# CHAPTER 9

# INTEGRATIVE SYNTHESIS

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# 9. INTEGRATIVE SYNTHESIS

## 9.1 INTRODUCTION

This chapter integrates key information drawn from the preceding detailed chapters, in order to provide coherent frameworks for assessment of human health and welfare risks posed by ambient PM in the United States. This chapter focuses on integrating newly available scientific information with the information available in the last review to address a series of overarching questions central to EPA's assessment of scientific information upon which the PM NAAQS review is to be based.

As such, this chapter is not intended merely as an Executive Summary of the information presented in the earlier chapters; nor is its goal to simply resummarize key information from those chapters. Rather, the goal of this chapter, in particular, is to provide an integrative exposition of the scientific basis for the Agency's review of the PM NAAQS. More specifically, this chapter attempts to provide an updated syntheses of scientific information in a manner so as to facilitate consideration of the key policy-related NAAQS issues to be addressed in the PM Staff Paper, prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) staff. These policy-related issues include consideration of information that will facilitate selection of appropriate indicators, averaging times, forms, and levels for primary and secondary PM NAAQS in the United States. EPA's consideration of these issues will be informed not only by the scientific information and integrative assessment presented here and throughout this document, but also by additional policy evaluations of scientific and technical information to be included in the PM Staff Paper so as to "bridge the gap" between the scientific review and the judgments required of the EPA Administrator in deciding whether to retain or revise the existing PM NAAQS.

While this synthesis focuses on what has been learned from the new information that has become available since the last PM NAAQS review, it also highlights important uncertainties that remain and recognizes the value of continuing research in a number of key areas. Although the delineation of detailed research recommendations in these areas is beyond the scope of this document, such recommendations are to be discussed in later PM research needs documents and/or research plans to be prepared by EPA.

In considering the PM-related health effects information, Section 9.2 builds specifically upon the integrative synthesis presented in Chapter 13 of the 1996 PM AQCD (U.S.

Environmental Protection Agency, 1996). The synthesis of PM-related health effects information in Section 9.2 is organized around five key questions dealing with the following central issues in assessing the available scientific information: (1) consideration of fine and coarse thoracic particles as separate subclasses of PM pollution, taking into account atmospheric science, exposure-related and dosimetric information; (2) the strengths and limitations of the epidemiological evidence of associations between health effects and fine and coarse thoracic PM within the mix of ambient air pollutants; (3) the extent to which effects observed in epidemiologic studies can plausibly be attributed to various indicators or constituents of ambient PM, acting alone and/or in combination with other pollutants, based on consideration of dosimetric, toxicologic, and other types of information; (4) characterization of susceptible subpopulations potentially at increased risk for PM-related health effects and factors enhancing such risk; and (5) potential public health impacts of human exposures to ambient PM in the United States.

With regard to considering PM-related welfare effects information important for decisions related to secondary standards, Section 9.3 then addresses each of the major types of welfare effects, first building upon information presented in the 1996 PM AQCD where possible. This includes allusion to key findings and conclusions on visibility and climate effects from Chapter 8 and on damage to manmade materials from Chapter 9 of the 1996 document and consideration of new findings discussed in Chapter 4 of this document. However, PM-related effects on vegetation and ecosystems were not addressed in the 1996 PM AQCD; and, so, the discussion of information concerning such effects is based entirely on pertinent findings characterized in Chapter 4 of this current document. Each subsection within Section 9.3 is organized around specific questions that serve to synthesize the available scientific information relevant to each of these classes of PM-related welfare effects.

## 9.2 SYNTHESIS OF AVAILABLE INFORMATION ON PM-RELATED HEALTH EFFECTS

The integrative synthesis of the latest available information on PM-related health effects poses especially large challenges in view of:

(1) The unprecedented amount of new information generated since the 1996 PM AQCD adds greatly to the complexity of any integrative assessment;

(2) Extensive new information available from epidemiologic studies, while reflecting much progress in addressing many research recommendations from the last review, also raises new issues or resurfaces issues earlier thought to have been adequately addressed but which remain important in interpreting the body of epidemiologic evidence and the characterization of its strengths and limitations;

(3) Much new information from dosimetric and toxicologic studies, making notable progress toward identifying and exploring potential mechanisms of action and characteristics of PM that may underlie health effects observed in experimental studies, but still leaving open many issues to be more fully addressed in the future.

Thus, despite substantial progress, uncertainties remain in integrating these different types of evidence into a coherent synthesis.

The present Section 9.2 is organized so as to first address the question of whether there is continued support for considering fine and coarse thoracic PM as separate subclasses of PM based on atmospheric science, air quality, exposure, and dosimetric information. Next, the strengths and limitations of epidemiologic evidence are evaluated, taking into account various factors, such as consideration of the magnitude, statistical significance, precision, and robustness of reported associations; assessment of the consistency or general concordance of study results and consideration of potential reasons for observed differences; and information from so-called intervention studies of "natural" or "found" experiments. Looking beyond just epidemiologic evidence, consideration is then given to toxicological and other information bearing on the biological plausibility of the PM-effects associations observed in the epidemiologic studies and the coherence of the effects associations to reach conclusions as to the extent to which observed effects can be attributed to ambient fine and coarse thoracic PM, acting alone and in combination with other pollutants. This is then followed by discussion of evidence regarding various risk factors (e.g., pre-existing disease and age-related factors) to reach conclusions as to which susceptible subpopulations may be potentially at special risk for health effects related to fine and coarse thoracic PM. Finally, information on the magnitude of population subgroups having health conditions thought to put them at increased risk for PM effects is discussed, to provide inputs to evaluation of potential public health impacts of exposures to ambient fine and coarse thoracic PM in the United States.

### 9.2.1 Does the Newly Available Information Continue to Support Consideration of Fine and Coarse Particles as Separate Subclasses of PM Pollution?

This question is addressed below by drawing upon the information and assessments found primarily in Chapters 2, 3, 5, and 6 of this document, concerning: the physics and chemistry of particle pollution, the measurement of airborne particles, relationships between ambient PM concentrations and population exposure, and PM dosimetry. The focus here is on whether the newly available science in these areas continues to support consideration of fine and coarse thoracic PM separately in the context of the Agency's periodic review of the PM NAAQS. The scientific bases for selecting certain key features of such standards, including health effects information and assessments presented in Chapters 7 and 8, will then be considered in addressing the subsequent questions posed and addressed beyond this Section.

#### 9.2.1.1 Key Points from Previous PM NAAQS Reviews

The primary focus in the last review was on thoracic particles, defined for regulatory purposes as being indexed by an indicator of $PM_{10}$, and whether fine and coarse thoracic particles should be addressed by separate standards with different indicators. The 1996 PM AQCD noted that the $PM_{10}$ indicator was established as a result of the 1987 PM NAAQS review, which concluded that the indicator for primary standards should represent those particles small enough to penetrate to the thoracic region (including the tracheobronchial and pulmonary regions) of the lower respiratory tract and generally exclude particles that deposit only in the extrathoracic region (the latter being particles previously included in the original TSP indicator).

As discussed in the 1996 PM AQCD, the natural division of ambient PM into fine particles and coarse particles has been understood since it was enunciated by Whitby (1978):

> "The distinction between "fine particles" and "coarse particles" is a fundamental one. There is now an overwhelming amount of evidence that not only are two modes in the mass or volume distribution usually observed, but that these fine and coarse modes are usually chemically quite different. The physical separation of the fine and coarse modes originates because condensation produces fine particles while mechanical processes produce mostly coarse particles . . . the dynamics of fine particle growth ordinarily operate to prevent the fine particles from growing larger than about 1 μm. Thus, the fine and coarse modes originate separately, are transformed separately, are removed separately, and are usually chemically different . . . practically all of the sulfur found in atmospheric aerosol is found in the fine particle fraction. Thus, the distinction between fine and coarse fractions is of fundamental importance to any discussion of aerosol physics, chemistry, measurement, or aerosol air quality standards."

Consistent with this view, the 1996 PM AQCD stated that the evidence indicates that "it would be appropriate to consider fine and coarse mode particles as separate subclasses" of PM pollution. This conclusion was based on various considerations:

(1) Differences in formation processes and sources of fine- and coarse-mode thoracic particles, as well as differences in chemical and physical properties, atmospheric residence times and distances transported in the atmosphere;

(2) Resulting differences in patterns of ambient population exposures to fine- and coarse-mode thoracic particles;

(3) Evidence from dosimetric studies showing differences in the fractions inhaled, deposited, and/or retained in various regions of the respiratory tract for fine- versus coarse-mode thoracic particles; and

(4) Evidence from health studies leading to conclusions that fine particles are more strongly associated with more serious health effects and that chemical components likely to have higher relative toxicity primarily occur in the fine fraction.

The EPA's selection of 2.5 μm as the appropriate cut-point between fine and coarse thoracic particles for use in defining an indicator for fine particle standards (i.e., $PM_{2.5}$) was based primarily on the following considerations:

(1) Recognition that overlap between fine and coarse thoracic particles occurs generally between 1 and 3 μm; within this range, no one cut-point would clearly separate fine- and coarse-mode particles in all areas. That is, although fine particles are generally below 1 μm in size, under high humidity conditions, constituent accumulation-mode particles may grow above 1 μm. Also, in clouds or fogs, accumulation-mode particles may grow to above 2.5 μm, and reactions of gases that dissolve in clouds or fog droplets may lead to formation of fine particles larger than 1 μm. As for coarse-mode particles, in dry dusty areas, resuspended coarse-mode soil particles may extend down to about 1 μm; and, in cities near oceans, coarse-mode sea salt particles may be found in the 1 to 2.5 μm range.

(2) The 2.5 μm cut-point was selected mainly to reflect the regulatory importance that was placed on defining an indicator for fine particle standards that would more completely capture fine-mode particles under all conditions likely to be encountered across the U.S., while recognizing that some small coarse-mode particles would also be captured by $PM_{2.5}$ monitoring.

(3) The decision to retain $PM_{10}$ as an indicator for standards to address coarse-mode particles, rather than an indicator that would not also encompass fine particles (e.g., $PM_{10-2.5}$), was based in large part on the very limited epidemiologic studies and air quality data specifically available for coarse-mode thoracic particles beyond that

which could be inferred or derived from $PM_{10}$ studies and data in areas dominated by coarse-mode particles.[1]

#### 9.2.1.2 Integration of New Information

The ensuing discussion builds upon the information base provided by the most salient key findings from the previous PM NAAQS review(s), while updating and integrating key findings and conclusions from the newly available studies assessed in earlier chapters of this document.

As a consequence of the decisions made by EPA in the last PM NAAQS review on the separate indicators for fine and coarse thoracic PM, a national $PM_{2.5}$ monitoring network was established that has provided extensive air quality data on $PM_{2.5}$ and, by difference between co-located $PM_{10}$ and $PM_{25}$ monitors, more limited data on $PM_{10-2.5}$. The availability of such air quality data has prompted the increased use of $PM_{2.5}$ and, to a far lesser degree, $PM_{10-2.5}$ as indicators in new epidemiologic studies, as well as increasing focus on these PM size fractions in other types of studies (exposure, dosimetry, toxicology, etc.).

##### *9.2.1.2.1 Physics and chemistry considerations*

Since the last PM NAAQS review, the physical and chemical properties of fine and coarse particles have become better understood. Nonetheless, the fundamental concept of the natural division of thoracic particles into somewhat overlapping ranges of fine and coarse particles, as illustrated in Figure 9-1, remains unchanged. Improved measurement techniques have provided additional information that refines the general characterization of particles below 0.1 μm diameter (i.e., ultrafine particles) from a single mode to a bi-modal structure. Thus, as shown in Figure 9-2, fine particles are now divided into three modes: a nucleation mode (< 0.01 μm); an Aitken mode (~0.01 to ~0.1 μm); and an accumulation mode (~0.1 to ~1.0 μm). The nucleation mode is transient and rapidly grows into the Aitken mode. The Aitken mode grows more slowly into the accumulation mode. Under normal atmospheric conditions, the accumulation mode does not grow into the coarse mode. However, as was previously recognized, an overlap between accumulation-mode fine particles and coarse particles can occur at times between 1 and 3 μm. For example, under high humidity conditions, accumulation-mode

[1] As discussed in Chapter 1, subsequent litigation resulted in the court finding the use of $PM_{10}$ as an indicator for coarse-mode particles (in conjunction with $PM_{2.5}$ standards) to be arbitrary, since $PM_{10}$ includes all fine particles; the court remanded this aspect of EPA's 1997 decision to the Agency for further consideration.

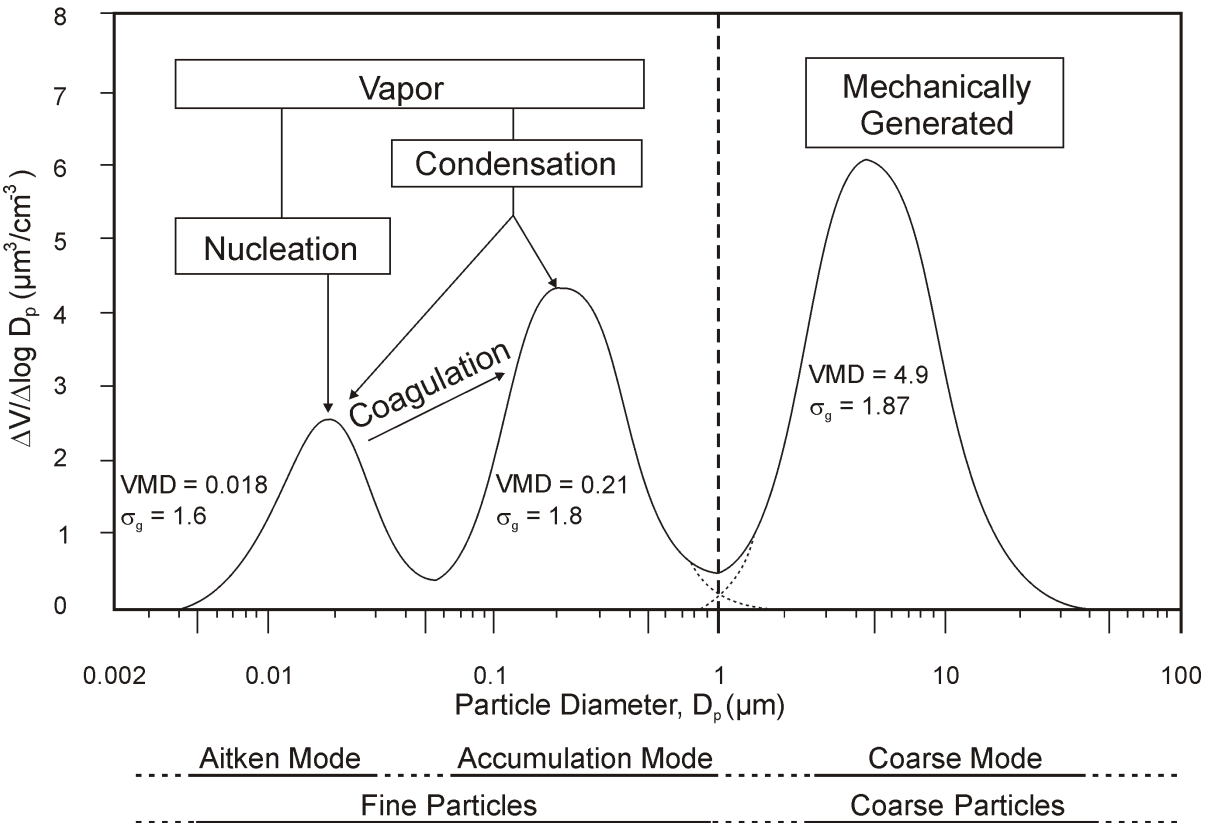


**Figure 9-1. Volume size distribution, measured in traffic, showing fine and coarse particles and the Aitken and accumulation modes of fine particles; VMD (volume median diameter) and $\sigma_g$ (geometric standard deviation); and formation and growth mechanisms.**

Source: Adapted from Wilson and Suh (1997).

particles may grow above 1 μm, and in dry dusty areas, coarse PM (e.g., resuspended soil) may have a tail reaching to 1 μm or below. Sampling fine and coarse particles using a cut point of 2.5 μm, as was specified as a regulatory choice in the last PM NAAQS review, thus helps to ensure that high concentrations of accumulation-mode particles will be collected even under high humidity conditions. However, it is recognized that a 1 μm cut point, using monitors that dehumidify the airstream before collecting particles, might give a better separation of fine- and coarse-mode particles, especially in dry, dusty areas.

It takes increasing amounts of energy to break non-biological materials into smaller and smaller particles. As a result, natural processes, such as suspension of soil dust by wind,

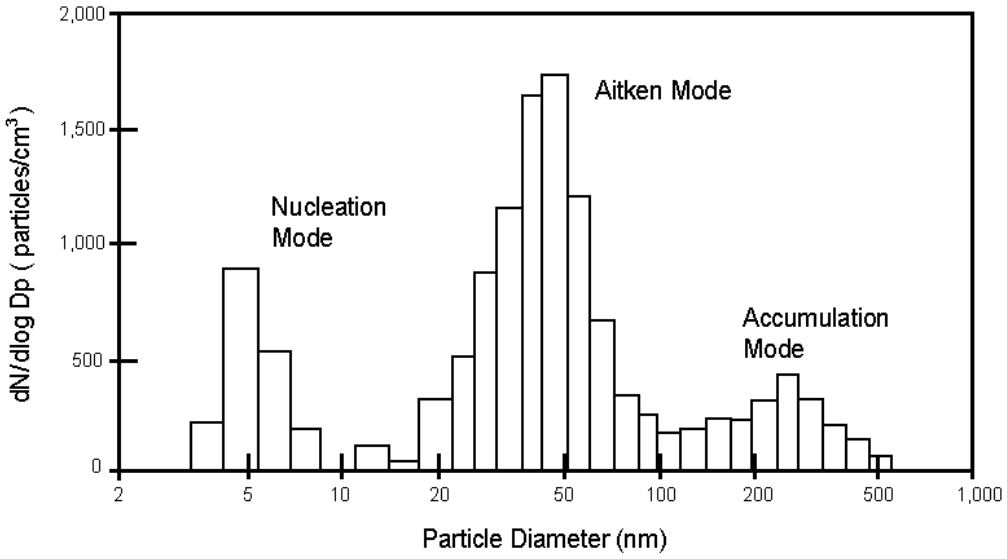


**Figure 9-2. Submicron number size distribution observed in a boreal forest in Finland showing the tri-modal structure of fine particles.**

Source: Mäkelä et al. (1997).

produce few particles below 1 μm in diameter. However, in the years since the 1996 PM AQCD, it has been discovered that biological material, although originally in the coarse mode, may deteriorate or fragment and produce particles in the fine-particle size range. Thus, fragments of pollen, endotoxins, and other biological material may be found in the fine-particle size range. Progress has also been made in understanding the semivolatile components of PM (particle-bound water, ammonium nitrate, and semivolatile organic compounds) and new techniques have been developed to measure the semivolatile components of mass, either separately or included with the nonvolatile component. Much progress has also been made in understanding the many organic compounds formed in the atmospheric reactions of biogenic and anthropogenic hydrocarbons, including condensible species that form organic particles. Progress also has been made in measurement of carbonaceous particles from diesel engines.

Progress of the above types has helped to enhance our understanding of ambient aerosol components and interrelationships between them that may contribute to ambient PM-related effects. Of much importance, for example, is emerging new evidence related to the role of particle-bound water and associated submicron PM constituents serving as vectors by which

water soluble gases (e.g., $SO_2$), short-lived reactive species (e.g., peroxides), and organic species (e.g., formaldehyde) present in atmospheric aerosol mixes can be delivered in enhanced proportions to lower regions of the respiratory tract (as discussed in Section 9.2.3). The importance of nonbiological ambient PM components serving as carriers or vectors enhancing deposition of bioaerosols (e.g., allergen-laden pollen fragments and endotoxins) in the lower respiratory tract is also noted in Section 9.2.3.

The 1996 PM AQCD listed properties of fine and coarse particles. Because of the increasing interest in ultrafine particles and additional information on their properties, this current document provides new information on the chemical and physical properties of ultrafine and accumulation-mode fine particles and coarse particles, as shown in Table 9-1. As shown, ultrafine and accumulation-mode particles share similar formation processes and mechanisms, sources, and compositions. However, their fate and transport are quite dissimilar. In breathing and infiltration into homes, ultrafine particles are removed rather efficiently by diffusion to surfaces. In the atmosphere, ultrafine particles are removed largely by coagulation with other ultrafine particles (or accumulation-mode particles) and grow into the accumulation mode. Coarse particles, however, are removed from the atmosphere rather rapidly by gravitational settling. With regard to the volume or mass of ambient PM, accumulation-mode and coarse-mode particles both contribute appreciably in most areas, with very little contribution from ultrafine particles. With regard to particle surface area, however, ultrafine and accumulation-mode particles both contribute appreciably, with very little contribution from coarse-mode particles.

Ultrafine, accumulation mode, and coarse particles also behave differently with regard to exposure and dosimetric considerations, as discussed below, as well as in toxicologic and epidemiologic studies, as discussed in subsequent sections of this chapter.

#### *9.2.1.2.2 Exposure-related considerations*

The critical relationship to be considered is that between ambient PM *concentrations* and *personal exposures* to ambient PM. (Ambient PM means that PM measured at a community monitoring site, or the average over several such sites.) It is convenient to consider two aspects of this relationship. One important aspect is the relationship between the ambient concentration measured at one or more monitoring sites, and the distribution of outdoor concentrations across

## TABLE 9-1. COMPARISON OF AMBIENT PARTICLES, FINE PARTICLES (Ultrafine Plus Accumulation-Mode) AND COARSE PARTICLES

| | Fine | | |
|---|---|---|---|
| | **Ultrafine** | **Accumulation** | **Coarse** |
| Formation Processes: | Combustion, high-temperature processes, and atmospheric reactions | | Break-up of large solids/droplets |
| Formed by: | Nucleation<br>Condensation<br>Coagulation | Condensation<br>Coagulation<br>Reactions of gases in or on particles<br>Evaporation of fog and cloud droplets in which gases have dissolved and reacted | Mechanical disruption (crushing, grinding, abrasion of surfaces)<br>Evaporation of sprays<br>Suspension of dusts<br>Reactions of gases in or on particles |
| Composed of: | Sulfate<br>Elemental carbon<br>Metal compounds<br>Organic compounds with very low saturation vapor pressure at ambient temperature | Sulfate, nitrate, ammonium, and hydrogen ions<br>Elemental carbon<br>Large variety of organic compounds<br>Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc.<br>Particle-bound water | Suspended soil or street dust<br>Fly ash from uncontrolled combustion of coal, oil, and wood<br>Nitrates/chlorides/sulfates from $HNO_3$/HCl/$SO_2$ reactions with coarse particles.<br>Oxides of crustal elements (Si, Al, Ti, Fe)<br>$CaCO_3$, $CaSO_4$, NaCl, sea salt<br>Pollen, mold, fungal spores<br>Plant and animal fragments<br>Tire, brake pad, and road wear debris |
| Solubility: | Probably less soluble than accumulation mode | Largely soluble, hygroscopic, and deliquescent | Largely insoluble and nonhygroscopic |
| Sources: | Combustion<br>Atmospheric transformation of $SO_2$ and some organic compounds<br>High temperature processes | Combustion of coal, oil, gasoline, diesel fuel, wood<br>Atmospheric transformation products of $NO_x$, $SO_2$, and organic compounds, including biogenic organic species (e.g., terpenes)<br>High-temperature processes, smelters, steel mills, etc. | Resuspension of industrial dust and soil tracked onto roads and streets<br>Suspension from disturbed soil (e.g., farming, mining, unpaved roads)<br>Construction and demolition<br>Uncontrolled coal and oil combustion<br>Ocean spray<br>Biological sources |
| Atmospheric half-life: | Minutes to hours | Days to weeks | Minutes to hours |
| Removal Processes: | Grows into accumulation mode<br>Diffuses to raindrops | Forms cloud droplets and rains out<br>Dry deposition | Dry deposition by fallout<br>Scavenging by falling rain drops |
| Travel distance: | < 1 to 10s of km | 100s to 1000s of km | < 1 to 10s of km (100s to 1000s in dust storms) |

Source: Adapted from Wilson and Suh (1997).

an area (e.g., outside homes and other microenvironments). This relationship will depend in part on the uniformity with which the PM indicator of interest is distributed across the community. For time-series epidemiologic analyses of associations between 24-h concentrations of ambient PM and health endpoints, another important parameter in this relationship is the day-to-day correlation of 24-hour concentration values at various monitoring sites in the community. For long-term epidemiologic analyses, the variation in the seasonal or yearly average at various sites in the community is the important parameter. Much new information on the uniformity of $PM_{2.5}$ and $PM_{10-2.5}$ concentrations across cities is available from the new monitoring networks and is presented in detail in Chapter 3. The data show that, in general, $PM_{2.5}$ is more evenly distributed than $PM_{10-2.5}$ in terms of both daily/seasonal/yearly averages and day-to-day correlations, although there are significant differences among cities. Little is known about the spatial distribution of ultrafine particle concentrations. However, because of their rapid growth into the accumulation mode, they probably tend to be concentrated most heavily near sources such as traffic and, thus, likely have a far more heterogeneous distribution across a community.

The second aspect is the relationship between the concentration of PM outdoors and the concentration of that outdoor PM which has infiltrated into the home or other microenvironment. The relationship between the concentrations of ambient particles outdoors, $C$, and the indoor concentrations of those ambient particles that have infiltrated indoors, $C_{ai}$, is given by

$$F_{INF} = C_{ai} / C = Pa /(a + k), \qquad 9\text{-}1$$

where $P$ is the penetration factor; $a$ is the air exchange rate; and $k$ is the particle deposition rate. $P$ and $k$ vary with particle size, so that infiltration factor, $F_{INF}$, also varies with particle size. As shown in Figure 9-3, the infiltration factor is high for accumulation-mode particles and decreases to low levels with decreasing size within the ultrafine range and with increasing size within the coarse-mode range. Exposure-related relationships for the three particle size classes are summarized in Table 9-2.

In most community time-series studies and long-term cohort studies, the ambient concentration is used as a surrogate for personal exposure to ambient PM (ambient exposure). For the ambient concentration to be a satisfactory surrogate, there must be a reasonable correlation between ambient concentration and ambient exposure. Because of the lower and

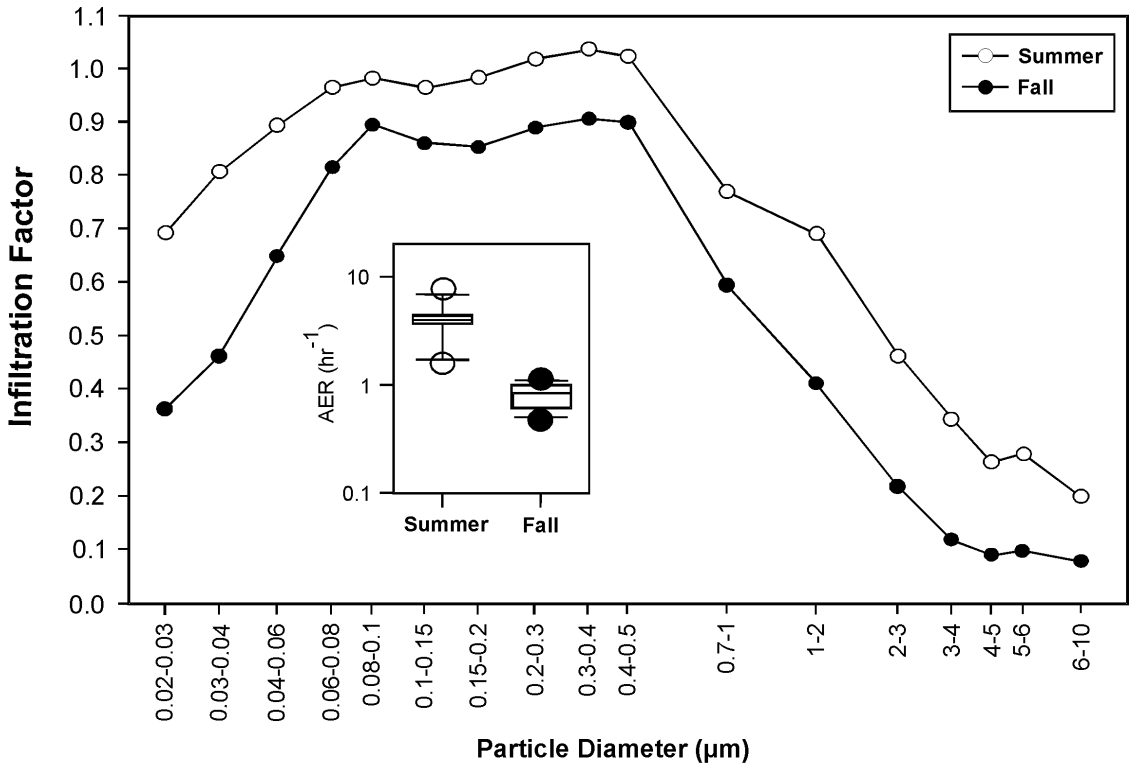


**Figure 9-3. Geometric mean infiltration factor (indoor/outdoor ratio) for hourly nighttime, nonsource data for two seasons. Box plots of air exchange rates are shown as inserts for each plot (Boston, 1998)**.

Source: Long et al. (2001).

**TABLE 9-2. EXPOSURE-RELATED RELATIONSHIPS FOR PARTICLE SIZE FRACTIONS**

| | Ultrafine | Accumulation-Mode | Thoracic-Coarse |
|---|---|---|---|
| Even distribution across city | probably not | frequently | seldom |
| Site-to-site correlation | probably low | frequently high | frequently low |
| Infiltration factor | generally low | high | generally low |

more variable infiltration factors for ultrafine and coarse particles and their less even distribution and lower site-to-site correlations across the community, it is likely that their ambient concentrations will be a poorer surrogate for their ambient exposures than is the case for $PM_{2.5}$. Nonambient PM may also be responsible for health effects. However, since the ambient and nonambient components of personal exposure are independent, the health effects due to nonambient PM exposures generally will not bias the risk calculated for ambient PM exposures.

#### *9.2.1.2.3 Dosimetric considerations*

The fraction of inhaled particles that are deposited in the various regions of the lung depends on the particle size, the breathing route (nasal or oral), the breathing frequency (breaths per minute), and the volume of air inhaled (tidal volume). The fractional depositions in the extrathoracic (ET), tracheobronchial (TB), and gas exchange or alveolar (A) regions of the respiratory tract are shown as a function of particle size in Figure 9-4 for nasal and oral breathing at two levels of activity (resting and light exercise). Particles in the accumulation-mode size range generally have very low deposition fractions, especially in the ET and TB regions, that are relatively insensitive to breathing pattern or exercise. However, for nose breathing the deposition of larger accumulation-mode particles in the ET region does increase with exertion. Thus, most accumulation mode particles that enter the lungs are exhaled rather than deposited.

Ultrafine particles generally have much higher fractional depositions than accumulation mode particles. However, the smaller nucleation-mode (< 0.01 μm) ultrafine particles behave differently from the larger Aitken mode (0.01 to 0.1 μm) ultrafine particles. With decreasing particle size below 0.1 μm, the total deposition of particles increases, and the pattern of deposition within the respiratory tract slowly moves proximally, i.e., toward the ET region. This shift in the pattern of deposition is quite obvious for decreases in particle size below 0.01 μm where A deposition fractions rapidly decline and the ET deposition fractions correspondingly increase. The TB deposition fraction increases to a maximum near 3 nm. For the Aitken mode particles, the deposition fraction for the A region increases with exertion whereas in the TB region it decreases. Deposition fractions in the A region for particles less than 1 μm are relatively insensitive to route of breathing.

The fractional deposition for coarse particles is even more complex. For both the A and TB regions, the deposition fraction increases with particle diameter above 1 μm, reaches a peak

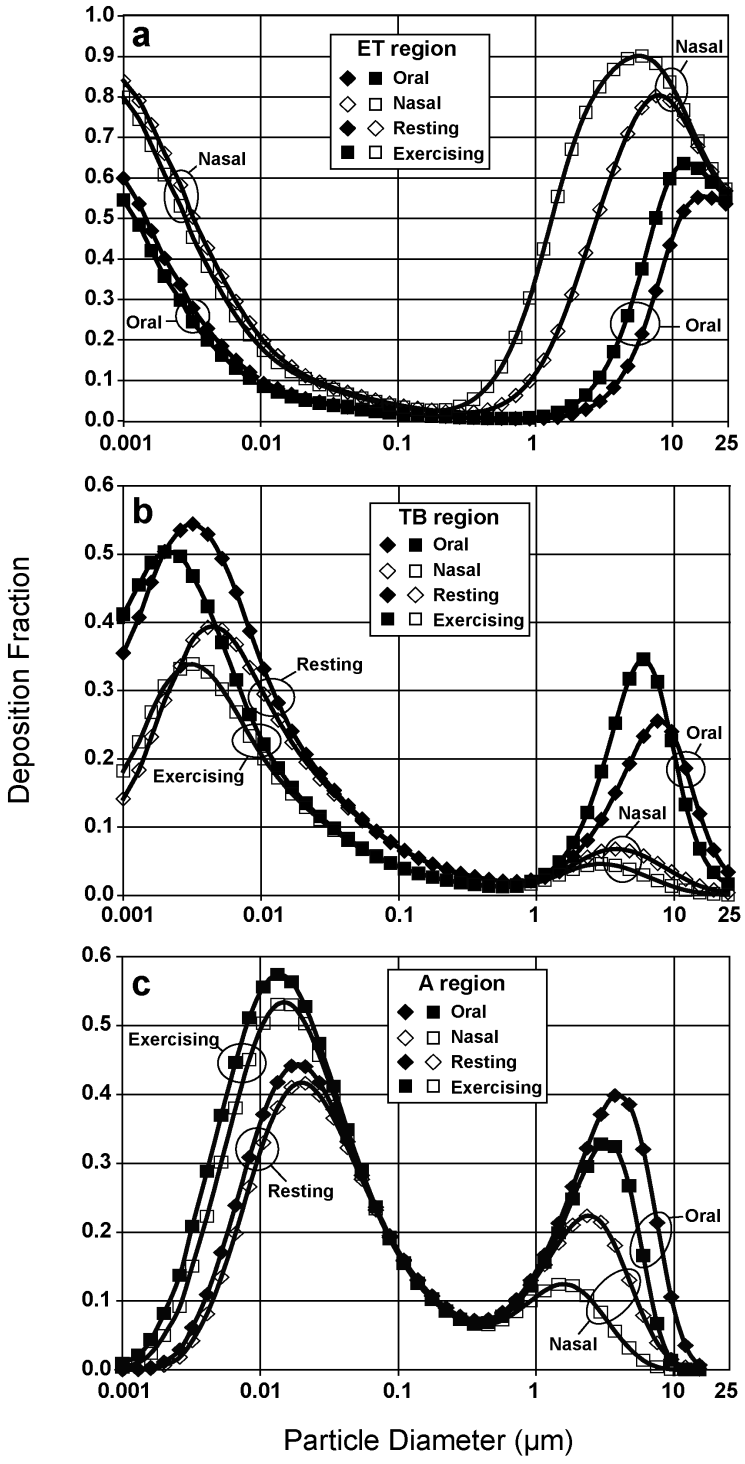


**Figure 9-4. Deposition fraction as a function of particle size for nasal and oral breathing during rest and exercise: (a) extrathoracic (ET), (b) tracheobronchial (TB), and (c) alveolar (A) regions. Data shown here were calculated with the ICRP model and were also shown in Figures 6-16 and 6-17 along with similar results from the MPPD model. The data below 0.01 μm are uncertain but are shown to indicate trends. Note the different scale for the ET region.**

before the diameter reaches 10 μm, and then declines. The deposition fractions for the A and TB regions are lower during nasal breathing because a large fraction of the coarse particles deposit within the nose. For mouth breathing, the A and TB deposition fractions are higher than during nasal breathing but not as high as those for the ultrafine mode during mouth breathing. For mouth breathing, the deposition fractions for both the A and the TB regions are greater for coarse particles than for accumulation-mode particles. Even for nose breathing, some coarse particles, of a specific size, will have higher deposition fractions than accumulation mode particles.

In general, given these complex deposition patterns, there are no sharp cut points that clearly distinguish between particle size ranges with relatively high versus relatively low fractional deposition rates. For example, in the ET region, particles ranging in size from roughly 0.01 μm on up to ~1 μm (for nasal breathing) to over 3 μm (for oral breathing) exhibit relatively low fractional deposition rates. For the TB region, relatively low rates are exhibited by particles ranging in size from roughly 0.05 μm up to ~2 μm (for oral breathing) to over 10 μm (for nasal breathing). For the A region, relatively low rates are exhibited not only by particles from ~0.1 to 1 μm, but also for particles in the low end of the ultrafine size range and in the upper end of the coarse-mode range. Thus, while differences in dosimetric properties also generally support the division of ambient particles into fine and coarse fractions, dosimetric considerations now further suggest subdividing fine particles, although appropriate size cut point(s) would depend in part on the relative importance placed on deposition in the different regions of the lung.

#### 9.2.1.3 Summary and Conclusions

The fundamental distinctions between fine and coarse ambient particles based on the physics and chemistry of ambient particles that were articulated in the last review, including differences in formation, sources, composition, fate, and transport, remain generally unchanged. However, some important advances have been made in our understanding of such distinctions, especially with regard to characteristics of particles below ~0.1 μm in diameter (ultrafine particles). In particular, whereas fine particles were previously characterized in two modes, they are now characterized in terms of three modes, and distinctions among these modes allow for more differentiation in characterizing properties of fine particles. Also, progress has been made in better understanding the size distribution of biological materials. While previously

understood mainly to be present in the coarse particle size range, newly available information indicates that such particles (e.g., pollen grains, endotoxins) may fragment or deteriorate into the fine particle size range. This information expands our understanding of the types of particles that can occur in particular within the intermodal size range of ~1 to ~3 μm.

Data now available from the new national $PM_{2.5}$ monitoring network and speciation sites have allowed for better assessments of exposure-related considerations which broaden but do not fundamentally change our understanding of the substantial differences between fine particles in the accumulation mode and coarse particles. Relationships between ambient PM concentrations and personal exposure to ambient PM are now better understood, primarily for fine particles, but also to a more limited degree for coarse particles. For example, new data reinforce our earlier understanding that ambient concentrations of fine particles (measured as $PM_{2.5}$) are typically more highly correlated and/or are more uniform across community monitors within an urban area than are coarse particles (measured as $PM_{10-2.5}$), although in some areas the differences are much less pronounced than in others. More limited data and knowledge of the behavior of ultrafine particles suggest that spatial distributions of their concentrations (which decrease quickly from peak levels around major highways) are likely more similar to those for coarse particles (which decrease quickly from peak levels around primary sources) than for other (accumulation-mode) fine particles. Further, new studies reinforce our earlier understanding that fine particles generally infiltrate indoors much better than do either coarse or ultrafine particles. Thus, central site ambient concentration measurements are a better surrogate for population exposure to accumulation-mode fine particles, measured as $PM_{2.5}$, than for either coarse or ultrafine particles. Such similarities between ultrafine particles and coarse particles are based on far more limited data, highlighting a need for further research on these particle size ranges. However, since ultrafine particles represent only a very small mass fraction of typical ambient fine particles, the most important exposure-related distinctions for particle mass, but not necessarily for surface area, remain between fine particles (measured as $PM_{2.5}$) and coarse particles (measured as $PM_{10-2.5}$).

Newly available dosimetry information continues to reinforce important distinctions between fine and coarse particles, and submodes within fine particles, with regard to deposition patterns within the respiratory tract. In general, while deposition patterns within the major respiratory tract regions as a function of particle size are complex and dependent in varying

degrees on breathing route and ventilation levels, accumulation-mode particles exhibit distinctly lower fractional deposition rates in any of the major respiratory tract regions than do ultrafine or coarse particles on average. With increasing levels of activity, associated increases in breathing rate, and associated increased oral nasal/oral breathing, the fractional deposition tends to increase in the TB and A regions for ultrafine and coarse particles, while decreasing in the ET region. Peak fractional deposition rates occur approximately in the mid-range of ultrafine and coarse particle sizes in the A region, with the peaks tending more to the lower end of the ultrafine size range and the upper end of the coarse particle range in the TB and ET regions. Thus, it is difficult to characterize more specific size fractions within the range of thoracic particles that would clearly delineate ranges of relatively high and relatively low fractional deposition across all respiratory tract regions.

Overall, then, the above considerations generally reinforce the recommendation made in the 1996 PM AQCD that fine and coarse atmospheric particles be considered as separate subclasses of PM pollution. Further progress in characterizing these subclasses of pollutants will depend upon obtaining additional ambient concentration/composition, exposure-related, and dosimetric data, especially to supplement the far more limited data on coarse particles. Also, new information suggests that important exposure-related and dosimetric distinctions exist between ultrafine and accumulation-mode particles within the fine fraction, although there is as yet only very limited data available to characterize these distinctions. Thus, it would also be particularly useful to obtain additional ambient measurements of ultrafine particles to facilitate future research to investigate their toxic potential.

### 9.2.2 How Does the Newly Available Information Inform Our Judgments about the Strengths and Limitations of the Epidemiologic Evidence for Health Effects Related to Ambient Fine and Coarse Thoracic PM, Acting Alone and/or in Combination With Other Pollutants?

In assessing the strengths and limitations of the epidemiologic evidence, information is drawn primarily from Chapter 8, as well as from Chapter 5 of this document. More specifically, as discussed in Section 8.1.4, the approach used here to assess the epidemiologic information focuses on a number of salient aspects of associations between mortality and morbidity effects and short- and long-term exposures to ambient thoracic PM and common copollutants. This includes consideration of: (1) the magnitude, statistical significance, precision/power, and

robustness of reported health effects associations for various size fractions of ambient PM, as well as for PM from various types of sources; (2) assessment of the consistency or general concordance of study results across the various PM size fractions, and consideration of potential reasons for observed differences; and (3) information from so-called "intervention" studies or "found experiments" as to the extent to which reductions in PM-related air pollution have been observed to be associated with improvements in health measures. In assessing the robustness of the PM-related health effects associations, consideration is given to potential confounding by looking at associations with PM alone and with other common gaseous air pollutants and associations based on different statistical modeling approaches. Exposure-related information is also considered to assess the potential consequences of exposure misclassification. In assessing these issues in light of the newly available information, Section 9.2.2.2 is organized primarily to focus on discussions of the evidence of associations for $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, and source-oriented PM.

### 9.2.2.1 Key Points from 1996 Integrative Synthesis

Based on the then available PM epidemiologic studies, the 1996 PM AQCD, arrived at the following overall conclusions:

> "The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiology studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS." (U.S. EPA, 1996, p. 13-92).

The 1996 PM AQCD went on to state further that, while the epidemiological studies indicate increased health risks associated with exposure to PM, alone or in combination with other air pollutants, the role of PM as an independent causal factor has not been completely resolved, based on the available studies using multiple air pollutants as predictors of health effects (U.S. EPA, 1996, p. 13-92).

#### 9.2.2.2 Integration of New Information

Many recent epidemiologic studies have built upon what was previously know, showing statistically significant associations of ambient PM with a variety of cardiovascular and respiratory health endpoints, including mortality, hospital admissions, emergency department visits, other medical visits, respiratory illness and symptoms, physiological or biochemical changes related to the cardiovascular system, and physiologic changes in pulmonary function. Associations have been consistently observed between short-term and all of these endpoints; and long-term PM exposure has been associated with increased risk of mortality, development of respiratory disease, and changes in lung function. As summarized in Appendices 8A and 8B, epidemiologic studies have been conducted in areas across the U.S. and Canada, as well as in Central and South America, Europe, Asia and Australia, and various methods have been used to measure ambient PM concentrations. Considering the evidence from the full body of epidemiologic studies using various PM indicators, the available findings demonstrate well that human health effects are associated with ambient PM. Discussions in the following sections will focus primarily on studies conducted in the U.S. and Canada using various mass measurements of thoracic particles (e.g., $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$).

The etiology of most air pollution-related health outcomes is highly multifactorial, and the impact of ambient air pollution exposure on these outcomes may be small in comparison to that of other etiologic factors (e.g., smoking). In contrast with the marked increase in health effects observed during historic episodes of very high air pollution levels, relatively small effect estimates would generally be expected with current ambient PM concentrations in the U.S.

In epidemiologic studies of ambient air pollution, associations with health outcomes have been observed quite consistently, frequently being statistically significant or nearly so. Also, magnitudes and significance levels of observed air pollution-related effects estimates would be expected to vary somewhat from place to place, if the observed epidemiologic associations denote actual effects, because (a) not only would the complex mixture of PM vary from place to place, but also (b) affected populations may differ in characteristics that could affect susceptibility to air pollution health effects, and (c) areas may differ in factors that affect population exposures to ambient pollutants.

#### *9.2.2.2.1 Strength of epidemiologic evidence on health effects associations with PM*

***Short-term Exposure Studies***

Many new epidemiologic studies have built upon what was available in the 1996 PM AQCD. These include several multi-city studies that can provide more precise estimates of effects than individual city studies, offer consistency in data handling and modeling, allow for systematic evaluation of geographic patterns in effects, and clearly do not suffer from potential omission of negative findings due to "publication bias." In addition, there are studies of new health indices (e.g., physician visits) and cardiovascular health outcomes, analyses that provide insight into the sensitivity of PM effects to alternative statistical modeling, new assessments on the potential for confounding by gaseous copollutants, and new evidence from "found experiments" that evaluate improvement in health with reductions in air pollution levels.

The results from key U.S. and Canadian studies on short-term PM exposure for several commonly-used health outcomes — mortality, hospitalization and medical visits – are presented in Figures 9-5 and 9-6. Epidemiologic studies of short-term air pollution exposures have also evaluated other health outcomes (e.g., respiratory symptoms, medical visits, cardiovascular health indicators, lung function changes). In addition, Chapter 8 also summarizes the results of numerous studies of health effects linked with long-term exposures (discussed later in Section 9.2.2.2.2). Thus, these figures do not attempt to present the full range of epidemiological study results, but rather to illustrate results for a few major health outcome categories commonly used in time-series epidemiology studies of short-term PM exposure effects. Appendix Tables 9A-1 and 9A-2 present a fuller array of results for short-term (24 h) ambient PM exposure effects on mortality and morbidity, respectively, including information on effect size estimates derived by varying models for different mortality and morbidity endpoints for U.S. and Canadian cities.

Figures 9-5 and 9-6 draw from findings presented in separate figures for the various endpoints in Chapter 8 to pull together results of studies for the three major PM mass indicators. As is the case for figures in Chapter 8, the results are drawn from U.S. and Canadian studies that either did not use GAM or were reanalyzed to address GAM-related questions. Single-pollutant (PM only) results are presented for purposes of comparison across studies, and it is noted that multipollutant model results are presented and discussed in Chapter 8 (see especially Section 8.4.3). In many studies, the authors identified the model or lag period that appeared to best fit

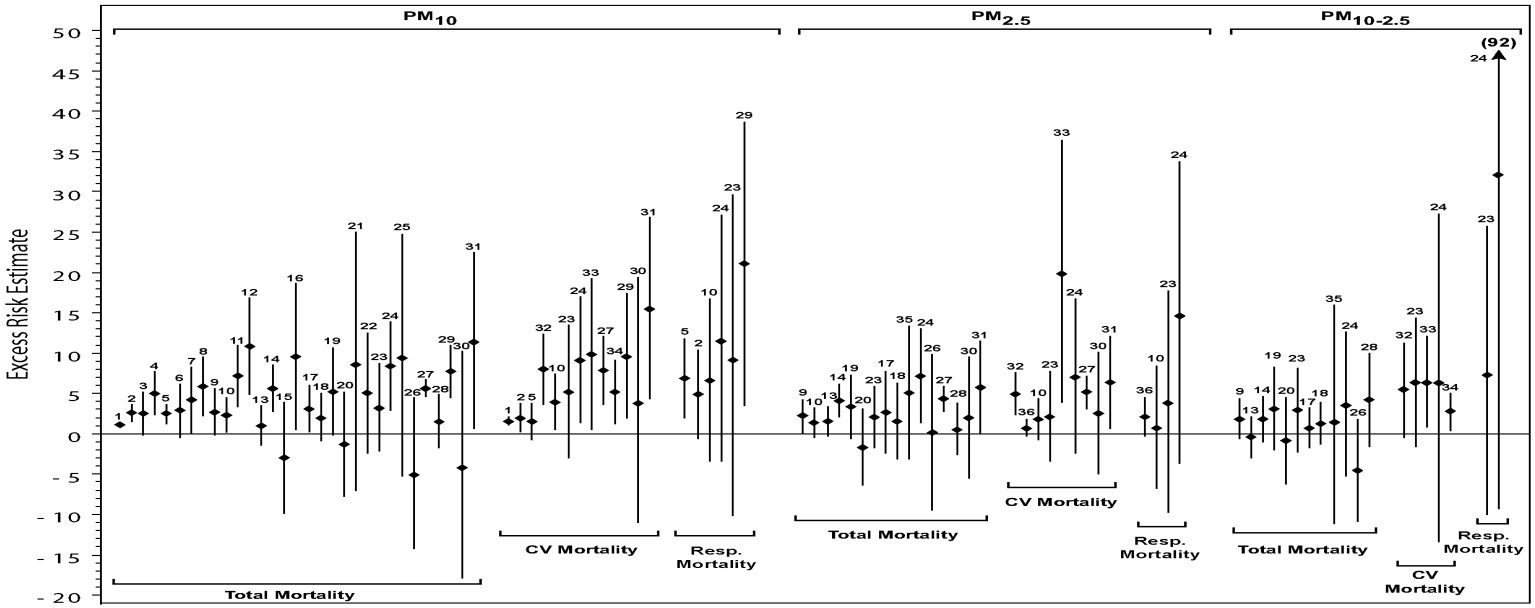


**Figure 9-5. Excess risk estimates for total non-accidental, cardiovascular, and respiratory mortality in single-pollutant models for U.S. and Canadian studies. PM increments: 50 µg/m$^3$ for $PM_{10}$ and 25 µg/m$^3$ for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.**

1. Dominici et al. (2003a), 90 U.S. cities
2. Moolgavkar (2003), Cook County
3. Kinney et al. (1995), Los Angeles
4. Schwartz (2003a), Chicago
5. Ito and Thurston (1996), Cook County
6. Schwartz (2003a), Pittsburgh
7. Styer et al. (1995), Cook County
8. Schwartz (2003a), Detroit
9. Burnett and Goldberg (2003), 8 Canadian cities
10. Moolgavkar (2003), Los Angeles
11. Schwartz (2003a), Seattle
12. Schwartz (2003a), Minneapolis
13. Klemm and Mason (2003), St. Louis
14. Klemm and Mason (2003), Boston
15. Schwartz (2003a), Birmingham
16. Schwartz (2003a), New Haven
17. Chock et al. (2000) Pittsburgh (< 75 y.o.)
18. Chock et al. (2000) Pittsburgh (75+ y.o.)
19. Klemm and Mason (2003), Kingston-Harriman
20. Klemm and Mason (2003), Portage
21. Schwartz (2003a), Canton
22. Schwartz (2003a), Spokane
23. Ito (2003), Detroit
24. Fairley (2003), Santa Clara County
25. Schwartz (2003a), Colorado Springs
26. Klemm and Mason (2003), Topeka
27. Tsai et al. (2000), Newark
28. Klemm and Mason (2003), Steubenville
29. Pope et al. (1992), Utah Valley
30. Tsai et al. (2000), Elizabeth
31. Tsai et al. (2000), Camden
32. Lipfert et al. (2000a), Philadelphia
33. Mar et al. (2003), Phoenix
34. Ostro et al. (2003), Coachella Valley
35. Klemm and Mason (2000), Atlanta
36. Ostro et al. (1995), Southern California

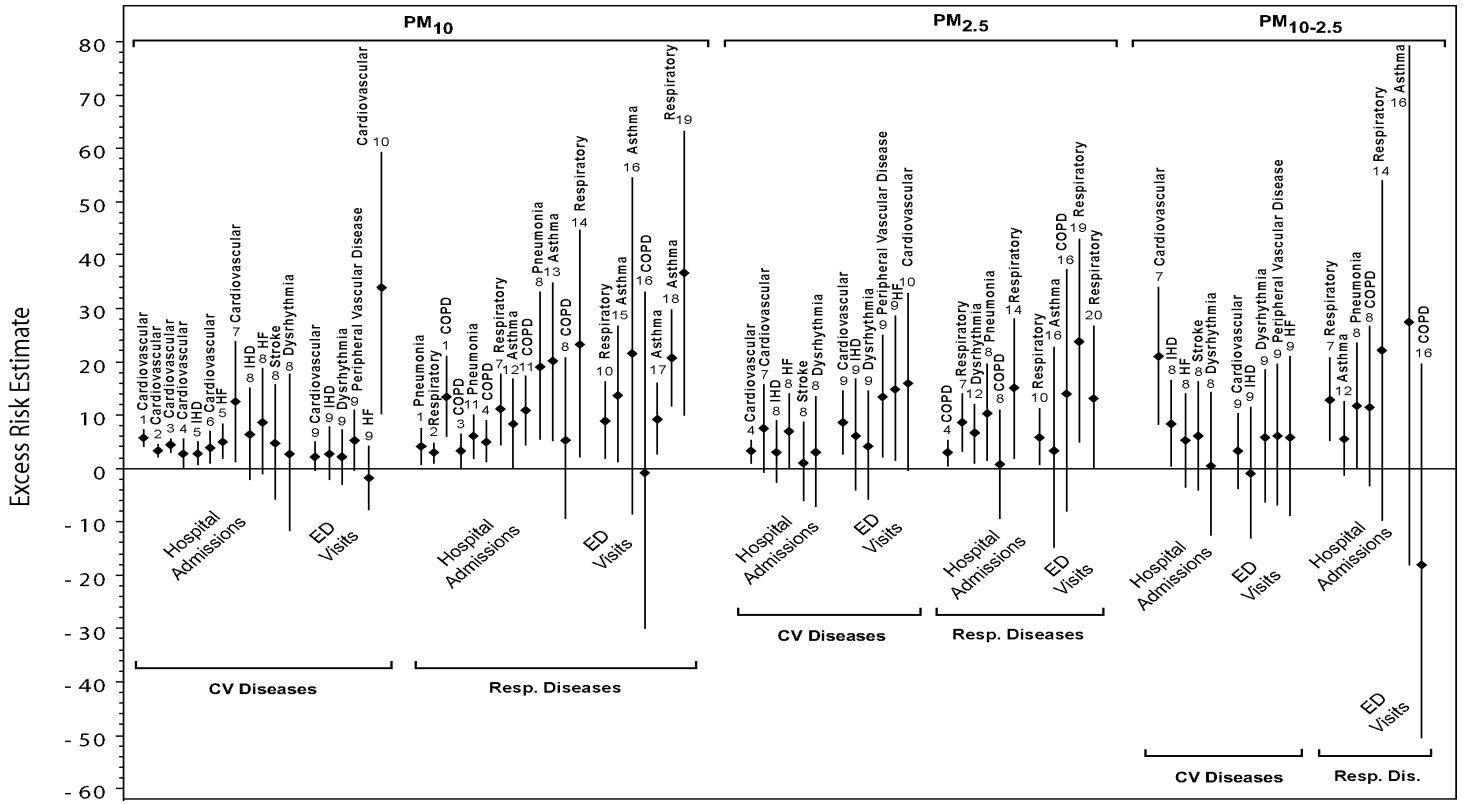


**Figure 9-6. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models from U.S. and Canadian studies. PM increments: 50 µg/m$^3$ for $PM_{10}$ and 25 µg/m$^3$ for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.**

1. Zanobetti and Schwartz (2003) U.S. 14 cities
2. Linn et al. (2000), Los Angeles
3. Moolgavkar (2003), Cook County
4. Moolgavkar (2003), Los Angeles
5. Schwartz and Morris (1995), Detroit
6. Morris and Naumova (1998), Chicago
7. Burnett et al. (1997), Toronto
8. Ito (2003), Detroit
9. Metzger et al. (2004), Atlanta
10. Stieb et al. (2000), St. John
11. Schwartz (1994), Detroit
12. Sheppard (2003), Seattle
13. Nauenberg and Basu (1999), Los Angeles
14. Thurston et al. (1994), Toronto
15. Tolbert et al. (2000b), Atlanta
16. Tolbert et al. (2000a), Atlanta
17. Lipsett et al. (1997), Santa Clara County
18. Choudhury et al. (1997), Montreal
19. Delfino et al. (1997), Montreal
20. Delfino et al. (1998), Montreal

the data, and those results are presented here. For other studies in which results for several lag periods are presented, results from the model with the most precise results (e.g., largest t-statistic) are shown. The results of models using different lag periods from time-series epidemiologic studies are also presented and discussed in Chapter 8 (see Section 8.4.4). Finally, for each health outcome, the results are presented in the figures in order (from left to right) of decreasing study power, using as an indicator the product of the number of study days and number of health events per day.

In Figure 9-5, effect estimates for associations between mortality and PM are grouped both by PM indicator ($PM_{10}$, $PM_{2.5}$, and $PM_{10-2.5}$) and by mortality category (total non-accidental, cardiovascular or cardiorespiratory, and respiratory). Looking across the results with particular focus on the more precise estimates, some general observations can be made:

(1) Most all of the associations between $PM_{10}$ and total mortality are positive and over half are statistically significant, including most all of those with more precise estimates. All associations reported between $PM_{10}$ and cardiovascular and respiratory mortality are positive; most of the cardiovascular mortality associations are also statistically significant, where as most of the respiratory associations are less precise and not statistically significant. In studies where all three types of mortality were evaluated, the effects estimates for respiratory mortality were generally larger and less precise. The more precise effect estimates range from ~1% to 8% increased risk of mortality per 50 $\mu g/m^3$ $PM_{10}$.

(2) A similar pattern can be seen for $PM_{2.5}$, though fewer studies are available, and the effects estimates are generally somewhat less precise and less frequently statistically significant. In particular, most all of the $PM_{2.5}$ associations with total mortality are positive, although less than half are statistically significant. All $PM_{2.5}$ associations with cardiovascular and respiratory mortality are positive; about half of the cardiovascular associations, but none of the respiratory associations, are statistically significant. The more precise effect estimates range from about 2% to 6% increased risk of mortality per 25 $\mu g/m^3$ $PM_{2.5}$.

(3) Still fewer studies have used $PM_{2.5}$ measurements. Though the effect estimates are most all positive and similar in magnitude to those reported for $PM_{2.5}$ and $PM_{10}$, few reach statistical significance. In this figure, statistically significant associations are seen only between cardiovascular mortality and $PM_{10-2.5}$, and only in Phoenix (Mar et al., 2003) and Coachella Valley, CA (Ostro et al., 2003).

The results for U.S. and Canadian studies are generally consistent with those presented in Chapter 8 based on all available epidemiologic studies world wide. These results indicate that there is substantial strength in the epidemiological evidence for association between $PM_{10}$

and $PM_{2.5}$ and mortality, especially for total and cardiovascular mortality, but also for respiratory mortality. For $PM_{10-2.5}$, the evidence for associations with mortality is more limited and clearly not as strong, though it will be important to consider the influence of issues such as exposure error in interpreting these results.

In Figure 9-5, the effect estimates presented for associations between morbidity and ambient PM are grouped by PM indicator ($PM_{10}$, $PM_{2.5}$, and $PM_{10-2.5}$), general health outcome category (cardiovascular and respiratory), and more specific outcome measures (hospital admissions and medical visits). Several general observations can be made:

(1) All associations between $PM_{10}$ and hospitalization for cardiovascular and respiratory diseases are positive and most are statistically significant, including all of the more precise estimates. Most all $PM_{10}$ associations with ED visits for cardiovascular and respiratory diseases are positive, and most respiratory (but not cardiovascular) associations are statistically significant. The more precise effect estimates range from about 2% to 6% increased risk per 50 $\mu g/m^3$ $PM_{10}$ for cardiovascular diseases, and 2% to 12% increased risk per 50 $\mu g/m^3$ $PM_{10}$ for respiratory diseases, with some effect estimates for respiratory medical visits up to about 30% per 50 $\mu g/m^3$ $PM_{10}$.

(2) For $PM_{2.5}$, all associations with hospitalization for cardiovascular and respiratory diseases are positive and many are statistically significant, especially for respiratory diseases. All $PM_{2.5}$ associations with ED visits for cardiovascular and respiratory diseases are positive, and about half are statistically significant. The more precise effect estimates range from about 1% to 10% increased risk per 25 $\mu g/m^3$ $PM_{2.5}$ for cardiovascular diseases, and 1% to 12% increased risk per 25 $\mu g/m^3$ $PM_{2.5}$ for respiratory diseases.

(3) Associations between $PM_{10-2.5}$ and hospitalization for cardiovascular and respiratory diseases are all positive, though the confidence intervals are broader than those for associations with $PM_{10}$ or $PM_{2.5}$ and few associations are statistically significant. Most $PM_{10-2.5}$ associations with ED visits are positive, but none are statistically significant.

(4) For all PM indicators, associations with medical visits tend to be less precise than those for hospital admissions. As was noted in Section 8.3.2.4, many of the medical/physician visits effect estimates are larger in magnitude than those for hospital admissions.

As was found for mortality, the epidemiologic evidence for associations between hospitalization and medical visits for cardiovascular and respiratory diseases is strong for $PM_{10}$ and $PM_{2.5}$. The few available $PM_{10-2.5}$ studies also provide some evidence, though not as strong,

for associations between hospitalization and medical visits for cardiovascular and respiratory diseases with $PM_{10-2.5}$.

For both mortality and morbidity effects, many more epidemiologic studies have used $PM_{10}$ than have used $PM_{2.5}$ and $PM_{10-2.5}$ measurements, since there is a much more extensive set of air quality monitoring data available for $PM_{10}$. It is not surprising that the strength of epidemiologic evidence for $PM_{10}$ may appear somewhat stronger than the epidemiologic evidence for $PM_{2.5}$ and certainly stronger than the evidence for effects of $PM_{10-2.5}$. It is important to recognize, however, that information summarized in the previous section strongly indicates that $PM_{2.5}$ and $PM_{10-2.5}$ are quite different pollutants and thus associations reported for $PM_{10}$ are representing some combination of effects of $PM_{2.5}$ and $PM_{10-2.5}$. The few studies that have tested multipollutant models that include both $PM_{2.5}$ and $PM_{10-2.5}$ have reported that the two PM size fractions have independent effects (e.g., Lippmann et al., 2000). In areas where $PM_{10}$ is predominantly fine particles, including most areas in the eastern U.S., it is likely that associations with $PM_{10}$ primarily reflect effects of fine particles. Likewise, associations reported in areas where $PM_{10}$ is predominantly coarse fraction particles, including many areas in the western U.S., effect estimates for $PM_{10}$ likely primarily reflect effects of $PM_{10-2.5}$. It should be noted that epidemiological effect estimates have been presented using standardized increments to allow for comparison across studies. As described in Section 8.1.1, based on current air quality data distributions, increments of 50 $\mu g/m^3$ for $PM_{10}$ and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$ were selected as representative of a realistic high-to-low range of concentrations for most U.S. communities. If one were to present the effect estimates per $\mu g/m^3$ for each PM mass measure, the effect estimates for both $PM_{2.5}$ and $PM_{10-2.5}$ are generally larger than those for $PM_{10}$.

In addition to studies using $PM_{10}$, $PM_{2.5}$, and $PM_{10-2.5}$, a few new studies have evaluated associations with ultrafine particle concentrations (using generally number of particles per $m^3$). One mortality study in Erfurt, Germany (Stölzel et al., 2003; Wichmann et al., 2000) reported associations for both $PM_{2.5}$ and ultrafine particles that were positive, but not statistically significant. Four panel studies of subjects with asthma, two in Germany and two in Finland, have included measurements of particle number. Peak expiratory flow and daily medication use in adults, but not children, were more closely associated with particle number than particle mass. One major source of ultrafine particles is motor vehicles, thus ultrafine particles may be used as

an indicator of traffic pollution, and, as discussed below, a number of studies have linked particles from motor vehicle emissions with mortality and other adverse health effects.

As discussed in more detail in Section 8.2.2.5, various PM components or characteristics have been associated with mortality. In general, evidence for associations have been reported for most components that have been studied. However, many PM components are correlated with each other and also with PM mass, making it is difficult to distinguish effects of the various components. Also, different PM components or characteristics would be expected to be more closely linked with different health outcomes.

One new approach used to evaluate effects associated with various PM components is to conduct a source apportionment analysis of the composition data base in conjunction with an epidemiologic analysis using source category factors as the surrogate for exposure. Three such studies were discussed in Section 8.2.2.5.3 (Laden et al., 2000, reanalyzed in Schwartz et al., 2003; Mar et al., 2000, 2003; Tsai et al., 2000). Motor vehicles, or more precisely particles associated with vehicular traffic, stand out clearly as a source category associated with mortality in all three studies. A regional sulfate source category was also identified as being associated with mortality in all three studies; however, particles of crustal origin were not significantly associated with mortality. Laden et al. (2000) and Tsai et al. (2000) reported associations with an oil combustion factor. In addition, a source category related to vegetative burning was also identified as being associated with mortality by Mar et al. (2000, 2003). These studies suggest that many different chemical components of fine particles and a variety of different types of source categories are all associated with, and probably contribute to, mortality, either independently or in combinations.

One key research question that has not been addressed in epidemiologic studies is the relationship between sources or composition of coarse fraction particles and health outcomes. The studies described above used source apportionment based on components of fine particles (Laden et al., 2000; Mar et al., 2000) or $PM_{15}$ in an area dominated by fine particles (Tsai et al., 2000). However, some limited information is available from air quality analyses that may help inform the assessment of epidemiological evidence for coarse fraction particles. Mar and colleagues (2000) conducted factor analysis of $PM_{10-2.5}$ data in Phoenix using the limited speciation data that were available, and reported that two major source factors for coarse fraction particles were crustal particles and coarse fraction metals. In addition to the studies described

above for fine particles, new studies have shown no increases in mortality on days with high concentrations of wind-blown dust (crustal particles), using $PM_{10}$ concentrations and data on wind speed as indicators of dust-storm days. Thus, it is possible that the association reported between $PM_{10-2.5}$ and cardiovascular mortality in Phoenix is influenced by the metal content of the coarse fraction particles, but perhaps not the crustal component. Clearly, further research is needed in this area.

In summary, as discussed in more detail in Chapter 8, there is strong evidence from epidemiologic studies that short-term increases in $PM_{10}$ and $PM_{2.5}$ are linked with increased risk of both mortality and morbidity. The more limited body of studies on $PM_{10-2.5}$ provides evidence that is suggestive of associations with morbidity and, perhaps less so, with mortality, but the evidence is less strong than that for $PM_{10}$ and $PM_{2.5}$. Some new epidemiological evidence also suggests associations between health effects and ultrafine particles and other fine particle components and sources, but the data are as yet too limited to characterize the relative toxicities of these various components or indicators of fine particles.

***Long-term Exposure Studies***

In the 1996 PM AQCD, results of prospective cohort studies linked long-term exposure to fine particles and mortality, and there was limited evidence indicating that long-term PM exposure was linked with chronic respiratory morbidity, such as the development of bronchitis. The more recent long-term exposure studies, summarized in Appendix Table 9A-3, have built upon these findings and provide further evidence for associations with both mortality and respiratory morbidity.

A series of analyses using data from the ACS cohort have shown significant associations between total and cardiopulmonary mortality and fine particles or sulfates, and the most recent analyses have also reported significant associations with lung cancer mortality. The Six Cities study found significant associations of $PM_{2.5}$ with total and cardiopulmonary (but not lung cancer) mortality, but not with coarse particle indicators. The results most recently reported for the AHSMOG study reported some significant associations between $PM_{10}$ and total mortality and deaths with contributing respiratory causes. In further investigation of the results found for $PM_{10}$ among males, the associations with $PM_{2.5}$ had larger effect estimates than those for $PM_{10-2.5}$ for

males in the AHSMOG cohort, though none reached statistical significance. For the VA study, inconsistent results were reported for associations between PM indicators and mortality.

Based on several factors – the larger study population in the ACS study, the larger air quality data set in the Six Cities study, the more generally representative study populations used in the Six Cities and ACS studies, and the fact that these studies have undergone extensive reanalyses – the greatest weight should be placed on the results of the ACS and Six Cities cohort studies in assessing relationships between long-term PM exposure and mortality. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient PM (especially fine PM) exposure and mortality.

For morbidity, results of studies in a cohort of children in Southern California have built upon the limited evidence available in 1996 PM AQCD to indicate that long-term exposure to PM is associated with development of chronic respiratory disease and reduced lung function growth. Long-term exposure to PM was associated with significant decreases in lung function growth among a cohort of Southern California school children, but the earlier cross-sectional analysis for the same cohort found no relationship between respiratory symptoms and annual average $PM_{10}$ levels. These findings support the results of the cross-sectional study in 24 U.S. and Canadian cities from the1996 PM AQCD, in which long-term PM exposure was associated with some effects on respiratory function changes and respiratory illness.

As was true in the 1996 PM AQCD, it is more difficult to assess strength of evidence for long-term exposure studies, since there are fewer studies available. For mortality, reanalyses and extended analyses of cohort studies provide strong evidence for the link between mortality and long-term exposure to fine particles; however, the available studies have provided no evidence for associations between long-term exposure to coarse fraction particles and mortality. In addition, prospective cohort and cross-sectional analyses have reported associations between respiratory morbidity and $PM_{10}$, and sometimes also $PM_{2.5}$, providing fairly strong evidence for effects of long-term fine particle exposures on respiratory morbidity. The morbidity studies have not generally included $PM_{10-2.5}$ data, so no conclusions can be drawn regarding long-term exposure to coarse fraction particles and morbidity.

#### *9.2.2.2.2 Assessment of robustness of associations for epidemiologic studies*

Many epidemiologic studies have also included assessment of whether the associations were robust to such factors as model specification and potential confounding by copollutants. Another factor that is relevant to robustness of epidemiologic findings is exposure error. Chapter 8 includes detailed discussions on each of these topics, and the following discussion will focus on the extent to which the current epidemiologic findings can be considered robust.

***Model Specification***

The 1996 PM AQCD included considerable discussion of issues regarding model specification for time-series epidemiologic studies, including results of reanalyses using several data sets, with a special focus on the large data set available from Philadelphia, PA. In this set of reanalyses, results reported with the use of alternative modeling strategies were not substantially different from the original investigators' findings. Also, at the time of completion of the 1996 PM AQCD, it appeared that issues related to model specifications used to control for weather effects in daily time-series analyses of ambient PM relationships to mortality/morbidity had largely been resolved. Based on two major studies extensively evaluating a number of different approaches to adjust for weather effects (including evaluations using synoptic weather patterns), it was concluded that significant PM-mortality associations were robust and verifiable via a variety of model specifications controlling for weather.

More recently, the influence of using default parameters in a widely used software package for GAM on epidemiologic study results has been investigated, and in this process, the question of appropriate adjustment for weather, temporal trends and other covariates in time- series models was reopened. Numerous study findings were reanalyzed to test the effect of using more stringent convergence criteria in the GAM program, as well as alternative modeling methods such as GLM. The results from the GAM reanalysis studies indicate that PM risk estimates from GAM models were often, but not always, reduced when more stringent convergence criteria were used, although the extent of the reduction was not substantial in most cases. Also, the extent of downward bias in standard errors reported for these data (a few percent to ~15%) appears not to be very substantial, especially when compared to the range of standard errors across studies due to differences in population size and numbers of days available. These GAM-related issues, however, were seen to have less influence on effect estimates than

investigator-to-investigator variations in model specifications, including the number of weather terms and extent of smoothing.

As observed in the HEI reanalysis report (HEI, 2003), the use of alternative modeling strategies tended to reduce the effect estimate size, but did not change the overall findings and qualitative conclusions of epidemiologic studies showing associations between PM and both mortality and morbidity. While it is clear that there will not be one "correct" model or approach for covariate adjustment, further research can help inform modeling strategies to adjust for temporal trends and weather variables in time-series epidemiology studies.

***Assessment of Confounding by Copollutants***

Airborne particles are found among a complex mixture of atmospheric pollutants, some of which are widely measured (such as gaseous criteria copollutants $O_3$, CO, $NO_2$, $SO_2$) and others which are not routinely measured. Because many of the pollutants are closely correlated due to emissions by common sources and dispersion by common meteorological factors, and some are in the pathway of formation of other pollutants (e.g., NO → $NO_2$ → $NO_3$- → PM nitrates), it is generally difficult to disentangle their effects. In addition, as described in Section 8.1.3.2, copollutants could possibly act as effect modifiers; for example, exposure to one pollutant could result in greater sensitivity to another pollutant. Potential effect modification between pollutants has been investigated in some toxicological or controlled human exposure studies (Section 7.9.3) but little evidence is available from epidemiologic studies to characterize any such effects.

The potential for co-pollutant confounding in the epidemiologic time-series studies was assessed in some detail in Section 8.4.3. Multipollutant modeling is the most common method used to test for potential confounding in epidemiologic studies; however, interpretation of the results of multipollutant models is complicated by the correlations that often exist between air pollutants. In interpreting the results of any of these studies, it is important to consider factors such as the biological plausibility of associations between the pollutants and health outcomes, and questions related to model specification and exposure error. Some new studies, described in Section 5.3.3.4 have reported that while ambient $PM_{2.5}$ concentrations are well correlated with personal $PM_{2.5}$ exposure measurements, this is not generally the case for $O_3$, $SO_2$ and $NO_2$. However, ambient gaseous pollutant concentrations were generally found to be correlated with personal $PM_{2.5}$ exposures, suggesting that ambient concentrations of $O_3$, $NO_2$, $SO_2$ may act as

surrogates, as opposed to confounders of $PM_{2.5}$ in the estimation of PM health effects based on multipollutant models.

Multipollutant modeling results for associations between a range of health outcomes and PM with gaseous pollutants in single-city studies are presented in Section 8.4.3 (Figures 8-16 through 8-19). For most studies, there was little change in coefficients for PM between single-pollutant and multipollutant models; however, in some cases the PM effect estimate was markedly reduced in size and lost statistical significance in models with one or more gaseous pollutants. Key results are also available from the NMMAPS evaluation of associations across many U.S. cities with varying climates and mixes of pollutants; associations between $PM_{10}$ and both mortality and morbidity were not changed with adjustment for gaseous pollutant concentrations. Thus, for the most part, effect estimates for PM were not substantially changed when gaseous copollutants were included in the models. PM and the gaseous copollutants were often highly correlated, especially for fine particles and CO, $SO_2$ and $NO_2$, and it was generally the case that high correlations existed between pollutants where PM effect estimates were reduced in size with the inclusion of gaseous copollutants.

In the prospective cohort and cross-sectional studies, the potential for confounding by copollutants has been assessed in some studies of mortality, but little studied for morbidity. The reanalysis of data from the ACS cohort indicated that the relationships with fine particles and sulfates were reduced in size in co-pollutant models including $SO_2$, but not the other gaseous pollutants. $SO_2$ is a precursor for fine particle sulfates, thus complicating the interpretation of multipollutant models including fine particles and $SO_2$ for this study. The authors concluded that their results suggested that mortality may be associated with more than one component of the ambient air pollutant mix, and that there were robust associations between mortality and fine particles and sulfates.

In summary, ambient PM exposure usually is accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical/chemical components. Assessment of the health effects attributable to ambient PM and its constituents within an already subtle total air pollution effect is therefore very challenging, even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects is not likely to characterize fully the effects that actually depend on simultaneous exposure to multiple air pollutants. Overall, the new evidence tends to substantiate that for both long-term and short-term exposures, observed PM

effects are at least partly due to ambient PM acting either alone or in conjunction with covarying gaseous pollutants.

***Exposure Error***

Numerous analyses of the potential influence of measurement error on time-series epidemiologic study results are discussed in Section 8.4.5. One consideration in comparing epidemiologic findings for different pollutants is the relative precision with which the pollutants are measured. If two pollutants have effects, and there is correlation between both the pollutants, the effect estimate of the pollutant that is less precisely measured may be attenuated when the pollutants are considered together. One would expect that $PM_{2.5}$, CO, and $NO_2$ would often have a high positive correlation due to common activity patterns, weather, and source emissions. $PM_{10-2.5}$ is generally less precisely measured than $PM_{2.5}$, but the two are not generally highly correlated. Several recent studies have focused on this question, and reported that for most situations, it is unlikely that differential measurement error would result in shifting apparent effects from one pollutant to another. The most extreme case, complete transfer of apparently causal effects from one pollutant to another, required very high correlation between the covariates, no error in measurement of the "false" covariate and moderate error in measurement of the "true" predictor. Thus, it is unlikely that effects attributed to PM (generally focusing on $PM_{10}$ or $PM_{2.5}$) are falsely transferred from other pollutants that are measured with less precision. Another facet of exposure error is the degree to which the measurements made at monitoring sites reflect population exposures to PM.

As discussed in Section 5.2, a number of studies have shown that ambient fine particle concentrations are well correlated with temporal changes in personal exposures to ambient fine particles. However, it should be noted that the spatial variability across the city is generally much greater for $PM_{10-2.5}$ than for $PM_{2.5}$. In addition, the infiltration factors for $PM_{10-2.5}$ and a number of the gases (e.g., ozone, $SO_2$) are lower and more variable that than of $PM_{2.5}$, likely leading to a lower correlation between ambient concentration, used as an exposure surrogate in community time-series studies, and personal exposure to the ambient pollutant for $PM_{10-2.5}$ and these gases. Thus, the new exposure studies indicate that fine particles measurements at central monitoring sites are good indicators of personal exposures to $PM_{2.5}$ in time-series studies. Exposure relationships for $PM_{10-2.5}$ have been less well studied, but exposure error and

measurement error would be expected to have greater influence for associations with $PM_{10-2.5}$ than for $PM_{2.5}$.

#### *9.2.2.2.3 Assessment of consistency in epidemiologic study results*

One key conclusion in the 1996 PM AQCD was that there was considerable consistency in findings among the PM time-series epidemiologic studies. The much larger set of studies available now includes evidence for somewhat greater heterogeneity among risk estimates from different locations, in studies of both mortality and morbidity effects.

This potential heterogeneity in risk estimates is most notable in the reports from multi- city studies conducted in the U.S., Canada and Europe, that have also included quantitative assessments of heterogeneity and potential factors that would influence heterogeneity. The city-specific and regional PM-mortality associations presented in NMMAPS results suggested greater variability in effect estimates than had been observed in the studies available in the 1996 PM AQCD. However, statistical analyses indicated that there was no significant heterogeneity in mortality effect estimates for 90 U.S. cities (Samet et al., 2000a, Dominici et al., 2003a). For eight Canadian cities, no evidence of heterogeneity was reported in the initial analysis, but in reanalysis to address GAM issues, there appeared to be greater heterogeneity in the PM-mortality associations (Burnett and Goldberg, 2003). Finally, initial analyses of mortality associations for 29 European cities indicated differences between eastern and western cities, but these differences were less clear with reanalysis to address GAM questions (Katsouyanni et al., 2003).

There are a number of reasons to expect variation in PM-health effect associations for different geographic regions. Regional differences can include differences in PM sources or composition, differences in population exposures, and differences in potentially susceptible groups. In the European multi-city study, APHEA, PM-mortality associations were found to be larger in areas with higher average $NO_2$ levels (considered an indicator of traffic pollution), warmer climates (possibly due to more open windows resulting in better exposure estimation) and lower overall mortality rates (potentially more susceptible people). In NMMAPS, no apparent associations were found between PM-mortality association and socioeconomic indicators or $PM_{2.5}/PM_{10}$ ratios, but there was also no statistically significant measure of heterogeneity in this study. However, for hospital admissions in the NMMAPS, the $PM_{10}$-

admissions associations were greater in areas with less use of central air conditioning (possibly an indicator of increased exposure to ambient pollutants) and with larger contributions of $PM_{10}$ emissions from vehicle emissions and oil combustion.

In general, it has been found that PM concentrations, especially for fine particles, are quite regional in distribution and concentrations measured at different monitors across a city are well correlated. However, as discussed in Section 8.4.5.2, some U.S. cities show more variability in PM measurements across monitoring sites. For larger metropolitan areas, including monitors in outlying areas can also increase variability in PM measurements across the area. From those U.S. cities in which epidemiological studies have been conducted, areas with more uniformity in $PM_{2.5}$ concentrations include Chicago and Detroit; areas with more variability include Seattle and Los Angeles. There are a number of factors that could influence spatial variability of PM concentrations, including topography, location of major PM sources and weather patterns. Greater spatial variability in PM concentrations would be expected to increase exposure error and thus potentially affect epidemiologic study results in those areas.

One factor unrelated to geographic location that would likely affect the consistency of results across studies is the amount of data available for analysis. For time-series studies, the number of days with measurements is one important indicator of study size, or statistical power. In Figure 9-5, the PM-mortality associations are plotted in order of decreasing statistical power, using the product of daily death rate and number of PM measurement days as the indicator. For single-city mortality studies, the number of PM measurement days ranges from about 150 (Tsai et al., 2000) to over 2000 days (e.g., Ito and Thurston, 1996). Multi-city studies included ranges of about 500-900 days for eight Canadian cities (Burnett and Goldberg, 2003), about 200-3000 days for 90 U.S. cities (Dominici, 2003), and 1500-3000 days for 10 U.S. cities (Schwartz, 2003a). For several studies, more data are available for $PM_{10}$ than for $PM_{2.5}$ or $PM_{10-2.5}$; for example, Fairley (2003) used a data set with approximately 800 days of $PM_{10}$ measurements and 400 days for $PM_{2.5}$ and $PM_{10-2.5}$. In the 1996 PM AQCD, studies conducted in the U.S. had about 300 to 4000 days of PM measurements, and a clear correlation between t-ratio and number of monitoring days could be seen (Figure 12-17, Table 12-25). Similarly, Figures 9-5 and 9-6 show a tendency for larger studies to have more consistent effect estimates that are more likely statistically significant. A number of the newer studies, however, particularly those using $PM_{2.5}$ and $PM_{10-2.5}$ data, are somewhat smaller in size than those available in the 1996 PM AQCD. This

would be expected to result in decreased precision, and more variability in effect estimate size for the smaller studies.

In addition, while many single-city epidemiologic studies have used availability of everyday monitoring data as a criterion for selecting study locations, a number of the newer studies have used $PM_{2.5}$ and $PM_{10-2.5}$ data measured every sixth day. Beyond limiting the number of days of data available, the use of 1-in-6 day data may also complicate the time-series analyses. As discussed in Section 8.4.5.2, one analysis of data from Chicago used data from an everyday monitor and created six 1-in-6 day data sets from these data; the resulting PM-mortality associations for these six data sets were quite inconsistent.

Focusing on the results of epidemiologic studies with larger study sizes, there remains an overall indication of consistency in effect estimate size for health effect associations with $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$. The new multi-city study results provide some evidence for differences in PM-mortality associations across locations. However, there are reasons to expect heterogeneity in study results across cities, based on different topographies, distribution of sources or emissions, mixes of pollutants, and population characteristics.

#### *9.2.2.2.4 Lag period between exposure and effect*

The lag time between exposure and health effect has been investigated in many time-series epidemiological studies, as described in more detail in Section 8.4.4. In considering the results of models for a series of lag days, it is important to consider the pattern of results that is seen across the series of lag periods. If there is an apparent pattern of results across the different lags, then selecting the single-day lag with the largest effect from a series of positive associations is reasonable. In fact, the single-day lag effect estimate is likely to underestimate the overall effect size since the largest single-lag day results do not fully capture the risk also distributed over adjacent or other days; a distributed lag model should more correctly capture the effect size. In addition, it should be noted that the pattern of results with different lag periods may depend on the pattern of persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city and from pollutant to pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and may tend to obscure important nuances of lag structures that might provide important clues to possible different lags between PM exposures and different cause-specific effects.

It would be expected that differing lag periods would be appropriate for different health outcome-pollutant associations. For example, the time-series studies of cardiovascular hospital admissions or emergency department visits suggest that PM effects are stronger with a lag 0 with some carryover to the day 1 lag. In a few studies of cardiac physiological changes, strongest associations were reported for some effects with 1- to 2-hour lag periods. In panel studies of respiratory symptoms and in several studies of asthma hospitalization or emergency department visits, longer moving average lag periods (up to 5- to 7-day moving averages) yielded larger PM effect estimates.

Studies have shown different lag days for different source categories and different size fractions. For example, Mar et al. (2000) found positive and significant associations with cardiovascular mortality for regional sulfate for lag day 0, for traffic-related PM on lag day 1, and for wood-burning related PM on lag day 3; for $PM_{10-2.5}$ on lag day 0 and $PM_{2.5}$ on lag day 1. $PM_{10}$, presumably due to its correlation with both $PM_{2.5}$ and $PM_{10-2.5}$, was positive and significant on both lag day 1 and 2.

Studies of long-term exposure have included less evaluation of temporal relationships between PM exposure and health effect. The prospective cohort studies have used air quality measurements made over a period of years as an indicator of long-term exposure to air pollution, The associations reported in these studies are for relationships with PM across various levels of exposure, not as a measure of latency of effect.

However, some new studies have included some assessment of temporal relationships between PM exposure and mortality. In the reanalysis of the Six City Study, the decline in fine particle levels over the monitoring period was included as a time-dependent variable, to assess the effect of changing PM concentrations over time on the association with mortality. The association between total mortality and fine particles was reduced in size, though still statistically significant, as compared with the model not allowing for temporal change in pollution level. This is likely indicative of the effectiveness of control measures in reducing source emissions importantly contributing to the toxicity of ambient particles in cities where PM levels were substantially decreased over time.

The VA study analysis tested associations between different subsets of pollution and mortality data. While the associations found between PM and mortality varied and were often negative and generally not statistically significant, it was observed that the associations were

larger and more likely to be statistically significant with the air quality data from the earliest time periods, as well as the average across all data. Further study is needed to evaluate the relationship between health effects and long-term PM exposure where PM concentrations are changing over time.

In summary, for time-series studies, it is likely that the most appropriate lag period for a study will vary depending on the health outcome under study and air quality patterns in the study area. Where effects are found for a series of lag periods, the effect estimate for any one lag period will likely underestimate the effect size and a distributed lag model will more accurately characterize the effect estimate size. Caution should be used in selecting results for single lag periods if the pattern of results across lag periods is highly variable. For effects of chronic exposure, less is known about the importance of different time windows for exposure and some recent studies indicate that further investigation will be important.

#### *9.2.2.2.5 Form of concentration-response function*

In the 1996 PM AQCD, the limitations of identifying possible "thresholds" in the concentration-response relationships in observational studies were discussed, including difficulties related to the low data density in the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Few studies had quantitatively assessed the form of PM-effect concentration-response functions and the potential for a threshold level.

A threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that should be noted. For example, since individual thresholds vary from person to person due to individual differences in genetic-level susceptibility and pre-existing disease conditions (and even can vary from one time to another for a given person), it is extremely difficult mathematically to demonstrate convincingly that a clear threshold exists in the population studies. This is especially true if the most sensitive members of a population are unusually sensitive even down to very low concentrations. The person-to-person difference in the relationship between personal exposure to PM of ambient origin and the concentration observed at a monitor may also add to the variability in observed exposure-response relationships, possibly obscuring otherwise more evident thresholds. Since one cannot directly

measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed population threshold biologically, without pertinent collateral dosimetric/toxicologic information. Despite these issues, several PM-related epidemiologic studies have attempted to address the question of threshold.

Analyses using data for 90 U.S. cities showed that, for total and cardiorespiratory mortality, the exposure-response spline curves for mean lag (0- and 1-day) were roughly linear, but less so for current and previous day $PM_{10}$, making it difficult to discern any evident threshold. For daily total or cardiorespiratory mortality, the likelihood of a threshold occurring above $PM_{10}$ levels of ~25 $\mu g/m^3$ seems to be essentially zero (see Figure 8-31); there was increasing probability of a threshold occurring at levels below 25 $\mu g/m^3$. The hypothesis of linearity was examined, with the results indicating that the linear model was preferred over the spline and the threshold models. In some single-city analyses, there were indications of potential population thresholds for associations between mortality and $PM_{10}$ in the range of 80 $\mu g/m^3$ to 100 $\mu g/m^3$, and with $PM_{2.5}$ in the range of 20-25 $\mu g/m^3$. However, other single-city analyses reported no evidence of a threshold level for PM-mortality associations.

In summary, the results from large multi-city studies suggest that there is no strong evidence of a clear threshold for PM mortality effect. Some single-city studies provide some suggestive hints for possible thresholds, but not in a statistically clear manner. More data need to be examined with alternative approaches, but, in the meantime, the use of linear PM effect models appears to be appropriate.

#### *9.2.2.2.6 Intervention studies*

Although many studies have reported short-term associations between PM indices and mortality, a largely unaddressed question remains as to the extent to which reductions in ambient air PM actually lead to reductions in health effects attributable to PM. This question is not only important in terms of "accountability" from the regulatory point of view, but it is also a scientific question that challenges the predictive validity of statistical models and their underlying assumptions used thus far to estimate excess mortality due to ambient PM.

The opportunities to address this question are rare. However, at the time of the 1996 PM AQCD, results were available from epidemiologic studies of a "natural" or "found experiment" in the Utah Valley, where mortality and respiratory hospital admissions were found to decrease

during the time a major PM source was closed. Recent toxicologic and controlled human exposure studies using particle extracts from ambient community $PM_{10}$ sampling filters from the Utah Valley have also shown reduced effects with exposure to particles collected during the time period when the source was not operating. A recent epidemiologic study in Dublin, Ireland also provides evidence for reductions in ambient PM being associated with reductions in mortality rates. Other "found experiments" also provide evidence for decreases in mortality and/or morbidity being associated with notable declines in PM (and/or gases such as SO2) as the result of interventions aimed at reducing air pollution.

By providing evidence for improvement in community health following reduction in air pollutant emissions, these studies add further support to the results of the hundreds of epidemiologic studies linking ambient PM exposure to an array of health effects. The studies available generally show improvements in health with reductions in emissions of both PM and gaseous pollutants and thus do not distinguish effects from the different pollutants. However, they provide strong evidence that reducing emissions of PM and gaseous pollutants has beneficial public health impacts.

#### *9.2.2.2.7 Summary and conclusions*

There is substantial evidence that both long-term and short-term exposures to $PM_{2.5}$ are associated with both mortality and morbidity. The fewer studies available for $PM_{10-2.5}$ provide less evidence for associations with mortality, but somewhat more support for associations between short-term exposures and morbidity effects; little evidence is available to allow conclusions to be drawn about long-term $PM_{10-2.5}$ exposures and morbidity. There is also extensive and convincing evidence for associations between short-term exposures to $PM_{10}$ and both mortality and morbidity; however, as discussed above, these $PM_{10}$ associations likely reflect underlying relationships with either $PM_{2.5}$ or $PM_{10-2.5}$ or with both PM mass fractions. Results of new source apportainment studies and "found experiments" lend support to the results of the other epidemiological studies.

### 9.2.3 How Does Newly Available Information Inform Assessment of Biological Plausibility and Coherence of Health Effects Attributed to Ambient Fine and Coarse Thoracic PM and/or Their Components?

In more broadly assessing the extent to which the overall body of evidence supports the attribution of observed health effects to exposure to fine and coarse thoracic PM and related chemical constituents, one needs to look beyond just epidemiologic evidence to consider the implications of newly available dosimetric, toxicologic, and other evidence as well. More specifically, the following assessment (a) evaluates information pertaining to the biological plausibility of the types of health effect associations observed in the epidemiologic studies, taking into account toxicologic findings and potential mechanisms of action; and (b) considers information about the coherence of the overall body of evidence relevant to PM-related health effects to reach conclusions regarding attribution of observed effects to ambient fine or coarse thoracic PM and related chemical constituents, acting alone and/or in combination with other pollutants.

#### 9.2.3.1 Key Points from 1996 Integrative Synthesis

The 1996 PM AQCD highlighted several key findings and conclusions concerning attribution of observed health effects to specific ambient PM size fractions or chemical compounds:

(1) "The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among [the] elderly population is bolstered by: (1) the more uniform distribution of fine particles across urban areas. . . ; (2) the penetration of ambient particles to indoor environments. . . ; and (3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles."

(2) The PM indices that have been "most consistently associated with health endpoints are fine particles (indexed by BS, COH, and $PM_{2.5}$), inhalable particles ($PM_{10}$ or $PM_{15}$), and sulfate ($S0_4^{=}$)," whereas "[l]ess consistent relationships have been observed for TSP, strong acidity ($H^+$), and coarse PM ($PM_{10-2.5}$). . . . [and] none of these indices can completely be ruled out as a biologically relevant indicator of PM exposure."

(3) "Based on current evidence from epidemiologic, controlled human, human occupational, and laboratory animal studies, no conclusions can be reached regarding the specific chemical components of $PM_{10}$ that may have the strongest biologic activity." Further, none of the various subclasses of PM [e.g., acid aerosols, bioaerosols, metals (including

> transition metals), and insoluble ultrafine particles] that have been considered "can be specifically implicated as the sole or even primary cause of specific morbidity and mortality effects." (U.S. EPA, 1996, p. 13-93)

Hence, although at the time of the 1996 PM AQCD, the epidemiologic evidence was viewed as substantiating well $PM_{10}$ or $PM_{2.5}$ associations with human mortality and morbidity, uncertainties remained with regard to (a) the relative toxicity of specific PM constituents and (b) the biological plausibility of the reported effects and/or the mechanisms of action underlying them.

#### 9.2.3.2 Integration of New Evidence

In the ensuing years since the 1996 PM AQCD evaluations, progress has been made in (1) further substantiating and expanding epidemiologic findings indicative of ambient PM-health effect associations, (2) identifying likely constituents contributing to observed effects, and (3) obtaining evidence bearing on the biological plausibility of observed effects and possible mechanisms of action involved. Efforts to interpret the overall meaning of the epidemiologic finds and to evaluate their biological plausibility and pertinent mechanisms of action are complicated by the fact that ambient PM exists as a component of a complex air pollution mixture that includes other criteria pollutants, as well as many other airborne contaminants that may convey risks to health. This section addresses these complexities by first considering the physical and chemical components and source categories that have been associated with health effects in epidemiologic studies. This is followed by a discussion of the toxicologic links that have been reported between specific PM components identified in epidemiologic studies and health effects and/or related biologic changes in controlled exposure human, animal, and in vitro studies. Potential mechanisms of actions are then summarized, followed by a discussion of inhaled particles as potential carriers of toxic agents. The coherence of findings from epidemiologic and toxicologic studies is then discussed, leading to conclusions with regard to the attribution of health effects to ambient fine and coarse thoracic PM and/or their constituents.

##### *9.2.3.2.1 Chemical components and source categories associated with health effects in epidemiologic studies*

As discussed above, the numerous newly available epidemiologic studies provide growing evidence that substantiates well statistical associations between (a) increased risk of total and cause-specific mortality, as well as various morbidity endpoints (e.g., hospital admissions,

doctors visits, etc.), and (b) short- or long-term exposures to ambient PM indexed by mass concentrations of several ambient PM size fractions and/or constituent components measured at community monitoring stations. Probably the most extensive database substantiating such associations is that demonstrating relationships between increased mortality/morbidity and ambient levels of $PM_{10}$, which subsumes both fine- and coarse-mode fractions of thoracic particles capable of reaching lower (thoracic) TB and A regions of the respiratory tract. Extensive new evidence also substantiates further the judgments made in the 1996 PM AQCD that significant associations exist between increased risk of mortality and morbidity and exposures to ambient fine particles (indexed mainly by $PM_{2.5}$ mass measurements), certain fine particle components (e.g., sulfates), and sources of fine particles (e.g., coal or oil combustion, motor vehicles, etc.). Less extensive, but growing, evidence has also begun to accumulate for the ambient coarse fraction ($PM_{10-2.5}$) of thoracic particles also being associated, at least under some circumstances, with increased risk of human morbidity and, possibly, mortality. For example, while the epidemiologic findings generally do not implicate crustal materials primarily in coarse fraction, they suggest that soil particles contaminated with metals (originally deposited as fine particle components) or serving as carriers for bioaerosol materials (e.g., pollen grain fragments, fungi spores, endotoxin) may contribute to observed effects.

Inherent in the PM research agenda recommended by the NRC (1998) was the recognition of the importance of evaluating the relative toxicity of various components or characteristics of PM so as to concentrate other aspects of future PM-related research (e.g., exposure monitoring) on components that may be relatively more toxic. However, currently a wide array of PM characteristics have been found to be associated with toxicity through epidemiologic studies, as listed in Table 9-3.

Epidemiologic studies using either individual chemical species or classes or using source category factors (SCF) derived from factor analysis have been particularly useful in helping to identify a variety of species whose ambient concentrations are statistically associated with either total mortality or more specific mortality groupings. A number of techniques have been developed that apportion PM in ambient samples to its sources (see Section 3.3 of this document and Section 5.5 of the 1996 PM AQCD for descriptions of these techniques). These powerful techniques are limited by their ability to differentiate between PM produced by sources having similar compositional profiles and by the lack of data for the composition (especially the organic

**TABLE 9-3. PARTICULATE MATTER CHARACTERISTICS, COMPONENTS, OR SOURCE CATEGORIES SHOWN TO BE ASSOCIATED WITH MORTALITY IN U.S., CANADIAN, OR EUROPEAN EPIDEMIOLOGIC STUDIES [1,2]**

| PM Size Fractions | Ions/Elements | Carbon/Organic Fractions | Source Categories (Tracers) |
|---|---|---|---|
| Mass TSP | Sulfate ($SO_4^{=}$) | TC (Total Carbon) | Motor Vehicles (CO, Pb) |
| Mass $PM_{10}$ | Nitrate ($NO_3^-$) | BC (Black Carbon) | Motor Vehicles plus resuspended road dust (CO, $NO_2$, EC, OC, Mn, Fe, Zn, Pb |
| Mass-thoracic coarse PM [$PM_{10-2.5}$ or $PM_{10-1}$] | Ammonium ($NH_{4-}$) | EC (Elemental Carbon) | |
| Mass-fine PM [$PM_{2.5}$ or $PM_{1.0}$] | Transition metals (e.g., Cd, Cu, Fe, Ni, Mn, Zn) | COH (Coefficient of Haze) | Fuel oil combustion (Ni, V) |
| Mass-ultrafine PM [$PM_{0.1}$] | Other toxic metals (e.g., Pb) | OC (Organic Carbon) | Coal burning (Se) |
| Particle number | Strong Acid ($H^+$) | CX (Cyclohexene-extractable Carbon) | Sulfate or regional sulfate (S) |
| Particle surface area | | Organic PM compounds | Industrial (Zn, Cd) |

1. Components measured in $PM_{2.5}$ unless otherwise specified.
2. Organic PM compounds extracted by three techniques.

composition) of emissions from many sources. This limitation may be mitigated in the future by further analytical developments in analyzing the composition of PM samples and broader availability of compositional data from the new PM speciation monitoring network.

Source categories found to be significantly associated with total, cardiovascular, or cardiovascular plus respiratory mortality in one or more cities are shown in Table 9-3, based on results from several studies (Laden et al., 2000; Schwartz, 2003a; Mar et al., 2000, 2003; and Tsai et al., 2000). A source category associated with motor vehicles was found in all three studies, which may include as causal elements one or more of: gaseous copollutants (CO and $NO_2$); soot particles from cars (indexed by BS, COH, or EC); organic PM from vehicles; Pb or transition metals emitted by vehicles (Mn, Fe, Zn); or other particles generated or

resuspended by vehicular traffic. Each of the three studies also identified a sulfate factor. The factor reported by Laden et al. (2000) as "coal burning" contains high loadings of both selenium and sulfur and could have also been called "regional sulfate." Mar et al. (2000) refer to the factor with high sulfate specifically as "regional sulfate," distinguishing it from a factor with a high loading of $SO_2$ (called a "local $SO_2$" factor). The regression with elemental S (assumed to be sulfate) was not significant, but the regression with the regional sulfate factor was significant, perhaps because the factor analysis tends to remove other more localized sulfate sources (e.g., $CaSO_4$ and $Na_2SO_4$), leaving only acid sulfates ($[NH_4]_2SO_4$, $NH_4HSO_4$, and $H_2SO_4$) for a regional sulfate factor. (In Phoenix, there was also a modest loading of S in the soil factor.) Thus, all three sulfate factors should be considered as regional sulfate. These studies of specific chemical components and source categories are also important because they indicate the association of human health effects with three major components of $PM_{2.5}$ mass: sulfate, nitrate, and organic PM. Examination of the lag structure from the Phoenix study reveals that neither the regional sulfate factor nor the vegetative burning factor was confounded by $NO_2$, CO, $SO_2$, or $O_3$. Also, in another study, examination of $PM_{2.5}$ and nitrate effects, alone and in multiple regressions, indicated that $PM_{2.5}$ and nitrate were not confounded by $NO_2$, CO or $O_3$ in Santa Clara, CA (Fairley, 1999).

Also of much importance, all of the above studies that investigated multiple source categories found a soil or crustal source that was negatively associated with mortality. This suggests that the components of natural soil may have minimal toxicity unless contaminated by toxic agents from anthropogenic sources, e.g., transition metals or polyaromatic hydrocarbons (PAHs).

Although results such as those presented above are illuminating, it should be noted that there can be ambiguity regarding the identification of source categories, as the marker elements used in many of the methods used (e.g., specific rotation factor analysis) can have more than one source. As an example, before Pb was phased down in gasoline, it was (and still is) both produced by smelters and other industries as well as used in gasoline (see Appendix 3D of Chapter 3). Also, there can be substantial spatial variability in source contributions across an urban area, increasing potential exposure characterization error. Still, these new epidemiologic findings suggest that various specific chemical components of PM and a variety of different

types of source categories are associated with and probably contribute to mortality, either acting alone or in combination with other agents in ambient aerosol mixes.

Based on the overall available epidemiologic information, then, one or more size fractions and/or constituent components of ambient PM have been most clearly shown to be associated with increased risk of mortality and/or morbidity manifested in terms of (1) cardiovascular/systemic, (2) respiratory, and (3) lung cancer effects. Acute, short-term (≤ 24-hr) exposures to ambient PM appear to exert cardiovascular/systemic effects rather quickly, with peak lags of 0-1 days being generally seen, and one study reporting myocardial infarction increases even as early as 2 h post exposure. Respiratory effects typically exhibit somewhat longer and more extended lag periods, from 1 to 2 days on out to a week or so. Both cardiovascular and respiratory risks have also been shown to be elevated in relation to long-term (years, decades) exposures to ambient PM (especially the fine fraction), as has lung cancer mortality and morbidity.

#### *9.2.3.2.2 Approaches to experimental evaluation of PM health effects*

As discussed in Chapter 7, various experimental approaches have been used to evaluate PM health effects, including: studies of human volunteers exposed to PM under controlled conditions; in vivo studies of laboratory animals including nonhuman primates, dogs, and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. A variety of exposure conditions have been employed, including: whole body, mouth-only, and nose-only inhalation exposures to concentrated ambient particles (CAPs) or laboratory-generated particles; intratracheal, intrapulmonary, and intranasal instillation; and in vitro exposures to test materials in solution or suspension. These approaches have been used mainly to test hypotheses regarding the role of PM in producing the types of health effects identified by PM-related epidemiologic studies. Thus, most new toxicological studies have thus far been designed to address the question of biologic plausibility of epidemiologically-demonstrated effects and mechanisms of action, rather than dose-response relationships.

Reflecting this, most of the toxicology studies have generally used exposure concentrations or doses that are relatively high compared to concentrations commonly observed in ambient air. One consideration underlying the use of such experimental exposure concentrations is the fact that healthy animals have most typically been used in many controlled-exposure toxicology studies, whereas epidemiologic findings often reflect ambient pollutant effects on compromised

humans (e.g., those with one or another chronic disease) or other susceptible groups at increased risk due to other factors. Implicit in using relatively high concentrations in experimental studies of healthy subjects is the assumption that increasing the dose makes up for compromised tissue/organ functions that may contribute to observed ambient PM effects. However, this may not be the case. Recognizing this, there has been growing attention to development and use of compromised animal models that are thought to mimic important characteristics contributing to increased human susceptibility to ambient PM effects.

One example is the use of monocrotaline (MCT)-treated rats, in which the MCT-induced pulmonary vasculitis/hypertension is thought to render them at possible increased risk for PM effects. Another example is a compromised animal model of chronic bronchitis (induced by repeated prolonged exposure to $SO_2$, before exposure to PM). Partial coronary artery occlusion is yet another example of a compromised animal model, evaluated for increased cardiovascular risk. Possible PM exacerbation of respiratory infections has also been evaluated in animals intratracheally exposed to various bacteria.

Given the relatively high concentrations used, much caution is needed in attempting to interpret and extrapolate effects seen in these studies to provide insight into the biological plausibility and mechanisms of action underlying effects seen in humans under "real world" exposure conditions. Some reported responses may only be seen at the higher concentrations (more typical of occupational exposures) and not necessarily at (usually much lower) ambient particle exposure levels. On the other hand, differences between humans and rodents with regard to the inhalability, deposition, clearance, and retention profiles for PM (see Chapter 6 for details) could conceivably make doses to some specific respiratory tract tissues from experimental exposures relatively similar to doses from human ambient exposures.

Since the 1996 PM AQCD, the effects of controlled exposures to ambient PM have been evaluated by use of urban air particles (UAP) collected from ambient samplers (e.g., impactors, diffusion denuders, etc.) and, more recently, by the use of aerosol concentrators. In the first type of study, particles from ambient air samplers are collected on filters or other media, then stored for varying time periods (hours to years or even decades) before later being resuspended in an aqueous medium and used in inhalation, instillation, or in vitro studies. Depending on the storage conditions for the filters (e.g., whether or not kept refrigerated or in the dark) varying

amounts of some originally collected materials (including highly biologically active semivolatile compounds) may be lost and their possible effects missed in UAP studies.

Particle concentrators allow exposure under controlled conditions of animals or humans by inhalation to concentrated "real-world" ambient particles (CAPs) at levels higher than typical ambient PM concentrations. However, CAPs studies cannot control closely the mass concentration and day-to-day variability in ambient particle composition, and they often lack detailed characterization of variations in chemical composition from one CAPs exposure to another. Because the composition of CAPs vary across both time and location, thorough physical-chemical characterization is needed (but rarely done or reported) in order to facilitate comparison of results between studies or even among exposures within studies, so as to better link specific particle composition to effects. Another limitation is the fact that concentrators used in many of the studies assessed here do not efficiently concentrate ambient particles $\leq 0.1$ μm. Thus, it is likely that a large portion of potentially important combustion-generated particles (e.g, from diesel, gasoline vehicle, wood smoke, coal smoke, etc.) were present only at ambient (not higher concentrated) levels in most or all of the CAPs studies assessed here; and many other potentially toxic co-components (e.g., $SO_2$, $O_3$, peroxides, etc.) of the ambient aerosols may be excluded from the CAPs exposure mix as well. Thus, even "real-world" CAPs exposures do not fully reflect important interactive effects of the overall aerosol mix (see also Section 9.2.3.2.4).

Controlled human and laboratory animal exposures to particulate material obtained from combustion-source bag house filters or other combustion-source collection devices have also been used to evaluate the in vitro and in vivo respiratory toxicity of complex combustion-related PM. Residual oil fly ash (ROFA) collected from large industrial sources (e.g., oil-fired power plants) has been extensively used, and, less often, domestic oil furnace ash (DOFA) or coal fly ash (CFA). The major disadvantage associated with the use of such materials derives from questions about the potential relevance of results obtained in understanding ambient PM exposure effects. Before extensive implementation of air pollution controls, ambient U.S. air contained mixtures of PM species (at higher than current concentrations) analogous to those in many of the source samples used in toxicologic studies during the past decade or so. However, it is unlikely that high concentrations of certain materials that typify such samples would be found or approached in ambient air PM samples from community monitoring sites in U.S., Canada, and

much of western Europe that generated the aerometric data (collected during the past 20 to 30 years) that were used to estimate PM exposures in most PM epidemiology studies assessed here. Very high concentrations of metals (especially Ni and V, for example) typify most ROFA samples, and experimental exposures to such materials have generally resulted in exposures and doses that are orders of magnitude (100s of times) higher than for usual concentrations of such metals in ambient PM measured routinely since the 1970s at community monitoring sites across the United States. Thus, significant issues arise concerning the extent to which the effects of high concentrations of ROFA or other combustion-source particle mixes can be extrapolated to help interpret ambient air PM effects.

Analogous issues arise with evaluation of the toxicity of PM emitted from mobile source combustion devices, e.g., diesel and gasoline vehicle engines. Complex combustion-related mixtures in such mobile source emissions include many different types of particles and gaseous compounds in high concentrations that are not necessarily representative of ambient PM derived from such sources after passage through particle traps, catalytic converters, exhaust pipes, etc. For example, ultrafine particles emitted from gasoline and diesel engines are reduced in numbers and concentrations as they agglomerate to form larger, accumulation-mode particles as they cool in passing through exhaust systems and/or as they undergo further physical and chemical transformation as they "age" in ambient air. Further complicating evaluation of the toxicity of mobile source emission components is: (1) the difficulty in separating out toxic effects attributable to particles versus those of gaseous components in automotive exhausts; and (2) the changing nature of those exhaust mixes as a function of variations in engine operating mode (e.g., cold start versus warm start or "light" versus "heavy" load operation, etc.) and changes in engine technology (e.g., "old diesels" versus "new diesels").

The in vivo and in vitro PM exposure studies have almost exclusively used $PM_{10}$ or $PM_{2.5}$ as particle size cutoffs for studying the effects of ambient PM. Collection and study of particles in these size fractions has been made easier by widespread availability of ambient sampling equipment for $PM_{10}$ and $PM_{2.5}$. However, other important size fractions, such as the coarse fraction ($PM_{10-2.5}$) and $PM_{1.0}$, largely have been ignored; and only limited toxicology data are now available to assess effects of these particle sizes. Similarly, relatively little research has addressed mechanisms by which organic compounds may contribute to ambient PM-related

effects. Both UAP extracts and CAPs have been used to evaluate effects in healthy and compromised laboratory animals and humans.

#### *9.2.3.2.3 Interspecies comparisons of experimental results*

Much of the new toxicologic data assessed in Chapter 7 and discussed here was derived from either: (a) in vivo exposures of human subjects or laboratory animals via inhalation exposures or instillation of PM materials; or (b) in vitro exposures of various (mostly respiratory tract) cells or tissues to diverse types of PM. As already noted, the experimental exposure conditions used in these studies are typically different from those experienced through inhalation of airborne PM by human populations in ambient environments. Thus, comparisons between experimental tissue doses leading to observed PM effects and exposure/doses associated with effects observed with human ambient PM exposures is useful, especially if any quantitative extrapolation of experimental results across species or to ambient conditions is to be attempted.

To help place the toxicologically relevant concentrations/doses into context in relation to ambient conditions, EPA carried out illustrative dosimetric/extrapolation modeling analyses to provide comparisons between the high doses typically used in toxicological studies and doses typical of human exposures under ambient conditions. Building upon advances in dosimetric modeling discussed in Chapter 6, the EPA analyses compare PM doses delivered to human or rat lung tissue from experimental exposures and PM doses to the human lung from exposures during normal activities. These analyses and interpretation of their results (see Appendix 7-A) provide context for exposure concentrations used and toxicological results assessed here.

***Dosimetric Considerations in Comparing Dosages for Inhalation, Instillation, and Exposure of Cultured Cells***

From among the three common experimental approaches for studying biological effects of PM, inhalation studies are the most realistic physiologically and, thus, the most applicable to risk assessment. However, because they are expensive, time consuming and require specialized equipment and personnel, they are often supplemented by other techniques (instillation and in vitro studies). Instillation studies, in which particles suspended in a carrier such as physiological saline are applied to the airways, have certain advantages over in vitro studies. The exposed cells have normal attachments to basement membranes and adjacent cells, circulatory support, surrounding cells and normal endocrine, exocrine and neuronal relationships. Although the TB

region is most heavily dosed in such studies, alveolar regions can also be exposed via instillation techniques. In vitro studies using live cells are cost-effective, allow for precise dose delivery, and provide a useful avenue by which to conduct rapid PM mechanistic and comparative toxicity studies. Often, the initial information on likely mechanisms of action of particles is obtained through in vitro techniques. For in vitro studies, dose selection is important because it is easy to overwhelm normal defense mechanisms.

It is difficult to compare particle deposition and clearance among different inhalation and instillation studies because of differences in experimental methods and in quantification of particle deposition and clearance. Key points from a discussion by Driscoll et al. (2000) of the role of instillation in respiratory tract dosimetry and toxicology studies are informative. In brief, inhalation may result in deposition within the ET region, the extent of which depends on the size of the particles used; but intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly into the TB tree. Although some studies indicate that short (0 to 2 days) and long (100 to 300 days postexposure) phases of clearance of insoluble particles delivered either by inhalation or intratracheal instillation are similar, others indicate that the percent retention of instilled particles is greater than for inhalation, at least up to 30 days postexposure. Also, inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs, but instillation is typified by heterogeneous distribution (especially in the A region) and high focal levels of particles. Most instilled material penetrates beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of particles. This difference is reflected in particle burdens within macrophages, those from animals inhaling particles being burdened more homogeneously and those from animals with instilled particles showing some populations of cells with heavy burdens and others with no particles, and is likely to impact clearance pathways, dose to cells and tissues, and systemic absorption. Exposure method, thus, clearly influences dose distribution; thus arguing for much caution in interpreting results from instillation studies.

Dosimetric calculations must be performed to relate TB cell exposures from instillation in terms of particle concentrations (on a number of particles per unit surface area basis) to those occurring in human environmental exposures. Such calculations require selecting characteristics associated with the particles, the exposed subject and the environmental exposure scenario. Hence each study can present a unique dosimetric analysis. In most cases, it will be useful to

know the relationship between the surface doses in instillation studies and realistic local surface doses that could occur in vivo in human subpopulations receiving the maximum potential dose. Some characteristics of individuals serve to enhance the local surface deposition doses to respiratory tract cells. These characteristics include: exercise and mouth breathing; non-uniform inhaled air distribution (such as occurs in chronic bronchitis and other COPD conditions), impaired particle clearance as occurs in some disease states; and location near pollutant sources. In addition, even normal subjects exposed by inhalation are expected to have numerous sites of locally high ("hot spots") particle deposition (specifically at airway bifurcations) within the TB tree.

In many studies, both toxicologic and epidemiologic, health endpoints are presented and analyzed as a function of exposure concentration. However, it is generally accepted that the dose to target cells or tissues, rather than exposure concentration per se, is responsible for adverse responses. Appendix 7A provides analyses of relationships between rat and human lung doses predicted for various exposure scenarios ranging from ambient PM exposures to PM instillations into the lung. As noted in Appendix 7A, establishing firm linkages between exposure and dose requires consideration of particle characteristics and biological normalizing factors. Optimally, the dose metrics and normalizing factors should be based on the biological mechanisms mediating an effect. For some effects, the mass of soluble PM depositing in a region of the lung may be an appropriate dose metric. For example, an appropriate normalizing factor for soluble PM could be the surface area of the airways for irritants, whereas body mass might be more suitable when considering systemic effects.

First, experimental exposure concentrations can be estimated that should result in the same tissue dose in a rat as received by a human exposed to various levels of ambient PM as a function of dose metric, normalizing factor, and level of human exertion. As no single dose metric nor normalizing factor appears to be appropriate for all situations, numerous scenarios were considered in Appendix 7A. The parameters chosen can dramatically affect the rat exposure concentration estimated to be required to provide a normalized dose equivalent to that occurring in a human, as illustrated in Appendix 7A, (Tables 7A-7a through 7A-9b).

Second, the dose to the lung can be estimated for both animal and human inhalation studies. These analyses make it possible to compare biological responses as a function of dose rather than just exposure. Equal lung doses should not be assumed in comparing studies, even if

PM mass concentrations, animal species, and exposure times are identical. Differences in the aerosol size distributions to which animals are exposed also affect dose delivered or retained. For example, in an Appendix 7A comparison of several CAPs studies, one study was estimated to have 1.7 times the alveolar dose of another study despite a 10% lower exposure concentration in the first study. Thus, to make accurate estimates of dose, it is essential to have accurate and complete information regarding exposure conditions, i.e., not only concentration and duration of exposure, but also the aerosol size distribution and the level of exertion (and hence breathing rates) for exposed subjects.

It was obviously not feasible, given the complexity involved, to attempt extrapolation modeling for more than a few illustrative health endpoints from among those evaluated in the vast array of studies assessed in Chapter 7 here. However, providing some illustrative modeling results here that estimate comparative exposure concentrations/doses shown experimentally in animal or human studies to be effective in producing a few important types of health endpoints should be of value in helping to provide a context by which to gauge the potential relevance of experimental results for ambient human exposure conditions.

***Dosimetric Intercomparison for PMN Influx as a Marker for Lung Inflammation***

Various types of particulate materials (both ambient PM and combustion source particles) have been shown to cause inflammation of the lung by migration of PMNs (predominantly neutrophils) into the airways as discussed in Chapter 7 and summarized below. These cells are initially produced by bone marrow and, along with alveolar macrophages (AM), constitute an important defense mechanism triggered by invasion of PM, bacteria, or some other foreign matter. The PMNs, once in the lung, ingest PM and then degranulate, forming hydrogen peroxide and superoxide anions. Excessive quantities of PM in the lung can cause the lysosomal enzymes in PMNs to enter the extracellular fluid, creating further inflammatory responses. Additionally, PMN produce thromboxanes, prostaglandins, and leukotrienes.

Three new studies discussed in Chapter 7 and Appendix 7A provide data on PMN increases following CAPs exposure that allow comparison of rat to human responses. (Clarke et al., 1999; Kodavanti et al., 2000a; Ghio et al., 2000a). Chapter 7 dosimetric intercomparison analysis of polymorphic neutrophil (PMN) data generated from exposures of rats and humans to CAPs in these studies demonstrated that healthy humans are more susceptible to the

inflammatory effects of CAPs than are rats. By assessing increases in PMN numbers in both species, a retained alveolar dose of 28 to 47 $\mu g/m^2$ causes a 60 to 500% increase in PMNs in rats, whereas it was estimated that a retained dose of 0.7 $\mu g/m^2$ causes a 267% increase in PMNs in humans. The full array of modeling results is presented in Table 9-4.

**TABLE 9-4. CAPS: RAT AND HUMAN INHALATION STUDY COMPARISONS**

| Study | Species | Particle | Exposure Conc. ($\mu g/m^3$) | MADD ($\sigma_g$) | Exposure duration | Analysis PE | Change in PMN | Estimated alveolar dose per surface area |
|---|---|---|---|---|---|---|---|---|
| Kodavanti et al. (2000a) | SD rat $SO_2$-SD | RTP CAPs | 740 | 0.98 (1.41) | 6 h/day for 2-3 days | < 3 h<br>18 h | 255% ↑PMN in 2 of 4 exp (bronchitic rats only) no change in PMN | ND<br>28 $\mu g/m^2$ retained |
| Clarke et al. (1999) | SD rat $SO_2$-SD | Boston CAPs | 515 | 0.18 (2.9) | 5 h/day for 3 days | 24 h | 500% ↑PMN<br>367% ↑PMN | 47 $\mu g/m^2$ retained |
| Ghio et al. (2000a) | humans | Chapel Hill CAPs | 120 | 0.65 (2.35) | 2 h | 18 h | 267% ↑PMN | 0.7 $\mu g/m^2$ retained |

***Inhibition of Phagocytosis by PM Exposure***

Phagocytosis is a form of endocytosis wherein bacteria, dead tissue, or other foreign material (e.g., inhaled ambient particles) are engulfed by cells such as AM, MO, or PMN as part of normal lung defense mechanisms. Hence, increased numbers of AM, MO, or PMN cells in lung tissue are an indicator of mobilization of lung defenses in response to infection or deposition of inhaled particles. Once ingested by AM, lysosomes act to digest engulfed materials. Inhibition of the phagocytosis by AM would signal interference with lung defense mechanisms by which inhaled bacteria and viruses are killed or other foreign particles are detoxified and/or cleared from the lung. Also, if an AM is overwhelmed by the amount or toxicity of ingested material, that material may be released along with the AM's digestive enzymes onto the alveolar surface and numbers of AM or their phagocytic activities may decrease.

Several experimental (especially in vitro) studies discussed in Chapter 7 have demonstrated, that in some instances, one or another type of PM has caused an inhibition of phagocytosis. As with other endpoints affected by PM, this inhibitory effect is determined by the size and composition of the specific particle mixes tested.

Analysis in Chapter 7 of in vitro exposure data evaluating inhibition of phagocytosis in rodent and humans showed some important species differences. Human AMs demonstrated inhibition of phagocytosis at 0.2 to 0.5 ng/cell (UAP and ROFA) and 0.05 ng/cell (Utah Valley PM). Hamster AMs showed no inhibition of phagocytosis at doses up to 0.04 ng/cell CAPs and 0.4 ROFA. A mouse AM cell line showed inhibition of phagocytosis at concentrations of 0.013 to 0.025 ng/cell. Differences in inhibition may be attributed to interspecies variability in the capacity of AM, wherein rodent AMs are smaller, have less capacity for phagocytosis, and are inhibited at a lower burden of PM per cell.

#### *9.2.3.2.4 General overview of toxicologic findings*

Dose-response relationships and extrapolation of experimental PM effects on both cardiovascular and respiratory endpoints were discussed in Chapter 7. Some of the more salient new toxicological findings that have emerged for the three general categories of effects implicated by the epidemiology studies are summarized below.

***Cardiovascular/Systemic Effects***

Controlled human exposure studies have yielded some limited but interesting evidence for ambient PM effects on cardiac physiological function (as indexed by ECG readings) or systemic endpoints (as indexed by vasopressor control, blood coagulation control, etc.) linked to more serious cardiovascular events. Cardiovascular and systemic effects of inhaled PM were observed with CAPs, UAP, and ROFA. Probably of most note, the controlled human exposure CAPs study by Ghio et al. (2000a) and another by Petrovic et al. (2000) did find evidence indicating that ambient levels (~25 to ~125 to 300 $\mu g/m^3$) of inhaled $PM_{2.5}$ can produce some biochemical changes (increased fibrinogen) in blood suggestive of PM-related increased risk for prothrombotic effects. Blood fibrinogen levels increased in humans with exposures of 125 to 330 $\mu g/m^3$ CAPs and in both normal and compromised dogs at 69 to 828 $\mu g/m^3$; and Ulrich et al. (2002) found a 20% increase in plasma fibrinogen in rats 2 days after instillation exposure to 6.7

or 22.2 mg/kg of Ottawa EHC93 UAP extract. Also, decreased Factor VII levels were observed by Gong et al. (2003) in humans (with 2-h CAPs exposure at ~174 $\mu g/m^3$) and by Reed et al. (2004) in rats (with DE exposure 6h/day, 7 day/wk, for 1 wk at 300 and 1000 $\mu g/m^3$), perhaps reflecting that enzyme being consumed in an ongoing coagulation process. Also, strain differences were found for effects on plasma fibrinogen levels, blood cell counts, and cardiac lesions in rats at doses of 10 to 15 $mg/m^3$ with exposures to ROFA via inhalation. On the other hand, the same and many other human and animal studies did not find significant changes in other factors (e.g., increased platelets or their aggregation) related to blood coagulation control. Additional other studies have shown no cardiovascular effects in rats and dogs with CAPs exposures of 3-360 $\mu g/m^3$. Inhalation of ROFA exposures demonstrated effects such as arrhythmias, ECG abnormalities, and decreased heart rate variability in rodents and dogs at 3 to 15 $mg/m^3$.

Instilled UAP and ROFA have been found to have cardiovascular and systemic effects in laboratory animals. Ottawa UAP instilled intratracheally at 7 mg/kg induced hypothermia and bradycardia in rats and at 1.6 to 2 mg/kg caused increases in circulating PMN band cell numbers and atherosclerotic lesions in rabbits. ROFA exposures of 0.7 mg/kg (compromised rats) and of 3 to 7 mg/kg (normal rat) have been shown to induce arrhythmias. The hypothermic response was also seen in a similar concentration range in rats. Increased fibrinogen has been observed in rats with exposures as low as 5 mg/kg. In many cases, compromised animals which model human cardiovascular disease show effects at lower doses than their normal counterparts. More rigorous characterizations of dose-response relationships with environmentally relevant levels and species of PM are necessary to evaluate more fully the risk posed by ambient exposures.

Among the most salient hypotheses proposed to account for cardiovascular/systemic effects of PM are: alterations in coagulability (Seaton et al., 1995; Sjögren, 1997); cytokine effects on heart tissue (Killingsworth et al., 1997); perturbations in both conductive and hypoxemic arrythmogenic mechanisms (Watkinson et al., 1998; Campen et al., 2000); altered endothelin levels (Vincent et al., 2001); and activation of neural reflexes (Veronesi and Oortgiesen, 2001). Only limited progress has been made in obtaining evidence bearing on such hypotheses, as discussed later; and much future research using controlled exposures to PM of laboratory animals and human subjects will be needed to test further such mechanistic

hypotheses so as to more fully understand pathways by which low concentrations of inhaled ambient PM may be able to produce life-threatening cardiovascular/systemic changes.

Overall, then, some available laboratory studies provide limited evidence suggesting that relatively high concentrations/doses of inhaled or instilled particles can exert cardiovascular-related systemic effects. However, many of the studies provide conflicting evidence, especially with regard to heart rate, heart rate variability, or other ECG markers of cardiac function. Thus, although some of the reported changes have been used as clinical "markers" for cardiovascular diseases, the causal relationship between such PM-related changes and potential life-threatening alterations in cardiovascular function remains to be better established.

***Respiratory Effects***

The respiratory effects of PM having varying physical and chemical characteristics have been extensively studied for more than 30 years using a wide range of techniques and with exposure durations ranging from brief periods to months. The most extensively studied materials have been sulfates and acid aerosols formed as secondary pollutants in the atmosphere. Fly ash from coal-fired power plants or other coal-combustion sources has been less extensively studied. The toxicological data available today provide little basis for concluding that these specific PM constituents have substantial respiratory effects at current ambient levels of exposure. Recently, ROFA, a very specific kind of PM, has been studied extensively and found to produce a range of respiratory effects, especially lung inflammation.

Probably of more direct relevance for present purposes, other recent studies evaluating controlled human exposures to concentrated ambient particles (CAPs) from diverse locations (e.g., Boston, New York City , Los Angeles, Toronto, and Chapel Hill, NC) have found little or no effects on pulmonary function or respiratory symptoms in healthy human adults acutely exposed (for 2 h) by inhalation to CAPs concentrations that ranged from about 25 up to about 300 $\mu g/m^3$. Some indications of mild lung inflammation were reported with such exposures in some of the studies, but not others. Analogous controlled exposures to CAPs of rats, hamsters, and dogs at concentrations varying across a range of ~100 to 1000 $\mu g/m^3$ for 1-6 h/day for 1 to 3 days yielded similar minimal effects on respiratory functions, but did find some signs of mild inflammation in normal healthy animals and somewhat enhanced indications of lung inflammation in at least one compromised animal model of chronic bronchitis. More

specifically, inhalation CAPs exposures of ~100 to 1055 μg/m$^3$ caused decreased respiratory rates and increased in BAL neurotrophils in dogs, 200 to 700 μg/m$^3$ caused functional changes in rats, and 650 μg/m$^3$ caused increased BAL protein and neutrophil in bronchitic rats. ROFA at concentrations of 10 to 15 mg/m$^3$ caused increases in PMN, AM, BAL protein, LDH, and airway hyperreactivity. Followup evaluations have produced new evidence for the transition metal components of ambient PM from diverse locations and of ROFA having a mediating role in producing inflammatory responses. Another inhalation study found indications of some impairment of lung immune defense functions and exacerbation of bacterial infection with an acute (3 h) exposure of rats to New York City CAPs (at 100-350 μg/m$^3$).

Instillation studies have also shown respiratory effects of PM on a variety of endpoints. Exposures of humans to Utah Valley dust at concentrations of 0.007 mg/kg caused increases in cytokines, fibronectin, fibrinogen, PMN, BAL protein, and tissue factor. Exposures of rats to 3 mg/kg caused similar changes, and 8 mg/kg caused lung lesions and airway reactivity. Respiratory effects from ROFA instillations were seen in rodents in dose ranges of ~1 to 10 mg/kg.

Also, CAPs, UAPs, and ROFA, have all been used in in vitro experiments to demonstrate effects and explore mechanisms whereby PM causes effects. Approximately 0.02 to 0.2 ng PM/cell is the concentration range where in vitro effects (e.g., cytokine production, inhibition of phagocytosis, and oxidant formation) were observed.

There still remains, however, a critical need for the systematic conduct of studies of the potential respiratory effects of major components of PM from different regions of the U.S., in recognition that PM of different composition and from different sources can vary markedly in its potency for producing different respiratory effects. Of particular importance are studies that more systematically evaluate mixtures of ambient constituents found in various airsheds, including short-lived species, e.g., peroxides.

***Mutagenic/Genotoxic Effects of PM***

As discussed in Chapter 8 and in Section 9.2.2, the Pope et al. (2002) extension of analyses evaluating long-term ambient PM exposure effects on total (non-accidental) and cause-specific mortality (using longer term follow-up data from the American Cancer Society or "ACS"

database) provides additional strong evidence for chronic ambient PM exposure being associated with increased risks for lung cancer.

Several recent in vivo and in vitro toxicological studies have suggested that ambient urban PM is mutagenic. Research evaluating the mutagenicity of ambient PM from the Los Angeles area has pointed to ubiquitous emission sources as being responsible for mutagenic activity observed in vitro (Hannigan et al., 1997, 1998). Fractionation of those ambient samples and subsequent mutagenicity assessments have indicated that six unsubstituted polyaromatic compounds and two semi-polar compounds are the likely mutagens. The former include pyrene compounds (mainly from non-catalyst equipped gasoline engines), and the latter fluoranthene compounds commonly found in vehicle exhaust or emitted by natural gas combustion. Mutagenicity of urban air from heavily industrialized or traffic urban areas of Germany has also been demonstrated (Hornberg et al., 1996, 1998; Seemayer and Hornberg, 1998) with evidence showing that ambient $PM_{2.5}$ exerted much stronger effects than $PM_{10}$. Additionally, ambient PM from high traffic areas in The Netherlands has also been shown to induce genotoxic activity.

Emissions from wood/biomass burning have been shown to be mutagenic. Studies of human exposures in The Netherlands (Heussen et al., 1994) and China (Vinitketkumnuen et al., 2002), examining both chronic seasonal and acute exposures, have demonstrated increased mutagenicity with environmental exposures. Characterization of wood smoke fractions to assign mutagenicity have shown that the gaseous fraction is more mutagenic than the PM component and that the condensate is not mutagenic (Putnam et al., 1999). Wood smoke emissions can cause both frameshift and base pair mutations but have not yet demonstrated the production of DNA adducts.

Coal combustion emissions have been shown to be mutagenic, especially the polar and aromatic fractions. Research in China examining populations with high lung cancer rates have shown that emission samples from homes burning smoky coal are mutagenic in the Ames assay, and implicate PAHs as contributors to the mutagenicity (Mumford et al., 1987, 1999; Lan et al, 2002). More recent work (Granville et al., 2003) characterizing the mechanism of genotoxicity has examined the mutation spectra of coal smoke emissions from these Chinese homes. Sequencing the revertants has demonstrated that the mutations in Salmonella exposed to coal smoke extract are similar to mutations seen in lung tumors of women exposed environmentally to the coal smoke.

Extensive past diesel exhaust (DE) studies have demonstrated mutagenic activity in both particulate and gaseous fractions of DE. By sequential fractionation of DE, apportionment of the mutagenicity is possible, which has implicated nitrated polynuclear aromatic compounds as being responsible for a substantial portion of the mutagenicity. Other mutagenically active compounds include ethylene, benzene, 1,3-butadiene, acrolein, and several PAHs in the gas phase. In addition to Ames assay studies, the induction of gene mutations has been reported in several in vitro mammalian cell lines after exposure to extracts of DPM. Structural chromosome aberrations and SCE in mammalian cells have been induced by DE particles and extracts.

Older studies comparing the mutagenicity of gasoline and diesel exhaust showed that the PM component of the exhaust is more mutagenic than the condensate fraction, and that overall, diesel exhaust is more mutagenic than gasoline exhaust. More mutagenicity is also observed in exhaust from cold starts than from exhausts at room temperature. Examining the fractional mutagenicity of gasoline and diesel exhausts, it was shown that, as with coal smoke, the polar component has the most mutagenicity, and further, that nitro-PAH is present in this fraction. A comprehensive study (Seagrave et al., 2002) comparing gasoline and diesel exhaust genotoxicity, using both the PM and SVOC fractions, demonstrated that both exhausts are mutagenic, but, in general, diesel exhaust is more mutagenic. Further, the study implicates PAH and nitroarenes in the genotoxicity. Another current study (Pohjola et al., 2003) corroborates these finding, and includes data suggesting that DNA adduct formation is a component of the mutagenicity.

Thus, there is qualitative evidence for the mutagenic/ genotoxic potential of both ambient PM and some fuel combustion products. Many of the published in vitro studies failed to provide details about the dose of PM extract delivered to the cells in vitro. In general, equal volumes of air or amounts of time were generally sampled and reported, but little characterization of the amount of PM mass or size was done or reported. Thus, any quantitative extrapolation of the reported findings would be quite difficult. Still, they collectively provide extensive credible evidence substantiating the biologic plausibility of, and/or elucidating potential mechanisms underlying reported epidemiologic associations between lung cancer and long-term human exposure to ambient fine particles.

#### *9.2.3.2.5 Links between specific PM components/characteristics and health effects*

The epidemiology evidence reviewed in the 1996 PM AQCD and updated in this document clearly shows positive associations between ambient PM pollution and mortality/morbidity.

Approaches to assessing likely "causation" and "biological plausibility" have attempted to integrate the wealth of epidemiologic data with the growing body of toxicology information in order to reveal coherence among the findings that support newly emerging sound hypotheses. Thus, while it is often difficult to separate the physicochemical attributes of PM that may be of health significance from the mechanisms by which individual factor(s) may function in the response, hypotheses have been proposed that focus on various PM characteristics as potentially significant contributors to the observed health effects (reviewed by Dreher, 2000). Each of the attribute-based hypotheses has a sufficient data base to merit consideration and further investigation.

To date, toxicologic studies on PM have provided important, albeit still limited, evidence for specific PM attributes being important factors involved in the induction of cardiopulmonary effects linked to ambient PM. In most cases, however, exposure concentrations in laboratory studies have been inordinately high compared to the exposures at which epidemiologic studies have found effects. Reasons for this dosimetric discrepancy include the typically limited use of very young, elderly, unhealthy, or otherwise at-high-risk animals or humans, especially in light of poorly understood risk factors. However, sufficient coherence in the epidemiologic and toxicological data has added a level of "plausibility" to the observational studies and has thus opened new avenues for investigation to link PM properties and constituents to specific sources and to health outcomes.

The plausibility of epidemiologically-demonstrated associations between ambient PM and increases in morbidity and mortality has been questioned because cardiovascular and pulmonary effects have been observed among human populations at very low ambient PM concentrations. To date, experimental toxicology studies have provided some intriguing, but limited, evidence for ambient PM mixes or specific PM components potentially being responsible for reported health effects of ambient PM. Overall, the new studies suggest that some types of particles are more toxic than others. New findings substantiating the occurrence of health effects in response to controlled exposures to (a) ambient PM mixes and/or (b) their constituent substances are

useful in demonstrating or clarifying potential contributions of physical/chemical factors of constituent particles.

***Physical Properties***

**Ultrafine Particles (Size, Surface Area, Number)**. The physical attributes of PM - size, surface area and number - are intimately interrelated. These properties influence lung deposition, penetrance and persistence in lung tissues, and systemic transport, and, in several studies, apparently the inherent toxicity of the particle itself. While a few epidemiologic studies (Wichmann et al., 2000) show correlations between health outcomes and ultrafine (< 100 nm) ambient PM, the bulk of the information regarding its toxic potential, and the role of surface area, has derived from studies of surrogate insoluble particles, such as mineral oxides (e.g., $TiO_2$) and carbon black. Studies of various types of ultrafine particles have demonstrated a significantly greater inflammatory response than that seen with fine particles of the same chemical composition at similar mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). Instillation of 125 μg of ultrafine carbon black (20 nm) caused substantially more inflammation per unit mass than did the same dose of fine particles of carbon black (200 to 250 nm), suggesting that ultrafine particles may cause more inflammation per unit mass than larger particles (Li et al., 1997). However, the chemical constituents of the two sizes of carbon black used in this study were not analyzed, and it cannot be assumed that the chemical composition was the same. Further, when the particle surface area is used as a dosimetric, the inflammatory response to both fine and ultrafine particles may be basically the same (Oberdörster, 1996; Oberdörster et al., 2000; Li et al., 1996). In other more limited studies, ultrafines also have generated greater oxidative stress in experimental animals. Inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge (100 $\mu g/m^3$ for 6 h) caused minimal lung inflammation per unit mass (Elder et al., 2000a,b), compared to ultrafine PTFE or metal particles.

These studies have shown that on an equivalent mass exposure-dose metric, ultrafine PM can induce more acute lung injury than fine PM. Similarly, surrogate PM with high surface areas induced more toxicity than those of like composition, but having smaller surface areas (Lison et al., 1997). On the other hand, studies have shown that composition also matters; for

example MgO ultrafines produce less injury than ZnO (Kuschner et al., 1997), as did sparked carbon versus similarly generated metal oxides (Elder et al., 2000a,b).

With regard to acid aerosols, studies of low concentrations of ultrafine sulfuric acid and metal oxide particles have demonstrated effects in the lung.

Studies of ultrafine particles have focused largely on effects in the lung, but inhaled ultrafine particles may also have the potential to be distributed systemically and have effects that are independent of lung effects. Recent epidemiologic studies evaluating blood viscosity as a biologic correlate of ultrafine exposures, have reported slight increases that raise the prospect of potential cardiovascular implications (Wichmann et al., 2000). Thus, there is still insufficient toxicological evidence to elucidate clearly the extent to which ambient concentrations or high number counts of ultrafine particles may differentially contribute to increased health effects risks associated with ambient PM air pollution.

**Fine and Thoracic Coarse Particles**. In contrast to ultrafine particles, the respective roles of $PM_{2.5}$ (indicator for fine PM) and $PM_{10-2.5}$ (indicator for thoracic coarse PM) in defining health outcomes have garnered considerable research attention because they are the most frequently measured size-fractions of ambient PM and for which most health effects data exist. The fine fraction comprises most of the combustion-related constituents discussed below under chemical properties. The fine fraction has greater surface area than the thoracic coarse fraction, but less surface area and much larger particle number than the ultrafine fraction. To the extent that inhaled PM may carry chemicals or reactive species on their surfaces, these smaller size fractions may have an additional dimension to their toxicity (in terms of surface chemical bioavailablilty) that is not found with coarse PM. For example, acute exposure to sulfate-coated carbon black was found to impair alveolar macrophage phagocytosis and intrapulmonary bactericidal activity in mice (Jakab et al., 1996; Clarke et al., 2000). On the other hand, coarse PM usually is of mineral (earthen) or biologic (discussed below) origin and, thus, has a less complex bioavailable chemical matrix than the finer PM mode. The relative toxicity of most earthen-derived PM has been observed to be less than that of the finer combustion-derived or surrogate ultrafine particles. However, because ambient coarse PM would tend to impact on the airways of humans, it is thought this fraction may be adverse to those with airways sensitivities or disease (e.g., asthma).

***Chemical Properties***

**Acid Aerosols.** Controlled exposure studies assessed in the 1996 PM AQCD showed that aqueous acid aerosols had little effect on pulmonary function or respiratory symptoms in healthy young adults with inhatim exposure at concentrations as high as 1000 $\mu g/m^3$. On the other hand, lung function effects were observed in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$; and modest bronchoconstriction was seen in adult asthmatics exposed to concentrations $\geq$ 400 $\mu g/m^3$, but the available data were not consistent. However, at concentrations as low as 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. That is, brief exposures ($\leq$ 1 h) to low concentrations (~100 $\mu g/m^3$ may accelerate clearance while longer (multihour) exposures to higher concentrations (> 100 $\mu g/m^3$) can depress clearance.

There is relatively little new information on the effects of acid aerosols, and the basic conclusions of the 1996 PM AQCD largely remain unchanged. As noted, It was previously concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects at levels well exceeding ambient concentrations, but asthmatics may experience small decrements in pulmonary function at distinctly lower (but supra-ambient) levels. Long-term exposures of animals to acid aerosols, on the other hand, have been shown to alter airway morphology with epithelial cell desquamation and an increase in secretory cells, but these changes have been considered relatively minor. The conclusions about acute health effects, however, appear to be supported by a newer study by Linn and colleagues (1997), in which healthy children (and children with allergy or asthma) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 hours. While there were no significant effects on symptoms or pulmonary function when the entire group was analyzed, the allergy group did have significant acid-related increases in symptoms, although the acid concentrations were distinctly higher than typical ambient concentrations. Also, Leduc et al. (1995) found no increased bronchoconstriction or bronchial hyperresponsiveness in asthmatic adults exposed via a facemask to 500 $\mu g/m^3$ of acid fog containing $H_2SO_4$ or ammonium sulfate aerosol.

Several other laboratory animal studies found little effect of sulfate (ammonium bisulfate, ammonium ferrosulfate) or ammonium nitrate aerosols on lung inflammation markers or indicators of AM function in normal, sensitized, or MCT-compromised mice with inhalation exposures (4 h/day for 3 days) at concentrations varying from 70 to ~970 $\mu g/m^3$ (Cassee et al., 1998a,b,c). In another study (Zelikoff et al., 1997), of 3 h exposures to 1000 $\mu g/m^3$ of $H_2SO_4$,

for both rabbits and humans, superoxide production by macrophages was somewhat depressed in both species, and macrophage phagocytosis and antimicrobial activity was reduced in the rabbits.

Although pulmonary effects of acid aerosols have been the subject of extensive research, the cardiovascular effects of acid aerosols have received little attention. One example which raises the issue is a study of acetic acid fumes where reflex mediated increases in blood pressure were found in normal and spontaneously hypertensive rats (Zhang et al., 1997). Similarly, acidic residual oil fly ash (ROFA),which also contains a considerable amount of metal sulfates, was found to alter ecocardiogram (ECG) patterns in the same strain of rats at high air concentrations (Kodavanti et al., 2000b). Thus, acidic components should not be entirely dismissed as possible mediators of ambient PM health effects, since so little is known about potential cardiovascular impacts or impacts in compromised subjects.

**Transition Metals.** The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) mainly relied on data related to occupational exposures to evaluate the potential toxicity of metals in contributing to health effects associated with ambient PM exposures. Since that time, numerous newly published in vivo and in vitro studies using exposures to ambient PM extracts, ROFA, other combustion source emission materials (e.g., CFA, etc.), or specific soluble transition metals have contributed substantial further information on the health effects of particle-associated soluble metals. Although there are some uncertainties about differential effects of one transition metal versus another, some water soluble metals (e.g., Ni, V, Zn, Fe) leached from ambient filter extracts or ROFA have been shown consistently (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro and in vivo.

**Other Inorganic Constituents.** The inorganic constituents of ambient PM comprise a number of compounds and elements that derive from either natural or combustion sources. The earthen or natural constituents of PM are typically silicates that contain surface and matrix bound metals such as calcium, magnesium, aluminum, and iron. As noted above, most of these silicates do not appear to contribute much toxicity to ambient PM, as considered in this document. Sulfate and nitrate anions derived from combustion or photochemical processes usually complex with other constituents in PM - often more water-soluble ammonium ions or

organic acids, as well as elemental cations, such as metals. The intrinsic, independent toxicities of sulfates (as per above) and nitrates appear to be rather low, but they may influence the toxicity or bioavailability of other PM components. Of the cations, metals represent a potential class of causal constituents for PM-associated health effects that have received considerable attention (discussed further below). Sulfate, nitrate, ammonium, and metals make up a substantial part of the mass of ambient PM, often with a silicate or carbonaceous (see below) core, layering, or matrix. The majority of PM-associated metals in fine PM are derived from stationary or mobile combustion sources whereas particle sulfate, nitrate and ammonium originate from secondary atmospheric transformation reactions of involving $SO_2$, $NO_x$ and biomass ammonia emissions. Organic PM has both primary and secondary sources.

**Organic Constituents.** Published research on the acute effects of PM-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles (DPM). Like metals, organics are common constituents of combustion-generated PM and are found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial portion of the mass of ambient PM (10 to 60% of the total dry mass [Turpin, 1999]). Although the organic fraction of PM is a poorly characterized heterogeneous mixture of a widely varying number of different compounds, strategies have been proposed for examining the health effects of potentially important organic constituents (Turpin, 1999). In contrast, the mutagenic effects of ambient PM and evidence of DNA-adducts have had more extensive study and have been linked to specific organic fractions (Binková et al., 1999; Chorąży et al., 1994; Izzotti et al., 1996). The extent to which organic constituents of ambient PM contribute to adverse health effects identified by current epidemiology studies is not known. Nevertheless, organic constituents remain of concern regarding PM health effects due in large part to the contribution of DE particles to the fine PM fraction and the health effects associated with exposure to these particles.

**Biological Constituents.** Recent studies do not fully support the strong conclusion of the 1996 PM AQCD that bioaerosols (e.g., fungal spores, plant and insect fragments, airborne bacteria, etc.), at concentrations present in the ambient environment, are unlikely to contribute to health effects of ambient PM. On the one hand, dose-response inhalation studies in healthy

volunteers exposed to 0.55 and 50 μg endotoxin showed the threshold for pulmonary and systemic effects for endotoxin to be between 0.5 and 5.0 μg (Michel et al., 1997). Urban ambient air PM contains variable amounts of endotoxin, but the levels typically are several orders of magnitude less. In vitro toxicological studies have also shown endotoxin associated with ambient PM to be pro-inflammatory, inducing cytokine expression in human and rat alveolar macrophages, which appears to depend heavily on the endotoxin dose to cell ratio (Becker et al., 1996; Dong et al., 1996). However, endotoxin content does appear to vary by PM size-mode. Monn and Becker (1999) demonstrated cytokine induction by human monocytes, characteristic of endotoxin activity, in the coarse size fraction of outdoor PM, but not in the fine fraction. Interestingly, while studies in animal models also require more endotoxin than typically found in ambient PM to induce inflammation, some findings suggest that endotoxin may have a priming effect on PM-induced inflammatory processes (Imrich et al., 1999). Thus, the role of biogenic material like endotoxin may have a subtle role that is poorly understood.

On the other hand, clearer new insights have been gained with regard to the fact that allergen-laden cytoplasmic fragments of pollen grains are produced that range to very small (0.1 - 0.4 μm) fine-mode size upon rupture of pollen granules, which is highly moisture dependent and thought to be the main cause of increased incidence of "thunderstorm" asthma characterized by dramatic post-storm increases in asthma attacks and medical visits/treatments. Important roles of pollen spores or grains as carriers of other biologic agents (e.g., endotoxins, fungi fragments) are discussed below in Section 9.2.3.2.4, as are the roles of non-biological particles in serving as carriers of allergen-laden pollen fragements or other toxic bioaerosol agents.

***Mixtures: Ambient and Source PM***

Ambient PM comprises a complex mix of constituents derived from many sources, both natural and anthropogenic. Hence, the physicochemical composition of PM generally reflects the major contributing sources locally and regionally. Within this framework of source or origin, PM composition also varies significantly by the size-mode within which it is classified (ultrafine, accumulation, or coarse). It should be clear that any given particle can differ appreciably from another individual particle of similar size, but that the region of origin with all of its contributing sources determines the general composition of the generic PM in that

classification mode. By its nature then, exposure to airborne ambient PM constitutes an exposure to what is very clearly a mixture of different particles of differing composition and to other gaseous copollutants that coexist in that air-shed. Particle concentrators are in use that separate particles between about 0.1 μm and 2.5 μm and concentrate them for use in inhalation exposure studies without removing the particles from the atmospheric gases in which they occur. Studies have also used diluted diesel without removing the particles from the diesel exhaust. Other studies make use of particles collected by impactors, filters, electrostatic precipitators, or bag houses and then resuspend them for inhalation studies or make extracts or suspensions for instillation or *in vitro* studies.

**Concentrated Ambient Particles (CAPs)**. Studies using CAPS are probably most useful in helping to substantiate that particles present in "real-world" ambient air mixes are indeed capable of inducing notable pathophysiological effects under controlled exposure conditions and to clarify further factors affecting increased susceptibility of "at risk" groups for PM effects. CAPs studies, on the other hand, have thus far been somewhat less helpful than other toxicologic approaches in helping to delineate the specific characteristics of PM producing toxicity and pertinent underlying mechanisms. Some, but not all, studies with inhaled CAPs have found cardiopulmonary changes in rodents and dogs at high concentrations of fine PM. However, no comparative studies to examine the effects of ultrafine and coarse ambient PM have been done.

Importantly, it has become evident that, although the concentrated ambient PM (CAPs) studies have provided important exposure-response information for some PM size fractions (especially $PM_{2.5}$), they have not, to date, been very helpful in identifying specific toxic components in urban PM. Insufficient attention has been accorded to characterization of day-to-day variations in specific PM constituents in order to relate such variations to observed variable health responses to CAPs exposures. New particle concentrator systems now coming on-line at the U.S. EPA and elsewhere that permit selective concentration of ultrafine, fine, and thoracic coarse PM hold promise for enhancing our future understanding of PM characteristics producing toxicity. Future CAPs studies also hold promise for helping to identify susceptibility factors in animal models and to permit examination of mechanisms related to PM toxicity.

**Collected Urban Air Particles.** Studies using extracts of collected urban air PM (UAP) for intratracheal administration to healthy and compromised animals have also produced interesting new information. Despite the difficulties associated with extrapolating from the bolus delivery used in such studies, they have provided evidence indicating that the chemical composition of ambient particles can have a major influence on toxicity. Instillation of rats with filter extracts of ambient air particles collected from Ottawa CN air (Watkinson, et al., 2002a,b) at 2.5 mg, for example, induced pronounced biphasic hypothermia, severe drop in heart rate, and increased arrhythmias; this was in contrast to no cardiac effects seen with comparable instilled dose of Mt. St. Helens volcanic ash (shown by many studies to be relatively inert toxicologically). Similarly, dose-dependent increases in polymorphonuclear leukocytes (PMNs), other markers of lung inflammation, and decreases in alveolar macrophages (AMs) were seen with intratracheal exposures of hamsters to urban ambient particles from St. Louis or to Kuwaiti oil file particles (Brain et al., 1998).

Perhaps most notable in this argument are the Utah Valley studies that have linked the toxicology (*in vitro* cell culture as well as human and rodent instillation) with published epidemiological findings. In these studies, filter extracts of Utah Valley PM collected from the State/Federal sampling sites yielding aerometric data used to ascribe the impact of PM on hospital admissions and population mortality rates showed remarkable qualitative coherence with toxicological and clinical endpoints (BAL fluid markers, lung dysfunction) among the human and rodent test subjects. Moreover, the data were themselves consistent with the hypothesized underlying mode of action (oxidant generation, inflammation) for metal-associated PM cardiorespiratory effects (Frampton et al., 1999; Dye et al., 2001; Ghio and Devlin, 2001; Soukup et al., 2000; Wu et al., 2001; Pagan et al., 2003). Studies comparing human (Ghio and Devlin, 2001) and rat (Dye et al., 2001) exposures to both high and low metal content PM collected near a steel plant, suggest that the metal content of the PM was an important contributor to the toxicity of the PM. Both species showed similar inflammatory responses to exposures from PM with high metal content (collected while the steel mill was operating). Hence, these findings provide an important linkages across study disciplines used in the human and animal toxicology as well as in the *in vitro* studies.

Since the Utah studies were completed, an analogous study has addressed differential exacerbation of allergic asthma-related responses by PM from two German cities (Hettstedt and

Zerbst) of contrasting industrial activity. An allergic mouse model (representing an allergic asthma population) was intratracheally instilled with filter extracts from each city and the appropriate allergen to activate the model. The respective responses of the model corresponded to the prevalence of allergy and respiratory disease in the cities and appeared to be influenced by the ambient PM metal content in the respective cities. Hence, the data base is growing for studies linking animal and human responses. Some of these linkages are in the laboratory while others are with epidemiology. Why these collective data show coherence despite exposure/dose discrepancies, not to mention species and other differences, is unclear, but the data and findings stand on their merits and attest to the legitimacy of the approach and the value of the animal data in establishing biologic plausibility and insight into potential mechanisms.

Even though it is clear that combustion particles that have a high content of soluble metals can cause lung injury in compromised animals and correlate well with epidemiological findings in some cases (e.g., the Utah Valley Studies), it has not been fully established that the small quantities of metals (typically $\leq$ 0.5 to 1.0 $\mu g/m^3$) associated with current U.S. ambient PM mass concentrations exhibit greater toxicity than other PM components typically present in ambient air. In studies in which various ambient and combustion-source particulates were instilled into rats, the soluble metal content did appear to be one important determinant of lung injury (Costa and Dreher, 1997). However, one published study (Kodavanti et al., 2000b) has compared the effects of inhaled ROFA (at 1 $mg/m^3$) to concentrated ambient PM (four experiments, at mean concentrations of 475 to 900 $\mu g/m^3$) in normal and $SO_2$-induced bronchitic rats. A statistically significant increase in at least one lung injury marker was seen in the bronchitic rats with one out of four of the CAPs exposures; whereas the inhaled ROFA had no effect, even though the content of soluble iron, vanadium, and nickel was much higher in the ROFA sample than in the concentrated ambient PM. This suggests that substances present in some ambient air (but perhaps not in ROFA) besides soluble metals may contribute to a stronger potency of ambient air, at times, than seen with some oil combustion source-related materials.

Other particularly interesting new findings do point toward ambient PM exacerbation of allergic airway hyperresponsiveness and/or antigen-induced immune responses. Both metal and diesel particles have been implicated, with an expanding array of new studies showing DPM in particular as being effective in exacerbating allergic asthmatic responses, as noted below.

**Diesel Exhaust Particles.** As described in Section 7.5.3, there is growing toxicological evidence that, analogously to several other types of PM (silica, carbon black, road dust, etc.), diesel PM may exacerbate allergic responses to inhaled antigens. The organic fraction of diesel exhaust has been linked to eosinophil degranulation and induction of cytokine production, suggesting that the organic constituents of diesel PM are the responsible part for the immune effects. It is known that the adjuvant-like activity of DEP is not unique, and that certain metals have analogous adjuvant effects (Lambert et al., 2000). It is important to compare the immune effects of other source-specific emissions, as well as concentrated ambient PM, to diesel PM to determine the extent to which exposure to diesel exhaust PM may contribute to the incidence and severity of allergic rhinitis and asthma. It is also notable that rather direct evidence has been obtained which demonstrates adherence of allergen-laden pollen cytoplasm fragments to diesel particles, providing a likely mechanism by which diesel PM acts to concentrate bioaerosol materials and to increase their focal accumulation in lower regions of the respiratory tract. Other evidence substantiates mutagenic/genotoxic effects of diesel emission particles (e.g., PAHs), consistent with qualitative findings in several studies of increased lung cancer effects being associated with long-term, occupational exposure to diesel emissions.

***Summary***

Toxicological studies have provided considerable supportive evidence that certain physicochemical particle attributes can provide elements of "causality" to observed health effects of ambient PM. There is probably no single primary causative attribute, but rather many attributes may contribute to complex mechanisms driven by the nature of a given type of PM and its contributing sources. The multiple interactions that may occur in eliciting a response in a host may make the identification of any single causal component difficult and may account for the fact that mass, as the most basic PM metric, shows the relationships to health outcomes that it does.

#### *9.2.3.2.6 Mechanisms of action*

As discussed in Chapter 7, the body of evidence supporting various hypotheses regarding induction of PM effects has grown substantially since the last review. Various toxicologic studies using PM having diverse physicochemical characteristics have shown that such

characteristics have a great impact on the specific response that is observed. Thus, there appear to be multiple biological mechanisms that may be responsible for observed morbidity/mortality due to exposure to ambient PM, and these mechanisms appear to be highly dependent on the type and dose of particle in the exposure atmosphere. It also appears that many biological responses are produced by PM whether it is composed of a single component or a complex mixture. The potential mechanisms for action on the cardiovascular and pulmonary systems that were discussed in more detail in Section 7.9.1 are summarized briefly below.

***Direct Pulmonary Effects:***

Lung Injury and Inflammation. Exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation. Recent studies have reported effects including increased levels of neutrophils, protein, and inflammatory cytokines, and increase in airway hyperresponsiveness. Some recent studies have implicated metal components of PM as contributing to inflammation and injury in the lung. In contrast, controlled exposures of animals to sulfuric acid aerosols, acid-coated carbon, and sulfate salts cause little lung injury or inflammation, even at high concentrations. Some (but not all) studies have shown CAPs exposure to cause mild pulmonary injury and inflammation. There are also new data indicating a potential neurogenic basis for the effects of particulate matter, with particles potentially activating certain receptors found on human airway epithelial cells and sensory terminals; this activation, could initiate and sustain inflammatory events in the pathophysiology of neurogenic inflammation. Particle surface change is important, with negatively charged particles surrounded by proton cloud being effective in activating the receptor.

Increased Airway Reactivity and Exacerbation of Asthma. The strongest evidence supporting this hypothesis is derived from studies on diesel particulate matter (DPM), which has been shown to increase production of antigen-specific IgE in mice and humans (as summarized in Chapter 7). Biological agents (e.g., pollen fragments) also contribute to asthma effects.

Increased Susceptibility to Respiratory Infections. A few newly published studies have provided some evidence for ambient PM potentially affecting lung defense mechanisms and increasing susceptibility to infection. Several new studies have suggested that particles can increase

numbers of alveolar macrophages and increase bacterial burden, slow clearance of the bacteria, reduce AM NO production, and decrease phagocytic activity of alveolar macrophages (AM). These data are suggestive of possible impairment of an important lung defense mechanism even in the absence of lung injury.

***Cardiovascular and Other Systemic Effects Secondary to Lung Injury***

**Decreased Pulmonary Function and Oxygenation Adversely Affect the Heart Secondary to Lung Injury**. Results from new toxicology studies in which animals (normal and compromised) were exposed to CAPs (at concentrations many times higher than would be encountered in the United States) indicate that ambient PM is unlikely to cause severe disturbances in oxygenation or pulmonary function. However, even a modest decrease in oxygenation can have serious consequences in individuals with ischemic heart disease. Evidence from some new studies indicate that it is plausible that instilled ROFA may cause severe hypoxemia leading to death; more information is needed, however, on the effects of PM on arterial blood gases and pulmonary function to fully address the above hypothesis.

**Systemic Hemodynamic Effects Secondary to Lung Inflammation and Increased Cytokine Production**. It has been suggested that systemic effects of ambient PM may result from activation of cytokine production in the lung, with cytokine releases in the lung resulting in systemic changes such as arrhythmias or changes in heart rhythm. While some new studies have provided suggestive evidence, further information is needed on the effects of mild pulmonary injury on cardiovascular function to more fully evaluate this hypothesis.

**Increased Blood Coagulability Secondary to Lung Inflammation**. Several new studies have investigated possible effects of ambient PM or surrogate particles on blood chemistry constituents that would be indicative of increased blood coagulability. There is abundant evidence linking small prothrombotic changes in the blood coagulation system to increased long-term risk of heart attacks and strokes. Some studies have shown both indicators of lung inflammation and increased coagulability; however, the published toxicological evidence bearing on whether moderate lung inflammation causes increased blood coagulability is very mixed and inconsistent. The coagulation system is multifaceted and complex; and there are

many other sensitive and clinically significant parameters that should, in addition to fibrinogen, show more extensive and consistent patterns of change reflective of PM effects on blood coagulation.

**Hematopoiesis Effects Secondary to PM Interactions With the Lung**. Some new studies have shown increased release of immune cells, such as PMNs, from bone marrow; however, consistent evidence that PM ambient concentrations can affect hematopoiesis remains to be demonstrated.

***Direct Effects on the Heart***

**Cardiac Effects Secondary to Uptake of Particles and/or Release of Soluble Substances into the Circulation**. Particles or particle components could conceivably be rapidly transported to the heart, where they might exert effects directly on cardiac vasculature (e.g., exacerbation of atherosclerosis) or heart muscle itself. Alternatively, they could also exert very rapid effects on cardiac function through stimulation of nerve ending receptors in lung tissue, resulting in secretion of inflammatory messenger substances and/or activation of neurally-mediated autonomic reflexes.

**Inhaled PM Effects on Autonomic Control of the Heart and Cardiovascular System**. Changes in sympathetic and parasympathetic input to the cardiovascular system can result in changes in heart rhythm; these changes may be mediated by neural reflexes. Though not always consistent and somewhat difficult to interpret, changes in heart rate variability and conductance system function associated with ambient PM exposure have been reported in some animal studies and in several epidemiologic studies.

#### *9.2.3.2.7 Inhaled particles as potential carriers of toxic agents*

***Particle-Bound Water***

In Chapter 2, it was noted that, although water vapor is not considered a pollutant per se and particle-bound water is not measured as part of the ambient PM mass typically monitored for regulatory purposes, particle bound water may serve as a carrier for other pollutants. Wilson (1995) proposed that water-soluble gases that are usually largely removed by deposition to wet

surfaces in the upper (ET) portion of the respiratory tract could be dissolved in particle bound water and, thereby, be carried into the lower regions of the respiratory tract. Such water-soluble gases commonly found in polluted air masses include: oxidant species (e.g., $O_3$, $H_2O_2$, and organic peroxides); acid gases (e.g., $SO_2$. HCl, $HNO_3$, HONO, and formic acid); and polar organic species (e.g., formaldehyde). Thus, water may be a vector by which these gases may be delivered in enhanced proportions to the TB and A regions of the deep lung.

Kao and Friedlander (1995) noted further that, in evaluating health effects of ambient aerosol components, it is "important to realize that the chemical analyses of routinely collected particulate samples are not necessarily an accurate representation of the atmosphere". They further noted that many short-lived chemical species in the gas or particle phase, such as free radicals, may not be present in the sampled materials when analyzed hours to weeks (or longer) after being collected on filters and stored. Also, the unmeasured metastable species may be much more biochemically active than "dead" components collected or remaining on analyzed filters. They concluded that, "since inhalation toxicology studies using both human and animal subjects often do not include the potential for metastable species and reactive intermediaries to be present, they could greatly underestimate the effects seen in field or epidemiologic studies."

Friedlander and Yeh (1998) elaborated further on the fact that the aqueous component of the atmospheric submicron aerosol contains short-lived reactive chemical species. That is, they explained that submicron atmospheric aerosols contain several types of components: (1) Primary components that include elemental (black) carbon; high molecular weight organic compounds emitted in aerosol form directly into the atmosphere; metallic compounds from smelting, welding, and other high temperature processes; and some small particles from soil dust or, in marine aerosols near coastal sites, sea salts; (2) Secondary components resulting from atmospheric reactions that yield inorganic ionic species ($NH_{4+}$, $SO_4$= and $NO_3$- being most important per mass basis) and, also, polar condensible products from atmospheric reactions involving organic vapors; (3) Water, the presence of which in the ambient submicron aerosol depends heavily on the relative humidity and the concentration of which can range from ~10 to 50 $\mu g/m^3$ in urban aerosols; and (4) Very short-lived reaction intermediates, such as hydrogen peroxides, aldehydes, and organic acids found in cloud and rain water.

Friedlander and Yeh (1998) further noted (1) that particle phase concentrations of hydrogen peroxide fall in a range for which significant biochemical effects were elicited with

treatment of respiratory tract epithelial calls; (2) that this may help to explain epidemiologic study results showing significant health effects to be associated with fine-mode aerosols or sulfate (the submicron sulfate-containing aerosol often being the product of atmospheric reactions involving hydrogen peroxide), and (3) that such aerosols may be serving as a surrogate or indicator for the hydrogen peroxide or other reactive species.

Wexler and Sarangapani (1998) used a physical model of "gas-particle-mucus heat and mass transport in the human airways" to investigate the transport by particles of soluble vapors to the tracheobronchial and air exchange regions of the lung. When the atmospheric aerosol is inhaled, water soluble gases will begin to dissolve in the mucus on the surface of the airways. However, hygroscopic particles will add particle-bound water in the high relative humidity of the respiratory tract and more soluble gas can dissolve in the particle. The amount of soluble gas in the particle will depend on the solubility of the gas (expressed as the Henry's Law coefficent), the size of the particle, and the position of the particle in the respiratory tract. In the presence of particles, the pattern of deposition of soluble gases may be moved deeper into the respiratory tract. Very soluble gases, such as $H_2O_2$ and formaldehyde will still be almost completely removed from the gas phase to the mucus on the airways. However, soluble gases dissolved in particles may be carried into the air exchange region. If equilibrium is reached rapidly, such highly soluble gases will evaporate from particles smaller than 0.1 μm diameter before the particles reach the air exchange region. However, particles larger than ~0.3 μm diameter can efficiently carry such gases into the air exchange region.

Wexler and Sarangapani (1998) point out that due to the small volume of particle-bound water, even in the case of highly soluble gases, only on the order of 1% of the soluble gas will be found in the particles. However, particles will change the pattern of vapor deposition and particles will carry dissolved gases deeper into the respiratory tract where the particles can deposit on air exchange surfaces not protected by mucus. Furthermore, the Wexler and Sarangapani (1998) analysis was based on considerations of physical solubility only. If adducts or complexes form, such peroxohydrates from $H_2O_2$ (Friedlander and Yeh, 1998; Elvers et al., 1991), or if the gas reacts chemically with water, as $SO_2$ does to form $SO_2$ (aq), $H_2SO_3$ (aq), and $HSO_{-3}$ (aq) (Schwartz, 1984), the solubility of the gas may be increased greatly and the time to reach equilibrium may be increased. Both factors would enable particles to transfer greater quantities of dissolved gases to the air exchange region.

Morio et al. (2001) evaluated whether hygroscopic components of PM may transport $H_2O_2$ into the lower respiratory tract and induce tissue injury. Rats were exposed via inhalation to $(NH_4)_2$ $SO_4$ (0.3 to 0.4 μm MMD) at 215 or 249 μg/$m^3$ or $H_2O_2$ at 10, 20, or 100 ppb alone or in combination for 2 h. No major effect was observed on BAL cell number or viability or on protein content or LDH levels immediately or 24 h post exposure. However, rats treated with the combination of sulfate and peroxide showed increased tumor necrosis factor (TNF – ∝) produced by alveolar macrophages and increased numbers of neutrophils in pulmonary capillaries (as seen via EM). These results and other effects on NO levels were interpreted by the authors as showing that biological effects of inhaled PM are augmented by coexposure to sulfate and peroxide, including altered production of cytokine mediators by AM.

Also of note, Hung and Wang (2001) observed high reactive oxygen species (ROS) activity (reflective of hydrogen peroxide levels) in atmospheric aerosols collected roadside in China, with higher ROS activity among fresh fine particles (~0.18 μm) than among ultrafine (< 0.1) or coarse (3.2 to 10 μm) particles. They noted that ambient temperature and water vapor content may affect ROS content of ambient particles.

The information summarized above has substantial implications for interpreting and understanding the vast array of epidemiological and toxicologic results discussed in preceding sections of this chapter and earlier chapters of this document. Their full significance becomes more evident when considered in light of dosimetric information discussed in Chapter 6. It is worth restating a few basic points here from Chapter 6 and expanding on them further with regard to the importance of dosimetric considerations in relation to particles as carriers of other toxic agents.

First, particle size is one of the most basic parameters governing particle behavior and deposition in the respiratory tract. Particles between 0.3 and 0.7 μm in diameter have minimal deposition in the respiratory tract. Above and below this range of minimum deposition, the efficiency of deposition increases. The pattern of deposition within the respiratory tract also slowly shifts from the alveolar region to the TB and ET regions with increasing particle size over 1 to 2 μm and with decreasing particle size below 0.1 μm.

Hygroscopicity, the propensity of a material for taking up and retaining moisture, is an important property of some ambient particle species and affects respiratory tract deposition. Such particles can increase in size in humid air in the atmosphere or in the respiratory tract and,

when inhaled, deposit according to their hydrated size rather than their initial size. Compared to nonhygroscopic particles of the same initial size, deposition of hygroscopic aerosols in different regions varies, depending on initial size: hygroscopicity generally increases total deposition for particles with initial sizes larger than ~0.5 μm, but decreases deposition for particles between ~0.01 and 0.5 and again increases deposition for particles < 0.01 μm. Thus, under high humidity conditions, there is increased deposition of smaller (nucleation-mode; < 0.01 μm) ultrafine particles and of larger accumulation-mode (≥ 0.5 μm) particles, the latter of which can grow to sizes exceeding 1.0 μm and both of which would contain enhanced amounts of particle bound water and other toxic agents (e.g., $O_3$, $SO_2$, peroxide, formaldehyde) dissolved therein.

Enhanced particle retention occurs on carinal ridges in the trachea and segmental bronchi; and deposition "hot spots" occur at airway bifurcations or branching points. Peak deposition sites shift from distal to proximal sites as a function of particle size, with greater surface dose in conducting airways than in the A region for all particle sizes. To some extent then, the growth of ultrafine and accumulation mode particles under humid conditions would also likely increase "hot spot" deposition at airway branching points and thereby increase PM doses to tissues at those points.

Ventilation rate, gender, age, and respiratory disease status all affect total and regional respiratory tract particle deposition. Of likely most concern from among all these factors affecting respiratory particle deposit patterns are altered PM deposition patterns due to respiratory disease status that may put certain groups of adults (including some elderly) and children at greater risk for PM effects. Importantly, COPD contributes to more heterogenous deposition patterns and differences in regional deposition. One study indicates that people with COPD tend to breathe faster and deeper than those with normal lungs (i.e., about 50% higher resting ventilation) and have ~50% greater deposition than age-matched healthy adults under typical breathing conditions, with average deposition rates 2.5 times higher under elevated ventilation rates. Enhanced deposition appears to be associated more with the chronic bronchitic than the emphysematous component of COPD. In this and other new studies, fine-particle deposition increased markedly with increased degree of airway obstruction. With increasing airway obstruction and uneven airflow because of irregular obstruction patterns, particles tend to penetrate more into remaining better ventilated lung areas, leading to enhanced focal deposition

at airway bifurcations and alveoli in those A region areas. In contrast, TB deposition increases with increasingly more severe bronchoconstrictive states, as occur with asthmatic conditions.

Disease states can also alter clearance rates for removal of deposited particles from the lung. Bronchial mucus transport is slowed by asthma, chronic bronchitis, bronchial carcinoma, and various acute respiratory infections - all being disease conditions expected to increase retention of deposited particle material and, thereby, increase the probability of toxic effects from inhaled ambient PM components reaching the TB region. Also, spontaneous coughing, an important TB region clearance mechanism, does not appear to fully compensate for impaired mucociliary clearance in small airways and may become depressed with worsening airway disease, as seen in COPD patients. Clearance of particles from the A region by alveolar macrophages and their mucociliary transport is usually rapid (< 24 h), but alveolar region clearance rates are decreased in human COPD sufferers and slowed by acute respiratory infections; and the viability and functioning of alveolar macrophages are reduced in human asthmatics and in animals with viral lung infections.

All this suggests that persons with asthma, chronic bronchitis, or acute lung infections are likely to experience increased deposition and retention of inhaled particles and to be at risk for ambient PM exposure effects. Such individuals can reasonably be expected to be put at even greater risk when inhaling ambient PM under high humidity conditions (with increased delivery of peroxides, $O_3$, $SO_2$, and other noxious agents into the deep lung in particle-bound water and enhanced "hot spot" deposition of hygroscopic aerosols at branching points in bronchial airways).

***Bioaerosols as Contributors to Ambient PM Effects***

Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 μm to > 20 μm. They comprise a small fraction of ambient PM, but likely contribute to the some types of ambient PM-related health effects exposure.

Intact pollen grains from flowering plants, trees and grasses are by far most abundant in warm/humid spring and summer months and can deposit in upper airways to induce allergic rhinitis. Allergen-laden cytoplasmic fragments (~0.1 to 0.4 μm in size) of pollen grains (which rupture under high moisture conditions) can enter the deep lung, where they can exacerbate asthma. Binding of allergen-laden pollen cytoplasmic fragments to ambient fine particles (e.g.,

DPM) has also been observed; and synergistic interactions between pollen debris and other ambient PM (e.g., the polycyclic hydrocarbon component of DE) are thought to be a mechanism that may explain the increased incidence of asthma morbidity and mortality. Pollen granules can also act as vectors for binding of other bioaerosols (e.g., endotoxins, fungi or fragments, glucans) and thereby enhance their inhalation and deposition in the respiratory tract.

Fungal spores and fungi fragments are among the largest and most consistently present bioaerosols found outdoors (levels being higher during warm/humid months). They cause allergic rhinitis and asthma, which is highly dependent on seasonal variations in concentration. Exposures have been linked to asthma hospitalization and death.

Bacteria and viruses are significant bioaerosols. Much of the toxicity of bacteria is due to the endotoxins present in the outer cell membrane, which trigger production of cytokines and a cascade of inflammation. Ambient airborne concentrations of endotoxins vary with seasons (being higher in warm/humid periods and low in colder months) and tend to be higher in samples of coarse-mode than in fine-mode ambient PM. Another cell wall component of bacteria and fungi, (1→3)-β-D-glucan, has also been shown to cause respiratory inflammation.

Animals and insects produce bioaerosols capable of producing hypersensitivity diseases. Most notably, exposure to dust mite and cockroach material has been linked to sensitization in children. However, indoor exposures to such materials probably are of most importance with regard to human exposures to such materials.

It thus appears that certain ambient bioaerosols (e.g., pollen, fungi, endotoxins, glucans) that become abundant during warm/humid weather may contribute to seasonal increases in PM-associated risk during spring/summer months, but not during colder winter months. The copresence of non-biological particles, serving as vectors concentrating such bioaerosols and enhancing their delivery into the deep lung, appears to likely be important.

***Summary and Conclusions***

It has been proposed that particles also may act as carriers to transport toxic gases into the deep lung. Water-soluble gases, which would be removed by deposition to wet surfaces in the upper respiratory system during inhalation, could dissolve in particle-bound water and be carried with the particles into the deep lung. Equilibrium calculations indicate that particles do not increase vapor deposition in human airways. However, these calculations do show that soluble

gases are carried to higher generation airways (i.e., deeper into the lung) in the presence of particles than in the absence of particles. In addition, species such as $SO_2$ and formaldehyde react in water, reducing the concentration of the dissolved gas-phase species and providing a kinetic resistence to evaporation of the dissolved gas. Thus, the concentration of the dissolved species may be greater than that predicted by the equilibrium calculations. Of much concern, particle-bound water appears to be a means by which dissolved hydrogen peroxide and other short-lived reactive oxygen species can be carried into lower respiratory tract regions and contribute to the induction of inflammatory responses. Also, certain other toxic species (e.g., nitric oxide [NO], nitrogen dioxide [$NO_2$], benzene, polycyclic aromatic hydrocarbons [PAH], nitro-PAH, a variety of allergens) may be absorbed onto solid particles and carried into the lungs. Thus, ambient particles may play important roles not only in inducing direct health impacts of their constituent components but also in facilitating delivery of toxic gaseous pollutants or bioagents into the lung and may, thereby, serve as key mediators of health effects caused by the overall air pollutant mix.

#### *9.2.3.2.8 Coherence of evidence*

One of the key factors for evaluating the associations between exposure and outcome variables derived from epidemiologic studies is the coherence in the evidence. As described in Section 13.4.2.5 of the 1996 PM AQCD, an assessment of the coherence across a body of evidence considers the logical and systematic relationships among various health outcomes that may be related to exposure. In assessing coherence, one should compare outcomes with similar time frames, for example, looking across various respiratory-related health outcomes linked with short-term (e.g., daily) ambient PM concentrations. An assessment of coherence is primarily qualitative in nature, not quantitative, since it involves consideration of evidence from across disciplines and varying study methodologies. For example, Bates (1992) suggested evaluating coherence not only within epidemiologic data, but also between epidemiologic and animal toxicologic data and among epidemiologic, controlled human exposure and animal data.

Looking first within the epidemiologic literature, considerable coherence can be seen to exist across the now extensive body of available epidemiologic study findings. In the 1996 PM AQCD, consideration was given to the coherence of evidence of various effects within the same geographic area. In particular, epidemiologic evidence from studies conducted in four U.S.

locations using varying indicators such as $PM_{10}$ and TSP – Detroit, Birmingham, Philadelphia and Utah Valley – generally showed coherence across cardiovascular and respiratory health outcomes within each area. The health outcomes included mortality from cardiovascular or respiratory diseases, hospital admissions for respiratory causes and for cardiovascular causes in the elderly, and respiratory symptoms.

The expanded body of epidemiological evidence available in this review provides further support for those findings. Effect estimates for associations between short-term exposure to $PM_{10}$ and various effects ranging from mortality to respiratory symptoms or cardiovascular health indicators are available from multiple studies in a number of urban areas, including Chicago, Los Angeles, Detroit, Seattle and Pittsburgh. As shown in Section 8.4.4, results for associations between $PM_{10}$ and various health outcomes are summarized in a series of figures, using single-pollutant model results from the available studies in each location. While in Detroit, Los Angeles, Seattle and Pittsburgh, some studies also reported associations with $PM_{2.5}$ and $PM_{10-2.5}$ (included in the presentation of results for mortality and hospitalization and medical visits studies in Figure 9-5 and 9-6), the more numerous results for $PM_{10}$ better allow for an assessment of coherence within these areas.

These results for $PM_{10}$ include an array of health outcome measures, summarized below, that expand upon the findings in the 1996 PM AQCD with much more extensive evidence on cardiovascular and respiratory morbidity outcomes. As discussed in Section 9.2.2, coherence can be observed in considering the pattern of findings across the studies within each area, especially focusing on those study results with greater precision, in that almost all studies report positive associations (at least for some of the lag periods examined in those studies that reported results for multiple lag periods), many of which are statistically significant.

- Chicago (Figure 8-24) - total, cardiovascular and respiratory mortality, hospital admissions for respiratory and cardiovascular diseases; especially for lag periods of day 0 and/or day 1.
- Los Angeles (Figure 8-25) - total, cardiovascular and respiratory mortality, hospital admissions for respiratory and cardiovascular diseases, hospital admissions for asthma, COPD, myocardial infarction, congestive heart failure, cardiac arrhythmia, cerebrovascular and occlusive stroke, and respiratory symptoms in asthmatic children. Positive, statistically significant results are more generally reported for lag periods of day 0 and/or day1, although less consistency is observed across different lag periods in some studies, perhaps due to inherent limitations in the 1-in-6-day ambient PM data used in some of these studies.

- Pittsburgh (Figure 8-26) - total mortality, hospital admissions for cardiovascular diseases, COPD and pneumonia.
- Detroit (Figure 8-27) - total, cardiovascular and respiratory mortality, and hospital admissions for pneumonia, COPD, ischemic heart disease, dysrrhythmia, heart failure and stroke.
- Seattle (Figure 8-28) - total mortality, hospital admissions for cardiovascular diseases, asthma, COPD and pneumonia, asthma symptoms; a notable exception is the negative risk estimate reported for sudden cardiac arrest, although the result is highly imprecise.

In addition to the evidence of associations with measures such as mortality or hospitalization, new epidemiological studies have reported associations between PM, primarily $PM_{10}$ or $PM_{2.5}$, and health outcome measures related to cardiovascular and respiratory disease such as physician visits for respiratory diseases, incidence of myocardial infarctions, and physiological or biochemical indicators of cardiovascular health. Epidemiologic panel studies have reported changes in blood characteristics (e.g., increased fibrinogen or C-reactive protein levels) related to increased risk of ischemic heart disease as also being associated with ambient PM exposures. New studies have also reported associations between PM and changes related to heart rhythm, including cardiac arrhythmia or changes in heart rate variability that may be linked with more serious cardiac effects. In addition, new evidence exists for ambient PM associations with reductions in pulmonary function and/or increased respiratory symptoms, especially of note in relation to asthmatic or other chronic lung disease individuals. In considering the evidence for different PM size fractions or components, it can be observed that most of these studies have data on fine particles or fine particle constituents. All these cardiovascular and respiratory morbidity effects add to the coherence of the overall evidence substantiating effects of short-term exposure to PM, especially fine PM, in susceptible population groups.

Beyond epidemiologic studies, there are now many more studies from other disciplines to use in considering the results of epidemiologic, toxicologic and controlled human exposure studies together than were available for the 1996 PM AQCD. For example, epidemiologic studies conducted in Boston have linked fine particle concentrations with increased risk of myocardial infarction, cardiac arrhythmia and changes in heart rate variability (discussed in Section 8.3.1.3.4) and toxicologic studies using Boston CAPs (fine particles) have also shown some evidence for changes in blood parameters or heart rhythm (summarized in Table 7-1). Section 9.2.3.2 summarizes the results of new toxicologic or controlled human exposure studies

that have shed light on potential mechanisms underlying cardiovascular and respiratory effects observed in epidemiologic studies, and thus provide support for the coherence of PM-related effects.

Compelling evidence of coherence is offered by a body of epidemiologic, toxicologic and controlled human exposure studies on effects of particles from the Utah Valley area. As discussed above, a series of epidemiologic studies from Utah Valley reported associations between PM and health outcomes ranging from increased respiratory symptoms to mortality. A special feature of these studies was the closure of a steel mill, a major source of PM emissions in the area, for a 13-month period. As discussed in Section 8.2.3.4, respiratory hospital admissions for children were reduced during the period the source was not operating, and assessment of mortality risk also indicated that mortality rates were 3.2% greater when the steel mill was operating. New toxicologic and human studies have used extracts of ambient particles collected on filters from ambient monitors operating during the time periods before, during and after steel mill closure. Intratracheal instillation of particle extracts in both human volunteers and animals resulted in greater lung inflammatory responses for materials obtained before and after the plant closure period (further discussed in section 7.3.1.2). The health responses were indicative of inflammatory changes in the lung, including increased levels of neutrophils, protein and inflammatory cytokines. As discussed previously, consideration of dosimetry information indicates that the doses of particles used in these experiments are equivalent to higher-level exposure concentrations that the community could experience during typical winter inversions in the Utah Valley. *In vitro* studies using human airway epithelial cell lines also showed evidence for inflammatory responses, such as increases in cytokine levels, indicators of oxidative response in alveolar macrophages and some evidence of cytotoxicity (see Section 7.4.2). This body of evidence links results of community epidemiologic studies reporting increases in respiratory hospitalization with toxicologic studies showing evidence of respiratory inflammation in humans and animals.

Further evidence was obtained from the toxicologic studies to suggest that metals were an important particle component for the inflammatory changes described above. The Utah Valley studies used particles collected from the $PM_{10}$ monitoring network, but further analysis was done on the extracted particle material. Notably larger proportions of metals (e.g., Cu, Zn, Fe, Pb, As, Mn, Ni), as well as sulfate and cationic salts (e.g., calcium, potassium, magnesium), were found

in the particles collected while the source was operating. The addition of a chelating agent to the particle extract was found to attenuate responses found in *in vitro* studies, providing further evidence that metals are an important particle component for this group of health responses.

More limited evidence is also available on the effects of long-term exposure to particles from all health disciplines. The epidemiologic studies indicate associations with mortality from cardiopulmonary diseases and lung cancer, and with potential development of chronic respiratory diseases or reduction in lung function. For lung cancer, there is substantial evidence for coherence in the results of recent epidemiologic studies and toxicologic studies on mutagenicity or genotoxicity, as described in Section 9.2.3.2.2. There have not been many toxicologic studies using chronic particle exposures to evaluate responses relevant to respiratory or cardiovascular health outcomes. In addition, epidemiologic studies have not as yet addressed potential links between long-term PM exposure and indicators for the development of cardiovascular disease that would provide coherence with findings of cardiovascular mortality risk. Thus, the evidence with regard to coherence of effects related to long-term particle exposures is somewhat limited.

The overall body of controlled human and/or laboratory animal exposure studies discussed earlier also add coherence to the evidence for ambient PM-related health impacts. A number of studies provide evidence that supports one or another hypothesis with regard to (a) PM components (by size, chemical composition, source) and/or (b) mechanisms likely contributing to PM effects on various cardiovascular or respiratory endpoints. For example, the results of instillation studies, using filter extracts from community monitoring stations in the Utah Valley before, during, and after temporary shut down of a steel mill there are particularly compelling on two accounts: (1) the evidence of greater lung inflammation from instilled extracts from periods of mill operation parallel epidemiologic findings of increased cardiorespiratory hospitalizations during such periods; and (2) dosimetric calculations indicate that concentrations of particulate extract materials likely delivered to affected lung tissue with the instillation would probably be reasonably comparable to those likely experienced in connection with ambient inhalation exposures over several weeks to $PM_{10}$ concentrations in the Utah Valley PM mixture.

Overall, new evidence from epidemiologic, toxicologic, and controlled human exposure studies has built a strong foundation for coherence for fine particle related effects. The evidence for coherence of effects related to $PM_{10-2.5}$, however, is far more limited, with some evidence for

related cardiopulmonary effects from epidemiologic studies but little supporting mechanistic evidence from toxicologic studies.

#### *9.2.3.2.9 Summary and conclusions*

Consideration of the plausibility and coherence of PM-related effects involves looking across evidence from dosimetric, toxicologic, and epidemiologic studies. In comparison with the 1996 PM AQCD, there is much more such evidence available in recent studies on fine particles or fine particle constituents.

Toxicological studies, largely studies of fine particles, contribute support for biological plausibility for the effects on the cardiovascular and respiratory systems observed in epidemiologic studies. While often high exposures/doses are used in toxicologic studies, the tissue doses achieved are often not necessarily that far removed from doses derived from exposures of humans at higher ambient levels, as indicated by the quantitative assessment of doses used in toxicologic and controlled human exposure studies, described in Appendix A to Chapter 7, along with the assessment of dose-response functions in toxicologic studies. The recent studies have linked components of fine particles with various health outcomes. There is probably no single primary causative attribute of fine particles, but rather many attributes may contribute to complex mechanisms for the different health outcomes. Overall, the toxicological evidence provides considerable evidence for biological plausibility for effects on the respiratory and cardiovascular systems, including new evidence for lung cancer. There is as yet little toxicological evidence available on coarse fraction particles.

Within the body of epidemiological evidence, there is good evidence of coherence across respiratory and cardiovascular health outcomes, especially for effects of short-term exposures. New toxicologic and controlled human exposure studies offer new insights into coherence for effects on the cardiovascular and respiratory systems; compelling new evidence is available, for example, from toxicological and controlled human exposure studies conducted in Utah Valley using particles collected in the same time period as the published epidemiological studies. The results of new studies build a strong foundation of coherence for fine particle effects; however, the evidence available on coherence of coarse fraction particles is far more limited.

There is also important new information highlighting potentially crucial roles that particle bound water plays in serving as a carrier or vector by which other toxic agents (e.g., $O_3$, $SO_2$,

peroxides, formaldehyde) can be accumulate within inhalable PM and delivered in enhanced quantities into the deep lung. The increased availability of certain bioaerosol materials (e.g., pollen fragments) in small (0.1 - 0.4 micrometers) fine particle sizes that deposit in TB and A regions of the lung (where they can exacerbate asthma effects) is also now recognized.

## 9.2.4 How Does Newly Available Information Inform Our Understanding of Subpopulations Potentially Susceptible to PM-Related Health Effects?

### 9.2.4.1 Key Points from 1996 Integrative Synthesis

The 1996 PM AQCD included only a relatively limited discussion of susceptible population groups potentially at increased risk for ambient PM effects, noting:

> "There is considerable agreement among different studies that the elderly are particularly susceptible to effects from both short-term and long-term exposures to PM, especially if they have underlying respiratory or cardiac disease. . . Children, especially those with respiratory diseases, may also be susceptible to pulmonary function decrements associated with exposure to PM or acid aerosols." (U.S. EPA, 1996, p. 13-92)

The term susceptibility generally encompasses innate or acquired factors that make individuals more likely to experience effects with exposure to pollutants. Genetic or developmental factors can lead to innate susceptibility, while acquired susceptibility may result from age, from disease, personal risk factors such as smoking or exercise, or socioeconomic factors such as reduced access to health care. Other factors can also increase an individual's vulnerability to adverse effects related to pollution exposure, such as having increased pollutant exposure due to characteristics of the home or due to residence near a specific pollution source.

The 1996 PM AQCD identified several population groups potentially as being at increased risk for experiencing health impacts of ambient PM exposure. Elderly individuals (> 65 years) were most clearly identified, along with people having preexisting cardiovascular or respiratory disease conditions. Individuals with asthma, especially children, also were identified as a potential susceptible population group.

New studies appearing since the 1996 PM AQCD provide additional evidence that substantiates the above named groups as likely being at increased risk for ambient PM-related morbidity or mortality effects. The newly available studies continue to indicate that the elderly and children are likely more susceptible to PM-related effects. There are also numerous new

studies which substantiate the finding that preexisting disease conditions represent an important risk factor for ambient PM health effects. Cardiovascular and respiratory diseases continue to appear to be of greatest concern in relation to increasing the risk for PM mortality and morbidity effects. Indeed, the fact that these disease "entities" often involve both organ systems, albeit to varying degrees, might argue for their compilation under a broader combined classification of "cardiopulmonary" disease.

### 9.2.4.2 Integration of Newly Available Information

#### *9.2.4.2.1 Preexisting disease as a risk factor for particulate matter health effects*

A number of epidemiologic studies have reported increased risk in study subsets of individuals with preexisting heart or lung diseases. For example, Sunyer et al. (2000) reported large relative risk estimates for total mortality in people with preexisting COPD. Also, Goldberg et al. (2000) originally reported larger effect sizes for total mortality in persons with cancer, diabetes, lower respiratory disease, cardiovascular disease, coronary artery disease, and congestive heart failure; however, upon reanalysis (Goldberg and Burnett, 2003) the pattern of results remained the same, but all lost statistical significance for new analyses using more stringent GAM or GLM. Both Linn et al. (2000) and Zanobetti and Schwartz (2001, 2002, not reanalyzed) reported increased risk of hospitalization for cardiovascular diseases in subgroups with diabetes. In addition, Boezen et al. (1998, Europe) reported significant effects in the subset of adults who had bronchial hyperreactivity or increased peak flow variability; and Vedal et al. (1998) reported greater effects in a subset of children who had asthma.

Toxicologists have used several animal models of cardiopulmonary disease to evaluate PM susceptibility aspects. Such animal models include rats with monocrotaline-induced pulmonary vasculitis/hypertension, $SO_2$-induced chronic bronchitis, spontaneously hypertensive rats, and animals infected with various viral or bacterial agents. As summarized in Section 7.5.1, increased magnitude or frequency of effects have been reported with PM exposure for these groups of animals relative to healthy animals. In addition, toxicologists have also studied effects of particles, including diesel exhaust particles, in animals with heightened allergic sensitivity and via *in vitro* studies (summarized in Section 7.5.2). Overall, the results from newly available toxicological studies provide evidence suggestive of enhanced susceptibility to inhaled PM in "compromised" hosts.

The underlying biology of lung diseases might also lead to heightened sensitivity to PM, but this attribute of disease remains hypothetical in the context of PM. The functional linkages with the cardiac system for maintenance of adequate gas exchange and fluid balance notwithstanding, the role of inflammation in the diseased respiratory tract (airways and alveoli) could play a key role. Studies in animals genetically or exogenously altered to induce inflammation are sometimes intrinsically more responsive to concentrated ambient PM, to specific combustion-source-generated PM, or to other laboratory-generated particles. While a PM-induced response may on the one hand be cumulative with the underlying injury or condition, the responses may, on the other hand, be magnified by any number of mechanisms that are poorly understood. There is sufficient basic biological data to hypothesize that the exudated fluids in the airspaces may either interact differently with deposited PM (e.g., to generate oxidants - Costa and Dreher, 1999; Ghio et al., 2001), to augment injury, or to predispose the lung (e.g., sensitize receptors - Undem and Carr, 2002) to enhance the response to a stereotypic PM stimulus through otherwise normal pathways. Less appreciated is the loss of reserve (functional or biochemical), wherein the susceptible individual may be incapable of sufficient compensation (e.g., antioxidant responses - Kodavanti et al., 2000b). Any of these or related mechanisms may contribute to increased "susceptibility" and may indeed be a common factor possibly attributable to other susceptible groups. Understanding these and other mechanisms will ultimately aid in better assessing any increased risk of susceptible groups to PM.

Studies with humans that might reveal more specific data have been limited both ethically, as well as by the absence of or limitations associated with biomarkers of response (such as interpretation of ECG indicators of cardiac function and disease). Measures of blood-gas saturation and lung function appear not to be sufficiently revealing or sensitive to mild physiologic changes in those with moderate disease conditions who might be amenable to participation in laboratory studies. In the field, assessing the degree of underlying disease and how that relates to responsiveness of these biomarkers is unclear. However, subjects with COPD and asthma have been studied under controlled conditions with inert aerosols for the purpose of assessing distribution of PM within the lung, and it is now quite clear that airways disease leads to very heterogeneous distribution of PM deposited within the lung. Studies have shown up to 10-fold higher than normal deposition at airway bifurcations, thus creating "hot-spots" that may

well have biologic implications, especially if the individual already has diminished function or other debilitations due to the underlying disease, even cardiovascular disease (CVD). Thus, the dosimetry of PM within the lung must be considered an important element of the susceptibility paradigm with most any cardiopulmonary disease condition.

#### *9.2.4.2.2 Age-related at-risk population groups: the elderly and children*

The very young and the very old apparently constitute two other groups thought to be especially at risk for ambient PM air pollution health effects. Numerous epidemiological studies have reported health responses to PM and other pollutants for one or another specific age group.

These studies, as summarized in Section 8.4.9 of Chapter 8, tend to support previous findings that, depending on the effect under study, older adults and children may be more susceptible to certain PM-related effects. More specifically, older adults (aged 65+ years) appear to be most clearly at somewhat higher risk for PM exacerbation of cardiovascular-related disease effects and, perhaps, tend to experience higher PM-related total (non-accidental) mortality risk, as well. On the other hand, more limited evidence points to children possibly being at somewhat higher risk for respiratory-related (especially asthma) PM effects than adults.

A major factor in increased susceptibility to air pollution is the presence of a preexisting illness and susceptibility related to age group may well be closely linked with the potential for preexisting cardiopulmonary diseases. Cardiopulmonary diseases more common to the elderly play into the risk within older age groups, but some panel studies of morbidity focusing on generally healthy people in retirement homes or elderly volunteers exposed to concentrated ambient PM in chambers show subtle alterations of autonomic control of cardiac function (e.g., slight depression of heart rate variability) and blood factors concordant with a putative response to ambient PM levels. However, given the overall patterns of results observed in these (and in controlled exposure) studies, there currently exists a conflicting array of evidence which makes it difficult to ascribe any clinical significance to the generally small changes observed, even though similar at times to changes indicative of increased risk based on studies of risk in cardiac patients and general population studies of cardiac disease progression. Over the long term, innate differences in metabolism or other mechanisms may impact the likelihood of chronic outcomes, e.g., COPD or lung cancer. To what extent progression occurs with repeated PM

exposures and how much disease or other risk factors add to or complicate the magnitude of response remains uncertain.

Although infection as a risk factor for PM has already been noted, it is important to emphasize that there are clear age differences in both the incidence and type of infections across age groups. Young children have the highest rates of respiratory illnesses related to infection (notably respiratory syncytial virus), while adults are affected by other infectious agents such as influenza that may also lend increased susceptibility to PM effects. Data to address fully the importance of these differences is incomplete, but some of the newly available toxicological studies (e.g., Zelikoff et al., 2003) provide evidence for ambient PM exposures affecting lung defense mechanisms so as to exacerbate preexisting respiratory infections.

In addition to their higher incidences of preexisting respiratory conditions, several other factors may render children and infants more susceptible to PM exposures, including more time spent outdoors, greater activity levels and ventilation, higher doses per body weight and lung surface area, and the potential for irreversible effects on the developing lung. For example, PM doses on a per kilogram body weight basis are much higher for children than for adults, as is displayed graphically in Figure 9-7. The amount of air inhaled per kilogram body weight decreases dramatically with increasing age, due in part to ventilation differences (in cubic meters per kilogram a day) of a 10-year-old being roughly twice that of a 30-year-old person, even without the consideration of activity level. Child-adult dosage disparities are even greater when viewed on a per lung surface-area basis.

As to potential lung developmental impacts of PM, there exist both experimental and epidemiologic data, which although limited, suggest that the early post-neonatal period of lung development is a time of high susceptibility for lung damage by environmental toxicants. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000); and acute injury to the lung during early postnatal development may impair normal repair processes, such as down-regulation of cellular proliferation (Smiley-Jewel et al., 2000, Fanucchi et al., 2000). These results in animals appear to be concordant with recent findings for young children growing up in the Los Angeles area, where both oxidants and high PM prevail (Gauderman et al., 2000).

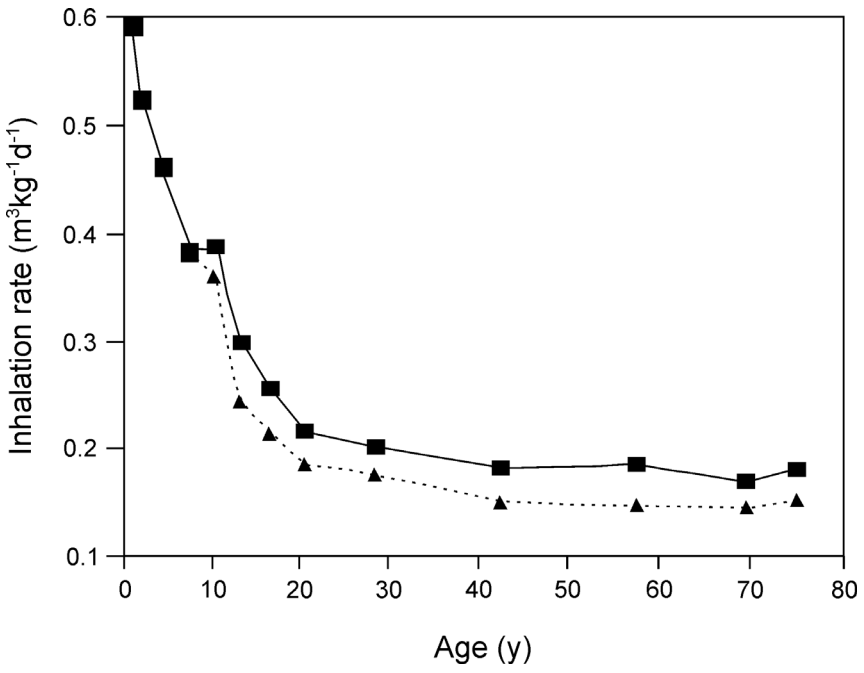


**Figure 9-7. Inhalation rates on a per body-weight basis for males (■) and females (▲) by age (Layton, 1993).**

1 ***9.2.4.2.3 Genetic susceptibility***

2 A key issue in understanding adverse health effects of inhaled ambient PM is the
3 identification of which classes of individuals are susceptible to PM. Although factors such as
4 age and health status have been studied in both epidemiology and toxicology studies, some
5 investigators have begun to examine the importance of genetic susceptibility in the response to
6 inhaled particles because of evidence that genetic factors play a role in the response to inhaled
7 pollutant gases. To accomplish this goal, toxicologists typically have sought to detect
8 inter-strain differences in responses to particles in rodents; little evidence is available from
9 epidemiological studies at this time. The small group of newly-available toxicological studies
10 have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled
11 particles (Section 7.5.2); for example, Kodavanti et al. (1996, 1997a) found a genetic based
12 difference in susceptibility to lung injury induced by instilled ROFA, using several strains of rats
13 with varying genetic characteristics.
14

#### *9.2.4.2.4 Gender*

There are significant gender differences in the homogeneity of deposition as well as the deposition rate of particles. These differences derive from differences between males and females in body size, conductive airway size, and ventilatory parameters. Females have a somewhat greater deposition of coarse mode particles in the ET and TB regions, but lower deposition in the A region. This gender effect appears to be particle-size dependent, showing a greater fractional deposition in females for very small ultrafine and large coarse thoracic particles. Total fractional lung deposition for 0.04 and 0.06 μm particles also appears to be somewhat greater in females than males but only negligibly so for particles in the size range 0.8 to 1.0 μm. As the particle size increases (3 to 5 μm), total fractional deposition increases in females. While deposition appears to be more localized in females than males, deposition rate appears to be greater in males.

Little evidence is available from toxicology studies regarding gender differences in susceptibility to pollution effects. In the epidemiology studies that have included stratified analyses based on gender, there is no clear pattern of increased vulnerability for either males or females. A number of studies using long-term and short-term PM exposures report no clear pattern of differences in effects across genders (e.g., Linn et al., 2000; Ostro et al., 2001; Dockery et al., 1996; Raizenne et al., 1996; Krewski et al., 2000). Where differences in effects between males and females were reported, they were generally not significantly different, and the findings are not consistent. For example, from $PM_{10}$-mortality studies conducted in Chicago, Styer et al. (1995) report larger effect estimates for men, but Ito and Thurston (1996) report larger effect estimates for women.

Thus, insufficient evidence exists overall to allow for any clear conclusions to be drawn as to potential gender differences with regard to PM health effects. More systematic research on the subject is needed.

#### *9.2.4.2.5 Socioeconomic status*

Epidemiological studies of long-term PM exposures have suggested that there is effect modification of PM-mortality associations due to socioeconomic factors. In the ACS and Six Cities cohort analyses on mortality risk with long-term exposure to $PM_{2.5}$, there was clear evidence of effect modification (though not confounding) by education level, with greater effects

being reported in the cohort subgroups with lower education levels (Krewski et al., 2000; Pope et al., 2002).

Among the studies of short-term PM exposure, the evidence is more mixed regarding potential influence of socioeconomic status on PM-related health risks. Schwartz (2000a) found no evidence of effect modification for $PM_{10}$-mortality associations in 10 U.S. cities using four measures of social or economic status: greater percent of population living in poverty status; higher unemployment rate; greater percent of population with college degrees; or greater percent of the population being nonwhite. Zanobetti and Schwartz (2003; reanalyzed Zanobetti et al., 2000) conducted similar analyses with data for hospital admissions in 10 U.S. cities, and none of the four measures of social or economic status mentioned above significantly modified the relationship between $PM_{10}$ and hospitalization for COPD or pneumonia. However, for CVD admissions, $PM_{10}$ effect estimates were greater in communities with greater percentages of the population being unemployed, nonwhite, or living in poverty. The authors postulate that this effect would be a result of increased exposure, increased prevalence of predisposing diseases or other factors. Tolbert et al. (2000b) found race (black vs. white) and insurance Medicaid vs. non-Medicaid) to be effect modifiers for emergency department admissions for asthma in children (< 17 years) in Atlanta, but no associations with interaction terms for these factors and $PM_{10}$ or ozone. Also, Norris et al. (1999) reported no effect estimate differences for asthma hospitalization in children (< 18 years) when comparing the inner city area with the rest of Seattle.

However, some studies have reported evidence for socioeconomic factors increasing risk of hospitalization or emergency department visits with PM and other pollutants. Gwynn and Thurston (2001, not reanalyzed) reported generally greater effect estimates for respiratory hospitalization for nonwhite persons, as compared to the white persons, and for the subgroup with no health insurance, compared with those who had insurance or Medicaid coverage; differences in effect estimates were more notable for ozone than $PM_{10}$. The authors suggest that a large portion of the apparent difference in pollutant risk estimates between racial subgroups can be explained by socioeconomic factors such as insurance status and poverty. Nauenberg and Basu (1998) analyzed associations between hospitalization for asthma with $PM_{10}$ and ozone in Los Angeles for subsets of patients who were uninsured, insured by MediCal, or had other insurance. Significant associations with $PM_{10}$ were reported only for the subset of patients using

MediCal, not for the privately insured or uninsured; the authors speculate that the small sample size for uninsured patients may have precluded detection of an effect.

In summary, evidence from cohort studies of long-term PM exposure effects indicates that PM-mortality risk may be greater for those with lower socioeconomic status. The time-series epidemiologic studies provide less evidence of effect modification for short-term exposure effects by socioeconomic status, though there is some limited evidence suggesting possible greater effects on respiratory hospitalization with lower socioeconomic status.

#### *9.2.4.2.6 Enhanced vulnerability due to heightened exposure levels*

Exercise may increase the potential health risks of inhaled particles because exercise increases the rate of oxygen consumption and changes ventilatory parameters affecting airflow rate and breathing patterns. The switch from nose breathing to mouth breathing, which occurs as exercise intensity increases, leads to an increase in fractional deposition of ultrafine and coarse thoracic particles in the tracheobronchial and alveolar regions. The higher breathing rate and larger tidal volume lead to a greater amount of deposition. Total lung deposition rate may be 3 to 4 times greater during exercise. The more rapid breathing of children also leads to a greater amount of deposition.

In several reports from the Southern California children's study, larger effect estimates for reduced lung function or increased respiratory illness with long-term exposure to PM and other pollutants were reported for the subset of children spending a larger amount of time outdoors (Peters et al., 1999a,b, Gauderman et al., 2000, 2002). Also, using data from 14 U.S. cities, Janssen et al. (2000; 2002; Zanobetti and Schwartz, 2003) reported that effect estimates between $PM_{10}$ and hospitalization for CVD and COPD increased with less air conditioning use in homes (such use being an indicator of decreased exposure due to less penetration of particles into the home). $PM_{10}$-hospital admission effect estimates were also found to increase with increasing population density, which was strongly correlated with estimates of vehicle miles traveled in these cities and, thus, is likely an indicator for increased exposure to vehicle-related pollution. Increased vulnerability to the effects of pollution may come from living near a source of PM and other pollutants, such as a major roadway. Numerous recent studies have linked adverse health effects with indicators of traffic-related pollution. For example, Hoek et al. (2002) reported

statistically significant associations for mortality with long-term ambient PM exposure (measured as black smoke, BS) and also with residence near a major road.

#### 9.2.4.3 Summary and Conclusions

In summary, host variability may come to be one of the most important factors in determining the response profile of any population exposed to PM. Studies to date suggest that certain subpopulations are indeed more acutely responsive to PM, perhaps due to differences in lung deposition (either in terms of dose and/or intrapulmonary distribution) or other biologic aspects of the cardiopulmonary system or disease thereof. The role of innate attributes of risk grounded in one's genetic code is largely unknown, but of potentially great importance. Animal models have been used to show clear differences in response to PM and other pollutants, and the critical involvement of varied genes in the induction of asthma, emphysema, and many other ailments is widely accepted, but poorly understood. Long-term epidemiologic studies indicate an increase in risk associated with various indications of lower socioeconomic status.

### 9.2.5 What Does the Newly Available Information Imply With Regard to Potential Public Health Impacts of Human Exposures to Ambient PM in the United States?

#### 9.2.5.1 Key Points from 1996 Integrative Synthesis

The 1996 PM AQCD highlighted the then considerable uncertainty related to estimating public health impact of ambient PM exposure, stating:

> "Efforts to quantify the number of deaths attributable to, and the years of life lost to, ambient PM exposure are currently subject to much uncertainty." (U.S. EPA, 1996, p. 13-87). Nonetheless, while "PM-related increases in individual health risks are small," they are "likely significant from an overall public health perspective because of the large numbers of individuals in susceptible risk groups that are exposed to ambient PM." (U.S. EPA, 1996, p. 1-21)

#### 9.2.5.2 Integration of New Information

##### *9.2.5.2.1 Magnitude of susceptible groups*

As summarized in Section 9.2.4, numerous U.S. population groups may be identified as having increased susceptibility or vulnerability to adverse health effects from PM. Considering together the subpopulations of persons with preexisting cardiopulmonary disease, older adults,

children, people of lower socioeconomic status and those with higher potential exposure levels as potentially susceptible or vulnerable, it is clear that the impact of PM on public health could be very extensive.

Table 9-5 summarizes information on the prevalence of chronic respiratory and circulatory conditions and diabetes in the U.S. population in 2000. It can be seen that people with preexisting cardiopulmonary disease constitute a fairly large proportion of the population, with tens of millions of people included in each disease category. For circulatory conditions, approximately 22 million people, or 11% of the U.S. adult population, have received a diagnosis of heart disease. Approximately 20% of the U.S. adult population has hypertension, with 6% reporting diagnoses of coronary heart disease. For respiratory conditions, approximately 9% of U.S. adults (and 11% of children) have been diagnosed with asthma, and 6% of adults diagnosed with conditions included in COPD. Table 9-6 provides further information on the number of various specific respiratory conditions per 100 persons by age among the U.S. population during the mid-1990s. In addition, approximately 6% of the U.S. adult population has diabetes. Both cardiovascular conditions and diabetes are more common among older age groups, while asthma prevalence is higher in children.

Potentially susceptible subpopulations based on age group or socioeconomic status would also comprise substantial segments of the population. Based on U.S. census data from 2000, about 26% of people in the U.S. are under 18 years of age, and 12% are 65 years of age or older. From among commonly-used indicators of socioeconomic status, about 12% of individuals and 9% of families are below the poverty level, and 20% of the U.S. population does not have a high school or higher level of education. Clearly, large proportions of the U.S. population are included in groups that are thought likely to be at increased risk (i.e., susceptible) to the effects of PM. Thus, even a small percentage reduction in PM-associated admissions or deaths from cardiopulmonary disease would predict a large number of avoided cases.

#### *9.2.5.2.2 Evidence of new endpoints and potentially susceptible groups*

The expanded body of epidemiologic studies have identified a number of health outcomes that are linked with exposure to ambient PM, in addition to data that were available in the 1996 PM AQCD on cardiopulmonary mortality, hospitalization for respiratory disease, respiratory symptoms and changes in lung function.

**TABLE 9-5. PREVALENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE GROUP AND BY GEOGRAPHIC REGION, 2000 (reported as percent or numbers of cases in millions)**

| | | | Age | | | | Regional | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Adults (18+)* | | 18-44 | 45-64 | 65-74 | 75+ | NE | MW | S | W |
| Chronic Condition/Disease | Number ($\times 10^6$) | % | % | % | % | % | % | % | % | % |
| **Respiratory conditions** | | | | | | | | | | |
| Asthma | 18.7 | 9.3 | 9.8 | 8.7 | 8.7 | 8.1 | 8.9 | 9.3 | 9 | 10.3 |
| *Asthma (<18 years)** | *8.92** | *12.4** | | | | | | | | |
| ***COPD***: | | | | | | | | | | |
| Chronic bronchitis | 9.36 | 4.6 | 3.6 | 5.5 | 6.4 | 6.6 | 3.9 | 4.6 | 5.4 | 4.1 |
| Emphysema | 3.13 | 1.6 | 0.2 | 1.9 | 4.7 | 5.9 | 1 | 1.7 | 2 | 1.2 |
| **Circulatory conditions** | | | | | | | | | | |
| All heart disease | 21.99 | 10.9 | 4.2 | 12.5 | 26.4 | 35 | 10.4 | 11.5 | 11.5 | 9.5 |
| Coronary heart disease | 11.23 | 5.6 | 0.7 | 6.6 | 17.3 | 22.7 | 5.1 | 5.3 | 6.3 | 5 |
| Hypertension | 39.21 | 19.5 | 6.4 | 27.3 | 46.3 | 51.5 | 17.9 | 18.8 | 21.6 | 18.1 |
| Stroke | 4.36 | 2.2 | 0.3 | 2.1 | 6.5 | 10.5 | 1.6 | 2.1 | 2.6 | 2.1 |
| **Diabetes** | 11.86 | 5.9 | 1.9 | 8.4 | 15.9 | 13.4 | 5.5 | 5.6 | 6.4 | 5.9 |

Source: Pleis et al. (2003).

*All data are for adults except asthma prevalence data for children under 18 years of age, responding to "ever told had asthma"; source for data on children is Blackwell et al. (2003).

**TABLE 9-6. NUMBER OF ACUTE RESPIRATORY CONDITIONS PER 100 PERSONS PER YEAR, BY AGE: UNITED STATES, 1996**

| Type of Acute Condition | All Ages | Under 5 Years | 5-17 Years | 18-24 Years | 25-44 Years | 45 Years and Over | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | 45-64 Years | 65 Years and Over |
| Respiratory Conditions | 78.9 | 129.4 | 101.5 | 86 | 76.9 | 53.3 | 55.9 | 49 |
| Common Cold | 23.6 | 48.6 | 33.8 | 23.8 | 18.7 | 16.1 | 16.4 | 15.7 |
| Other Acute Upper Respiratory Infections | 11.3 | 13.1 | 15 | 16.1 | 11.6 | 7 | 7.5 | 6.1 |
| Influenza | 36 | 53.7 | 44.3 | 40.5 | 38.1 | 23.3 | 26.1 | 18.6 |
| Acute Bronchitis | 4.6 | *7.2 | 4.3 | *3.9 | 5.1 | 3.8 | 3.5 | *4.4 |
| Pneumonia | 1.8 | *3.9 | *1.7 | *1.4 | *1.3 | *2.0 | *0.9 | *3.8 |
| Other Respiratory Conditions | 1.7 | *2.9 | *2.4 | *0.4 | *2.0 | *1.1 | *1.5 | *0.5 |

Source: Adams et al. (1999).

*All data are for adults except asthma prevalence data for children under 18 years of age, responding to "ever told had asthma"; source for data on children is Blackwell et al. (2003).

New information from prospective cohort studies has suggested that long-term exposure to PM is linked not only with mortality due to cardiovascular diseases, but also with lung cancer mortality. This new data adds to what had been reported in earlier cross-sectional studies and provides strong supporting evidence for the link between ambient pollution and lung cancer mortality.

The recent appreciation for underlying cardiovascular dysfunction as a risk factor for PM health effects derives from a growing and diverse body of literature. A number of epidemiologic studies had reported associations with cardiopulmonary mortality, and limited evidence was available on hospitalization for cardiovascular diseases in the 1996 PM AQCD. Numerous new epidemiologic studies have built upon those findings, and new studies summarized in Section 8.3.1.3 have reported associations between PM and risk of myocardial infarction, measures of heart beat rhythm, and changes in electrocardiographic (ECG) markers of cardiac function, e.g., altered heart rate variability (HRV), shown in other studies to be indicators of increased risk for serious cardiovascular outcomes (e.g., heart attacks), though it is noted that interpretation of changes in heart rate variability is complicated. Other studies point toward changes in blood characteristics (e.g., alterations in C-reactive protein levels, fibrinogen levels, blood viscosity,

etc.) related to increased risk of ischemic heart disease also being associated with ambient PM exposures. These results provide suggestive evidence indicative of potential pathophysiologic alterations contributing to serious PM-related cardiovascular effects (e.g. myocardial infarction, stroke, death). Collectively, these new epidemiologic and toxicologic studies provide important new insights into potential cardiac responses to PM.

As noted above, studies using data on visits to physicians' offices or outpatient clinics provide new evidence on respiratory morbidity. That is, comparing the number of admissions in London from an earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study, Hajat et al. (1999) observed about 24 asthma GP visits for every asthma hospital admission in that city. This suggests that looking only at numbers of hospital admissions and emergency hospital visits may markedly underestimate the overall numbers of respiratory morbidity events due to acute ambient PM exposure.

PM-related health effects in infants and children are emerging as an area of more concern than in the 1996 PM AQCD; and ultimately, such health effects could have very substantial implications for life expectancy calculations. However, only very limited evidence currently exists about potential ambient PM relationships with some of the more serious pertinent health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions, and mortality in older children). Also, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue, because childhood illness or death may cost a very large number of productive life-years.

Small relative risk estimates for health effects have generally been observed for ambient air pollutants, as would be expected on biological and epidemiologic grounds. In contrast to effect estimates for mortality derived for the 1952 London smog episode, i.e., relative risk (RR) exceeding 4.0 (i.e., 400% increase over baseline) for extremely high ($\geq$2 mg/m3) ambient PM levels, effects estimates in most current epidemiology studies at distinctly lower PM concentrations (often $\leq$100 $\mu g/m^3$) are relatively small.

It is important to recognize that even a small percentage reduction in PM health impacts on respiratory-related diseases would reflect a large number of avoided cases. As described earlier, the potentially susceptible population subgroups can include a large portion of the U.S. population. Data available from national surveys can provide some useful information on U.S.

annual health outcome statistics, and also provide background information on what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 millions deaths per year in the U.S. population, with about 900,000 deaths due to cardiovascular diseases, and 100,000 from chronic lower respiratory diseases (Arias et al., 2003). For measures of cardiovascular disease morbidity, there are approximately 6 million hospital discharges per year (Hall and DeFrances, 2003), nearly 5 million emergency department visits (McCaig et al., 2004), to over 70 million ambulatory care visits for circulatory system disorders (Cherry et al., 2003). For chronic respiratory health diseases, there are over 3 million hospital discharges for respiratory diseases (Hall and DeFrances, 2003), nearly 13 million emergency department visits (McCaig et al., 2004), over 200 million ambulatory care visits per year for respiratory conditions (Cherry et al., 2003) and an estimated 700 million restricted activity days per year due to respiratory conditions (Adams et al., 1999). Combining small risk estimates with relatively large baseline estimates of health outcomes can result in quite large public health impacts.

#### *9.2.5.2.3 Impact on life-expectancy*

Conceptually, ambient PM exposures may be associated with both the long-term development of underlying health problems ("frailty") and with the short-term variations in timing of mortality among a susceptible population with some underlying health condition (Künzli et al. 2001). New evidence from toxicological studies have provided insights into potential mechanisms for PM-related health effects, but this evidence is not sufficient to allow direct conclusions to be drawn regarding specific effects linked with short-term or long-term PM exposures. Epidemiologic studies of the mortality effects of short-term exposure to particulate matter using time-series studies can only capture PM's association with short-term variations in mortality and, therefore, must systematically underestimate the proportion of total mortality attributable to PM. The relative risk estimates for mortality from the prospective cohort studies have converged in the range of 7 to 13 percent increase in the non-external mortality rate associated with a 10 $\mu g/m^3$ increment in a long-term average of $PM_{2.5}$. Risk estimates from short-term exposure studies are considerably smaller in magnitude, on the order of 2 to 6% increased risk of mortality per 25 $\mu g/m^3$ change in 24-hour average $PM_{2.5}$. A recent time-series study that examined the contribution of daily PM levels over an extended lag period (42 days) could only partially bridge the gap between the effects of short-term and long-term exposures to

particulate matter (Zanobetti et al., 2002). The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflect cumulative PM effects above and beyond those exerted by short-term exposure events.

Recent investigations of the public health implications of effect estimates for long-term PM exposures also were reviewed in Chapter 8. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to ambient airborne PM can have substantial effects on life expectancy. For example, a calculation for the 1969 to 1971 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of ~1.3 years for the entire population's life expectancy at age 25. The new evidence noted above of infant mortality associations with PM exposure suggests that life shortening in the entire population from long-term PM exposure could well be significantly larger than estimated by Brunekreef (1997).

It is also useful to highlight the newer results of the extension of the ACS study analyses (that include more years of participant follow-up and address previous criticisms of the earlier ACS analyses), which provide the strongest evidence to date that long-term ambient PM exposures are associated with increased risk of lung cancer. That increased risk appears to be in about the same range as that seen for a non-smoker residing with a smoker and, therefore, passively exposed chronically to tobacco smoke, with any consequent life-shortening impacts due to lung cancer.

#### 9.2.5.3 Summary and Conclusions

Clearly, the public health impact of exposures to ambient PM can be quite large. The population groups that are likely more susceptible to the effects of ambient particles, including those with heart or lung diseases, children and older adults, comprise substantial portions of the U.S. population. Even relatively small increases in PM-related risks for serious health effects (e.g., premature mortality, hospital admissions) in such large population groups result in substantial public health impacts. In addition, somewhat larger increases in PM-related risks for less serious health effects (e.g., medical visits, respiratory symptoms) can add substantially to this overall public health burden. Looking beyond the question of how many PM-related premature deaths are likely to occur, it is also important to address the question of the extent of life lost due to PM-related premature mortality. Findings from recent studies indicate that loss

of population life expectancy may be substantial, on the order of a year or so, with long-term exposure to PM; however, further research is needed on this question. Further research is also needed to build upon currently only very limited evidence about potential PM-related health endpoints in infants and children, which is emerging as an area of more concern than in the previous review.

## 9.3 SYNTHESIS OF AVAILABLE INFORMATION ON PM-RELATED WELFARE EFFECTS

The synthesis of available information on PM-related welfare effects presented in this section focuses on four types of effects, i.e., PM-related effects on: visibility, vegetation and ecosystems, man-made materials, and climate change processes. The resulting synthesis of information and conclusions are intended to provide the scientific bases for options to be considered by the EPA Administrator as to whether currently available scientific information supports retention or revision of existing secondary PM NAAQS.

### 9.3.1 Airborne Particle Effects on Visibility

The following discussion of the effects of airborne particles on visibility is drawn primarily from information in Chapter 4 of this document, which itself is supplementary to several other significant reviews of the science of visibility. These reviews include reports of the National Acid Precipitation Assessment Program (1991, 1998), the National Research Council's report on Protecting Visibility in National Parks and Wilderness Areas (1993), and U.S. EPA's Interim Findings on the Status of Visibility Research (1995). The focus here is on characterizing: (a) how ambient PM (in particular ambient fine PM) affects visibility, and (b) how the public values improvements in visibility, especially in urban areas.

#### 9.3.1.1 How Does Newly Available Information Inform Our Understanding of How Ambient PM and Its Major Constituents Affect Visibility?

The role of ambient PM in impairing visibility has long been well understood, as was recognized in the 1996 PM AQCD as follows:

> "The relationships between air quality and visibility are well understood. Ambient fine particles are the major cause of visibility impairment. Significant scientific evidence exists showing that reducing fine particle concentrations will improve visibility." (U.S. EPA, 1996, p. 1-18).

More specifically, the efficiency with which airborne particles cause visibility impairment depends on not just the mass of fine particles, but also on particle composition, particle size, and relative humidity. Airborne particles degrade visibility due to their optical properties of light scattering and absorption, which can be well characterized in terms of a light extinction coefficient. The contribution of airborne particles to total light extinction can be derived from well-established relationships for the major fine particle components, with relative-humidity adjustment factors to account for the hygroscopic behavior of the sulfate and nitrate components; coarse mode particles generally play a much smaller role. Sulfates, nitrates, and organic carbon are the primary light-scattering components of fine particles, with each component being relatively more important to visibility impairment in different parts of the U.S. (e.g., sulfates being the most important contributor in the eastern U.S., organic carbon in the western U.S., and nitrates in southern California). Elemental carbon and, to a much smaller degree, crustal materials are the primary light-absorbing components of fine particles. Some minerals in coarse-mode crustal particles also absorb light and, during events such as dust storms, can be a significant factor in visibility impairment.

Particle-related light scattering efficiency depends on particle size, with peak efficiency resulting from particles that are about 0.5 to 0.8 μm in diameter, falling off rapidly for particles below 0.3 or above 1.0 μm in diameter. Therefore, fine particles within the accumulation mode are most effective in scattering light and are more important in visibility degradation than either ultrafine (nuclei-mode) or coarse-mode particles.

The overall effect of increasing humidity on light scattering by particles was quantified nearly 20 years ago, but current research is greatly increasing the detailed understanding of the response of aerosol particles to changing humidities and the relationship of this response to the chemical composition of the particles. Humidity effects generally become important at relative humidities between 60 and 70%, and increase particle-related light scattering by a factor of 2 at approximately 85% relative humidity. Light scattering by particles increases rapidly with relative humidity when the humidity exceeds 90%.

As discussed in Chapter 4, a number of studies available since the last review have resulted in refinements both (a) in the algorithms and related parameters used to calculate light extinction based on particle properties and (b) in related measurements methods and monitoring instrumentation. For example, a few studies have focused on better characterizing the hygroscopic properties of particles, with a particular focus on organic compounds and mixtures associated with different sources (e.g., Cocker et al., 2001; Chughtai et al., 1999; Hemming and Senfield, 2001). More broadly, Malm (2000) used data from a special study at the Great Smoky Mountain National Park to compare the performance of a number of models for calculating light extinction and found that significant model improvement could be obtained by including the degree of sulfate ammoniation in the model. These studies have served primarily to reinforce and refine our understanding of how airborne particles affect visibility.

Our understanding of how ambient PM affects visibility has historically focused on visibility impairment in rural areas, particularly in national parks and wilderness areas (i.e., Federal Class I areas). Visibility in such areas varies substantially between eastern and western sites in the U.S., with the haziest days in the West typically being roughly equivalent to the clearest days in the East. The largest monitoring network that measures both visibility and aerosol conditions is the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, formed in 1987 as a collaborative effort between Federal, regional, and state entities responsible for visibility protection in such areas. This network has been used in visibility-related research, including the advancement of visibility monitoring instrumentation and analysis techniques and source attribution field studies. This network and related research have provided substantial support to regulatory programs established to protect Federal Class I areas from local and regional sources of visibility impairment.

Particle-related visibility impairment also occurs in urban areas, although historically the relationship between ambient PM and visibility has been less well studied in such areas. More recent attention has been given to such efforts, however, drawing upon data now available from the new national monitoring networks designed to assess $PM_{2.5}$ concentrations and composition in urban areas across the country that have been deployed in conjunction with establishment in 1997 of the $PM_{2.5}$ NAAQS. In addition, higher resolution visibility data are now becoming available from the Automated Surface Observing System (ASOS) monitoring network in operation at airports across the U.S. These and other sources of visibility and ambient fine

particle data provide important information that helps to facilitate the characterization of relationships between ambient PM and visibility especially in urban areas.

In addition to empirically derived relationships between ambient PM and visibility measurements, photographic modeling techniques that have been refined in recent years are useful in portraying changes in visibility specifically due to changes in ambient PM levels. For example, the WinHaze system developed by Molenar et al. (1994) has been used to simulate changes in visibility as a function of changes in air quality for both rural and urban areas. This modeling system can produce a simulated photograph that accurately depicts a cloud-free scene as it would appear to a human observer. Such photographic representations have facilitated the evaluation of how the public values improvements in visibility in a number of urban areas, as discussed below.

#### 9.3.1.2 How Does Newly Available Information Inform Our Understanding of How the Public Values Improvements in Visibility, Especially in Urban Areas?

Information about how the public values improvements in visibility comes from both economic studies and from local and/or state initiatives in a number of areas to adopt local visibility goals and standards. There is an extensive scientific literature on the theory and application of economic valuation methods, although, as summarized in Chapter 4, study results vary substantially across different valuation methods and concerns remain about the use of this general approach for quantitative purposes. Initiatives over the past few years in the Denver, CO and Phoenix, AZ areas provide important evidence of public interest in addressing visibility impairment in these urban areas, although uncertainty would be involved in extending the public values implied by these examples to other areas.

More specifically, the initiative in Denver began with a series of visibility-related studies in the 1970's through the 1980's, leading to the adoption of a visibility standard for the city of Denver in 1990. This standard is based on a light extinction level of 0.076 $km^{-1}$, averaged over four daylight hours, reflecting the short-term nature of the perception of changes in visibility conditions. This standard is equivalent to a visual range of approximately 50 km and reflects citizen judgments about acceptable and unacceptable levels of visual air quality. In Phoenix, a study conducted between 1988 and 1990 led to establishment of a Blue Sky Index, which focuses on days in which the visual range, averaged over six daylight hours, is 40 km or more. This target is based on a method very similar to that used in Denver for obtaining citizen's

judgments as to acceptable levels of visual air quality. While in practice these standard target values are exceeded many times per year in these areas, they reflect a reasonable degree of consistency in the outcome of the approach used to characterize the value that citizens in these two urban areas place on visual air quality.

## 9.3.2 Effects of Ambient PM on Vegetation and Ecosystems

### 9.3.2.1 What Are the Direct and Indirect Effects of Ambient PM?

The direct and indirect effects of deposited ambient PM can span the full range, scale and properties of biological organization listed under Biotic condition (Chapter 4) and can vary widely depending on the (1) sensitivity of each ecosystem and/or its component biota (biotic receptors) to a given concentration and chemical composition (acid/base, trace metal or nutrients, e.g., nitrates or sulfates) of PM components; (2) the pre-existing buffering capacity of the soils and/or waters (freshwater streams, rivers, ponds, and lakes; estuaries and ocean); (3) the magnitude (rate, deposition velocity), mode, and meteorology of the deposition; and (4) other site specific features (e.g., terrain, hydrology, climate, land use, etc.). The ability of an ecosystem to maintain integrity in the presence of the different stressors in PM deposition is a direct function of the sensitivity level of the ecosystem to the different PM constituents and to the ability of the ecosystem components to ameliorate the effects that can result. Changes in structural patterns and the functioning of ecological processes must be scaled in both time and space and propagated to the more complex levels of community interaction to produce observable ecosystem changes.

Direct effects result when PM is deposited onto sensitive receptors. Such effects can be either chemical and/or physical; and they have been observed largely downwind of point sources as the result of dust from limestone quarries and cement kilns or heavy metals from iron and lead smelting factories (Chapter 4). Because these effects tend to be very limited in scope, they do not warrant the level of attention given the more widespread indirect, ecosystem-level, effects discussed below.

The indirect effects of major concern are mediated via the soil or aquatic environment and have the potential of degrading ecosystem functioning by altering species diversity, structure, and sustainability of ecosystems to the detriment of animals and plant life, so that ecosystems provide fewer benefits and services for humans (Moomaw, 2002).

Ecosystems within the U.S. span the range from remote to urban. Most of the ecosystem impacts of PM that have been reported occurred at non-urban sites and, as such, non-urban ecosystems are the primary focus of the discussion that follows in subsequent subsections. In briefly considering urban ecosystems here, it is recognized that despite a large body of knowledge on concentrations and chemical reactions of air pollutants in cities, there has been little work on the rates of atmospheric deposition to urban ecosystems. However, urban ecosystems are likely to be subjected to large rates of deposition of anthropogenic pollutants (Lovett et al.2000). Decades of research on urban air quality indicate that cities are often sources of nitrogen oxides, sulfur oxides, and dust, among many other pollutants. Some of these air pollutants are major plant nutrients (e.g., nitrogen) and may be affecting nutrient cycles in plant-dominated areas in and around cities. Studying the deposition rates of atmospheric pollutants in urban areas can provide a quantitative estimate of the amounts of gaseous and particulate air pollutants that are removed by urban vegetation. Though these effects of PM as such appear not to have been measured at this time, the deployment of new $PM_{2.5}$ speciated urban monitors and concern over urban visibility impairment could lead to additional information being developed that would be relevant to assessing PM effects on urban ecosystems.

#### 9.3.2.2 What are the Components in Ambient PM that are Major Ecosystem Stressors?

In order for any component of ambient PM to impact ecosystems, it must first be removed from the atmosphere through deposition. Deposition can occur in three modes: wet, dry, or occult. The factors that influence the magnitude and mode of particle deposition are numerous and complex and depend in part on particle size, shape, chemistry, atmospheric conditions (e.g., relative humidity, wind speed) and ecosystem surface features (e.g., elevation, complexity of terrain, land over type, etc.). National deposition monitoring networks routinely measure total wet or dry deposition of certain compounds. Data from these networks demonstrate that nitrogen and sulfur compounds are being deposited onto soils and aquatic ecosystems in sufficient amounts to impact ecosystems at local, regional and national scales. Though the ambient PM contribution to total wet or dry deposition has rarely been characterized and the percentages of nitrogen and sulfur containing compounds in PM vary spatially and temporally, nitrates and sulfates make up a substantial portion of the chemical composition of PM.

Therefore, the components of PM that are considered of greatest environmental significance are nitrates, sulfates and the associated hydrogen ($H^+$) ion (Chapter 4).

#### *9.3.2.2.1 Nitrogen*

Nitrogen is required by all organisms as it is a major constituent of the nucleic acids that determine the genetic character of all living things and the enzyme proteins that drive the metabolic machinery of every living cell (Galloway, 1998; Galloway and Cowling, 2002). It has long been recognized as the nutrient most important for plant metabolism and, to a large extent it governs the utilization of phosphorus, potassium, and other nutrients. Typically, the availability of nitrogen via the nitrogen cycle controls net primary productivity, and possibly, the decomposition rate of plant litter. Plants usually obtain nitrogen directly from the soil by absorbing $NH_4^+$ or $NO_3^-$ through their roots, or it is formed in their roots by symbiotic organisms (bacteria, blue-green algae). However, nitrogen (N), unlike other essential nutrients, is not readily available and usually is in short supply.

Nitrogen in nature can be divided into two groups: nonreactive ($N_2$) and reactive (Nr). Molecular nitrogen ($N_2$), though the most abundant element in the Earth's atmosphere, is not available to more than 99% of living organisms unless converted into reactive forms (Galloway et al., 2003). Reactive Nr includes the inorganic reduced forms of nitrogen (e.g., ammonia [$NH_3$] and ammonium [$NH_4^+$]), inorganic oxidized forms (e.g., nitrogen oxide [$NO_x$], nitric acid [$HNO_3$], nitrous oxide [$N_2O$], and nitrate [$NO_3^-$]) , and the organic compounds (e.g., urea, amine, proteins, and nucleic acids)]) (Galloway and Cowling, 2002).

Anthropogenic Nr creation now exceeds the rate of natural terrestrial Nr creation and its conversion back to $N_2$ by denitrification (Galloway and Cowling, 2002). Thus, increase in global Nr is the result of three main causes: (1) widespread cultivation of legumes, rice and other crops that promote conversion of $N_2$ to organic nitrogen through biological nitrogen fixation (BNF); (2) combustion of fossil fuels which converts both atmospheric $N_2$ and fossil N to reactive $NO_x$ ; and (3) the Haber-Bosch process, developed in 1913, which converts nonreactive $N_2$ to reactive $NH_3$ to sustain food production and some industrial activities (Galloway and Cowling, 2002; Galloway et al., 2003). As a result, Nr is now accumulating in the atmosphere and terrestrial and aquatic ecosystems on all spatial scales – local, regional and global (Galloway and Cowling, 2002; Galloway et al., 2003).

Nitrogen oxides is the only ambient air criteria pollutant that has not decreased since the passage of the Clean Air Act. Despite decreases in emissions from fossil fuel burning industries, emissions from automobiles have increased approximately 10% since 1970 due to greater total miles driven (Howarth et al., 2002). Nitrogen oxides emissions from fuel burning increased exponentially from 1940 until the 1970s, leveled off after the passage in of the Clean Air Act in 1970, and stabilized at approximately 7 Tg $NO_x$ /yr in the late 1990s. Contemporary emissions of $NO_x$ in the U.S. from fossil fuel burning are nearly two-thirds the rate of Nr releases from the use of inorganic fertilizers and comprise 30% of the global emissions of $NO_x$ from fossil fuel combustion.

***Environmental Effects of Nr***

The term "nitrogen cascade" refers to the sequential transfers and transformations of Nr molecules as they move from one environmental system or reservoir (atmosphere, biosphere, hydrosphere) to another and the multiple linkages that develop among the different ecological components. Because of these linkages, the addition of anthropogenic Nr alters a wide range of biogeochemical processes and exchanges as it moves among the different environmental reservoirs, with the consequences becoming magnified through time (Figure 4-15; Galloway and Cowling, 2002; Galloway et al., 2003). These changes in the nitrogen cycle are contributing to both beneficial and detrimental effects to the health and welfare of humans and ecosystems (Rabalais, 2002; van Egmond et al., 2002; Galloway, 1998).

Some of the detrimental effects resulting from increased inputs of atmospheric Nr include: (1) increases in productivity of Nr-limited forests and grasslands followed by decreases wherever increase in atmospheric deposition of Nr significantly exceeds critical thresholds; Nr additions have also been shown to decrease biodiversity in many natural habitats (Aber et al., 1995); (2) formation of $O_3$ and ozone-induced injury to crops, forests, and natural ecosystems and the resulting predisposition to attack by pathogens and insects; (3) nitrogen saturation of soils in forests and other natural ecosystems, leading to shifts in community composition and leaching of Nr into streams, lakes and rivers; (4) eutrophication, hypoxia, loss of biodiversity, and habitat degradation in coastal ecosystems, now considered the biggest pollution problem in coastal waters (Rabalais, 2002); (5) acidification and loss of biodiversity in lakes and streams in many regions of the world when associated with sulfur (Vitousek et al., 1997); and (6) alteration

of ecosystem processes through changes in the functioning of beneficial soil organisms (Galloway and Cowling 2002).

Indirect effects of Nr on societal values include: (1) increases in fine PM resulting in regional hazes that decrease visibility at scenic rural and urban vistas and airports; (2) depletion of stratospheric ozone by $N_2O$ emissions which can in turn affect ecosystems and human health; (3) global climate change induced by emissions of $N_2O$; and (4) formation of acidic deposition when in association with sulfate (Galloway et al., 2002).

Large uncertainties, however, still exist concerning the rates of Nr accumulation in the various environmental reservoirs which limits our ability to determine the temporal and spatial distribution of environmental effects for a given input of Nr. These uncertainties are of great significance because of the sequential nature of Nr effects on environmental processes. Reactive nitrogen does not cascade at the same rate through all environmental systems. The only way to eliminate Nr accumulation and stop the cascade is to convert Nr back to nonreactive $N_2$ (Galloway et al., 2003).

***Nitrogen Saturation and Ecosystem Response***

A major environmental concern is nitrogen saturation of soils. Nitrogen saturation occurs when chronic additions of nitrogen (including nitrate deposition from ambient PM) to soil background levels (nitrogen loading) exceeds the capacity of plants and soil microorganisms to utilize and retain nitrogen (Aber et al., 1989, 1998; Garner 1994; U.S. Environmental Protection Agency, 1993). Nitrogen saturation implies that some resource other than nitrogen is now limiting biotic functions. The appearance of nitrogen in soil solution (leaching) is an early symptom of excess nitrogen.

Nitrogen saturation does not occur at a specific point in time, but is a set of gradually developing critical changes in ecosystem processes which represent the integrated response of a system to increased nitrogen availability over time (Aber, 1992). The chronic additions and accumulation of nitrogen alter normal nitrogen cycling and many of the soil and plant processes involving nitrogen that affect an ecosystems's nutrient balance (Waring, 1987; Figure 4-16, Chapter 4).

Not all vegetation or ecosystems react in the same manner to nitrogen deposition. Responses vary depending on numerous factors, including soil composition and the length of

time nitrate deposition has been occurring. For example, ecosystems comprised of older, mature forests with high stores of soil nitrogen and low C:N ratios receiving high nitrogen deposition are prone to nitrogen saturation (Fenn et al., 1998).

Variations in the response of forest ecosystems in the eastern and the western U.S. to differing amounts of nitrate deposition illustrate this point (Chapter 4, Table 4-14). Although soils of most North American forest ecosystems are nitrogen limited, some exhibit severe symptoms of nitrogen saturation (See Figure 4-17; Chapter 4 (Aber et al., 1989). In the east, these include the Great Smoky Mountains National Park (3.1 to 26.6 kg N $ha^{-1}$ yr) (Johnson and Lindberg, 1992); the Fernow Experimental Forest, WV (15 to 20 kg N $ha^{-1}$ yr) (Gilliam et al., 1996); Whitetop Mountain, VA (32 kg N $ha^{-1}$ yr); the Catskill Mountains in southeastern NY (10.2 kg N $ha^{-1}$ yr); and the Adirondack Mountains of northeastern NY (9.3 kg N $ha^{-1}$ yr) (see Table 4-14).

In the west, wildland ecosystems within the South Coast Air Basin of California receive the highest nitrogen deposition in the United States (Fenn et al., 1998; 2003). The areas receiving the greatest deposition are the south-facing slopes of the San Gabriel Mountains and the western and southern edges of the San Bernardino Mountains where deposition ranges from 23.3 to 30 kg N $ha^{-1}$ per yr. Deposition in the low- and mid-elevation chaparral and mixed conifer forests ranges from 20 to 45 kg N $ha^{-1}$ per yr in the most exposed areas. However, when fog occurs in late summer with unusually high $NO_3^-$ and $NH_4^+$ concentrations, deposition values can be higher than 90 kg N $ha^{-1}$ yr (Fenn et al., 2003). The forests in the southwestern Sierra Nevada of Central California receive 6-11 kg N $ha^{-1}$ yr as throughfall (Fenn et al; 1998). Nitrogen deposition since the 1980s has resulted in saturation in the high-elevation Front Range in northern Colorado where deposition values currently range from 8 to 10 kg N $ha^{-1}$ yr (Bowman and Steltzer, 1998; Bowman, 2000; Baron et al., 2000) (Chapter 4, Table 4-14.)

On the other hand, the Harvard Forest hardwood stand in Massachusetts has absorbed over 900 kg N $ha^{-1}$ without significant nitrate leaching during a nitrogen amendment study of 8 years. However, leaching losses were high in Harvard pine sites suggesting that deciduous forests may have a greater capacity for nitrogen retention (Fenn et al., 1998). Magill et al. (2000) suggest that the sharp contrasts that exist between hardwood and pine forests indicate that the mosaic of community types across the landscape must be considered when determining regional scale response to nitrogen deposition.

Increases in soil nitrogen can also play a selective role in ecosystems, by affecting competition among species, resulting in changes in biodiversity, i.e., community composition. In general, plants adapted to living in an environment of low nitrogen availability will be replaced by nitrophilic plants capable of using increased nitrogen because they have a competitive advantage when nitrogen becomes more readily available (Fenn et al., 1998). Several long-term fertilization studies have observed these effects. For example, fertilization and nitrogen gradient experiments at Mount Ascutney, VT suggest that nitrogen saturation may lead to the slow-growing, slow nitrogen-cycling spruce-fir forest stands being replaced by fast-growing deciduous forests that cycle nitrogen rapidly. Similarly, experimental studies of the effects of nitrogen deposition over a 12-year period on Minnesota grasslands dominated by native warm-season grasses observed the shift to low-diversity mixtures dominated by cool-season grasses at all but the lowest rates of nitrogen addition (Wedin and Tilman, 1996). The shift to low-diversity mixtures was associated with the decrease in biomass carbon to nitrogen (C:N) ratios, increased nitrogen mineralization, increased soil nitrate, high nitrogen losses, and low carbon storage (Wedin and Tilman, 1996).

The mutualistic relationship between plant roots, fungi, and microbes is critical for the growth of the organisms involved. The rhizosphere, the soil that surrounds and is influenced by plant roots is an important region of nutrient dynamics. Bacteria are essential components of the nitrogen and sulfur cycles while fungi in association with plant roots form mycorrhizae that are essential in the uptake of mineral nutrients. The action of bacteria make N, S, Ca, P, Mg, K available for plant growth while mycorrhizae are of special importance in the uptake of N and P (Section 4.3.3; Wall and Moore, 1999; Rovira and Davy, 1974). Changes in soil nitrogen influence the mycorrhizal-plant relationship. Mycorrhizal fungal diversity is associated with above-ground plant biodiversity, ecosystem variability, and productivity (Wall and Moore, 1999). During nitrogen saturation, soil microbial communities change from being fungal, and dominated by mycorrhizae, to being dominated by bacteria. The decline in the coastal sage scrub species can be directly linked to the decline of the arbuscular mycorrhizal community (Edgerton-Warburton and Allen, 2000; Allen et al., 1998; Padgett et al., 1999).

***Nitrate Effects on Aquatic Habitats***

Aquatic ecosystems (streams, rivers, lakes, estuaries or oceans) receive increased nitrogen inputs either from direct atmospheric deposition (including nitrogen-containing particles), surface runoff, or leaching from saturated soils into ground or surface waters. The primary pathways of nitrogen loss from forest ecosystems are hydrological transport beyond the rooting zone into groundwater or stream water, or surface flows of organic nitrogen as nitrate and nitrogen loss associated with soil erosion (Fenn et al., 1998). Based on data from a number of hydrologic, edaphic, and plant indicators, the mixed conifer forest and chaparral watershed with high smog exposure in the Los Angeles Air Basin exhibited the highest stream water $NO_3^-$ concentrations in wilderness areas of North America (Bytnerowicz and Fenn, 1996; Fenn et al., 1998). High nitrate concentrations have also been observed in streams draining watersheds in the Great Smoky Mountains National Park in Tennessee and North Carolina (Fenn et al., 1998).

Estuaries are among the most intensely fertilized systems on Earth (Fenn et al., 1998). They receive far greater nutrient inputs than other systems. For example, atmospheric nitrogen deposition into soils in watershed areas feeding into estuarine sound complexes (e.g., Chesapeake Bay, the Pamlico Sound of North Carolina) contribute to excess nitrogen flows that also include runoff from agricultural practices or other uses (e.g., fertilization of lawns or gardens). Especially during and after heavy rainfall events such as hurricanes, massive influxes of nitrogen into watersheds and sounds can lead to dramatic decreases of oxygen in water and increases in algae blooms that can cause extensive fish kills and damage to commercial fish and sea food harvesting (Paerl et al., 2001).

#### *9.3.2.2.2 Acidification from PM deposition*

Acidic deposition is composed of ions, gases, and particles derived from the precursor gaseous emissions of sulfur dioxide ($SO_2$), nitrogen oxides ($NO_x$), ammonia ($NH_3$) and particulate emissions of acidifying and neutralizing compounds. It connects air pollution to diverse terrestrial and aquatic ecosystems and alters the interactions of the ($H^+$) and many elements (e.g., S, N, Ca, Mg, Al, and Hg) (Driscoll et al., 2001). Linked also to the nitrogen cascade (see Figure 4-15), acidic precipitation is a critical environmental stress that affects forest landscapes and aquatic ecosystems in North America, Europe, and Asia (Driscoll et al., 2001).

Acidic deposition and acidification of soils can lead to high Al-to-nutrient ratios that limit plant uptake of essential nutrients, such as Ca and Mg. Calcium is essential in the formation of wood and the maintenance of the primary plant tissues necessary for tree growth (Shortle and Smith, 1988), and tree species can be adversely affected if altered Ca/Al ratios impair calcium or Mg uptake. A region-wide increase in Ca above expected levels followed by decreasing changes in wood Ca suggests that Ca mobilization began possibly 30 to 40 years ago and has been followed by reduced accumulation in wood, presumably associated with decreasing Ca availability in soil (Chapter 4; Bondietti and McLaughlin, 1992).

#### 9.3.2.3 How can Exposures of Concern for Ecosystem Stressor Components of PM be Characterized?

The critical loads concept has been used in Europe for estimating the amounts of pollutants that sensitive ecosystems can absorb on a sustained basis without experiencing measurable degradation (Lokke et al., 1996). The estimation of ecosystem critical loads requires an understanding of how an ecosystem will respond to different loading rates in the long term and can be of special value for ecosystems receiving chronic deposition of Nr and sulfur independently and as acidic deposition when in combination. Time scales must be considered when selecting and evaluating ecosystems response(s) to changes in atmospheric deposition. Indicators of ecosystems at risk of nitrogen saturation should include those that can be identified when nitrogen availability exceeds biotic demand. The cardinal indicator of nitrogen saturation in all ecosystem types is increased and prolonged $NO_3^-$ loss below the main rooting zone in stream water (Fenn and Poth, 1998). A paucity of baseline data makes it difficult to determine the time scale for critical loading of most U.S. ecosystems because nitrogen deposition began so many years ago. Though atmospheric sources of nitrogen, including ambient PM, are clearly contributing to the overall excess nitrogen load/burden entering ecosystems annually, there is still insufficient data available at this time to quantify the contribution of ambient PM to total nitrogen or acidic deposition its role varies both temporally and spatially along with a number of other factors.

#### 9.3.2.4 Summary and Conclusions

A number of ecosystem-level conditions (e.g., nitrogen saturation, terrestrial and aquatic acidification, coastal eutrophication) that can lead to negative impacts on human health and welfare have been associated with chronic, long-term exposure of ecosystems to elevated inputs of compounds containing Nr, sulfur and/or associated hydrogen ions. Some percentage of total ecosystem inputs of these chemicals is contributed by deposition of atmospheric particles, although the percentage greatly varies temporally and geographically and has not generally been well quantified. Unfortunately, our ability to relate ambient concentrations of PM to ecosystem response is hampered by a number of significant data gaps and uncertainties.

First, U.S. monitoring networks have only recently begun to measure speciated PM. Historically, measurements were focused only on a particular size fraction such as $PM_{10}$ and, more recently, $PM_{2.5}$. An exception to this is the IMPROVE network, which collects speciated measurements. Additionally, except for the IMPROVE and some CASTNet sites, much of the PM monitoring effort has focused on urban or near urban exposures, rather than on those in sensitive ecosystems. Thus, the lack of a long-term, historic database of annual speciated PM deposition rates precludes establishing relationships between PM deposition (exposure) and ecosystem response at this time.

A second source of uncertainty lies in predicting deposition velocities based on ambient concentrations of PM. There are a multitude of factors that influence the amounts of PM that get deposited from the air onto sensitive receptors, including the mode of deposition (wet, dry, occult), windspeed, surface roughness/stickiness, elevation, particle characteristics (e.g., size, shape, chemical composition, etc.) relative humidity, etc. Therefore, modeled deposition rates, used in the absence of monitored data, can be highly uncertain.

Third, each ecosystem has developed within a context framed by the topography, underlying bedrock, soils, climate, meteorology, hydrologic regime, natural and land use history, species associations that co-occur at that location (i.e., soil organisms, plants, etc.), and successional stage, making it unique from all others. Because of this variety, and insufficient baseline data on each of these features for most ecosystems, it is currently impossible to extrapolate with much confidence any effect from one ecosystem to another, or to predict an appropriate "critical load." Thus, for example, a given PM deposition rate or load of nitrates in

one ecosystem may produce entirely different responses than the same deposition rate at another location.

Finally, related in part to the complexity and unique set of characteristics belonging to each ecosystem as discussed above, there remain large uncertainties associated with the length of residence time of Nr in a particular ecosystem component or reservoir, and thus, its impact on the ecosystem as it moves through the various levels of the N cascade. As additional PM speciated air quality and deposition monitoring data become available, there is much room for fruitful research into the areas of uncertainty identified above.

## 9.3.3 What Does the Available Information Indicate About the Relationships Between Atmospheric PM and Climate Change Processes?

### 9.3.3.1 Key Points from 1996 PM AQCD

With regard to the role of ambient PM in affecting climate change-related processes, the 1996 PM AQCD stated:

> "Particles [primarily fine particles] suspended in the atmosphere affect the earth's energy budget and thus exert an impact on climate: (a) directly by increasing the reflection of solar radiation by cloud-free portions of the atmosphere, and (b) indirectly by affecting cloud microphysical properties in ways that increase the brightness and stability of clouds." Since aerosol lifetimes are much shorter than the time required for global mixing, "aerosol radiative effects are most likely to exert their influence on a regional rather than on a global basis." (U.S. EPA, 1996, p. 1-19, 1-21)

### 9.3.3.2 Integration of New Information

The same physical processes (i.e., light scattering and absorption) responsible for visibility degradation are also responsible for airborne particle effects on transmission of solar visible and ultraviolet radiation. Scattering of solar radiation back to space and absorption of solar radiation determine the effects of an aerosol layer on solar radiation. Atmospheric particles greatly complicate projections of future trends in global warming processes because of emissions of greenhouse gases; consequent increases in global mean temperature; resulting changes in regional and local weather patterns; and mainly deleterious (but some beneficial) location-specific human health and environmental effects. Available evidence, ranging from satellite to in situ measurements of aerosol effects on radiation receipts and cloud properties, is strongly indicative of an important role in climate for aerosols, but this role is poorly quantified. No

significant advances have been made since the 1996 PM AQCD in reducing the uncertainties assigned to forcing estimates for aerosol-related forcing, especially for black carbon-containing aerosol. The IPCC characterizes the scientific understanding of greenhouse gas-related forcing as "high" in contrast to that for aerosol, which it describes as "low" to "very low."

In addition to direct climate effects through the scattering and absorption of solar radiation, particles also exert indirect effects on climate by serving as cloud condensation nuclei, thus affecting the abundance and vertical distribution of clouds. The direct and indirect effects of particles appear to have significantly offset global warming effects caused by the buildup of greenhouse gases on a globally averaged basis. However, because the lifetime of particles is much shorter than that required for complete mixing within the Northern Hemisphere, the climate effects of particles generally are felt much less homogeneously than are the effects of long-lived greenhouse gases.

Quantification of the effect of anthropogenic aerosol on hydrological cycles requires more information than is presently available regarding ecosystems responses to reduced solar radiation and other changes occurring in the climate system. However, several global-scale studies indicate that aerosol cooling alone can slow down the hydrological cycle, while cooling plus the nucleation of additional cloud droplets can dramatically reduce precipitation rates.

Any effort to model the impacts of local alterations in particle concentrations on projected global climate change or consequent local and regional weather patterns would be subject to considerable uncertainty.

Atmospheric particles also complicate estimation of potential future impacts on human health and the environment projected as possible to occur because of increased transmission of solar ultraviolet radiation (UV-B) through the Earth's atmosphere, secondary to stratospheric ozone depletion due to anthropogenic emissions of chlorofluorcarbons (CFCs), halons, and certain other gases. The transmission of solar UV-B radiation is strongly affected by atmospheric particles. Measured attenuations of UV-B under hazy conditions range up to 37% of the incoming solar radiation. Measurements relating variations in PM mass directly to UV-B transmission are lacking. Particles also can affect the rates of photochemical reactions occurring in the atmosphere, e.g., those involved in catalyzing tropospheric ozone formation. Depending on the amount of absorbing substances in the particles, photolysis rates either can be increased or decreased. Thus, atmospheric particle effects on UV-B radiation, which vary depending on size

and composition of particles, can differ substantially over different geographic areas and from season to season over the same area. Any projection of effects of location-specific airborne PM alterations on increased atmospheric transmission of solar UV radiation (and associated potential human health or environmental effects) due to stratospheric ozone-depletion would, therefore, also be subject to considerable uncertainty.

## 9.3.4 What Does the Available Information Indicate About the Effects on Man-Made Materials Associated With Ambient PM and its Major Constituents?

### 9.3.4.1 Key Points from 1996 PM AQCD

The 1996 PM AQCD arrived at the following key findings and conclusions related to PM effects on man-made materials:

> "Particle exposure results in the soiling of painted surfaces and other building materials, increasing the cleaning frequency for exposed surfaces and possibly reducing their useful lifetimes." (U.S. EPA, 1996, p. 1-19) Damage to materials can result from the deposition of acid aerosols and the dissolution of acid forming gases on metal surfaces, increasing the corrosion of metals; "exposure to acid forming gases may also limit the life expectancy of paints and may damage various building stones and cement products beyond that resulting from natural weathering processes." (U.S. EPA, 1996, p. 1-20).

### 9.3.4.2 Integration of New Information

As noted in the 1996 PM AQCD and restated in Chapter 4 (Section 4.4), building materials (metals, stones, cements, and paints) undergo natural weathering processes from exposure to environmental elements (wind, moisture, temperature fluctuations, sun light, etc.). Metals form a protective film of oxidized metal (e.g., rust) that slows environmentally induced corrosion. On the other hand, the natural process of metal corrosion from exposure to natural environmental elements is enhanced by exposure to anthropogenic pollutants, in particular $SO_2$ or other acidic substances, that render the protective film less effective. For example, dry deposition of $SO_2$ enhances the effects of environmental elements on calcereous stones (limestone, marble, and cement) by converting calcium carbonate (calcite) to calcium sulfate dihydrate (gypsum). The rate of deterioration is determined by the $SO_2$ concentration, the deposition rate, and the stone's permeability and moisture content; however, the extent of the damage to stones produced by the pollutant species above and beyond that from the natural weathering processes is uncertain.

Sulfur dioxide also has been found to limit the life expectancy of paints by causing discoloration and loss of gloss and thickness of the paint film layer.

As also highlighted in the 1996 PM AQCD, the soiling of painted surfaces and other building materials is a significant detrimental effect of particle pollution. Soiling changes the reflectance of a material from opaque and reduces the transmission of light through transparent materials; it is also a degradation process that requires remediation by cleaning or washing and, depending on the soiled surface, repainting. Available data indicate that airborne particles can result in increased cleaning frequency of exposed surfaces and may reduce the usefulness of soiled materials. Attempts have been made to quantify the pollutant exposure levels at which materials damage and soiling have been perceived; but, to date, insufficient data are available to advance our knowledge regarding perception thresholds with respect to pollutant concentration, particle size, and chemical composition.

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# APPENDIX 9A

## Key Quantitative Estimates of Relative Risk for Particulate Matter-Related Health Effects Based on Epidemiologic Studies of U.S. and Canadian Cities

## TABLE 9A-1. ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** | | | | | |
| Ito and Thurston (1996)<br>Chicago, IL | GAM not used | 2.47 (1.26, 3.69) | — | — | $PM_{10}$ 38 (max 128) |
| Styer et al. (1995)<br>Chicago, IL | GAM not used | 4.08 (0.08, 8.24) | — | — | $PM_{10}$ 37 (4, 365) |
| Kinney et al. (1995)<br>Los Angeles, CA | GAM not used | 2.47 (−0.17, 5.18) | — | — | $PM_{10}$ 58 (15, 177) |
| Pope et al. (1992)<br>Utah Valley, UT | GAM not used | 7.63 (4.41, 10.95) | — | — | $PM_{10}$ 47 (11, 297) |
| Schwartz (1993)<br>Birmingham, AL | GAM not used | 5.36 (1.16, 9.73) | — | — | $PM_{10}$ 48 (21, 80) |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>Boston, MA | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 5.3 (3.5, 7.1)<br>5.7 (3.7, 7.6)<br>5.0 (3.1, 7.0)<br>4.5 (2.5, 6.5) | 0.7 (−1.9, 3.4) | $PM_{10}$ 24.5 (SD 12.8)<br>$PM_{2.5}$ 15.7 (SD 9.2)<br>$PM_{10-2.5}$ 8.8 (SD 7.0) |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>Kingston-Harriman, TN | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 3.1 (0.0, 6.2)<br>3.0 (−0.3, 6.6)<br>2.8 (−0.5, 6.3)<br>2.6 (−0.8, 6.1) | 1.7 (−2.7, 6.3) | $PM_{10}$ 32.0 (SD 14.5)<br>$PM_{2.5}$ 20.8 (SD 9.6)<br>$PM_{10-2.5}$ 11.2 (SD 7.4) |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>St. Louis, MO | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 2.6 (0.9, 4.3)<br>2.4 (0.6, 4.1)<br>2.6 (0.9, 4.4)<br>2.3 (0.6, 4.1) | 0.3 (−2.1, 2.7) | $PM_{10}$ 30.6 (SD 16.2)<br>$PM_{2.5}$ 18.7 (SD 10.5)<br>$PM_{10-2.5}$ 11.9 (SD 8.5) |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>Steubenville, OH | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 2.4 (−0.4, 5.3)<br>1.7 (−1.3 4.8)<br>1.5 (−1.5, 4.6)<br>1.8 (−1.2, 4.9) | 5.2 (0.0, 10.7) | $PM_{10}$ 45.6 (SD 32.3)<br>$PM_{2.5}$ 29.6 (SD 21.9)<br>$PM_{10-2.5}$ 16.1 (SD 13.0) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** (cont'd) | | | | | |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>Topeka, KS | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 1.6 (−5.3, 9.0)<br>2.7 (−5.0, 10.9)<br>1.3 (−6.2, 9.3)<br>1.4 (−6.3, 9.6) | <br><br><br>−3.0 (−8.1, 2.3) | $PM_{10}$ 26.7 (SD 16.1)<br>$PM_{2.5}$ 12.2 (SD 7.4)<br>$PM_{10-2.5}$ 14.5 (SD 12.2) |
| Schwartz et al. (1996)<br>Schwartz (2003a)<br>6 Cities, Overall | GAM Strict<br>GLM NS<br>GLM BS<br>GLM PS | — | 3.5 (2.5, 4.5)<br>3.3 (2.2, 4.3)<br>3.0 (2.0, 4.0)<br>2.9 (1.8, 4.0) | — | $PM_{10}$ means 17.8-45.6<br>$PM_{2.5}$ means 11.2-29.6<br>$PM_{10-2.5}$ means 6.6-16.1 |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis-St. Louis | GAM Strict<br>GLM NS | 2.0 (0.0, 4.1)<br>1.0 (−1.5, 3.6) | 2.0 (0.5, 3.5)<br>1.3 (−0.5, 3.0) | 0.0 (−2.2, 2.3)<br>−0.5 (−3.0, 2.0) | $PM_{10}$ 30.6 (SD 16.2)<br>$PM_{2.5}$ 18.7 (SD 10.5)<br>$PM_{10-2.5}$ 11.9 (SD 8.5) |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis-Steubenville | GAM Strict<br>GLM NS | 2.5 (−1.7, 7.0)<br>1.5 (−1.7, 4.9) | 1.5 (−1.6, 4.7)<br>0.5 (−2.7, 3.8) | 4.6 (−0.7, 10.1)<br>4.0 (−1.6, 10.0) | $PM_{10}$ 45.6 (SD 32.3)<br>$PM_{2.5}$ 29.6 (SD 21.9)<br>$PM_{10-2.5}$ 16.1 (SD 13.0) |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis-Topeka | GAM Strict<br>GLM NS | −3.5 (−11.6, 5.4)<br>−5.4 (−14.3, 4.4) | 1.5 (−6.5, 10.2)<br>−0.5 (−9.5, 9.4) | −3.7 (−9.2, 2.1)<br>−4.7 (−10.8, 1.8) | $PM_{10}$ 26.7 (SD 16.1)<br>$PM_{2.5}$ 12.2 (SD 7.4)<br>$PM_{10-2.5}$ 14.5 (SD 12.2) |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis - Kingston-Harriman | GAM Strict<br>GLM NS | 6.1 (1.5, 11.0)<br>5.1 (−0.2, 10.7) | 4.3 (0.9, 7.8)<br>3.8 (−0.1, 7.8) | 3.5 (−1.0, 8.2)<br>3.0 (−1.9, 8.2) | $PM_{10}$ 32.0 (SD 14.5)<br>$PM_{2.5}$ 20.8 (SD 9.6)<br>$PM_{10-2.5}$ 11.2 (SD 7.4) |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis - Boston | GAM Strict<br>GLM NS | 6.1 (3.6, 8.8)<br>5.6 (2.8, 8.5) | 5.1 (3.3, 6.9)<br>4.0 (1.9, 6.2) | 1.3 (−1.1, 3.7)<br>1.8 (−1.0, 4.6) | $PM_{10}$ 24.5 (SD 12.8)<br>$PM_{2.5}$ 15.7 (SD 9.2)<br>$PM_{10-2.5}$ 8.8 (SD 7.0) |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis - Portage | GAM Strict<br>GLM NS | 1.0 (−4.6, 7.0)<br>−1.5 (−7.7, 5.1) | 1.5 (−2.7, 5.9)<br>−1.2 (−5.7, 3.5) | 0.0 (−4.8, 5.0)<br>−1.0 (−6.2, 4.5) | $PM_{10}$ 17.8 (SD 11.7)<br>$PM_{2.5}$ 11.2 (SD 7.8)<br>$PM_{10-2.5}$ 6.6 (SD 6.8) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** (cont'd) | | | | | |
| Klemm et al. (2000)<br>Klemm and Mason (2003)<br>Six City reanalysis - overall | GAM Strict<br>GLM NS | 3.5 (2.0, 5.1)<br>2.5 (0.8, 4.3) | 3.0 (2.0, 4.1)<br>2.0 (0.9, 3.2) | 0.8 (−0.6, 2.1)<br>0.5(−1.0, 2.0) | $PM_{10}$ means 17.8-45.6<br>$PM_{2.5}$ means 11.2-29.6<br>$PM_{10-2.5}$ means 6.6-16.1 |
| Samet et al. (2000a,b)<br>Dominici et al. (2002, 2003a)<br>90 Largest U.S. Cities | GAM strict<br>GLM NS | 1.4 (0.9, 1.9)<br>1.1 (0.5, 1.7) | — | — | $PM_{10}$ mean range 15.3-52.0 |
| Schwartz (2000a)<br>Schwartz (2003b)<br>10 U.S. cities | GAM Strict<br>GLM NS | 3.4 (2.6, 4.1)<br>2.8 (2.0, 3.6) | — | — | $PM_{10}$ mean range 27.1-40.6 |
| Schwartz (2000a)<br>Chicago, IL<br>Schwartz (2003a) | Strict GAM<br>(dist. lag) | 5.41 (2.36, 8.56) | — | — | $PM_{10}$ mean 36.5 |
| Schwartz (2000a)<br>Pittsburgh, PA<br>Schwartz (2003) | Strict GAM<br>(dist. lag)<br>GLM PS | 3.14 (0.25, 6.11)<br>2.83 (−0.44, 6.21) | — | — | $PM_{10}$ mean 36.4 |
| Schwartz (2000a)<br>Detroit, MN<br>Schwartz (2003b) | Strict GAM<br>(dist. lag)<br>GLM PS | 6.83 (3.73, 10.02)<br>5.83 (2.26, 9.52) | — | — | $PM_{10}$ mean 36.9 |
| Schwartz (2000a)<br>Seattle, Wa<br>Schwartz (2003b) | Strict GAM<br>(dist. lag)<br>GLM PS | 7.46 (3.94, 11.10)<br>7.04 (3.33, 10.88) | — | — | $PM_{10}$ mean 32.5 |
| Schwartz (2000a)<br>Minneapolis, MN<br>Schwartz (2003a) | Strict GAM<br>(dist. lag)<br>GLM PS | 10.25 (4.67, 16.12)<br>10.68 (4.87, 16.81) | — | — | $PM_{10}$ mean 27.5 |
| Schwartz (2000a)<br>Birmingham, AL<br>Schwartz (2003a) | Strict GAM<br>(dist. lag)<br>GLM PS | 1.71 (−3.44, 7.13)<br>−3.21 (−9.80, 3.87) | — | — | $PM_{10}$ mean 34.8 |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** (cont'd) | | | | | |
| Schwartz (2000a)<br>New Haven, CT<br>Schwartz (2003a) | Strict GAM<br>(dist. lag)<br>GLM PS | 9.17 (1.04, 17.96)<br><br>9.22 (0.49, 18.71) | — | — | $PM_{10}$ mean 28.6 |
| Schwartz (2000a)<br>Canton, OH<br>Schwartz (2003) | Strict GAM<br>(dist. lag)<br>GLM PS | 8.79 (−4.69, 24.18)<br><br>7.78 (−7.04, 24.97) | — | — | $PM_{10}$ mean 29.31 |
| Schwartz (2000a)<br>Spokane, WA<br>Schwartz (2003a) | Strict GAM<br>(dist. lag)<br>GLM PS | 5.62 (−0.31, 11.91)<br><br>4.79 (−2.35, 12.45) | — | — | $PM_{10}$ mean 40.6 |
| Schwartz (2000a)<br>Colorado Springs, CO<br>Schwartz (2003a) | Strict GAM<br>(dist. lag)<br>GLM PS | 8.58 (−3.94, 22.73)<br><br>8.69 (−5.25, 24.67) | — | — | $PM_{10}$ mean 27.1 |
| Burnett et al. (2000)<br>Burnett and Goldberg (2003)<br>8 Canadian Cities | GAM Strict<br>GLM NS<br>(6 knots/yr) | 3.2 (1.1, 5.5)<br>2.7 (−0.1, 5.5) | 2.8 (1.2, 4.4)<br>2.1 (0.1, 4.2) | 1.9 (−0.1, 3.9)<br>1.8 (−0.6, 4.4) | $PM_{10}$ 25.9 (max 121)<br>$PM_{2.5}$ 13.3 (max 86)<br>$PM_{10-2.5}$ 12.9 (max 99) |
| Chock et al. (2000)<br>Pittsburgh, PA | GAM not used | < 75 years 3.1 (0.2, 6.1)<br>> 75 years 2.0 (−0.9, 5.0) | < 75 years 2.6 (−2.0, 7.3)<br>> 75 years 1.5 (−3.0, 6.3) | < 75 years 0.7 (−1.7, 3.7)<br>> 75 years 1.3 (−1.3, 3.8) | NR |
| Clyde et al. (2000)<br>Phoenix, AZ | GAM not used | 6 (> 0, 11) | — | — | $PM_{10}$ mean 45.4 |
| Fairley (1999)<br>Fairley (2003)<br>Santa Clara County, CA | GAM Strict<br>GLM NS | 7.8 (2.8, 13.1)<br>8.3 (2.9, 13.9) | 8.1 (1.6, 15.0)<br>7.0 (1.4, 13.0) | 4.5 (−7.6, 18.1)<br>3.3 (−5.3, 12.6) | $PM_{10}$ 34 (6, 165)<br>$PM_{2.5}$ 13 (2, 105)<br>$PM_{10-2.5}$ 11 (0, 45) |
| Gamble (1998)<br>Dallas, TX | GAM not used | −3.56 (−12.73, 6.58) | — | — | $PM_{10}$ 24.5 (11, 86) |
| Goldberg et al. (2000)<br>Goldberg and Burnett (2003)<br>Montreal, CAN | GAM Strict<br>GLM NS | — | 4.2 ($p < 0.05$)<br>1.5 ($p > 0.05$) | — | $PM_{2.5}$ 17.6 (4.6, 71.7) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** (cont'd) | | | | | |
| Klemm and Mason (2000)<br>Atlanta, GA | GAM not used | 8.7 (−5.2, 24.7) | 4.8 (−3.2, 13.4) | 1.4 (−11.3, 15.9) | $PM_{2.5}$ 19.9 (1.0, 54.8)<br>$PM_{10-2.5}$ 10.1 (0.2, 39.5) |
| Levy (1998)<br>King Co., WA | GAM not used | 7.2 (−6.3, 22.8) | 1.76 (−3.53, 7.34) | — | $PM_{10}$ 29.8 (6.0, 123.0)<br>$PM_1$ 28.7 (16.3, 92.2) |
| Lipfert et al. (2000a)<br>Philadelphia, PA | GAM not used | 5.99 ($p > 0.055$) | 4.21 ($p < 0.055$) | 5.07 ($p > 0.055$) | $PM_{10}$ 32.20 (7.0, 95.0)<br>$PM_{2.5}$ 17.28 (−0.6, 72.6)<br>$PM_{10-2.5}$ 6.80 (−20.0, 28.3) |
| Lippmann et al. (2000)<br>Ito (2003)<br>Detroit, MI | GAM Strict<br>GLM NS | 3.3 (−2.0, 8.9)<br>3.1 (−2.2, 8.7) | 1.9 (−1.8, 5.7)<br>2.0 (−1.7, 5.8) | 3.2 (−1.9, 8.6 )<br>2.8 (−2.2, 8.1) | $PM_{10}$ 31 (12, 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50)<br>mean (5%, 95%) |
| Moolgavkar (2000a)<br>Moolgavkar (2003)<br>Los Angeles, CA | GAM Strict 30df<br>GLM NS 30df | 2.4 (0.5, 4.2)<br>2.3 (0.5, 4.1) | 1.5 (0, 3.0)<br>1.4 (−0.4, 3.2) | — | $PM_{10}$ median 44 (7, 166)<br>$PM_{2.5}$ 22 (4, 86) |
| Moolgavkar (2000a)<br>Moolgavkar (2003)<br>Cook Co., IL | GAM Strict 100df<br>GLM NS 100df | 2.4 (1.4, 3.5)<br>2.6 (1.6, 3.6) | — | — | $PM_{10}$ median 35 (3, 365) |
| Ostro (1995)<br>San Bernadino and Riverside Counties, CA | GAM not used | — | 0.28 (−0.61, 1.17) | — | $PM_{2.5}$ 32.5 (9.3, 190.1)<br>(estimated from visibility) |
| Schwartz (2000b)<br>Schwartz (2003a)<br>Boston, MA | GLM NS | — | 5.8 (4.5, 73) (15-day)<br>9.7 (8.2, 11.2) (60-day) | — | $PM_{2.5}$ 15.6 (±9.2) |
| Laden et al. (2000)<br>Schwartz (2003a)<br>Six City source-oriented analysis | GLM PS | — | −5.1 (−13.9, 4.6) crustal<br>9.3 (4.0, 14.9) traffic<br>2.0 (−0.3, 4.4) coal | — | $PM_{2.5}$ same as Six City |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **MORTALITY: Total (nonaccidental) Mortality** (cont'd) | | | | | |
| Tsai et al. (2000)<br>Newark, NJ | GAM not used | 5.65 (4.62, 6.70) | 4.34 (2.82, 5.89) | — | $PM_{15}$ 55 (SD 6.5)<br>$PM_{2.5}$ 42.1 (SD 22.0) |
| Tsai et al. (2000)<br>Camden, NJ | GAM not used | 11.07 (0.70, 22.51) | 5.65 (0.11, 11.51) | — | $PM_{15}$ 47.0 (SD 20.9)<br>$PM_{2.5}$ 39.9 (SD 18.0) |
| Tsai et al. (2000)<br>Elizabeth, NJ | GAM not used | −4.88 (−17.88, 10.19) | 1.77 (−5.44, 9.53) | — | $PM_{15}$ 47.5 (SD 18.8)<br>$PM_{2.5}$ 37.1 (SD 19.8) |
| **Cardiorespiratory Mortality:** | | | | | |
| Samet et al. (2000a, b)<br>90 U.S. Cities<br>Domenici, 2002 | GLM NS | 1.6 (1.1, 2.0) | — | — | $PM_{10}$ mean range:<br>15.3 - 52.0 |
| Tsai et al. (2000)<br>Newark, NJ | GAM not used | 7.79 (3.65, 12.10) | 5.13 (3.09, 7.21) | — | $PM_{15}$ 55 (SD 6.5)<br>$PM_{2.5}$ 42.1 (SD 22.0) |
| Tsai et al. (2000)<br>Camden, NJ | GAM not used | 15.03 (4.29, 26.87) | 6.18 (0.61, 12.06) | — | $PM_{15}$ 47.0 (SD 20.9)<br>$PM_{2.5}$ 39.9 (SD 18.0) |
| Tsai et al. (2000)<br>Elizabeth, NJ | GAM not used | 3.05 (−11.04, 19.36) | 2.28 (−4.97, 10.07) | — | $PM_{15}$ 47.5 (SD 18.8)<br>$PM_{2.5}$ 37.1 (SD 19.8) |
| **Total Cardiovascular Mortality** | | | | | |
| Schwartz (2003b)<br>10 U.S. Cities | GAM Strict | 4.1 (2.5, 5.6) | — | — | $PM_{10}$ mean range<br>27.1- 40.6: |
| Ito and Thurston (1996)<br>Chicago, IL | GAM not used | 1.49 (−0.72, 3.74) | — | — | $PM_{10}$ 38 (max 128) |
| Pope et al. (1992)<br>Utah Valley, UT | GAM not used | 9.36 (1.91, 17.36) | — | — | $PM_{10}$ 47 (11, 297) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Total Cardiovascular Mortality** (cont'd) | | | | | |
| Fairley (1999)<br>Fairley (2003)<br>Santa Clara County, CA | GAM Strict<br>GLM NS | 8.5 (0.6, 17.0)<br>8.9 (1.3, 17.0) | 6.3 (−4.1. 17.9)<br>6.7 (−2.5, 16.7) | 5.0 (−13.3,27.3) | $PM_{10}$ 34 (6, 165)<br>$PM_{2.5}$ 13 (2, 105)<br>$PM_{10-2.5}$ 11 (0, 45) |
| Goldberg et al. (2000)<br>Goldberg and Burnett (2003)<br>Montreal, CAN | GAM Strict<br>GLM NS | — | 3.48 (−0.16, 7.26) | — | $PM_{2.5}$ 17.6 (4.6, 71.7) |
| Lipfert et al. (2000a)<br>Philadelphia, PA<br>(7-county area) | GAM not used | 8.0 (3.7, 12.3) | 5.0 (2.4, 7.5) | 5.4 (−0.4, 11.2) | $PM_{10}$ 32.20 (7.0, 95.0)<br>$PM_{2.5}$ 17.28 (−0.6, 72.6)<br>$PM_{10-2.5}$ 6.80 (−20.0, 28.3) |
| Lippmann et al. (2000)<br>Ito (2003)<br>Detroit, MI | GAM Strict<br>GLM NS | 5.4 (−2.6, 14.0)<br>4.9 (−3.0, 13.5) | 2.2 (−3.2, 7.9)<br>2.0 (−3.4, 7.7) | 6.7 (−1.0, 15.0)<br>6.0 (−1.6, 14.3) | $PM_{10}$ 31 (12, 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50)<br>mean (10%, 90%) |
| Mar et al. (2000)<br>Mar et al. (2003)<br>Phoenix, AZ | GAM Strict<br>GLM NS | 9.7 (1.7, 18.3)<br>9.5 (0.6, 19.3) | 18.0 (4.9, 32.6)<br>19.1 (3.9, 36.4) | 6.4 (1.3, 11.7)<br>6.2 (0.8, 12.0) | $PM_{10}$ 46.5 (5, 213)<br>$PM_{2.5}$ 13.0 (0, 42)<br>$PM_{10-2.5}$ 33.5 (5, 187) |
| Moolgavkar (2000a)<br>Moolgavkar (2003)<br>Los Angeles, CA | GAM Strict 30df<br>GLM NS 100df | 4.5 (1.6, 7.5)<br>3.9 (0.6, 7.4) | 2.6 (0.4, 4.9)<br>1.7 (−0.8, 4.3) | — | $PM_{10}$ median 44 (7, 166)<br>$PM_{2.5}$ median 22 (4, 86) |
| Moolgavkar (2000a)<br>Moolgavkar (2003)<br>Cook Co., IL | GAM Strict 100df<br>GLM NS 100df | 2.0 (0.3, 4.1)<br>2.0 (0.2, 3.7) | — | — | $PM_{10}$ median 35 (3, 365) |
| Ostro et al. (2000)<br>Ostro et al. (2003)<br>Coachella Valley, CA | GAM Strict<br>GLM NS | 5.5 (1.6, 9.5)<br>5.1 (1.2, 9.1) | 9.8 (−5.7, 27.9)<br>10.2 (−5.3, 28.3) | 2.9 (0.7, 5.2)<br>2.7 (0.4, 5.1) | $PM_{10}$ 47.4 (3, 417)<br>$PM_{2.5}$ 16.8 (5, 48)<br>$PM_{10-2.5}$ 17.9 (0, 149) |
| Ostro (1995)<br>San Bernadino and<br>Riverside Counties, CA | GAM not used | — | 0.69 (−0.34, 1.74) | — | $PM_{2.5}$ 32.5 (9.3, 190.1)<br>(estimated from visibility) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Total Respiratory Mortality:** | | | | | |
| Ito and Thurston (1996)<br>Chicago, IL | GAM not used | 6.77 (1.97, 11.79) | — | — | $PM_{10}$ 38 (max 128) |
| Pope et al. (1992)<br>Utah Valley, UT | GAM not used | 19.78 (3.51, 38.61) | — | — | $PM_{10}$ 47 (11, 297) |
| Fairley (1999)<br>Fairley (2003)<br>Santa Clara County, CA | GAM Strict<br>GLM NS | 10.7 (−3.7, 27.2)<br>10.8 (−3.4, 27.1) | 11.7 (−9.8, 38.3)<br>13.5 (−3.6, 33.7) | (GAM strict)<br>32.1 (−9.1, 92.2) | $PM_{10}$ 34 (6, 165)<br>$PM_{2.5}$ 13 (2, 105)<br>$PM_{10-2.5}$ 11 (0, 45) |
| Goldberg et al. (2000)<br>Goldberg and Burnett (2003)<br>Montreal, CAN | GAM Strict<br>GLM NS | — | 21.6 (13.0, 31.0) | — | $PM_{2.5}$ 17.6 (4.6, 71.7) |
| Lippmann et al. (2000)<br>Ito (2003)<br>Detroit, MI | GAM Strict<br>GLM NS | 7.5 (−10.5, 29.2)<br>7.9 (−10.2, 29.7) | 2.3 (−10.4, 16.7)<br>3.1 (−9.7, 17.7) | 7.0 (−9.5, 26.5)<br>6.4 (−10.0, 25.7) | $PM_{10}$ 31 (12, 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50)<br>mean (10%, 90%) |
| Ostro (1995)<br>San Bernadino and Riverside Counties, CA | GAM not used | — | 2.08 (−0.35, 4.51) | — | $PM_{2.5}$ 32.5 (9.3, 190.1)<br>(estimated from visibility) |

## TABLE 9A-1 (cont'd). ESTIMATED TOTAL, CARDIOVASCULAR, AND RESPIRATORY MORTALITY EFFECT SIZES PER INCREMENTS IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ FROM U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **COPD Mortality:** | | | | | |
| Schwartz (2003b)<br>10 U.S. Cities | GAM Strict | 7.7 (4.1, 11.5) | — | — | $PM_{10}$ mean range 27.1 - 40.6: |
| Moolgavkar (2000a)<br>Moolgavkar (2003)<br>Cook Co., IL | GAM Strict 30df<br>GLM NS 100df | 4.0 (−0.2, 10.1)<br>4.8 (−0.6, 10.4) | — | — | $PM_{10}$ median 35 (3, 365) |
| Moolgavkar (2000a)<br>Mookgavkar (2003)<br>Los Angeles, CA | GAM Strict 30 df<br>GLM NS 100df | 4.4 (−3.2, 12.6)<br>6.2 (−3.4, 16.7) | 1.0 (−5.1, 7.4)<br>0.5 (−6.8, 8.4) | — | $PM_{10}$ median 44 (7, 166)<br>$PM_{2.5}$ 22 (4, 86) |

* Both original published studies and recent reanalyses reported in HEI (2003) Special Report for many cited here. Original studies published before 1996 and Schwartz et al. (1996) were assessed in 1996 PM AQCD.

** Where GAM not used in original analysis cited, original results are reported here. Otherwise reanalyses results are reported here if GAM (default) was used in original analysis. GAM strict = GAM with stringent criteria; GLM = general linear model; NS = natural splines; BS = B splines; PS = penalized splines.

*** Mean (minimum, maximum) 24-h PM level in parentheses unless otherwise noted.

## TABLE 9A-2. CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 µg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 µg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 µg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **CARDIOVASCULAR MORBIDITY** | | | | | |
| **Total Cardiovascular Hospital Admissions or Medical Visits:** | | | | | |
| Samet et al. (2000a,b)<br>14 U.S. Cities<br>(> 65 years)<br>Zanobetti and Schwartz (2003) | strict GAM<br>GLM NS<br>GLM PS<br>GLM PS | 4.95 (3.95-5.95)<br>4.8 (3.55-6.0)<br>5.0 (4.0-5.95)<br>5.7 (4.2-7.30) | — | — | $PM_{10}$ means 24.4-45.3 |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 3.25 (2.04, 4.47) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Metzger et al. (2004)<br>Atlanta, GA<br>Period 1 (1993 - 2000)<br>Period 2 (1998 - 2000) | GAM not used | <br>5.1 (−7.9, 19.9)<br>2.3 (−0.4, 5.0) | <br><br>8.2 (2.6, 14.7) | <br><br>3.0 (−3.7, 10.3) | <br>$PM_{10}$ median 26.3<br>$PM_{2.5}$ median 17.8<br>$PM_{10-2.5}$ median 9.1 |
| Moolgavkar (2000b)<br>Moolgavkar (2003)<br>Cook Co., IL<br>(> 65 years) | strict GAM 100df<br>GLM NS100df | 4.05 (2.9-5.2)<br>4.25 (3.0-5.5) | — | — | $PM_{10}$ median 35 (3, 365) |
| Moolgavkar (2000b)<br>Moolgavkar (2003)<br>Los Angeles, CA<br>(> 65 years) | GAM30df<br>GAM100df<br>GLM NS100df | 3.35 (1.2-5.5)<br>2.7 (0.6-4.8)<br>2.75 (0.1-5.4) | 3.95 (2.2-5.7)<br>2.9 (1.2-4.6)<br>3.15 (1.1-5.2) | — | $PM_{10}$ median 44 (7, 166)<br>$PM_{2.5}$ median 22 (4, 86) |
| Morris and Naumova (1998)<br>Chicago, IL (> 65 years) | GAM not used | 3.92 (1.02, 6.90) | — | — | $PM_{10}$ 41 (6, 117) |
| Stieb et al. (2000)<br>St. John, CAN (all ages) | GAM not used | 32.5 (10.2, 59.3) | 15.11 (−0.25, 32.8) | — | Summer 93<br>$PM_{10}$ 14.0 (max 70.3)<br>$PM_{2.5}$ 8.5 (max 53.2) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Total Cardiovascular Hospital Admissions:** (cont'd) | | | | | |
| Burnett et al. (1997)<br>Toronto, CAN (all ages) | GAM not used | 12.07 (1.43, 23.81) | 7.18 (−0.61, 15.60) | 20.46 (8.24, 34.06) | $PM_{10}$ 28.4 (4, 102)<br>$PM_{2.5}$ 16.8 (1, 66)<br>$PM_{10-2.5}$ 11.6 (1, 56) |
| **Ischemic Heart Disease Hospital Admissions:** | | | | | |
| Schwartz and Morris (1995)<br>Detroit (> 65 years) | GAM not used | 2.8 (0.7, 5.0) | — | — | $PM_{10}$ (98 (22, 82)<br>(10%, 90%) |
| Lippmann et al. (2000)<br>Detroit, MI (> 65 years)<br>Ito 2003 | Strict GAM<br>GLM NS | 8.0 (−0.3-17.1)<br>6.2 (−2.0-15.0) | 3.65% (−2.05-9.7)<br>3.0% (−2.7-9.0) | 10.2% (2.4-18.6)<br>8.1% (0.4-16.4) | $PM_{10}$ 31 (max 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50) |
| Metzger et al. (2004)<br>Atlanta, GA<br>Period 1 (1993 - 2000)<br>Period 2 (1998 - 2000) | GAM not used | 2.8 (−1.9, 7.7) | 5.8 (−4.1, 16.9) | −1.5 (−13.0, 11.6) | $PM_{10}$ median 26.3<br>$PM_{2.5}$ median 17.8<br>$PM_{10-2.5}$ median 9.1 |
| **Dysrhythmias Hospital Admissions:** | | | | | |
| Lippmann et al. (2000)<br>Detroit, MI (> 65 years)<br>Ito (2003) | Strict GAM<br>GLM NS | 2.8 (−10.9-18.7)<br>2.0 (−11.7-17.7) | 3.2 (−6.6-14.0)<br>2.6 (−7.1-13.3) | 0.1% (−12.4-14.4)<br>0.0% (−12.5-14.3) | $PM_{10}$ 31 (max 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50) |
| Metzger et al. (2004)<br>Atlanta, GA<br>Period 1 (1993 - 2000)<br>Period 2 (1998 - 2000) | GAM not used | 2.0 (−2.9, 7.2) | 3.8 (−5.8, 14.4) | 5.3 (−6.3, 18.5) | $PM_{10}$ median 26.3<br>$PM_{2.5}$ median 17.8<br>$PM_{10-2.5}$ median 9.1 |
| **Heart Failure Hospital Admissions:** | | | | | |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 2.02 (−0.94, 5.06) | — | — | $PM_{10}$ 45.5 (5, 132) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 µg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 µg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 µg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Heart Failure Hospital Admissions:** (cont'd) | | | | | |
| Lippmann et al. (2000) | Strict GAM | 9.2 (−0.3-19.6) | 8.0 (1.4-15.0) | 4.4% (−4.0-13.5) | $PM_{10}$ 31 (max 105) |
| Ito (2003) | GLM NS | 8.4 (−1.0-18.7) | 6.8 (0.3-13.8) | 4.9% (−3.55-14.1) | $PM_{2.5}$ 18 (6, 86) |
| Detroit, MI (> 65 years) | | | | | $PM_{10-2.5}$ 13 (4, 50) |
| Metzger et al. (2004) | GAM not used | | | | |
| Atlanta, GA | | | | | |
| Period 1 (1993 - 2000) | | 2.0 (7.7, 4.1) | | | $PM_{10}$ median 26.3 |
| Period 2 (1998 - 2000) | | | 14.3 (1.7, 28.6) | 5.1 (−8.7, 21.0) | $PM_{2.5}$ median 17.8 |
| | | | | | $PM_{10-2.5}$ median 9.1 |
| Schwartz and Morris (1995) | GAM not used | 5.0 (1.9, 8.3) | | | |
| Detroit (> 65 years) | | | | | |
| **Myocardial Infarction Hospital Admissions:** | | | | | |
| Linn et al. (2000) | GAM not used | 3.04 (0.06, 6.12) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Los Angeles, CA (> 29 years) | | | | | |
| **Cardiac arrhythmia Hospital Admissions:** | | | | | |
| Linn et al. (2000) | GAM not used | 1.01 (−1.93, 4.02) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Los Angeles, CA (> 29 years) | | | | | |
| **Cerebrovascular Hospital Admissions:** | | | | | |
| Linn et al. (2000) | GAM not used | 0.30 (−2.13, 2.79) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Los Angeles, CA (> 29 years) | | | | | |
| Metzger et al. (2004) | GAM not used | 5.1 (−0.4, 10.9) | 13.0 (2.1, 25.0) | 5.6 (−6.8, 19.6) | $PM_{10}$ median 26.3 |
| Atlanta, GA | | | | | $PM_{2.5}$ median 17.8 |
| | | | | | $PM_{10-2.5}$ median 9.1 |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **RESPIRATORY MORBIDITY** | | | | | |
| **Stroke Hospital Admissions:** | | | | | |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 6.72 (3.64, 9.90) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Lippmann et al. (2000)<br>Ito (2003)<br>Detroit, MI (> 65 years) | GLM NS | 4.4 (−5.8, 15.7) | 1.0 (−6.1, 8.5) | 5.6 (−4.0, 16.2) | $PM_{10}$ 31 (max 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50) |
| **Total Respiratory Hospital Admissions or Medical Visits:** | | | | | |
| Thurston et al. (1994)<br>Toronto, Canada | GAM not used | 23.26 (2.03, 44.49) | 15.00 (1.97, 28.03) | 22.25 (−9.53, 54.03) | $PM_{10}$ 29.5-38.8 (max 96.0)<br>$PM_{2.5}$ 15.8-22.3 (max 66.0)<br>$PM_{10-2.5}$ 12.7-16.5 (max 33.0) |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 2.89 (1.09, 4.72) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Schwartz et al. (1996)<br>Cleveland, OH<br>(> 65 years) | GAM not used | 5.8 (0.5, 11.4) | — | — | $PM_{10}$ 43 |
| Lumley and Heagerty (1999)<br>King County, WA<br>(all ages) | GAM not used | — | 5.91 (1.10, 10.97) | — | $PM_1$ NR |
| Burnett et al. (1997)<br>Toronto, CAN (all ages) | GAM not used | 10.93 (4.53, 17.72) | 8.61 (3.39, 14.08) | 12.71 (5.33, 20.74) | $PM_{10}$ 28.1 (4, 102)<br>$PM_{2.5}$ 16.8 (1, 66)<br>$PM_{10-2.5}$ 11.6 (1, 56) |
| Delfino et al. (1997)<br>Montreal, CAN<br>(> 64 years) | GAM not used | 36.62 (10.02, 63.21) | 23.88 (4.94, 42.83) | — | summer 93<br>$PM_{10}$ 21.7 (max 51)<br>$PM_{2.5}$ 12.2 (max 31) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Total Respiratory Hospital Admissions:** (cont'd) | | | | | |
| Delfino et al. (1998)<br>Montreal, CAN<br>(> 64 years) | GAM not used | — | 13.17 (−0.22, 26.57) | — | $PM_{2.5}$ 18.6 (SD 9.3) |
| Stieb et al. (2000)<br>St. John, CAN (all ages) | GAM not used | 8.8 (1.8, 16.4) | 5.69 (0.61, 11.03) | — | summer 93<br>$PM_{10}$14.0 (max 70.3)<br>$PM_{2.5}$ 8.5 (max 53.2) |
| **Pneumonia Hospital Admissions:** | | | | | |
| Schwartz, 1995<br>Detroit (> 65 years) | GAM not used | 5.9 (1.9, 10.0) | — | — | $PM_{10}$ 48 (22, 82)<br>mean (10%, 90%) |
| Samet et al. (2000a,b)<br>14 U.S. Cities<br>(> 65 years)<br>Zanobetti and Schwartz (2003) | Strict GAM<br>GLM NS<br>GLM PS<br>(dist. lag) | 8.8 (5.9, 11.8)<br>2.9 (0.2, 5.6)<br>6.3 (2.5, 10.3)<br>4.1 (0.7, 7.5) | — | — | $PM_{10}$ means 24.4-45.3 |
| Lippmann et al. (2000)<br>Detroit, MI (> 65 years)<br>Ito (2003) | Strict GAM<br>GLM NS | 18.1 (5.3, 32.5)<br>18.6 (5.6, 33.1) | 10.5 (1.8, 19.8)<br>10.1 (1.5, 19.5) | 9.9 (−0.1, 22.0)<br>11.2 (−0.02, 23.6) | $PM_{10}$ 31 (max 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50) |
| **COPD Hospital Admissions:** | | | | | |
| Schwartz, 1995<br>Detroit (> 65 years) | GAM not used | 10.6 (4.4, 17.2) | — | — | $PM_{10}$ 48 (22, 82)<br>mean (10, 90) |
| Samet et al. (2000a,b)<br>14 U.S. Cities<br>(> 65 years)<br>Zanobetti and Schwartz (2003) | Strict GAM<br>GLM NS<br>GLM PS<br>(dist. lag) | 8.8 (4.8, 13.0)<br>6.8 (2.8, 10.8)<br>8.0 (4.3, 11.9)<br>13.4 (6.2, 21.0) | — | — | $PM_{10}$ means 24.4-45.3 |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 1.5 (−0.5, 3.5) | — | — | $PM_{10}$ 45.5 (5, 132) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **COPD Hospital Admissions:** (cont'd) | | | | | |
| Tolbert et al. (2000a)<br>Atlanta, GA (all ages) | GAM not used | −3.5 (33.0, −29.9) | 12.44 (−7.89, 37.24) | −23.03 (−50.69, 20.15) | $PM_{10}$ 29.1 (SD 12.0)<br>$PM_{2.5}$ 19.4 (SD 9.35)<br>$PM_{10-2.5}$ 9.39 (SD 4.52) |
| Lippmann et al. (2000)<br>Detroit, MI (> 65 years)<br>Ito (2003) | Strict GAM<br>GLM NS | 6.5 (−7.8, 23.0)<br>4.6 (−9.4, 20.8) | 3.0(−6.9, 13.9)<br>0.3(−9.3, 10.9) | 8.7 (−4.8, 24.0)<br>10.8 (−3.1, 26.5) | $PM_{10}$ 31 (max 105)<br>$PM_{2.5}$ 18 (6, 86)<br>$PM_{10-2.5}$ 13 (4, 50) |
| Moolgavkar (2000c)<br>Cook Co., IL<br>(> 65 years)<br>Moolgavkar 2003 | Strict GAM 100df | 3.24 (.031, 6.24) | — | — | $PM_{10}$ median 35 (3, 365) |
| Moolgavkar (2000c)<br>Los Angeles, CA<br>(> 65 years)<br>Moolgavkar 2003 | Strict GAM: 100df<br>GLM NS: 100df | 5.52 (2.53-8.59)<br>5.00 (1.22, 8.91) | 2.87 (0.53, 5.27)<br>2.59 (−0.29, 5.56) | | $PM_{10}$ median 44 (7, 166)<br>$PM_{2.5}$ median 22 (4.86) |
| **Asthma Hospital Admissions or Medical Visits:** | | | | | |
| Choudbury et al. (1997)<br>Anchorage, AK<br>Medical Visits (all ages) | GAM not used | 20.9 (11.8, 30.8) | — | — | $PM_{10}$ 42.5 (1, 565) |
| Jacobs et al. (1997)<br>Butte County, CA<br>(all ages) | GAM not used | 6.11 (p > 0.05) | — | — | $PM_{10}$ 34.3 (6.6, 636) |
| Linn et al. (2000)<br>Los Angeles, CA<br>(> 29 years) | GAM not used | 1.5 (−2.4, 5.6) | — | — | $PM_{10}$ 45.5 (5, 132) |
| Lipsett et al. (1997)<br>Santa Clara Co., CA<br>(all ages) | GAM not used | 34.7 (16, 56.5)<br>(min. temp. 20° F)<br>9.1 (2.7, 15.9)<br>(min. temp. 40° F) | — | — | $PM_{10}$ 61.2 (9, 165) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Asthma Hospital Admissions or Medical Visits:** (cont'd) | | | | | |
| Nauenberg and Basu (1999)<br>Los Angeles, CA<br>(all ages) | GAM not used | 20.0 (5.3, 35) | — | — | 44.8 (SE 17.23) |
| Tolbert et al. (2000b)<br>Atlanta, GA (< 17 years) | GAM not used | 13.2 (1.2, 26.7) | — | — | $PM_{10}$ 38.9 (9, 105) |
| Tolbert et al. (2000a)<br>Atlanta, GA (all ages) | GAM not used | 18.8 (−8.7, 54.4) | 2.3 (−14.8, 22.7) | 21.1 (−18.2, 79.3) | $PM_{10}$ 29.1 (SD 12.0)<br>$PM_{2.5}$ 19.4 (SD 9.35)<br>$PM_{10-2.5}$ 9.39 (SD 4.52) |
| Sheppard et al. (1999)<br>Seattle, WA (< 65 years) | Strict GAM<br>GLM NS | 10.9 (2.8, 19.6)<br>8.1 (0.1, 16.7) | 8.7 (3.2, 14.4)<br>6.5 (1.1,12.0) | 5.5 (0, 14.0)<br>5.5 (−2.7, 11.1) | $PM_{10}$ 31.5 (90% 55)<br>$PM_{2.5}$ 16.7 (90% 32)<br>$PM_{10-2.5}$ 16.2 (90% 29) |
| **Respiratory Symptoms** | | Odds Ratio (95% CI) for 50 ug/m$^3$ increase in $PM_{10}$ | Odds Ratio (95% CI) for 25 ug/m$^3$ increase in $PM_{2.5}$ | Odds Ratio (95% CI) for 25 ug/m$^3$ increase in $PM_{10-2.5}$ | $PM_{10-2.5}$ Mean (Range) Levels Reported** |
| Schwartz et al. (1994)<br>6 U.S. cities<br>(children, cough) | GAM not used | 1.39 (1.05, 1.85) | 1.24 (1.00, 1.54) | — | $PM_{10}$ median 30.0 (max 117)<br>$PM_{2.5}$ median 18.0 (max 86) |
| Schwartz et al. (1994)<br>6 U.S. cities<br>(children, lower respiratory symptoms) | GAM not used | 2.03 (1.36, 3.04) | 1.58 (1.18, 2.10) | — | $PM_{10}$ median 30.0 (max 117)<br>$PM_{2.5}$ median 18.0 (max 86) |
| Neas et al. (1995)<br>Uniontown, PA<br>(children, cough) | GAM not used | — | 2.45 (1.29, 4.64) | — | $PM_{2.5}$ 24.5 (max 88.1) |
| Ostro et al. (1991)<br>Denver, CO<br>(adults, cough) | GAM not used | 1.09 (0.57, 2.10) | — | — | $PM_{10}$ 22 (0.5, 73) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study* Reanalysis study Study location | Analysis Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Respiratory Symptoms** (cont'd) | | | | | |
| Pope et al. (1991) Utah Valley, UT (lower respiratory symptoms, schoolchildren) | GAM not used | 1.28 (1.06, 1.56) | — | — | $PM_{10}$ 44 (11, 195) |
| Pope et al. (1991) Utah Valley, UT (lower respiratory symptoms, asthmatic patients) | GAM not used | 1.01 (0.81, 1.27) | — | — | $PM_{10}$ 44 (11, 195) |
| Neas et al. (1996) State College, PA (children, cough) | GAM not used | NR | 1.48 (1.17, 1.88) (1-d) | — | $PM_{10}$ 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8) |
| Neas et al. (1996) State College, PA (children, wheeze) | GAM not used | NR | 1.59 (0.93, 2.70) (1-d) | — | $PM_{10}$ 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8) |
| Neas et al. (1996) State College, PA (children, cold) | GAM not used | NR | 1.61 (1.21, 2.17) (0-d) | — | $PM_{10}$ 31.9 (max 82.7) $PM_{2.1}$ 23.5 (max 85.8) |
| Ostro et al. (1995) Los Angeles, CA (children, asthma episode) | GAM not used | 1.05 (0.64, 1.73) | — | — | $PM_{10}$ 55.87 (19.63, 101.42) |
| Ostro et al. (1995) Los Angeles, CA (children, shortness of breath) | GAM not used | 1.51 (1.04, 2.17) | — | — | $PM_{10}$ 55.87 (19.63, 101.42) |
| Schwartz and Neas (2000) Six Cities reanalysis (children, cough) | GAM not used | — | 1.28 (0.98, 1.67) | 1.77 (1.23, 2.54) | $PM_{2.5}$ (same as Six Cities) $PM_{10-2.5}$ NR |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Respiratory Symptoms** (cont'd) | | | | | |
| Schwartz and Neas (2000)<br>Six Cities reanalysis<br>(children, lower respiratory symptoms) | GAM not used | — | 1.61 (1.20, 2.16) | 1.51 (0.66, 3.43) | $PM_{2.5}$ (same as Six Cities)<br>$PM_{10-2.5}$ NR |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, cough) | GAM not used | 1.40 (1.14, 1.73) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, phlegm) | GAM not used | 1.40 (1.03, 1.90) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, nose symptoms) | GAM not used | 1.22 (1.00, 1.47) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, sore throat) | GAM not used | 1.34 (1.06, 1.69) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, wheeze) | GAM not used | 1.16 (0.82, 1.63) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, chest tightness) | GAM not used | 1.34 (0.86, 2.09) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| Vedal et al. (1998)<br>Port Alberni, CAN<br>(children, dyspnea) | GAM not used | 1.05 (0.74, 1.49) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study* Reanalysis study Study location | Analysis Comments** | % increase (95% CI) per 50 μg/m³ $PM_{10}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{2.5}$ Increase | % increase (95% CI) per 25 μg/m³ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Respiratory Symptoms** (cont'd) | | | | | |
| Vedal et al. (1998) Port Alberni, CAN (children, any symptom) | GAM not used | 1.16 (1.00, 1.34) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |
| **Lung Function Changes** | | Lung Function change (L/min) (95% CI) for 50 ug/m³ increase in $PM_{10}$ | Lung Function change (L/min) (95% CI) for 25 ug/m³ increase in $PM_{2.5}$ | Lung Function change (L/min) (95% CI) for 25 ug/m³ increase in $PM_{10-2.5}$ | $PM_{10-2.5}$ Mean (Range) Levels Reported** |
| Neas et al. (1995) Uniontown, PA (children) | GAM not used | — | −2.58 (−5.33, +0.35) | — | $PM_{2.5}$ 24.5 (max 88.1) |
| Thurston et al. (1997) Connecticut summer camp (children) | GAM not used | — | PEFR −5.4 (−12.3, 1.5) (15 μg/m³ $SO_4^=$) | — | $SO_4^=$ 7.0 (1.1, 26.7) |
| Naeher et al. (1999) Southwest VA (adult women) | GAM not used | am PEFR −3.65 (−6.79, −0.51) pm PEFR −1.8 (−5.03, 1.43) | am PEFR −1.83 (−3.44, −0.21) pm PEFR −1.05 (−2.77, 0.67) | am PEFR −6.33 (−12.50, −0.15) pm PEFR −2.4 (−8.48, 3.68) | $PM_{10}$ 27.07 (4.89, 69.07) $PM_{2.5}$ 21.62 (3.48, 59.65) $PM_{10-2.5}$ 5.72 (0.00, 19.78) |
| Neas et al. (1996) State College, PA (children) | GAM not used | — | pm PEFR −0.64 (−1.73, 0.44) | — | $PM_{2.5}$ 23.5 (max 85.8) |
| Neas et al. (1999) Philadelphia, PA (children) | GAM not used | am PEFR −8.17 (−14.81, −1.56) pm PEFR −1.44 (−7.33, 4.44) | am PEFR −3.29 (−6.64, 0.07) pm PEFR −0.91 (−4.04, 2.21) | am PEFR −4.31 (−11.44, 2.75) pm PEFR 1.88 (−4.75, 8.44) | $PM_{2.5}$ 22.2 (IQR 16.2) $PM_{10-2.5}$ 9.5 (IQR 5.1) |
| Schwartz and Neas (2000) Uniontown, PA (reanalysis) (children) | GAM not used | — | pm PEFR −1.52, (−2.80, −0.24) | pm PEFR +1.73 (−2.2, 5.67) | $PM_{2.5}$ 24.5 (max 88.1) $PM_{10-2.5}$ NR |

## TABLE 9A-2 (cont'd). CARDIOVASCULAR AND RESPIRATORY-RELATED MORBIDITY EFFECT SIZE ESTIMATES PER INCREMENT IN 24-h CONCENTRATIONS OF $PM_{10}$, $PM_{2.5}$, AND $PM_{10-2.5}$ IN U.S. AND CANADIAN STUDIES

| Original study*<br>Reanalysis study<br>Study location | Analysis<br>Comments** | % increase (95% CI) per 50 µg/m$^3$ $PM_{10}$ Increase | % increase (95% CI) per 25 µg/m$^3$ $PM_{2.5}$ Increase | % increase (95% CI) per 25 µg/m$^3$ $PM_{10-2.5}$ Increase | $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ Mean (Range) Levels Reported*** |
|---|---|---|---|---|---|
| **Lung Function Changes (cont'd)** | | Lung Function change (L/min) (95% CI) for 50 ug/m$^3$ increase in $PM_{10}$ | Lung Function change (L/min) (95% CI) for 25 ug/m$^3$ increase in $PM_{2.5}$ | Lung Function change (L/min) (95% CI) for 25 ug/m$^3$ increase in $PM_{10-2.5}$ | $PM_{10-2.5}$ Mean (Range) Levels Reported** |
| Schwartz and Neas (2000) State College PA (reanalysis) (children) | GAM not used | — | pm PEFR −0.93 (−1.88, 0.01) | pm PEFR −0.28 (−3.45, 2.87) | $PM_{2.5}$ 23.5 (max 85.8) $PM_{10-2.5}$ NR |
| Vedal et al. (1998) Port Alberni, CAN (children) | GAM not used | PEF −1.35 (−2.7, −0.05) | — | — | $PM_{10}$ median 22.1 (0.2, 159.0) (north site) |

*Both original published studies and recent reanalyses reported in HEI (2003) Special Report for many cited here. Original studies published before 1996 and Schwartz et al. (1996) were assessed in 1996 PM AQCD.

**Where GAM not used in original analysis cited, original results reported here. Otherwise reanalyses results reported here if GAM (default) used in original analysis. GAM strict = GAM with stringent criteria. GLM = general linear model; NS = natural splines; BS = B splines; PS = penalized splines.

***Mean (minimum, maximum) 24-h PM level in parentheses unless otherwise noted.

## TABLE 9-A3. EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

| Type of Health Effect Study and Location | Indicator (PM Increment) | Change in Health Indicator per Increment in PM | Range of City PM Levels ** Means ($\mu g/m^3$) |
|---|---|---|---|
| **Increased Total Mortality in Adults** | | **Relative Risk (95% CI)** | |
| Six City[A] | $PM_{15/10}$ (20 $\mu g/m^3$) | 1.18 (1.06-1.32) | 18-47 |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.13 (1.04-1.23) | 11-30 |
| | $SO_4^=$ (15 $\mu g/m^3$) | 1.46 (1.16-2.16) | 38119 |
| Six City Reanalysis[C] | $PM_{15/10}$ (20 $\mu g/m^3$) | 1.19 (1.06-1.34) | 18.2-46.5 |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.14 (1.05-1.23) | 11.0-29.6 |
| ACS Study[B] (151 U.S. SMSA) | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.07 (1.04-1.10) | 9-34 |
| | $SO_4^=$ (15 $\mu g/m^3$) | 1.10 (1.06-1.16) | 4-24 |
| ACS Study Reanalysis[C] | $PM_{15/10}$ (20 $\mu g/m^3$) (dichot) | 1.04 (1.01, 1.07) | 58.7 (34-101) |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.07 (1.04-1.10) | 9.0-33.4 |
| | $PM_{15-2.5}$ (10$\mu g/m^3$) | 1.00 (0.99, 1.02) | 9-42 |
| ACS Study Extended Analyses[D] | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.04 (1.01-1.08) | 21.1 (SD=4.6) |
| Southern California[E] | $PM_{10}$ (20 $\mu g/m^3$) | 1.091 (0.985-1.212; males) | 51 (±17) |
| | $PM_{10}$ (cutoff = 30 days/year > 100 $\mu g/m^3$) | 1.082 (1.008-1.162; males) | |
| | $PM_{10}$ (20 $\mu g/m^3$) | 0.950 (0.873-1.033; females) | 51 (±17) |
| | $PM_{10}$ (cutoff = 30 days/year > 100 $\mu g/m^3$) | 0.958 (0.899-1.021; females) | |
| Southern California[F] | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.09 (0.98, 1.21) (males) | 32 (17, 45) |
| | $PM_{10-2.5}$ (10 $\mu g/m^3$) | 1.05 (0.92, 1.21) (males) | 27 (4, 44) |
| Veterans Cohort[G] | $PM_{2.5}$ (10 $\mu g/m^3$) (mortality period 1976-96) | 1.003 (NS) **** | 5.6-42.3 |
| | $PM_{2.5}$ (10 $\mu g/m^3$) (mortality period 1982-88) | 0.90 (SS) **** | 5.6-42.3 |
| | $PM_{15-2.5}$ (10 $\mu g/m^3$) (mortality period 1976-96) | 1.007 (NS)**** | 3.6-64.2 |
| | $PM_{15-2.5}$ (10 $\mu g/m^3$) (mortality period 1982-88) | 0.98 (NS)**** | 3.6-64.3 |
| | $PM_{15}$ (10 $\mu g/m^3$) (mortality period 1976-96) | 1.007 (NS)**** | 9.74-101.7 |
| | $PM_{15}$ (10 $\mu g/m^3$) (mortality period 1982-88) | 0.92 (NS)**** | 9.74-101.7 |

## TABLE 9A-3 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

| Type of Health Effect Study and Location | Indicator (PM Increment) | Change in Health Indicator per Increment in PM | Range of City PM Levels ** Means ($\mu g/m^3$) |
|---|---|---|---|
| **Increased Cardiopulmonary Mortality in Adults** | | **Relative Risk (95% CI)** | |
| Six City[A] | $PM_{15/10}$ (20 $\mu g/m^3$) | *** | 18-47 |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.18 (1.06, 1.32) | 37954 |
| Six City Reanalysis[C] | $PM_{15/10}$ (20 $\mu g/m^3$) | 1.20 (1.29, 1.41) | 18.2-46.5 |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.19 (1.07, 1.33) | 11.0-29.6 |
| ACS Study[B] (151 U.S. SMSA) | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.12 (1.07-1.17) | 9-34 |
| ACS Study Reanalysis[C] | $PM_{15/10}$ (20 $\mu g/m^3$) (dichot) | 1.07 (1.03, 1.12) | 58.7 (34-101) |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.12 (1.07-1.17) | 9.0-33.4 |
| | $PM_{15-2.5}$ (10 $\mu g/m^3$) | 1.00 (0.98, 1.03) | 9-42 |
| | $PM_{10}$ (20 $\mu g/m^3$) | 1.01 (0.92, 1.10) | 51 (±17) |
| ACS Study Extended Analyses[D] | $PM_{2.5}$ (10 $\mu g/m^3$) (1979-83) | 1.06 ( 1.02, 1.10) | 21 (10, 30)*** |
| | $PM_{2.5}$ (10 $\mu g/m^3$) (1999-00) | 1.08 (1.02, 1.14) | 14 (5, 20)(*** |
| | $PM_{2.5}$ (10 $\mu g/m^3$) (average) | 1.09 (1.03, 1.16) | 18 (±4) |
| Southern California[E] | $PM_{10}$ (20 $\mu g/m^3$) | 1.01 (0.92, 1.10) | 51 (0, 84) |
| Southern California[F] | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.23 (0.97, 1.55) (males) | 32 (17, 45) |
| | $PM_{10-2.5}$ (10 $\mu g/m^3$) | 1.20 (0.87, 1.64) (males) | 27 (4, 44) |
| **Increased Lung Cancer Mortality in Adults** | | | |
| Six City[A] | $PM_{15/10}$ (20 $\mu g/m^3$) | **** | NR (18, 47) |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.18 (0.89, 1.57) | NR (11, 30) |
| Six City Reanalysis[C] | $PM_{15/10}$ (20 $\mu g/m^3$) | 1.14 (0.75, 1.74) | NR (18, 47) |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.21 (0.92, 1.60) | NR (11, 30) |
| ACS Study[B] | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.01 (0.91, 1.12) | 18** (9, 34) |
| ACS Study Reanalysis[C] | $PM_{15/10}$ (10 $\mu g/m^3$) (dichot) | 1.01 (0.91, 1.11) | 59 (34, 101) |
| | $PM_{2.5}$ (10 $\mu g/m^3$) | 1.01 (0.91, 1.11) | 20 (10, 38) |
| | $PM_{15-2.5}$ (10 $\mu g/m^3$) | 0.99 (0.93, 1.05) | 7.1 (9, 42) |
| ACS Study Extended Analyses[D] | $PM_{2.5}$ (10 $\mu g/m^3$) (1979-83) | 1.08 (1.01, 1.16) | 21 (10, 30)*** |
| | $PM_{2.5}$ (10 $\mu g/m^3$) (1999-00) | 1.13 (1.04, 1.22) | 14 (5, 20)*** |
| | $PM_{2.5}$ (average) | 1.14 (1.05, 1.24) | 18 (±4) |
| Southern California[E] | $PM_{10}$ (20$\mu g/m^3$) | 1.81 (1.14, 2.86) (males) | 51 (0, 84) |
| Southern California[F] | $PM_{2.5}$(10 $\mu g/m^3$) | 1.39 (0.79, 2.50) (males) | 32 (17, 45) |
| | | 1.26 (0.62, 2.55) (males) | 27 (4, 44) |

**TABLE 9A-3 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES**

| Type of Health Effect Study and Location | Indicator (PM Increment) | Change in Health Indicator per Increment in PM | Range of City PM Levels ** Means ($\mu g/m^3$) |
|---|---|---|---|
| **Increased Bronchitis in Children** | | **Odds Ratio (95% CI)** | |
| Six City[H] | $PM_{15/10}$ (50 $\mu g/m^3$) | 3.26 (1.13, 10.28) | 20-59 |
| 24 City[I] | $SO_4^=$ (15 $\mu g/m^3$) | 3.02 (1.28, 7.03) | 18.1-67.3 |
| 24 City[I] | $PM_{2.1}$ (10 $\mu g/m^3$) | 1.31 (0.94, 1.84) | 9.1-17.3 |
| 24 City[I] | $PM_{10}$ (20 $\mu g/m^3$) | 1.60 (0.92, 2.78) | 22.0-28.6 |
| Southern California[J] | $SO_4^=$ (15 $\mu g/m^3$) | 1.39 (0.99, 1.92) | — |
| 12 Southern California communities[K] (all children) | $PM_{10}$ (20 $\mu g/m^3$) | 0.95 (0.79, 1.15) | 28.0-84.9 |
| 12 Southern California communities[L] (children with asthma) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$) | 1.4 (1.1, 1.8)<br>1.3 (0.9, 1.7) | 13.0-70.7<br>6.7-31.5 |
| **Increased Cough in Children** | | **Odds Ratio (95% CI)** | |
| 12 Southern California communities[K] (all children) | $PM_{10}$ (20 $\mu g/m^3$) | 1.05 (0.94, 1.16) | 28.0-84.9 |
| 12 Southern California communities[L] (children with asthma) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$) | 1.1 (0.7, 1.8)<br>1.2 (0.8, 1.8) | 13.0-70.7<br>6.7-31.5 |
| **Increased Airway Obstruction in Adults** | | **Odds Ratio (95% CI)** | |
| Southern California[M] | $PM_{10}$ (20 $\mu g/m^3$) | 1.19 (0.84, 1.68) | NR |
| **Decreased Lung Function in Children** | | **Odds Ratio (95% CI)** | |
| Six City[H] | $PM_{15/10}$ (50 $\mu g/m^3$) | NS Changes | 20-59 |
| 24 City[N] | $PM_{2.1}$ (10 $\mu g/m^3$) | −2.15% (−3.34, −0.95) FVC | 18.1-67.3 |
| 24 City[N] | $SO_4^=$ (7 $\mu g/m^3$) | −3.06% (−4.50, −1.60) FVC | 9.1-17.3 |
| 24 City[N] | $PM_{10}$ (20 $\mu g/m^3$) | −2.80% (−4.97, −0.59) FVC | 22.0-28.6 |
| 12 Southern California communities[O] (all children) | $PM_{10}$ (20 $\mu g/m^3$) | −19.9 (−37.8, −2.6) FVC | 28.0-84.9 |

**TABLE 9A-3 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES**

| Type of Health Effect Study and Location | Indicator (PM Increment) | Change in Health Indicator per Increment in PM | Range of City PM Levels ** Means ($\mu g/m^3$) |
|---|---|---|---|
| **Decreased Lung Function in Children** (cont'd) | | **Odds Ratio (95% CI)** | |
| 12 Southern California communities[O] (all children) | $PM_{10}$ (20 $\mu g/m^3$) | −25.6 (−47.1, −5.1) MMEF | 28.0-84.9 |
| 12 Southern California communities[P] ($4^{th}$ grade cohort) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$)<br>$PM_{10-2.5}$ (10 $\mu g/m^3$) | −0.23 (−0.44, −0.01) FVC % growth<br>−0.18 (−0.36, 0.0) FVC % growth<br>−0.22 (−0.47, 0.02) FVC % growth | NR |
| 12 Southern California communities[P] ($4^{th}$ grade cohort) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$)<br>$PM_{10-2.5}$ (10 $\mu g/m^3$) | −0.51 (−0.94, −0.08) MMEF % growth<br>−0.4 (−0.75, −0.04) MMEF % growth<br>−0.54 (−1.0, −0.06) MMEF % growth | NR |
| 12 Southern California communities[Q] (second $4^{th}$ grade cohort) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$) | −0.23 (−0.46, −0.0) FVC % growth<br>−0.19 (−0.39, 0.01) FVC % growth | NR |
| 12 Southern California communities[Q] (second $4^{th}$ grade cohort) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$) | −0.55 (−1.0, −0.08) MMEF % growth<br>−0.42 (−0.85, 0.01) MMEF % growth | NR |
| 12 Southern California communities[Q] (second $4^{th}$ grade cohort) | $PM_{10}$ (20 $\mu g/m^3$)<br>$PM_{2.5}$ (10 $\mu g/m^3$) | −0.49 (−0.84, −0.14) PEFR % growth<br>−0.37 (−0.70, −0.04) PEFR % growth | NR |
| Southern California[R] | $PM_{10}$ (20 $\mu g/m^3$) | −3.6 (−18, 11) FVC growth | 15.0-66.2 |
| Southern California[R] | $PM_{10}$ (20 $\mu g/m^3$) | −33 (−64, −2.2) MMEF growth | 15.0-66.2 |
| Southern California[R] | $PM_{10}$ (20 $\mu g/m^3$) | −70 (−120, −20) PEFR growth | 15.0-66.2 |

**TABLE 9A-3 (cont'd). EFFECT ESTIMATES PER INCREMENTS* IN LONG-TERM MEAN LEVELS OF FINE AND COARSE FRACTION PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES**

| Type of Health Effect Study and Location | Indicator (PM Increment) | Change in Health Indicator per Increment in PM | Range of City PM Levels ** Means ($\mu g/m^3$) |
|---|---|---|---|
| **Lung Function Changes in Adults** | | | |
| Southern California[S] (% predicted $FEV_1$, females) | $PM_{10}$ (cutoff of 54.2 days/year > 100 $\mu g/m^3$) | +0.9 % (−0.8, 2.5) $FEV_1$ | 52.7 (21.3, 80.6) |
| Southern California[S] (% predicted $FEV_1$, males) | $PM_{10}$ (cutoff of 54.2 days/year > 100 $\mu g/m^3$) | +0.3 % (−2.2, 2.8) $FEV_1$ | 54.1 (20.0, 80.6) |
| Southern California[S] (% predicted $FEV_1$, males whose parents had asthma, bronchitis, emphysema) | $PM_{10}$ (cutoff of 54.2 days/year > 100 $\mu g/m^3$) | −7.2 % (−11.5, −2.7) $FEV_1$ | 54.1 (20.0, 80.6) |
| Southern California[S] (% predicted $FEV_1$, males) | $SO_4^=$ (1.6 $\mu g/m^3$) | −1.5 % (−2.9, −0.1) $FEV_1$ | 7.3 (2.0, 10.1) |

* Results calculated using PM increment between the high and low levels in cities, or other PM increments given in parentheses; NS Changes = No significant changes.

** Range of mean PM levels given unless, as indicated, studies reported overall study mean (min, max), or mean (±SD); NR=not reported.

*** Results only for smoking category subgroups.

**** NS = not significant. SS = statistically significant; as reported by the author.

**References:**


[A] Dockery et al. (1993)
[B] Pope et al. (1995)
[C] Krewski et al. (2000)
[D] Pope et al. (2002)
[E] Abbey et al. (1999)
[F] McDonnell et al. (2000)
[G] Lipfert et al. (2000b)
[H] Dockery et al. (1989)
[I] Dockery et al. (1996)
[J] Abbey et al. (1995a,b,c)
[K] Peters et al. (1999b)
[L] McConnell et al. (1999)
[M] Berglund et al. (1999)
[N] Raizenne et al. (1996)
[O] Peters et al. (1999a)
[P] Gauderman et al. (2000)
[Q] Gauderman et al. (2002)
[R] Avol et al. (2001)
[S] Abbey et al. (1998)