CHAPTER 9

INTEGRATIVE SYNTHESIS

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9. INTEGRATIVE SYNTHESIS

9.1 INTRODUCTION

This chapter integrates key information from the preceding chapters to provide coherent frameworks for assessment of human health and welfare risks posed by ambient particulate matter (PM) in the United States. Rather than simply resummarizing information from earlier chapters, the focus here is on integrating newly available scientific information with that available from the last review so as to address a set of issues central to EPA's assessment of scientific information upon which the PM NAAQS review is to be based.

In particular, this chapter provides an updated synthesis of the scientific information that is intended 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 selection of appropriate indicators, averaging times, forms, and levels for primary and secondary PM NAAQS in the United States. Ultimately, 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. As such, the PM Staff Paper serves to "bridge the gap" between scientific assessments 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 since the last PM NAAQS review, it also highlights important remaining uncertainties that remain and recognizes the value of continuing PM research efforts in a number of key areas. Although detailed delineation of research needs 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.

9.1.1 Chapter Organization

As part of this opening introduction, Section 9.1.2 first summarizes important information on U.S. PM air quality trends and current ambient concentrations, to provide the context for ensuing discussions of ambient PM characteristics, exposures, and effects.

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

Environmental Protection Agency, 1996). The Section 9.2 synthesis of PM-related health effects information is organized around five key issues: (1) consideration of fine and coarse thoracic particles as separate subclasses of PM pollution, taking into account atmospheric science, exposure, and dosimetric information; (2) assessment of strengths and limitations of the epidemiological evidence for associations between health effects and fine and coarse thoracic PM within the mix of ambient air pollutants; (3) integration of epidemiologic and experimental (e.g., dosimetric and toxicologic) evidence supporting judgments about the extent to which causal inferences can be made about observed associations between health endpoints and various indicators or constituents of ambient PM, acting alone and/or in combination with other pollutants; (4) characterization of susceptible and vulnerable subpopulations potentially at increased risk for PM-related health effects; and (5) discussion of potential public health impacts (including newly emerging evidence for adverse cardiovascular effects) of human exposures to ambient PM in the United States.

Building upon information presented in the 1996 PM AQCD where possible, Section 9.3 addresses the major PM-related welfare effects of importance for decision-making for secondary standards. This includes drawing upon 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, as well as consideration of new findings discussed in Chapter 4 of this document. Since PM-related effects on vegetation and ecosystems were not addressed in the 1996 PM AQCD, the present discussion is based entirely on findings characterized in Chapter 4 of this document.

9.1.2 Trends in United States PM Air Quality

PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ Concentrations and Trends

The nationwide average concentration of PM_{10} decreased from about 28 $\mu g/m^3$ to 24 $\mu g/m^3$ from 1992 through 2001 (U.S. Environmental Protection Agency, 2003). Most of this decrease occurred during the first half of that time period. There was considerable variability in the trends for various geographic subregions, with the largest decreases being found in the northwest (-9.6 $\mu g/m^3$) and the smallest in the south-central United States (-1.3 $\mu g/m^3$). These trends reflect the continuation of longer-term declines in U.S. PM concentrations. For example, Lipfert (1998) estimated that TSP concentrations may have declined by two- to three-fold in urban areas

between 1950 and 1980. Data for quantifying nationwide trends in $PM_{2.5}$ concentrations are not available over this period. However, it may be surmised that notable declines in $PM_{2.5}$ concentrations also likely occurred over the same period. The consistent reductions in PM_{10} concentrations found in a wide variety of environments may have resulted from common controls that affected $PM_{2.5}$ more strongly than $PM_{10-2.5}$ particles (Darlington et al., 1997). These considerations suggest that $PM_{10-2.5}$ concentrations likely decreased to a smaller extent over this period.

Annual mean $PM_{2.5}$ concentrations in the United States currently average about 13 $\mu g/m^3$, based on data collected from 1999 through 2001. Such fine particle concentrations can be less than a few $\mu g/m^3$ in many remote areas in the western United States and in many urban areas immediately after it has rained. However, 24-h $PM_{2.5}$ concentrations on individual days can also exceed 100 $\mu g/m^3$ at certain locations, especially if there are events such as wild fires or dust storms. These values indicate a high degree of spatial and temporal variability in $PM_{2.5}$ concentrations. $PM_{2.5}$ concentrations observed in a number of urban areas across the United States are characterized in Chapter 3; see Section 3.2 and Appendices 3A (for urban areas) and 3E (for relatively remote areas).

It should be noted that the mean $PM_{2.5}$ concentrations given above are considerably lower than those obtained and used in many air pollution-health outcome studies conducted during the 1980s. Lipfert (1998) has estimated that $PM_{2.5}$ concentrations decreased by about 4 to 5% per year from 1970 to 1990; some of that change may be attributable to use of different monitoring methods during earlier versus later years.

The Composition of $PM_{2.5}$ and $PM_{10-2.5}$ Particles

Data for $PM_{2.5}$, $PM_{10-2.5}$ and PM_{10} from earlier monitoring studies, spanning the time period from the late 1970s to the mid 1990s, were presented in Appendix 6A of the 1996 PM AQCD. The data from such studies were summarized in Appendix 6A as pie charts showing the gross composition of the three size fractions for the eastern, central, and western United States. The chemical composition of particles in the $PM_{2.5}$ size range, as determined most recently by the speciation network in 13 urban areas across the United States during 2001 to 2002 is summarized in Chapter 3.

As summarized in Chapter 3 (Section 3.2 and Appendix 3B), sulfate and organic carbon compounds constitute the major identified components of the aerosol in the eastern and central United States. In the western United States, organic compounds and nitrate and/or sulfate constitute the major identified aerosol components. Other important components are: elemental carbon, ammonium and crustal materials. Even though total organic compounds constitute 10 to 60% of $PM_{2.5}$, only about 10 to 20% of organic compounds in ambient samples can be quantified due to analytical limitations resulting largely from the polar nature of the organic compounds. Results of studies characterizing the composition of organic compounds in ambient particles are summarized in Appendix 3C. The attribution of organic carbon to primary or secondary sources is still under study in different regions of the country. Three mechanisms have been identified for the formation of secondary organic components in ambient PM: (1) condensation of oxidized end- products of photochemical reactions (e.g., ketones, aldehydes, organic acids, and hydroperoxides), (2) adsorption of semivolatile organic compounds (e.g., polycyclic aromatic compounds) onto existing particles, and (3) dissolution of soluble gases (e.g., aldehydes) that can undergo reactions in particle bound water (PBW). Primary biological particles (or bioaerosols) are also usually lumped into the broad category of organic compounds. In addition to soluble organic compounds, soluble oxidants (e.g., H_2O_2) can be taken up or formed in PBW, as discussed further below. As will be seen later, these considerations have implications for the delivery of these and other soluble components to lower respiratory tract regions.

Trace metals typically constitute a much smaller fraction of PM than the components given above. Typically, their average combined air concentrations constitute less than 1% of $PM_{2.5}$ levels (or on the order of 0.1 $\mu g/m^3$ or less), as shown in Appendix 3B. There are exceptions to this general pattern in industrial cities (e.g., St. Louis, MO), where metals can constitute closer to 2% of $PM_{2.5}$. However, maximum concentrations of Fe, typically the most abundant trace metal, can be on the order of several tenths of a $\mu g/m^3$ in any of the urban areas characterized. Prior to the phaseout of leaded gasoline, Pb was often found to be the most abundant trace metal in urban atmospheres (Tables 6A2a-c, PM AQCD 1996) at quarterly-average concentrations in the range of 0.1 to 1.0 $\mu g/m^3$. Currently, ambient air Pb concentrations for most U.S. urban areas are in the range of several ng/m^3. The second most abundant trace metal, Zn, is typically present at < 0.1 $\mu g/m^3$, whereas other transition elements (e.g., Ni, V) are typically < 10 ng/m^3. Many

transition elements are currently nondetectable in most U.S. 24-h ambient air filter samples, using X-ray fluorescence spectrometry.

The composition of $PM_{10-2.5}$ particles has not been characterized to the same extent as for $PM_{2.5}$. In general, the inorganic composition of $PM_{10-2.5}$ particles is dominated by crustal particles; and, at times, there is also some evidence of combustion-related PM in some U.S. locations. Photomicrographs obtained by scanning electron microscopy also indicate that large numbers of biologic particles, such as pollen spores, are often present among coarse ($PM_{10-2.5}$) ambient air particles. The contributions of organic compounds and elemental carbon to $PM_{10-2.5}$ particles are poorly known.

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:

- The unprecedented amount of new information generated since the 1996 PM AQCD, which adds greatly to the complexity of any integrative assessment;
- Extensive new information available from epidemiologic studies, which reflects much progress in addressing many research recommendations from the last review, but 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;
- Much new information from dosimetric and toxicologic studies, which makes 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, challenges remain in integrating these different types of evidence into a coherent synthesis.

As discussed in Section 8.1.4, concepts underlying an integrative assessment of statistical associations reported in epidemiologic public health studies have been discussed in numerous publications, from the historic publication by Hill (1965) to the most recent report by the U.S. Surgeon General on the health consequences of smoking (Centers for Disease Control and Prevention, 2004). All such discussions recognize that making causal inferences based on such

associations requires expert judgment, and criteria to aid such judgments generally derive from those originally put forward by Hill. Such criteria are not intended to serve as a checklist or a set of rigid rules of evidence, but rather as a means of organizing an evaluation of the evidence to facilitate reaching such judgments and conclusions. The criteria used in this assessment are generally consistent with those defined in the Surgeon General's report and include the following:

- *Strength of association*, which includes "the magnitude of the association and its statistical strength."
- *Consistency*, which refers to the "persistent finding of an association between exposure and outcome in multiple studies of adequate power, and in different persons, places, circumstances, and times." This criterion serves to address issues related to potential confounding, which in this assessment are separately considered in a discussion of the *robustness* of the associations to the inclusion of potential confounding factors.
- *Temporality,* which most simply refers to "the occurrence of a cause before its purported effect." In this assessment, temporality is more broadly defined to include consideration of lag periods between exposure and effect.
- *Biologic gradient*, or concentration-response relationships, which refers to "the finding of an increment in effect with an increase in the strength of the possible cause. . . ."
- *Experiment*, which refers to "situations where natural conditions might plausibly be thought to imitate conditions of a randomized experiment, producing a 'natural experiment' whose results might have the force of a true experiment."
- *Coherence and plausibility*, which in combination address the idea "that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data . . . ." (Centers for Disease Control and Prevention, 2004, pp. 21-23).

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 the criteria outlined above, including the strength and robustness of the reported associations; assessment of the consistency or general concordance of study results and consideration of potential reasons for observed differences; information related to lags and concentration-response relationships; and information from so-called intervention studies of "natural" or "found" experiments. Looking beyond the epidemiologic evidence, consideration is then also given to toxicological and other

information bearing on the biological plausibility and coherence of the PM-effects associations observed in the epidemiologic studies to make causal inferences with regard to different categories of health effects (cardiovascular, respiratory, etc.) and to reach conclusions regarding 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 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 and vulnerable subpopulations are most likely to be at risk for health effects related to fine and coarse thoracic PM. Finally, information on the magnitude of susceptible subpopulations is discussed, to provide context for the consideration of potential public health impacts of exposures to ambient fine and coarse thoracic PM in the U.S.

9.2.1 Fine and Coarse Particles as Separate Subclasses of PM Pollution

The question of whether fine and coarse particles should continue to be considered as separate subclasses of ambient PM is addressed below, drawing upon information and assessments found primarily in Chapters 2, 3, 5, and 6 of this document related to 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, and if so, on appropriate indicators for these subclasses of PM.

The primary focus in the last review was on thoracic particles (with PM_{10} defined as the index for regulatory purposes) and on the question of 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 should generally exclude particles that deposit only in the extrathoracic region (the latter being particles previously included in the original TSP indicator). The PM_{10} cut-point closely matches the definition for thoracic PM given by the American Conference of Government and Industrial Hygienists (1994), as shown in Chapter 2 (Figure 2-6).

As discussed in the 1996 PM AQCD, the natural division of ambient PM into fine particles and coarse particles is a fundamental distinction based on the recognition that "the fine and coarse modes originate separately, are transformed separately, are removed separately, and are usually chemically different . . ." (Whitby, 1978). Consistent with this distinction, the 1996 PM AQCD stated that the evidence indicates that "it would be appropriate to consider fine and coarse particles as separate subclasses" of PM pollution. This conclusion was based on various considerations:

- Differences in formation processes and sources of fine and coarse thoracic particles, as well as differences in chemical and physical properties, atmospheric residence times and distances transported in the atmosphere;
- Resulting differences in patterns of ambient population exposures to fine and coarse thoracic particles;
- 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 thoracic particles; and
- 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 occur primarily in the fine fraction.

The evidence available in the last review strongly focused on particle size as the basis for distinguishing between the fine and coarse particles. In selecting a size-based cut point between fine and coarse thoracic particles for use in defining an indicator for fine particle standards, EPA recognized that overlap between fine and coarse thoracic particles occurs generally between 1 and 3 μm, and that within this intermodal region, no one size cut-point would clearly separate fine and coarse particles in all areas. For example, published size distributions from Philadelphia, Phoenix, and Los Angeles (shown in Figure 2-9) manifest considerable variability in this intermodal region. Very little mass is seen in the intermodal region in Philadelphia; in Phoenix, the coarse mode can be seen to extend to below 1 μm; and in Los Angeles, a droplet mode, comprising the upper end of the fine mode, occurs under high relative humidity conditions (usually associated with very high fine particle concentrations) and extends above 2.5 μm. EPA's decision to select a nominal cut-point of 2.5 μm in the last review mainly reflected the regulatory importance that was placed on defining an indicator for fine

particle standards that would more completely capture fine particles under all conditions likely to be encountered across the United States, especially high humidity conditions when fine particle concentrations are also likely to be high, while recognizing that some small coarse-mode particles would also be captured by $PM_{2.5}$ monitoring.

In selecting an indicator for coarse thoracic particles in the last review, EPA concluded that the available dosimetric evidence continued to support the use of the same nominal upper cut-point of 10 μm that had previously been selected as the basis for the standards set in 1987. While recognizing that this cut point is on a part of the size distribution curve where the concentration is changing rapidly, such that the amount of PM collected is sensitive to small changes in the effective cut point of the sampler, it still represents the most appropriate cut point to be used as the basis for an indicator of thoracic particles. EPA's decision in the last review to retain PM_{10} as an indicator for standards to address coarse particles, rather than an indicator that would generally exclude fine particles (e.g., $PM_{10-2.5}$), was based largely on the limited epidemiologic studies and air quality data specifically available for coarse thoracic particles beyond that which could be inferred or derived from PM_{10} studies in areas dominated by coarse particles.[1]

As a consequence of these decisions made by EPA in the last PM NAAQS review, 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 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.).

In considering the distinctions between fine and coarse thoracic particles based on currently available information, the following discussion builds upon the most salient key findings from the previous PM NAAQS reviews, while updating and integrating key findings and conclusions from the newly available studies assessed in earlier chapters of this document.

[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.

9.2.1.1 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, with a minimum in the mass distribution between 1 and 3 μm, as illustrated by the idealized distribution shown 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, fine particles are now divided into three modes: a nucleation mode, an Aitken mode, and an accumulation mode. Nucleation mode applies to newly formed particles that have had little chance to grow by condensation or coagulation. Aitken mode particles are also recently formed particles that are still actively undergoing coagulation but have grown to larger sizes. The accumulation mode applies to the final stage, as particles originally formed as nuclei grow to a point where growth slows down, such that accumulation-mode particles normally do not grow into the coarse particle size range. However, during conditions of high relative humidity, hygroscopic accumulation mode particles grow in size, increasing the overlap of fine and coarse particles. The accumulation mode may split into a hygroscopic droplet mode and a non-hygroscopic condensation mode. In addition, gas-phase pollutants may dissolve and react in the particle-bound water (PBW) of hygroscopic particles, e.g., forming more sulfate or nitrate, leading to particle growth beyond the original size even after removal of PBW. These three modes, which comprise fine particles (sometimes called fine-mode particles), are formed primarily by combustion or chemical reactions of gases that yield products with low saturated vapor pressures. Fine particles include metals, black or elemental carbon, and organic carbon (primary PM) and sulfate, nitrate, ammonium and hydrogen ions, and organic compounds (secondary PM).

The coarse mode refers to particles formed by mechanical breakdown of minerals, crustal material, and organic debris. The composition includes primary minerals and organic material. The coarse mode may also include sea salt, nitrate formed from the reaction of nitric acid with sodium chloride, and sulfate formed from the reaction of sulfur dioxide with basic particles. The accumulation mode and the coarse mode overlap in the region between 1 and 3 μm (and occasionally over an even larger range). In this intermodal region, the chemical composition of

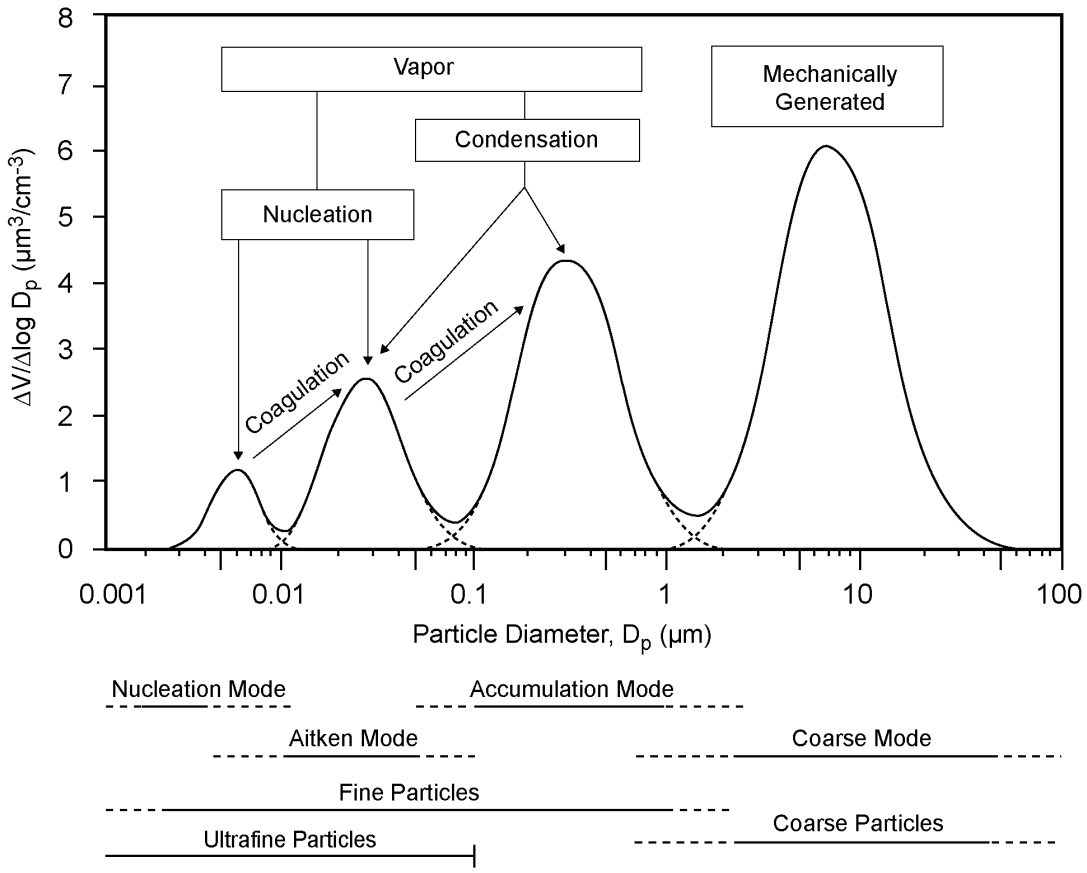

Figure 9-1. An idealized size distribution, as might be observed in traffic, showing fine and coarse particles and the nucleation, Aitken, and accumulation modes that comprise fine particles. Also shown are the major formation and growth mechanisms of the four modes of atmospheric particles.

individual particles can usually, but not always, allow identification of a source or formation mechanism and so permit identification of a particle as belonging to the accumulation or coarse mode.

Since the 1966 PM AQCD, several studies have sought to better characterize particles present in the intermodal region (e.g., indexed by $PM_{2.5}$ - PM_1) and to assess the importance of coarse mode particles present in the intermodal region on associations reported in epidemiologic studies. For example, studies conducted in Phoenix suggested that inclusion of such particles would not likely affect reported associations with $PM_{2.5}$. Studies using Salt Lake City data suggest that coarse particles due to windblown dust are less toxic than PM_{10} present during

non-windblown dust events. Studies in Spokane show that windblown dust contributes to $PM_{2.5}$ but not to PM_1. Thus, the inclusion of days with high windblown dust events could obscure associations with fine particles if $PM_{2.5}$ were used as the indicator.

Natural processes, such as the suspension of soil dust by wind, produce few particles below 1 μm in diameter. However, studies now suggest 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. The many organic compounds formed in the atmospheric reactions of biogenic and anthropogenic hydrocarbons, including condensible species that form organic particles, are now better understood, and progress has been made in measurement of carbonaceous particles.

This progress has helped to enhance our understanding of ambient aerosol components and interrelationships among 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. 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 has also been noted. It is notable that rather direct evidence has also been obtained which demonstrates adherence of allergen-laden pollen cytoplasm fragments to diesel particles, providing a likely mechanism by which diesel PM may act to concentrate bioaerosol materials and to increase their focal accumulation in lower regions of the respiratory tract.

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,

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

Source: Adapted from Wilson and Suh (1997).

ultrafine and accumulation-mode particles share similar formation processes and mechanisms, sources, and compositions. However, their fate and transport are quite dissimilar. 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 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 particles. 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 bioavailability) that is not found with coarse PM.

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 Exposure-Related Considerations

The critical relationship to be considered is that between ambient PM *concentrations* and *personal exposures* to ambient PM (ambient PM refers to 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 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, the relevant measurement of this relationship is the day-to-day correlation of 24-h 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 relevant parameter. Much new information on the distribution 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. 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, except that their concentrations are highest in and near heavy traffic areas and rapidly fall off with distance from traffic due to coagulation and dispersion. Because of their rapid growth into the accumulation mode, their concentrations are probably highest near sources such as traffic. Thus, they likely have a more heterogeneous distribution across a community than accumulation-mode particles.

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, characterized by an infiltration factor which is a function of particle size. As shown in Figure 9-2, 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.

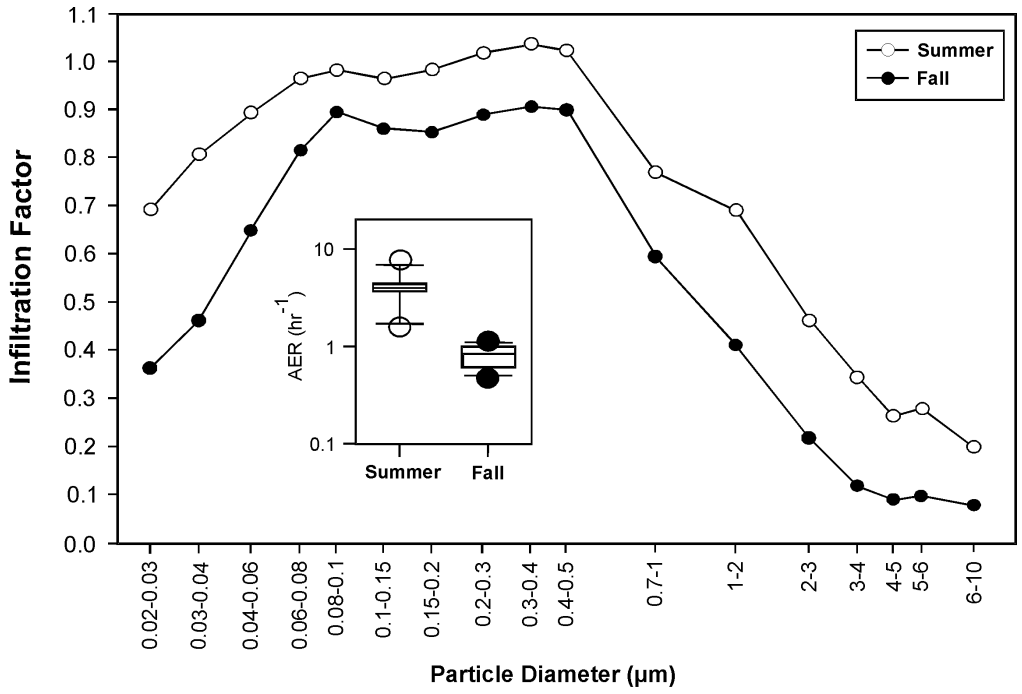

Figure 9-2. Geometric mean infiltration factor (indoor/outdoor ratio) for hourly nighttime, nonsource data for two seasons. Box plots of air exchange rates are shown as inserts for each plot (Boston, 1998).

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

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, as appears to be the case for fine particles ($PM_{2.5}$). However, because of the lower and 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 somewhat 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 estimated for ambient PM exposures.

9.2.1.3 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), the volume of air inhaled (tidal volume), the anatomy of the respiratory tract of the individual, and deposition mechanisms (diffusion, sedimentation, impaction) which affect different-sized particles to varying extents. Because of differing effects of all the above-noted factors, fractional deposition patterns in various respiratory tract regions can vary considerably for particles in different size ranges. 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 9-3 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. As particle size decreases 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 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 A and TB 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

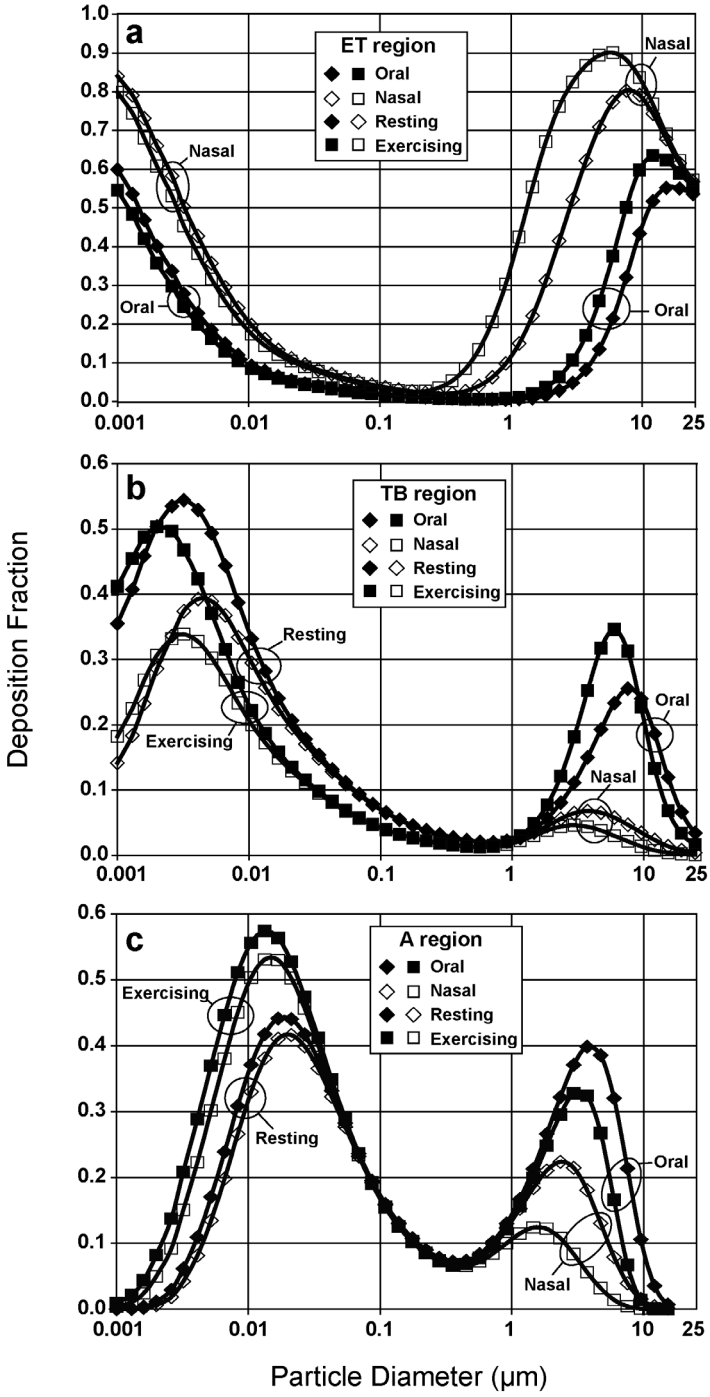

Figure 9-3. Deposition fraction as a function of particle size for nasal and oral breathing during rest and exercise: (a) extrathoracic (ET), (b) tracheobronchial (TB), and (c) alveolar (A) regions. Deposition estimates shown here were calculated with the ICRP model and were also shown in Figures 6-16 and 6-17 along with similar results from the MPPD model. The estimates below 0.01 μm are uncertain but are shown to indicate trends. Note the different scale for the ET region.

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 as well as for particles in the upper end of the coarse-mode range. Thus, while differences in dosimetric properties continue to support the general division of ambient particles into fine and coarse fractions, dosimetric considerations now also suggest that further distinctions can be made between subclasses (ultrafine, accumulation-mode) within the range of fine particles.

9.2.1.4 Summary and Conclusions

The distinction articulated in the last review between fine and coarse ambient particles (as indicators of of fundamentally different sources and composition, formation mechanisms, transport, and fate) remains 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. New information indicates that atmospheric particles may carry components of biological particles (allergens and endotoxin) to the lower respiratory tract and confirms earlier suggestions that water soluble gases can dissolve in particle-bound water and be delivered in enhanced proportions to the lower respiratory tract.

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, although there may be large differences in $PM_{2.5}$ concentrations across many urban areas. 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 (indexed as $PM_{2.5}$) and thoracic coarse particles (indexed 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. The factional deposition of ultrafine, accumulation-mode, and coarse thoracic particles in the ET, TB, and A regions show complex variations with increasing levels of activity, associated increases in breathing rate, and associated increased oral nasal/oral breathing. 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; that particle size remains an appropriate basis for distinguishing between fine and coarse particles; and that cut points of 2.5 μm and 10 μm remain appropriate as the bases for indicators of fine and thoracic coarse particles.

9.2.2 Assessment of Epidemiologic Evidence

Based on the PM epidemiologic evidence available at the time, 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. Environmental Protection Agency, 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 outcomes (U.S. Environmental Protection Agency, 1996, p. 13-92).

In assessing the strengths and limitations of the extensive body of new epidemiologic evidence of associations between health effects and fine and coarse thoracic PM, information discussed in this section is drawn primarily from Chapter 8, as well as from Chapter 5 of this document. The information is considered here in relation to several criteria noted at the outset of Section 9.2: (1) the *strength* of reported associations, in terms of magnitude, statistical significance, and statistical power/precision of effects estimates; (2) the *robustness* of reported associations to the use of alternative model specifications, potential confounding by co-pollutants, and exposure misclassification related to measurement error; (3) the *consistency* or

general concordance of findings in multiple studies of adequate power, and in different persons, places, circumstances and times; (4) *temporality*, in terms of lag periods between exposure and observed effects; (5) the nature of *concentration-response* relationships; and (6) information from so-called *natural experiments* or intervention studies as to the extent to which reductions in PM-related air pollution have been observed to be associated with improvements in health measures. The body of epidemiologic evidence is further considered in the following section in terms of its coherence within itself and in relation to toxicologic findings derived from controlled exposure studies which, overall, provide insights on the plausibility of reported PM-related health effects reflecting causal relationships.

Many recent epidemiologic studies have built upon what was previously known, 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 PM exposure 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 Chapter 8, Appendices 8A and 8B, epidemiologic studies have been conducted in areas across the U.S. and Canada, as well as in Mexico 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 outcomes are associated with ambient PM. Discussions in the following sections focus primarily on studies conducted in the U.S. and Canada using various mass measurements of thoracic particles (e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$) and source-oriented PM analyses.

9.2.2.1 Strength of Epidemiologic Associations

As quoted above, the 1996 PM AQCD concluded that the epidemiological evidence for cardiorespiratory effects was “fairly strong” considering both magnitude and statistical significance of results available at that time. At that time, it was recognized that the relative risk estimates from time-series studies were generally small in magnitude, and the results of recent

reanalyses to address GAM-related issues has led to smaller effect estimates in some cases. 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 United States. The etiology of most air pollution-related health outcomes is multifactorial, and the impact of ambient air pollution exposure on these outcomes may be small in comparison to that of other risk factors (e.g., smoking, diet).

9.2.2.1.1 Short-term Exposure Studies

Many new epidemiologic studies have built upon what was available in the 1996 PM AQCD. These include several multicity 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 co-pollutants, and new evidence from "found experiments" that evaluate improvement in health with reductions in air pollution levels.

The results from key United States and Canadian studies on short-term PM exposure for several commonly-used health outcomes — mortality, hospitalization and medical visits – are presented in Figures 9-4 and 9-5. While recognizing that epidemiologic studies of short-term air pollution exposures have also evaluated other health outcomes (e.g., respiratory symptoms, cardiovascular health indicators, lung function changes), these figures illustrate results for a few major health outcome categories commonly used in PM time-series epidemiologic analyses.

The results are drawn from studies using one or more of the three major PM mass indicators (PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$) that either did not use GAM or were reanalyzed to address GAM-related questions. Single-pollutant (PM only) results are presented here 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). 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). For each health outcome, the results are presented in Figures 9-4 and 9-5 in

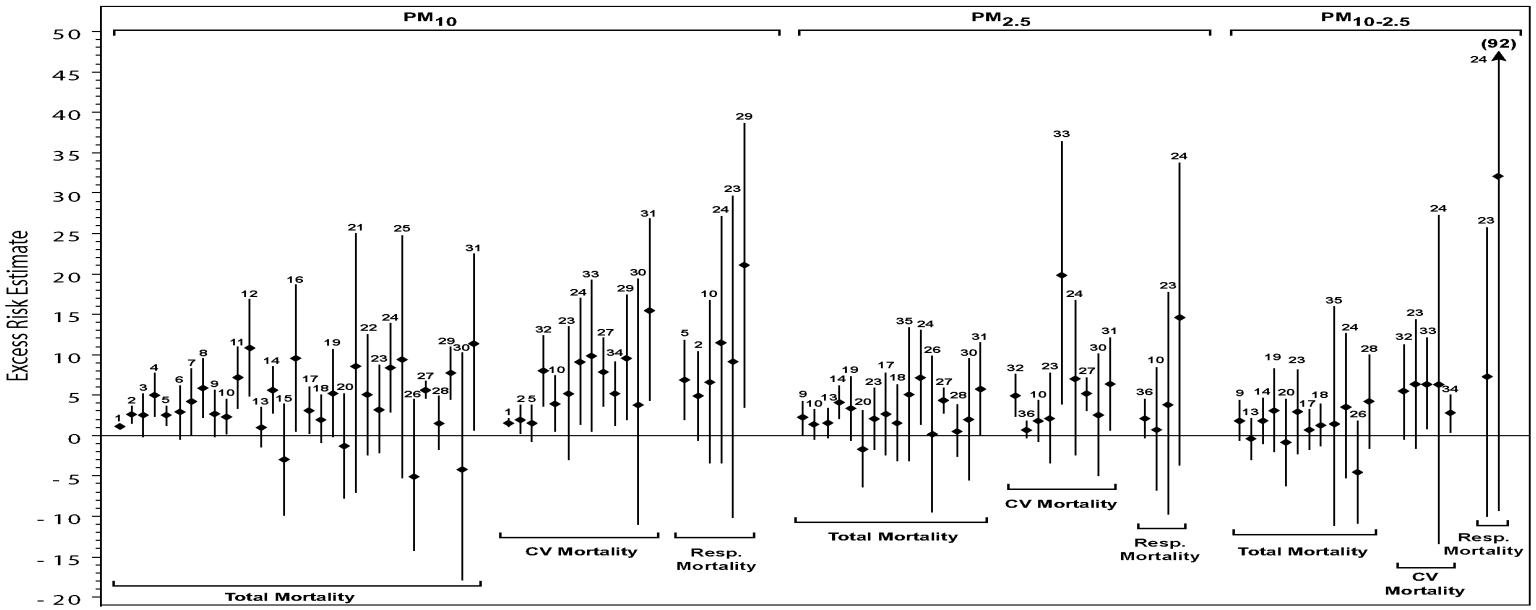

Figure 9-4. Excess risk estimates for total nonaccidental, cardiovascular, and respiratory mortality in single-pollutant models for U.S. and Canadian studies. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use 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

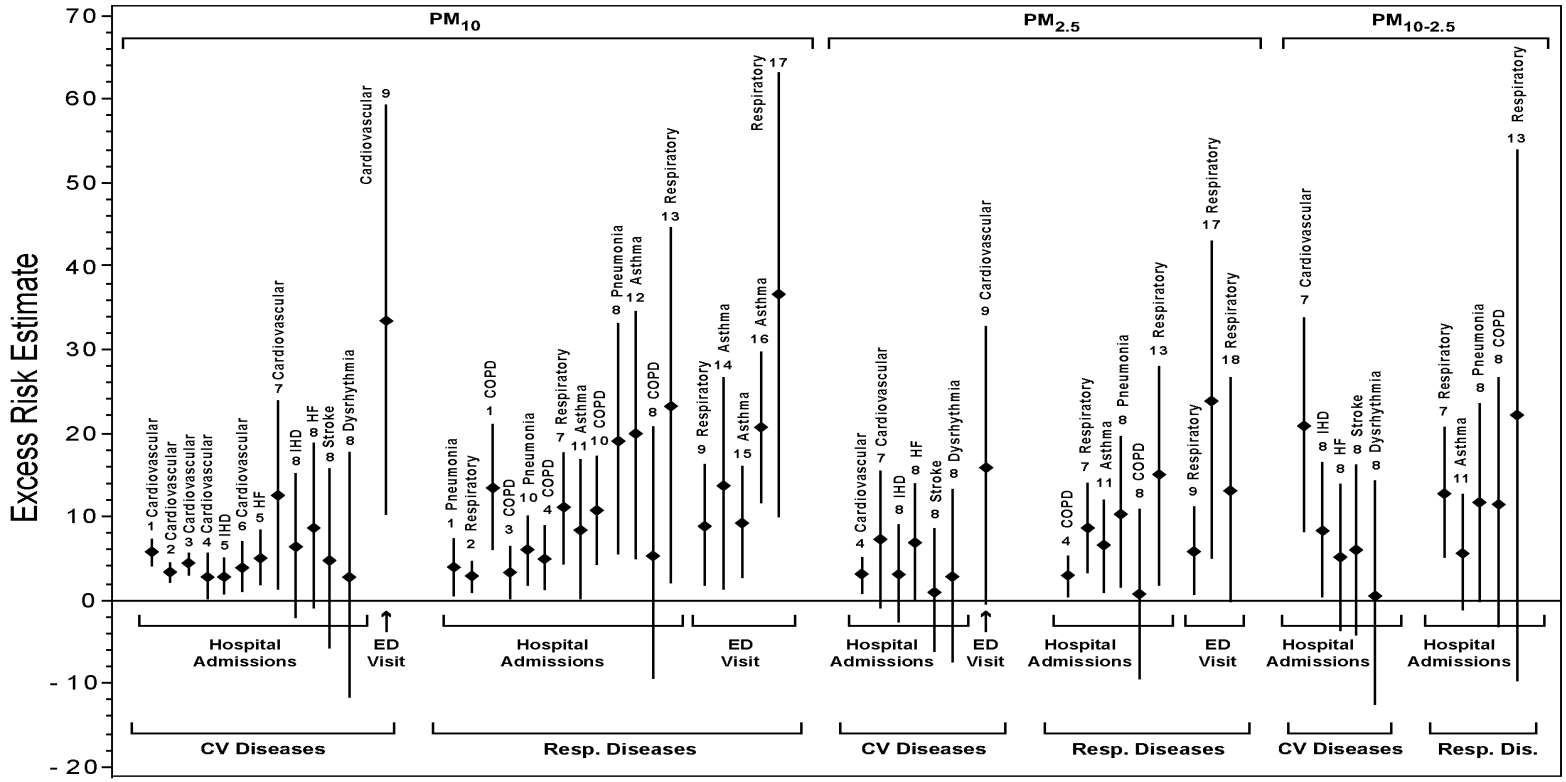

Figure 9-5. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models from U.S. and Canadian studies. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. PM effect size estimate (±95% confidence intervals) are depicted for the studies listed below.

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. Stieb et al. (2000), St. John
10. Schwartz (1994), Detroit
11. Sheppard (2003), Seattle
12. Nauenberg and Basu (1999), Los Angeles
13. Thurston et al. (1994), Toronto
14. Tolbert et al. (2000b), Atlanta
15. Lipsett et al. (1997), Santa Clara County
16. Choudhury et al. (1997), Montreal
17. Delfino et al. (1997), Montreal
18. Delfino et al. (1998), Montreal

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 9-4, 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 nonaccidental, cardiovascular or cardiorespiratory, and respiratory). Looking across the results with particular focus on the more precise estimates, some general observations can be made:

- Almost 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, whereas most of the respiratory associations are generally larger in size but less precise and not statistically significant; less precision would be expected since respiratory deaths comprise only a small portion of total nonaccidental mortality. The more precise effect estimates range from ~1 to 8% increased risk of mortality per 50 $\mu g/m^3$ PM_{10}; for the multicity studies, effect estimates ranged from ~1.0 to 3.5% per 50 $\mu g/m^3$ PM_{10}.

- 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, almost 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; and 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 $\mu g/m^3$ $PM_{2.5}$ and ~1 to 3.5% per 25 $\mu g/m^3$ $PM_{2.5}$ in multicity studies.

- Still fewer studies have used $PM_{10-2.5}$ measurements. The effect estimates are almost all positive and similar in magnitude to those reported for $PM_{2.5}$ and PM_{10}, but few reach statistical significance. Measurement error likely contributes to greater uncertainty, reflected by wider confidence intervals, in effect estimates for $PM_{10-2.5}$ than for $PM_{2.5}$ and PM_{10}.

The results for United States 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 is 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:

- 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. Almost all PM_{10} associations with emergency department (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}.

- 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.

- Associations between $PM_{10-2.5}$ and hospitalization for cardiovascular and respiratory diseases are all positive, and the effect estimates are of the same general magnitude as for PM_{10} and $PM_{2.5}$. In general, as was the case for mortality, the confidence intervals for the $PM_{10-2.5}$ estimates are broader than those for associations with PM_{10} or $PM_{2.5}$ and some, but not all, of the associations are statistically significant.

- 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.

These figures include effect estimates from both recent studies and those available in the previous PM NAAQS review, and it can be seen that the results fall within similar ranges. For example, in the 1996 PM AQCD, a 50 $\mu g/m^3$ increase in PM_{10} was associated with a 2.5 to 5% increase in mortality risk, and results of the Six Cities analysis showed a 3% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$. The effect estimates from the more recent mortality studies, especially those with greater statistical power, can be seen to fall in the same ranges. It is expected that results of multicity studies would more accurately reflect the magnitude of PM-health associations, and it is important to note that the effect estimates from the new multicity studies, such as NMMAPS,

are at the low end of the effect estimate ranges; these results are, however, statistically significant and the precision of the multicity estimates is notably greater than for single-city studies.

For both mortality and morbidity outcomes, 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}. 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 outcomes (e.g., Lippmann et al., 2000; Ito, 2003). In areas where PM_{10} is predominantly fine particles, including most areas in the eastern United States, 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 United States, 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 United States 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}.

As discussed in more detail in Section 8.2.2.5 and summarized in Table 9-3, various PM components or characteristics, including ultrafine particles, have been associated with various health outcomes. In general, evidence for associations have been reported for most components that have been studied; and several new studies have reported associations between ultrafine particles and mortality or respiratory morbidity. However, many PM components are correlated with each other and also with PM mass, making it 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 and to use the resulting daily source factors as surrogates for exposure in an epidemiologic analysis. Motor vehicles, or more precisely particles associated with vehicular traffic, stand out clearly as a source category

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) [3]
Mass fractions:	Sulfate ($SO_4^=$)	TC (Total Carbon)	Motor Vehicles (CO, Pb)
TSP	Nitrate (NO_3^-)	BC (Black Carbon)	Motor Vehicles plus resuspended road dust (CO, NO_2, EC, OC, Mn, Fe, Zn, Pb)
PM_{10}	Ammonium (NH_4^-)	EC (Elemental Carbon)	
Thoracic coarse PM (e.g., $PM_{10-2.5}$)	Transition metals (e.g., Cd, Cu, Fe, Ni, Mn, Zn)	COH (Coefficient of Haze)	Fuel oil combustion (Ni, V)
Fine PM (e.g., $PM_{2.5}$)		OC (Organic Carbon)	Coal burning (Se)
Ultrafine PM ($PM_{0.1}$)	Other toxic metals (e.g., Pb)	CX (Cyclohexene-extractable Carbon)	Sulfate or regional sulfate (S)
Particle number	Strong Acid (H^+)	Organic PM compounds	Industrial (Zn, Cd)
Particle surface area			

[1] Components measured in $PM_{2.5}$ unless otherwise specified.
[2] Organic PM compounds extracted by three techniques.
[3] Source: Laden et al. (2000); reanalyzed in Schwartz et al. (2003); Mar et al. (2000, 2003); Tsai et al. (2000).

associated with mortality in all three studies that used this approach[2]. A regional sulfate source category was also identified as being associated with mortality in all three studies (although regional sulfate may be acting as a surrogate for $PM_{2.5}$, given the high correlation between the two); however, particles of crustal origin in $PM_{2.5}$ were not significantly associated with mortality. Also, associations were reported with an oil combustion factor and a source category related to vegetative burning. 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.

[2] Multivariate techniques such as factor analyses and principal component analyses were used with speciation data to determine PM contributions from source categories (Section 8.2.2.5.3, Table 8-4). For example, factors for particles from motor vehicle emissions from studies using older air quality data used as indicators Pb (Laden et al., 2000; Schwartz et al., 2003) or Pb and CO (Tsai et al., 2000), but in a study with more recent air quality data, the source category included several metals, OC, EC, CO and NO_2 (Mar et al., 2000, 2003).

One key research question that has not been addressed in epidemiologic studies is the relationship between sources or composition of thoracic coarse particles and health outcomes. The studies described above used source apportionment based on components of fine particles or PM_{15} in an area dominated by fine particles. Some limited information is available from air quality analyses that may help inform the assessment of epidemiological evidence for thoracic coarse fraction particles; however, no studies are available to indicate potential differences in thoracic coarse particle composition in relation to morbidity (for which there appears to be more epidemiologic evidence suggesting coarse particle effects). As summarized in Chapter 3, crustal material is an important contributor to thoracic coarse particles. Based on studies described above, crustal components of $PM_{2.5}$ have not been found to be important contributors to associations with mortality, although such thoracic coarse particles ($PM_{10-2.5}$) may be associated with morbidity endpoints. Thoracic coarse fraction particles also include substantial contributions from metals and biological constituents, both of which may be linked with adverse health effects.

In summary, considering results from studies conducted both within and outside the U.S. and Canada, the epidemiological evidence is strong for associations between PM_{10} and $PM_{2.5}$ and mortality, especially for total and cardiovascular mortality. The magnitude of the associations is relatively small, especially for the multicity studies. However, there is a pattern of positive and often statistically significant associations across studies for cardiovascular and respiratory health outcomes, including mortality and hospitalization and medical visits for cardiovascular and respiratory diseases, with PM_{10} and $PM_{2.5}$. The few available $PM_{10-2.5}$ studies also provide some evidence for associations between hospitalization for cardiovascular and respiratory diseases with $PM_{10-2.5}$. $PM_{10-2.5}$-hospitalization effect estimates were similar in magnitude to those for PM_{10} and $PM_{2.5}$, but with less precision. For $PM_{10-2.5}$, the evidence for associations with mortality is more limited; the magnitude of the effect estimates is very similar to those for $PM_{2.5}$ and PM_{10}, but in terms of precision, the evidence is not as strong. While there is some new epidemiological evidence suggesting possible associations between health outcomes and ultrafine particles and other fine particle components and sources, the data are as yet too sparse to characterize the relative toxicities of these various components or indicators of fine particles for different health outcomes.

9.2.2.1.2 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. More recent long-term exposure studies 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 of total and cardiopulmonary mortality with 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, although none reached statistical significance. For the VA study, indices of long-term exposures to PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ were not associated with mortality.

Based on several factors – the larger study population in the ACS study, better characterization of exposure 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 is placed here 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 (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. Nor can any conclusions yet be drawn regarding possible effects of long-term exposures to ultrafine particles, given the lack of relevant data.

9.2.2.2 Robustness of Epidemiologic Associations

Many epidemiologic studies have also included assessment of whether the associations were robust to such factors as model specification and potential confounding by co-pollutants. 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 focuses on the extent to which the current epidemiologic findings can be considered robust.

9.2.2.2.1 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 observation days available.

Thus, as observed in the HEI reanalysis report (Health Effects Institute, 2003), revised analyses using GAM with more stringent convergence criteria or GLM with natural splines and the use of alternative modeling strategies tended to reduce the PM 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. In general, PM effect estimates were more sensitive to different controls for time-varying (e.g., weather or seasonal) effects. In some studies, with use of different methods or degrees of control for temporal variables, PM effects estimates were largely unchanged, whereas in several other studies the changes were enough to alter study conclusions. 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.

9.2.2.2.2 Assessment of Confounding by Co-pollutants

Airborne particles are found among a complex mixture of atmospheric pollutants, only some of which are widely measured (e.g., gaseous criteria co-pollutants O_3, CO, NO_2, SO_2). Because many of the pollutants are closely correlated due to emission 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 → HNO_3 → particulate nitrates), it is generally difficult to disentangle their effects. In addition, as described in Section 8.1.3.2, co-pollutants 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, as well as questions related to model specification and exposure error. For example, some new studies described in Section 5.3.3.4 have reported that ambient $PM_{2.5}$ concentrations are well correlated with personal $PM_{2.5}$ exposure measurements; in contrast, that is generally not the case for O_3, SO_2, and NO_2.

Multipollutant modeling results for associations of a range of health outcomes with PM and 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 that included 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; the NMMAPS 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 co-pollutants were included in the models. Often, PM and the gaseous co-pollutants were 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 co-pollutants.

In the prospective cohort and cross-sectional studies, the potential for confounding by co-pollutants 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 of mortality with 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 outcomes 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 newly available epidemiologic evidence substantiates that, for both long-term and short-term exposures, there are PM associations with mortality or morbidity that are robust to confounding by co-pollutants.

9.2.2.2.3 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 in a model 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. The results of these analyses indicate that it is unlikely that effects attributed to PM (generally focusing on PM_{10} or $PM_{2.5}$) are falsely transferred from other less-precisely measured pollutants.

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 (a) the spatial variability across a city is generally much greater for $PM_{10-2.5}$ than for $PM_{2.5}$ and (b) there may still be substantial variability in $PM_{2.5}$ concentrations across some urban areas, as discussed in Chapter 3. In addition, the infiltration factors for $PM_{10-2.5}$ and a number of gases (e.g., O_3, SO_2) are lower and more variable than that 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. Also, studies which included subjects limited to those living near the air monitoring site (and, therefore, presumably have lower exposure error due to spatial heterogeneity of PM concentrations) tend to yield higher effect estimates. Thus, the new exposure studies indicate that fine particle 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 $PM_{2.5}$; this likely contributes to larger confidence intervals around $PM_{10-2.5}$ effect estimates.

9.2.2.3 Consistency of Findings Across Epidemiologic Studies

In the 1996 PM AQCD, it was observed that PM was associated with mortality and morbidity in studies conducted in numerous locations in the United States as well as in other countries. The expanded body of studies available in this review includes studies conducted in a wider range of locations; as described above, many of those studies, especially those with greater statistical power, report statistically significant associations. 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 increase susceptibility to air pollution health effects, and (c) areas may differ in factors that affect population exposures to ambient pollutants.

Multicity studies conducted in the United States, Canada, and Europe have included quantitative assessments of heterogeneity in PM effect estimates. 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 outcome 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 multicity study, APHEA, PM-mortality associations were found to be larger in areas with higher average NO_2 levels (considered an indicator of traffic pollution), and warmer climates (possibly due to more open windows resulting in better exposure estimation). In NMMAPS, no apparent associations were found between PM-mortality associations and either/or $PM_{2.5}/PM_{10}$ ratios or socioeconomic indicators, 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.

Variability in PM concentrations across study areas could influence epidemiologic study results. For larger metropolitan areas, including monitors in outlying areas may bias the exposure estimate and reduce the correlation between the averaged concentration and the true population exposure. From among those U.S. cities in which epidemiological studies have been conducted, areas with more uniformity in $PM_{2.5}$ concentrations include Chicago and Detroit, whereas areas with more spatial 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 levels would be expected to increase exposure error, potentially affecting 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 9-4, 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 2,000 days (e.g., Ito and Thurston, 1996). Multicity studies included ranges of about 500 to 900 days for eight Canadian cities (Burnett and Goldberg, 2003), about 200 to 3,000 days for 90 U.S. cities (Dominici et al., 2003a), and 1,500 to 3,000 days for 10 U.S. cities (Schwartz, 2003a). For several studies, more data are available for PM_{10} than for $PM_{2.5}$ or $PM_{10-2.5}$; Fairley (2003) as an example, 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 United States had about 300 to 4,000 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 9-4 and 9-5 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 time-series analyses. As discussed in Section 8.4.5.2, one analysis of data from Chicago first used data from an everyday monitor and then six 1-in-6 day data sets were created from the same data. Whereas the resulting analysis using all the daily data showed clearly statistically significant positive PM-mortality associations, the results for the analyses using 1-in-6 day data sets were quite

inconsistent. Hence, the use of air quality data with many missing days adds uncertainty to results for PM-health outcome associations.

Thus, there are numerous reasons to expect study results to vary across cities, based on different topographies, distribution of sources or emissions, mixes of pollutants, and population characteristics. The new multicity studies have provided some initial evidence for some of these factors that may affect the magnitude or significance of PM-health associations. Effect estimates reported for set of studies of the same location generally fall well within the range of the confidence intervals of all studies. With multicity studies, statistical tests for heterogeneity among effect estimates have been conducted with inconsistent findings. It seems likely that some apparent variation in effect estimate size is simply statistical variability, while factors such as differential exposures based on housing characteristics or population characteristics may contribute to real variations in effects between locations. Overall, the epidemiological studies indicate that there are associations between PM_{10} and $PM_{2.5}$ and mortality from cardiorespiratory diseases in numerous locations, and between PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ and hospitalization for respiratory or cardiovascular causes in various places across the United States.

9.2.2.4 Temporality and the Question of Lags

As discussed in Section 8.4.4, differing lag periods are likely 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 same day PM concentrations, with some effects also linked with PM from the previous day. In a few studies of cardiac physiological changes, the strongest associations were reported for some outcomes with 1- to 2-hour lag periods, indicating that for certain health outcomes very short-term fluctuations in pollution are most important. 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, suggesting that these health responses may have a longer and more extended latency period than indicated by single day lag analyses.

Where results are presented 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 a jumbled pattern of results across the different lags, then the single-day lag with the largest effect is likely biased.

However, when there is a pattern of effects across lag periods, selecting any one of the single-day lag effect estimates 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 days. In these cases, a distributed lag model should more correctly capture the effect size.

Studies of long-term exposure have included less evaluation of temporal relationships between PM exposure and health outcome. 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 long-term exposure to 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 outcomes 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 and the specific pollutant under study. 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 associated with chronic

exposure, less is known about the importance of different time windows for exposure, and some recent studies indicate that further investigation is needed.

9.2.2.5 Concentration-Response Relationships

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 and toxicologic information.

Recognizing these difficulties, several recent epidemiologic studies evaluated potential thresholds in time-series mortality studies. Analyses using data for 90 U.S. cities from NMMAPS showed that, for total and cardiorespiratory mortality, it was difficult to discern any threshold level for PM_{10}, with the results of statistical tests indicating that a linear concentration-response model was preferred over the spline and the threshold models. In this study, 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); but there was increasing probability of a threshold occurring at levels below 25 $\mu g/m^3$. In some single-city analyses, there were indications of potential population thresholds

for associations between mortality and PM_{10} in the range of 80 to 100 $\mu g/m^3$, and with $PM_{2.5}$ in the range of 20 to 25 $\mu g/m^3$. However, other single-city analyses reported no evidence of a threshold level for PM-mortality associations.

In summary, available studies do not provide strong evidence of a clear threshold for the relationship between PM concentration and mortality. The multicity and most single-city studies have not identified threshold levels for mortality, and have indicated that the associations generally show linear concentration-response relationships; where potential threshold levels have been suggested in single-city studies, they are at fairly low levels. It is possible that there are no clear threshold levels for population responses, especially for health endpoints that include multiple causes such as total nonaccidental mortality.

9.2.2.6 Natural Experiment 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 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 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 SO_2) 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.

9.2.2.7 Summary and Conclusions

Epidemiological evidence can help to inform judgments about causality; and, the present discussion evaluated the epidemiologic evidence in relation to the first five criteria set for the beginning of Section 9.2, including key considerations with regard to criteria such as the strength (magnitude, precision) and robustness of reported associations. Information related to last of the six criteria (coherence and biological plausibility of the evidence) is discussed in the following section.

Overall, there is strong epidemiological evidence linking (a) short-term (hours, days) exposures to $PM_{2.5}$ with cardiovascular and respiratory mortality and morbidity, and (b) long-term (years, decades) $PM_{2.5}$ exposure with cardiovascular and lung cancer mortality and respiratory morbidity. The associations between $PM_{2.5}$ and these various health endpoints are positive and often statistically significant. There are fewer studies available for $PM_{10-2.5}$ and the magnitude of the effect estimates for associations with mortality and morbidity effects (especially respiratory morbidity) is similar to that for $PM_{2.5}$, but the lesser precision reduces the strength of the evidence. 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, as was reported in the previous review.

With regard to the robustness of the associations, research questions remain on modeling issues with time-varying variables, but extensive reanalyses conducted for both time-series and prospective cohort studies provide further support for the results of the original analyses. Recent reanalyses of a number of time-series studies found that results were little changed with adjustments to deal with GAM-related issues, but some results were sensitive to different adjustment for time-varying factors such as weather. However, the recent studies, using a

variety of approaches to control for weather effects, still appear to demonstrate increased PM-related mortality and morbidity risks beyond those attributable to weather influences alone.

Much progress has been made in sorting out contributions of ambient PM_{10} and its components to observed health effects relative to other co-pollutants. Despite continuing uncertainties, the evidence overall tends to support the above conclusions that ambient PM_{10} and $PM_{2.5}$ are most clearly associated with mortality/morbidity effects, acting either alone or in combination with other covarying gaseous pollutants, with more limited support being available with regard to $PM_{10-2.5}$. Likely contributing to this is the fact that greater measurement error associated with exposure estimates for a given pollutant or indicator will result in less precise effect size estimates that are less robust in multipollutant models. Of importance here, directly measured PM_{10} and $PM_{2.5}$ values likely have less measurement error than $PM_{10-2.5}$ values derived by subtracting $PM_{2.5}$ values from PM_{10} concentrations, especially if obtained from non-collocated PM_{10} and $PM_{2.5}$ monitors at different locations in a given urban area. Thus, the current paucity of statistical significance for a pattern of positive associations with $PM_{10-2.5}$ may reflect measurement imprecision, not necessarily lack of effects.

Focusing on the studies with the most precision it can be concluded that there is much consistency in epidemiological evidence regarding associations between short-term and long-term exposures to fine particles and cardiopulmonary mortality and morbidity. For coarse fraction particles, there is also some consistency in effect estimates for hospitalization for cardiovascular and respiratory causes based on the few studies available for several locations across the United States. Some variability in effect estimate size can be seen across locations, especially in the recent multicity studies. Factors likely contributing to this variability include geographic differences in air pollution mixtures, composition of ambient PM components, and personal and sociodemographic factors potentially affecting PM exposure (e.g., use of air conditioning), as well as differences in PM mass concentration.

Temporality, or the occurrence of the health outcome following the exposure, has been found to hold well for the time-series epidemiological studies. The length of the lag period for exposure and effect varies for different health outcomes, with short acute exposures of an hour or more seemingly more important for some cardiovascular health endpoints and longer average exposures or distributed lag exposure windows being more closely associated with other health endpoints. For long-term exposures, the existing studies generally use spatial variation in

concentrations to estimate exposure changes, thus temporality is not directly tested, but some new evidence suggests that changes in pollutant mix over time may influence relationships with health effects.

In conclusion, the epidemiological evidence continues to support likely causal associations between $PM_{2.5}$ and PM_{10} and both mortality and morbidity from cardiovascular and respiratory diseases, based on an assessment of strength, robustness, and consistency in results. For $PM_{10-2.5}$, less evidence is available, but the studies using short-term exposures have reported results that are of the same magnitude as those for PM_{10} and $PM_{2.5}$, though less often statistically significant and thus having less strength, and the associations are generally robust to alternative modeling strategies or consideration of potential confounding by co-pollutants. This evidence is suggestive of associations for morbidity with short-term changes in $PM_{10-2.5}$. Epidemiologic studies suggest no strong evidence for a threshold in PM-mortality relationships. Important new results from source apportionment studies and found experiments indicating that reductions in PM and other pollutants result in improvements in community health lend support to the results of the other epidemiological studies.

9.2.3 Integration of Experimental and Epidemiologic Evidence

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 outcome 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 outcomes supporting 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.

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

- "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."

- 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."

- "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. Environmental Protection Agency, 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 contribution of specific PM constituents to PM toxicity and (b) the biological plausibility of the reported effects and/or the mechanisms of action underlying them.

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 possible 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 findings 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 pollutants. This section addresses these complexities by considering the extent of coherence observed among findings reported for specific PM components identified in epidemiologic studies for specific health outcome categories (cardiovascular; respiratory; lung cancer; fetal and infant development/mortality) and related toxicologic links to biologic changes

observed in controlled exposure human, animal, and in vitro studies. Hypothesized potential mechanisms of actions and other supporting pieces of evidence are also summarized.

As discussed at the outset of Section 9.2, several criteria were listed as useful in evaluating scientific evidence as supporting conclusions regarding potential causal relationships between two variables. In addition to those criteria addressed in the preceding discussion of PM-related epidemiologic evidence, it is important to take into account still other information or criteria which combine consideration of biological plausibility and coherence, so as to help ensure: "that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data. . . ."

For the purposes of this assessment: the ensuing discussion of plausibility and coherence considers both: (a) the extent to which the available epidemiologic evidence (of adequate power) shows associations in the same location (urban area) with a range of logically linked health endpoints (i.e., endpoints within a "pyramid of effects" ranging from the most severe outcome, mortality, to physiological changes in the cardiovascular or respiratory systems, e.g., altered fibrinogen levels or lung function changes); and (b) the extent to which the available toxicologic evidence and mechanistic information provide support for the plausibility of the array of observed epidemiologic associations likely reflecting causal relationships.

Before embarking on the plausibility and coherence discussions in Section 9.2.3.2 for each of several health endpoints (cardiovascular, respiratory, etc.) evaluated as likely being impacted by ambient PM, the next section first provides important background information on three cross-cutting issues that help to place the ensuing discussions in context.

9.2.3.1 Background on Cross-Cutting Issues

Background information on several cross-cutting issues is provided here to help place the ensuing discussions in perspective. First, important considerations related to strengths and weaknesses of experimental approaches used to study PM health effects area summarized along with relevant caveats. Next, interspecies dosimetric comparisons are discussed and representative examples are provided for extrapolation of PM exposure/doses between rats and humans. Lastly, information on inhaled particles as carriers of other toxic agents and consequent potential implications are discussed.

9.2.3.1.1 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 used, 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 mainly addressed the question of biologic plausibility of epidemiologically-demonstrated effects and mechanisms of action, rather than attempting to delineate 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, but this may not be so.

Recognizing this, there has been growing attention to the development and use of compromised animal models 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. A limitation of this model is that pathology is induced acutely in rats to model a chronic illness in humans. 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. There is a need to search for relevant new animal models to better simulate human pathophysiology in PM exposure studies.

Given the relatively high concentrations used, 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 in some instances 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 closely control the mass concentration and day-to-day variability in ambient particle composition; and they have sometimes lacked 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 not always done or reported) 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 lose concentrating efficiency below 0.3 μm, and do not concentrate ambient particles in the ultrafine range ≤ 0.1 μm. Thus, it is possible that portions 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 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 not have been concentrated or were excluded from the CAPs exposure mix as well. Newer versions of CAPs concentrators being used in ongoing research do allow for concentrating of particles ≤ 0.1 μm and for exposure to gaseous co-pollutants present in the ambient air along with the particles being concentrated. These improvements should enable CAPs exposures in ongoing and/or future research studies to more fully reflect potentially important interactive effects of overall "real-world" aerosol mixes.

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 the United States, 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 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. However, these studies provide some insight into the relative toxicity of contributing sources or specific PM components.

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 $PM_{1.0}$, have largely 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.

9.2.3.1.2 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.

Of the three common experimental approaches for studying PM health effects, inhalation studies provide the most realistic exposure scenarios and physiologically best mimic biological reactions to ambient PM. However, because they are expensive, typically require large samples, are time consuming, and require specialized equipment and personnel, they are often supplemented by 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, initial information on the likely mechanisms of action of particles is obtained through in vitro techniques. For PM toxicologic studies, dose selection is important to avoid overwhelming normal defense mechanisms.

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. To help place the toxicologically relevant concentrations/doses into context in relation to ambient conditions, EPA carried out illustrative dosimetric/extrapolation modeling analyses (described in Appendix 7A) to provide comparisons between the high exposure doses typically used in toxicological studies and doses more typical of human exposures under ambient conditions. Building upon advances in dosimetric modeling discussed in Chapter 6, 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. These analyses and interpretation of their results provide context for exposure concentrations used and toxicological results assessed here.

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. 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. Inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs, relative to instillation, which is typified by heterogeneous distribution and high focal levels of particles. This disparity in distribution likely impacts clearance pathways, dose to cells and tissues, and systemic absorption. This is reflected, for example, by particle burdens within macrophages, those from animals inhaling particles being burdened more homogeneously and those with instilled particles showing some populations of cells with heavy burdens and others with no particles. Also, some studies have found greater percent retention of instilled than inhaled particles, at least up to 30 days postexposure, while others report similar clearance rates. Exposure method, thus, clearly influences dose distribution; and, possibly clearance, thus necessitating much caution in interpreting results from instillation studies.

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. 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 potential exposure scenarios were considered in Appendix 7A. 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. 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 Tables 7A-7a through 7A-9b of Appendix 7A.

Representative dosimetric calculations provided in Appendix 7A indicate that higher PM concentration exposures in rats than in humans are needed under certain conditions in order to achieve nominally similar acute doses per lung tissue surface area in exercising humans exposed to ambient PM while undergoing moderate to high exertion. However, for resting or light

exertion situations, lower rat exposure concentrations are adequate to produce equivalent lung tissue doses. Also, given that rats clear PM much faster than humans, Appendix 7A dosimetric modeling predicted that much higher exposure concentrations in the rat are required to simulate the retained burden of poorly soluble particles which builds up over years of human ambient PM exposure. In resuspended PM, used in some inhalation studies, the smaller particles found in the accumulation and Aitken modes of the original atmospheric aerosol are aggregated onto (or into) larger particles. Thus, for dose metrics based on particle surface area or number, very high exposure concentration of resuspended PM for rats would be required to provide a dose equivalent to that received by humans exposed to ambient atmospheric aerosols.

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. 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. Such calculations require knowledge about the 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 is useful to know the relationship between the surface doses in instillation studies and realistic local surface doses that could occur in humans. However, providing some illustrative modeling results here 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.

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. PMNs, along with alveolar macrophages (AM), constitute an important lung defense mechanism triggered by invasion of PM, bacteria, and 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. Also, PMN produce thromboxanes, leukotrienes, and prostaglandins.

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. Analysis of PMN data from exposures of rats and humans to CAPs in these studies suggest that healthy humans may be 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 $\mu g/m^2$ was estimated to be associated with a 60 to 500% increase in PMNs in rats, whereas an estimated retained dose of 0.7 $\mu g/m^2$ induced a 267% increase in PMNs in humans. The apparent greater sensitivity (magnitude of PMN response) of humans observed through these comparisons, however, may be affected by differences in PMN baseline levels across species and between studies.

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. Increased numbers of these cells in lung tissue are an indicator of normal mobilization of lung defenses in response to infection or deposition of inhaled particles. Inhibition of phagocytosis signals interference with lung defense mechanisms. 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 the numbers of AM or their phagocytic activities may decrease. Several in vitro studies discussed in Chapter 7 have shown that, in certain 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.

Comparison in Chapter 7 rodent and human data evaluating inhibition of phagocytosis 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 ng/cell ROFA. A mouse AM cell line showed inhibition of phagocytosis at concentrations of 0.013 to 0.025 ng/cell of TiO_2 and carbon black. 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 than human AM. It must be noted that these in vitro exposures are at extremely high doses, exposing each cell to tens to hundreds of particles at physiologically improbable levels unlikely to be experienced as the result of human exposures to current U.S. ambient air PM (except possibly, under very extreme conditions).

9.2.3.1.3 Inhaled Particles as Carriers of Other Toxic Agents

In Chapter 2, it was noted that, although water vapor is not considered an air pollutant per se, particle bound water (PBW) may serve as a carrier for other toxic pollutants. Wilson (1995) proposed that water-soluble gases that are usually removed by deposition to wet surfaces in the upper (ET) regions of the respiratory tract may be dissolved in PBW and be carried into lower regions (TB, A) of the respiratory tract. Thus, PBW could be a vector by which certain toxic gases commonly found in polluted air masses may be delivered in enhanced proportions to deep lung regions, including water-soluble gases such as: oxidants (e.g., H_2O_2, organic peroxides); acid gases (e.g., SO_2, HCl, HONO, formic acid); and polar organic species.

Kao and Friedlander (1995) also noted that many short-lived chemical species in the gas or particle phase (such as free radicals) in ambient aerosols may not still be present in sampled materials when analyzed hours to weeks (or even longer) after collection on filters and being stored. Also, the unmeasured metastable species may be much more biochemically active than the "dead" components collected or remaining on analyzed filters. They also noted that since inhalation toxicology studies often do not include the potential for metastable species and reactive intermediaries to be present, then such studies could greatly underestimate the effects

seen in field or epidemiological studies. Friedlander and Yeh (1998) further noted that atmospheric submicron (< 1.0 μm) aerosols contain: (1) primary components (e.g., elemental or black carbon; high molecular weight organic compounds; metallic compounds from smelting, welding, etc.; small soil dust particles; or sea salt near coastal areas); (2) secondary components from atmospheric reactions yielding inorganic ionic species (e.g., NH_{4+}; $SO_4^{=}$; NO_3^{-}); (3) water; and (4) short-lived reaction intermediaries (e.g., hydrogen peroxides, aldehydes, and organic acids) formed in clouds and rain water. Also, they indicated that: (1) hydrogen peroxide particle phase concentrations fall in a toxicologic range capable of eliciting biochemical effects on respiratory tract airway epithelial cells; (2) this may help to explain epidemiologic results indicating health effects to be associated with sulfate or other fine particle aerosols; and (3) such aerosols may be surrogate indicators for hydrogen peroxide or other species.

Certain physical modeling of gas-particle-mucus heat and mass transport in human airways suggests that very soluble gases (e.g., H_2O_2, formaldehyde) may be largely evaporated from particles < 0.1 μm diameter before reaching A regions of the lung, but particles > ~0.3 μm can efficiently carry such gases into the air exchange region of the lung. Also one new toxicological study discussed in Chapter 7 (Section 7.9.1) evaluated whether certain commonly present hygroscopic components of ambient PM can transport H_2O_2 into the lower lung and thereby exert or enhance toxic effects. More specifically, rats exposed by inhalation to combinations of $(NH_4)\ SO_4$ (0.3 to 0.4 MMD) and H_2O_2 exhibited enhanced biochemical effects that 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 alveolar macrophages.

The information summarized above has important implications for interpreting and understanding epidemiologic and experimental toxicology results discussed in ensuing sections of this chapter. Also, of much importance is dosimetric information discussed in Chapter 6 which indicates that hygroscopicity affects particle deposition patterns in the respiratory tract, such that under high humidity conditions one can expect increased deposition of small nucleation (< 0.1 μm) ultrafine particles and larger accumulation-mode (≥ 0.5 μm) particles, the latter of which are able to grow to exceed 1.0 μm and both of which would contain enhanced amounts of PBW and other toxic agents (e.g., SO_2, peroxide, aldehydes, etc.). Also, to some extent, growth of ultrafine and accumulation mode particles under high humidity conditions

would likely enhance particle "hot spot" deposition at airway branching points and increase PM doses to lung tissue at those points. Enhanced deposition and tissue doses would likely exacerbate PM respiratory effects in particularly susceptible population groups, e.g., asthmatics, COPD patients, and others with severe cardiopulmonary conditions.

In addition to recognition that particle-bound water may serve as a carrier of other toxic agents, there is growing recognition that bioaerosols as likely have potential to contribute to some ambient PM effects, in part, via their serving as carriers of toxic agents or via their attaching to and being carried by non-biological particles. Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 μm to > 20 μm. Although they typically only comprise a small fraction of ambient PM, they likely contribute to some types of ambient PM-related health effects.

Intact pollen grains from plants, trees and grasses are most abundant during warm/humid spring/summer months. When they deposit in upper airways, they induce allergic rhinitis. However, 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 diesel exhaust) may be a mechanism that increases incidence of asthma morbidity and mortality. Pollen granules can also act as vectors for binding of other bioaerosols (e.g., endotoxins, fungi or fungal fragments, glucans) and thereby enhance their inhalation and deposition in the respiratory tract, as well.

Fungal spores and fungal 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 in epidemiologic studies. They proliferate very effectively on wet cellulose materials (at times posing serious indoor contamination problems), thus raising the possibility that airborne cellulose-containing plant debris (which otherwise may be non-toxic when dry) may serve as effective vectors for proliferation of fungi and their delivery into the lung under high humidity ambient conditions.

Bacteria and viruses are also significant bioaerosols. Bacteria have endotoxins in their outer cell membrane, which trigger production of cytokines and a cascade of inflammation.

Ambient airborne levels of endotoxins vary with seasons (being higher in warm/humid periods and low in colder months). Another cell wall component of bacteria and fungi, (1→3)-β-D-glucan, has also been shown to cause respiratory inflammation.

Based on the above, it appears that certain ambient bioaerosols (e.g., pollen, fungi, endotoxins, glucans) that become abundant during warm/humid weather have the potential to contribute to seasonal increases in PM-associated risk during spring/summer months in many U.S. areas, but not during colder winter months. In addition, the copresence of non-biological particles, serving as vectors concentrating such bioaerosols and enhancing their delivery into the deep lung, also appears likely to be important. For example, airborne endotoxins have been shown to be associated with both fine and coarse thoracic ambient particles (albeit higher with the coarse PM); and cytoplasmic pollen fragments have been found attached to airborne diesel particles. It thusly appears that airborne anthropogenic particles (both in fine and coarse size ranges) as well as naturally-generated biological particles likely enhance the risk for bioaerosols-stimulated effects.

9.2.3.2 Biological Plausibility and Coherence of Evidence for Different Health Endpoint Categories

This section is organized to integrate epidemiologic, toxicologic, and mechanistic information for each of four major categories of health endpoints, i.e., (a) cardiovascular; (b) respiratory; (c) lung cancer; and (d) fetal/infant development and mortality, purported to be associated epidemiologically with either short- or long-term ambient PM exposures. Each subsection concisely summarizes pertinent key information and then arrives at conclusions as to the plausibility of effects being reasonably attributable to fine and coarse thoracic particles and/or subcomponents.

9.2.3.2.1 Cardiovascular-related Health Endpoints

As noted in Section 9.2.2, a number of epidemiologic studies (a) show associations between short-term and/or chronic ambient PM exposures and increases in cardiac-related deaths and/or morbidity indicators and (b) indicate that the risk of PM-related cardiac effects may be as great or greater than those attributed to respiratory causes (see Chapter 8). Hypothesized mechanisms thought to be involved in cardiovascular responses to PM exposure (as discussed in Chapter 7) include: (a) effects on autonomic nervous system control of cardiovascular functions

and (b) pathophysiologic effects on certain blood chemistry parameters involved in control of blood clotting or otherwise impacting cardiovascular integrity.

With regard to autonomic nervous system control, the heart receives both parasympathetic and sympathetic inputs that decrease or increase heart rate, respectively. Vasoconstriction, possibly due to release of endothelin elicited by PM, could cause increased blood pressure and its detection by baroreceptors. Parasympathetic neural input may then be increased to the heart, slowing heart rate and decreasing cardiac output (which is sensed by aortic and carotid chemoreceptors). These, in turn, may stimulate a sympathetic response, manifested by increased heart rate and contractile force, thus increasing cardiac output. This arrhythmogenesis and altered cardiac output in either direction can be life-threatening to susceptible individuals.

Pathophysiological changes in cardiac function can be detected by electrocardiographic (ECG) recordings, with certain ECG parameters (e.g., heart rate variability or HRV) now often being used as indicators of PM-induced cardiac effects. HRV is a reflection of the overall autonomic control of the heart and can be divided into time and frequency measures. Frequency measures of variability help to resolve parasympathetic and sympathetic influences on the heart better than do time domain measurements. Under some circumstances (as discussed in Chapter 7), HRV provides insight into sympathetic nervous activity, but more commonly it is a good measure of parasympathetic modulation. Heart rate variability can be used to judge the relative influences of sympathetic and parasympathetic forces on the heart, but short-term spectral parameters (i.e., measures averaged over five minute intervals) can vary as much as 4-fold during the course of a 1-h period. Despite the inherent variability of short-term HRV measures during routine daily activity, long-term measures show excellent day-to-day reproducibility. Given the inherent variability in the minute-to-minute spectral measurements, much care is required in the design of studies using HRV techniques and in interpretation of HRV results. Still, studies utilizing measures of HRV can provide insight into relationships between perturbations of the internal or external environment and subsequent changes in the modulation of autonomic neural input to the heart.

Using both time and frequency domain parameters, HRV has been studied as a marker of medical prognosis in human clinical populations, most frequently in coronary artery disease populations, particularly in the post-myocardial infarction (post-MI) population. Those variables most closely correlated with parasympathetic tone appear to have the strongest predictive value

in heart disease populations. The altered HRV itself is not the causative agent, but rather altered HRV (including changes in HRV associated with exposure to PM) is simply a marker for enhanced risk of serious cardiac events (e.g., heart attack, stroke).

Another route by which PM could exert deleterious cardiovascular effects may involve ambient PM effects on endothelial function. PM exposure may affect blood coagulation through endothelial injury that results in platelet activation. This then could initiate a cascade of effects (e.g., platelet activation and/or aggregation, increased blood fibrinogen and fibrin formation modulated by Factor VII, etc.), leading to increased formation of blood clots. Or PM taken up into the systemic circulation could possibly affect clot lysing events that normally terminate the blood coagulation cascade. Newly available studies have measured various blood substances to evaluate possible PM-induced effects on blood coagulation. Another significant effect of PM exposure could be vascular inflammation, which induces release of C-reactive proteins and cytokines that may cause further inflammatory responses which, on a chronic basis, can lead to atherosclerosis. In narrowed coronary arteries, clots formed by the aforementioned cascade may block blood flow, resulting in acute myocardial infarction.

Small prothrombotic changes in blood coagulation parameters in a large population can have substantial effects on the incidence and prevalence of cardiovascular disease events (Di Minno and Mancini, 1990; Braunwald, 1997; Lowe et al., 1997). Altered coagulation, for example, could increase heart attack risk through formation of clots on atherosclerotic plaques in coronary arteries that cut off blood supply to the myocardium or induce ischemic strokes via clots forming or lodging in the carotid arteries and blocking blood flow to the brain. Also, evidence exists for formation of small thrombi being common in persons with atherosclerosis (Meade et al., 1993); and whether such thrombi lead to more serious effects (heart attack, stroke) depends in part on the balance between thrombogenic factors underlying blood clot formation and fibrinolytic factors that lyse clots. Increased sympathetic activity is thought to cause prothrombotic changes in blood coagulation parameters such that even small, homeostatic modulations of coagulation within a normal range could translate into significant increased risk for heart attack.

Another possible effect of PM exposure could be plasma extravasation from post-capillary venules. The mechanisms by which this occurs are thought to include the release of peptides (such as neurokinin A, substance P, and calcitonin-gene-related peptide) from unmyelinated

sensory nerves near to or on the blood vessels. These peptides bind to receptors on the endothelial cells of vessels and create gaps, allowing leakage of plasma, which is one component of neurogenic inflammation (Piedimonte et al., 1992; Baluk et al., 1992).

Thus, alterations in cardiovascular functions due to PM exposure could be signaled by small PM-related (a) changes in blood coagulation cascade indicators, e.g., increased blood platelet, fibrinogen, or Factor VII levels or decreased tissue plasma activator (TPA) levels; (b) increased C-reactive protein or cytokines, possibly contributing to increased atherosclerosis plaque formation and/or blood coagulation; (c) increased blood pressure; and/or (d) certain alterations in heart rate, heart rate variability, or other ECG indicators indicative of shifts in parasympathetic/sympathetic neural inputs to the heart or other underlying cardiac pertubations. These alterations, while not likely to have significant impact in healthy individuals, may be deleterious in susceptible individuals with underlying cardiopulmonary disease.

Coherence Between Epidemiologic and Experimental Evidence

Considering first the evidence from epidemiological studies conducted within a given location, recent studies have reported associations for PM with both mortality and hospital admissions for cardiovascular diseases in several U.S. cities. For example, in Chicago (Figure 8-24), associations were reported between PM_{10} and cardiovascular mortality and cardiovascular hospital admissions. In Los Angeles (Figure 8-25), associations were found between PM_{10} and cardiovascular mortality, cardiovascular hospital admissions, and admissions for specific categories of cardiovascular disease (e.g., myocardial infarction, congestive heart failure, cardiac arrhythmia, cerebrovascular and occlusive stroke); some studies included associations with $PM_{2.5}$. In addition, one recent study in a group of Los Angeles residents with COPD reported associations between PM_{10} and diastolic and systolic blood pressure, although no associations were reported for heart rhythm measures (Section 8.3.1.3.4). In Detroit (Figure 8-27), as well, associations were seen between PM_{10} and cardiovascular mortality, cardiovascular hospital admissions and admissions for specific categories of cardiovascular disease (including ischemic heart disease, heart failure, dysrrhythmia, stroke); associations were also reported with $PM_{2.5}$ and $PM_{10-2.5}$.

More broadly, the fuller array of epidemiologic studies shows associations between various ambient PM indices and a range of cardiovascular health outcomes, from mortality and

hospitalization for various cardiovascular diseases to recent evidence for associations with incidence of myocardial infarctions and physiological or biochemical indicators of cardiovascular health. The newer evidence includes epidemiologic panel studies reporting changes in blood characteristics (e.g., increased fibrinogen or C-reactive protein levels) related to increased risk of ischemic heart disease, and changes related to heart rhythm, including cardiac arrhythmia or changes in heart rate variability that may be linked with more serious cardiac effects. While further research is needed to more firmly establish and understand links between particles and these more subtle endpoints, the newly available results provide suggestive evidence for a chain of endpoints linked to potential mechanisms for cardiac effects. These more recent studies have mainly found associations for PM_{10} and $PM_{2.5}$; only one study included $PM_{10-2.5}$ and reported no associations with heart rate variability changes (Section 8.3.1.3.4). As for lags seen epidemiologically between PM exposure and observed effects, acute short-term ($\leq$ 24-h) 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.

There were few toxicologic studies assessed in the 1996 PM AQCD that evaluated cardiovascular system effects of exposures to particulate matter. Since 1996, numerous studies have now become available that evaluated cardiovascular effects of exposures (via inhalation or instillation) of ambient PM, constituent components, complex mixtures from PM emission sources and/or exposures to single PM substances or binary/ternary combinations of particles of varying chemical composition. Whereas earlier studies tended to focus on healthy animals, the more recent studies have, in addition, begun to focus on evaluation of PM effects in animal models of disease states thought to mimic aspects of pathophysiologic states experienced by compromised humans at increased risk for PM effects.

A growing number of studies have used extracts of collected/stored ambient PM or real-time generated concentrated ambient particles (CAPs) drawn from various airsheds (e.g., Boston, New York City, etc.) to evaluate cardiovascular and other systemic effects of PM. Many other new animal studies have also used metal-associated ROFA as one type of combustion source particle mix and others have used other combustion source materials, e.g., domestic oil fly ash (DOFA), coal fly ash (CFA), or diesel exhaust (DE).

The ensuing discussion focuses mainly on those toxicology studies using ambient or near-ambient PM concentrations thought to be most relevant to ambient PM exposure situations in the United States. Controlled human exposure studies have yielded limited 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 also observed with CAPs, UAP, and ROFA. Probably of most note, two controlled human exposure CAPs studies found evidence that ambient levels (~50 to 300 $\mu g/m^3$) of inhaled $PM_{2.5}$ can produce biochemical changes (increased fibrinogen) in blood suggestive of PM-related increased risk for prothrombotic effects. Also, blood fibrinogen levels increased in both normal and compromised dogs at 69 to 828 $\mu g/m^3$; and decreased Factor VII levels were observed by other investigators in humans with 2-h CAPs exposure at ~174 $\mu g/m^3$, perhaps reflecting that enzyme being consumed in an ongoing coagulation process. 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 $\mu g/m^3$.

One excellent example of linkage between cardiovascular results from epidemiological and toxicological studies is provided by a series of studies conducted in Boston. Recent epidemiological studies have linked daily or hourly changes in $PM_{2.5}$ with several cardiovascular health outcomes: incidence of myocardial infarction was increased in association with PM exposures 2 hours prior to the health event; increases in recorded discharges from implanted cardiovertex defibrillators (an indicator of cardiac arrhythmia) were positively associated with daily $PM_{2.5}$ concentrations; and decreases in heart rate variability measures were reported (a) in young healthy boilermakers to be associated with personal $PM_{2.5}$ measurements and (b) in elderly residents of a retirement community with ambient $PM_{2.5}$ (Section 8.3.1.3.4). Results of toxicological studies in Boston using $PM_{2.5}$ CAPs exposures in dogs are suggestive of changes in cardiac rhythm with $PM_{2.5}$ mass and changes in blood parameters with certain $PM_{2.5}$ components (Table 7-1). These findings in both humans and animals, using the same general mix of particles and co-pollutants, are suggestive of changes in cardiac rhythm and changes in blood parameters. Also, in addition to the epidemiologic studies conducted in Los Angeles, results from controlled human inhalation exposures (for 2 h) of healthy adult volunteers to

Los Angeles $PM_{2.5}$ CAPs suggest effects on some cardiovascular outcomes (decreased Factor VII blood levels and some cardiac symptoms), but not with other cardiovascular indicator measures (such as changes in blood fibrinogen levels) (Table 7-1). More rigorous characterizations of dose-response relationships with environmentally relevant levels and species of PM will be necessary to evaluate more fully cardiovascular risks posed by ambient PM exposures.

Limited new evidence is available regarding the effects of different components or attributes of particles on the cardiovascular system. Recent epidemiological studies reported slight increases in blood viscosity with ultrafine particle exposures. Little or no evidence is available on cardiovascular effects of PM components, such as sulfates or acid aerosols. Particle constituents such as transition metals (e.g., Ni, V, Zn, Fe) have been shown to cause cell injury and inflammatory responses in toxicologic studies, that may possibly be linked with cardiovascular health outcomes. Since particles are complex mixtures, studies using factor analysis or source apportionment methods may be more relevant than studies of individual components, and the few studies available to date have linked cardiovascular mortality with several fine particle source categories (Table 9-3).

More limited evidence is also available on cardiovascular effects of long-term exposure to particles. Epidemiologic studies indicate associations between fine particles and mortality from cardiovascular diseases, although no evidence is currently available regarding long-term PM exposure and cardiovascular morbidity. Toxicologic studies have not yet been conducted to investigate potential cardiovascular effects with chronic PM exposures.

Beyond the evidence of coherence and plausibility described above, it is useful to consider salient-hypotheses that have been proposed to account for PM-related effects. The most salient hypotheses proposed to account for cardiovascular 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; and, to date, the strongest evidence found thus far most clearly supports the plausibility of the first mechanism being involved. Both epidemiologic and toxicologic studies have found evidence of ambient PM effects on blood

fibrinogen and/or other measures indicative of increased blood coagulability within 2 to 24 hours following short-term (≤ 24 h) exposures to ambient or near-ambient concentrations of urban PM aerosols. Much future research using controlled exposures to PM of laboratory animals and human subjects will be needed, however, 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.

9.2.3.2.2 Respiratory-related Health Endpoints

As noted in Section 9.2.2, a number of epidemiologic studies show associations between short-term and/or chronic ambient PM exposure and respiratory effects ranging from respiratory-related mortality to hospitalization or medical visits for respiratory diseases to increased respiratory symptoms or decreased lung function. Respiratory system effects of PM may be exerted via several different types of mechanisms of action, including involving direct pulmonary effects and others secondary to lung injury. Direct pulmonary effects include lung injury and inflammation; increased airway reactivity and exacerbation of asthma; and increased susceptibility to infection.

Numerous toxicological studies point towards lung injury and inflammation being associated with exposure of lung tissue to complex combustion-related PM materials. Important evidence pointing towards ambient PM causing lung injury and inflammation derives from the study of ambient PM materials on filter extracts collected from community air monitors before, during the temporary closing of a steel mill in Utah Valley, and after its reopening. Studies in animals and human volunteers reported greater lung inflammatory responses with exposure to materials obtained before and after the temporary closing versus that collected during the plant closing. Further analyses suggested that the metal constituents of particles may be important contributors to the pulmonary toxicity observed in these studies. Rats with SO_2-induced bronchitis and monocrotaline-treated rats have been reported to have a greater inflammatory response to concentrated ambient PM than normal rats. The toxicologic studies suggest that exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

Toxicologic studies have also indicated that PM exposure can affect pulmonary defense responses to microbial agents. Studies using combustion related particles, albeit at high doses,

have shown effects such as increased inflammatory responses or mortality rate from respiratory infections, compared with animals exposed to infectious agents without PM exposure (as discussed in Section 7.5.4).

Finally, PM exposure may result in increased airway reactivity and exacerbation of asthma. The strongest evidence supporting this hypothesis is from studies on diesel particulate matter (DPM). Diesel particulate matter has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 7.2.1.2).

Coherence Between Epidemiologic and Experimental Evidence

Recent time series epidemiologic studies have reported associations between short-term (24-h) PM exposures and respiratory-related mortality and hospital admissions for respiratory diseases in cities such as Chicago, Los Angeles and Detroit. These studies, and others in Seattle and Pittsburgh, have also reported associations between PM and hospitalization or emergency department visits for asthma, pneumonia and COPD, as well as physicians visits for respiratory diseases. 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. Respiratory effects typically exhibit somewhat longer and more extended lag periods, from 1 to 2 days on out to a week or so after PM exposure, than do cardiovascular effects.

Some epidemiologic studies also indicate associations between long-term (years to decades) exposures to ambient PM (especially fine particles) and mortality due to cardiopulmonary causes, although other recent studies indicated that such fine PM associations may be more strongly linked to cardiovascular diseases than respiratory disease. Long-term exposure to PM has also been found to be associated with potential development of chronic respiratory diseases and reductions in lung function.

The respiratory effects of PM with 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. Controlled exposures to crustal materials, e.g., those in Mt. St. Helens volcanic ash, have also

been studied. The toxicological data available today provide little basis for concluding that these types of specific PM constituents have substantial respiratory effects at current U.S. ambient levels of exposure. Recently, ROFA, a very specific kind of PM derived from oil combustion, has been studied extensively and found to produce a range of respiratory effects, especially lung inflammation, mainly attributable to its very high metal content that is several orders of magnitude (100's of times) higher than ambient concentrations typically found in U.S. ambient air.

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 at 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 yield 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. Followup evaluations have produced new evidence implicating transition metal components of ambient PM from diverse locations and of ROFA as inducing 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 $\mu g/m^3$). Although ranges of concentration were reported in the above inhalation studies, it is not possible to determine the actual lowest concentration at which effects were observed.

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, though these doses are extremely high and are unlikely to be approached with exposures to ambient levels of PM currently found in U.S.

airsheds (except, possibly, under unusual circumstances, e.g., exposure to dense smoke from forest fires).

A set of epidemiologic, toxicologic and controlled human exposure studies on effects of particles from the Utah Valley area has linked PM_{10} with respiratory system effects or, more specifically, lung inflammation. 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. An epidemiologic study reported that respiratory hospital admissions for children were reduced during the period when the source was not operating (see Chapter 8, Section 8.2.3.4). New toxicologic and human studies then used extracts of ambient particles collected on filters from ambient PM_{10} 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 (as discussed in Chapter 7, 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. However, consideration of dosimetric analyses (see Appendix 7A) indicates that the bolus instillation doses of particles used in these experiments were equivalent to a single-dose exposure to amounts of particles that would result from extended (for 6-9 weeks) continuous exposure to the higher-end of the range of concentrations of PM_{10} that the community might have experienced during wintertime inversions in the Utah Valley. In vitro studies using a human airway epithelial cell line and primary rat airway epithelial cells 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). Additional evaluations indicate that the in vivo and in vitro inflammatory responses observed were attributable to elevated metal content present in the particle extracts during the periods when the steel mill was operating. This body of evidence provides coherent links between results of community epidemiologic studies reporting increases in respiratory hospitalization with toxicologic evidence of respiratory inflammation in humans and animals.

Some evidence is also available on respiratory effects of different components or attributes of particles, especially fine particles. A few epidemiologic studies have reported associations between ultrafine particles (measured as particle number) with respiratory symptoms or decreased lung function. In addition, toxicologic studies have used various types of ultrafine

particles (e.g., carbon black), and reported greater inflammatory responses than those seen with fine particle mass for the same type of particles. The relative importance of differing composition or surface area for these effects remains to be determined.

Fine particulate sulfates and acid aerosols have been associated with respiratory hospitalization, symptoms or and decreased pulmonary function in epidemiological studies, in both short-term and long-term exposure studies. Toxicological studies, however, have reported pulmonary or inflammatory effects with acid aerosol or sulfate exposures only at fairly high (hundreds of $\mu g/m^3$). It appears likely that, in the epidemiological studies, sulfates are serving as an indicator of particle mixtures or sources of particles. Toxicological studies have also reported that transition metals on fine particles (e.g., Ni, V, Zn, Fe) cause cell injury and inflammatory responses and, so, they may contribute to associations with respiratory health outcomes reported in epidemiological studies. Also, recent studies also show that diesel exhaust particles may exacerbate allergic responses to inhaled antigens.

As summarized above (Section 9.2.3.3.1) and discussed in more detail in Chapter 7 (Section 7.3.6) biological constituents of particles (e.g., fungal spores, plant and insect fragments, airborne bacteria) have been clearly linked with allergic, pulmonary or inflammatory responses in toxicological studies, and with respiratory symptoms or lung function changes in epidemiologic studies. Though the 1996 PM AQCD had concluded that bioaerosols at ambient levels were unlikely to contribute to PM-related health effects, more recent findings suggest that biogenic materials in ambient air may be attached to either natural or anthropogenic particles and be carried by them into the deep lung and concentrated at “hot spots”, where enhanced doses to tissue may produce exacerbation of lung inflammatory and allergic responses to of the bioaerosols.

For the most part, information regarding components of particles has come from studies of fine particles. Some of these components, particularly biogenic material and metals, can also be important components of coarse fraction particles. More research involving the systematic conduct of studies of potential respiratory effects of major components of PM from different regions of the United States is needed, in recognition that PM of different composition and from different sources can vary markedly in its potency for producing respiratory toxicity.
Of particular importance are studies that more systematically evaluate mixtures of ambient constituents found in various airsheds, including short-lived species, e.g., peroxides.

9.2.3.2.3 Lung Cancer

Historical evidence linking cancer with PM exposures includes epidemiological studies of lung cancer trends, studies of occupational groups, comparisons of urban and rural populations, and case-control and cohort studies using diverse exposure metrics. Numerous past ecological and case-control studies of PM and lung cancer have generally found lung cancer relative risks greater than 1.0 to be associated with living in areas having higher PM exposures despite possible problems with respect to potential measurement errors for exposure and other risk factors. The 1996 PM AQCD (Section 8.4.6.4) further noted certain recently published prospective cohort study results (e.g., those from the ACS study) which found positive, but not statistically significant,associations between $PM_{2.5}$ and lung cancer mortality — leading to a bottom line conclusion in that document that insufficient evidence then existed by which to link ambient PM exposures to increased risk of lung cancer.

More recent epidemiologic studies published since the 1996 PM AQCD have expanded upon and extended the earlier findings, including both (a) reported significant associations between long-term exposure to fine particles and lung cancer mortality in further analyses of data for the ACS and AHSMOG cohorts, and (b) suggestive evidence for PM -related increases in lung cancer incidence in analyses using AHSMOG cohort data (see Section 8.4.6.4, Tables 8-10 and 8-12). The 2002 extended ACS analysis included additional data from that cohort, inclusion of more recent air quality data , incorporation of statistical modeling advances, and additional data on potential confounders (such as dietary information); and it showed a 13% increase in lung cancer mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The AHMOG analysis also included follow-up data from the ASHMOG cohort and yielded a significant association between PM_{10} and lung cancer mortality in males, but not in females. In further follow-up of the results in males only, positive but not statistically significant associations were reported with $PM_{2.5}$ and $PM_{10-2.5}$, and the authors observed that the association was larger in magnitude for $PM_{2.5}$ than for $PM_{10-2.5}$.

Toxicological studies have shown extensive evidence that certain types of particles are mutagenic or otherwise genotoxic in various types of bioassays, and several recent *in vivo* and *in vitro* studies have suggested that ambient particles are mutagenic. These latter studies have included exposures to ambient particles collected in Los Angeles, urban areas of Germany, and high traffic areas in the Netherlands (Section 7.8.1). In Germany, $PM_{2.5}$ extracts were found to

have more mutagenicity than extracts of PM_{10} samples. Also, evidence of mutagenicity has been reported in studies using exposures to emissions from wood/biomass burning, coal combustion, and gasoline and diesel engine exhaust. Some of these studies identified PAHs as well as some gaseous components of the emissions as being more mutagenic than other portions (Sections 7.8.2, 7.8.3). Such results appear to provide experimental evidence that adds some degree of plausibility for the reported epidemiologic findings of ambient PM associations with increased risk of lung cancer. However, this should be caveated by noting that some of the bioassay results were not indicative of particularly strong mutagenic responses to the PM sample extracts or components tested, nor is there necessarily a high degree of correspondence between some of the types of in-vitro genotoxic effects observed and demonstrated tumerogenic/cancer-causing potential across a broad array of different types of gaseous and particulate compounds tested over many years.

Thus, recent epidemiological studies support an association between long-term exposure to fine particles and lung cancer mortality; and the new toxicological studies provide credible evidence for the biological plausibility of these associations.

9.2.3.2.4 Fetal and Infant Development/Mortality

A few older cross-sectional studies reviewed in the 1996 PM AQCD reported findings suggestive of (a) possible TSP relationship to increased postnatal mortality among U.S. infants, children, and adolescents (aged 0-14 yrs.) and (b) possible associations between early postnatal mortality among Czech infants (1-12 mo). Several more recent studies conducted in the U.S. have focused on the possible effects of air pollution exposures during pregnancy on the occurrence of preterm or low birth weight births, both of these being risk factors for a myriad of later health problems (childhood morbidity/mortality; possible adult morbidity). One study found results suggestive of prenatal PM_{10} exposures during the 1st month of pregnancy or averaged over 6 weeks prior to birth being associated with increased risk of preterm birth, even in multipollutant models. However, another large scale U.S. study found little evidence indicative of prenatal PM_{10} exposures being related to increased risk of low birth weight, whereas a new Czech study did find evidence indicative of interuterine growth retardation (leading to low birth weight) being related to $PM_{2.5}$ exposures during the first gestational month. Similarly, analogously mixed results were reported for some new studies that evaluated ambient

PM relationships to early postnatal mortality among U.S., Czech, and Mexican infants. These results, overall, highlight the need for more research to elucidate potential ambient PM effects on fetal development/mortality and for postnatal morbidity/mortality.

9.2.3.3 Summary and Conclusions

Consideration of the plausibility and coherence of PM-related effects involves the integration of the epidemiologic evidence with information derived from other types of studies (e.g., exposure, dosimetry, toxicology). As discussed in Section 9.2.2, consideration of epidemiologic evidence alone gave evidence supporting causality for associations between PM and a range of cardiovascular and respiratory health outcomes. In this section, evidence from both epidemiologic and toxicologic studies for health outcomes that are logically linked together was considered.

Epidemiologic studies have reported associations between ambient PM and cardiovascular effects across a range of endpoints, from cardiovascular mortality to more subtle effects, such as changes in electrocardiographic markers of cardiac function, including evidence of cardiac arrhythmia and altered heart rate variability, or 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. The new epidemiological findings for physiological changes suggest links to mechanistic pathways that would result in observed cardiovascular morbidity or mortality, but as described earlier, there are caveats to be considered in the interpretation of these studies. Important new evidence is available from toxicologic studies that builds support for plausibility of associations between particles, especially fine particles (or constituents) with physiological endpoints indicative of increased risk of ischemic heart disease, development or exacerbation of atherosclerosis or changes in cardiac rhythm. While many research questions remain, the convergence of evidence related to cardiac health from epidemiologic and toxicologic studies indicates both coherence and plausibility in this body of evidence.

For respiratory effects, notable new evidence from epidemiological studies substantiates positive associations between ambient PM concentrations and not only respiratory mortality, but (a) increased respiratory-related hospital admissions, emergency department, and other medical visits; (b) increased incidence of asthma and other respiratory symptoms; and (c) decrements in pulmonary functions. Of much interest are new findings tending to implicate not only fine

particle components but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of various respiratory conditions (e.g., asthma). Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure. The biological pathways underlying such effects can include inflammatory responses, increased airway responsiveness or altered responses to infectious agents. Toxicological studies have provided evidence that supports plausible biological pathways for respiratory effects of fine particles; little evidence is yet available on coarse fraction particles.

New epidemiological reanalyses or extensions of earlier prospective cohort studies of long-term ambient PM exposure also show substantial evidence for increased lung cancer risk being associated with such PM exposures, especially exposure to fine PM or specific fine particles subcomponents (e.g., sulfates) and/or associated precursors (e.g., SO_2). Toxicological evidence of mutagenicity or genotoxicity in ambient or combustion-related particles supports the plausibility of a relationship between fine particles and lung cancer mortality.

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). Most studies have used PM_{10} or other measures of thoracic particles; little evidence is available regarding $PM_{2.5}$ or $PM_{10-2.5}$. 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.

Taken together, new evidence from mechanistic studies suggesting plausible biological response pathways, and the extensive body of epidemiology evidence on associations between short- and long-term exposures to ambient thoracic particles (typically indexed by PM_{10}) and a range of health effects, supports the general conclusion that ambient thoracic particles, acting alone and/or in combination with gaseous co-pollutants, are likely causally related to cardiovascular and respiratory mortality and morbidity. A growing body of evidence both from epidemiologic and toxicologic studies also supports the general conclusion that $PM_{2.5}$ (or one or

more $PM_{2.5}$ components), acting alone and/or in combination with gaseous co-pollutants, are likely causally related to cardiovascular and respiratory mortality and morbidity. The strength of the evidence varies across such endpoints, with relatively stronger evidence of associations with cardiovascular than respiratory endpoints, potentially due to reduced statistical power where respiratory outcomes are seen less frequently than cardiovascular outcomes. In addition, mortality associations with long-term exposures to $PM_{2.5}$, in conjunction with evidence of associations with short-term exposures, provide strong evidence in support of a casual inference.

A much more limited body of evidence is suggestive of associations between short-term (but not long-term) exposures to ambient coarse-fraction thoracic particles (generally indexed by $PM_{10-2.5}$) and various mortality and morbidity effects observed at times in some locations. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may contribute under some circumstances to increased human health risks. The strength of the evidence varies across endpoints, with somewhat stronger evidence for coarse-fraction particle associations with morbidity (especially respiratory) endpoints than for mortality. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, and much remains to be learned about the contribution of different sources or thoracic coarse particle components to different health outcomes. Reduced precision for $PM_{10-2.5}$ effect estimates may be heavily influenced by the increased error in $PM_{10-2.5}$ measurements obtained by subtraction, and exposure error related to greater spatial variability and reduced penetration indoors, as compared with $PM_{2.5}$.

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., SO_2, peroxides, aldehydes) can be accumulated within inhalable PM and delivered in enhanced quantities 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. 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 important mediators of health effects caused by the overall air pollutant mix.

The increased availability of certain bioaerosol materials (e.g., allergen-laded 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. Such bioagents have been found attached to non-biologic particles of anthropogenic origin, as well as natural biologic particles, which may serve to concentrate the biologic agents and enhance their delivery into TB and A regions of the lung and exacerbate consequent inflammatory and allergic asthmatic responses.

9.2.4 Potentially Susceptible and Vulnerable Subpopulations

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, or personal risk factors such as smoking, diet, or exercise; personal risk factors such as smoking, diet, or exercise habits are also associated with the development of heart and lung diseases. In addition, new attention has been paid to the concept of some population groups having increased *vulnerability* to pollution-related effects due to factors including socioeconomic status (e.g., reduced access to health care) or particularly elevated exposure levels.

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. Environmental Protection Agency, 1996, p. 13-92)

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; and the evidence related to preexisting disease, age groups, and genetic susceptibility is summarized below. In addition, recent studies have explored potential new risk factors related to potential increased vulnerability for certain population groups, and evidence regarding factors such as socioeconomic status or exposure status are also discussed below.

9.2.4.1 Preexisting Disease as a Risk Factor

A number of time-series epidemiologic studies have reported increased risk in study subsets of individuals with preexisting heart or lung diseases. Several studies have suggested that people with diabetes are also susceptible to PM effects, possibly due to cardiovascular complications associated with diabetes. One study reported large relative risk estimates for total mortality in people with preexisting COPD living in Barcelona. Another study in Montreal showed larger effect sizes for total mortality in persons with cancer, diabetes, lower respiratory disease, cardiovascular disease, coronary artery disease, and congestive heart failure. In addition, an European study found significant effects in the subset of adults who had bronchial hyperreactivity or increased peak flow variability; and a Canadian study 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 of Chapter 7, 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 (see Section 7.4.9 of

Chapter 7). 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. 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), to augment injury, or to predispose the lung (e.g., sensitize receptors) so as 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). Any of these or related mechanisms may contribute to increased "susceptibility" and may indeed be a common factor possibly contributing to increased risk for various susceptible groups.

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).

9.2.4.2 Age-related At-risk Population Groups: the Elderly, Infants, 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 (nonaccidental) 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. Some newly emerging studies provide suggestive evidence for increased neonatal mortality and adverse birth outcomes being associated with ambient PM exposures, but other new studies have found contradicting results.

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 contribute to the potentially higher risk within older age groups. Also, some recent studies have reported evidence suggestive of associations between ambient PM exposure and effects on total development or neonatal mortality (see Section 8.3.4 of Chapter 8). 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 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 or vulnerable 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. 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).

9.2.4.3 Genetic Susceptibility

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

9.2.4.4 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. Results from two of the prospective cohort studies evaluating long-term PM exposure effects have reported greater mortality (and cancer) risks in males than in females (e.g., Abbey et al., 1999; Pope et al., 2002), but 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 in the time-series studies, they were generally not significantly different and the findings were 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.

9.2.4.5 Factors Related to Enhanced Vulnerability

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 (Chapter 8, Appendices 8A and 8B), the evidence is more mixed regarding potential influence of socioeconomic status on PM-related health risks. No evidence of effect modification for PM_{10}-mortality associations in 10 U.S. cities was found 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. Similarly, in a study of hospital admissions in 10 U.S. cities, 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. This may be a result of increased exposure, increased prevalence of predisposing diseases, or other factors. Also, one study in Atlanta found race (black vs. white) and insurance (Medicaid vs. non-Medicaid) to be effect modifiers for emergency department admissions for asthma in children, but no associations with interaction terms for these factors and PM_{10} or ozone. Another study 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. However, a Seattle study reported no effect estimate differences for asthma hospitalization in children (< 18 years) when comparing the inner city area with the rest of Seattle.

Vulnerability to PM-related effects may also be increased in populations experiencing enhanced exposure to ambient aerosols in comparison to other groups. In some cases, e.g., proximity to roadways or other PM sources, there may be overlap with other factors (e.g., socioeconomic statuses).

As summarized in Chapter 8, 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. Also, using data from 14 U.S. cities, other investigators found 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). 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 and with residences near a major road.

In addition to the above factors contributing to increased vulnerability, exercise may also 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.

9.2.4.6 Summary and Conclusions

The existence of heart and lung disease, including possibly diabetes, is clearly linked with increased susceptibility to effects from PM exposure, based on epidemiological and toxicological studies and dosimetric evidence. The epidemiological evidence of susceptibility is primarily from studies of short-term exposure. Long-term exposure studies have suggested that PM exposure may result in chronic respiratory disease or decreased lung function growth, thus there is the potential that chronic PM exposure can also increase susceptibility to acute changes in PM. More recent studies also support considering older adults and children, including possibly infants, as susceptible groups, recognizing that there is likely overlap between age categories and preexistence of cardiopulmonary diseases. Some new evidence from toxicologic studies indicates that there may be populations who are genetically predisposed to PM-related effects. In addition, beyond consideration of innate or acquired factors related to susceptibility, some population groups can be considered to be more vulnerable to PM-related effects due to factors such as socioeconomic status or residing near roadways or other sources.

9.2.5 Potential Public Health Impacts in the United States

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. Environmental Protection Agency, 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. Environmental Protection Agency, 1996, p. 1-21)

9.2.5.1 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.

One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with PM-related air pollution exposure. Table 9-4 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 9-5 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.

In addition, as discussed previously, subpopulations based on age group or socioeconomic status would also comprise substantial segments of the population that may be potentially more vulnerable to PM-related health impacts. 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. Hence, large proportions of the U.S. population are included in groups that are thought likely to be at increased risk for ambient PM-related health effects.

TABLE 9-4. 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 9-5. 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).

The health statistics data also illustrate what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 millions deaths from all causes 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. Thus, even a small percentage reduction in PM health impacts on cardiorespiratory-related diseases would reflect a large number of avoided cases.

Another key input for public health impact assessment is the range of concentration-response functions for various health outcomes. As described in Chapter 8, epidemiological studies have reported associations between short-term exposure to PM, especially PM_{10} and $PM_{2.5}$, with: mortality, hospitalization and medical visits for cardiovascular and respiratory diseases; changes in heartbeat rhythm or electrocardiographic markers of cardiac function; incidence of myocardial infarction; changes in blood characteristics (e.g., C-reactive protein, fibrinogen levels); incidence of respiratory symptoms; and reduced lung function. As discussed previously, the fewer studies using $PM_{10-2.5}$, measurements have reported evidence for associations with hospitalization for cardiovascular and respiratory causes, and increased respiratory symptoms, and suggestions of associations with cardiopulmonary mortality. Associations with long-term exposure to fine particles have been reported for cardiovascular and lung cancer mortality, increased incidence of respiratory disease and decreased lung function and lung function growth. The magnitude of the concentration-response function, measured or anticipated change in air concentration, and size of population group are three major components of a public health impact assessment.

Of concentration-response functions for PM-related effects, it can generally be said that the effect estimates are small in magnitude. In historical episodes with very high air pollution levels, risks on the order of 4-fold (400%) increases in mortality were estimated, but much smaller risk estimates have been reported from recent studies at current pollution levels.

Risk estimates from long-term exposure studies are often larger in magnitude than those for the same health outcome associated with short-term PM exposure. These estimates can reflect different responses — long-term exposure perhaps being linked with development of disease and short-term exposure with acute exacerbation of existing conditions — but there may also be some overlap in the effect estimates. Relative risk estimates for total mortality from the prospective cohort studies fall in the range of 7 to 13% increase per 10 $\mu g/m^3$ increase in $PM_{2.5}$; there are no significant associations with long-term exposure to $PM_{10-2.5}$. Risk estimates from the short-term exposure studies are considerably smaller in magnitude, on the order of 2 to 6% increase in mortality per 25 $\mu g/m^3$ increase in $PM_{2.5}$ and $pM_{10-2.5}$. Time-series studies using distributed lag periods over more extended time periods (e.g., 40-60 days) partially bridge these results.

Effect estimates for morbidity responses to short-term changes in PM tend to be larger in magnitude than those for mortality; those for hospitalization generally range from 4-10% increases for cardiovascular diseases and 5-15% increases for respiratory diseases per 25 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10-2.5}$. From the more recent studies on visits to the emergency department or physicians' offices for respiratory conditions, effect estimate sizes have been somewhat larger, ranging up to about 35% per 25$\mu g/m^3$ increase in $PM_{2.5}$.

Other important considerations for public health impact assessment that have been discussed previously include questions about the concentration-response function form and potential identification of threshold levels, and attribution of risks for the varying health outcomes to PM, sources or components of particles, and co-pollutants. Taken together, however, it can be concluded that small incremental risks for large groups of the U.S. population would result in large public health impact estimates.

9.2.5.2 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 PM 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.

Finally, as discussed in Section 8.4.10 of Chapter 8, there appears to be no strong evidence to suggest that PM exposures are shortening life by only a few days (i.e., for "harvesting"). To the contrary, the 1996 PM AQCD noted that results from the Harvard Six City Study suggested that long-term exposure to $PM_{2.5}$ was associated with ~2 yr loss of life expectancy. More recent investigations of the public health implications of effect estimates for long-term PM exposures were also reviewed in Chapter 8. Using results from prospective cohort studies of mortality in adults, it has been estimated 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 may ultimately significantly increase estimates of the extent of life shortening due to PM-related premature mortality.

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 indicate 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, with any consequent life-shortening due to lung cancer.

Lastly, new epidemiologic studies of a broader array of health endpoints indicate ambient PM associations with increased non-hospital medical visits (physician visits) and asthma effects. Such new findings suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed either by just hospital admissions/visits and/or mortality.

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, climate change processes, and man-made materials. 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 (1993) report on Protecting Visibility in National Parks and Wilderness Areas, and U.S. EPA's Interim

Findings on the Status of Visibility Research (U.S. Environmental Protection Agency, 1995). The focus here is on characterizing: (a) how ambient PM (in particular ambient fine PM) impairs visibility, and (b) how the public perceives and values improvements in visibility, especially in urban areas.

9.3.1.1 Relationships Between Ambient PM and 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 the dry mass of fine particles, as modulated by particle composition, size, hygroscopic characteristics, and by 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 measurement 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, so as to better estimate the ambient aerosol water content. These studies have served primarily to reinforce and refine our understanding of how airborne particles affect visibility.

Effects to address visibility impairment have historically been focused on 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 rural 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.

More recent attention has been given to addressing visibility impairment in urban areas, as well. Such efforts can now draw upon data 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 perceives and values improvements in visibility in a number of urban areas, as discussed below.

9.3.1.2 Public Perception and Valuation of Visibility Improvements

The Clean Air Act (Section 169A) establishes a national visibility goal to "remedy existing impairment" and prevent future impairment in national parks and wilderness areas across the U.S., and requires that long-term strategies be put in place to make reasonable progress toward this national goal. The 1990 Amendments to the Act (Section 169B) place additional emphasis on improving visibility, leading to EPA's promulgation of a Regional Haze Rule in 1999 that establishes specific goals for improving visibility in such areas. These national goals and regulations provide clear evidence of the value society places on visibility improvements that add to enjoyment of scenic vistas in special areas.

More specific information about how the public perceives and values improvements in visibility in rural and urban areas comes from both economic studies and from local and/or state initiatives in a number of areas to adopt local visibility goals and standards. As summarized in Chapter 4, there is an extensive scientific literature on the theory and application of economic valuation methods. Such studies have estimated the value of visibility improvements in the range of billions of dollars annually, for example, in analyses of visibility improvements in national parks in the Southwest (e.g., Chestnut and Rowe, 1990) and in an analysis of benefits to residents in the eastern U.S. due to visibility improvements associated with the Federal acid rain program (Chestnut and Dennis, 1997). Study results vary substantially across different valuation methods, however, and concerns remain about the use of these general approaches for quantitative purposes. Local initiatives over the past few years, for example in the Denver, CO and Phoenix, AZ areas, also provide important information about how the public perceives and values efforts to address 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. In addition, similar threshold determinations, convergent on a minimal visual range of 40 to 60 km, have also been identified in visibility standards in the Lake Tahoe area, the lower Fraser Valley in British Columbia, CN, and the State of Vermont.

9.3.1.3 Summary and Conclusions

Impairment of visibility in rural and urban areas is directly related to ambient concentrations of fine particles, as modulated by particle composition, size, and hygroscopic characteristics, and by relative humidity. Refinements in algorithms that relate these factors to light extinction, and thus, to visual range, as well as the availability of much expanded databases of PM2.5 concentrations and related compositional information and higher resolution visibility data all contribute to the ability to develop improved characterizations of relationships between ambient fine particle levels and visibility impairment.

Various local initiatives to address visibility impairment have demonstrated the usefulness of approaches now being used to evaluate public perceptions and attitudes about visibility impairment and public judgments as to the importance of standards to improve visibility relative to current conditions. Various such initiatives, conducted in areas with notable scenic vistas (e.g., Denver, CO), have resulted in local standards that reflect what might be referred to as "adverse thresholds" associated with a minimum visual range of approximately 40 to 60 km. These various local standards take into account that visibility impairment is an instantaneous effect of ambient $PM_{2.5}$ levels and that the public primarily values enhanced visibility during daylight hours. These considerations are reflected in local standards that are based on sub-daily averaging times (e.g., 4 to 6 hours), typically averaged across mid-day hours. This general convergence of visual range values and averaging times that have been determined to be acceptable to the public in a number of such locations suggests that these values and averaging times are relevant for consideration in assessing the need for a national secondary standard to protect visibility in such areas.

9.3.2 Effects of Ambient PM on Vegetation and Ecosystems

9.3.2.1 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 (streams, rivers, ponds, and lakes, estuaries and ocean); (3) the magnitude

(ambient concentration and 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. These effects were the usually 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.

Indirect effects of major concern (such as nitrogen saturation, acidification, and eutrophication) 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).

Ecosystem effects 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. Though the effects of urban PM as such, appear not to have been sufficiently 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 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).

Due mainly to three anthropogenically-driven activities, 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 (a compound of Nr) 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. Some NO_x emissions get converted/transformed into a portion of ambient air PM (particulate nitrate) and deposited onto sensitive ecosystems.

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 (e.g., particulate nitrates) 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 and species composition 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 nitrate 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).

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 carbon/nitrogen (C:N) ratios receiving high nitrogen deposition are prone to nitrogen saturation (Fenn et al., 1998).

Variations in the response of different forest types ecosystems across the eastern and the western United States 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^{-1}) (Johnson and Lindberg, 1992); the Fernow Experimental Forest, WV (15 to 20 kg N ha^{-1} yr^{-1}) (Gilliam et al., 1996); Whitetop Mountain, VA (32 kg N ha^{-1} yr^{-1}); the Catskill Mountains in southeastern NY (10.2 kg N ha^{-1} yr^{-1}); and the Adirondack Mountains of northeastern NY (9.3 kg N ha^{-1} yr^{-1}) (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 that result 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 which are 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 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 Characterization of PM-related Ecosystem Stressors

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 as 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 Relationships Between Atmospheric PM and Climate Change Processes

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. Environmental Protection Agency, 1996, p. 1-19, 1-21)

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 Effects of Ambient PM on Man-made Materials

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. Environmental Protection Agency, 1996, p. 1-20).

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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