# Integrated Science Assessment
# for Particulate Matter

# First External Review Draft

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**As immediate past CASAC Chair, Dr. Henderson is invited to participate in CASAC advisory activities for FY 2009.

# Chapter 1. Introduction

1        The first external review draft Integrated Science Assessment (ISA) is a concise review, synthesis,

2    and evaluation of the most policy-relevant science, and communicates critical science judgments relevant

3    to the National Ambient Air Quality Standards (NAAQS) review. As such, the ISA forms the scientific

4    foundation for the review of the primary (health-based) and secondary (welfare-based) NAAQS for

5    particulate matter (PM). The ISA accurately reflects "the latest scientific knowledge useful in indicating

6    the kind and extent of identifiable effects on public health which may be expected from the presence of

7    [a] pollutant in ambient air" (42 U.S.C. 7408). Key information and judgments formerly contained in the

8    Air Quality Criteria Document (AQCD) for PM are incorporated in this assessment. Additional details of

9    the pertinent scientific literature published since the last review, as well as selected older studies of

10   particular interest, are included in a series of annexes. This ISA thus serves to update and revise the

11   information available at the time of the previous review of the NAAQS for PM in 2006.

12       The *Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter*

13   identifies a series of policy-relevant questions that provide a framework for this review of the scientific

14   evidence (U.S. EPA, 2008b). These questions frame the entire review of the NAAQS for PM, and thus are

15   informed by both science and policy considerations. The ISA organizes and presents the scientific

16   evidence such that, when considered along with findings from risk analyses and policy considerations,

17   will help the EPA address these questions during the NAAQS review for PM. Briefly, the focus of this

18   assessment will be on scientific evidence that is most relevant to the following:

19   - What new scientific evidence is available to better understand the relationship between health
20     effects and short- or long-term exposure to PM? To what extent has scientific evidence
21     improved our understanding of the nature and magnitude of visibility, climate, and ecosystem
22     responses to PM?

23   - What evidence is available from recent studies focused on specific size fractions, chemical
24     components, sources, or environments (e.g., urban and non-urban areas) of PM to inform our
25     understanding of the nature of PM exposures that are linked to various health or public
26     welfare effects?

1      ▪    At what levels of PM exposure are health or welfare effects observed? What is the nature of

2            the dose-response relationships of PM for the various effects evaluated?

3      ▪    To what extent is key evidence becoming available that could inform our understanding of

4            subpopulations that are particularly susceptible or vulnerable to PM exposures[1]?

5      ▪    To what extent have important uncertainties identified in the last review been reduced? Have

6            new uncertainties emerged?

## 1.1. Legislative Requirements

7      Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS.

8    Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list "air pollutants" that "in his

9    judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence…

10   in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality

11   criteria for those that are listed (42 U.S.C. 7408). Air quality criteria are intended to "accurately reflect the

12   latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health

13   or welfare which may be expected from the presence of [a] pollutant in ambient air…" 42 U.S.C. 7408(b).

14   Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and

15   "secondary" NAAQS for pollutants listed under Section 108. 42 U.S.C. 7409(a). Section 109(b)(1)

16   defined a primary standard as one "the attainment and maintenance of which in the judgment of the

17   Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect

18   the public health."[2] 42 U.S.C. 7409(b)(1). A secondary standard, as defined in Section 109(b)(2), must

19   "specify a level of air quality the attainment and maintenance of which, in the judgment of the

20   Administrator, based on such criteria, is required to protect the public welfare from any known or

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[1] "Susceptibility" refers to innate (e.g., genetic or developmental) or acquired (e.g., age, disease, or smoking) factors that make individuals more likely to experience effects with exposure to PM. "Vulnerability" refers to PM-related effects due to factors including socioeconomic status (e.g., reduced access to health care) or particularly elevated exposure levels.

[2] The legislative history of section 109 indicates that a primary standard is to be set at "the maximum permissible ambient air level…which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" [S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970)].

1    anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[1]

2    42 U.S.C. 7409(b)(2).

3        The requirement that primary standards include an adequate margin of safety was intended to

4    address uncertainties associated with inconclusive scientific and technical information available at the

5    time of standard setting. It was also intended to provide a reasonable degree of protection against hazards

6    that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154

7    (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d

8    1176, 1186 (D.C. Cir. 1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of uncertainties are

9    components of the risk associated with pollution at levels below those at which human health effects can

10   be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an

11   adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been

12   demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk

13   of harm, even if the risk is not precisely identified as to nature or degree.

14       In selecting a margin of safety, the EPA considers such factors as the nature and severity of the

15   health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of the

16   uncertainties that must be addressed. The selection of any particular approach to providing an adequate

17   margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries*

18   *Association v. EPA*, supra, 647 F.2d 1161-62.

19       In setting standards that are "requisite" to protect public health and welfare, as provided in

20   Section 109(b), the Administrator's task is to establish standards that are neither more nor less stringent

21   than necessary. In so doing, EPA may not consider the costs of implementing the standards. See generally

22   *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (2001).

23       Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year

24   intervals thereafter, the Administrator shall complete a thorough review of the criteria published under

25   Section 108 and the national ambient air quality standards…and shall make such revisions in such criteria

26   and standards and promulgate such new standards as may be appropriate…" 42 U.S.C. 7409(d)(1).

27   Section 109(d)(2) requires that an independent scientific review…committee "shall complete a review of

28   the criteria and the national primary and secondary ambient air quality standards…and shall recommend

29   to the Administrator any new standards and revisions of existing criteria and standards as may be

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[1] Welfare effects as defined in Section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation,

1 appropriate…" 42 U.S.C. 7409(d)(2). Since the early 1980s, this independent review function has been

2 performed by the Clean Air Scientific Advisory Committee (CASAC).

# 1.2. History of Reviews of the NAAQS for PM

3 PM is the generic term for a broad class of chemically and physically diverse substances that exist

4 as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety

5 of anthropogenic stationary and mobile sources as well as from natural sources. Particles may be emitted

6 directly or formed in the atmosphere by transformations of gaseous emissions such as sulfur oxides

7 $(SO_X)$, nitrogen oxides $(NO_X)$, and volatile organic compounds (VOC). The chemical and physical

8 properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the

9 assessment of health and welfare effects. Table 1-1 summarizes the NAAQS that have been promulgated

10 for PM to date. These reviews are briefly described below, and further details are provided in the

11 Integrated Review Plan (U.S. EPA, 2008b).

as well as effects on economic values and on personal comfort and well-being."

**Table 1-1.    Summary of NAAQS promulgated for PM, 1971-2006.**

| Final Rule | Indicator | Avg Time | Level | Form |
|---|---|---|---|---|
| 1971 (36 FR 8186) | TSP (Total Suspended Particulates) | 24-h | 260 µg/m³ (primary) <br> 150 µg/m³ (secondary) | Not to be exceeded more than once per year |
| | | Annual | 75 µg/m³ (primary) | Annual average |
| 1987 (52 FR 24634) | PM₁₀ | 24-h | 150 µg/m³ | Not to be exceeded more than once per year on average over a 3-year period |
| | | Annual | 50 µg/m³ | Annual arithmetic mean, averaged over 3 years |
| 1997 (62 FR 38652) | PM₂.₅ | 24-h | 65 µg/m³ | 98th percentile, averaged over 3 years |
| | | Annual | 15 µg/m³ | Annual arithmetic mean, averaged over 3 years[1] |
| | PM₁₀ | 24-h | 150 µg/m³ | Initially promulgated 99th percentile, averaged over 3 years; when 1997 standards were vacated in 1999, the form of 1987 standards remained in place (not to be exceeded more than once per year on average over a 3-year period) |
| | | Annual | 50 µg/m³ | Annual arithmetic mean, averaged over 3 years |
| 2006 (71 FR 61144) | PM₂.₅ | 24-h | 35 µg/m³ | 98th percentile, averaged over 3 years |
| | | Annual | 15 µg/m³ | Annual arithmetic mean, averaged over 3 years[2] |
| | PM₁₀ | 24-h | 150 µg/m³ | Not to be exceeded more than once per year on average over a 3-year period |

Note: When not specified, primary and secondary standards are identical.

1       EPA first established NAAQS for PM in 1971 (36 FR 8186, April 30, 1971), based on the original

2   criteria document (NAPA, 1969). The reference method specified for determining attainment of the

3   original standards was the high-volume sampler, which collects PM up to a nominal size of 25 to 45

4   micrometers (µm) (referred to as total suspended particulates or TSP). The primary standards (measured

5   by the indicator TSP) were 260 µg/m³, 24-h average, not to be exceeded more than once per year, and

6   75 µg/m³, annual geometric mean. The secondary standard was 150 µg/m³, 24-h average, not to be

7   exceeded more than once per year. In October 1979 (44 FR 56730, October 2, 1979), EPA announced the

8   first periodic review of the air quality criteria and NAAQS for PM, and significant revisions to the

9   original standards were promulgated in 1987 (52 FR 24634, July 1, 1987). In that decision, EPA changed

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[1] The level of the 1997 annual PM₂.₅ standard was to be compared to measurements made at the community-oriented monitoring site recording the highest level, or, if specific constraints were met, measurements from multiple community-oriented monitoring sites could be averaged ("spatial averaging"). These criteria and constraints were intended to ensure that spatial averaging would not result in inequities in the level of protection afforded by the PM₂.₅ standards. Community-oriented monitoring sites were specified to be consistent with the intent that a spatially averaged annual standard provide protection for persons living in smaller communities, as well as those in larger population centers.

[2] In the revisions to the PM NAAQS finalized in 2006, EPA tighten the constraints on the spatial averaging criteria by further limiting the conditions under which some areas may average measurements from multiple community-oriented monitors to determine compliance (see 71 FR 61165-61167, October 17, 2006).

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1   the indicator for particles from TSP to $PM_{10}$, the latter including particles with a mean aerodynamic

2   diameter[1] less than or equal to 10 μm, which delineated that subset of inhalable particles small enough to

3   penetrate to the thoracic region (including the tracheobronchial and alveolar regions) of the respiratory

4   tract (referred to as thoracic particles). EPA also revised the level and form of the primary standards by

5   (1) replacing the 24-h TSP standard with a 24-h $PM_{10}$ standard of 150 μg/m$^3$ with no more than one

6   expected exceedence per year; and (2) replacing the annual TSP standard with a $PM_{10}$ standard of

7   50 μg/m$^3$, annual arithmetic mean, averaged over three years.

8   The secondary standard was revised by replacing it with 24-h and annual standards identical in all

9   respects to the primary standards. The revisions also included a new reference method for the

10   measurement of $PM_{10}$ in the ambient air and rules for determining attainment of the new standards. On

11   judicial review, the revised standards were upheld in all respects. Natural Resources Defense Council v.

12   Administrator, 902 F. 2d 962 (D.C. Cir. 1990, cert. denied, 498 U.S. 1082, 1991).

13   In April 1994, EPA announced its plans for the second periodic review of the air quality criteria and

14   NAAQS for PM, and promulgated significant revisions to the NAAQS in 1997 (62 FR 38652, July 18,

15   1997). In that decision, EPA revised the PM NAAQS in several respects. While EPA determined that the

16   PM NAAQS should continue to focus on $PM_{10}$, EPA also determined that the fine and coarse[1] fractions of

17   $PM_{10}$ should be considered separately. The Administrator's decision to modify the standards was based on

18   evidence that serious health effects were associated with short- and long-term exposure to fine particles in

19   areas that met the existing $PM_{10}$ standards. The EPA added new standards, using $PM_{2.5}$ as the indicator for

20   fine particles (with $PM_{2.5}$ referring to particles with a nominal mean aerodynamic diameter less than or

21   equal to 2.5 μm), and using $PM_{10}$ as the indicator for purposes of regulating the coarse fraction of $PM_{10}$

22   (referred to as thoracic coarse particles or coarse-fraction particles; generally including particles with a

23   nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm, or $PM_{10-2.5}$).

24   The EPA established two new $PM_{2.5}$ standards: an annual standard of 15 μg/m$^3$, based on the 3-year

25   average of annual arithmetic mean $PM_{2.5}$ concentrations from single or multiple community-oriented

26   monitors; and a 24-h standard of 65 μg/m$^3$, based on the 3-year average of the 98th percentile of 24-h

27   $PM_{2.5}$ concentrations at each population-oriented monitor within an area. Also, EPA established a new

28   reference method for the measurement of $PM_{2.5}$ in the ambient air and adopted rules for determining

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[1] The more precise term is 50 percent cut point or 50 percent diameter ($d_{50}$). This is the aerodynamic particle diameter for which the efficiency of particle collection is 50 percent. Larger particles are not excluded altogether, but are collected with substantially decreasing efficiency and smaller particles are collected with increasing (up to 100 percent) efficiency.

1   attainment of the new standards. To continue to address thoracic coarse particles, EPA retained the annual

2   $PM_{10}$ standard, while revising the form, but not the level, of the 24-h $PM_{10}$ standard to be based on the

3   99th percentile of 24-h $PM_{10}$ concentrations at each monitor in an area. The EPA revised the secondary

4   standards by making them identical in all respects to the primary standards.

5       Following promulgation of the 1997 PM NAAQS, petitions for review were filed by a large

6   number of parties, addressing a broad range of issues. In May 1999, a three-judge panel of the U.S. Court

7   of Appeals for the District of Columbia Circuit issued an initial decision that upheld EPA's decision to

8   establish fine particle standards, holding that "the growing empirical evidence demonstrating a

9   relationship between fine particle pollution and adverse health effects amply justifies establishment of

10  new fine particle standards." *American Trucking Associations v. EPA* (175 F. 3d 1027, 1055-56 [D.C. Cir.

11  1999; rehearing granted in part and denied in part, 195 F. 3d 4 [D.C. Cir. 1999]), affirmed in part and

12  reversed in part, *Whitman v. American Trucking Associations* (531 U.S. 457, 2001). The Panel also found

13  "ample support" for EPA's decision to regulate coarse particle pollution, but vacated the 1997 $PM_{10}$

14  standards, concluding that EPA had not provided a reasonable explanation justifying use of $PM_{10}$ as an

15  indicator for coarse particles (175 F. 3d at 1054-55). Pursuant to the court's decision, EPA removed the

16  vacated 1997 $PM_{10}$ standards. The pre-existing 1987 $PM_{10}$ standards remained in place (65 FR 80776,

17  December 22, 2000). The Court also upheld EPA's determination not to establish more stringent

18  secondary standards for fine particles to address effects on visibility (175 F. 3d 1027).

19      More generally, the panel held (over one judge's dissent) that EPA's approach to establishing the

20  level of the standards in 1997, both for PM and for ozone ($O_3$) NAAQS promulgated on the same day,

21  effected "an unconstitutional delegation of legislative authority" (Id. at 1034-40). Although the panel

22  stated that "the factors EPA uses in determining the degree of public health concern associated with

23  different levels of ozone and PM are reasonable," it remanded the rule to EPA, stating that when EPA

24  considers these factors for potential non-threshold pollutants "what EPA lacks is any determinate criterion

25  for drawing lines" to determine where the standards should be set. Consistent with EPA's long-standing

26  interpretation and D.C. Circuit precedent, the panel also reaffirmed prior rulings holding that in setting

27  NAAQS EPA is "not permitted to consider the cost of implementing those standards" (Id. at 1040-41).

28      Both sides filed cross appeals on these issues to the U.S. Supreme Court, and the Court granted

29  *certiorari*. In February 2001, the Supreme Court issued a unanimous decision upholding EPA's position

30  on both the constitutional and cost issues. *Whitman v. American Trucking Associations*, 531 U.S. 457,

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[1] See definitions of "fine" and "coarse" particles in Section 3.2.

1    464, 475-76. On the constitutional issue, the Court held that the statutory requirement that NAAQS be

2    "requisite" to protect public health with an adequate margin of safety sufficiently guided EPA's discretion,

3    affirming EPA's approach of setting standards that are neither more nor less stringent than necessary. The

4    Supreme Court remanded the case to the Court of Appeals for resolution of any remaining issues that had

5    not been addressed in that court's earlier rulings. Id. at 475-76. In March 2002, the Court of Appeals

6    rejected all remaining challenges to the standards, holding under the traditional standard of judicial

7    review that $PM_{2.5}$ standards were reasonably supported by the administrative record and were not

8    "arbitrary and capricious" *American Trucking Associations v. EPA*, 283 F. 3d 355, 369-72 (D.C. Cir.

9    2002).

10    In October 1997, EPA published its plans for the third periodic review of the air quality criteria and

11    NAAQS for PM (62 FR 55201). After CASAC and public review, EPA's NCEA finalized the 2004 PM

12    AQCD (U.S. EPA, 2004). The final Office of Air Quality Planning and Standards (OAQPS) Staff Paper

13    (U.S. EPA, 2005b), took into account the advice and recommendations of CASAC and public comments

14    received on the earlier drafts of this document and presented additional advice and recommendations

15    submitted by CASAC to the Administrator.

16    On December 20, 2005, EPA announced its proposed decision to revise the NAAQS for PM (71 FR

17    2620; hereafter "proposal"). In the proposal, EPA identified proposed revisions, based on the air quality

18    criteria for PM, and solicited public comments on alternative primary and secondary standards. EPA

19    proposed to revise the level of the 24-h $PM_{2.5}$ standard to 35 µg/m$^3$ to provide increased protection against

20    health effects associated with short-term $PM_{2.5}$ exposures, including premature mortality and increased

21    hospital admission and emergency room visits and to retain the level of the annual $PM_{2.5}$ standard at

22    15 µg/m$^3$, continuing protection against health effects associated with long-term exposure including

23    premature mortality and development of chronic respiratory disease. With regard to the primary standards

24    for $PM_{10}$, EPA proposed to revise the 24-h $PM_{10}$ standard in part by establishing a new indicator for

25    thoracic coarse particles (particles generally between 2.5 and 10 µm in $PM_{10-2.5}$ diameter), qualified so as

26    to include any ambient mix of $PM_{10-2.5}$ that was dominated by resuspended dust from high density traffic

27    on paved roads and PM generated by industrial sources and construction sources, and proposed to exclude

28    any ambient mix of $PM_{10-2.5}$ that was dominated by rural windblown dust and soils and PM generated by

29    agricultural and mining sources. The EPA proposed to set a 24-h $PM_{10-2.5}$ standard at a level of 70 µg/m$^3$

30    to continue to provide a level of protection against health effects associated with short-term exposure

31    (including hospital admissions for cardiopulmonary diseases, increased respiratory symptoms and

32    possibly premature mortality) generally equivalent to the level of protection provided by the existing 24-h

33    $PM_{10}$ standard. Also, EPA proposed to revoke, upon finalization of a primary 24-h standard for $PM_{10-2.5}$,

34    the 24-h $PM_{10}$ standard as well as the annual $PM_{10}$ standard. EPA proposed to revise the secondary

1    standards by making them identical to the suite of proposed primary standards for fine and coarse

2    particles, providing protection against PM-related public welfare effects including visibility impairment,

3    effects on vegetation and ecosystems, and materials damage and soiling. EPA also solicited comment on

4    adding a new sub-daily $PM_{2.5}$ secondary standard to address visibility impairment in urban areas. CASAC

5    provided additional advice to EPA in a letter to the Administrator requesting reconsideration of CASAC's

6    recommendations for both the primary and secondary $PM_{2.5}$ standards as well as standards for thoracic

7    coarse particles (Henderson, 2006).

8        On September 21, 2006, EPA announced its final decisions to revise the primary and secondary

9    NAAQS for PM to provide increased protection of public health and welfare, respectively (71 FR 61144).

10   With regard to the primary and secondary standards for fine particles, EPA revised the level of the 24-h

11   $PM_{2.5}$ standard to 35 $\mu g/m^3$, retained the level of the annual $PM_{2.5}$ annual standard at 15 $\mu g/m^3$, and

12   revised the form of the annual $PM_{2.5}$ standard by narrowing the constraints on the optional use of spatial

13   averaging. With regard to the primary and secondary standards for $PM_{10}$, EPA retained the 24-h $PM_{10}$

14   standard at 150 $\mu g/m^3$ and revoked the annual standard because available evidence generally did not

15   suggest a link between long-term exposure to current ambient levels of coarse particles and health or

16   welfare effects.

# 1.3. Document Development

17       EPA initiated the current formal review of the NAAQS for PM on June 28, 2007 with a call for

18   information from the public (72 FR 35462). In addition to the call for information, publications were

19   identified through an ongoing literature search process that includes extensive computer database mining

20   on specific topics. Additional publications were identified by EPA scientists in a variety of disciplines by

21   combing through relevant, peer-reviewed scientific literature obtained through these ongoing literature

22   searches, reviewing previous EPA reports, and a review of reference lists from key publications; studies

23   were also identified in the course of CASAC and public review.

24       All relevant epidemiologic, human clinical, and animal toxicological studies, including those

25   related to exposure-response relationships, mode(s) of action (MOA), or susceptible or vulnerable

26   subpopulations, and ecological or welfare effects studies published since the last review were considered.

27   Added to the body of research were EPA's analyses of air quality and emissions data, studies on

28   atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure to PM.

29   Further information was acquired from consultation with content and area experts and the public.

30       In the 2008 $NO_X$-$SO_X$ ISA (U.S. EPA, 2008e), EPA focused on ecological effects related to the

31   deposition of nitrogen (N)- and sulfur (S)-containing compounds, including particle-phase compounds

1 (e.g., nitrates and sulfates) primarily including effects from acidification and N-nutrient enrichment and
2 eutrophication. In this draft ISA, EPA focused on recent data on direct welfare effects of particle-phase
3 $NO_X$ and $SO_X$ in the ambient air — primarily visibility impairment, damage to materials, and positive and
4 negative climate interactions.

# 1.4. Document Organization

5    The ISA is composed of nine chapters. This introductory chapter presents background information,
6 and provides an overview of EPA's framework for making causal judgments. Key findings and
7 conclusions from the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry,
8 and health effects for consideration in the review of the NAAQS for PM, including judgments on
9 causality for the health effects of PM exposure, are presented in Chapter 2. More detailed summaries,
10 evaluations and integration of the evidence are included in Chapters 3 through 8.
11    Chapter 3 highlights key concepts or issues relevant to understanding the atmospheric chemistry,
12 sources, and exposure of PM following a "source-to-exposure" paradigm. Chapter 4 summarizes key
13 concepts and recent findings on the dosimetry of PM and Chapter 5 discusses possible pathways and
14 MOA for the effects of PM. Chapters 6 and 7 evaluate and integrate epidemiologic, human clinical, and
15 animal toxicological information relevant to the review of the primary NAAQS for PM. Effects related to
16 short-term exposures to PM are the focus of Chapter 6. Chapter 7 evaluates evidence related to long-term
17 exposures to PM. Chapters 6 and 7 are organized by health outcome categories, such as cardiovascular or
18 respiratory effects, and each section includes effects of the various types of PM studied. For each health
19 outcome category, summary sections then integrate the findings to draw conclusions on the evidence for
20 the main size classes of PM (i.e., $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, and ultrafine particles). Chapter 6 also includes a
21 summary and synthesis of the recent evidence on various health effects related to short-term exposure to
22 different components or sources of PM. Chapter 8 evaluates evidence related to the public health impact
23 of ambient PM exposure, including potentially susceptible and vulnerable population groups.
24    Chapter 9 evaluates ecological and welfare effects evidence that is relevant to the review of the
25 secondary NAAQS for PM. That chapter includes consideration of evidence on visibility impairment,
26 materials damage, effects of PM on climate, and ecological effects of PM that were not addressed in the
27 2008 $NO_X$-$SO_X$ ISA (U.S. EPA, 2008e); the chapter also includes the integrative synthesis of the evidence
28 and presents key conclusions and scientific judgments regarding causality for welfare and ecological
29 effects of PM.

1    A series of annexes supplement this ISA. The annexes provide additional details of the pertinent

2    literature published since the last review, as well as selected older studies of particular interest. These

3    annexes contain information on:

4    ▪    atmospheric chemistry of PM as well as the sampling and analytic methods for measurement

5         of PM (Annex A)

6    ▪    concentrations, emissions, sources and human exposure to PM (Annex A)

7    ▪    studies on the dosimetry of PM (Annex B)

8    ▪    human clinical studies of health effects related to exposure to PM (Annex D)

9    ▪    toxicological studies of health effects in laboratory animals (Annex C); and

10   ▪    epidemiologic studies of health effects from short- and long-term exposure to PM (Annex E)

11   Within the Annexes, detailed information about methods and results of health studies is

12   summarized in tabular format, and generally includes information about: concentrations of PM and

13   averaging times; study methods employed; results and comments; and quantitative results for

14   relationships between effects and exposure to PM.

# 1.5. EPA Framework for Causal Determination

15   The EPA has developed a consistent and transparent basis to evaluate the causal nature of air

16   pollution-induced health or environmental effects. The framework described below establishes uniform

17   language concerning causality and brings more specificity to the findings. It drew standardized language

18   from across the federal government and wider scientific community, especially from the recent National

19   Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive*

20   *Disability Decision-Making Process for Veterans* (IOM, 2008), the most recent comprehensive work on

21   evaluating causality.

22   This introductory section focuses on the evaluation of health effects evidence, particularly

23   epidemiologic study results, since this is a crucial element of the PM ISA. While focusing on human

24   health outcomes, the concepts are also generally relevant to causality determination for welfare effects.

25   This section:

26   ▪    describes the kinds of scientific evidence used in establishing a general causal relationship

27        between exposure and health effects;

28   ▪    defines cause, in contrast to statistical association;

1    ▪  discusses the sources of evidence necessary to reach a conclusion about the existence of a
2         causal relationship;

3    ▪  highlights the issue of multifactorial causation;

4    ▪  identifies issues and approaches related to uncertainty; and

5    ▪  provides a framework for classifying and characterizing the weight of evidence in support of
6         a general causal relationship.

7        Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, human
8    clinical, and animal toxicological studies) have been formulated by a number of regulatory and science
9    agencies, including the IOM of the NAS (IOM, 2008), International Agency for Research on Cancer
10   (IARC, 2006), EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), Centers for Disease
11   Control and Prevention (CDC, 2004), and National Acid Precipitation Assessment Program (NAPAP)
12   (1991). These formalized approaches offer guidance for assessing causality. The frameworks are similar
13   in nature, although adapted to different purposes, and have proven effective in providing a uniform
14   structure and language for causal determinations. Moreover, these frameworks have supported
15   decision-making under conditions of uncertainty.

# 1.5.1. Scientific Evidence Used in Establishing Causality

16       Causality determinations are based on the evaluation and synthesis of evidence from across
17   scientific disciplines; the type of evidence that is most important for such determinations will vary by
18   pollutant or assessment. The most compelling evidence of a causal relationship between pollutant
19   exposures and human health effects comes from human clinical studies. This type of study experimentally
20   evaluates the health effects of administered exposures in human volunteers under highly-controlled
21   laboratory conditions.

22       In epidemiologic or observational studies of humans, the investigator does not control exposures or
23   intervene with the study population. Broadly, observational studies can describe associations between
24   exposures and effects. These studies fall into several categories: cross-sectional, prospective cohort, and
25   time-series studies. "Natural experiments" offer the opportunity to investigate changes in health with a
26   change in exposure; these include comparisons of health effects before and after a change in population
27   exposures, such as closure of a pollution source.

28       Experimental animal data complement the clinical and observational data; these studies can help
29   characterize effects of concern, exposure-response relationships, susceptible subpopulations and MOAs.

1  In the absence of clinical or epidemiologic data, animal data alone may be sufficient to support a likely

2  causal determination, assuming that humans respond similarly to the experimental species.

## 1.5.2. Association and Causation

3  "Cause" is a significant, effectual relationship between an agent and an effect on health or public

4  welfare. "Association" is the statistical dependence among events, characteristics, or other variables. An

5  association is prima facie evidence for causation; alone, however, it is insufficient proof of a causal

6  relationship between exposure and disease. Unlike an association, a causal claim supports the creation of

7  counterfactual claims; that is, a claim about what the world would have been like under different or

8  changed circumstances (IOM, 2008). Much of the newly available health information evaluated in this

9  ISA comes from epidemiologic studies that report a statistical association between ambient exposure and

10  health outcome.

11  Many of the health and environmental outcomes reported in these studies have complex etiologies.

12  Diseases such as asthma, coronary heart disease or cancer are typically initiated by a web of multiple

13  agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status,

14  immune competence, and social factors (Gee and Payne-Sturges, 2004; IOM, 2008). Effects on

15  ecosystems are often also multifactorial with a complex web of causation. Further, exposure to a

16  combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk represents

17  the net effect of many actions and counteractions.

## 1.5.3. Evaluation of Evidence for Going beyond Association to Causation

18  Moving from association to causation involves elimination of alternative explanations for the

19  association. In estimating the causal influence of an exposure on health or environmental effects, it is

20  recognized that scientific findings incorporate uncertainty. Uncertainty can be defined as a state of having

21  limited knowledge where it is impossible to exactly describe an existing state or future outcome; the lack

22  of knowledge about the correct value for a specific measure or estimate. Uncertainty characterization and

23  uncertainty assessment are two activities that lead to different degrees of sophistication in describing

24  uncertainty. Uncertainty characterization generally involves a qualitative discussion of the thought

25  processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. The uncertainty

26  assessment is more quantitative. The process begins with simpler measures (e.g., ranges) and simpler

27  analytical techniques and progresses, to the extent needed to support the decision for which the

1    assessment is conducted, to more complex measures and techniques. Data will not be available for all

2    aspects of an assessment and those data that are available may be of questionable or unknown quality. In

3    these situations, evaluation of uncertainty can include professional judgment or inferences based on

4    analogy with similar situations. The net result is that the assessments will be based on a number of

5    assumptions with varying degrees of uncertainty.

6        Uncertainties commonly encountered in evaluating health evidence for the criteria air pollutants are

7    outlined below for epidemiologic and experimental studies. Various approaches to characterizing

8    uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis,

9    in order of increasing complexity and data requirements. The ISA generally evaluates uncertainties

10   qualitatively in assessing the evidence from across studies; in some situations quantitative analysis

11   approaches, such as meta-regression may be used.

12       Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants in a

13   highly controlled laboratory setting. Also referred to as human clinical studies, these experiments allow

14   investigators to expose subjects to fixed concentrations of air pollutants under carefully regulated

15   environmental conditions and activity levels. Controlled human exposures to PM typically involve

16   exposing subjects either at rest or while engaged in intermittent exercise in a whole-body exposure

17   chamber, although mouthpiece and facemask systems can also be used. A variety of different types of

18   particles are used in these studies including ambient outdoor particles, concentrated ambient particles

19   (CAPs), diesel exhaust (DE) from a diesel engine, wood smoke (WS) generated in a wood stove,

20   laboratory generated surrogate particles (e.g., elemental carbon [EC]or zinc oxide [ZnO]), or particles

21   collected on a filter, resuspended in saline, and administered either through instillation or inhalation

22   (aerosolized and delivered using a nebulizer). The recovery of particles on filters is variable and some

23   components, such as organics, may be too volatile to be collected. Exposures to artificially generated

24   particles may provide important information on the health effects of PM, but are not truly representative

25   of ambient air pollution particles. The direct exposure of humans to ambient air pollution particles may be

26   complicated by factors that cannot be controlled such as co-exposures to other air pollutants (e.g., $O_3$,

27   $SO_2$, and $NO_2$). In concentrating ambient particulates, gaseous copollutants are not proportionately

28   concentrated and interactions between PM and the copollutants cannot be investigated unless the latter are

29   re-introduced. These limitations as well as daily variability in concentration and composition can make it

30   difficult to compare the results from human clinical studies employing particles from different sources.

31       In some instances, controlled human exposure studies can also be used to characterize

32   concentration-response relationships at pollutant concentrations relevant to ambient conditions.

33   Controlled human exposures are typically conducted using a randomized crossover design with subjects

34   exposed both to PM and a clean air control. In this way, subjects serve as their own controls, effectively

1    controlling for many potential confounders. However, human clinical studies are limited by a number of

2    factors including a small sample size and short exposure time. The repetitive nature of ambient PM

3    exposures may lead to cumulative health effects, but this type of exposure is not practical to replicate in a

4    laboratory setting. In addition, although subjects do serve as their own controls, personal exposure to

5    pollutants in the hours and days preceding the controlled exposures may vary significantly between and

6    within individuals. Finally, human clinical studies require investigators to adhere to stringent health

7    criteria for a subject to be included in the study, and therefore the results cannot necessarily be

8    generalized to an entire population. Although some human clinical studies have included health

9    comprised individuals such as asthmatics or individuals with chronic obstructive pulmonary disease

10   (COPD) or coronary artery disease, these individuals must also be relatively healthy and do not represent

11   the most sensitive individuals in the population. Thus, a lack of observation of effects from human

12   clinical studies does not necessarily mean that a causal relationship does not exist. While human clinical

13   studies provide important information on the biological plausibility of associations observed between air

14   pollutant exposure and health outcomes in epidemiologic studies, observed effects in these studies may

15   underestimate the response in certain subpopulations.

16       Epidemiologic studies provide important information on the associations between health effects

17   and exposure of human populations to ambient air pollution. These studies also help to identify

18   susceptible or vulnerable subgroups and associated risk factors. There are important methodological

19   issues that to be considered in evaluating results from air pollution epidemiologic studies, especially the

20   potential for confounding and/or effect modification; and exposure measurement error.

21       Scientific judgment is needed regarding sources and magnitude of potential confounding by

22   covariates, together with judgment about how well the existing constellation of study designs, results, and

23   analyses address this potential threat to inferential validity. One key consideration is evaluation of the

24   potential contribution of PM to health effects, when it is a component of a complex air pollutant mixture.

25   There are multiple ways by which PM might cause or be associated with adverse health effects. First, the

26   reported PM effect estimates in epidemiologic studies may reflect independent PM effects on respiratory

27   and cardiovascular health. Second, ambient PM may be serving as an indicator of complex ambient air

28   pollution mixtures that share the same source as PM (i.e., combustion of sulfur-containing fuels or motor

29   vehicle emissions). Finally, copollutants may mediate the effects of PM or PM may influence the toxicity

30   of copollutants.

31       Epidemiologists use the term "interaction" or "effect modification" to denote the departure from

32   the observed joint risk from what might be expected based on the separate effects of the factors. These

33   possibilities are not necessarily exclusive. In addition, confounding can result in the production of an

34   association between adverse health effects and PM that is actually attributable to another factor that is

1  associated with PM in a particular study. Multivariate models are the most widely used strategy to address

2  confounding in epidemiologic studies, but such models are not always easily interpreted when assessing

3  effects of covarying pollutants such as $O_3$, $SO_2$ and $NO_2$.

4  　　Inferring causation requires consideration of potential confounders. In confounding, the apparent

5  effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or

6  mixed with the actual exposure effect, which may be null. When associations are found in epidemiologic

7  studies, one approach to remove spurious associations from possible confounders is to control for

8  characteristics that may differ between exposed and unexposed persons; this is frequently termed

9  "adjustment." Multivariable regression models constitute one tool for estimating the association between

10  exposure and outcome after adjusting for characteristics of participants that might confound the results.

11  The use of multipollutant regression models has been the prevailing approach for controlling potential

12  confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant

13  from multipollutant regression models is made difficult by the possibility that one or more air pollutants

14  may be acting as a surrogate for an unmeasured or poorly-measured pollutant or for a particular mixture

15  of pollutants. Further, the correlation between the air pollutant of interest and various copollutants may

16  show temporal and spatial discongruities that can influence exposures and health effects. Thus, results of

17  models that attempt to distinguish gaseous and particle effects must be interpreted with caution. Despite

18  these limitations, the use of multipollutant models is still the prevailing approach employed in most air

19  pollution epidemiologic studies, and may provide some insight into the potential for confounding or

20  interaction among pollutants.

21  　　Another way to adjust for potential confounding is through stratified analysis, i.e., examining the

22  association within homogeneous groups with respect to the confounding variable. Stratified analysis can

23  also be used to examine potential effect modification. The use of stratified analyses has an additional

24  benefit: it allows examination of effect modification through comparison of the effect estimates across

25  different groups. If investigators successfully measured characteristics that distort the results, adjustment

26  of these factors help separate a spurious from a true causal association. Appropriate statistical adjustment

27  for confounders requires identifying and measuring all reasonably expected confounders. Deciding which

28  variables to control for in a statistical analysis of the association between exposure and disease depends

29  on knowledge about possible mechanisms and the distributions of these factors in the population under

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

31  spurious association.

32  　　Measurement error is another problem encountered when adjusting for spurious associations.

33  Controlling for confounders, whether by adjustment or stratification, is only successful when the

34  confounder is well-measured. Considered together, the effects of a well-measured covariate may be

1     overestimated in contrast to a covariate measured with greater error. There are several components that

2     contribute to exposure measurement error in these studies, including the difference between true and

3     measured ambient concentrations, the difference between average personal exposure to ambient pollutants

4     and ambient concentrations at central monitoring sites, and the use of average population exposure rather

5     than individual exposure estimates. Previous assessments have examined the role of measurement error in

6     time-series epidemiologic studies using simulated data and mathematical analyses and suggested that

7     "transfer of effects" would only occur under unusual circumstances (i.e., "true" predictors having high

8     positive or negative correlation; substantial measurement error; or extremely negatively correlated

9     measurement errors) (U.S. EPA, 2004).

10          Confidence that unmeasured confounders are not producing the findings is increased when multiple

11     studies are conducted in various settings using different subjects or exposures; each of which might

12     eliminate another source of confounding from consideration. Thus, multicity studies which use a

13     consistent method to analyze data from across locations with different levels of covariates can provide

14     insight on potential confounding in associations. The number and degree of diversity of covariates, as

15     well as their relevance to the potential confounders, remain matters of scientific judgment. Intervention

16     studies, because of their experimental nature, can be particularly useful in characterizing causation.

17          In addition to clinical and epidemiologic studies, the tools of experimental biology have been

18     valuable for developing insights into human physiology and pathology. Laboratory tools have been

19     extended to explore the effects of putative toxicants on human health, especially through the study of

20     model systems in other species. Background knowledge of the biological mechanisms by which an

21     exposure might or might not cause disease can prove crucial in establishing, or negating, a causal claim.

22     At the same time, species can differ from each other in fundamental aspects of physiology and anatomy

23     (e.g., metabolism, airway branching, hormonal regulation) that may limit extrapolation. Testable

24     hypotheses about the causal nature of proposed mechanisms or MOAs are central to utilizing

25     experimental data in causal determinations.

26          Interpretations of experimental studies of air pollution effects in animals, as in the case of

27     environmental comparative toxicology studies, are affected by limitations associated with extrapolation

28     models. The differences between humans and rodents with regard to pollutant absorption and distribution

29     profiles based on breathing pattern, exposure dose, and differences in lung structure and anatomy all have

30     to be taken into consideration. Also, in spite of a high degree of homology and the existence of a high

31     percentage of orthologous genes across human and rodents (particularly mice), extrapolation of molecular

32     alterations at the gene level is complicated by species-specific differences in transcriptional regulation.

33     Given these molecular differences, there are uncertainties associated with quantitative extrapolations at

1 this time between laboratory animals and humans of observed pollutant-induced pathophysiological

2 alterations under the control of widely varying biochemical, endocrine, and neuronal factors.

## 1.5.4. Application of Framework for Causal Determination

3      EPA uses a two-step approach to evaluate the scientific evidence on health or environmental effects

4 of criteria pollutants. The first step determines the weight of evidence in support of causation and

5 characterizes the strength of any resulting causal classification. The second step includes further

6 evaluation of the quantitative evidence regarding the concentration-response relationships and the loads or

7 levels, duration and pattern of exposures at which effects are observed.

8      To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and

9 scientists. The most widely cited aspects of causality in epidemiology, and public health, in general, were

10 articulated by Sir Austin Bradford Hill in 1965 and have been widely used (CDC, 2004; IARC, 2006;

11 IOM, 2008; U.S. EPA, 2005a). Several adaptations of the Hill aspects have been used in aiding causality

12 judgments in the ecological sciences (Adams, 2003; Buck et al., 2000; Collier, 2003; Fox, 1991; Gerritsen

13 et al., 1998). These aspects (Hill, 1965) have been modified (Table 1-2) for use in causal determinations

14 specific to health and welfare effects or pollutant exposures.[2] Some aspects are more likely than others to

15 be relevant for evaluating evidence on the health or environmental effects of criteria air pollutants. For

16 example, the analogy aspect does not always apply, especially for the gaseous criteria pollutants, and

17 specificity would not be expected for multi-etiologic health outcomes such as asthma or cardiovascular

18 disease, or ecological effects related to acidification. Aspects that usually play a larger role in

19 determination of causality are consistency of results across studies, coherence of effects observed in

20 different study types or disciplines, biological plausibility, exposure-response relationship, and evidence

21 from "natural" experiments.

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

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

**Table 1-2.     Aspects to aid in judging causality.**

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

6    **Strength of the observed association.** The finding of large, precise risks increases confidence
7         that the association is not likely due to chance, bias, or other factors. However, given a truly
8         causal agent, a small magnitude in the effect could follow from a lower level of exposure, a
9         lower potency, or the prevalence of other agents causing similar effects. While large effects
10        support causality, modest effects therefore do not preclude it.

11   **Specificity of the observed association.** As originally intended, this refers to increased inference
12        of causality if one cause is associated with a single effect or disease (Hill, 1965). Based on
13        our current understanding this is now considered one of the weaker guidelines for causality;
14        for example, many agents cause respiratory disease and respiratory disease has multiple
15        causes. At the scale of ecosystems, as in epidemiology, complexity is such that single agents
16        causing single effects, and single effects following single causes, are extremely unlikely. The
17        ability to demonstrate specificity under certain conditions remains, however, a powerful
18        attribute of experimental studies. Thus, although the presence of specificity may support
19        causality, its absence does not exclude it.

20   **Temporal relationship of the observed association.** Evidence of a temporal sequence between
21        the introduction of an agent, and appearance of the effect, constitutes another argument in
22        favor of causality.

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

30   **Biological plausibility**. An inference of causality tends to be strengthened by consistency with data
31        from experimental studies or other sources demonstrating plausible biological mechanisms. A

1    proposed mechanistic linking between an effect, and exposure to the agent, is an important

2    source of support for causality, especially when data establishing the existence and

3    functioning of those mechanistic links are available. A lack of biologic understanding,

4    however, is not a reason to reject causality.

5    **Coherence.** An inference of causality from epidemiologic associations may be strengthened by

6    other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect

7    interpretation of the association. Evidence on ecological or welfare effects may be drawn

8    from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and

9    subdisciplines of ecology (e.g., community ecology, biogeochemistry and

10   paleological/historical reconstructions). The coherence of evidence from various fields

11   greatly adds to the strength of an inference of causality. The absence of other lines of

12   evidence, however, is not a reason to reject causality.

13   **Experimental evidence.** The strongest evidence for causality can be provided when a change in

14   exposure brings about a change in occurrence or frequency of health or welfare effects.

15   **Analogy.** Structure activity relationships and information on the agent's structural analogs can

16   provide insight into whether an association is causal. Similarly, information on mode of

17   action for a chemical, as one of many structural analogs, can inform decisions regarding

18   likely causality.

19   While these aspects provide a framework for assessing the evidence, they do not lend themselves to

20   being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about

21   causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically

22   significant results or statistically nonsignificant results and reach credible conclusions about the relative

23   weight of the evidence and the likelihood of causality. Rather, these important considerations are taken

24   into account with the goal of producing an objective appraisal of the evidence, informed by peer and

25   public comment and advice, which includes weighing alternative views on controversial issues.

26   Additionally, it is important to note that the aspects in Table 1-2 cannot be used as a strict checklist, but

27   rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or

28   more of the principles does not automatically preclude a determination of causality (e.g., see discussion in

29   CDC, 2004).

## 1.5.5. First Step—Determination of Causality

30   In the ISA, EPA assesses the results of recent relevant publications, building upon evidence

31   available during the previous NAAQS review, to draw conclusions on the causal relationships between

1    relevant pollutant exposures and health or environmental effects. This ISA uses a five-level hierarchy that

2    classifies the weight of evidence for causation, not just association[1]; that is, whether the weight of

3    scientific evidence makes causation at least as likely as not, in the judgment of the reviewing group. In

4    developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the

5    IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2008), EPA's

6    Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), and the U.S. Surgeon General's smoking

7    reports (CDC, 2004). In the ISA, EPA uses a series of five descriptors to characterize the weight of

8    evidence for causality. This weight of evidence evaluation is based on various lines of evidence from

9    across the health and environmental effects disciplines. These separate judgments are integrated into a

10   qualitative statement about the overall weight of the evidence and causality. The five descriptors for

11   causal determination are described in Table 1-3.

12       For PM, this determination of causality step involved a rather complex evaluation of evidence for

13   different PM indices, different types of health or environmental effects, and for short- and long-term

14   exposure periods. Determination of causality was made for both the PM measure ($PM_{10}$, $PM_{10-2.5}$, $PM_{2.5}$,

15   and ultrafine particles, to the extent evidence was available for each measure) and for the overall effect

16   category. In the evaluation of health effects findings in Chapter 6 (for short-term exposure) and Chapter 7

17   (for long-term exposure), evidence was evaluated for health outcome categories, such as cardiovascular

18   effects, and then conclusions were drawn based upon the integration of evidence from across disciplines

19   (e.g., epidemiology, clinical studies and toxicology) and also across the suite of related individual health

20   outcomes. These chapters initially summarize and evaluate findings for individual health outcomes, then

21   integrate the results in summary sections to draw conclusions on causality for each PM indicator. In the

22   integrative synthesis and conclusions in Chapter 2, the ISA presents causality determinations and a

23   summary of the underlying basis for those determinations for the PM indicator (e.g., $PM_{2.5}$), for the

24   exposure time period (e.g., short- and long-term exposure) and for the major health endpoint categories.

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

**Table 1-3.    Weight of evidence for causal determination.**

| | Health Effects | Ecological and Welfare Effects |
|---|---|---|
| **Causal relationship** | Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposures and the health outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Evidence includes, for example, controlled human exposure studies; or observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g. animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators. | Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposure and the outcome. Causality is supported when an association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure (laboratory or small- to medium-scale field studies) provides the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other. |
| **Likely to be a causal relationship** | Evidence is sufficient to conclude that a causal relationship is likely to exist between relevant pollutant exposures and health outcome but important uncertainties remain. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators. | Evidence is sufficient to conclude that there is a likely causal association between relevant pollutant exposures and the outcome. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups. |
| **Suggestive of a causal relationship** | Evidence is suggestive of a causal relationship between relevant pollutant exposures and the health outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent. | Evidence is suggestive of an association between relevant pollutant exposures and the outcome, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an association, but the results of other studies are inconsistent. |
| **Inadequate to infer a causal relationship** | Evidence is inadequate to determine that a causal relationship exists between relevant pollutant exposures and health outcome. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. | The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome. |
| **Suggestive of no causal relationship** | Evidence is suggestive of no causal relationship between relevant pollutant exposures and health outcome. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible or vulnerable subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposure. | Several adequate studies, examining relationships between relevant exposures and outcomes, are consistent in failing to show an association between exposure and the outcome at any level of exposure. |

# 1.5.6. Second Step—Evaluation of Response

1    Beyond judgments regarding causality are questions relevant to quantifying health or

2    environmental risks based on our understanding of the quantitative relationships between pollutant

3    exposures and health or welfare effects.

## *Effects on Human Populations*

4    Important questions regarding quantitative relationships include:

5    ▪  What is the concentration-response or dose-response relationship in the human population?

1    ▪ What is the interrelationship between incidence and severity of effect?

2    ▪ What exposure conditions (dose or exposure, duration and pattern) are important?

3    ▪ What subpopulations appear to be differentially affected i.e., more susceptible or vulnerable
4        to effects?

5    To address these questions the second step of the EPA framework evaluated the entirety of

6    policy-relevant quantitative evidence regarding the concentration-response relationships including levels

7    of pollutant and exposure durations at which effects were observed, and subpopulations that differ from

8    the general population. This integration of evidence resulted in identification of a study or set of studies

9    that best approximated the concentration response relationship for the U.S. population, given the current

10   state of knowledge and the uncertainties that surrounded these estimates.

11   To accomplish this integration, evidence from multiple and diverse types of studies was considered.

12   Response was evaluated over a range of observations which was determined by the type of study and

13   methods of exposure or dose and response measurements. Results from different protocols were

14   compared and contrasted. Animal data also informed evaluation of concentration-response, particularly

15   relative to dosimetry, modes of action, and characteristics of susceptible subpopulations. For some health

16   outcomes, the probability and severity of health effects and associated uncertainties can be characterized.

17   Chapter 2 presents the integrated findings informative for evaluation of population risks.

18   An important consideration in characterizing the public health impacts associated with exposure to

19   a pollutant is whether the concentration-response relationship is linear across the full concentration range

20   encountered, or if nonlinear relationships exist along any part of this range. Of particular interest is the

21   shape of the concentration-response curve at and below the level of the current standards. The shape of

22   the concentration-response curve varies, depending on the type of health outcome, underlying biological

23   mechanisms and dose. At the human population level, however, various sources of variability and

24   uncertainty tend to smooth and "linearize" the concentration-response function (such as the low data

25   density in the lower concentration range, possible influence of measurement error, and individual

26   differences in susceptibility to air pollution health effects). Additionally, many chemicals and agents may

27   act by perturbing naturally occurring background processes that lead to disease, which also linearizes

28   population concentration-response relationships (Clewell and Crump, 2005; Crump et al., 1976; Hoel,

29   1980). These attributes of population dose-response may explain why the available human data at ambient

30   concentrations for some environmental pollutants (e.g., PM, ozone, lead [Pb], secondhand tobacco smoke,

31   radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though likely

32   mechanisms include nonlinear processes for some key events. These attributes of human population

1 dose-response relationships have been extensively discussed in the broader epidemiologic literature (e.g.,

2 Rothman and Greenland, 1998).

### Effects on Ecosystems or Public Welfare

3 Key questions for understanding the quantitative relationships between exposure (or concentration

4 or deposition) to a pollutant and risk to ecosystems or the public welfare include:

- 5 What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations,
  6 functions, etc.) appear to be affected, or are more sensitive to effects?

- 7 Under what exposure conditions (amount deposited or concentration, duration and pattern)
  8 are effects seen?

- 9 What is the shape of the concentration-response or exposure-response relationship?

10 Evaluations of causality typically characterize how the probability of ecological and welfare effects

11 change in response to exposure. A challenge to the quantification of exposure-response relationships for

12 ecological effects is the variability across ecosystems. Ecological responses are evaluated within the range

13 of observations, so a quantitative relationship may be determined for a given ecological system and scale.

14 There is great regional and local variability in ecosystems, thus an exposure-response relationship

15 generally cannot be determined at the larger national or even regional scale. Quantitative relationships

16 therefore are available site by site. For example, an ecological response to deposition of a given pollutant

17 can differ greatly between ecosystems. Where results from greenhouse or animal ecotoxicological studies

18 are available, they may be used to aid in characterizing exposure-response relations, particularly relative

19 to mechanisms of action, and characteristics of sensitive biota.

# 1.5.7. Concepts in Evaluating Adversity of Health Effects

20 In evaluating the health evidence, a number of factors can be considered in determining the extent

21 to which health effects are "adverse" for health outcomes such as changes in lung function. What

22 constitutes an adverse health effect may vary between populations. Some changes in healthy individuals

23 may not be considered adverse while those of a similar type and magnitude are potentially adverse in

24 more susceptible individuals.

25 The American Thoracic Society (ATS) published an official statement titled *What Constitutes an*

26 *Adverse Health Effect of Air Pollution?* (ATS, 2000). This statement updated the guidance for defining

27 adverse respiratory health effects that had been published 15 years earlier (ATS, 1985), taking into

28 account new investigative approaches used to identify the effects of air pollution and reflecting concern

for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality of life measures as indicators of adversity and a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no identifiable individual experiences clinically relevant effects; this shift toward decreased lung function, however, would be considered adverse because individuals within the population would have diminished reserve function and, therefore, would be at increased risk to further environmental insult.

# 1.6. Summary

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

# Chapter 2. Integrative Health Effects Overview

1    The subsequent chapters of this ISA will present the most policy-relevant information related to the
2    review of the NAAQS for PM. This chapter integrates the key findings from the disciplines evaluated in
3    this current assessment of the PM scientific literature, which includes the atmospheric sciences, ambient
4    air data analyses, exposure assessment, dosimetry, and health studies (e.g., toxicological, human clinical,
5    and epidemiologic). The EPA framework for causal determinations described in Chapter 1 has been
6    applied to the body of evidence in order to judge the scientific data that examines the association between
7    exposure to PM and health effects in a two-step process. The first step wass to determine the weight of
8    evidence in support of causation at relevant pollutant exposures and characterize the strength of any
9    resulting causal classification. The EPA framework applied here employed a five-level hierarchy for
10   causal determination:

11        ▪   Causal relationship

12        ▪   Likely to be a causal relationship

13        ▪   Suggestive of a causal relationship

14        ▪   Inadequate to infer a causal relationship

15        ▪   Suggestive of no causal relationship

16   The second step evaluated the entirety of policy-relevant quantitative evidence regarding the
17   concentration-response relationships including levels and exposure durations at which effects were
18   observed, and subpopulations that were more susceptible or vulnerable to PM exposure than the general
19   population. This integration of evidence resulted in identification of a study or set of studies that best
20   estimated the concentration-response relationships for the U.S. population, given the current state of
21   knowledge. Together the two steps in the framework led to: (1) causal determinations for a range of health
22   outcomes, and (2) characterization of the magnitude of these responses, including susceptible or
23   vulnerable subpopulations, over a range of ambient concentrations.
24   This chapter summarizes and integrates the newly available scientific evidence that best informs
25   consideration of the policy-relevant questions that frame this assessment, presented in Chapter 1.
26   Section 2.1 discusses the trends in ambient concentrations and sources of PM and provides a brief
27   summary of ambient air quality for short- and long-term exposure durations. Section 2.2 presents the
28   evidence regarding personal exposure to ambient PM in outdoor and indoor microenvironments, and it

1 discusses the relationship between ambient PM concentrations and exposure to PM from ambient sources.
2 Section 2.3 integrates the evidence for studies that examine the development of health effects in response
3 to short- and long-term exposure to PM and discusses important uncertainties identified in the
4 interpretation of the scientific evidence. In addition, the section discusses the evidence from recent studies
5 that examined the association between PM components or sources, instead of mass and health effects.
6 Finally, Section 2.4 presents the public health impacts associated with exposure to PM, which includes
7 evidence for potentially susceptible and vulnerable populations to PM exposure.

# 2.1. Concentrations and Sources of Atmospheric PM

## 2.1.1. Ambient PM Variability and Correlations

8 Advances in understanding the spatiotemporal distribution of PM mass and constituents have
9 recently been made, particularly with regard to $PM_{2.5}$ mass and chemical composition and ultrafine
10 concentrations. Emphasis in this ISA was on the period from 2005-2007 so that the most recent validated
11 EPA Air Quality System (AQS) data were used. Note, however, that a majority of U.S. counties were not
12 represented in AQS data, since their population densities fell below the regulatory monitoring threshold
13 for PM. Moreover, monitors reporting to AQS were not uniformly distributed across the U.S. or within
14 counties, and conclusions drawn from AQS data may not apply equally to all parts of a geographic region.
15 Furthermore, biases can exist for some PM constituents (and hence total mass) owing to volatilization
16 losses of nitrates and other semi-volatile compounds, and, conversely, to retention of particle-bound water
17 by hygroscopic species. The degree of spatial variability in PM was likely to be region-specific and
18 strongly influenced by region-specific sources and meteorological and topographic conditions.

### 2.1.1.1. Spatial Variability across the U.S.

19 County-scale, 24-h average concentration data for $PM_{10}$ and $PM_{2.5}$ for 2005–2007 showed
20 considerable variability across the U.S. Figures 3-6 and 3-7 show county-scale coverage and average
21 concentrations for $PM_{10}$ and $PM_{2.5}$. For $PM_{10}$, the highest reported annual average concentrations
22 (>51 µg/m$^3$) occurred in two counties in southern California and five counties in southern Arizona and
23 central New Mexico. The lowest reported annual average $PM_{10}$ concentrations ($\leq$ 20 µg/m$^3$) were within
24 114 counties distributed fairly uniformly across the U.S. For $PM_{2.5}$, the highest reported annual average
25 concentration (>20 µg/m$^3$) were reported for six counties within the San Joaquin Valley and inland
26 southern California, as well as Jefferson County, AL (containing Birmingham) and Allegheny County, PA

1    (containing Pittsburgh). The lowest reported annual average $PM_{2.5}$ concentrations ($\leq 12$ µg/m$^3$) were

2    contained within 237 counties distributed throughout the west, northeast, Florida and the Carolinas.

3         The concentration of $PM_{2.5}$ relative to that of $PM_{10}$ varied substantially by location, with a larger

4    fraction of PM mass in the coarse mode in cities with dryer climates (e.g., Phoenix and Denver) and a

5    larger fraction in the fine mode in eastern U.S. cities (e.g., Pittsburgh and Philadelphia). Limiting the

6    differential calculation of $PM_{10-2.5}$ to low volume federal reference method (FRM) $PM_{10}$ and $PM_{2.5}$

7    monitors helps reduce sampling artifacts resulting from subtracting two independent mass measurements.

8    However, this results in poor geographic coverage since few sites have the appropriate co-located

9    monitors for computing this difference. Figure 3-8 contains all U.S. counties where co-located low

10   volume FRM data was available for this calculation. Although the general understanding of PM

11   differential settling leads to an expectation of greater spatial heterogeneity in the $PM_{10-2.5}$ fraction,

12   deposition of particles as a function of size depends strongly on local meteorological conditions. Current

13   data coverage is insufficient to draw any meaningful conclusions regarding the spatial distribution of

14   $PM_{10-2.5}$.

15        Spatial variability in $PM_{2.5}$ components obtained from the Chemical Speciation Network (CSN)

16   varied considerably by species, including organic carbon (OC), elemental carbon (EC), sulfate ($SO_4^{2-}$),

17   nitrate ($NO_3^-$) and ammonium ($NH_4^+$) (see Section 3.5.1.1). The highest annual average OC

18   concentrations (>5 µg/m$^3$) were observed in the western and southeastern U.S. Concentrations in the

19   western U.S. peaked in the fall and winter, while concentrations in the Southeast peaked anytime between

20   spring and fall. EC exhibited less seasonality than OC and was particularly stable in the eastern half of the

21   U.S. Annual average EC concentrations greater than 1.5 µg/m$^3$ were present in Los Angeles, Pittsburgh,

22   New York and El Paso. Concentrations of $SO_4^{2-}$ were higher in the eastern U.S. as a result of higher $SO_2$

23   emissions in the East, compared with the West. There is also considerable seasonal variability with higher

24   $SO_4^{2-}$ concentrations in the summer months when the oxidation of $SO_2$ proceeds at a faster rate than

25   during the winter. $NO_3^-$ concentrations were highest in California, with annual averages >4 µg/m$^3$ at

26   many monitoring locations. There were also elevated levels of $NO_3^-$ in the Upper Midwest (>2 µg/m$^3$),

27   particularly in the winter. In general, $NO_3^-$ was higher in the winter across the country, in part as a result

28   of temperature-driven partitioning and volatilization. Exceptions existed in Los Angeles and Riverside,

29   where high $NO_3^-$ readings appeared year round. Concentrations of $NH_4^+$ were similar to concentrations of

30   $NO_3^-$ or $SO_4^{2-}$ throughout the U.S. Clearly, there is variation in both $PM_{2.5}$ mass and composition by city,

31   some of which might be due to regional differences; however, there are too many controlling variables

32   (e.g. meteorology, sources, topography) which are too poorly characterized at this scale to allow

33   conclusions to be drawn regarding $PM_{2.5}$ composition across all cities within a given geographic region.

1        Variability in $PM_{2.5}$ components across the U.S. was examined by focusing on fifteen metropolitan

2    areas chosen based on their geographic distribution and coverage in recent health effects studies (see

3    Section 3.5.1.1). The urban areas selected were Atlanta, Birmingham, Boston, Chicago, Denver, Detroit,

4    Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. On

5    an annual average basis, sulfate was the dominant $PM_{2.5}$ component in the eastern cities, ranging from

6    42% of $PM_{2.5}$ mass in Chicago to 56% in Pittsburgh. Organic carbon mass (OCM) was the next largest

7    component. In the western cities, OCM was the largest constituent of $PM_{2.5}$ on an annual basis, ranging

8    from 34% in Los Angeles to 58% in Seattle. Sulfate, nitrate and crustal material were all important

9    components in the western cities analyzed. Sulfate ranged from 18% in Denver to 32% in Los Angeles.

10    Nitrate was particularly large in Riverside (22%), Los Angeles (19%) and Denver (15%); crustal material

11    constituted a substantial fraction of $PM_{2.5}$ year-round in Phoenix (28%) and Denver (16%), and during the

12    summer in Houston (26%), even though the annual average was much lower (11%).

## 2.1.1.2. Spatial Variability on the Urban and Neighborhood Scales

13        In general, $PM_{10}$ has a shorter atmospheric lifetime than $PM_{2.5}$ because $PM_{10}$ contains larger

14    particles which have higher settling velocity. As a result, local emission sources often dominate $PM_{10}$

15    annual average mass concentrations at particular monitors, while $PM_{2.5}$ mass concentrations are more

16    homogeneously distributed (see Section 3.5.1.2). Therefore, as an example, using the 15 cities listed

17    above, there was considerably less decline in the correlation between monitors as a function of distance

18    for $PM_{2.5}$ than for $PM_{10}$. Furthermore, correlations between $PM_{2.5}$ concentrations exhibited substantially

19    less scatter. For $PM_{10}$, Atlanta, Boston, Denver, Los Angeles, New York City, Philadelphia, Phoenix,

20    Pittsburgh and Riverside all showed relatively high correlations as a function of distance (average

21    correlation of 0.75 at 40 km or greater monitor separation), while Birmingham, Chicago, Detroit, Houston

22    and St. Louis had correlations that dropped off much more quickly with distance (average correlation of

23    0.75 at 6 km or less monitor separation). The Seattle data only included two $PM_{10}$ monitoring sites, thus

24    providing insufficient information to draw any conclusions. For $PM_{2.5}$, most metropolitan areas exhibited

25    high correlations (generally >0.75) out to a distance of 100 km. Notable exceptions were Denver, Los

26    Angeles and Riverside, where correlations dropped below 0.75 somewhere between 20 and 50 km.

27    Insufficient data were available in the 15 metropolitan areas to perform similar analyses for $PM_{10-2.5}$ using

28    co-located, low volume FRM monitors.

29        Population density and associated building density are important determinants of the spatial

30    distribution of PM concentrations. Inter-sampler correlations as a function of distance between monitors

31    obtained for sampler pairs located less than 4 km apart (i.e., on a neighborhood scale) showed a shallower

1    slope for $PM_{2.5}$ than for $PM_{10}$. Average correlation was maintained at 0.93 for $PM_{2.5}$, while it dropped to

2    0.70 for $PM_{10}$ (see Section 3.5.1.3).

3          Few studies performed direct comparisons of ultrafine particle measurements at multiple locations

4    within an urban area. A decrease in the number of ultrafine particles was demonstrated with shifts from a

5    dominant mode at around 10 nm within 20 m of a freeway to a flattened dominant mode at around 50 nm

6    at a distance of roughly 100–150 m. At the same time, accumulation mode particle number concentration

7    remained relatively constant to within ~300 m from the freeway. These findings suggest a high degree of

8    spatial heterogeneity in ultrafine particles compared with accumulation mode particles on the urban scale.


## 2.1.2. Temporal Variability

9          Trends in $PM_{10}$ concentrations show a steady decline from 1988 to 2007 in all 10 EPA Regions. A

10   steady decrease in $PM_{2.5}$ concentrations from 1999 (the beginning of nationwide monitoring for $PM_{2.5}$) to

11   2007 was observed in all 10 EPA Regions, with the three-year average of the 98th percentile of 24-h

12   $PM_{2.5}$ concentrations dropping 10% over this time period.

13         Using hourly PM observations in the 15 metropolitan areas, diel variation showed peaks that differ

14   by pollutant and region. For $PM_{10}$, all areas showed a gradual morning increase in mean concentrations

15   starting at approximately 6:00 am on weekdays, corresponding with both the start of morning rush hour

16   and break-up of the overnight inversion layer. The magnitude and duration of this peak varied

17   considerably by metropolitan area. For $PM_{2.5}$, a similar morning peak was observed starting at

18   approximately 6:00 am in all cities except Pittsburgh, where elevated overnight $PM_{2.5}$ obscures any

19   morning peak. There was also an evening $PM_{2.5}$ concentration peak that was broader than the morning

20   peak and extended into the overnight period, reflecting the concentration increase caused by the usual

21   collapse of the mixed layer after sundown (see Section 3.5.2.3).

22         Studies indicate that ultrafine particles in urban environments exhibit similar two-peaked diel

23   patterns in Los Angeles and the San Joaquin Valley as well as in Kawasaki City, Japan and Copenhagen,

24   Denmark (see Section 3.5.2.3). The afternoon peak in ultrafine particles likely represents the combination

25   of primary source emissions such as evening rush hour traffic and photochemical formation of secondary

26   organic aerosol.


## 2.1.3. Correlations between Copollutants

27         Correlations between PM and gaseous copollutants including $SO_2$, $NO_2$, carbon monoxide (CO)

28   and $O_3$ varied both seasonally and spatially between and within metropolitan areas. On average, $PM_{10}$ and

1   PM$_{2.5}$ were correlated with each other better than with the gaseous copollutants. There was relatively little

2   seasonal variability in the mean correlation between PM in both size fractions and SO$_2$ and NO$_2$. CO,

3   however, showed higher correlations with PM$_{10}$ and PM$_{2.5}$ on average in the winter compared with the

4   other seasons. This seasonality results in part because a larger fraction of PM is primary in origin during

5   the winter. To the extent that this primary component of PM is associated with common sources of NO$_2$

6   and CO, then higher correlations with these gaseous co-pollutants are to be expected. Increased

7   atmospheric stability in colder months would also reinforce these associations.

8       The correlation between daily maximum 8-h average O$_3$ and PM showed the highest degree of

9   seasonal variability with positive correlations on average in the spring, summer and fall, and negative

10  correlations on average in the winter. This situation arises as the result of seasonal differences in sources

11  and photochemical production of secondary PM$_{2.5}$ and O$_3$. However, this relationship is not found in all

12  cities examined (e.g., Birmingham, Boston and St. Louis).


## 2.1.4. Measurement Techniques

13      Reliable methods have been developed to measure real-time PM mass concentrations (e.g., FDMS-

14  TEOM). Real-time (or continuous and semi-continuous) measurement techniques are also available for

15  PM species, such as PILS for multiple ions analysis and AMS for multiple components analysis.

16  Advances have also been achieved in PM organic speciation (e.g. TD-GC-MS) (For additional

17  information see Section 3.4).


## 2.1.5. PM Source Characteristics

18      PM in the atmosphere contains both primary (i.e., emitted directly by sources) and secondary

19  components, which can be anthropogenic or natural in origin. Secondary components are produced by the

20  oxidation of precursor gases such as SO$_2$, NO$_X$ and ammonia (NH$_3$) and organic compounds. The largest

21  sources of primary PM$_{2.5}$ on a nationwide basis are wildfires, road dust, and electricity-generating units

22  (EGUs), with road dust being the largest single source of PM$_{10}$ according to the National Emissions

23  Inventory (NEI).

24      Developments in the chemistry of formation of secondary organic aerosol (SOA) indicate that

25  oligomers are likely a major component of OC in aerosol samples. Until a few years ago, the oxidation of

26  terpenes and aromatic compounds were considered as sources of SOA, but not the oxidation of isoprene.

27  However, recent observations suggest that small, but important quantities of SOA are formed from

28  isoprene oxidation. Gasoline engines have been found to emit a mix of nucleation-mode heavy and large

1    polycyclic aromatic hydrocarbons on which unspent fuel and trace metals condense, while diesel particles

2    are composed of a soot nucleus on which $SO_4^{2-}$ and hydrocarbons condense. Current inventories of

3    emissions from combustion sources overestimate the primary component of organic aerosol and

4    underestimate the semi-volatile components in the emissions. This situation results from the lack of

5    capture of evaporated semi-volatile components upon dilution in standard emissions tests. As a result,

6    near-traffic sources of organic aerosol are underestimated, however, farther downwind the overall

7    formation rate of SOA increases as a result of the oxidation of these semi-volatile components.

## 2.1.6. Source Contributions to PM

8    Results of receptor modeling calculations indicate that $PM_{2.5}$ is produced mainly by combustion of

9    fossil fuel, either by stationary sources or by transportation. It is apparent that a relatively small number

10    of source categories, compared to the total number of chemical species that typically are measured in

11    ambient monitoring source receptor model studies, are needed to account for the majority of the observed

12    mass of PM in these studies. A compilation of study results shows that secondary sulfate (mainly from

13    EGUs), nitrate (from the oxidation of NO emitted mainly from transportation and EGUs), and primary

14    mobile source categories constitute most of $PM_{2.5}$ (and $PM_{10}$) in the East. Fugitive dust, found mainly in

15    the $PM_{10-2.5}$ size range, represents the largest source of ambient $PM_{10}$ in many locations in the western

16    U.S. Quoted uncertainties in the source apportionment of constituents in ambient aerosol samples

17    typically range from 10 to 50%. An intercomparison of source apportionment techniques indicated that

18    the same major source categories of $PM_{2.5}$ were consistently identified by several independent groups

19    working with the same data sets. Soil-, sulfate-, residual oil-, and salt-associated mass were most clearly

20    identified by the groups. Other sources with more ambiguous signatures, such as vegetative burning and

21    traffic-related emissions were less consistently identified.

22    Spatial variability in source contributions across urban areas is an important consideration in

23    assessing the likelihood of exposure error in epidemiologic studies relating health endpoints to sources.

24    Concepts similar to those for using ambient concentrations as surrogates for personal exposures apply

25    here. Studies for $PM_{2.5}$ indicate that intra-urban variability increases in the following order: regional (e.g.

26    secondary $SO_4^{2-}$ from EGUs) < area (e.g. on road mobile sources) < point (e.g. stacks) sources. Only one

27    study was available for $PM_{10-2.5}$, indicating a similar ordering, but without a regional component (resulting

28    from the short lifetime of $PM_{10-2.5}$ compared to transport times on the regional scale).

## 2.1.7. Policy-Relevant Background

1    The background concentration of PM that is useful for risk and policy assessments informing

2    decisions about the NAAQS are referred to as policy-relevant background (PRB) concentrations. PRB

3    concentrations are those concentrations that would occur in the U.S. in the absence of anthropogenic

4    emissions in continental North America (defined here at the U.S., Canada and Mexico). PRB

5    concentrations include contributions from natural sources everywhere in the world and from

6    anthropogenic sources outside these three countries. Background levels so defined facilitate separation of

7    pollution levels that can be controlled by U.S. regulations (or through international agreements with

8    neighboring countries) from levels that are generally uncontrollable by the U.S. Contributions to policy-

9    relevant background (PRB) levels of PM include both primary and secondary natural and anthropogenic

10   components (see Section 3.6). PRB concentrations for the continental U.S. were estimated using a

11   deterministic, continental scale chemistry-transport model (CTM) using results from the GEOS-Chem

12   global scale CTM as boundary conditions. PRB concentrations of $PM_{2.5}$ were estimated to be less than 1

13   $\mu g/m^3$ on an annual basis and maximum daily average values generally range from 3.1 to 20 $\mu g/m^3$ with a

14   peak as high as 63 $\mu g/m^3$ at the nine national park sites across the U.S. that were used for model

15   evaluation.


# 2.2. Human Exposure

16   This section summarizes the findings from the recent exposure assessment literature, which include

17   the assessment of exposure to ambient PM, infiltration of ambient PM to indoor environments, and source

18   apportionment of exposure. This summary is intended to support the interpretation of the findings from

19   epidemiologic studies. For a more detailed explanation see Section 3.7.


## 2.2.1. Outdoor Exposure to Ambient PM

20   The correlation between the PM concentration measured at a central community ambient monitor

21   and the true community average concentration depends on the spatial distribution of the PM, selection of

22   the monitoring site chosen to represent the community average, and division of the community by terrain

23   features or source locations into several sub-communities that differ in the temporal pattern of pollution.

24   Some studies, conducted mainly in Europe, have found that personal $PM_{2.5}$ and $PM_{10}$ exposures for

25   pedestrians in street canyons could be much higher than ambient concentrations measured by urban

26   background ambient monitors. As a result, ambient monitors located at background, central urban, road

1   side, or near-residential sites might not reflect peak exposures to some individuals in a community.

2   Ambient monitor height also affects estimates of exposure because PM concentration varies as a function

3   of height. Within a street canyon, changes in wind direction and speed cause significant variability over a

4   small distance, with findings showing up to a two order of magnitude change in benzo[a]pyrene

5   concentrations across a street canyon. Wind tunnel studies have shown street canyon effects exist for

6   suburban and not just for downtown, heavily urbanized settings.

## 2.2.2. Indoor and Personal Exposure to Ambient PM

7       PM infiltration factors, $F_{inf}$, depend on particle size, chemical composition, season, and region of

8   the country. Infiltration can best be modeled dynamically based on a distribution of air exchange and

9   deposition PM loss rates rather than being represented by a single value. There is significant variability

10  within and across regions of the country with respect to indoor exposures to ambient PM. Infiltrated

11  ambient PM concentrations depend in part on the ventilation properties of the building or vehicle in which

12  the person is exposed. Season is important to PM infiltration because it affects the ventilation practices

13  used, and ambient temperature and humidity conditions affect the transport, dispersion, and size

14  distribution of PM. Residential air exchange rates have been observed to be higher in summer for regions

15  with low air conditioning usage, and regional differences in air exchange rates (Southwest < Southeast

16  < Northeast < Northwest) also reflect ventilation practices. Differential infiltration occurs as a function of

17  PM size and composition. PM infiltration is largest for accumulation mode particles, and decreases for

18  ultrafine PM lost to diffusion and for coarse particles lost through inertial impaction mechanisms.

19  Infiltration is also affected by variations in particle composition and volatility. For example, EC or black

20  carbon (BC) infiltrates more readily than OC. Differential infiltration can affect both exposure estimates

21  and PM toxicity.

22      Emission inventories and source apportionment studies suggest that sources of PM exposure vary

23  by region. Comparison of studies performed in the eastern U.S. with studies performed in the western

24  U.S. suggest that the contribution of $SO_4^{2-}$ to personal exposure is higher for the East (16-46%) compared

25  with the West (~4%) and that motor vehicle emissions and secondary $NO_3^-$ are larger sources of personal

26  exposure for the West (~9%) as compared with the East (~4%). Results of source apportionment studies

27  of personal exposure to $SO_4^{2-}$ indicate that personal $SO_4^{2-}$ exposures are mainly attributable to ambient

28  sources. Source apportionment for OC and EC is difficult because they originate from both indoor and

29  outdoor sources. Exposure to OC of indoor and outdoor origin can be distinguished by the presence of

30  aliphatic C-H groups generated indoors, since outdoor concentrations of aliphatic C-H are low. Trace

31  metal studies have shown variable results regarding personal exposure to ambient constituents with

1    significant variation among cities and over seasons that can be related to incinerator operation, fossil fuel

2    combustion, biomass combustion (wildfires), and presence of crustal materials in the built environment,

3    among other sources.

## 2.2.3. Implications for Epidemiologic Studies

4    Variations in PM and its components could lead to errors in using ambient PM measures as

5    surrogates for exposures to PM. $PM_{2.5}$ and $PM_{10}$ concentrations are relatively well-correlated across

6    monitors in the urban areas examined. Correlation coefficients tend to be lower, and concentration

7    differences tend to be higher between $PM_{10}$ monitoring sites than between $PM_{2.5}$ monitoring sites. Even if

8    $PM_{2.5}$ and $PM_{10}$ concentrations measured at sites within an urban area are highly correlated, significant

9    differences in their concentrations can occur on any given day. The degree of spatial uniformity in $PM_{10}$

10   and $PM_{2.5}$ concentrations in urban areas varies across the country. Current information suggests that

11   $PM_{10-2.5}$ and some PM components are more spatially variable than $PM_{2.5}$. These factors should be

12   considered in using data obtained from monitoring networks to estimate community-scale human

13   exposure to ambient PM, and caution should be exercised in extrapolating conclusions obtained from one

14   urban area to another.

15   Community, time-series epidemiologic studies use the average community PM concentration as a

16   surrogate for the average personal exposure to ambient PM. The resulting health effect risk estimate,

17   based on the average community ambient concentration, differs from the risk that would be estimated if

18   the average community ambient exposure were used in the epidemiologic study. This difference is given

19   by the average ambient exposure factor. However, the risk estimate based on the ambient concentration

20   gives the change in health effects resulting from a change in ambient concentration of PM and is,

21   therefore, an appropriate measure for risk assessment and risk management. Variations in ambient

22   concentrations across a community, variations in individual ambient exposures around the community

23   average, and seasonal or daily variation in the ambient exposure factor may increase standard errors of

24   PM health effects estimates, making it more difficult to detect a true underlying association between the

25   correct exposure metric and the health outcome studied. The use of the community average ambient PM

26   concentration as a surrogate for the community average personal exposure to ambient PM is not expected

27   to change the principal conclusions from PM epidemiologic studies that use community average health

28   and pollution data (U.S. EPA, 2004). Several recent studies support this by showing how the ambient

29   component of personal exposure to $PM_{2.5}$ could be estimated using various tracer and source

30   apportionment techniques and that is highly correlated with ambient concentrations of $PM_{2.5}$. These

31   studies also show that the non-ambient component of personal exposure to $PM_{2.5}$ is basically uncorrelated

1    with ambient $PM_{2.5}$ concentrations. For long-term studies that use differences in long-term community

2    average ambient PM concentrations as an exposure metric, the effect of possible community-to-

3    community differences in the average ambient exposure factor or in the average non-ambient exposure

4    are less understood. For panel epidemiologic studies, the most appropriate exposure metric may depend

5    on the health outcome measured. However, sufficient information should be obtained to enable

6    determining the association of the health outcome with ambient concentration, ambient exposure, non-

7    ambient exposure, and total personal exposure.

8        A number of studies have examined whether gaseous copollutants could act as surrogates for

9    exposure to ambient PM. Several studies have concluded that ambient concentrations of $O_3$, $NO_2$, and

10   $SO_2$ are associated with the ambient component of personal exposure to total $PM_{2.5}$ as opposed to the

11   ambient component of personal exposures to the gases. However, in some studies this result may have

12   arisen in part because personal exposure to the gases was often beneath the detection limits of the

13   personal monitoring devices. Thus, the evidence that ambient gases can be considered surrogates of $PM_{2.5}$

14   exposure is mixed. It is likely that associations between ambient gases and personal exposure to $PM_{2.5}$ of

15   ambient origin exist, but they are complex and vary by season and location.

# 2.3. Health Effects

16       This section evaluates the evidence from toxicological, human clinical, and epidemiologic studies

17   that examined the health effects associated with short- and long-term exposure to PM (i.e., $PM_{10}$, $PM_{2.5}$,

18   $PM_{10-2.5}$ and ultrafine particles [0.01-0.1 µm]). Within this section a discussion of the causal

19   determinations will be presented by PM size fraction and exposure type (i.e., short- or long-term

20   exposure) for only those health endpoints in which sufficient evidence was available to conclude that a

21   specific PM size fraction **causes** or **likely causes** a health effect (i.e., cardiovascular morbidity,

22   respiratory morbidity, mortality). Although an extensive amount of research has been conducted to

23   examine PM-related health effects, a limited body of evidence is currently available to examine the

24   presence or absence of associations between some health outcomes and PM size fractions. Thus, based on

25   currently available evidence, it is not possible to causally link exposure duration, PM size fraction and

26   health outcome for all combinations evaluated in this ISA. The evaluation of the aforementioned factors

27   together has resulted in evidence that is **suggestive** of a causal relationship for mortality and respiratory

28   morbidity in response to short-term exposure to $PM_{2.5}$, mortality, cardiovascular morbidity and

29   reproductive and developmental effects in response to long-term exposure to $PM_{10}$, and reproductive and

30   developmental effects in response to long-term exposure to $PM_{2.5}$. In addition, **inadequate** evidence to

1    infer a causal relationship exists for all other health outcomes (due to both short- and long-term exposure)

2    to $PM_{10-2.5}$ and ultrafine PM. A detailed discussion of the underlying evidence used to formulate each

3    causal determination can be found in Chapters 6 and 7.


# 2.3.1. Exposure to $PM_{10}$

## 2.3.1.1. Effects of Short-Term Exposure to $PM_{10}$

| Size Fraction | Outcome | Causality Determination |
|---|---|---|
| $PM_{10}$ | Cardiovascular morbidity | Likely to be causal |
| | Respiratory morbidity | Likely to be causal |
| | Mortality | Likely to be causal |


### *Cardiovascular Morbidity*

4    The majority of recent evidence for an association between short-term exposure to $PM_{10}$ and

5    cardiovascular (CV) health effects is derived from epidemiologic studies of hospital admissions (HAs)

6    and emergency room (ED) visits (see Section 6.2.10). Although some regional heterogeneity is evident in

7    the single-city effect estimates, consistent increases in HAs and ED visits for cardiovascular diseases

8    (CVD), has been observed across studies, with the majority of estimates ranging from 0.5–1.0% per 10

9    $\mu g/m^3$ increase in $PM_{10}$ (see Figure 6-1). A detailed examination of specific CV health outcomes has

10   suggested that ischemic heart disease (IHD) and chronic heart failure (CHF) are responsible for the

11   majority of PM-related CVD HAs rather than cerebrovascular diseases; however, one large multicity

12   U.S.-based study provides evidence of an association between $PM_{10}$ and ischemic stroke. Overall, the new

13   literature provides consistent evidence for associations between short-term exposure to $PM_{10}$ and

14   increased risk of cardiovascular HAs and ED visits in cities with mean 24-h average concentrations

15   ranging from 16.8 to 48 $\mu g/m^3$.

16   Human clinical studies which evaluate the effect of $PM_{10}$ on measures of cardiovascular function

17   have not been conducted; however, a few recent animal toxicological studies demonstrated impacts on the

18   cardiovascular system. A new inhalation study in animals found lowered cardiac contractility upon

19   exposure to $PM_{10}$, while several intratracheal instillation studies found altered vasoreactivity and elevated

20   levels of systemic inflammatory and blood coagulation markers (see Sections 6.2.1. through 6.2.9). In

21   addition, several epidemiologic studies have observed physiologic alterations in CV function including:

1  heart rate variability (HRV), systemic markers of inflammation, coagulation, and oxidative stress in cities

2  with mean 24-h average concentrations ranging from 10.5 to 46.1 μg/m$^3$. These findings, along with those

3  reported in the toxicological literature contribute to the biological plausibility of $PM_{10}$-related

4  cardiovascular effects.

5      Overall, consistent and coherent evidence exists across recent toxicological and epidemiologic

6  studies, which supports the conclusion that short-term exposure to $PM_{10}$ is associated with an increased

7  risk of cardiovascular morbidity. Furthermore, findings of altered autonomic function, cardiac

8  contractility, systemic inflammation, coagulation, and vasoreactivity provide biological plausibility that

9  exposure to $PM_{10}$ could lead to more severe effects, including HAs or ED visits for IHD, CHF, or

10  ischemic stroke. Collectively, the studies evaluated provide sufficient evidence to conclude that **a causal**

11  **relationship is likely to exist between short-term exposure to ambient concentrations of $PM_{10}$ and**

12  **cardiovascular morbidity.**

### *Respiratory Morbidity*

13      Epidemiologic studies that examined the association between short-term exposure to $PM_{10}$ and

14  respiratory morbidity found consistent positive effects in asthmatic children and adults, but no evidence

15  of an association in healthy individuals. The majority of the studies that examined the association between

16  $PM_{10}$ and respiratory symptoms and medication use found an increased risk ranging from ~1.0 to 1.75 for

17  cough, phlegm, difficulty breathing, and bronchodilator use in asthmatic children in cities with mean 24-h

18  average concentrations ranging from 16.8 to 64.5 μg/m$^3$. Positive, but less consistent effects for

19  respiratory symptoms and medication use were observed in asthmatic adults (see Figure 6-7). One study

20  in the new epidemiologic literature examined the effects of $PM_{10}$ on pulmonary inflammation, and

21  observed an association between $PM_{10}$ and exhaled nitrogen oxide (eNO). An evaluation of respiratory

22  ED visit and HA studies found consistent positive associations at ambient $PM_{10}$ concentrations ranging

23  from 13.3 to 60.8 μg/m$^3$ (see Section 6.3.8.), among asthmatic children (~ 2% increase) and older adults

24  with COPD (~ 0 to 3% increase). Although no toxicological or human clinical studies in the new body of

25  literature examined the effect of short-term exposure to $PM_{10}$ on respiratory morbidity, the consistent

26  epidemiologic evidence alone is sufficient to conclude that **a causal relationship is likely to exist**

27  **between short-term exposure to ambient concentrations of $PM_{10}$ and respiratory morbidity**.

### *Mortality*

28      The epidemiologic literature indicates consistent positive associations between short-term exposure

29  to $PM_{10}$ and all-cause mortality. The multicity studies evaluated reported an approximate 0.12–0.81%

30  increase in all-cause mortality per 10 μg/m$^3$ increase in $PM_{10}$ with 24-h average $PM_{10}$ concentrations

1  ranging from 13 to 53.2 µg/m$^3$ (see Section 6.5). Although respiratory and cardiovascular-related

2  mortality also show consistent positive effects, only a few multicity studies conducted cause-specific

3  mortality analyses. Heterogeneity in $PM_{10}$ mortality risk estimates was observed between cities and

4  studies, which could be attributed to the lag, averaging time, number of cities and/or copollutants included

5  in the regression models. An evaluation of the lag structures used in the multicity studies found that the

6  greatest effects were observed using the previous day's $PM_{10}$ concentration (lag 1) or the average of the

7  same day's and previous day's concentrations (lag 0-1). In addition, the use of a distributed lag model

8  resulted in slightly larger (by ~30%) estimates compared to single-day lags. Regional heterogeneity and

9  seasonal patterns in $PM_{10}$ risk estimates were also observed, with the greatest effects occurring in the

10  Eastern U.S. and during the summer and transition seasons, spring and fall, respectively. An examination

11  of potential confounders (i.e., temperature and copollutants) using different study designs (i.e., time series

12  and case crossover) observed that neither is likely to account for differences in $PM_{10}$-mortality risk

13  estimates between studies. However, one Canadian-based multicity study did observe a reduction in the

14  $PM_{10}$ mortality risk estimate upon the inclusion of $NO_2$ in the model. Overall, the consistent evidence

15  found across epidemiologic studies is sufficient to conclude that **a causal relationship is likely to exist**

16  **between short-term exposure to ambient concentrations of $PM_{10}$ and mortality**.

## 2.3.1.2. Effects of Long-Term Exposure to $PM_{10}$

| Size Fraction | Outcome | Causality Determination |
|---|---|---|
| $PM_{10}$ | Cardiovascular morbidity | Suggestive |
| | Respiratory Morbidity | Likely to be causal |
| | Mortality | Suggestive |
| | Reproductive and Developmental | Suggestive |
| | Cancer | Inadequate |

### *Respiratory Morbidity*

17  The recent epidemiologic literature focuses on prospective cohort studies, which found consistent

18  positive associations between long-term exposure to $PM_{10}$ and respiratory morbidity (see Section 7.3).

19  U.S.- and European-based multi- and single-city studies have observed an increase in respiratory

20  symptoms (e.g., bronchitis and cough) in children at annual average concentrations ranging from 7.0 to

21  34.8 µg/m$^3$. The strength of the observed association is increased through the results of a cohort

1   consisting of school children in Switzerland, which found a reduction in respiratory symptoms

2   (i.e., chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis symptoms) that

3   coincided with a reduction in ambient $PM_{10}$ levels. Additional epidemiologic studies conducted in both

4   the U.S. and abroad also found a relationship between ambient $PM_{10}$ levels and decrements in lung

5   function and lung function growth (Figure 7-4). Although the epidemiologic evidence supports an

6   increase in respiratory health effects in response to long-term exposure to $PM_{10}$, a high correlation

7   between $PM_{10}$ and other pollutants has also been observed, which could potentially confound the $PM_{10}$-

8   respiratory morbidity relationship. Overall, the consistent associations observed across studies and

9   locations provide sufficient evidence to conclude that **a causal relationship is likely to exist between**

10  **long-term exposure to ambient concentrations of $PM_{10}$ and respiratory morbidity**.


## 2.3.2. Exposure to $PM_{2.5}$

### 2.3.2.1. Effects of Short-Term Exposure to $PM_{2.5}$

| Size Fraction | Outcome | Causality Determination |
|---|---|---|
| $PM_{2.5}$ | Cardiovascular morbidity | Causal |
| | Respiratory morbidity | Likely to be causal |
| | Mortality | Likely to be causal |


### *Cardiovascular Morbidity*

11  The large body of evidence from studies that examined the effect of short-term exposure to $PM_{2.5}$

12  on cardiovascular morbidity found consistent cardiovascular health effects across epidemiologic, human

13  clinical and toxicological studies. Epidemiologic studies that examined the effect of $PM_{2.5}$ on

14  cardiovascular ED visits and HAs reported consistent positive associations, with the majority ranging

15  from ~ 0.5 to 3.4%, for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in cities with mean 24-h average concentrations of

16  13.8–18.8 µg/m3 (see Section 6.2.10). The largest U.S.-based multicity study, Medicare Air Pollution

17  Study (MCAPS), also observed regional heterogeneity (i.e., the largest excess risks occurred in the

18  Northeast [1.08%]) and seasonal variation (i.e., the largest excess risks occurred during the winter season

19  [1.49%]) in $PM_{2.5}$ risk estimates. The $PM_{2.5}$ ED visit and HA effects observed appear to be driven by IHD

20  and CHF rather than cerebrovascular diseases. Additional epidemiologic studies that examined

21  physiologic alterations in cardiovascular function observed changes in HRV, electrocardiogram (ECG)

1 abnormalities, vasomotor function, systemic inflammation, coagulation and oxidative stress at mean 24-h

2 average concentrations ranging from 7.7–23.7 μg/m$^3$, which provides biological plausibility for the

3 development of cardiovascular health effects at ambient PM$_{2.5}$ concentrations.

4      Controlled human exposure studies have consistently demonstrated changes in various measures of

5 cardiovascular function following exposure to PM$_{2.5}$. The majority of the new studies described have been

6 conducted using diesel exhaust (DE) or concentrated ambient particles (CAPs), and provide strong

7 evidence of PM$_{2.5}$-induced decreases in HRV and vasomotor function, as well as increases in markers of

8 systemic oxidative stress (see Section 6.2). An additional study observed a decrease in ST-segment

9 depression following exposure to DE in a group of older adults with prior myocardial infarction (MI).

10 Although not consistently observed across studies, some investigators have reported PM$_{2.5}$-induced

11 changes in blood pressure (BP), blood coagulation markers, and markers of systemic inflammation (see

12 Section 6.2).

13      Additional new toxicological studies have demonstrated that short-term exposure to PM$_{2.5}$ can

14 result in cardiovascular health effects. Consistent with evidence from human clinical studies, the most

15 significant contributions from the current toxicological literature for acute PM$_{2.5}$-induced cardiovascular

16 effects are decreased myocardial blood flow following ischemia, changes in vascular reactivity, and

17 increased cardiac oxidative stress (see Section 6.2). The results for additional cardiovascular health effects

18 such as HRV, arrhythmia, systemic inflammation, and blood coagulation are mixed, while very few or

19 weakly designed studies were evaluated for BP and cardiac contractility. Taken together, the results from

20 the new human clinical and toxicological studies provide coherence and support the biological plausibility

21 of an association between short-term exposure to PM$_{2.5}$ and cardiovascular morbidity.

22      Overall, the consistent and coherent results from epidemiologic, human clinical, and toxicological

23 studies provides sufficient evidence to conclude that **a causal relationship exists between short-term**

24 **exposure to ambient concentrations of PM$_{2.5}$ and cardiovascular morbidity**.

## *Respiratory Morbidity*

25      The recent epidemiologic literature that examined the association between short-term exposure to

26 PM$_{2.5}$ and respiratory morbidity focused on both respiratory symptoms, which includes medication use,

27 along with respiratory-related HAs and ED visits. The majority of the studies that examined the

28 association between PM$_{2.5}$ and respiratory symptoms and medication use found a consistent increase in

29 asthmatic children (effect estimates ranging from ~1.0–1.3) with less consistent evidence for an

30 association in asthmatic adults in cities with mean 24-h average PM$_{2.5}$ concentrations ranging from 6.1 to

31 19.2 μg/m$^3$ (see Section 6.3). An evaluation of epidemiologic studies that examined specific physiologic

32 alterations in the respiratory health of asthmatic children (i.e., pulmonary function and pulmonary

1  inflammation) found: (1) a decrease in forced expiratory volume ($FEV_1$) ranging from 1-3.4% per

2  10 $\mu g/m^3$ increase in $PM_{2.5}$; and (2) an increase in eNO ranging from 0.46 to 6.99 ppb, respectively. In

3  addition, epidemiologic studies that examined the effect of short-term exposure to $PM_{2.5}$ on respiratory

4  HAs and ED visits found consistent associations (ranging from ~0 to 5%) for respiratory diseases (e.g.

5  COPD and respiratory infections) among older adults (Figure 6-20), but less consistent effects were

6  reported for asthma HAs and ED visits. These respiratory HA and ED visit studies were conducted in

7  cities with mean 24-h average $PM_{2.5}$ concentrations ranging from 13.8 to 18.9 $\mu g/m^3$.

8  Human clinical studies provide supporting evidence of an association between short-term exposure

9  to $PM_{2.5}$ and respiratory morbidity through increased markers of pulmonary inflammation following DE

10  and other traffic-related exposures, oxidative responses to DE and woodsmoke, and exacerbation of

11  allergic responses and allergic sensitization in response to diesel exhaust particles (DEP) (see

12  Section 6.3).

13  Toxicological studies have also demonstrated respiratory-related effects following acute $PM_{2.5}$

14  exposure, including altered pulmonary function, mild pulmonary inflammation and injury, oxidative

15  responses, airway hyperresponsiveness (AHR) in allergic and non-allergic animals, exacerbations of

16  allergic responses and increased susceptibility to infections in a large number of studies involving

17  exposure to CAPs, DE, other traffic-related PM, and woodsmoke (see Section 6.3). The numerous and

18  wide range of respiratory responses observed in both the human clinical and toxicological studies provide

19  biological plausibility for an association between short-term exposure to $PM_{2.5}$ and respiratory morbidity.

20  The consistent and coherent results found in the epidemiologic, human clinical, and toxicological

21  literature provide sufficient evidence to conclude that **a causal relationship is likely to exist between**

22  **short-term exposures to ambient concentrations of $PM_{2.5}$ and respiratory morbidity**.

### Mortality

23  An evaluation of the epidemiologic literature indicates consistent positive associations between

24  short-term exposure to $PM_{2.5}$ and all-cause, respiratory- and cardiovascular-related mortality. The analysis

25  of multicity studies found that risk estimates for all-cause (non-accidental) mortality ranged from

26  0.29-1.21% per 10 $\mu g/m^3$ increase in $PM_{2.5}$ at mean 24-h average concentrations ranging from

27  6.7-34.4 $\mu g/m^3$ (see Section 6.5.2.2). Cardiovascular-related mortality risk estimates (0.34-0.94%) were

28  found to be similar to those for all-cause mortality. However, the risk estimates for respiratory-related

29  mortality were slightly larger (1.01-2.2%) using the same lag and averaging indices. A regional and

30  seasonal pattern in $PM_{2.5}$ risk estimates was observed with the greatest effects occurring in the Eastern

31  U.S. and during the spring. An evaluation of potential confounding of risk estimates by gaseous pollutants

32  found that $PM_{2.5}$ mortality risk estimates remained robust to the inclusion of copollutants in regression

1    models; however, one Canadian-based study did observe potential confounding by $NO_2$. An examination

2    of effect modifiers (e.g., demographic and socioeconomic status [SES] factors), specifically air

3    conditioning use, which is sometimes used as a surrogate for ventilation rate, suggests that $PM_{2.5}$ risk

4    estimates increase as the percent of the population with access to air conditioning decreases. The

5    epidemiologic evidence, along with the results from the examination of potential confounders and effect

6    modifiers of the $PM_{2.5}$–mortality relationship, provide sufficient evidence to conclude that **a causal**

7    **relationship is likely to exist between short-term exposure to ambient concentrations of $PM_{2.5}$ and**

8    **mortality**.

## 2.3.2.2. Effects of Long-Term Exposure to $PM_{2.5}$

| Size Fraction | Outcome | Causality Determination |
|---|---|---|
| $PM_{2.5}$ | Cardiovascular morbidity | Likely to be causal |
| | Respiratory Morbidity | Likely to be causal |
| | Mortality | Likely to be causal |
| | Reproductive and Developmental | Suggestive |
| | Cancer | Inadequate |

### *Cardiovascular Morbidity*

9    Epidemiologic and toxicological studies have provided evidence of the adverse effects of long-term

10   exposure to $PM_{2.5}$ on clinical and subclinical markers of cardiovascular morbidity (see Section 7.2). The

11   epidemiologic evidence consists of a large U.S. based cohort of post-menopausal women, which reported

12   an association between one-year average $PM_{2.5}$ concentrations (mean = 13.5 $\mu g/m^3$) and MI,

13   revascularization, and their combination with CHD death. However, assocations were not found in a

14   cohort of both men and women in Germany with mean one-year average $PM_{2.5}$ concentrations of

15   23.3 $\mu g/m^3$. The examination of subclinical markers of atherosclerosis (i.e., coronary artery calcification

16   [CAC], abdominal aortic calcium [AAC], and carotid intimal-medial thickness [CIMT]) through

17   epidemiologic studies found consistent associations with chronic exposure to $PM_{2.5}$. In addition, these

18   studies reported a modification of atherosclerotic effects in former or current smokers and individuals

19   taking anti-hyperlipidemic medications.

20   Several toxicological studies provide evidence for the accelerated development of atherosclerosis

21   (i.e., increased lipid deposition, increased plaque and lesion areas) in ApoE$^{-/-}$ mice exposed to CAPs from

1    Tuxedo, NY for 4–6 months. Increased expression of tissue factor, an important initiator of thrombosis,

2    was also observed in aortic plaques. Another CAPs study conducted in southern California demonstrated

3    increased lesion area similar to that observed by the other research groups and the effect was attributable

4    to ultrafine traffic PM that contained particles in the accumulation mode (0.18 μm). In addition, long-term

5    exposure to CAPs from Tuxedo, NY resulted in enhanced BP responses in an animal model of

6    hypertension. These experimental studies provide biological plausibility for adverse cardiovascular

7    outcomes observed in epidemiologic studies.

8        A limited amount of new literature is available that examines clinical cardiovascular disease

9    outcomes. Although inconsistent results were reported in these long-term exposure studies, the evidence

10   from epidemiologic, human clinical, and animal toxicological studies that examined the cardiovascular

11   outcomes associated with short-term exposure to $PM_{2.5}$ (discussed in Section 6.2.), supports a role for the

12   development of cardiovascular morbidity in response to long-term exposure to $PM_{2.5}$. Based on the

13   consistent and coherent evidence from epidemiologic and toxicological studies that examined the

14   association between long-term and short-term exposure to $PM_{2.5}$ and cardiovascular morbidity, sufficient

15   evidence is available to conclude that **a causal relationship is likely to exist between long-term**

16   **exposure to ambient concentrations of $PM_{2.5}$ and cardiovascular morbidity**.

### *Respiratory Morbidity*

17       Recent epidemiologic studies conducted in the U.S. and abroad provide consistent evidence of

18   associations between long-term exposure to $PM_{2.5}$ and respiratory symptoms, asthma, and decrements in

19   lung function growth in children from cities with annual average concentrations ranging from 5.0–

20   15.5 μg/m$^3$ (see Section 7.3). Subchronic and chronic toxicological studies provide some evidence of

21   altered pulmonary function, mild inflammation, oxidative responses and histopathological changes

22   including mucus cell hyperplasia and immune suppression in response to CAPs, DE, roadway air and

23   woodsmoke. An examination of allergic animals demonstrated AHR in response to DE, but in some cases

24   adaptation to prolonged exposures was observed. In addition, pre- and postnatal exposure to ambient

25   levels of urban particles was found to affect mouse lung development. Impaired lung development is an

26   important mechanism by which PM exposure may decrease lung function growth in children.

27   Collectively, the results from the toxicological studies provide biological plausibility for the development

28   of respiratory-related health effects resulting from long-term exposure to $PM_{2.5}$. Overall, the consistent

29   and coherent evidence from epidemiologic and toxicological studies is sufficient to conclude that **a**

30   **causal relationship is likely to exist between long-term exposure to ambient concentrations of $PM_{2.5}$**

31   **and respiratory morbidity**.

*Mortality*

1    The new epidemiologic evidence reports a consistent association between long-term exposure to

2    $PM_{2.5}$ and an increased risk of mortality (with the majority of the effects ranging from >1 to 1.20) in cities

3    with annual average $PM_{2.5}$ concentrations ranging from 10.2–29 μg/m$^3$ (see Section 7.6). New evidence

4    from the Harvard Six Cities cohort study shows a relatively large reduction in mortality risk associated

5    with a decrease in $PM_{2.5}$ concentrations. Additional analyses of the Harvard Six Cities cohort and the

6    American Cancer Society (ACS) study in Los Angeles suggest that previous and current studies may have

7    underestimated the magnitude of the $PM_{2.5}$-mortality association. Overall, the consistent evidence

8    reported across epidemiologic studies is sufficient to conclude that **a causal relationship is likely to**

9    **exist between long-term exposure to ambient concentrations of $PM_{2.5}$ and mortality**.

## 2.3.3. PM$_{2.5}$ Constituents or Sources Linked to Health Outcomes

10    Recently, epidemiologic, human clinical and toxicological studies have begun to evaluate the health

11    effects associated with ambient PM constituents and sources, as opposed to PM mass. This evaluation is

12    conducted using a variety of quantitative methods applied to the full set of PM constituents, rather than

13    selecting constituents a priori. A review of the recent literature identified key studies that examined the

14    association between specific PM constituents, PM sources and health effects (Section 6.6). Health studies

15    found some associations between various $PM_{2.5}$ constituents or sources, and respiratory- and

16    cardiovascular-related effects and mortality. However, results varied by study location, the health outcome

17    assessed, $PM_{2.5}$ constituents considered, and $PM_{2.5}$ constituents from a specific source.

18    Table 2-1 provides an overview of the PM source categories, along with the study-specific $PM_{2.5}$

19    constituent groupings or tracers that comprise the sources. Also included are the $PM_{2.5}$ constituents for

20    which an association with various health effects was found. Overall, a consistent trend or pattern that

21    links particular constituents or sources with specific health outcomes was not observed, but a number of

22    $PM_{2.5}$ constituent groupings that are commonly associated with sources such as crustal/soil, salt,

23    secondary sulfate/long-range transport, traffic, oil combustion and woodsmoke/vegetative burning were

24    linked with health effects.

25    Comparisons among these studies are difficult because of differences in handling the data, in

26    approaches used to model source contributions, and in the level of experience in applying source

27    apportionment techniques among research groups. In an intercomparison study, several research groups

28    used the same data sets (which contained the composition of ambient $PM_{2.5}$ and daily mortality counts)

29    and their choice of source apportionment models to identify PM sources (see Section 6.5.2.6.). In these

30    studies, when examining the association between various PM sources and mortality risk estimates, it was

1    found that the between source category variation in risk estimates for daily mortality was significantly

2    larger than the between group variation in reported risks. The results of this exercise indicated that the

3    choice of source apportionment models has a much smaller effect on variations in risk estimates

4    compared to the variations in risk caused by the different source components. In addition, the most

5    strongly associated source types were consistent across all of the groups. This study indicates that source

6    apportionment methods can add useful insights into those source components that contribute to $PM_{2.5}$

7    health effects. Additionally, as more studies are conducted that increase the number of different

8    geographic locations in relation to similar health effects, it is probable that linkages between PM

9    constituents or sources and health effects will become more apparent.


**Table 2-1.    Study-specific PM$_{2.5}$ factor/source categories associated with health effects.**

| Source Category | Health Effects | Time | Type of Study[1] | Species | Reference |
|---|---|---|---|---|---|
| *CRUSTAL/SOIL* | | | | | |
| Al, Si, Fe | negative association with total mortality | Lag 2 | E | Human | Mar et al. (2000) |
| Al, Si, Ca, K, Fe | ST-segment depression | Lag 3 | E | Human | Lanki et al. (2006b) |
| Al, Si, Ti, Fe | ↑ uric acid ↑ mean cycle length | Lag 15 h | E | Human | Riediker et al. (2004b) |
| Al, Si, Ca, K, Fe | ↓ ST-segment voltage | 2 days post-exposure | H | Human | Gong et al. (2003b) |
| Al, Si | ST-segment change | Following exposure | T | Dog | Wellenius et al. (2003) |
| Al, Si | ↑ blood PMN % ↓ blood lymphocytes % ↑ WBC | Following exposure | T | Dog | Clarke et al. (2000) |
| Al | ↓ airway irritation (penh) | During exposure | T | Dog | Nikolov et al. (2008) |
| Al, Si, Ca | ↓ lumen/wall ratio | 24 h post-exposure | T | Rat | Batalha et al. (2002) |
| Al, Si, Ca, Fe | ↓ H ↑ H ↑ SDNN, ↑ RMSSD | During exposure Afternoon post-exposure Night post-exposure | T | Mouse | Lippmann et al. (2005b) |
| *SALT* | | | | | |
| Na, Cl | ST-segment depression | Lag 3 | E | Human | Lanki et al. (2006a) |
| Na, Cl | ↑ blood lymphocyte % | Following exposure | T | Dog | Clarke et al. (2000) |
| Na, Cl | ↑ lung PMN density | 24 h post-exposure | T | Rat | Saldiva et al. (2002) |
| *SECONDARY SULFATE / LONG-RANGE TRANSPORT* | | | | | |

| Source Category | Health Effects | Time | Type of Study[1] | Species | Reference |
|---|---|---|---|---|---|
| S | ↑ total mortality<br>negative association with total mortality | Lag 0<br>Lag 5 | E | Human | Mar et al. (2000) |
| $SO_4^{2-}$, $NH_4^+$, OC | ↑ respiratory ED visits | Lag 0 | E | Human | Sarnat et al. (2008) |
| S, K, Zn, Pb | ST-segment depression | Lag 2 | E | Human | Lanki et al. (2006a) |
| $SO_4^{2-}$ | ↓ systolic BP | 4 h post-exposure | H | Human | Gong et al. (2003a) |
| $SO_4^{2-}$ (+$NO_2$) | ↓ $FEV_1$<br>↓ FVC | Following exposure | H | Human | Gong et al. (2005) |
| S | ↓ RBC<br>↑ hemoglobin | Following exposure | T | Dog | Clarke et al. (2000) |
| S, Si, OC | ↓ H<br>↓ SDNN, ↓ RMSSD | Afternoon post-exposure<br>Night post-exposure | T | Mouse | Lippmann et al. (2005b) |
| *TRAFFIC* | | | | | |
| Pb, Br, Cu | ↑ mortality | Lag 0-1 | E | Human | Laden et al. (2000) |
| Mn, Fe, Zn, Pb, OC, EC, CO, $NO_2$ | ↑ CV mortality | Lag 1 | E | Human | Mar et al. (2000) |
| $NO_X$, EC, ultrafine count | ST-segment depression | Lag 2 | E | Human | Lanki et al. (2006a) |
| Gasoline (OC, $NO_3^-$, $NH_4^+$) | ↑ CVD ED visits | Lag 0 | E | Human | Sarnat et al. (2008) |
| Diesel (EC, OC, $NO_3^-$) | ↑ CVD ED visits | Lag 0 | E | Human | Sarnat et al. (2008) |
| Speed-change factor (Cu, S, aldehydes) | ↑ blood urea nitrogen<br>↑ mean red cell volume<br>↑ blood PMN %<br>↓ blood lymphocytes %<br>↑ von Willebrand factor (vWF)<br>↓ protein C<br>↑ mean cycle length<br>↑ SDNN<br>↑ PNN50<br>↑ supraventricular ectopic beats | Lag 15 h | E | Human | Riediker et al. (2004b) |
| Motor vehicle/other (Br, Pb, Se, Zn, $NO_3^-$) | ↓ RMSSD | Afternoon post-exposure | T | Mouse | Lippmann et al. (2005b) |
| Gasoline+secondary nitrate* | cytotoxic responses (potency) | 24 h post-exposure | T | Rat | Seagrave et al. (2006) |
| Gasoline+diesel* | inflammatory responses (potency) | 24 h post-exposure | T | Rat | Seagrave et al. (2006) |
| *OIL COMBUSTION* | | | | | |
| V, Ni | ↑ BALF AM %<br>↑ blood PMN %<br>↓ blood lymphocytes % | 24 h post-exposure<br>Following exposure<br>Following exposure | T | Dog | Clarke et al. (2000) |
| Ni | ↓ respiratory rate | During exposure | T | Dog | Nikolov et al. (2008) |
| V, Ni | ↑ lung PMN density | 24 h post-exposure | T | Rat | Saldiva et al. (2002) |
| V, Ni, Se | ↓ SDNN, ↓ RMSSD | Afternoon post-exposure | T | Mouse | Lippmann et al. (2005b) |

| Source Category | Health Effects | Time | Type of Study[1] | Species | Reference |
|---|---|---|---|---|---|
| *COAL COMBUSTION* | | | | | |
| Se, $SO_4^{2-}$ | ↑ mortality | Lag 0-1 | E | Human | Laden et al. (2000) |
| *OTHER METALS* | | | | | |
| Metal processing ($SO_4^{2-}$, Fe, $NH_{4+}$, EC, OC) | ↑ CVD ED visits | Lag 0 | E | Human | Sarnat et al. (2008) |
| *WOODSMOKE / VEGETATIVE BURNING* | | | | | |
| OC, K | ↑ CV mortality | Lag 3 | E | Human | Mar et al. (2000) |
| OC, EC, K, $NH_{4+}$ | ↑ CVD ED visits | Lag 0 | E | Human | Sarnat et al. (2008) |
| *UNNAMED FACTORS* | | | | | |
| Zn-Cu-V | ↑ blood fibrinogen | 18 h post-exposure | H | Human | Huang et al. (2003c) |
| Fe-Se-sulfate | ↑ BALF PMN | 18 h post-exposure | H | Human | Huang et al. (2003c) |
| Br, Pb | ↑ BALF PMN % | 24 h post-exposure | T | Dog | Clarke et al. (2000) |
| Br, Pb | ↑ lung PMN density | 24 h post-exposure | T | Rat | Saldiva et al. (2002) |

*Constituents not provided.
[1] E = Epigemiologic study; H = Human clinical study; T = Toxicologic study

# 2.3.4. Public Health Impacts

## 2.3.4.1. PM Concentration-Response Relationship

1     The examination of the PM concentration-response curve has primarily occurred in large multi-city

2 studies that have analyzed the association between short- and long-term exposure to PM and mortality

3 (see Sections 6.5.2.7, 7.3.8, and 8.1). These studies have used various statistical methods, but overall have

4 consistently found that a no-threshold log-linear model most adequately portrays the PM-mortality

5 concentration-response relationship. However, some heterogeneity in the shape of the concentration-

6 response curve has been observed in an analysis that compared the concentration-response relationship

7 across individual cities. Therefore, although a consensus has been reached regarding the most likely shape

8 of the PM concentration-response curve in multicity analyses, uncertainty still exists surrounding the

9 PM-mortality concentration-response relationship on a city-to-city basis.

## 2.3.4.2. Potentially Susceptible and Vulnerable Subpopulations

1   During the evaluation of the PM literature, numerous studies were identified that examined

2   whether underlying factors increased the susceptibility or vulnerability of an individual to PM-related

3   health effects. In this ISA, a susceptible subpopulation is defined as those individuals that might exhibit

4   an adverse health effect to a pollutant at concentrations lower than those needed to elicit the same

5   response in the general population or those individuals that might elicit a more adverse health effect at the

6   same concentration. A vulnerable subpopulation is defined as those individuals that might be differentially

7   exposed to higher concentrations of a pollutant than the general population, regardless of the health

8   outcome. The examination of both susceptible and vulnerable subpopulations to PM exposure allows for

9   the NAAQS to provide an adequate margin of safety for both the general population and sensitive

10  subpopulations (see Chapter 8 for a more detailed discussion).

### *Susceptibility Characteristics*

11  Epidemiologic, human clinical, and toxicological studies provide evidence for a diverse group of

12  characteristics that could potentially increase the susceptibility of an individual to PM-related health

13  effects (see Table 8.1 for a comprehensive list of characteristics that could potentially increase the

14  susceptibility of an individual to PM-related health effects). The susceptibility characteristics examined in

15  the PM literature can theoretically be divided into two categories: (1) innate (e.g., age, gender,

16  race/ethnicity) and (2) pre-existing disease (see Section 8.2.1). Although the strength of the evidence for

17  each characteristic varies, the recent literature provides a basis for understanding the increased

18  susceptibility of an individual to PM-related health effects.

19  The literature provides mixed evidence that innate characteristics lead to increased susceptibility to

20  health effects upon exposure to PM. The evaluation of epidemiologic and human clinical studies found

21  some evidence, which demonstrates an increase in cardiovascular health effects in older individuals (65+)

22  along with some support for an increase in mortality. In addition, the epidemiologic literature suggests an

23  increase in respiratory-related health effects in children. When examining gender and race/ethnicity, it

24  remains unclear if either modifies the association between PM and health effects. The new literature

25  indicates no clear pattern of effect modification when stratifying effects by gender or race/ethnicity. But,

26  there is some evidence, albeit from two studies conducted in southern California with 6 overlapping

27  cities, that individuals of Hispanic ethnicity are more susceptible to mortality upon short-term exposure to

28  $PM_{2.5}$.

29  Recent toxicological studies have also examined the effects of exposure to PM during pregnancy

30  through the use of animal models. These studies suggest that exposure to particles, both immunologically

1    inert and toxic, result in local and systemic inflammation in the pregnant animal. Inflammation during

2    pregnancy can potentially lead to allergic susceptibility in the offspring.

3        The new literature has continued to examine the role of genetic factors on PM-related health

4    effects. These studies found some evidence that individuals with polymorphisms in genes that mediate an

5    antioxidant response confer a greater degree of susceptibility to PM exposure. However, it has also been

6    observed that in some cases genetic polymorphisms can result in a gain of function, leading to a

7    protective effect.

8        A large amount of literature examined the role of underlying diseases on PM-related health effects.

9    Epidemiologic, human clinical and toxicological studies have found some evidence of an increase in

10   cardiovascular effects in individuals with a pre-existing cardiovascular disease. However, the

11   cardiovascular health effect observed upon exposure to PM was found to vary depending on the pre-

12   existing cardiovascular condition.

13       The evaluation of studies that examined the association between exposure to PM and health effects

14   in individuals with pre-existing respiratory diseases also observed a difference in effects depending on the

15   underlying respiratory condition. The epidemiology literature indicated some evidence of an increase in

16   respiratory-related health effects in individuals with asthma, but less consistent evidence in those with

17   COPD. In addition, an increase in mortality was observed in individuals with underlying pneumonia and

18   respiratory illnesses. The toxicological literature presented evidence that suggested that individuals with

19   allergic airways disease are more susceptible to allergic responses upon exposure to PM. Interestingly, the

20   human clinical and animal toxicological literature also found evidence of cardiovascular effects (e.g.,

21   acute responses in the cardiovascular system and reduced pulmonary artery lumen-to-wall ratio) in

22   individuals or subjects with underlying respiratory illnesses.

23       As obesity and diabetes have increased in the U.S., studies have also examined the potential

24   susceptibility of these individuals to PM-related health effects. The epidemiologic literature provides

25   some evidence that individuals with diabetes are at increased risk of mortality along with cardiovascular

26   HAs and ED visits following short-term exposure to ambient concentrations of PM. In addition, human

27   clinical studies provide evidence of an increase in biomarkers associated with inflammation, oxidative

28   stress and acute phase response potentially leading to cardiovascular effects. Only a few studies have

29   examined the role of obesity on PM-related health effects, but there is evidence of HRV modification and

30   increased inflammatory markers with PM exposure.

### Vulnerability

31       The recent epidemiologic literature has also examined characteristics that potentially increase the

32   vulnerability of subpopulations to PM-related health effects. These analyses, which primarily focus on the

1 association between PM and mortality, examine health effects in individuals that are potentially

2 disproportionately exposed to PM due to the location of their residence, their socioeconomic status (SES),

3 their educational attainment, or the geographic area of the country where they live (see Section 8.2).

4 There is some evidence that individuals residing in an urban environment are at increased risk of

5 PM-related health effects, specifically mortality, due to higher exposures to traffic-derived PM. However,

6 when examining other factors that potentially contribute to whether an individual lives in an urban

7 environment, such as SES and educational attainment, it remains unclear whether either characteristic

8 results in disproportionate exposure to PM. This is because, specifically for SES, which is closely tied to

9 educational attainment, there has not been a consistently-observed trend that characterizes the impact of

10 SES on exposure to PM or other air pollutants. Additional analyses of air conditioning (AC) use, which is

11 sometimes used as a surrogate for SES, provide some evidence that AC use reduces exposure to PM.

12 However, it has been argued that AC use may not be an appropriate measure when examining PM

13 exposure because of differences in building ventilation rate, which differs by season and community.

14 Finally, analyses conducted that examine the PM-mortality association (for both $PM_{10}$ and $PM_{2.5}$) by

15 geographic location tend to see the greatest effects in the Eastern U.S. Additional regional analyses have

16 also suggested that regional effects may vary by season with an increase in $PM_{10}$ mortality risk estimates

17 during the summer in the Northeast and industrial Midwest.

# Chapter 3. Source to Human Exposure

## 3.1. Introduction

1　　　This chapter contains basic information about concepts and findings in atmospheric sciences and
2　human exposure assessment relevant to recent PM studies and results to help establish a foundation for
3　the detailed discussions of health effects data in subsequent chapters. Section 3.2 presents an overview of
4　basic information related to the size distribution and composition of airborne particles. Section 3.3
5　provides a brief description of the sources and emissions of PM. It includes discussions of mechanisms of
6　secondary PM formation from gaseous precursors. Issues related to the measurement of PM and its
7　components and to the deployment of monitors in networks are covered in Section 3.4. Analyses of data
8　for ambient concentrations of PM and its components are characterized in Section 3.5. This Section also
9　includes results from receptor modeling studies of source contributions to PM based on ambient data.
10　Policy relevant background concentrations of PM, i.e., those concentrations defined to result from
11　uncontrollable sources, are presented in Section 3.6. Issues related to personal exposure to PM and its
12　components are discussed in Section 3.7. See the 2004 PM AQCD (U.S. EPA, 2004) for a detailed
13　characterization of PM properties.

14　　　The intent of this chapter is to build on previous AQCDs with newly available data and studies.
15　This information includes new knowledge of PM chemistry, latest developments in monitoring
16　methodologies, recent national and local trends in PM concentration as a function of size range and
17　species, revised estimates of policy-relevant background PM, and recent work on exposure assessment.
18　This information is compiled to support interpretation of the epidemiologic studies presented in
19　subsequent chapters.

20　　　Developments in our ability to identify organic components in PM and in the chemistry of
21　formation of secondary organic aerosols indicate that oligomers are likely a major component of OC in
22　aerosol samples. Until a few years ago, the oxidation of terpenes and aromatic compounds were
23　considered as sources of SOA, but not the oxidation of isoprene. However, recent observations suggest
24　that small but important quantities of SOA are formed from isoprene oxidation. Gasoline engines have
25　been found to emit a mix of OC, EC, and nucleation mode heavy and large polycyclic aromatic
26　hydrocarbons (PAHs), on which unspent fuel and trace metals condense, while diesel particles are
27　composed of a soot nucleus on which $SO_4^{2-}$ and hydrocarbons condense. After initial emission from the
28　vehicle, evolution of the PM distribution within the plume is a function of turbulence diluting the plume
29　and cycling of semi-volatile components between the gas and aerosol phases. Emissions of ultrafine

1 particles tend to be higher during cold engine starts and when ambient temperatures are low, such as

2 during the winter. Current inventories of emissions from combustion sources overestimate the primary

3 component of organic aerosol and underestimate the semi-volatile components in the emissions. This

4 situation results from the lack of capture of evaporated semi-volatile components upon dilution in

5 standard emissions tests. Near traffic, sources of organic aerosol are underestimated. However, further

6 downwind the overall formation rate of SOA increases as a result of the oxidation of these semi-volatile

7 components. Evaluation of federal reference monitors (FRMs) and equivalent monitors strengthens

8 conclusions about their performance. Issues still remain regarding the recently promulgated FRM for

9 $PM_{10-2.5}$. These data are still subject to large errors, resulting in negative numbers in a number of

10 locations.

11 In general, levels and spatial distributions of $PM_{2.5}$ (based on 2005 to 2007 data) have remained

12 relatively unchanged since the last review (based on 1999 to 2001 data). Improvements in QA have

13 resulted in slightly greater homogeneity across urban areas for $PM_{2.5}$. Spatial variability in $PM_{2.5}$ across

14 urban areas is related to differences in topography and source characteristics. Data for ultrafine particles

15 are still sparse, but recent studies suggest a high degree of spatial variability with motor vehicle exhaust

16 as the major primary source. Data from the CSN indicate West to East gradients in a number of

17 components. OC and EC are higher in the West than in the East, conversely sulfate is higher in the East.

18 Nitrate shows highest values in the valleys of central California, but similarly high values are also found

19 in the Midwest during winter. Studies of intra-urban variation in PM concentration have shown

20 neighborhood scale variability, particularly with respect to $PM_{10}$ and ultrafine PM. Within a street canyon,

21 changes in wind direction and speed can cause significant variability over a small distance in

22 concentrations of PM components.

23 Receptor modeling studies indicate that the main sources for most of the $PM_{2.5}$ found in the East

24 are power plants and motor vehicles. An intercomparison of source apportionment techniques indicated

25 that the same major source categories of $PM_{2.5}$ were consistently identified by several independent

26 groups. Soil-, sulfate-, residual oil-, and salt-associated mass were most clearly identified by the groups.

27 Other sources such as vegetative burning and traffic related emissions were less consistently identified in

28 large part because of collinearity in the source profiles or the level of experience of the investigators.

29 Significant associations were reported between PM and certain source categories and mortality. The

30 between-source variation in predicting daily RR was found to be statistically significant and significantly

31 larger than the between group variation in this intercomparison.

32 Policy relevant background concentrations of $PM_{2.5}$ were estimated using CMAQ nested inside a

33 global chemistry-transport model. On average they are $<1$ μg/m$^3$ but daily maximum values ranged from

34 ~3 to ~63 μg/m$^3$ at nine National Park sites across the U.S.

1    Of major concern is the ability of $PM_{2.5}$ and $PM_{10}$ measured by ambient monitors to serve as a

2    reliable indicator of personal exposure to $PM_{2.5}$ and $PM_{10}$ of ambient origin. The key question is what

3    errors are associated with using PM measured by ambient monitors as a surrogate for personal exposure.

4    Exposure to PM of ambient origin is subject to a number of factors, including: season; region; intra-urban

5    spatiotemporal variability; proximity to sources; and time spent indoors and outdoors. Studies of on-street

6    PM exposure suggest that personal outdoor local environmental exposures to fine and coarse PM are

7    higher than ambient concentrations measured at urban background ambient monitors as a result of local

8    sources and trapping within street canyons. As a result, data reported by ambient monitors located at

9    background, central urban, roadside, or near-residential sites will likely be variable across an urban area.

10   Several recent studies have shown how the ambient component of personal exposure to $PM_{2.5}$ could be

11   estimated using various tracer and source apportionment techniques and that it is highly correlated with

12   ambient concentrations of $PM_{2.5}$. These studies also show that the non-ambient component of personal

13   exposure to $PM_{2.5}$ is basically uncorrelated with ambient $PM_{2.5}$ concentrations. A number of studies have

14   examined whether gaseous copollutants act as confounders or surrogates for PM in exposure assessments.

15   Many of these studies have shown that ambient $O_3$, $NO_2$, and $SO_2$ are associated with personal exposure

16   to total $PM_{2.5}$ and to $PM_{2.5}$ of ambient origin as opposed to personal exposures to the gases, themselves.

17   This result may have arisen in part because personal exposures to the gases were often beneath detection

18   limits of the personal monitoring devices. The association between ambient $O_3$ and ambient $PM_{2.5}$ was

19   also generally found to be seasonal with a positive association in the summer and a negative association

20   in the winter. This situation arises because of seasonal differences in sources of $PM_{2.5}$ and $O_3$. The

21   evidence is mixed regarding the association between SES and ambient personal exposures to PM.

## 3.2. Overview of Basic Aerosol Properties

22   Unlike gas-phase pollutants such as $SO_2$, CO, $H_2CO$ and $O_3$, which are well-defined chemical

23   entities, atmospheric PM varies in size, shape, and chemical composition. Atmospheric chemical and

24   microphysical processing of direct emissions of PM and precursors and mechanical generation of

25   particles tend to produce distinct lognormal modes (Whitby, 1978) as shown in Figure 3-1. To the extent

26   that information is available, discussions in this and subsequent chapters will focus on particles in specific

27   size ranges (i.e., $PM_{2.5}$, $PM_{10-2.5}$ and $PM_{10}$). The subscripts for $PM_{2.5}$ through $PM_{10}$ refer to the

28   aerodynamic diameters in micrometers (µm) of 50% cut points of sampling devices. For example, EPA

29   defines $PM_{10}$ as particles collected by a sampler with an upper 50% cut point of 10 µm aerodynamic

30   diameter and a specific, fairly sharp, penetration curve, as defined in the Code of Federal Regulations (40

CFR Part 58). $PM_{2.5}$ is defined in an analogous way. Ultrafine particles, 0.01 to 0.1 μm, thermodynamic diameter, which is related to the diffusion coefficient of the particle, will also be discussed.

The terms "fine particles" and "coarse particles" have lost the precise meaning given in Whitby's (1978) definition, where "fine particles" refers to all particles in the nucleation, Aitken, and accumulation modes; and "coarse particles" characterizes all particles larger than these. Ultrafine particles correspond loosely to the nucleation plus Aitken modes (in earlier literature, these modes were not separated and the combination, unresolved by older instruments, was called the Aitken mode). Now, the term "fine particles" has come to be often associated with the $PM_{2.5}$ fraction, which includes the nucleation, Aitken and accumulation modes and some of the lower-size tail of the coarse particle mode between about 1 and 2.5 μm aerodynamic diameter. "Thoracic coarse" is frequently used to refer to $PM_{10-2.5}$, which does not include all of the smaller coarse particles. Under high relative humidity conditions, the larger particles in the accumulation mode may also extend into the 1 to 3 μm size range. These relationships can be seen in Figure 3-1, which shows the number distribution for ultrafine particles and the volume distribution (or mass distribution if particle density is constant across the size range) for fine and (thoracic) coarse particles. The figure is arranged this way because particle number is most highly concentrated in the ultrafine size range but volume (or mass) is most concentrated in the larger size ranges.

Particles can penetrate to different regions of the human respiratory tract depending on size. Thoracic particles refer to particles that travel past the larynx to reach the lung airways and the gas-exchange region of the lung, and respirable particles are those that reach the gas-exchange region. The selection of $PM_{10}$ as an indicator of thoracic particles was based in large part on dosimetry (U.S. EPA, 1984). However, dosimetric considerations do not provide insight into the selection of a size cut to characterize fine mode particles. The American Conference of Governmental Industrial Hygienists (ACGIH, 2005), the International Standards Organization (ISO), and the European Standardization Committee (CEN) have adopted a 50% cut point of 4 μm as an indicator of respirable particles. $PM_{10}$ is an indicator of thoracic particles; $PM_{2.5}$ is an indicator of fine mode particles; and $PM_{10-2.5}$ is an indicator of the thoracic component of coarse mode particles that is sometimes refered to as thoracic coarse (noting that it excludes some coarse particles below 2.5 μm and above 10 μm).

As can be seen from Table 3-1, particles in individual size modes are characterized by rather distinct sources, composition, chemical properties, lifetimes in the atmosphere (τ) and distances over which they can travel. Whereas particles in the smaller size modes are formed mainly by combustion processes and by nucleation and condensation of gases, coarse mode particles are generated mainly by mechanical activity, such as by the action of wind on either the ground or the sea surface. Further details are given in subsequent sections of this chapter.
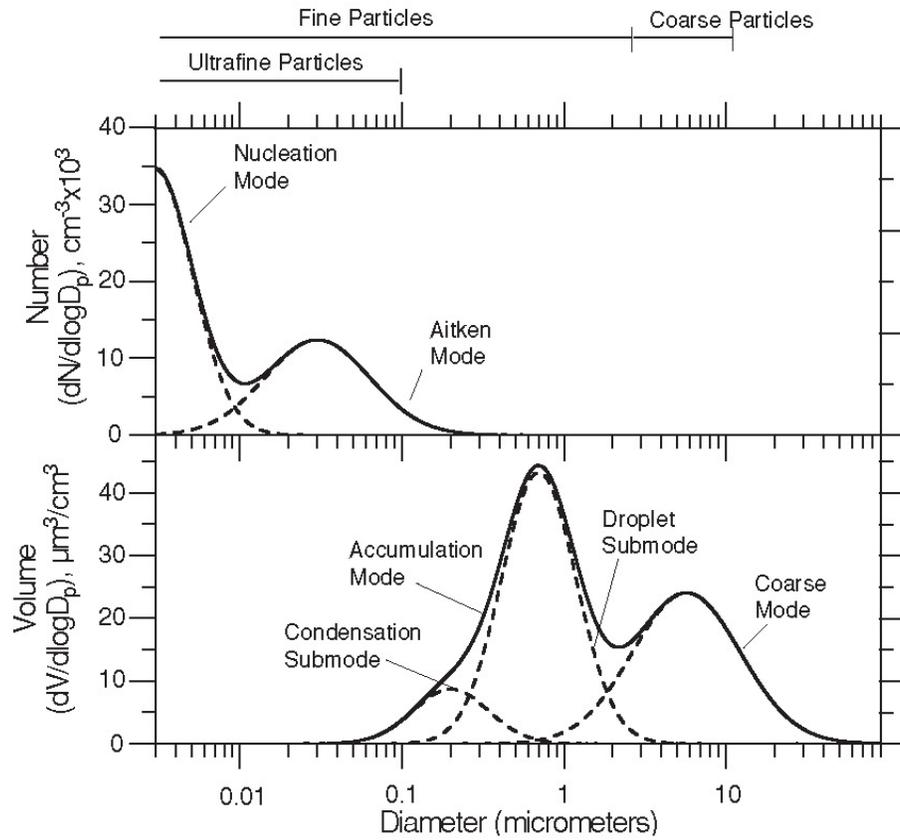
Source: Pandis (2004)

**Figure 3-1.    Particle size distributions by number and volume.**

**Table 3-1.** Characteristics of ambient fine (ultrafine plus accumulation-mode) and coarse particles.

| | Fine | | Coarse |
|---|---|---|---|
| | **Ultrafine** | **Accumulation** | |
| Formation Processes | Combustion, high-temperature processes, and atmospheric reactions | | Break-up of large solids/droplets |
| Formed by | Nucleation of atmospheric gases including $H_2SO_4$, $NH_3$ and some organic compounds<br>Condensation of gases | Condensation of gases<br>Coagulation of smaller particles<br>Reactions of gases in or on particles<br>Evaporation of fog and cloud droplets in which gases have dissolved and reacted | Mechanical disruption (crushing, grinding, abrasion of surfaces)<br>Evaporation of sprays<br>Suspension of dusts<br>Reactions of gases in or on particles |
| Composed of | Sulfate<br>EC<br>Metal compounds<br>Organic compounds with very low saturation vapor pressure at ambient temperature | Sulfate, nitrate, ammonium, and hydrogen ions<br>EC<br>Large variety of organic compounds<br>Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc.<br>Particle-bound water<br>Bacteria, viruses | Suspended soil or street dust<br>Fly ash from uncontrolled combustion of coal, oil, and wood<br>Nitrates/chlorides/sulfates from $HNO_3/HCl/SO_2$ reactions with coarse particles<br>Oxides of crustal elements (Si, Al, Ti, Fe)<br>$CaCO_3$, $CaSO_4$, NaCl, sea salt<br>Bacteria, pollen, mold, fungal spores, plant and animal debris<br>Tire, brake pad, and road wear debris |
| Solubility | Not well characterized | Largely soluble, hygroscopic, and deliquescent | Largely insoluble and nonhygroscopic |
| Sources | High temperature combustion<br>Atmospheric reactions of primary, gaseous compounds. | Combustion of fossil and biomass fuels, and high temperature industrial processes, smelters, refineries, steel mills etc.<br>Atmospheric oxidation of $NO_2$, $SO_2$, and organic compounds, including biogenic organic species (e.g., terpenes) | Resuspension of particles deposited onto roads<br>Suspension from disturbed soil (e.g., farming, mining, unpaved roads)<br>Construction and demolition<br>Uncontrolled coal and oil combustion<br>Ocean spray |
| Atmospheric half-life | Minutes to hours | Days to weeks | Minutes to hours |
| Removal Processes | Grows into accumulation mode<br>Diffuses to raindrops | Forms cloud droplets and rains out<br>Dry deposition | Dry deposition by fallout<br>Scavenging by falling rain drops |
| Travel distance | <1 to 10s of km | 100s to 1000s of km | <1 to 10s of km (small size tail, 100s to 1000s in dust storms) |

Source: Adapted from Wilson and Suh (1997).

# 3.3. Sources of Primary and Secondary PM

1      Table 3-2 summarizes anthropogenic and natural sources for the major primary and secondary

2    aerosol constituents of fine and coarse particles. Anthropogenic sources can be further divided into

3    stationary and mobile sources. Stationary sources include fuel combustion for electrical utilities,

4    residential space heating and cooking; industrial processes; construction and demolition; metals, minerals,

5    and petrochemicals; wood products processing; mills and elevators used in agriculture; erosion from tilled

6    lands; and waste disposal and recycling. Mobile or transportation-related sources include direct emissions

1    of primary PM and secondary PM precursors from highway vehicles and non-road sources as well as

2    fugitive dust from paved and unpaved roads. In addition to fossil fuel combustion, biomass in the form of

3    wood is burned for fuel. Vegetation is burned to clear new land for agriculture and for building

4    construction, to dispose of agricultural and domestic waste, to control the growth of animal or plant pests,

5    and to manage forest resources (prescribed burning). Wildlands also burn due to lightning strikes and

6    arson. Also shown in Table 3-2 are sources for several precursor gases, the oxidation of which can form

7    secondary PM.

8        In general, the sources of fine PM are very different from those of coarse PM. Some of the mass in

9    the fine size fraction forms during combustion from material that has volatilized in combustion chambers

10   and then recondensed before emission to the atmosphere. Some ambient $PM_{2.5}$ forms in the atmosphere

11   from photochemical reactions involving precursor gases. PM formed by the first mechanism is referred to

12   as primary, and PM formed by the second mechanism is referred to as secondary. $PM_{10-2.5}$ is mainly

13   primary in origin, as it is produced by surface abrasion or by suspension of biological material composed

14   of microorganisms (e.g., bacteria, viruses, fungal spores, pollens) and fragments of living things

15   (e.g., plant and insect debris). Because precursor gases undergo mixing during transport from their

16   sources and reactions in the atmosphere can produce the same products, it is difficult to identify

17   individual sources of secondary PM constituents. Transport and transformation of precursors can occur

18   over distances of hundreds of kilometers. Coarse PM has a shorter lifetime in the atmosphere, so its

19   effects tend to be more localized.

20       Only major sources for each constituent within each broad category shown at the top of Table 3-2

21   are listed. Not all sources are equal in magnitude. Chemical characterizations of primary particulate

22   emissions for a wide variety of natural and anthropogenic sources (as shown in Table 3-2) were given in

23   Chapter 5 of the 1996 PM AQCD (U.S. EPA, 1996). Summary tables of the composition of source

24   emissions presented in the 1996 PM AQCD (U.S. EPA, 1996) and updates to that information are

25   provided in Appendix 3D to the 2004 PM AQCD (U.S. EPA, 2004). Source composition profiles are

26   archived by the EPA at http://www.epa.gov/ttn/chief/software/speciate/index.html. The profiles of source

27   composition were based in large measure on the results of studies that collected source signatures for use

28   in source apportionment studies.

29       Natural sources of primary PM include windblown dust from undisturbed land, sea spray, and

30   biological material. The oxidation of a fraction of terpenes emitted by vegetation and reduced sulfur

31   species from anaerobic environments leads to secondary PM formation. Ammonium ($NH_4^+$) ions, which

32   play a major role in regulating the pH of particles, are derived from emissions of $NH_3$ gas. Source

33   categories for $NH_3$ have been divided into emissions from undisturbed soils (natural) and emissions that

34   are related to human activities (e.g., fertilized lands, domestic and farm animal waste). There is ongoing

1  debate about characterizing emissions from wildfires (i.e., unwanted fire) as either natural or

2  anthropogenic. Wildfires have been listed in Table 3-2 as natural in origin, but land management practices

3  and other human actions affect the occurrence and scope of wildfires. For example, fire suppression

4  practices allow the buildup of fire fuels and increase the susceptibility of forests to more severe and

5  infrequent fires from whatever cause, including lightning strikes. Similarly, prescribed burning is listed as

6  anthropogenic, but can be viewed as a substitute for wildfires that would otherwise occur eventually on

7  the same land.

8    Information about the nature of sources directly emitting ultrafine particles is still sparse compared

9  to that for the larger size modes. The composition of motor vehicle has been most widely studied. Matti

10  Maricq (2007) presents a model of diesel PM as a mix of nucleation-mode $SO_4^{2-}$ and hydrocarbons from

11  unspent fuel and soot embedded with trace metals on which $SO_4^{2-}$ and hydrocarbons condense, although

12  the $SO_4^{2-}$ portion of the diesel PM is now substantially reduced following mandate of ultra-low sulfur

13  diesel fuel production (Lim et al., 2007b). Similarly, gasoline PM is a mix of OC, EC and small quantities

14  of trace metals and sulfates, with OC constituting anywhere from 26-88% of PM (Cadle et al., 1999)

15  (Geller et al., 2006; Schauer et al., 2002). Much of the OC mass has yet to be identified. Riddle et al.

16  (2007) have shown that large and heavy PAHs are present in OC. Phuleria et al. (2006) have also found

17  spikes of high molecular weight and large PAHs from gasoline-fueled vehicles in the Caldecott Tunnel.

18  The diameter of semi-volatile near-road PM is highly dependent on the temperature at which the particles

19  exit the engine and the ambient temperature, so that hot driving conditions and/or hot ambient conditions

20  can cause the mode of the ultrafine size distribution to decrease in diameter and magnitude (Kuhn et al.,

21  2005b).

22    An overview of estimates of emissions of primary PM and precursors to secondary PM from major

23  sources is given in Section 3.3.1. The transformations from gaseous precursors to secondary PM shown in

24  Table 3-2 are described in Section 3.3.2.

**Table 3-2.    Constituents of atmospheric particles and their major sources.**

| Aerosol species | Primary (PM <2.5 µm) | | Primary (PM >2.5 µm) | | Secondary PM Precursors (PM <2.5 µm) | |
|---|---|---|---|---|---|---|
| | Natural | Anthropogenic | Natural | Anthropogenic | Natural | Anthropogenic |
| Sulfate ($SO_4^{2-}$) | Sea spray | Fossil fuel combustion | Sea spray | — | Oxidation of reduced sulfur gases emitted by the oceans and wetlands and $SO_2$ and $H_2S$ emitted by volcanism and forest fires | Oxidation of $SO_2$ emitted from fossil fuel combustion |
| Nitrate ($NO_3^-$) | — | — | — | — | Oxidation of $NO_X$ produced by soils, forest fires, and lighting | Oxidation of $NO_X$ emitted from fossil fuel combustion and in motor vehicle exhaust |
| Minerals | Erosion and re-entrainment | Fugitive dust from paved and unpaved roads, agriculture, forestry, construction, and demolition | Erosion and re-entrainment | Fugitive dust, paved and unpaved road dust, agriculture, forestry, construction, and demolition | — | — |
| Ammonium ($NH_4^+$) | — | — | — | — | Emissions of $NH_3$ from wild animals, and undisturbed soil | Emissions of $NH_3$ from animal husbandry, sewage, and fertilized land |
| Organic carbon (OC) | Wildfires | Prescribed burning, wood burning, motor vehicle exhaust, cooking and industrial processes | Soil humic matter | Tire and asphalt wear, paved and unpaved road dust | Oxidation of hydrocarbons emitted by vegetation (terpenes, waxes) and wild fires | Oxidation of hydrocarbons emitted by motor vehicles, prescribed burning, wood burning, solvent use and industrial processes |
| EC | Wildfires | Motor vehicle exhaust (mainly diesel), wood biomass burning, and cooking | — | Tire and asphalt wear, paved and unpaved road dust | — | — |
| Metals | Volcanic activity | Fossil fuel combustion, smelting and other metallurgical processes, and brake wear | Erosion, re-entrainment, and organic debris | — | .— | — |
| Bioaerosols | Viruses and bacteria | — | Plant and insect fragments, pollen, fungal spores, and bacterial agglomerates | — | — | — |

Dash (—) indicates either very minor source or no known source of component.
Source: U.S. EPA (2004).

# 3.3.1. Emissions of Primary PM and Precursors to Secondary PM

1        Emissions of primary $PM_{2.5}$, $PM_{10}$ and gaseous precursor species ($SO_2$, $NO_X$, $NH_3$ and VOCs) from

2    different source categories are shown in Figure 3-2. Note that the entries refer mainly to anthropogenic

1   sources, with little information about natural sources. However, for categories such as VOCs, the

2   contribution from biogenic emissions of isoprene and terpenes can be quite large. The entries are

3   continually undergoing revision and are subject to varying degrees of uncertainty. For example, almost all

4   of the sulfur in fuel is released as volatile components ($SO_2$ or $SO_3$) during combustion. Hence, sulfur

5   emissions can be calculated on the basis of sulfur content in fuel stocks to greater accuracy than can be

6   done for other pollutants like nitrogen oxides or primary PM. There have been notable downward

7   revisions to the inventories since 2002 in the emissions of dust from roads. These have resulted in large

8   measure from incorporation of emissions test data that relies on updated measurement methods. Also, the

9   spatial and temporal nature of wildland fire emissions has improved since 2002 by integrating satellite-

10  derived fire detection and state-of-art fuels characterization and consumption models (Pouliot et al.,

11  2008). Many estimates for emissions from high temperature combustion sources are subject to artifacts

12  due to inadequate dilution and thermal equilibration of the samples (England et al., 2007a; England et al.,

13  2007b; Sheya et al., 2008). Note that the estimates given in Figure 3-2 are U.S. national averages and may

14  not accurately reflect the contribution of specific local sources determining a person's exposures to PM at

15  any given time and location.
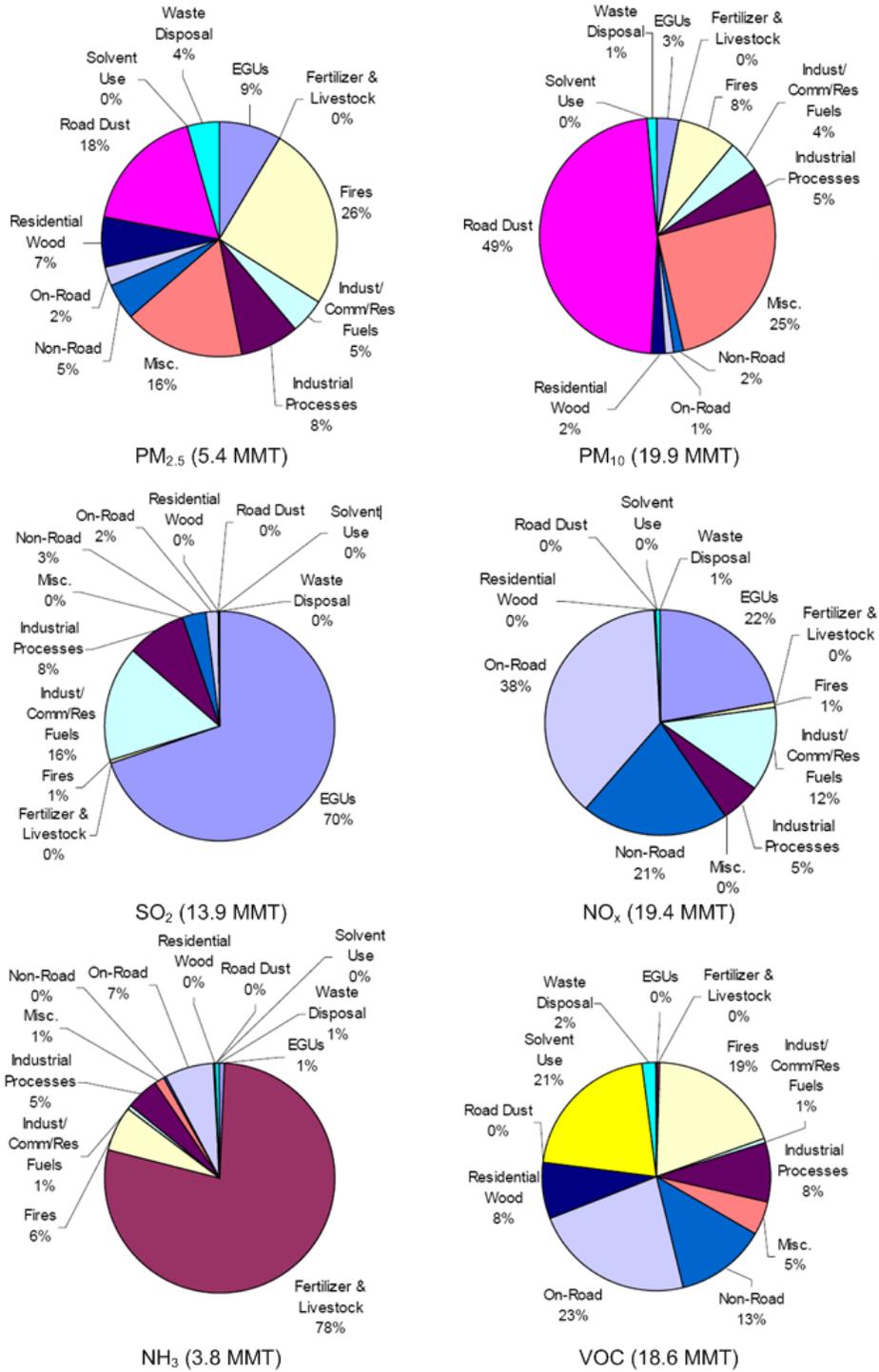
Source: U.S. EPA (2006a)

**Figure 3-2.** Detailed source categorization of emissions of primary PM$_{2.5}$, PM$_{10}$ and gaseous precursor species SO$_2$, NO$_X$, NH$_3$ and VOCs for 2002 in units of million metric tons.

EGUs = Electricity Generating Units.

# 3.3.2. Formation of Secondary PM

1    Precursors to secondary PM have natural and anthropogenic sources, just as primary PM has

2    natural and anthropogenic sources. A substantial fraction of the fine particle mass, especially during the

3    warmer months of the year, is secondary in nature, formed as the result of atmospheric reactions

4    involving both inorganic and organic gaseous precursors. The major atmospheric chemical

5    transformations leading to the formation of particulate nitrate ($pNO_3$) and sulfate ($pSO_4$) are relatively

6    well understood; whereas those involving the formation of SOA are less so and are subject to much

7    current investigation. A large number of organic precursors are involved and many of the kinetic details

8    still need to be determined. Also, many of the actual products of the oxidation of hydrocarbons have yet to

9    be identified. However, there has been substantial progress made in understanding the chemistry of SOA

10   formation in the past few years.

## 3.3.2.1. Formation of Nitrate and Sulfate

11   The basic mechanism of the gas and aqueous phase oxidation of $NO_2$ and $SO_2$ has long been

12   studied and can be found in numerous texts on atmospheric chemistry, e.g., Seinfeld and Pandis (1998),

13   Finlayson-Pitts and Pitts (2000), Jacob (1999), and Jacobson (2002a). The reader is referred to the 2004

14   PM AQCD (U.S. EPA, 2004), where these processes are described in great detail, as well as the 2008

15   $NO_X$ ISA (U.S. EPA, 2008c) and the 2008 $SO_X$ ISA (U.S. EPA, 2008d).

## 3.3.2.2. Formation of Secondary Organic Aerosol

16   Some key new findings have altered perceptions of secondary organic aerosol (SOA) formation

17   since the 2004 PM AQCD (see especially the reviews by Kroll and Seinfeld (2008) and Rudich et al.

18   (2007). Robinson et al. (2007a) noted that emissions from combustion sources overestimates the primary

19   component of organic aerosol and underestimates the semi-volatiles in the emissions. This situation

20   results from the lack of capture of evaporated semi-volatile components upon dilution in standard

21   emissions tests. Near traffic, sources of organic aerosol are underestimated. However, further downwind

22   the overall formation rate of SOA increases as a result of the oxidation of these semi-volatile components.

23   Until a few years ago, the oxidation of terpenes and aromatic compounds were considered as sources of

24   SOA, and the oxidation of isoprene was not considered as a source of SOA. However, observations of

25   2-methyl tetrols in ambient samples from a number of different environments suggest that small but

26   important quantities of SOA are formed (Claeys et al., 2004). Laboratory studies also indicate the

27   formation of 2-methyl tetrols from isoprene oxidation (Edney et al., 2005; Kleindienst et al., 2006).

1    Kroll and Seinfeld (2008) and Rudich et al. (2007) stressed that the composition of SOA evolves

2    from repeated cycles of volatilization and condensation of chemical reaction products in both the particle

3    and gas phases. Rudich et al. (2007) focused on the oxidation of particle phase species by reaction with

4    gas phase oxidants. Kroll and Seinfeld (2008) identified three factors that determine the SOA forming

5    potential of organic compounds in the atmosphere:

6    1. Oxidation reactions of gas-phase organic species. These species include alkanes, alkenes,

7        aromatics, cyclic olefins, isoprene and terpenes. Note that oxidation reactions can either

8        lower volatility by addition of functional groups or increase volatility by cleavage of

9        carbon-carbon bonds;

10   2. Reactions in the particle, or condensed, phase that can change volatility either by oxidation or

11       formation of high-molecular-weight species. These reactions can lead to the formation of

12       oligomers e.g. to decrease volatility or to the formation of products that can volatilize; and

13   3. Ongoing reactions that result from the varied volatility of oxidation products.

14   Other detailed work has focused on the formation of higher molecular weight particle-phase

15   oligomers (Gao et al., 2004b; Kalberer et al., 2004; Tolocka et al., 2004), the importance of cloud

16   processing in the evolution of SOA (Blando and Turpin, 2000; Gelencser and Varga, 2005), and the role

17   of acid seeds in oligomer formation (Tolocka et al., 2004). These results imply that ambient samples could

18   contain mixtures of SOA from different sources at different stages of processing, some with common

19   reaction products making source identification of SOA problematic. Figure 3-3 shows a schematic of

20   processes involved in the formation of SOA.
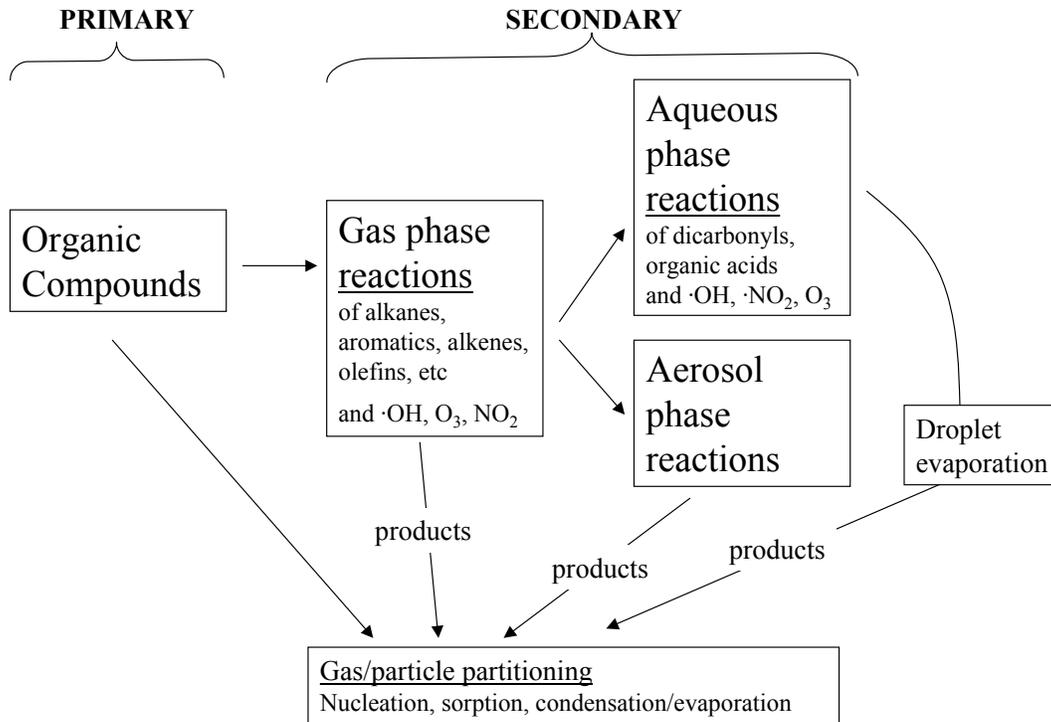
**Figure 3-3.** **Primary emissions and formation of secondary organic aerosol through gas, cloud and condensed phase reactions.**

# 3.4. Monitoring Issues

## 3.4.1. Ambient Measurement Techniques

### 3.4.1.1. Federal Reference Method and Federal Equivalent Method Evaluation

1    The FRM and Federal Equivalent Method (FEM) are designed to measure the mass concentrations

2  of ambient particles. The FRMs for measuring $PM_{10}$ and $PM_{2.5}$ are specified in CFR 40 Part 50, Appendix

3  J and L, respectively. The $PM_{10}$ FRM is a performance based method in which particles are inertially

4  separated with a penetration efficiency of 50% at $10 \pm 0.5$ μm aerodynamic diameter. The collection

5  efficiency specified in the CFR approaches 100% as particle size decreases and approaches 0% as particle

6  size increases. Particles are collected on filters for which mass concentrations are determined

7  gravimetrically. In contrast, the FRM for $PM_{2.5}$ is a design based method that specifies certain details of

8  the sampler design, as well as of sample handling and analysis, whereas other aspects (e.g., flow control)

9  have performance specifications (U.S. EPA, 2004). $PM_{10-2.5}$ concentration is computed as the difference

10  between concurrent and co-located $PM_{10}$ (as specified in 40 CFR Part 50, Appendix O) and $PM_{2.5}$

concentrations obtained from select co-located FRM samplers. FRMs and FEMs for $PM_{2.5}$, $PM_{10}$, and $PM_{10-2.5}$ were discussed in detail in the 2004 PM AQCD (U.S. EPA, 2004). Issues discussed there include the definition or description of FRMs and FEMs for $PM_{10}$, $PM_{2.5}$ and $PM_{10-2.5}$ with detailed descriptions of the WINS impactor, virtual and cascade multi-stage impactors for $PM_{10-2.5}$ measurement, and real-time or continuous FEMs for $PM_{10}$ and $PM_{2.5}$ including:

- Tapered Element Oscillating Microbalance (TEOM) operated at various temperatures;

- Sample Equilibration System (SES)-TEOM;

- Differential TEOM,

- Beta-Gauge Techniques (BGT);

- Piezoelectric Microbalance;

- Real-Time Total Ambient Mass Sampler (RAMS);

- Continuous Ambient Mass Monitor (CAMM);

- Continuous Coarse Particle Monitor (CCPM);

- Micro-orifice Uniform Deposit Impactor (MOUDI);

- Multichannel diffusion denuder sampling system (BOSS); and

- Light scattering photometric instruments.

In 2006, EPA finalized new performance criteria (40 CFR Part 53) for the approval of FEMs as Class II equivalent methods when based on integrated filter sampling and as Class III equivalent methods when based on continuous technologies that can provide at least hourly data reporting. The performance criteria include evaluating additive bias (intercept) and multiplicative bias (slope) as well as correlation from co-located candidate and FRM methods at field studies covering multiple seasons and locations. As a result of these new performance criteria, EPA approved the first Class III FEM for $PM_{2.5}$ on March 12, 2008. The approved method is the Met One BAM 1020 incorporating the same techniques described in the 2004 PM Criteria Document; however, several features have been improved such as the distance of the beta source to the filter tape and the conditioning of the sample stream relative humidity for better sensitivity and comparison to filter-based methods. A complete list of FRMs and FEMs can be found at the EPA web site http://www.epa.gov/ttn/amtic/files/ambient/criteria/reference-equivalent-methods-list.pdf and in Annex A. This ISA will focus on new methodologies and evaluation techniques.

Several new innovations have emerged since 2004 to measure both fine and coarse PM fractions in the ambient air. These techniques include approval of a very sharp cut cyclone (VSCC) as a $PM_{2.5}$ FEM

1    method (Kenny et al., 2004), a high-volume dichotomous sampler (1000 l/min) (Sardar et al., 2006), and a

2    Filter Dynamics Measurement System-TEOM (FDMS-TEOM) (Grover et al., 2006). The VSCC provides

3    superior performance over long sampling periods under heavy loading and was also incorporated as an

4    optional second-stage separator for the PM 2.5 FRM (71 FR 61214, October 17, 2006). The

5    FDMS-TEOM system is a self-referencing system operated at 4°C integrated with the measurement

6    capability of the TEOM technology operated at 30°C. With oscillating measurements of 6 minutes each

7    for ambient air and chilled clean air - under which conditions the volatile PM loses mass on the TEOM

8    filter and is therefore quantified - the instrument provides measurements of total particulate mass,

9    including the semivolatile $NH_4NO_3$ and organic material. Several particle sizing instruments have also

10   been developed to measure PM concentration and particle size; these are discussed later in Section 3.4.1.3

11   along with ultrafine particles and PM size distribution.

12   Evaluation of all the instruments mentioned above was conducted both in supersite studies and in

13   other research studies (Ayers, 2004; Brown et al., 2006; Butler et al., 2003; Cabada et al., 2004; Chang

14   and Tsai, 2003; Charron et al., 2004; Chow et al., 2006; Grover et al., 2005; Hains et al., 2007; Hering et

15   al., 2004; Jaques et al., 2004; Krieger, 2007; 2005b; 2005c; Lee et al., 2005d; Price et al., 2003; Rees et

16   al., 2004; Russell et al., 2004; Salminen and Karlsson, 2003; Schwab et al., 2004; 2006; Solomon et al.,

17   2003; Tsai et al., 2006a; Vega et al., 2003; Wilson et al., 2006; Yi et al., 2004; Zhu et al., 2007) (Annex

18   A). In general, the co-located FRMs showed very good precision with CV <5%. For different co-located

19   FRMs, the regression slope of one sampler on another is commonly close to unity and with an $R^2$ >0.95.

20   The $PM_{2.5}$ and $PM_{10}$ concentrations measured by dichotomous samplers were within 10% of the FRM

21   methods, and the differences can be attributed to the sampling artifacts of semi-volatile components; see

22   Section 3.4.1.2 for details. The precision of various TEOMs ranges from 10%-30%. The concentration

23   measured by the TEOM operated at 50°C was consistently lower than those measured by the TEOM

24   operated at 30°C. The TEOM operated at 30°C provided concentrations 50% lower than the

25   FDMS-TEOM, and the FDMS-TEOM provided concentrations 10-30% higher than the FRM. The

26   differences between these monitors were also found to be a function of season and location. BGTs were

27   highly correlated with FRMs but BGT mass could be higher than the FRM mass (30% higher at the

28   Fresno supersite) (Chow et al., 2008). CAMMs didn't show a consistent pattern when compared with

29   FRMs. These differences could be largely attributed to the sampler operating principles and design,

30   ambient conditions (copollutants and meteorological parameters), and the built-in default calibration

31   factors for non-FRM/FEM instruments. Additionally, a number of new techniques have been developed to

32   reduce positive and negative sampling artifacts. These are described in the ISA for $NO_X$ and $SO_X$ –

33   Environmental Criteria (U.S. EPA, 2008e).

1    Several papers (Buser et al., 2007a, b, c) published since the 2004 PM AQCD claim that the EPA

2    FRM samplers for $PM_{10}$ (and $PM_{2.5}$) "oversample certain agricultural and other source emissions." These

3    claims are based on the erroneous assumption that the "true" $PM_{10}$ concentration is what would be given

4    by a $PM_{10}$ sampler that excluded all particles greater than 10 μm aerodynamic diameter and included all

5    particles less than 10 μm. As noted earlier (Section 2.2) the legal definitions for $PM_{2.5}$ and $PM_{10}$, as

6    defined in the Code of Federal Regulations include both a 50% cut-point and a penetration curve. For

7    $PM_{10}$, the 50% cut-point of 10 μm diameter means that 50% of particles with aerodynamic diameter of

8    $10 \pm 0.5$ μm are removed by the inlet and 50% pass through the inlet and are collected on the filter. The

9    penetration curve specifies, as a function of particle size, the fraction of particles larger than 10 μm that

10   pass through the inlet and the fraction of particles less than 10 μm that are intercepted by the inlet. No

11   effort was made in the development of the FRM to have the $PM_{10}$ sampler collect all particles less than

12   10 μm and no particles greater than 10 μm since the sampler was designed to collect a fraction of

13   atmospheric particles similar to the "inhalable" or thoracic fraction, i.e., those particles that would pass

14   through the nose and throat and reach the lungs (Miller et al., 1979). Thus, the FRM $PM_{10}$ sampler

15   correctly and intentionally collects particles greater than 10 μm.

## 3.4.1.2. PM Speciation

16   The following sections describe recent developments regarding measurement techniques to

17   ascertain quantities of particle-bound water, cations and anions, elemental composition, carbon, and

18   organic species.

### *Particle-Bound Water*

19   Particle-bound water is an important component of ambient PM (U.S. EPA, 2006d). Recently, a

20   differential method was developed to measure particle-bound water (Santarpia et al., 2004; Stanier et al.,

21   2004). The dry ambient aerosol size spectrometer (DAASS) can measure particle-bound water in the

22   particle size range from 3 nm-10 μm (Stanier et al., 2004), by alternatively measuring ambient PM size

23   distribution at low relative humidity (RH) and ambient RH. A comparison of the two size distributions

24   provides information on the water absorption and change in particle size due to RH. Khlystov et al.

25   (2005) reported that the particle-bound water, measured by DAASS, was underestimated for particles

26   <200 nm, and overestimated for particles >200 nm, compared with thermodynamic models. The loss of

27   semi-volatile components during measurement may also bias the measurement results. Methods and

28   analytical specifications for particle-bound water are listed in Annex A.

### Cation and Anion

1    The measurement of cations and anions including $SO_4^{2-}$, $NO_3^-$, $NH_4^+$, Cl⁻, $Na^+$, and $K^+$ still heavily

2    relies on filter-based collection (denuders might be used in the sampling system to adjust sampling

3    artifacts), water based extraction and ion chromatography (IC) based chemical speciation and

4    quantification. These methods have been reviewed in the 2004 PM AQCD (U.S. EPA, 2004).

5    Filter-denuder based integrated sample methods for $SO_4^{2-}$, $NO_3^-$, and $NH_4^+$ have been detailed in the 2008

6    $SO_X$ ISA and 2008 $NO_X$-$SO_X$ ISA (U.S. EPA, 2008d, e).

7    Recent developments in multiple ion measurements have focused on the coupling of IC and a

8    sample dissolution system, represented by the Particle into Liquid Sampler-Ion Chromatography

9    (PILS-IC) and the Ambient Ion Monitor (AIM) (Dasgupta et al., 2007; Orsini et al., 2003; Weber et al.,

10   2001). When ambient PM passes through the PILS-IC system, water droplets are generated by mixing

11   ambient PM with saturated water vapor and collected by impaction. The resulting liquid stream is then

12   introduced into the IC system for ion speciation and quantification. Hourly concentrations of multiple

13   ions can be obtained with the system, with a coefficient of variation of 10%. For the AIM system, a

14   parallel plate denuder is used to remove the interfering gases, and then particles enter a super-saturation

15   chamber to form droplets. The collected droplets are then introduced into the IC for analysis. The AIM

16   system can provide hourly concentrations for multiple ions. The particle mass spectrometer is another

17   advance in multiple PM component measurements, but most of these types of measurements are

18   semi-quantitative and will be detailed later in Section 3.4.1.4. Note that measurement and analytical

19   specifications for ions other than $NO_3^-$ and $SO_4^{2-}$ are listed in Annex A.

### Sulfate

20   Methods used for continuous (sampling interval of minutes) measurements of $SO_4^{2-}$ include

21   Aerosol Mass Spectrometry (AMS) (Drewnick et al., 2003; Hogrefe et al., 2004), PILS (Weber et al.,

22   2001), flash volatilization techniques (Bae et al., 2007a; Stolzenburg and Hering, 2000), and the Harvard

23   School of Public Health (HSPH) tube furnace to convert $SO_4^{2-}$ to $SO_2$ for detection by a $SO_2$ analyzer

24   (Allen et al., 2001). These methods are described in detail by Drewnick et al. (2003), along with an inter-

25   sampler comparison that found overall agreement within 2.9% for all continuous instruments with $R^2$ of

26   0.87 or better. When compared with filter samples, Drewnick et al. (2003) showed differences were less

27   than 25% for the AMS, PILS, flash vaporization, and HSPH continuous $SO_4^{2-}$ monitors. Annex A lists

28   detailed methods and analytical specifications for sampling $SO_4^{2-}$.

### Nitrate

1      In addition to the filter-based method and the new developments mentioned above, methods based

2    on flash volatilization-chemiluminescence analysis and catalytic conversion-chemiluminescence analysis

3    have also been developed for continuous $NO_3^-$ measurement (averaging time 30 s-10 min). For the flash

4    volatilization system (Fine et al., 2003; Stolzenburg and Hering, 2000; Stolzenburg et al., 2003), particles

5    are collected by a humidified impaction process and analyzed in place by flash vaporization and

6    chemiluminescent detection of the evolved $NO_X$. For the catalytic conversion-chemiluminescence

7    analysis system (e.g. ARA N, Weber et al., 2003), $NO_3^-$ was measured by conversion of particle $NO_3^-$ into

8    NO, and then detected with the chemiluminescence method. Field and lab comparisons were conducted to

9    compare the different instruments mentioned above. Although the R&P 8400N ambient particulate $NO_3^-$

10   monitor could provide 10-min resolution data and showed excellent precision (with a CV <10%)

11   (Harrison et al., 2004; Hogrefe et al., 2004; Long and McClenny, 2006; Rattigan et al., 2006), it

12   consistently reported $NO_3^-$ concentrations ~30% lower than the denuder-filter systems in both the

13   Baltimore supersite and the multi-year field sampling in New York (Harrison et al., 2004; Hogrefe et al.,

14   2004; Rattigan et al., 2006). In the New York measurement campaign, an AMS was also co-located with

15   other instruments to obtain the real-time $NO_3^-$ information. AMS did not always agree well with the

16   denuder-filter system for reasons not entirely apparent. However, Bae et al. (2007b) reported that some

17   organic compounds can also produce signals at mass-to-charge ratio $m/z = 30$, which is one of the

18   characteristic $m/z$ for $NO_3^-$. Therefore, the disagreement between the AMS and the filter-based method

19   could be a result of the interference of organic compounds using the AMS. Annex A lists methods and

20   analytical specifications for sampling $NO_3^-$.

### Ammonium

21      Field and lab comparisons were conducted to compare the continuous measurement methods

22   mentioned above. Several continuous and semi-continuous instruments could be applied to monitor

23   ambient ammonium concentrations (Al-Horr et al., 2003; Bae et al., 2007a). Bae et al. (2007a) conducted

24   an inter-comparison of three semi-continuous instruments during the New York multi-year air sampling

25   campaign: a PILS-IC, an AMS, and a wet scrubbing-long path absorption photometer. Bae et al. (2007a)

26   reported the inter-sampler coefficients of determination ($R^2$) between these instruments were above 0.75

27   and the slopes (intercepts were forced to be zero) were between 0.71 and 1.04. Annex A describes

28   measurement of ions other than $NO_3^-$ and $SO_4^{2-}$, including $NH_4^+$.

## Elemental Composition

1    Techniques for measuring the elemental composition of PM samples were reviewed in the 2004

2    PM AQCD (U.S. EPA, 2004). These methods include:

3    ▪ Energy dispersive X-ray fluorescence (ED-XRF);

4    ▪ Synchrotron X-ray fluorescence (SXRF);

5    ▪ Particle-induced X-ray emission (PIXE);

6    ▪ Particle elastic scattering analysis (PESA);

7    ▪ Total reflection X-ray fluorescence (TR-XRF);

8    ▪ Instrumental neutron activation analysis (INAA);

9    ▪ Atomic absorption spectrophotometry (AAS);

10   ▪ Inductively-coupled plasma-atomic emission spectroscopy (ICP-AES);

11   ▪ Inductively-coupled plasma-mass spectrometry (ICP-MS); and

12   ▪ Scanning electron microscopy (SEM).

13   Recent development in this area focused on the semi-continuous measurement methods, in which

14   elements were analyzed in the lab using the methods mentioned above on time-resolved and/or size

15   resolved samples (Kidwell and Ondov, 2004). The concentrated slurry/graphite furnace atomic absorption

16   spectrometry (GFAAS) method collects ambient PM as a slurry using impactors and then the collected

17   PM is analyzed by AAS in the lab. Laser induced breakdown spectroscopy (LIBS) was used to measure

18   seven metals at the Pittsburgh supersite. LIBS concentrates ambient PM using a virtual impactor into a

19   sample cell, and then a Nd: YAG laser-spectrometer is used to identify and quantify different elements. A

20   full listing of measurement techniques and analytical specifications for trace elements is provided in

21   Annex A.

## Elemental and Organic Carbon

22   The large variety of aspects of carbon analyses were reviewed in the 2004 PM AQCD (U.S. EPA,

23   2004). Measurement and analytical specifications for carbon measurements are listed in Annex A. Aspects

24   of the measurements include sampling artifacts associated with the integrated filter-based OC and EC

25   sampling methods, the IMPROVE vs. the National Institute for Occupational Safety and Health (NIOSH)

26   thermal optical protocols (i.e., different thermal optical methods) and optical techniques to measure

27   light-absorption or BC. One significant change taking place in the CSN is that the method for carbon

28   measurements began switching from the NIOSH method to the IMPROVE carbon analysis protocol in

1   2007. This is a phased process and the CSN will not be fully converted to IMPROVE–like sampling and

2   IMPROVE analysis until late 2009 (Henderson, 2005). The CSN network was implemented to support the

3   PM$_{2.5}$ NAAQS and began providing data for PM$_{2.5}$ mass, SO$_4^{2-}$, NO$_3^-$, NH$_4^+$, Na, K, EC, OC, and select

4   trace elements (Al through Pb) at many sites across the U.S. This move increased consistency between

5   these two networks. Also, since the release of the 2004 PM AQCD, more studies have been conducted to

6   extend the understanding of sampling artifact issues (Chow et al., 2008; Watson et al., 2005b), to evaluate

7   different thermal and optical procedures (Chen et al., 2004a; Chow et al., 2004; 2005a; 2007; Conny et

8   al., 2003; Han et al., 2007; Subramanian et al., 2006; Watson et al., 2005b ), to develop reference

9   materials (Klouda et al., 2005; Lee, 2007), to develop water soluble organic carbon (WSOC)

10  measurement techniques (Andracchio et al., 2002; Yang et al., 2003b), and

11  semi-continuous/continuous/real-time carbon measurement techniques (Chow et al., 2008; Watson et al.,

12  2005b), as well as to introduce isotope identification into the OC/EC measurement (Huang et al., 2006).

13      OC sampling artifact issues were further addressed in various studies (Arhami et al., 2006; Bae et

14  al., 2004; Chow et al., 2005a; Fan et al., 2003; Fan et al., 2004; Grover et al., 2008; Lim et al., 2003;

15  Mader et al., 2003; Matsumoto et al., 2003; Müller et al., 2004; Offenberg et al., 2007; Olson and Norris,

16  2005; Park et al., 2006a; Rice, 2004; Subramanian et al., 2004; ten Brink et al., 2004; 2005; Viana et al.,

17  2006), and were well summarized by Watson et al. (2005b) and Chow et al. (2008). There are two

18  commonly used methods to correct OC sampling artifacts: the filter with backup filter system (TBQ:

19  placing a backup quartz-fiber filter behind the front Teflon-membrane; or QBQ: placing a backup

20  quartz-fiber filter behind the front quartz-fiber filter), and the denuder-filter-adsorbent system.

21  Subramanian et al. (2004) and Chow et al. (2006) reported that during the Pittsburgh and Fresno supersite

22  studies the positive artifact (organic gases condense on filters) from TBQ (24–34%, up to 4 µg/m$^3$ OC)

23  was nearly twice that from QBQ (13–17%). With the denuder-filter-adsorbent system, the negative

24  artifact (OC evaporating from the filter) was 5–10%. Watson and Chow (2002) reported that the

25  XAD-coated denuder could function as efficiently as a parallel plate denuder using carbon-impregnated

26  charcoal filters (CIF) with frequent denuder changes. Huebert and Charlson (Huebert and Charlson)

27  reported that using tandem filter packs may hinder a quantitative analysis of the artifacts.

28      Different temperature protocols and optical correction methods in thermal-optical analyses were

29  further evaluated by Watson et al. (2005b), Chow et al. (2005a; 2007), Subramanian et al. (2006), Conny

30  et al. (2003), Han et al. (2007), Chen et al. (2004a), and Chow et al. (2004). Solomon et al. (2003)

31  reported a 20-50% difference for OC and a 20-200% difference for EC using 11 filter samples and 4

32  different analytical protocols. In an assessment of the different thermal-optical analysis protocols used

33  around the world, Watson et al. (2005b) reported that differences of a factor of 2 to 7 in EC between

34  different methods could be observed, and a factor of 2 was common, while the relative differences in OC

1    between different methods were relatively small. As Watson et al. (2007) stated, there are 12 major

2    differences among the thermal methods: (1) analysis atmosphere; (2) temperature ramping rates; (3)

3    temperature plateaus; (4) residence time at each plateau; (5) optical pyrolysis monitoring configuration

4    and wavelength; (6) standardization; (7) oxidation and reduction catalysts; (8) sample aliquot and size; (9)

5    evolved carbon detection method; (10) carrier gas flow through or across the sample; (11) location of the

6    temperature monitor relative to the sample; and (12) oven flushing conditions. Chow et al. (2004) and

7    Chen et al. (2004a) addressed the difference between optical transmission and optical reflectance methods

8    for charring correction, and they reported that the charring OC on the surface of a filter or inside a filter

9    dominated the differences between these two charring correction methods. The differences between

10   different sampling and measurement methods are also applied to the in-situ/semi-continuous methods,

11   since most of these methods are also based on thermal-optical analysis of collected filters, and most of

12   these methods agree with integrated filter methods within 30%.

13       The differences observed between methods for OC and EC come largely from how OC and EC are

14   defined. They are defined on an operational basis, as there are no standard reference materials. Initial

15   efforts have been made to produce OC/EC reference materials at the National Institute of Science and

16   Technology (NIST) (Klouda et al., 2005; Lee, 2007). Klouda et al. (2005) described the development of

17   Reference Material 8785: Air Particulate Matter on Filter Media. Each reference filter is uniquely

18   identified by its air PM number and its gravimetrically determined mass of fine SRM 1649a, and each

19   filter has values assigned for total carbon, EC, and organic carbon mass fractions measured according to

20   both IMPROVE and NIOSH protocols. Lee et al. (2007) reported a method to create a reference filter

21   with a known amount of OC (as potassium hydrogen phthalate), and EC (as carbon black hydrosol).

22       Measurement methods for WSOC have been been developed recently (Greenwald et al., 2007;

23   Miyazaki et al., 2006; 2007; Sullivan et al., 2004; Sullivan et al., 2006; 2006; Yu et al., 2004). WSOC can

24   be measured on integrated filter samples, or in-situ measurement can be conducted by coupling with the

25   PILS-IC (Sullivan et al., 2004). For integrated filter samples, filters are extracted with deionized water

26   and followed by oxidation of total WSOC to $CO_2$. $CO_2$ can then be detected by either infrared

27   spectroscopy (IR) (Decesari et al., 2000; Kiss et al., 2002; Yang et al., 2003b), or FID (Yang et al.,

28   2003b), or pyrolysis gas chromatography/mass spectrometry (GC/MS) (Gelencsér et al., 2000). A

29   correlation coefficient of 0.84 was reported by Sullivan et al. (2004) between in-situ and filter based

30   measurement of WSOC.

31       Further development and evaluation has been conducted on the measurement of BC with light

32   absorption instruments (Andreae and Gelencsér, 2006; Arnott et al., 2003; Bae et al., 2004; Borak et al.,

33   2003; Cyrys et al., 2003; Hitzenberger et al., 1999; Kurniawan and Schmidt-Ott, 2006; Park et al., 2006a;

34   Saathoff et al., 2003; Sadezky et al., 2005; Slowik, 2007; Taha, 2007; Virkkula et al., 2007; Wallace,

1    2000; Weingartner et al., 2003; Williams et al., 2006b; Wu et al., 2005). These instruments include the

2    aethalometer, particle absorption photometer, and photoacoustic analyzer. However, these instruments are

3    subject to interferences by particle scattering, interactions with the filter substrate, particle loading on

4    filters, and other pollutants (e.g. $NO_2$). Uncertainties of up to 50% were observed in the studies mentioned

5    above by comparing these methods and integrated filter methods.

6           Huang et al. (2006) reported the measurement of a stable isotope, $^{13}C$, in OC and EC with a thermal

7    optical transmission analyzer coupled with gas chromatography-isotope ratio mass spectrometer

8    (TOT-GC-IRMS). The ratio of $^{13}C/^{12}C$ in OC and EC can provide useful information on OC/EC source

9    categories and origin. The method was applied to Pacific2001 aerosol samples from the Greater

10   Vancouver area in Canada and produced a precision of ~0.03%.

## Organic Speciation

11          Organic matter makes up a substantial fraction of PM in all regions of the U.S. (U.S. EPA, 2004),

12   and 10 to 40% of the total organic matter is currently quantifiable at the individual compound level

13   (Pöschl, 2005). Recent advancements in traditional solvent extraction gas chromatography/mass

14   spectrometry (GC/MS) and high pressure liquid chromatography (HPLC) as well as application of

15   thermal desorption (TD) techniques are helping to expand our understanding of the composition of

16   organic matter as well as improving detection limits for quantification of organic molecular marker

17   (OMM) compounds (Robinson et al., 2006; Schnelle-Kreis et al., 2005; Sheesley, 2007; Shrivastava et al.,

18   2007). In addition, information about organic functional groups can be obtained with Fourier transform

19   infrared spectrometry (FTIR) (Tsai and Kuo, 2006).

20          Recent advancements in GC/MS technology including inert electron ionization sources and

21   improved instrument sensitivity and scan rates for better OMM quantification, have increased its

22   application in organic aerosol characterization studies (Cass, 1998; Fraser et al., 2003; Graham et al.,

23   2003; Hays et al., 2002; Robinson et al., 2006; Schauer et al., 1996; Sheesley, 2007; Subramanian et al.,

24   2006; Watson et al., 1998; Zheng et al., 2002; 2006). Incorporation of high volume injection using

25   programmable temperature vaporization (PTV) (Engewald et al., 1999) has further increased detection

26   limits for trace level OMM compounds. High volume injection has the added benefit of preventing the

27   loss of semivolatile compounds (Swartz et al., 2003), and has been applied for analysis of PAHs using

28   low volume samplers (down to 5 Lpm), allowing for smaller required mass loadings (Bruno et al., 2007;

29   Crimmins and Baker, 2006). Since last review, HPLC analysis with fluorescence detection has also been

30   used frequently for quantification of semivolatile organic compounds in both the particle and gas phase

31   (Albinet et al., 2007; Barreto et al., 2007; Eiguren-Fernandez et al., 2003; Goriaux et al., 2006;

1     Murahashi, 2003; Rynö et al., 2006; Schauer et al., 2003; Stracquadanio et al., 2005; Temime-Roussel et

2     al., 2004a, b). Lengthy extraction and analysis times remain a limiting factor for these methods.

3         TD techniques bypass one of the time consuming steps in traditional solvent extraction analysis for

4     nonpolar organic compounds (n-alkanes, branched alkanes, cyclohexanes, hopanes, steranes, alkenes,

5     phthalates and PAHs). This is achieved by vaporizing and analyzing organic constituents directly from the

6     collection substrate, thereby bypassing the extraction step (Chow, 2007). Methods exist for both off-line

7     TD analysis of previously collected filter samples and semi-continuous TD analysis. Annex A is adapted

8     from Chow et al. (2007) and summarizes recent TD-GC/MS studies. The most common off-line method is

9     thermal desorption-gas chromatography/mass spectrometry (TD-GC/MS) (Hays and Lavrich, 2007).

10     Continuous or semi-continuous methods have been developed for direct analysis of individual organic

11     constituents by coupling TD with various forms of mass spectrometry (Smith et al., 2004; Tobias and

12     Ziemann, 1999; 2000; Voisin et al., 2003; Williams et al., 2006a). A comparison of measurement and

13     analytical specifications for filter analysis using solvent extraction and TD methods for organic speciation

14     are summarized in Annex A.

## 3.4.1.3. Ultrafine PM and PM Size Distribution

15         Instruments for measuring ultrafine PM developed during the past decade permit measurement of

16     size distributions of particles down to 3 nm in diameter with mobility particle sizers. Concentrations

17     down to this size range can be obtained by a Micro-Orifice Uniform Deposit Impactor (MOUDI). The

18     recently developed low pressure-drop ultrafine particle impactor coupled with a Beta Attenuation Monitor

19     (nano-BAM) can also provide ultrafine PM mass concentrations (Chakrabarti et al., 2004). A high

20     correlation coefficient was observed between MOUDIs and nano-BAMs, with a correlation of 0.96. A

21     50% cutpoint ($d_{50}$) of 13-200 nm can be achieved by a high-volume slot-type ultrafine PM virtual

22     impactor (Middha and Wexler, 2006).

23         Methods are also being developed to measure the surface area of ultrafine particles. Wilson et al.

24     (2007b) suggested that the electrical aerosol detector (EAD) measurement might be a useful indicator of

25     the particle surface area deposited in the lung. This method can be potentially useful for examining the

26     association between health effects and particle surface areas.

27         Developments involving the condensation particle counter include use of de-ionized water as a

28     condensation media in lieu of butanol or n-propanol in condensation particle counters (Hering et al.,

29     2005; Hermann et al., 2007; Petäjä, 2006). This development makes the condensation particle counter

30     (CPC) easier to use in field studies because water does not have some of the same chemical properties

31     (with respect to hazard and odor) as butanol or n-propanol. The performance of this CPC was reported to

32     be similar to the conventional butanol based CPC (Hering et al., 2005). Use of a battery of water and

1   butanol-based CPCs was demonstrated to detect a range of solubilities in nucleation-mode particles
2   (Kulmala et al., 2007). Additionally, CPCs have been used to measure particles in the smaller end of the
3   ultrafine scale through adjustment of CPC cut-off diameters through tuning the temperature difference
4   between the CPC saturator and condenser (Kulmala et al., 2007) and improved charge reduction
5   techniques (Winkler et al., 2008). The latter method was effective in reducing the size of particles
6   detected by a CPC to less than 2 nm. These studies include assessment of errors related to these
7   developments with the CPC and generally show that counting efficiencies with these devices is upwards
8   of 95% (Hermann et al., 2007). Additionally, recent advancements have been made in development of fast
9   scanning methods for ultrafine particle size distributions, including diffusion screens (DS) (Feldpausch et
10  al., 2006) and fast integrated mobility scanners (FIMS) (Olfert et al., 2008).
11      It is also important to characterize the particle size distribution. For particles >0.1 µm, several
12  instruments (e.g. DRUM, MOUDIs, and aerodynamic particle sizer [APS]) are available to measure
13  mass-based or count-based particle size distribution. For example, a PM monitoring system
14  (Aerodynamic Particle Sizer) with very sharp cut points between 0.1 and 10 µm is now available (Peters,
15  2006; Zeng, 2006). For particles in this range, inertial forces are used to separate particles based on
16  impaction. For particles <0.1 µm, particles can be separated by their electrical mobility, and as a result,
17  electrical mobility diameter, which is often used to describe ultrafine PM size distribution in lieu of
18  aerodynamic diameter. It has been necessary to develop techniques to change mobility diameters,
19  measured by the scanning mobility particle sizer (SMPS), to aerodynamic diameters, measured by the
20  APS, or vice versa, in order to merge the distributions spanning the ultrafine, accumulation, and coarse
21  modes. A variety of techniques for combining SMPS and APS diameters have been reported in the
22  literature (Hand and Kreidenweis, 2002; Khlystov et al., 2004; Morawska et al., 1999; 2007; Shen et al.,
23  2002; TSI., 2005). However, each of these techniques incurs some error of which the user must be aware.

### 3.4.1.4. Multiple-Component Measurements on Individual Particles

24      The 2004 PM AQCD discussed the aerosol time-of-flight mass spectrometry (ATOFMS). Recently,
25  the ATOFMS and several other aerosol mass spectrometry methods have been further developed. Both lab
26  and field comparisons have been conducted to evaluate the reliability of these types of instruments.
27      There are four types of commonly used aerosol mass spectrometry: (1) particle analysis by laser
28  MS (PALMS; National Oceanic and Atmospheric Administration [NOAA]); (2) rapid single particle mass
29  spectrometer (RSMS; University of Delaware); (3) aerosol time-of-flight MS (ATOFMS; TSI, Inc.); and
30  (4) AMS (Aerodyne) (Chow et al., 2008; Nash et al., 2006). The differences between these instruments
31  primarily come from the particle sizing methods of mass spectrometers, as shown in Annex A. Although
32  the technique varies, the underlying principle is to fragment each particle into ions, using either a

1  high-power laser or a heated surface, and then a mass spectrometer to measure the mass to charge ratio of

2  each ion fragment in a vacuum.

3     These instruments were evaluated at the Atlanta, Houston, Fresno, Pittsburgh, New York, and

4  Baltimore supersites (Bein et al., 2005; Drewnick et al., 2004a; 2004b; Hogrefe et al., 2004; Jimenez et

5  al., 2003; Lake et al., 2003, 2004; Middlebrook et al., 2003; Phares et al., 2003; Qin and Prather, 2006;

6  Wenzel et al., 2003; Zhang et al., 2008). Measurements of the gross composition and abundance of

7  particles by these instruments were generally semi-quantitative, with the exception of AMS. Particles of

8  similar composition (e.g. $OC/SO_4^{2-}$, $Na/K/SO_4^{2-}$, soot/hydrocarbon, and mineral particle types) were

9  characterized by these instruments during the studies mentioned above. $NO_3^-$ and $SO_4^{2-}$ concentrations

10  measured with AMS were comparable with other continuous and filter-based methods, as mentioned in

11  Section 3.4.1.2. In addition, concentrations of different particle types can be obtained by the co-location

12  of these aerosol mass spectrometers and other particle sizing instruments, such as particle counters or the

13  MOUDI.

## 3.4.1.5. Emerging Methods

14     Alternative methods for measuring PM concentrations have been developed or improved since

15  2004. These include passive sampler development (discussed in Section 3.7.2.1) and satellite inference

16  techniques. Satellite remote-sensing techniques have been employed to infer ground-level $PM_{2.5}$ mass

17  concentrations (Gupta et al., 2006; Pelletier et al., 2007; Schafer et al., 2008). Although the satellite

18  measurements can provide global coverage and concentrations in remote areas, the spatial resolution of

19  these measurements is still relatively large. Other shortcomings relating to operating principle and

20  interferences also exist.

# 3.4.2. Ambient Network Design

## 3.4.2.1. Monitor Siting Requirements

21     Where SLAMS $PM_{10}$ and $PM_{2.5}$ monitoring is required, at least one of the sites must be a maximum

22  concentration site for that specific area. In 2007, there were 4,693 $PM_{10}$ monitors and 2,194 $PM_{2.5}$

23  monitors reporting values to the EPA Air Quality System database (AQS). The AQS contains

24  measurements of air pollutant concentrations in the 50 states, plus the District of Columbia, Puerto Rico,

25  and the Virgin Islands, for the 6 criteria air pollutants and hazardous air pollutants. Criteria for siting

26  ambient monitors for PM at these sites are given in the CFR 40 Part 58 Appendix D, and

1  SLAMS/NAMS/PAMS Network Review Guidance (U.S. EPA, 1998). The criteria described below are

2  summarized from CFR 40 Part 58 Appendix D.

3      The appropriate spatial scales for $PM_{10}$ and $PM_{2.5}$ SLAMS monitoring vary given differences in the

4  inertial behavior of coarse PM in contrast with fine. The scales at which networks are maintained are

5  listed below, and relevant scales for each size classification are provided in the subsections that follow.

6      ▪ *Micro (~5 – 100 m) and Middle (~100 – 500 m) scales*—Some data uses associated with

7          microscale and middle scale measurements for $PM_{10}$ and $PM_{2.5}$ include assessing the effects

8          of control strategies to reduce concentrations (especially for the 24-h averaging times), and

9          monitoring air pollution episodes.

10     ▪ *Neighborhood scale (~500 m – 4 km)*—This scale applies where there is a need to collect air

11         quality data as part of an ongoing $PM_{10}$ and $PM_{2.5}$ stationary source impact investigation.

12         Typical locations might include suburban areas adjacent to $PM_{10}$ and $PM_{2.5}$ stationary

13         sources, for example, or for determining background concentrations as part of studies of

14         population responses to PM exposure.

15     ▪ *Urban scale (~4 – 50 km)*—This scale applies for assessment of air quality at an urban scale,

16         although any given sampler is probably not representative of air quality as a whole across the

17         urban scale.

18     ▪ *Regional scale (~50 – 100s km)*—This scale defines a fairly homogeneous rural area without

19         large sources. It can also be used to examine inter-urban variability and transport of pollution

20         across regions of the country.


### $PM_{10}$

21     Cities with populations in excess of one million are required to have between 2 and 10 monitors

22  (depending on concentration) while cities with populations less than one million are required to have

23  between 0 and 8 monitors (40 CFA Part 58, Appendix D). Except some circumstances where microscale

24  (<100 m, for maximum $PM_{10}$ exposure) monitoring may be appropriate, the most important scales to

25  characterize the emissions of $PM_{10}$ effectively from both mobile and stationary sources are the middle

26  scales (for short-term public exposure) and neighborhood scales (for trends and compliance with

27  standards). $PM_{10}$ measurements are obtained at standard temperature and pressure across the

28  NAMS/SLAMS networks (40 CFR Part 58).

**PM$_{2.5}$**

1    Monitor requirements for PM$_{2.5}$ based on city population are similar to those for PM10 above.

2    Continuous PM$_{2.5}$ monitors must be operated in no fewer than one-half of the minimum required sites in

3    each area. Most PM$_{2.5}$ monitoring in urban areas should be representative of a neighborhood scale (for

4    trends and compliance with standards). Urban or regional scale sites are built to characterize regional

5    transport of PM$_{2.5}$. In certain instances where population-oriented micro- or middle-scale PM$_{2.5}$

6    monitoring are determined by the Regional Administrator to represent many such locations throughout a

7    metropolitan area, these smaller scales can be considered to represent community-wide air quality. PM$_{2.5}$

8    measurements are obtained at the NAMS/SLAMS networks (40 CFR Part 58).

9    PM Species are monitored at both mostly urban (CSN) and mostly rural (IMPROVE) locations.

10    PM$_{2.5}$ chemical speciation monitoring is currently conducted at 197 CSN sites

11    (http://www.epa.gov/ttn/amtic/specgen.html). Within the CSN network, 53 locations are recognized as the

12    Speciation Trends Network (STN) operating on a sample schedule of one in every three days, while the

13    rest of the CSN typically operates very sixth day.


**PM$_{10-2.5}$**

14    PM$_{10-2.5}$ is not required to be monitored at SLAMS sites, but is required at NCore Stations. Middle

15    and neighborhood scale measurements are the most important station classifications for PM$_{10-2.5}$ to assess

16    the variation in coarse particle concentrations that would be expected across populated areas that are in

17    proximity to large emissions sources. PM$_{10-2.5}$ chemical speciation monitoring and analyses is required at

18    NCore sites. Probing and monitoring path siting criteria for any specific monitoring site are given in CFR

19    40 Part 58 Appendix E, including horizontal and vertical placement, spacing from minor source, spacing

20    from obstructions, spacing from trees, and spacing from roadways. PM$_{10}$ measurements are converted to

21    local conditions to facilitate calculation of the difference between PM$_{10}$ and PM$_{2.5}$.


## 3.4.2.2. Spatial and Temporal Coverage

### *Locations of PM$_{2.5}$ and PM$_{10}$ Monitors in Selected Metropolitan Areas in the U.S.*

22    Fifteen metropolitan regions were chosen for closer investigation of monitor siting based on their

23    relevance to health studies analyzed in subsequent chapters of this ISA. These regions were: Atlanta,

24    Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York City, Philadelphia,

1    Phoenix, Pittsburgh, Riverside, Seattle, and St. Louis. Core-Based Statistical Areas (CBSAs) and

2    Combined Statistical Areas (CSAs), as defined by the U.S. Census Bureau (http://www.census/gov/),

3    were used to determine which counties, and hence monitors, to include for each metropolitan region.[1]

4    Appendix A displays $PM_{2.5}$ and $PM_{10}$ monitor density with respect to population density for the fifteen

5    metropolitan regions. As an example, Figures 3-4 and 3-5 display $PM_{10}$ and $PM_{2.5}$ monitor density with

6    respect to population density for Boston.

7        Tables 3-3 to 3-10 break down the population density around $PM_{2.5}$ and $PM_{10}$ monitors for the total

8    population and for sub-populations of children aged 0-4 and 5-17 and elderly adults aged 65 and over for

9    each CSA/CBSA. Variation in percentage within a certain radius of the monitor was generally fairly low

10   for each city across the total population and child age groups. In the cases of Boston, Phoenix, Riverside,

11   and St. Louis for $PM_{2.5}$ and Atlanta, Denver, and Riverside for $PM_{10}$, the elderly population's distribution

12   around the samplers varied more from the other groups. Between-city disparities in population density

13   were larger. For $PM_{2.5}$, Denver (84%) and Los Angeles (82%) had the largest proportion of the total

14   population within 15 km of a monitor. Houston (30%) had the least population coverage with their $PM_{2.5}$

15   monitors. For $PM_{10}$, Phoenix (89%) had the largest proportion of the total population within 15 km of a

16   monitor. Detroit (28%), Boston (36%), Seattle (37%), and Philadelphia (38%) had the smallest proportion

17   of the population within 15 km of a $PM_{10}$ monitor. Proximity to monitoring stations is considered further

18   in sections 3.5 and 3.7 regarding spatial variability within cities. Figure 3-5 shows that the $PM_{2.5}$ network

19   more closely samples near population centers compared with the $PM_{10}$ network shown in Figure 3-4 for

20   Boston, although both $PM_{10}$ and $PM_{2.5}$ networks place at least one monitor in the city center.

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[1] A CBSA represents a county-based region surrounding an urban center of at least 10,000 people determined using 2000 census data and replaces the older Metropolitan Statistical Area (MSA) definition from 1990. The CSA represents an aggregate of adjacent CBSAs tied by specific commuting behaviors. The broader CSA definition was used when selecting monitors for the cities listed above with the exception of Los Angeles, Riverside and Phoenix. Los Angeles and Riverside are contained within the same CSA, so the smaller CBSA definition was used to delineate these two cities. Phoenix is not contained within a CSA, so the smaller CBSA definition was used for this city as well.
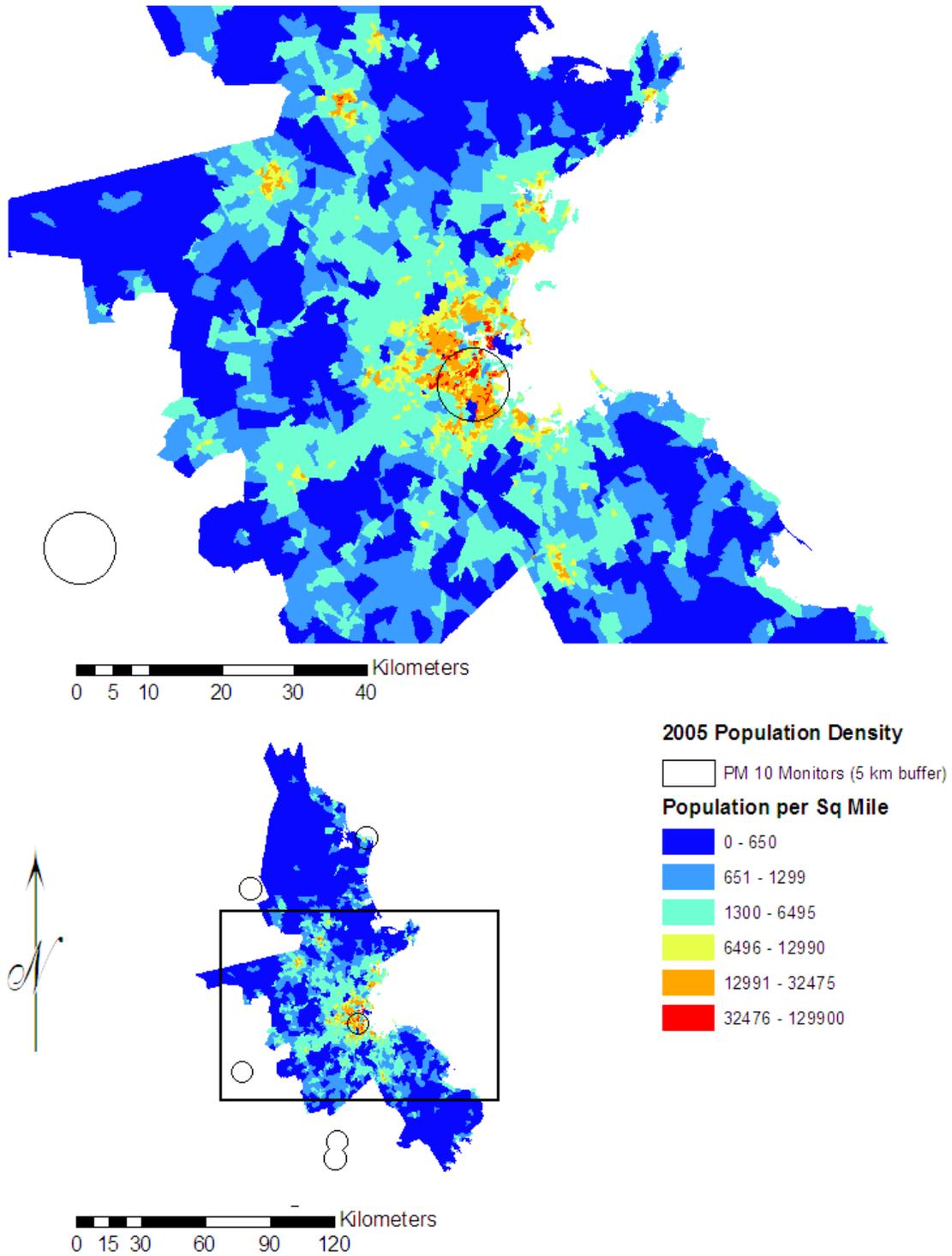
**Figure 3-4.** PM$_{10}$ monitor distribution in comparison with population density, Boston CSA.

**2005 Population Density**

☐ PM 2.5 Monitors (5 km buffer)

**Population per Sq Mile**

■ 0 - 650
■ 651 - 1299
■ 1300 - 6495
■ 6496 - 12990
■ 12991 - 32475
■ 32476 - 129900
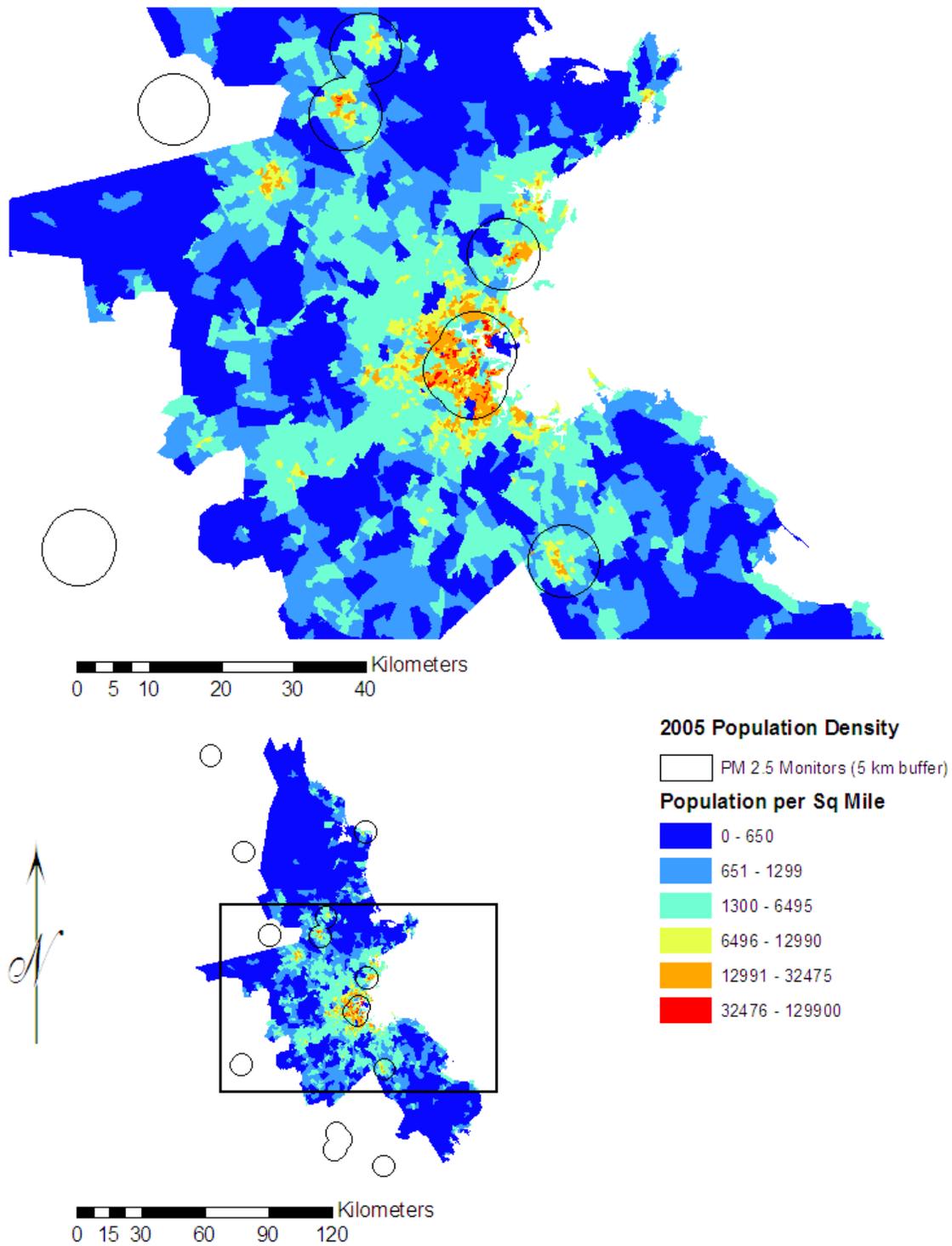
**Figure 3-5.** **PM$_{2.5}$ monitor distribution in comparison with population density, Boston CSA.**

**Table 3-3.** Proximity to PM$_{2.5}$ monitors for the total population by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 4980447 | 30973 | 0.62 | 416440 | 8.36 | 1090497 | 21.90 | 1837983 | 36.90 |
| Birmingham | 1087703 | 23943 | 2.20 | 251309 | 23.10 | 473052 | 43.49 | 638471 | 58.70 |
| Boston | 4453936 | 21432 | 0.48 | 459019 | 10.31 | 1089852 | 24.47 | 1610722 | 36.16 |
| Chicago | 9537620 | 55646 | 0.58 | 844705 | 8.86 | 2374966 | 24.90 | 3843908 | 40.30 |
| Denver | 2379716 | 20401 | 0.86 | 330202 | 13.88 | 899951 | 37.82 | 1440920 | 60.55 |
| Detroit | 4590501 | 14050 | 0.31 | 309619 | 6.74 | 748977 | 16.32 | 1300705 | 28.33 |
| Houston | 5398706 | 36795 | 0.68 | 832767 | 15.43 | 2227314 | 41.26 | 3141028 | 58.18 |
| Los Angeles | 13057686 | 52054 | 0.40 | 1404370 | 10.76 | 4899179 | 37.52 | 9075754 | 69.51 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 5848871 | 23988 | 0.41 | 376968 | 6.45 | 1091530 | 18.66 | 2238306 | 38.27 |
| Phoenix | 3818147 | 99520 | 2.61 | 1255430 | 32.88 | 2615738 | 68.51 | 3416682 | 89.49 |
| Pittsburgh | 2419053 | 61291 | 2.53 | 667265 | 27.58 | 1234171 | 51.02 | 1618336 | 66.90 |
| Riverside | 3781063 | 61356 | 1.62 | 895615 | 23.69 | 2360272 | 62.42 | 2922799 | 77.30 |
| Seattle | 3246877 | 4771 | 0.15 | 219722 | 6.77 | 709070 | 21.84 | 1205927 | 37.14 |
| St. Louis | 2810628 | 27872 | 0.99 | 380411 | 13.53 | 891695 | 31.73 | 1212543 | 43.14 |

Percentages are given with respect to the total population per city provided.

**Table 3-4.** Proximity to PM$_{10}$ monitors for the total population by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 4980447 | 30973 | 0.62 | 416440 | 8.36 | 1090497 | 21.90 | 1837983 | 36.90 |
| Birmingham | 1087703 | 23943 | 2.20 | 251309 | 23.10 | 473052 | 43.49 | 638471 | 58.70 |
| Boston | 4453936 | 21432 | 0.48 | 459019 | 10.31 | 1089852 | 24.47 | 1610722 | 36.16 |
| Chicago | 9537620 | 55646 | 0.58 | 844705 | 8.86 | 2374966 | 24.90 | 3843908 | 40.30 |
| Denver | 2379716 | 20401 | 0.86 | 330202 | 13.88 | 899951 | 37.82 | 1440920 | 60.55 |
| Detroit | 4590501 | 14050 | 0.31 | 309619 | 6.74 | 748977 | 16.32 | 1300705 | 28.33 |
| Houston | 5398706 | 36795 | 0.68 | 832767 | 15.43 | 2227314 | 41.26 | 3141028 | 58.18 |
| Los Angeles | 13057686 | 52054 | 0.40 | 1404370 | 10.76 | 4899179 | 37.52 | 9075754 | 69.51 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 5848871 | 23988 | 0.41 | 376968 | 6.45 | 1091530 | 18.66 | 2238306 | 38.27 |
| Phoenix | 3818147 | 99520 | 2.61 | 1255430 | 32.88 | 2615738 | 68.51 | 3416682 | 89.49 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pittsburgh | 2419053 | 61291 | 2.53 | 667265 | 27.58 | 1234171 | 51.02 | 1618336 | 66.90 |
| Riverside | 3781063 | 61356 | 1.62 | 895615 | 23.69 | 2360272 | 62.42 | 2922799 | 77.30 |
| Seattle | 3246877 | 4771 | 0.15 | 219722 | 6.77 | 709070 | 21.84 | 1205927 | 37.14 |
| St. Louis | 2810628 | 27872 | 0.99 | 380411 | 13.53 | 891695 | 31.73 | 1212543 | 43.14 |

Percentages are given with respect to the total population per city provided.

### Table 3-5.    Proximity to PM$_{2.5}$ monitors for children aged 0-4 by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 317949 | 1263 | 0.40 | 34671 | 10.90 | 122351 | 38.48 | 197996 | 62.27 |
| Birmingham | 70482 | 884 | 1.25 | 15768 | 22.37 | 44086 | 62.55 | 55224 | 78.35 |
| Boston | 277628 | 6245 | 2.25 | 66920 | 24.10 | 123763 | 44.58 | 177769 | 64.03 |
| Chicago | 675274 | 14081 | 2.09 | 234890 | 34.78 | 465860 | 68.99 | 580204 | 85.92 |
| Denver | 153531 | 1066 | 0.69 | 24149 | 15.73 | 80140 | 52.20 | 117083 | 76.26 |
| Detroit | 312177 | 3817 | 1.22 | 74109 | 23.74 | 169820 | 54.40 | 223174 | 71.49 |
| Houston | 379467 | 972 | 0.26 | 18781 | 4.95 | 77667 | 20.47 | 125829 | 33.16 |
| Los Angeles | 953522 | 9187 | 0.96 | 204772 | 21.48 | 583222 | 61.17 | 820231 | 86.02 |
| New York | 1243377 | 48129 | 3.87 | 471327 | 37.91 | 787795 | 63.36 | 955967 | 76.88 |
| Philadelphia | 369018 | 7285 | 1.97 | 125606 | 34.04 | 223485 | 60.56 | 275691 | 74.71 |
| Phoenix | 254040 | 3314 | 1.30 | 41675 | 16.40 | 89794 | 35.35 | 128482 | 50.58 |
| Pittsburgh | 134859 | 2260 | 1.68 | 31406 | 23.29 | 72557 | 53.80 | 102891 | 76.30 |
| Riverside | 264700 | 3785 | 1.43 | 60346 | 22.80 | 144522 | 54.60 | 175659 | 66.36 |
| Seattle | 198596 | 942 | 0.47 | 19252 | 9.69 | 57459 | 28.93 | 92985 | 46.82 |
| St. Louis | 179092 | 2695 | 1.50 | 36535 | 20.40 | 86315 | 48.20 | 112672 | 62.91 |

Percentages are given with respect to the total population per city provided.

**Table 3-6.**     Proximity to PM$_{10}$ monitors for children aged 0-4 by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 317949 | 1465 | 0.46 | 23703 | 7.45 | 66981 | 21.07 | 117010 | 36.80 |
| Birmingham | 70482 | 1675 | 2.38 | 16691 | 23.68 | 31553 | 44.77 | 41457 | 58.82 |
| Boston | 277628 | 1530 | 0.55 | 22486 | 8.10 | 57300 | 20.64 | 87595 | 31.55 |
| Chicago | 675274 | 4259 | 0.63 | 61898 | 9.17 | 177799 | 26.33 | 293181 | 43.42 |
| Denver | 153531 | 786 | 0.51 | 22534 | 14.68 | 60633 | 39.49 | 94729 | 61.70 |
| Detroit | 312177 | 1260 | 0.40 | 24363 | 7.80 | 56992 | 18.26 | 98211 | 31.46 |
| Houston | 379467 | 3109 | 0.82 | 67631 | 17.82 | 173298 | 45.67 | 235197 | 61.98 |
| Los Angeles | 953522 | 3740 | 0.39 | 112759 | 11.83 | 384078 | 40.28 | 693715 | 72.75 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 369018 | 1821 | 0.49 | 24351 | 6.60 | 65371 | 17.71 | 133324 | 36.13 |
| Phoenix | 254040 | 8450 | 3.33 | 95136 | 37.45 | 184308 | 72.55 | 232869 | 91.67 |
| Pittsburgh | 134859 | 3239 | 2.40 | 36237 | 26.87 | 67452 | 50.02 | 89153 | 66.11 |
| Riverside | 264700 | 4502 | 1.70 | 71812 | 27.13 | 178212 | 67.33 | 212080 | 80.12 |
| Seattle | 198596 | 378 | 0.19 | 13916 | 7.01 | 40826 | 20.56 | 68559 | 34.52 |
| St. Louis | 179092 | 2266 | 1.27 | 26457 | 14.77 | 61592 | 34.39 | 79845 | 44.58 |

Percentages are given with respect to the total population per city provided.


**Table 3-7.**     Proximity to PM$_{2.5}$ monitors for children aged 5-17 by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 813107 | 2739 | 0.34 | 78623 | 9.67 | 297032 | 36.53 | 492499 | 60.57 |
| Birmingham | 192830 | 2404 | 1.25 | 44556 | 23.11 | 119723 | 62.09 | 151012 | 78.31 |
| Boston | 748858 | 15347 | 2.05 | 176638 | 23.59 | 329170 | 43.96 | 475482 | 63.49 |
| Chicago | 1772017 | 35584 | 2.01 | 602396 | 33.99 | 1195980 | 67.49 | 1505243 | 84.95 |
| Denver | 398461 | 2505 | 0.63 | 60214 | 15.11 | 196983 | 49.44 | 293694 | 73.71 |
| Detroit | 869389 | 11105 | 1.28 | 207420 | 23.86 | 474076 | 54.53 | 615848 | 70.84 |
| Houston | 988206 | 2464 | 0.25 | 46060 | 4.66 | 187215 | 18.94 | 309878 | 31.36 |
| Los Angeles | 2482440 | 23781 | 0.96 | 516653 | 20.81 | 1474428 | 59.39 | 2118897 | 85.36 |
| New York | 3266360 | 117638 | 3.60 | 1200357 | 36.75 | 2043076 | 62.55 | 2480535 | 75.94 |
| Philadelphia | 1074283 | 20096 | 1.87 | 361257 | 33.63 | 652630 | 60.75 | 807584 | 75.17 |
| Phoenix | 619044 | 7037 | 1.14 | 92828 | 15.00 | 199177 | 32.17 | 302349 | 48.84 |

| | | | | | | | | |
|------|--------|------|------|--------|-------|--------|-------|--------|-------|
| Pittsburgh | 406762 | 6777 | 1.67 | 90122 | 22.16 | 214227 | 52.67 | 309488 | 76.09 |
| Riverside | 756027 | 9182 | 1.21 | 160971 | 21.29 | 398432 | 52.70 | 495123 | 65.49 |
| Seattle | 548642 | 2556 | 0.47 | 52257 | 9.52 | 155593 | 28.36 | 253031 | 46.12 |
| St. Louis | 528319 | 7394 | 1.40 | 103816 | 19.65 | 250730 | 47.46 | 331111 | 62.67 |

Percentages are given with respect to the total population per city provided.

### Table 3-8. Proximity to PM₁₀ monitors for children aged 5-17 by city.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|--------|----------------|--------|------|--------|-------|---------|-------|---------|-------|
| | **N** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Atlanta | 813107 | 3064 | 0.38 | 51765 | 6.37 | 155239 | 19.09 | 280891 | 34.55 |
| Birmingham | 192830 | 4745 | 2.46 | 47958 | 24.87 | 86186 | 44.70 | 114890 | 59.58 |
| Boston | 748858 | 4182 | 0.56 | 61075 | 8.16 | 148703 | 19.86 | 226634 | 30.26 |
| Chicago | 1772017 | 11096 | 0.63 | 165032 | 9.31 | 473575 | 26.73 | 783967 | 44.24 |
| Denver | 398461 | 1551 | 0.39 | 50915 | 12.78 | 139990 | 35.13 | 228485 | 57.34 |
| Detroit | 869389 | 3126 | 0.36 | 61201 | 7.04 | 150762 | 17.34 | 269196 | 30.96 |
| Houston | 988206 | 6960 | 0.70 | 149188 | 15.10 | 406773 | 41.16 | 567427 | 57.42 |
| Los Angeles | 2482440 | 9169 | 0.37 | 285327 | 11.49 | 968855 | 39.03 | 1801841 | 72.58 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 1074283 | 4848 | 0.45 | 68349 | 6.36 | 189689 | 17.66 | 388207 | 36.14 |
| Phoenix | 619044 | 18456 | 2.98 | 208231 | 33.64 | 425518 | 68.74 | 562374 | 90.85 |
| Pittsburgh | 406762 | 9562 | 2.35 | 103569 | 25.46 | 198260 | 48.74 | 267091 | 65.66 |
| Riverside | 756027 | 11877 | 1.57 | 193891 | 25.65 | 492092 | 65.09 | 601629 | 79.58 |
| Seattle | 548642 | 729 | 0.13 | 34323 | 6.26 | 106779 | 19.46 | 178574 | 32.55 |
| St. Louis | 528319 | 6593 | 1.25 | 80897 | 15.31 | 180583 | 34.18 | 232835 | 44.07 |

Percentages are given with respect to the total population per city provided.

**Table 3-9.    Proximity to PM$_{2.5}$ monitors for adults aged 65 and older by city.**

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 326656 | 1400 | 0.43 | 33070 | 10.12 | 127765 | 39.11 | 194901 | 59.67 |
| Birmingham | 134563 | 1618 | 1.20 | 29954 | 22.26 | 84200 | 62.57 | 106389 | 79.06 |
| Boston | 550114 | 10919 | 1.98 | 127385 | 23.16 | 266527 | 48.45 | 380376 | 69.14 |
| Chicago | 990352 | 17116 | 1.73 | 339558 | 34.29 | 700994 | 70.78 | 869475 | 87.79 |
| Denver | 93460 | 1847 | 0.95 | 38143 | 19.72 | 113825 | 58.84 | 163801 | 84.67 |
| Detroit | 532845 | 4983 | 0.94 | 123179 | 23.12 | 307678 | 57.74 | 408426 | 76.65 |
| Houston | 366637 | 1010 | 0.28 | 14911 | 4.07 | 66728 | 18.20 | 117629 | 32.08 |
| Los Angeles | 1206715 | 9653 | 0.80 | 229893 | 19.05 | 688833 | 57.08 | 984878 | 81.62 |
| New York | 2306151 | 76951 | 3.34 | 814370 | 35.31 | 1422463 | 61.68 | 1779594 | 77.17 |
| Philadelphia | 758833 | 13323 | 1.76 | 251459 | 33.14 | 487003 | 64.18 | 605663 | 79.82 |
| Phoenix | 388150 | 2738 | 0.71 | 39833 | 10.26 | 90304 | 23.27 | 142084 | 36.61 |
| Pittsburgh | 430748 | 8933 | 2.07 | 111050 | 25.78 | 249269 | 57.87 | 345281 | 80.16 |
| Riverside | 342334 | 3024 | 0.88 | 50901 | 14.87 | 129836 | 37.93 | 170933 | 49.93 |
| Seattle | 308746 | 1721 | 0.56 | 29426 | 9.53 | 101223 | 32.79 | 156484 | 50.68 |
| St. Louis | 350324 | 5401 | 1.54 | 83528 | 23.84 | 192532 | 54.96 | 244929 | 69.92 |

Percentages are given with respect to the total population per city provided.


**Table 3-10.    Proximity to PM$_{10}$ monitors for adults aged 65 and older by city.**

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| Atlanta | 326656 | 2115 | 0.65 | 35448 | 10.85 | 93903 | 28.75 | 139240 | 42.63 |
| Birmingham | 134563 | 3663 | 2.72 | 35628 | 26.48 | 66839 | 49.67 | 86299 | 64.13 |
| Boston | 550114 | 1983 | 0.36 | 43421 | 7.89 | 125579 | 22.83 | 205946 | 37.44 |
| Chicago | 990352 | 7619 | 0.77 | 107539 | 10.86 | 291704 | 29.45 | 441729 | 44.60 |
| Denver | 193460 | 2100 | 1.09 | 28705 | 14.84 | 88653 | 45.83 | 143801 | 74.33 |
| Detroit | 532845 | 1555 | 0.29 | 41832 | 7.85 | 99682 | 18.71 | 167716 | 31.48 |
| Houston | 366637 | 2085 | 0.57 | 57413 | 15.66 | 166715 | 45.47 | 219603 | 59.90 |
| Los Angeles | 1206715 | 4693 | 0.39 | 126694 | 10.50 | 422716 | 35.03 | 810068 | 67.13 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 758833 | 2740 | 0.36 | 49413 | 6.51 | 154535 | 20.36 | 322700 | 42.53 |
| Phoenix | 388150 | 8605 | 2.22 | 119306 | 30.74 | 267456 | 68.91 | 348464 | 89.78 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pittsburgh | 430748 | 12222 | 2.84 | 124874 | 28.99 | 231658 | 53.78 | 297674 | 69.11 |
| Riverside | 342334 | 4181 | 1.22 | 65499 | 19.13 | 182615 | 53.34 | 236900 | 69.20 |
| Seattle | 308746 | 498 | 0.16 | 22283 | 7.22 | 72929 | 23.62 | 122424 | 39.65 |
| St. Louis | 350324 | 4316 | 1.23 | 55833 | 15.94 | 117743 | 33.61 | 172535 | 49.25 |

Percentages are given with respect to the total population per city provided.

1    Annex A shows the locations of $PM_{2.5}$ and $PM_{10}$ monitors for the 15 CSAs/CBSAs in relation to

2  major roadways, including Interstate highways, U.S. highways, state highways, and other major roadways

3  required for network connectivity. In most cases, the monitors are concentrated near the center of the

4  CSA/CBSA. Regional background sites are not included on the maps unless they lie within the

5  CSA/CBSA.

## *Comparison of Monitors at Supersites*

6    Annex A lists parameters and findings for various supersite mass monitoring efforts, with

7  methodology for the various sites listed in this table along with results. Inter-sampler comparison results

8  varied widely. Conditions impacting agreement between samplers included volatility of the particles and

9  related operation temperature of the monitor, particle shape, and hygroscopicity of the particles. Particle

10  agglomeration may also impact results for laser photometric methods. Annex A compares supersite

11  monitoring results for particle-bound water, $NO_3^-$, $SO_4^{2-}$, carbon, and mass spectrometry, respectively.

12  Example results are highlighted here; more detail can be found in the tables. For particle-bound water,

13  variability in the results was reported at 20-43% (Kidwell and Ondov, 2004). Khlystov et al. (2005) and

14  Stanier et al. (2007) reported growth factors of 2-14%, and measurement agreement varied from 20-35%

15  (Solomon et al., 2003; Weber et al., 2008). For $SO_4^{2-}$, Solomon (2003) reported greater than 50%

16  variability of analyzed $SO_4^{2-}$ compared with a reference filter, although Weber et al. (2008) and Zhang et

17  al. (2005b) reported agreement within 16%. Drewnick et al. (2003) and Hogrefe et al. (2004) reported

18  25% inlet losses but only 2-3% loss for the AMS. For carbon, Solomon et al. (2003) showed that that OC

19  measured with denuded samplers was lower than reference, while non-denuded samples had higher OC.

20  Subramanian et al. showed a positive artifact when QBT was used. At the same time, they measured a

21  negative artifact of approximately 6.3% of particulate OC. Bae et al. (2004) noted denuder breakthrough

22  of only 5%. Solomon et al. (2003) showed EC agreement to vary from 20-200% of the reference filter.

23  The variable responses reported in these studies reflect the fact that sampler operating conditions and

24  properties of the aerosol (i.e. size, chemical composition, volatility, shape) are also highly variable and

25  present challenges for identification of errors and interpretation of results.

# 3.5. Ambient PM Concentrations

1    This section describes measurements of ambient PM and its components made since the 2004 PM
2    AQCD (U.S. EPA, 2004) and recent advancements in understanding of the spatiotemporal concentration
3    distribution of PM and its constituents. Emphasis is placed on the period from 2005-2007, which
4    incorporates the most recent, validated EPA Air Quality System (AQS) data available at the time this
5    document was prepared.

6    When the 2004 PM AQCD was written, the full nationwide $PM_{2.5}$ compliance monitoring network
7    had only recently been deployed, providing three years (1999 to 2001) of measurements. For this PM
8    ISA, the network has been active for eight or nine years depending on location. Therefore, this document
9    contains substantial new data for examining the spatiotemporal distribution of $PM_{2.5}$. Furthermore, by
10   selecting locations where $PM_{10}$ and $PM_{2.5}$ measurements are co-located, further information about the
11   spatiotemporal distribution of the $PM_{10-2.5}$ size fraction has been gained since the last AQCD. A large
12   amount of new information has emerged over the last several years regarding $PM_{2.5}$ composition and
13   ultrafine particle concentrations. Compliance monitoring does not apply for ultrafine particles because
14   there is no ambient standard for them.

15   Spatial distributions of PM across a range of geographic scales are covered in Section 3.5.1.
16   Temporal behavior including trends, seasonality and hourly variability are covered in Section 3.5.2.
17   Statistical associations between different size fractions of PM and copollutants including CO, $NO_2$, $O_3$
18   and $SO_2$ are included in Section 3.5.3. Finally, source attribution methodologies, results and uncertainties
19   are covered in Section 3.5.4.

20   Unless otherwise specified, the PM data utilized throughout this section comes from the AQS.
21   Monitors reporting to the AQS are not uniformly distributed across the U.S. Monitors are far more
22   abundant in urban areas than rural ones, so true rural spatiotemporal distributions may differ from those
23   reported here. Furthermore, biases exist for some PM constituents (and hence total mass) owing to
24   volatilization losses of $NO_3^-$ and other semi-volatile compounds and, conversely, retention of
25   particle-bound water with hygroscopic species. The magnitude of these effects is likely to be
26   region-specific. Such regional differences are addressed in the following section.

## 3.5.1. Spatial Distribution

27   Spatial scales of interest for PM include global and continental (>1000 km), regional (100 to 1000
28   km), urban (4 to 100 km) and neighborhood (<4 km) scales (Watson et al., 1997). Focusing primarily on
29   data available from the AQS, this section has been divided into three sub-sections based on spatial scale:

1    variability across the U.S., urban-scale variability and neighborhood-scale variability. Variation in PM

2    concentration depends on the spatial scale and magnitude of PM sources, formation and removal

3    mechanisms, and transport and dispersion of PM. These different sources and processes can cause

4    substantial variation in particle size distribution and chemistry. Consequently, the following sections are

5    further subdivided to the extent possible into PM size fractions and composition.

## 3.5.1.1. Variability across the U.S.

### $PM_{10}$

6    Figure 3-6 shows the 3-y mean of the 24-h $PM_{10}$ concentrations by county across the U.S. for

7    2005-2007. The data used in generating this map are from the AQS database after applying a

8    completeness criteria of 75 % per quarter (or 11/15 measurements for a one-in-six-day sampling

9    schedule). The highest annual averages for $PM_{10}$ (>51 $\mu g/m^3$) generally occur in inland southern

10   California and the populous counties of southern Arizona and central New Mexico. Of the 3,225 U.S.

11   counties, 676 (12%) contained $PM_{10}$ data meeting the completeness criteria in all three years (2005-2007)

12   and have been included in Figure 3-6. These 676 counties incorporate approximately 43% of the U.S.

13   population. The fraction of the population for each reported concentration level is also shown in the

14   figure. Given the number of counties with no data, the non-uniform spacing of the monitors, and the

15   population within each reporting county, this should only be taken as a rough estimate of the relationship

16   between population and ambient monitors and concentrations.
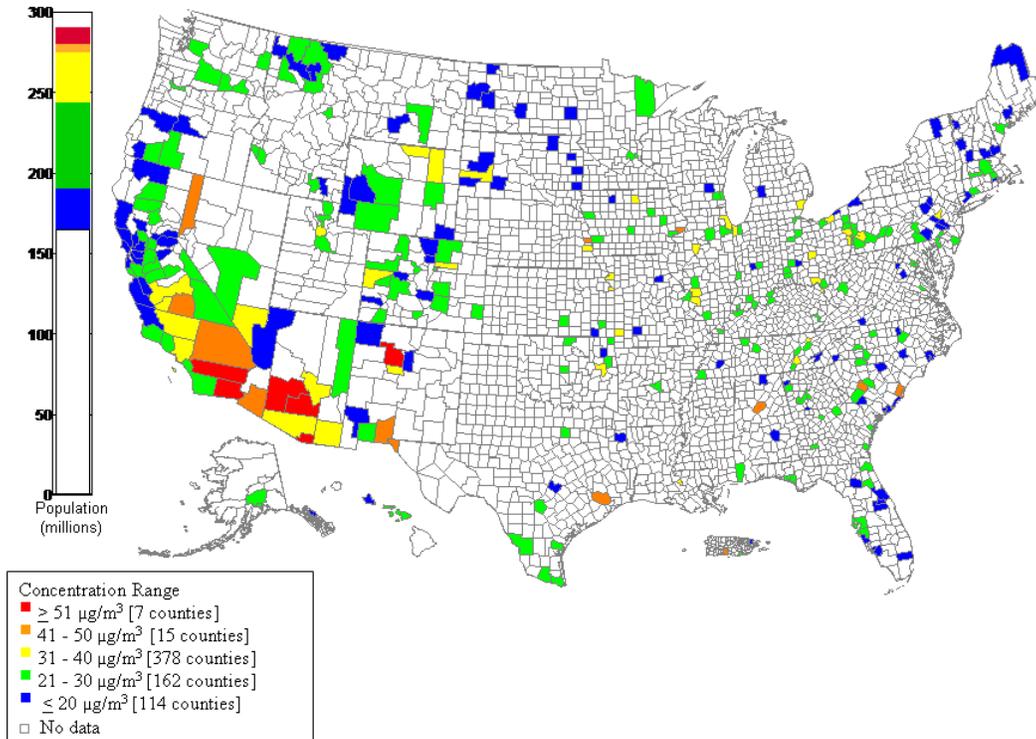
**Figure 3-6.** Average 24-h PM$_{10}$ concentration by county derived from FRM or FEM monitors, 2005–2007. The population bar shows the number of people residing within counties that reported county-wide average values in each of the concentration ranges.

**Table 3-11.** PM$_{10}$ distributions derived from AQS data (concentration in µg/m$^3$).

| | n | Mean | Percentiles | | | | | | | | | Max |
| | | | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 99 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *2005-2007 PM$_{10}$ FOR DIFFERENT AVERAGING PERIODS* | | | | | | | | | | | | |
| Annual avg.* (24-h FRM and 1-h FEM) | 674 | 25 | 9 | 14 | 16 | 19 | 22 | 28 | 35 | 43 | 58 | 81 |
| 24-h avg. (24-h FRM and 1-h FEM) | 326,675 | 26 | 3 | 6 | 9 | 14 | 21 | 32 | 46 | 59 | 97 | 8299 |
| 24-h avg. (24-h FRM) | 167,310 | 25 | 2 | 6 | 9 | 14 | 21 | 31 | 45 | 57 | 91 | 8299 |
| 24-h avg. (1-h FEM) | 156,931 | 26 | 4 | 7 | 9 | 14 | 21 | 32 | 48 | 62 | 105 | 979 |
| 1-h avg. (1-h FEM) | 3,767,533 | 27 | 1 | 4 | 6 | 11 | 19 | 32 | 51 | 69 | 145 | 8540 |
| *PM$_{10}$ ANNUAL AND SEASONAL STRATIFICATION USING 24-H AVG. FRM AND FEM DATA* | | | | | | | | | | | | |
| 2005 | 107,524 | 25 | 2 | 6 | 9 | 13 | 21 | 31 | 46 | 58 | 93 | 1441 |
| 2006 | 109,505 | 26 | 3 | 6 | 9 | 13 | 21 | 32 | 46 | 59 | 101 | 8299 |
| 2007 | 109,646 | 26 | 4 | 7 | 9 | 14 | 21 | 32 | 47 | 60 | 99 | 2253 |
| Winter (December-February) | 80,959 | 23 | 2 | 5 | 7 | 11 | 17 | 27 | 42 | 57 | 99 | 8299 |
| Spring (March-May) | 82,772 | 25 | 2 | 6 | 8 | 13 | 20 | 31 | 45 | 58 | 96 | 2253 |
| Summer (June-August) | 81,351 | 29 | 6 | 10 | 12 | 18 | 25 | 35 | 49 | 60 | 92 | 1839 |
| Fall (September-November) | 81,593 | 26 | 3 | 7 | 9 | 14 | 21 | 32 | 48 | 62 | 102 | 1212 |

| 2005-2007 PM$_{10}$ IN INDIVIDUAL CSAS/CBSAS USING 24-H AVG. FRM AND FEM DATA | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Atlanta | 1,868 | 24 | 6 | 9 | 11 | 16 | 23 | 31 | 39 | 44 | 57 | 108 |
| Birmingham | 5,478 | 34 | 6 | 9 | 12 | 19 | 28 | 43 | 64 | 82 | 120 | 241 |
| Boston | 1,412 | 17 | 2 | 5 | 7 | 10 | 15 | 22 | 30 | 36 | 50 | 58 |
| Chicago | 6,165 | 26 | 6 | 9 | 11 | 16 | 23 | 32 | 45 | 55 | 78 | 214 |
| Denver | 4,706 | 28 | 5 | 10 | 12 | 18 | 25 | 35 | 47 | 54 | 75 | 118 |
| Detroit | 1,407 | 30 | 7 | 10 | 12 | 18 | 26 | 38 | 53 | 64 | 81 | 182 |
| Houston | 1,397 | 31 | 7 | 10 | 12 | 17 | 23 | 34 | 56 | 80 | 137 | 248 |
| Los Angeles | 2,020 | 27 | 4 | 8 | 11 | 18 | 25 | 33 | 42 | 51 | 74 | 489 |
| New York | 514 | 19 | 2 | 6 | 7 | 11 | 17 | 25 | 35 | 40 | 51 | 83 |
| Philadelphia | 4,207 | 19 | 4 | 7 | 9 | 12 | 17 | 24 | 34 | 40 | 52 | 84 |
| Phoenix | 12,005 | 52 | 7 | 14 | 19 | 29 | 44 | 65 | 91 | 112 | 166 | 2253 |
| Pittsburgh | 12,677 | 24 | 4 | 7 | 9 | 13 | 19 | 31 | 45 | 57 | 83 | 157 |
| Riverside | 4,327 | 35 | 4 | 8 | 11 | 19 | 30 | 45 | 64 | 75 | 111 | 1212 |
| Seattle | 2,136 | 19 | 5 | 7 | 9 | 12 | 17 | 23 | 31 | 37 | 52 | 79 |
| St. Louis | 2,464 | 33 | 6 | 10 | 12 | 18 | 28 | 42 | 59 | 74 | 114 | 315 |
| All 15 CSAs/CBSAs | 62,783 | 32 | 5 | 8 | 10 | 16 | 25 | 39 | 60 | 77 | 120 | 2253 |
| Not in the 15 CSAs/CBSAs | 263,892 | 24 | 2 | 6 | 8 | 13 | 20 | 30 | 43 | 54 | 88 | 8299 |

*straight annual average without quarterly weighting

1    Table 3-11 contains summary statistics for PM$_{10}$ reported to AQS for the period 2005-2007. Both

2    FRM and FEM data are included in the table. The majority of observations are 24-h filter-based FRM

3    measurements, but numerous sites also report 1-h FEM data. To facilitate a distributional comparison

4    between 24-h and 1-h data reporting, the FRM and FEM data have been separated in Table 3-11. The

5    table also includes the data stratified by year (2005, 2006 and 2007) and season: winter

6    (December-February), spring (March-May), summer (June-August), and fall (September-November).

7    Fifteen CSAs/CBSAs were chosen for their importance in recent PM health studies, as described in

8    Section 3.4.


### PM$_{2.5}$

9    Figure 3-7 shows the 3-y mean of the 24-h PM$_{2.5}$ concentrations by county across the U.S. for

10   2005-2007. These data are obtained from the same source as PM$_{10}$ with the same 11+ days per quarter

11   completeness criteria applied. The San Joaquin Valley and inland southern California reported high PM$_{2.5}$

12   24-h concentrations above 20 μg/m$^3$. In addition, Jefferson County containing Birmingham, AL and

13   Allegheny County containing Pittsburgh, PA show annual average PM$_{2.5}$ concentrations above 18 μg/m$^3$.

14   Of the 3,225 U.S. counties, 540 (17%) had PM$_{2.5}$ data meeting the completeness criteria in all three years

15   (2005-2007) and have been included in Figure 3-7. These 540 counties represent roughly 63% of the U.S.

16   population.

1    Table 3-12 contains summary statistics for $PM_{2.5}$ reported to AQS for the period 2005-2007. All

2    24-h FRM and 1-h FRM-like[1] data reported to AQS are included in the table. On a national basis using

3    the 2005-2007 data in Tables 3-11 and 3-12, the mean 24-h $PM_{10}$ concentration (26 µg/m$^3$) is slightly

4    more than twice the mean 24-h $PM_{2.5}$ concentration (12 µg/m$^3$). Therefore, approximately half the PM

5    mass is in the fine mode and half in the coarse mode. The distribution between fine and coarse PM varies

6    substantially by location with a larger fraction of PM mass in the coarse mode in drier climates like

7    Phoenix and Denver and a larger fraction in the fine mode in cities like Pittsburgh and Philadelphia.

8    Comparisons of $PM_{2.5}$ to $PM_{10}$ as reported to AQS should be used with caution, however, since $PM_{2.5}$

9    concentrations are reported for local conditions while $PM_{10}$ concentrations are converted to STP before

10   reporting.

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[1] FRM-like refers to $PM_{2.5}$ concentration data associated with the parameter code "88502 - Acceptable $PM_{2.5}$ AQI and Speciation Mass" in the EPA Air Quality System. These data were collected by continuous instruments which are not approved as FRM or FEM, and consequently EPA does not use these data for regulatory purposes. These data are denoted as "FRM-like" because state and local monitoring agencies have individually decided that the continuous instruments reporting these data have a degree of agreement with FRM/FEM methods that is sufficient in their opinion for the data to be used in public advisories regarding current air quality. In some cases, these data include statistical adjustments by the state/local monitoring agency based on one-time or ongoing correlation analysis with co-located FRM/FEM monitors, intended to improve the "FRM-likeness" of the continuous concentration data (see, for example, (Bortnick et al., 2002). State/local monitoring agency decisions about whether to adjust continuous PM2.5 data and whether their raw or adjusted continuous PM2.5 data should be associated with parameter code 88502 were informed by non-binding EPA guidance issued in 2006 (Technical Note on Reporting $PM_{2.5}$ Continuous Monitoring and Speciation Data to the Air Quality System (AQS) http://www.epa.gov/ttn/amtic/files/ambient/pm25/datamang/contrept.pdf).
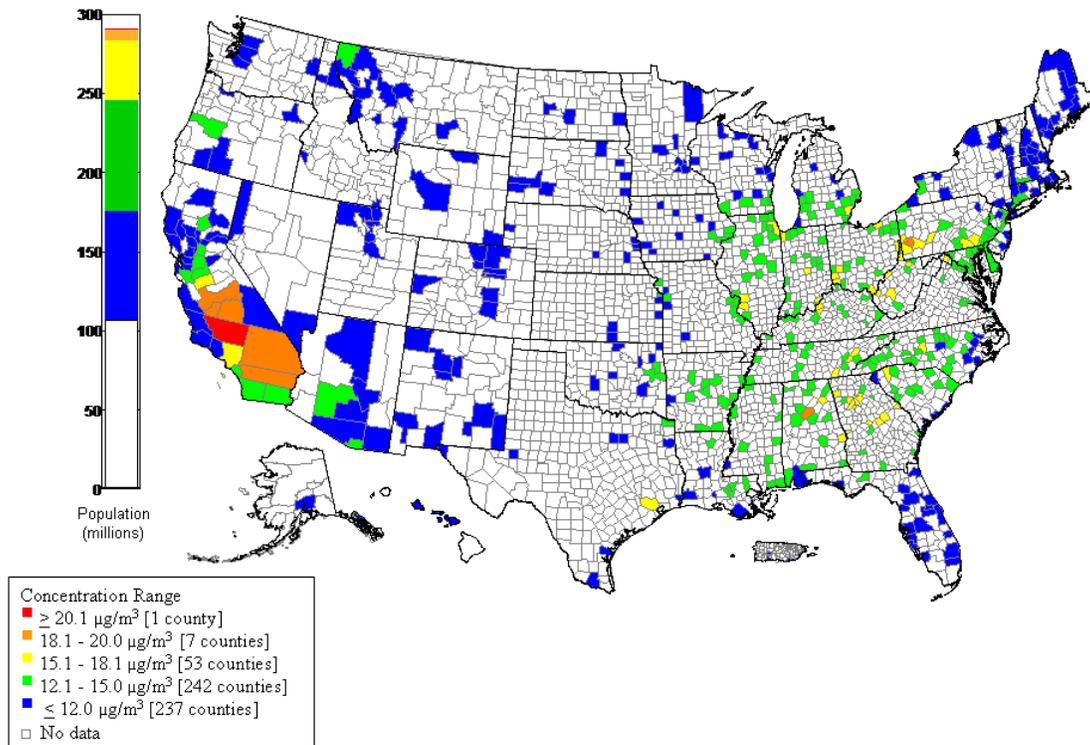
**Figure 3-7.** Average 24-h PM$_{2.5}$ concentration by county derived from FRM or FRM-like data, 2005-2007. The population bar shows the number of people residing within counties that reported county-wide average values in each of the concentration ranges.

### PM$_{10-2.5}$

1    Co-located PM$_{10}$ and PM$_{2.5}$ measurements from the AQS network were used to generate the

2    PM$_{10-2.5}$ concentrations by county across the U.S. for 2005-2007 in Figure 3-8. Only FRM or FRM-like

3    samplers were considered in calculating PM$_{10-2.5}$ to avoid complications with vastly different sampling

4    protocols (e.g., flow rates) between the independent PM$_{10}$ and PM$_{2.5}$ measurements. The PM$_{2.5}$

5    concentrations are reported to AQS using local conditions; the PM$_{10}$ data were adjusted to local conditions

6    on a daily basis using temperature and pressure measurements from the nearest National Weather Service

7    station. Figure 3-8 has considerably less coverage than the corresponding PM$_{10}$ and PM$_{2.5}$ figures as a

8    result of the monitor selection criteria and the fact that not all PM$_{10}$ and PM$_{2.5}$ monitors in a given region

9    are co-located. The 40 counties included in Figure 3-8 incorporate less than 5% of the U.S. population. Of

10   the 3,225 U.S. counties, only 40 (1%) met the completeness and co-location criteria in all three years

11   (2005-2007) and therefore the available measurements do not provide sufficient information to assess

12   regional-scale coarse PM concentration distributions.

**Table 3-12. PM$_{2.5}$ distributions derived from AQS data (concentration in µg/m$^3$).**

| | n | Mean | Percentiles | | | | | | | | | Max |
| | | | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 99 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *2005-2007 PM$_{2.5}$ FOR DIFFERENT AVERAGING PERIODS* | | | | | | | | | | | | |
| Annual avg.* (24-h FRM) | 794 | 12 | 5 | 6 | 8 | 10 | 13 | 14 | 15 | 16 | 19 | 22 |
| 24-h avg. (24-h FRM) | 349,028 | 12 | 2 | 4 | 4 | 7 | 10 | 16 | 23 | 28 | 39 | 193 |
| 24-h avg. (1-h FRM-like) | 183,057 | 10 | 1 | 2 | 3 | 5 | 8 | 13 | 19 | 24 | 35 | 126 |
| 1-h avg. (1-h FRM-like) | 4,403,817 | 10 | 0 | 1 | 2 | 4 | 8 | 13 | 21 | 27 | 42 | 828 |
| *PM$_{2.5}$ ANNUAL AND SEASONAL STRATIFICATION USING 24-H AVG. FRM DATA* | | | | | | | | | | | | |
| 2005 | 114,346 | 13 | 2 | 4 | 5 | 7 | 11 | 17 | 24 | 30 | 42 | 133 |
| 2006 | 113,197 | 12 | 2 | 4 | 4 | 7 | 10 | 15 | 21 | 26 | 36 | 193 |
| 2007 | 121,485 | 12 | 2 | 4 | 4 | 7 | 10 | 16 | 22 | 27 | 40 | 145 |
| Winter (December-February) | 86,286 | 12 | 2 | 4 | 5 | 7 | 10 | 15 | 22 | 27 | 44 | 193 |
| Spring (March-May) | 88,489 | 11 | 2 | 3 | 4 | 6 | 9 | 14 | 20 | 24 | 33 | 145 |
| Summer (June-August) | 86,830 | 14 | 2 | 4 | 5 | 8 | 12 | 19 | 26 | 31 | 40 | 133 |
| Fall (September-November) | 87,423 | 12 | 2 | 3 | 4 | 6 | 10 | 15 | 22 | 26 | 39 | 126 |
| *2005-2007 PM$_{2.5}$ IN INDIVIDUAL CSAS/CBSAS USING 24-H AVG. FRM DATA* | | | | | | | | | | | | |
| Atlanta | 4,939 | 15 | 4 | 6 | 7 | 10 | 14 | 19 | 25 | 29 | 37 | 145 |
| Birmingham | 4,869 | 16 | 4 | 6 | 7 | 10 | 15 | 21 | 29 | 34 | 47 | 64 |
| Boston | 8,464 | 10 | 2 | 3 | 4 | 5 | 9 | 13 | 20 | 24 | 32 | 50 |
| Chicago | 10,308 | 14 | 3 | 4 | 6 | 8 | 13 | 18 | 25 | 31 | 42 | 65 |
| Denver | 4,192 | 9 | 2 | 3 | 4 | 6 | 8 | 10 | 14 | 18 | 31 | 61 |
| Detroit | 5,223 | 14 | 2 | 3 | 5 | 7 | 12 | 19 | 26 | 31 | 45 | 82 |
| Houston | 1,342 | 15 | 4 | 6 | 8 | 10 | 14 | 18 | 23 | 26 | 34 | 44 |
| Los Angeles | 6,600 | 15 | 3 | 5 | 6 | 9 | 13 | 18 | 25 | 32 | 50 | 133 |
| New York | 15,826 | 13 | 2 | 4 | 4 | 6 | 10 | 17 | 24 | 29 | 39 | 58 |
| Philadelphia | 7,541 | 14 | 3 | 4 | 5 | 8 | 12 | 18 | 25 | 30 | 38 | 63 |
| Phoenix | 1,634 | 10 | 2 | 3 | 4 | 6 | 9 | 12 | 17 | 21 | 32 | 77 |
| Pittsburgh | 5,783 | 16 | 3 | 5 | 6 | 9 | 13 | 20 | 29 | 36 | 52 | 101 |
| Riverside | 2,751 | 17 | 3 | 5 | 6 | 10 | 14 | 21 | 31 | 40 | 58 | 106 |
| Seattle | 1,297 | 9 | 2 | 3 | 3 | 4 | 7 | 10 | 20 | 29 | 43 | 68 |
| St. Louis | 6,887 | 14 | 3 | 5 | 6 | 9 | 13 | 18 | 24 | 29 | 40 | 50 |
| All 15 CSAs/CBSAs | 87,656 | 14 | 2 | 4 | 5 | 7 | 12 | 17 | 25 | 30 | 42 | 145 |
| Not in the 15 CSAs/CBSAs | 261,372 | 12 | 2 | 3 | 4 | 6 | 10 | 15 | 22 | 27 | 38 | 193 |

*Straight annual average without quarterly weighting.

PM$_{10-2.5}$ 24-hour Average Concentration, 2005-2007
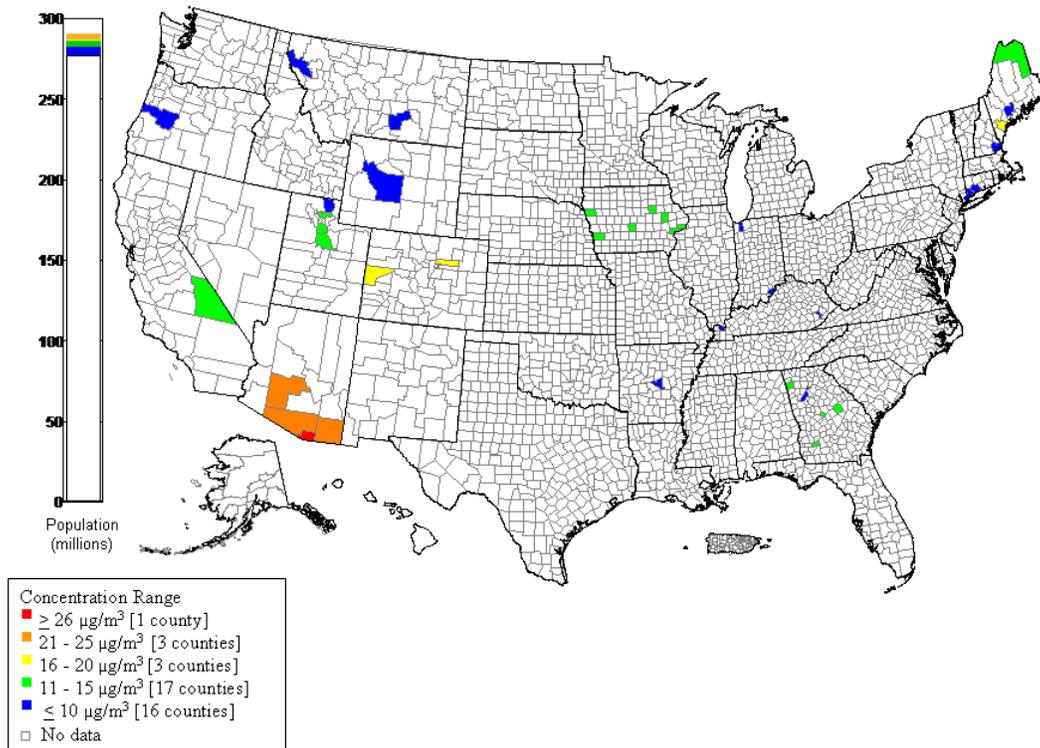


**Figure 3-8.** **Average 24-h PM$_{10-2.5}$ concentration by county derived from co-located low volume FRM PM$_{10}$ and PM$_{2.5}$ monitors, 2005-2007. The population bar shows the number of people residing within counties that reported county-wide average values in each of the concentration ranges.**

1       Table 3-13 contains summary statistics for PM$_{10-2.5}$ for the period 2005-2007 similar to those above

2    for PM$_{10}$ and PM$_{2.5}$. Given the FRM requirement applied here for calculating PM$_{10-2.5}$, no continuous data

3    were incorporated into this table. Using all available co-located PM measurements from 2005-2007, the

4    mean 24-h PM$_{10-2.5}$ concentration (13 µg/m$^3$) is roughly equivalent to the mean 24-h PM$_{2.5}$ concentration

5    (12 µg/m$^3$).

### PM Constituents

6       Figures 3-9 through 3-13 contain U.S. concentration maps for OC, EC, SO$_4$, NO$_3$, and NH$_4$ from

7    the CSN network for the period 2005-2007.

## Table 3-13. $PM_{10-2.5}$ distributions derived from AQS data (concentration in $\mu g/m^3$).

| | n | Mean | Percentiles | | | | | | | | | Max |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 99 | |
| *2005-2007 $PM_{10-2.5}$ FOR DIFFERENT AVERAGING PERIODS* | | | | | | | | | | | | |
| Annual avg.* (low volume FRM) | 43 | 12 | 4 | 5 | 6 | 9 | 11 | 14 | 20 | 22 | 40 | 40 |
| 24-h avg. (low volume FRM) | 12,027 | 13 | -3 | 1 | 2 | 6 | 10 | 17 | 26 | 33 | 54 | 246 |
| *$PM_{10-2.5}$ ANNUAL AND SEASONAL STRATIFICATION USING 24-H AVG. LOW VOLUME FRM DATA* | | | | | | | | | | | | |
| 2005 | 3,990 | 12 | -5 | 0 | 2 | 5 | 10 | 16 | 26 | 33 | 52 | 246 |
| 2006 | 4,037 | 13 | -2 | 1 | 2 | 6 | 10 | 17 | 27 | 34 | 56 | 182 |
| 2007 | 4,000 | 13 | -2 | 1 | 3 | 6 | 11 | 18 | 26 | 33 | 56 | 148 |
| Winter (December-February) | 2,942 | 11 | -5 | -1 | 1 | 4 | 8 | 15 | 27 | 34 | 56 | 246 |
| Spring (March-May) | 3,088 | 13 | -2 | 1 | 2 | 5 | 10 | 17 | 26 | 33 | 62 | 151 |
| Summer (June-August) | 2,968 | 14 | -2 | 3 | 5 | 8 | 12 | 18 | 25 | 31 | 44 | 93 |
| Fall (September-November) | 3,029 | 14 | -2 | 1 | 3 | 6 | 11 | 18 | 28 | 34 | 60 | 148 |
| *2005-2007 $PM_{10-2.5}$ IN INDIVIDUAL CSAS/CBSAS USING 24-H AVG. LOW VOLUME FRM DATA** | | | | | | | | | | | | |
| Atlanta | 167 | 10 | -4 | 1 | 2 | 5 | 9 | 13 | 18 | 21 | 30 | 46 |
| Boston | 340 | 7 | -2 | 1 | 2 | 4 | 6 | 9 | 12 | 16 | 25 | 27 |
| Chicago | 161 | 5 | -8 | -4 | -3 | 1 | 4 | 8 | 14 | 19 | 37 | 37 |
| Denver | 353 | 20 | 0 | 4 | 6 | 11 | 19 | 28 | 36 | 42 | 59 | 78 |
| New York | 338 | 9 | -16 | -2 | 1 | 5 | 8 | 12 | 17 | 23 | 34 | 56 |
| Phoenix | 163 | 22 | -3 | 8 | 11 | 16 | 20 | 29 | 35 | 46 | 67 | 70 |
| All 6 CSAs/CBSAs | 1,522 | 12 | -6 | 0 | 2 | 5 | 10 | 17 | 27 | 34 | 51 | 78 |
| Not in the 6 CSAs/CBSAs | 10,505 | 13 | -2 | 1 | 2 | 6 | 10 | 17 | 26 | 33 | 56 | 246 |

*straight annual average without quarterly weighting
**no co-located FRM $PM_{10}$ and FRM-like $PM_{2.5}$ monitors present in Birmingham, Detroit, Houston, Los Angeles, Philadelphia, Pittsburgh, Riverside, Seattle or St. Louis.
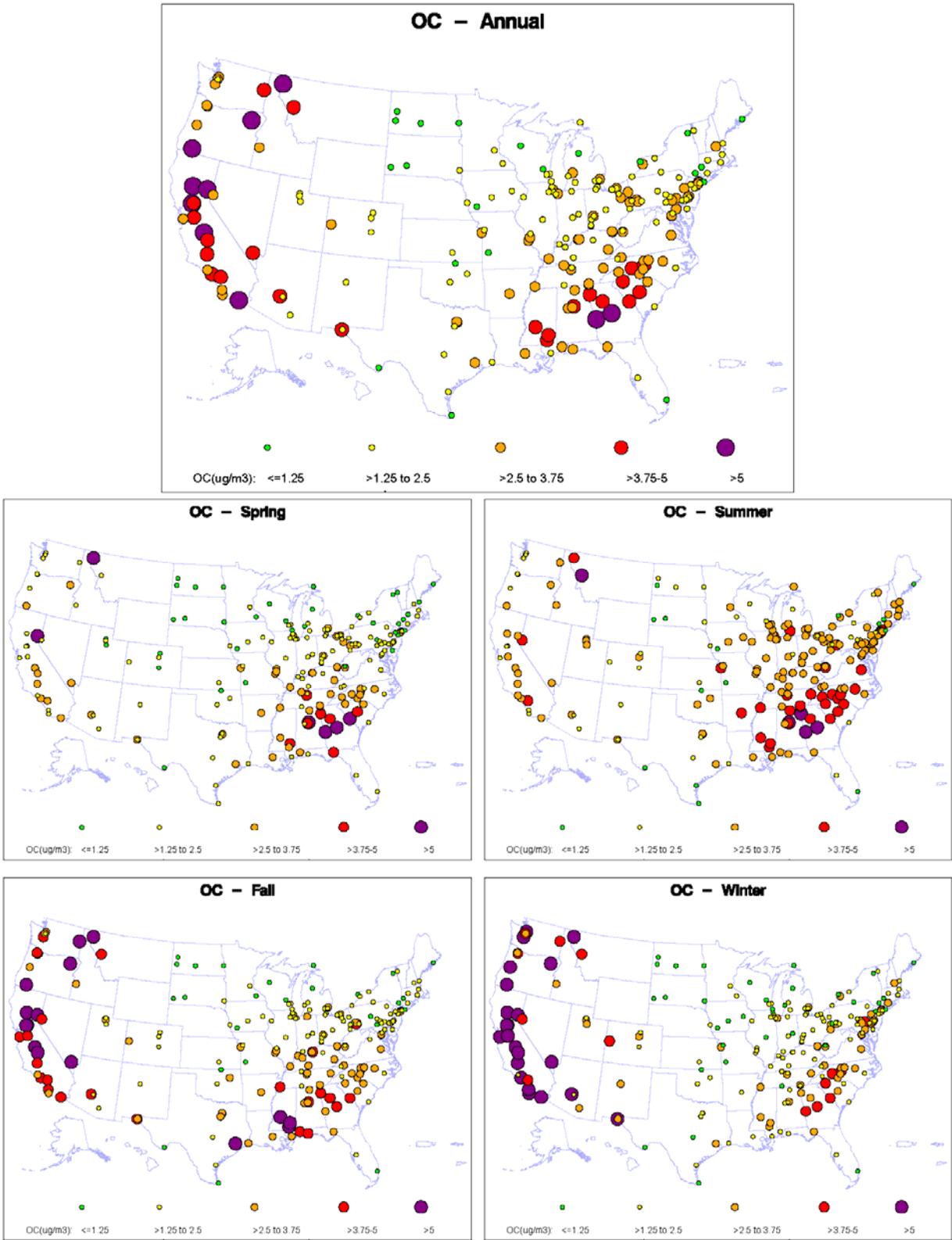
**Figure 3-9.** OC concentrations measured at CSN sites across the U.S., 2005-2007.
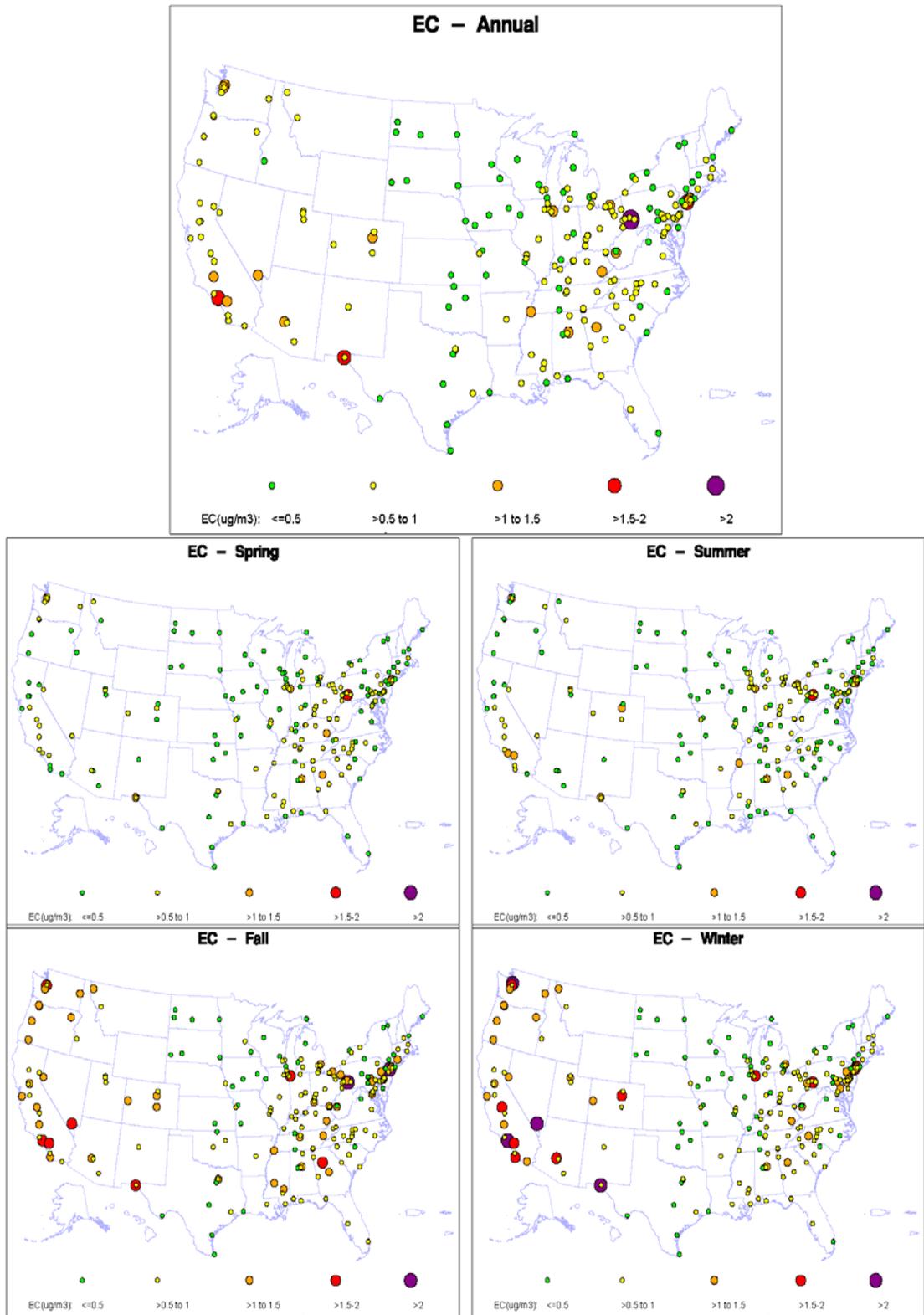
**Figure 3-10. EC concentrations measured at CSN sites across the U.S., 2005-2007.**
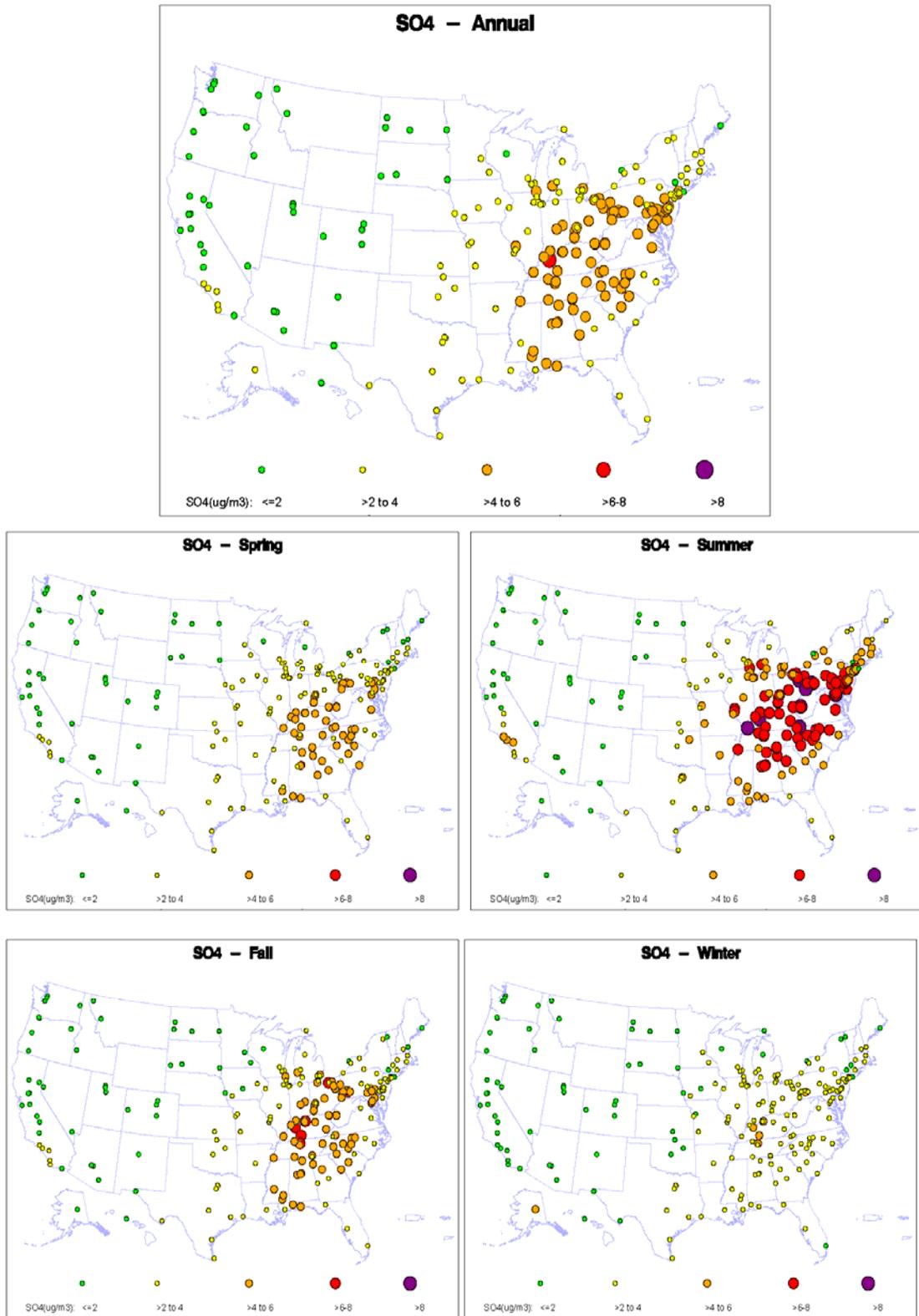
**Figure 3-11.   SO$_4^{2-}$ concentrations measured at CSN sites across the U.S., 2005-2007.**
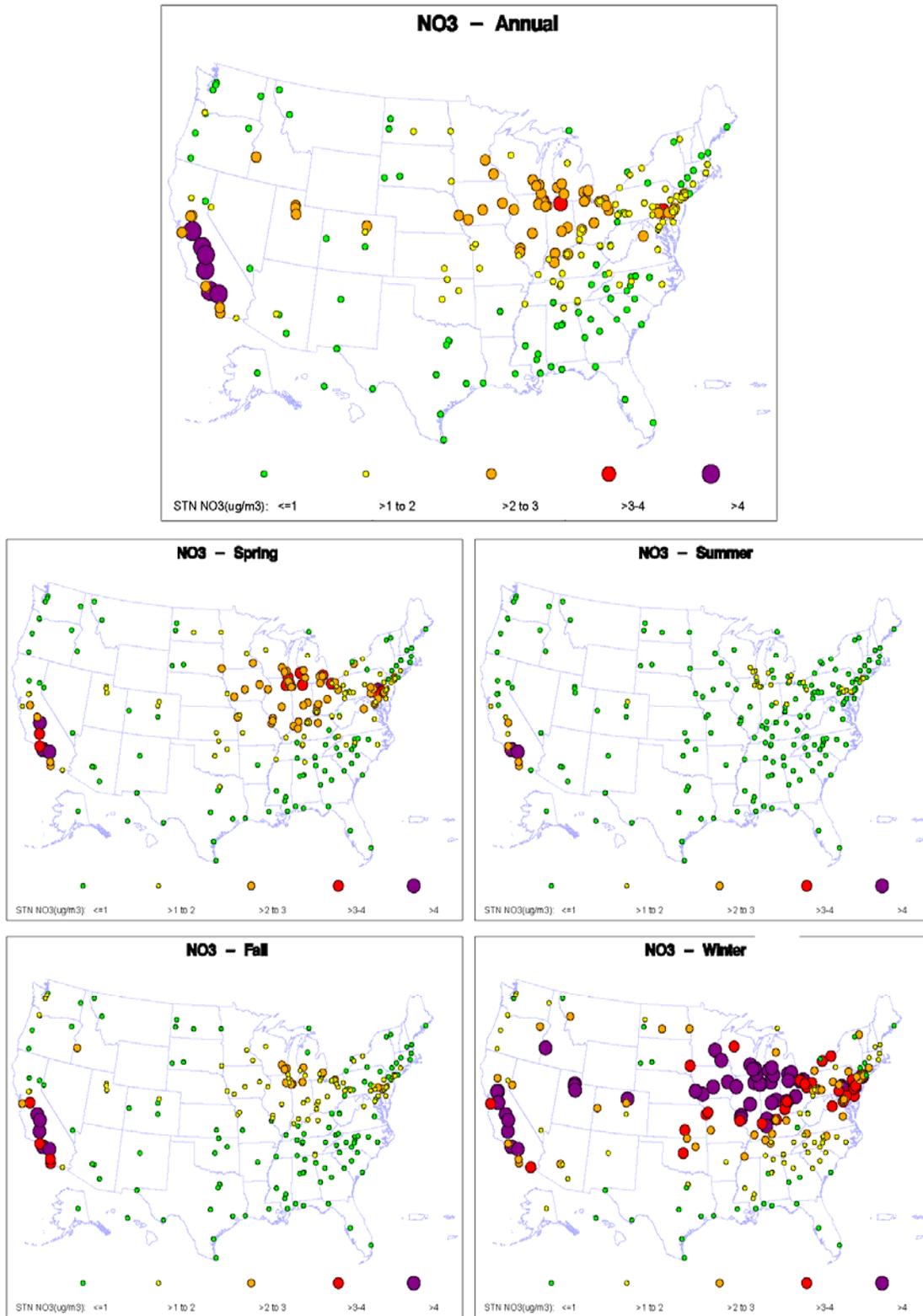
**Figure 3-12. NO₃⁻ concentrations measured at CSN sites across the U.S., 2005-2007.**
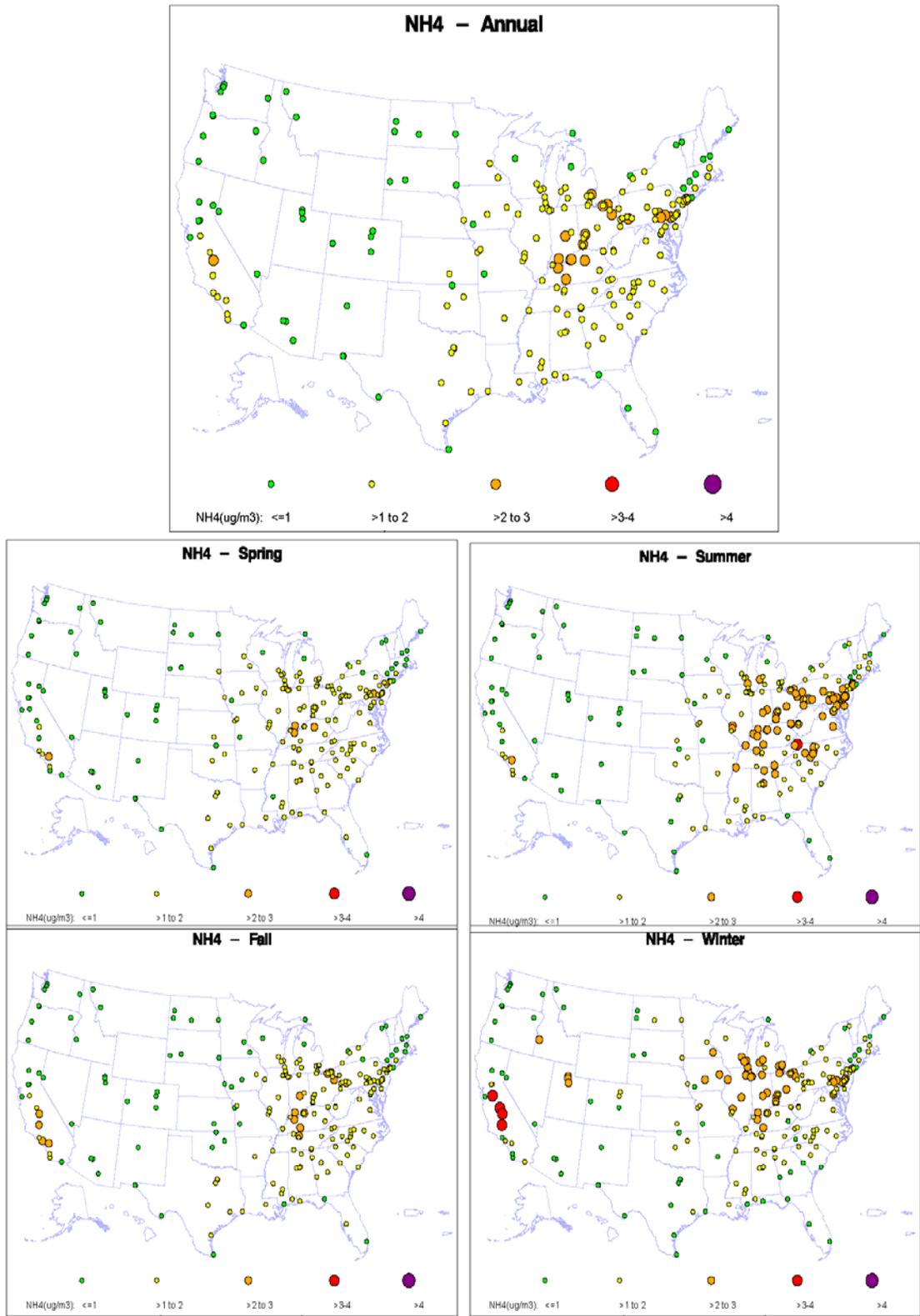
**Figure 3-13.** NH$_4^+$ concentrations measured at CSN sites across the U.S., 2005-2007.

1   Figure 3-9 shows regions of high OC with annual average concentrations greater than 5 $\mu g/m^3$ in

2 the western and the southeastern U.S. Concentrations at the western monitors peak in the fall and winter

3 while those in the Southeast peak anywhere from spring through fall. The central and northeastern

4 portions of the U.S. generally contain lower measured OC. Bell et al. (2007a) present a similar map for

5 estimated OCM (2000-2005) calculated by multiplying the blank corrected OC measurement by 1.4 to

6 account for non-carbon mass. This differs from the raw OC values that have not been multiplied by a

7 scaling factor, shown in Figure 3-9. There are a range of estimates in the literature for suggested scaling

8 factors (Turpin and Lim, 2001), depending predominantly on how highly oxygenated the aerosol is (Pang

9 et al., 2006). Fresh PM, more common in urban regions, has undergone limited chemical transformation.

10 As the aerosol is transported to rural regions, it becomes more oxygenated and hence heavier. As a result,

11 the necessary correction factor to account for non-carbon mass is higher in rural locations with estimates

12 ranging from 1.6 to 2.6 for IMPROVE monitors (El-Zanan et al., 2005). Therefore, applying one

13 correction factor of 1.4 across the entire U.S. will lead to an underestimate of the OCM in rural regions.

14 Therefore, the data presented in Figure 3-9 represent OC as measured and with a national blank

15 correction, but have not been adjusted to OCM by use of a scaling factor.

16   Figure 3-10 contains a similar map for EC that exhibits smaller seasonal variability than OC,

17 particularly in the eastern half of the U.S. There are isolated monitors spread throughout the country that

18 measure high annual average EC levels. These EC 'hot spots' are primarily associated with larger

19 metropolitan areas such as Los Angeles, Pittsburgh, and New York, but El Paso, TX, also reported high

20 annual average EC levels (driven by a wintertime average concentration greater than 2 $\mu g/m^3$). In a

21 similar analysis for EC by Bell et al. (2007a) for 2000-2005 data, there were also high wintertime EC

22 levels in eastern Kentucky and western Montana. These particular locations do not stand out in the

23 2005-2007 data in Figure 3-10.

24   Figure 3-11 contains a map for $SO_4^{2-}$ which shows that $SO_4^{2-}$ is more prevalent in the eastern U.S.

25 owing to the strong west-to-east gradient in $SO_2$ emissions. This gradient is magnified in the summer

26 months when more sunlight is available for photochemical formation of $SO_4^{2-}$. In contrast, $NO_3^-$ in Figure

27 3-12 is highest in the west, particularly in California. There are also elevated levels of $NO_3^-$ in the upper

28 midwest. The seasonal plots show generally higher $NO_3^-$ in the wintertime as a result of temperature

29 driven partitioning. Exceptions exist in Los Angeles and Riverside where high $NO_3^-$ readings appear year

30 round. The $NH_4$ concentration maps in Figure 3-13 shows spatial patterns related to both $SO_4^{2-}$ and $NO_3^-$

31 resulting from its presence in both $(NH_4)_2SO_4$ and $NH_4NO_3$. Annex A contains similar concentration maps

32 for Cu, Fe, Ni, Pb, Se and V as measured by XRF. There is considerably less seasonal variation in the

33 concentration profile for these metals than OC or the ions.

1        For the fifteen metropolitan areas identified earlier, the contribution of the major component

2    classes to total $PM_{2.5}$ mass was derived using the measured $SO_4^{2-}$, adjusted $NO_3^-$, derived water, inferred

3    carbonaceous mass approach (SANDWICH) (Frank, 2006). This approach uses the measured FRM $PM_{2.5}$

4    mass and co-located CSN chemical constituents to perform a mass balance-based estimation of the $PM_{2.5}$

5    fraction attributed to $SO_4^{2-}$, $NO_3^-$, EC, OCM, and crustal material. $SO_4^{2-}$ and $NO_3^-$ include associated

6    $NH_4^+$ mass and estimated particle-bound water. Furthermore, $NO_3^-$ is assumed to be fully neutralized as

7    $NH_4NO_3$ and has been adjusted to represent the amount retained by the FRM monitor. EC is taken as

8    measured, and the crustal component is derived from common oxides contained in the Earth's crust

9    (Pettijohn, 1957). Finally, OCM is estimated using mass balance by subtracting the sum of all other

10    constituents from the FRM $PM_{2.5}$ mass. The SANDWICH method takes into account passive collection of

11    semi-volatile or handling-related mass on the FRM filters in the mass balance calculation. The magnitude

12    of this artifact is assigned a nominal value of 0.5 $\mu g/m^3$ which is derived from limited analysis of FRM

13    field blanks. Other constituents such as salt and other metallic oxides, however, are not included in these

14    calculations and therefore the OCM fraction represents an upper bound on the FRM retained OC. The

15    calculations and assumptions that go into the SANDWICH method are discussed in detail in Frank (2006)

16    with further information available on EPA's AirExplorer web site

17    (http://www.epa.gov/cgi-bin/htmSQL/mxplorer/query_spe.hsql).
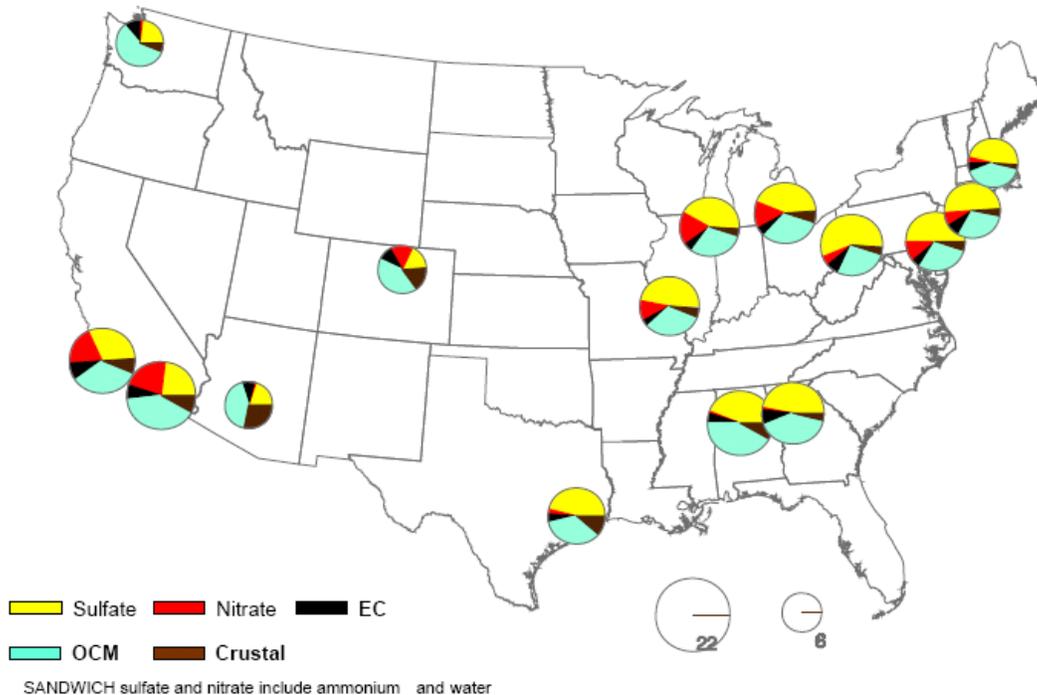
**Figure 3-14. Annual average FRM PM$_{2.5}$ speciation data for 2005-2007 derived using the SANDWICH method in fifteen CSAs/CBSAs: Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Pie diameters are scaled to PM$_{2.5}$ mass ($\mu$g/m$^3$).**

1    Figure 3-14 shows the PM$_{2.5}$ compositional breakdown for the fifteen CSAs/CBSAs. All available

2    monitoring sites with co-located FRM PM$_{2.5}$ and speciation data reporting in all four seasons for at least

3    one calendar year from 2005-2007 were included. Furthermore, each season was required to contain five

4    reported values for mass and the major PM$_{2.5}$ constituents. This resulted in a varying number of sites

5    (ranging from one to seven) used to create the averages shown in Figure 3-14.

6    On an annual average basis, SO$_4^{2-}$ is a dominant PM component in the eastern U.S. cities. For the

7    presented cities, this spans Houston to Boston where SO$_4^{2-}$ makes up between 42 and 56% of PM$_{2.5}$ on an

8    annual average basis. OCM is the next largest component in the east. In the west, OCM is the largest

9    constituent on an annual basis, ranging from 34% in Los Angeles to 58% in Seattle. SO$_4^{2-}$, NO$_3^-$ and

10   crustal material are also important in many of the included western cities. Fractional SO$_4^{2-}$ ranges from

11   18% in Denver to 32% in Los Angeles. Fractional NO$_3^-$ is relatively large in Denver (15%), Los Angeles

12   (19%) and Riverside (22%) and less important on an annual basis in Phoenix (1%) and Seattle (2%).

13   Crustal material is particularly prevalent in Phoenix (28%). EC makes up a smaller fraction of the PM$_{2.5}$

14   (4 to 11%), but it is consistently present in all included cities regardless of region.

15   The seasonal variation in PM$_{2.5}$ composition across the fifteen CSAs/CBSAs is shown in Figures

16   3-15 through 3-18 where the seasons are defined as before. SO$_4^{2-}$ dominates in most metropolitan areas in

1 the summertime, while $NO_3^-$ becomes important in the colder wintertime months. Notable summertime

2 exceptions include Denver, Phoenix, and Seattle, where $SO_4^{2-}$ makes up a smaller fraction of the $PM_{2.5}$

3 mass. Likewise, $NO_3^-$ is less pronounced in the wintertime in Atlanta, Birmingham, Houston, Phoenix,

4 and Seattle. Los Angeles and Riverside exhibit elevated $NO_3^-$ from spring through fall. Crustal material is

5 a substantial summertime component in Houston (26%), and is generally low elsewhere in the East in all

6 seasons. In the West, crustal material represents a substantial component year-round in Phoenix and

7 Denver.
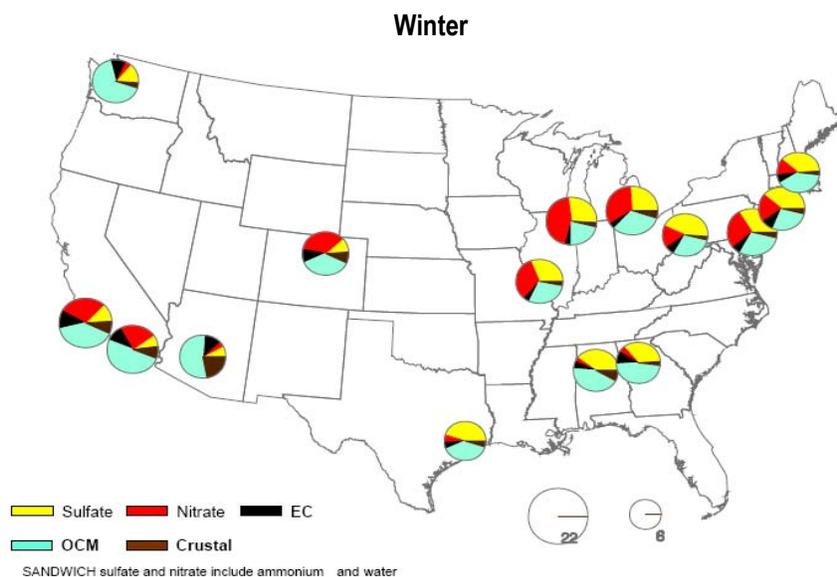
**Winter**



**Figure 3-15.** **Seasonally averaged FRM PM$_{2.5}$ speciation data for 2005-2007 for winter derived using the SANDWICH method in fifteen CSAs/CBSAs:  Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Pie diameters are scaled to PM$_{2.5}$ mass ($\mu$g/m$^3$).**
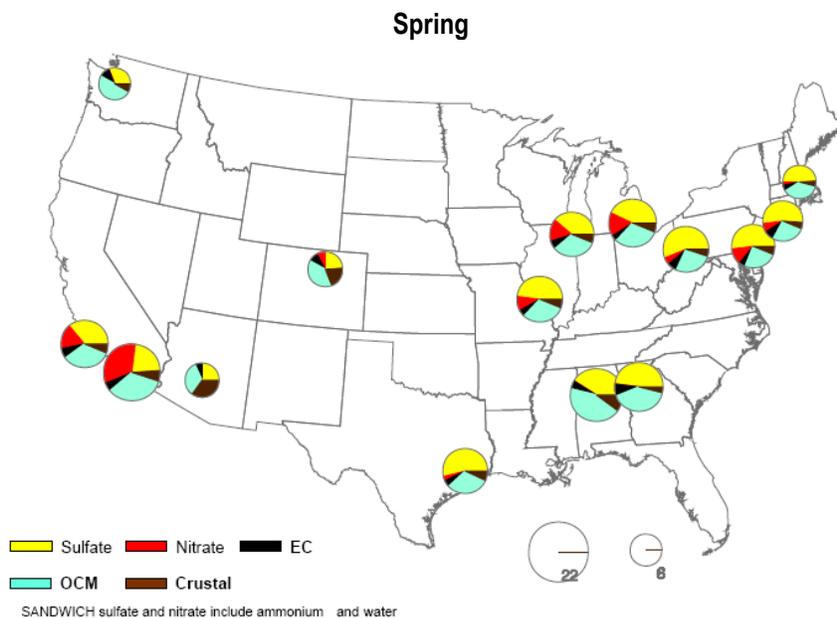
**Spring**



**Figure 3-16.** Seasonally averaged FRM PM₂.₅ speciation data for 2005-2007 for spring derived using the SANDWICH method in fifteen CSAs/CBSAs: Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Pie diameters are scaled to PM₂.₅ mass (µg/m³).
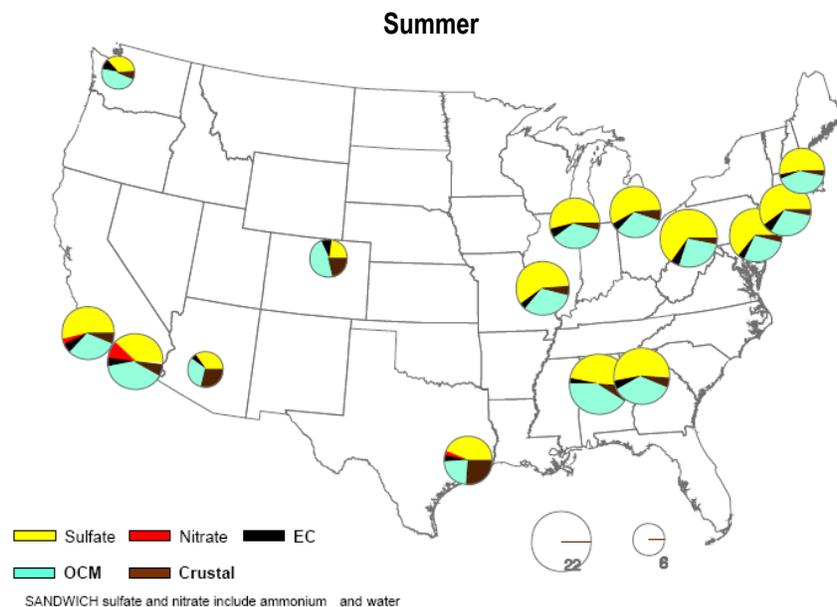
**Summer**



**Figure 3-17.** Seasonally averaged FRM PM₂.₅ speciation data for 2005-2007 for summer derived using the SANDWICH method in fifteen CSAs/CBSAs: Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Pie diameters are scaled to PM₂.₅ mass (µg/m³).
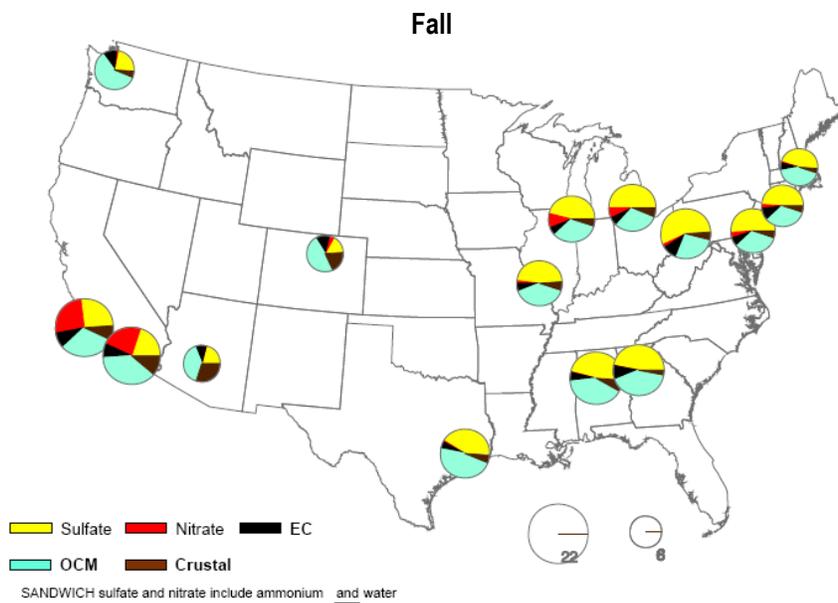
**Fall**



**Figure 3-18. Seasonally averaged FRM PM₂.₅ speciation data for 2005-2007 for fall derived using the SANDWICH method in fifteen CSAs/CBSAs: Atlanta, Birmingham, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. Pie diameters are scaled to PM₂.₅ mass (μg/m³).**

1   As noted in the 2004 PM AQCD (U.S. EPA, 2004), primary biological particles (PBPs), which
2   include microorganisms, fragments of living things, and organic compounds of miscellaneous origin in
3   surface deposits on filters, are not distinguishable in analyses of total OC. A clear distinction should be
4   made between PBP and primary OC produced by organisms (e.g. waxes coating the surfaces of
5   organisms) and precursors to secondary OC such as isoprene and terpenes. Indeed, the fields of view of
6   many photomicrographs of PM samples obtained by scanning electron microscopy are often dominated
7   by large numbers of pollen spores, plant and insect fragments, and microorganisms. Bioaerosols such as
8   pollen, fungal spores, and most bacteria are expected to be found mainly in the coarse size fraction.
9   However, allergens from pollens can also be found in respirable particles (Monn, 2001; Taylor et al.,
10  2002). Matthias-Maser et al. (2000) summarized information about the size distribution of PBP in and
11  around Mainz, Germany in what is perhaps the most complete study of this sort. Matthias-Maser found
12  that PBP constituted up to 30% of total particle number and volume in the approximate size range from
13  0.35 μm to 50 μm on an annual basis. Additionally, whereas the contribution of PBP to the total aerosol
14  volume did not change appreciably with season, the contribution of PBP to total particle number ranged
15  from about 10% in December and March to about 25% in June and October.

*Ultrafine Particles*

1    Very little is known about the spatiotemporal distribution or composition of ultrafine particles on a
2    regional scale. In an urban setting, a large percentage of ultrafine particles come from combustion-related
3    emissions from mobile sources (Sioutas et al., 2005). Ultrafine particle number concentrations drop off
4    quickly with distance from the roadway (Levy et al., 2003; Reponen et al., 2003; Zhu et al., 2005), and
5    therefore concentrations can be highly heterogeneous. Studies characterizing spatial variability in
6    ultrafines are currently limited to a handful of close proximity locations and therefore are discussed in the
7    next section on urban-scale variability. As for composition, OC makes up the majority of ultrafine
8    particles in most regions. Herner et al. (2005) reported a gradual increase in OC mass fraction as particle
9    size decreases from 1 μm (20% OC) to 100 nm (80% OC) in the San Joaquin Valley of California. Sardar
10   et al. (2005) found OC to be the major component of ultrafine particles at four locations in California,
11   with higher OC mass fraction in the wintertime relative to summertime. EC and $SO_4^{2-}$ were also present
12   in the ultrafine samples but at much smaller mass fractions; EC was present year-round whereas $SO_4^{2-}$
13   had a summertime preference. More detailed chemical characterization of the OC fraction of ambient
14   ultrafine particles is extremely limited, but recent studies have identified specific organic molecular
15   markers affiliated with motor vehicle emissions including hopanes and polycyclic aromatic hydrocarbons
16   (Fine et al., 2004; Ning et al., 2007; Phuleria et al., 2007).

## 3.5.1.2. Urban-Scale Variability

*$PM_{10}$*

17   $PM_{10}$ mass concentration has been shown to vary as much as a factor of five over urban-scale
18   distances of 100 km or less, and by a factor of 2 or more on scales as small as 30 km in an analysis of
19   California air quality (Alexis et al., 2001). This can be attributed to the rapid settling velocity and
20   resulting short atmospheric lifetime of the coarse-mode particles making up the majority of $PM_{10}$ mass.
21   As a result, local emission sources often dominate $PM_{10}$ annual average mass at certain monitors. Data
22   from the fifteen CSAs/CBSAs were used to investigate urban variability in PM reported to the AQS
23   database. Maps of $PM_{10}$ monitor locations and box plots of seasonal $PM_{10}$ mass concentration data are
24   provided for Boston (Figures 3-19 and 3-20), Pittsburgh (Figures 3-21 and 3-22), and Los Angeles
25   (Figures 3-23 and 3-24). Annex A shows the $PM_{10}$ monitor locations and box plots of seasonal $PM_{10}$ mass
26   concentration for all 15 CSAs/CBSAs. Boston is an example of a city with a wide range in concentrations
27   measured at different sites. Inter-monitor variation in $PM_{10}$ is frequently larger than the seasonal variation
28   measured at any given site. Pittsburgh is an example of a city with a large number of $PM_{10}$ monitors
29   providing consistent values with a select few reporting higher concentrations (sites D, H, I and K in

1    Figure 3-22). This illustrates the potential influence of localized point or area sources or topography. Los

2    Angeles shows a high degree of between-season and within-season variability, which is on the order of

3    the between-monitor variation.
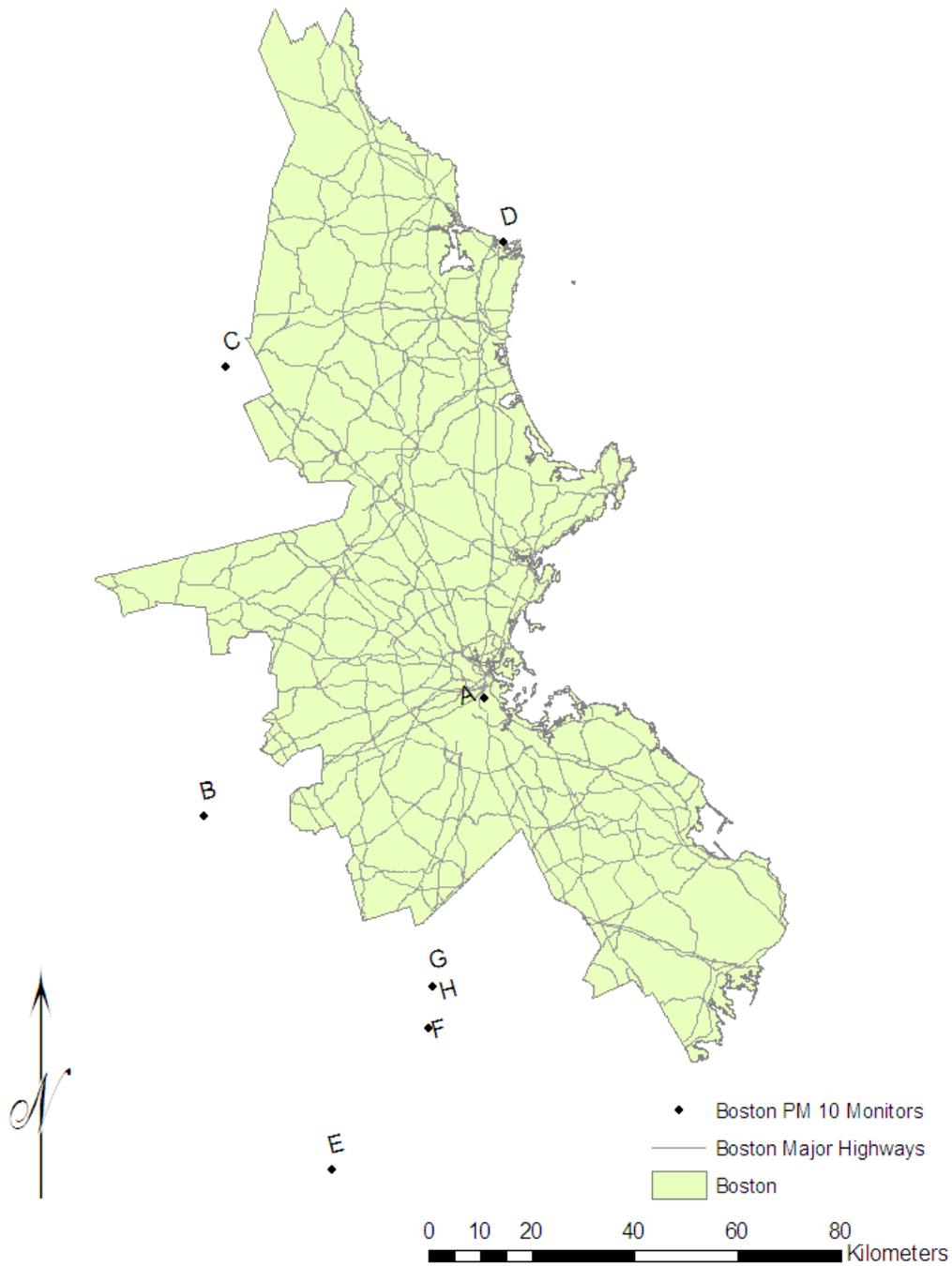


**Figure 3-19.   Map of PM$_{10}$ FRM distribution with AQS Site IDs for Boston, MA.**

| | A | B | C | D | E | F | G | H |
|------|------|------|------|------|------|------|------|------|
| Mean | 16.4 | 21.6 | 16.5 | 14.8 | 10.7 | 17.0 | 21.3 | 18.8 |
| Obs | 191 | 174 | 182 | 175 | 171 | 182 | 169 | 168 |
| SD | 7.7 | 11.9 | 9.2 | 8.2 | 7.0 | 8.7 | 10.8 | 9.4 |

|        | AQS Site ID |
|--------|-------------|
| Site A | 25-025-0042 |
| Site B | 25-027-0023 |
| Site C | 33-011-0020 |
| Site D | 33-015-0014 |
| Site E | 44-003-0002 |
| Site F | 44-007-0022 |
| Site G | 44-007-0026 |
| Site H | 44-007-0027 |

concentration ($\mu g/m^3$)

1=winter
2=spring
3=summer
4=fall
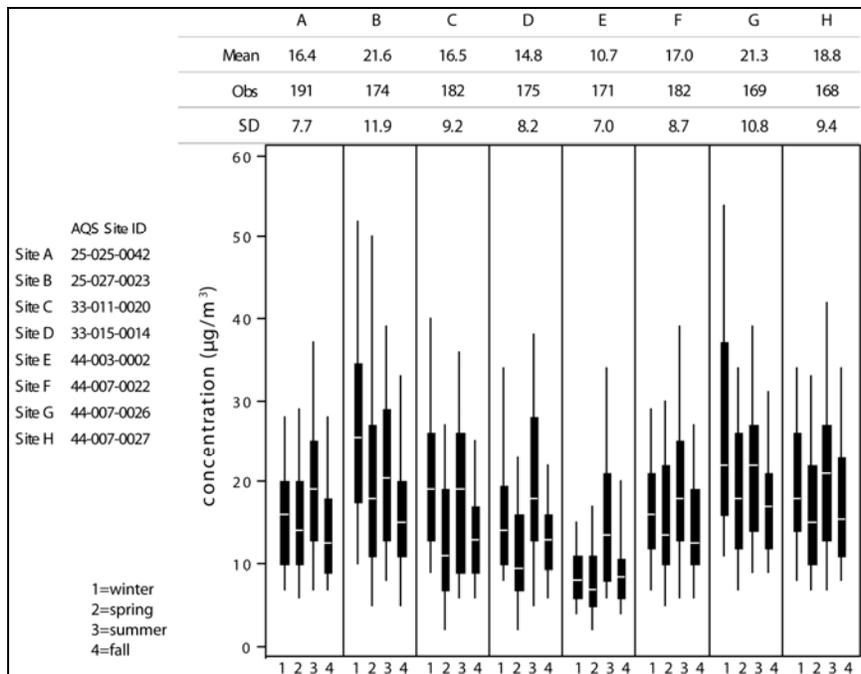
**Figure 3-20.** Box plot illustrating the seasonal distribution of 24-h average $PM_{10}$ concentrations for Boston, MA.

**Table 3-14.** Inter-sampler correlation statistics for each pair of $PM_{10}$ AQS data for Boston, MA.

| Site | A | B | C | D | E | F | G | H |
|------|------|------|------|------|------|------|------|------|
| **A** | 1.00 | 0.69 | 0.69 | 0.73 | 0.71 | 0.84 | 0.70 | 0.79 |
| | (0.0, 0.00) | (15.0, 0.22) | (12.0, 0.20) | (10.0, 0.22) | (13.0, 0.30) | (8.0, 0.14) | (15.0, 0.20) | (10.0, 0.17) |
| | 191 | 169 | 179 | 173 | 171 | 182 | 169 | 167 |
| **B** | | 1.00 | 0.66 | 0.56 | 0.45 | 0.69 | 0.77 | 0.65 |
| | | (0.0, 0.00) | (17.0, 0.24) | (19.0, 0.28) | (24.0, 0.39) | (15.0, 0.21) | (12.0, 0.17) | (16.0, 0.20) |
| | | 174 | 167 | 161 | 158 | 169 | 156 | 154 |
| **C** | | | 1.00 | 0.72 | 0.47 | 0.62 | 0.64 | 0.59 |
| | | | (0.0, 0.00) | (10.0, 0.22) | (17.0, 0.33) | (12.0, 0.21) | (16.0, 0.26) | (16.0, 0.24) |
| | | | 182 | 170 | 168 | 179 | 166 | 164 |
| **D** | | | | 1.00 | 0.63 | 0.68 | 0.59 | 0.69 |
| | | | | (0.0, 0.00) | (11.0, 0.29) | (10.0, 0.23) | (19.0, 0.30) | (13.0, 0.26) |
| | | | | 175 | 163 | 173 | 161 | 158 |
| **E** | | *KEY* | | | 1.00 | 0.84 | 0.58 | 0.80 |
| | | Pearson R | | | (0.0, 0.00) | (13.0, 0.29) | (22.0, 0.38) | (15.0, 0.33) |
| | | (90th Percentile, COD) | | | 171 | 171 | 161 | 157 |
| **F** | | n | | | | 1.00 | 0.81 | 0.95 |
| | | | | | | (0.0, 0.00) | (11.0, 0.16) | (5.0, 0.11) |
| | | | | | | 182 | 169 | 167 |
| **G** | | | | | | | 1.00 | 0.79 |
| | | | | | | | (0.0, 0.00) | (10.0, 0.13) |
| | | | | | | | 169 | 154 |
| **H** | | | | | | | | 1.00 |
| | | | | | | | | (0.0, 0.00) |
| | | | | | | | | 168 |
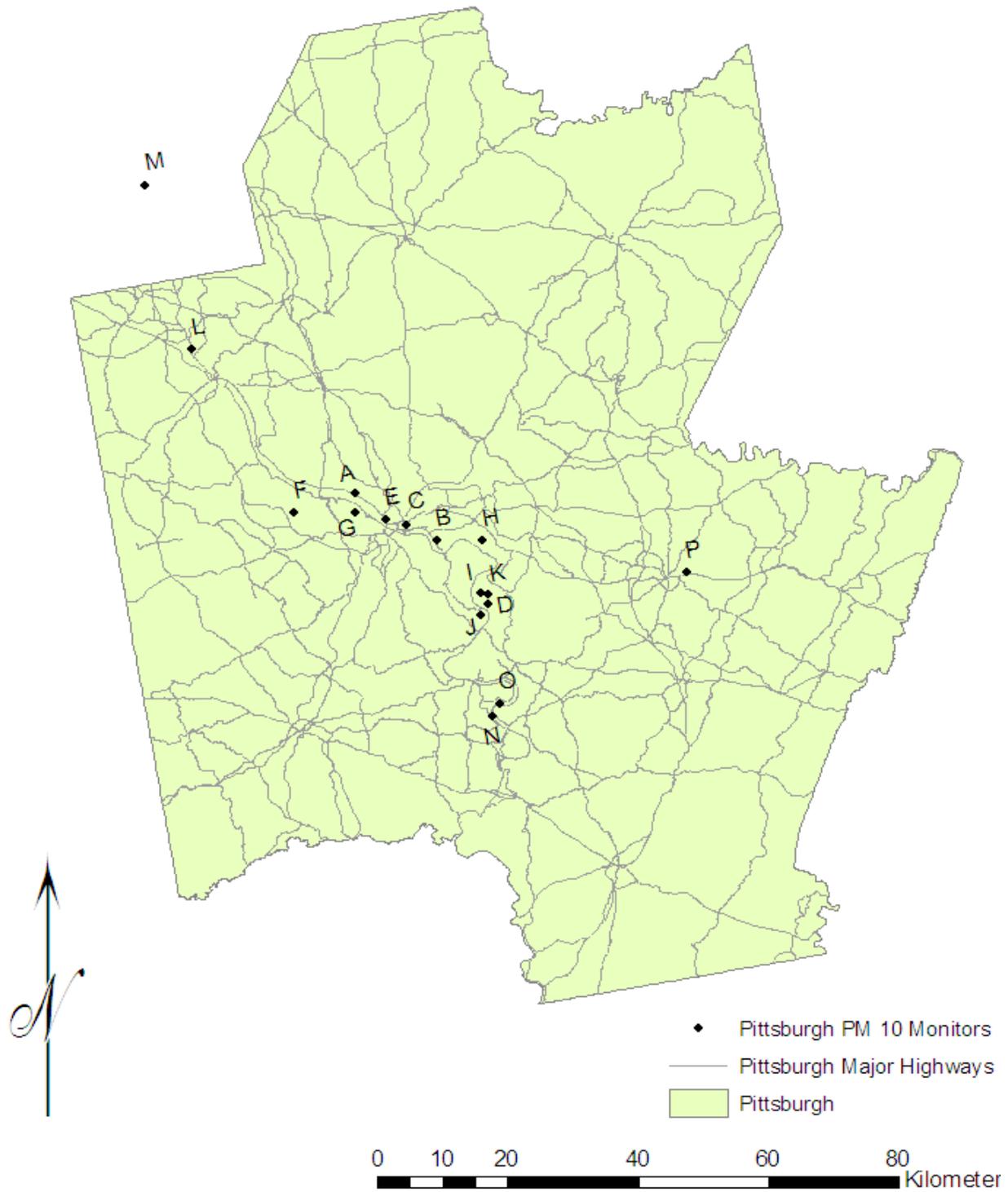
**Figure 3-21. Map of PM$_{10}$ FRM distribution with AQS Site IDs for Pittsburgh, PA.**

| | A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 21.2 | 18.2 | 21.8 | 27.7 | 23.4 | 19.6 | 18.4 | 29.7 | 25.2 |
| Obs | 1077 | 1019 | 1083 | 1087 | 176 | 179 | 978 | 182 | 1022 |
| SD | 12.9 | 11.4 | 12.3 | 20.3 | 11.1 | 9.9 | 11.7 | 16.8 | 19.3 |

AQS Site ID

Site A 42-003-0002
Site B 42-003-0021
Site C 42-003-0031
Site D 42-003-0064
Site E 42-003-0092
Site F 42-003-0095
Site G 42-003-0116
Site H 42-003-1301

1=winter
2=spring
3=summer
4=fall

| | J | K | L | M | N | O | P | Q |
|---|---|---|---|---|---|---|---|---|
| Mean | 20.1 | 36.5 | 26.3 | 26.4 | 21.7 | 19.7 | 27.3 | 21.1 |
| Obs | 177 | 1061 | 1051 | 1069 | 1092 | 167 | 178 | 1079 |
| SD | 10.3 | 26.7 | 16.3 | 15.0 | 12.4 | 11.0 | 12.0 | 11.4 |

AQS Site ID

Site I 42-003-3006
Site J 42-003-3007
Site K 42-003-7004
Site L 42-007-0014
Site M 42-073-0015
Site N 42-125-0005
Site O 42-125-5001
Site P 42-129-0007
Site Q 42-129-0008

1=winter
2=spring
3=summer
4=fall

**Figure 3-22.  Box plots illustrating the seasonal distribution of 24-h average PM$_{10}$ concentrations in Pittsburgh, PA.**

## Table 3-15. Inter-sampler correlation statistics for each pair of PM$_{10}$ AQS data for Pittsburgh, PA.

KEY
Pearson R
(90th Percentile, COD)
n

| Site | A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|---|
| A | 1.00 (0.0, 0.00) 1077 | 0.93 (9.0, 0.15) 1002 | 0.93 (8.0, 0.14) 1065 | 0.80 (23.0, 0.21) 1070 | 0.92 (8.0, 0.12) 175 | 0.89 (14.0, 0.18) 178 | 0.93 (8.0, 0.14) 960 | 0.79 (16.0, 0.17) 181 | 0.86 (18.0, 0.18) 1005 |
| B | | 1.00 (0.0, 0.00) 1019 | 0.96 (8.0, 0.15) 1007 | 0.80 (29.0, 0.24) 1012 | 0.91 (11.0, 0.20) 163 | 0.92 (6.0, 0.16) 166 | 0.97 (5.0, 0.10) 911 | 0.81 (25.0, 0.29) 169 | 0.89 (22.0, 0.20) 954 |
| C | | | 1.00 (0.0, 0.00) 1083 | 0.81 (23.0, 0.20) 1075 | 0.94 (6.0, 0.11) 173 | 0.93 (7.0, 0.12) 176 | 0.94 (8.0, 0.13) 966 | 0.77 (21.0, 0.22) 179 | 0.87 (19.0, 0.17) 1010 |
| D | | | | 1.00 (0.0, 0.00) 1087 | 0.72 (21.0, 0.20) 176 | 0.66 (26.0, 0.24) 179 | 0.76 (27.0, 0.24) 970 | 0.83 (14.0, 0.18) 182 | 0.88 (16.0, 0.14) 1014 |
| E | | | | | 1.00 (0.0, 0.00) 176 | 0.90 (10.0, 0.14) 173 | 0.90 (10.0, 0.17) 154 | 0.78 (20.0, 0.20) 175 | 0.77 (20.0, 0.19) 166 |
| F | | | | | | 1.00 (0.0, 0.00) 179 | 0.94 (7.0, 0.12) 157 | 0.70 (25.0, 0.27) 178 | 0.74 (25.0, 0.22) 168 |
| G | | | | | | | 1.00 (0.0, 0.00) 978 | 0.70 (22.0, 0.28) 160 | 0.87 (20.0, 0.19) 910 |
| H | | | | | | | | 1.00 (0.0, 0.00) 182 | 0.76 (17.0, 0.20) 171 |
| I | | | | | | | | | 1.00 (0.0, 0.00) 1022 |

| Site | J | K | L | M | N | O | P | Q |
|---|---|---|---|---|---|---|---|---|
| A | 0.84 (14.0, 0.20) 176 | 0.76 (40.0, 0.30) 1044 | 0.88 (15.0, 0.18) 1033 | 0.85 (16.0, 0.19) 1052 | 0.86 (11.0, 0.16) 1074 | 0.77 (16.0, 0.22) 166 | 0.78 (15.0, 0.19) 177 | 0.86 (11.0, 0.15) 1061 |
| B | 0.93 (7.0, 0.16) 164 | 0.76 (43.0, 0.36) 986 | 0.88 (19.0, 0.23) 982 | 0.81 (20.0, 0.26) 994 | 0.91 (10.0, 0.16) 1016 | 0.76 (12.0, 0.19) 157 | 0.83 (18.0, 0.28) 165 | 0.88 (10.0, 0.18) 1003 |
| C | 0.90 (8.0, 0.13) 174 | 0.75 (39.0, 0.30) 1049 | 0.88 (14.0, 0.17) 1039 | 0.83 (15.0, 0.19) 1057 | 0.89 (9.0, 0.12) 1080 | 0.78 (12.0, 0.18) 164 | 0.88 (13.0, 0.19) 175 | 0.90 (9.0, 0.12) 1067 |
| D | 0.73 (24.0, 0.22) 177 | 0.84 (24.0, 0.22) 1055 | 0.80 (20.0, 0.18) 1043 | 0.78 (20.0, 0.20) 1061 | 0.76 (25.0, 0.20) 1084 | 0.57 (28.0, 0.26) 167 | 0.64 (20.0, 0.25) 178 | 0.74 (26.0, 0.21) 1071 |
| E | 0.86 (10.0, 0.16) 171 | 0.65 (36.0, 0.29) 169 | 0.83 (16.0, 0.16) 169 | 0.80 (14.0, 0.17) 172 | 0.84 (12.0, 0.14) 176 | 0.77 (14.0, 0.19) 161 | 0.84 (13.0, 0.16) 172 | 0.85 (11.0, 0.15) 174 |
| F | 0.90 (7.0, 0.12) 174 | 0.57 (41.0, 0.34) 172 | 0.82 (20.0, 0.20) 172 | 0.75 (19.0, 0.22) 175 | 0.86 (11.0, 0.14) 179 | 0.83 (9.0, 0.15) 164 | 0.84 (16.0, 0.22) 175 | 0.86 (9.0, 0.14) 177 |
| G | 0.92 (7.0, 0.13) 156 | 0.73 (45.0, 0.35) 955 | 0.87 (18.0, 0.21) 938 | 0.78 (19.0, 0.24) 952 | 0.89 (9.0, 0.15) 975 | 0.81 (11.0, 0.17) 146 | 0.84 (17.0, 0.26) 157 | 0.86 (10.0, 0.16) 967 |
| H | 0.74 (23.0, 0.26) 176 | 0.68 (26.0, 0.22) 175 | 0.77 (15.0, 0.18) 175 | 0.78 (17.0, 0.18) 178 | 0.74 (21.0, 0.22) 182 | 0.60 (27.0, 0.29) 167 | 0.65 (19.0, 0.22) 177 | 0.76 (21.5, 0.24) 180 |
| I | 0.79 (22.0, 0.20) 166 | 0.83 (30.0, 0.25) 992 | 0.82 (16.0, 0.17) 978 | 0.78 (18.0, 0.20) 998 | 0.81 (20.0, 0.17) 1019 | 0.66 (26.0, 0.24) 158 | 0.69 (21.0, 0.25) 167 | 0.78 (22.0, 0.19) 1009 |
| J | 1.00 (0.0, 0.00) 177 | 0.66 (44.5, 0.33) 170 | 0.79 (18.0, 0.20) 170 | 0.72 (18.0, 0.22) 173 | 0.88 (8.0, 0.13) 177 | 0.78 (11.0, 0.17) 163 | 0.86 (16.0, 0.21) 173 | 0.86 (8.0, 0.15) 175 |
| K | | 1.00 (0.0, 0.00) 1061 | 0.74 (31.0, 0.26) 1017 | 0.75 (33.0, 0.24) 1035 | 0.70 (40.0, 0.30) 1058 | 0.47 (44.0, 0.36) 160 | 0.58 (34.0, 0.30) 171 | 0.68 (43.0, 0.30) 1048 |
| L | | | 1.00 (0.0, 0.00) 1051 | 0.87 (13.0, 0.16) 1025 | 0.85 (16.0, 0.17) 1048 | 0.70 (22.0, 0.24) 160 | 0.74 (17.0, 0.21) 171 | 0.80 (18.0, 0.19) 1035 |
| M | | | | 1.00 (0.0, 0.00) 1069 | 0.74 (18.0, 0.21) 1067 | 0.64 (19.0, 0.26) 163 | 0.67 (17.0, 0.22) 174 | 0.77 (18.0, 0.19) 1053 |
| N | | | | | 1.00 (0.0, 0.00) 1092 | 0.72 (13.0, 0.18) 167 | 0.86 (14.0, 0.20) 178 | 0.86 (10.0, 0.14) 1076 |
| O | | | | | | 1.00 (0.0, 0.00) 167 | 0.75 (18.0, 0.25) 163 | 0.69 (14.0, 0.19) 165 |
| P | | | | | | | 1.00 (0.0, 0.00) 178 | 0.84 (15.0, 0.21) 176 |
| Q | | | | | | | | 1.00 (0.0, 0.00) 1079 |

**Figure 3-23.   Map of PM$_{10}$ FRM distribution with AQS Site IDs for Los Angeles, CA.**
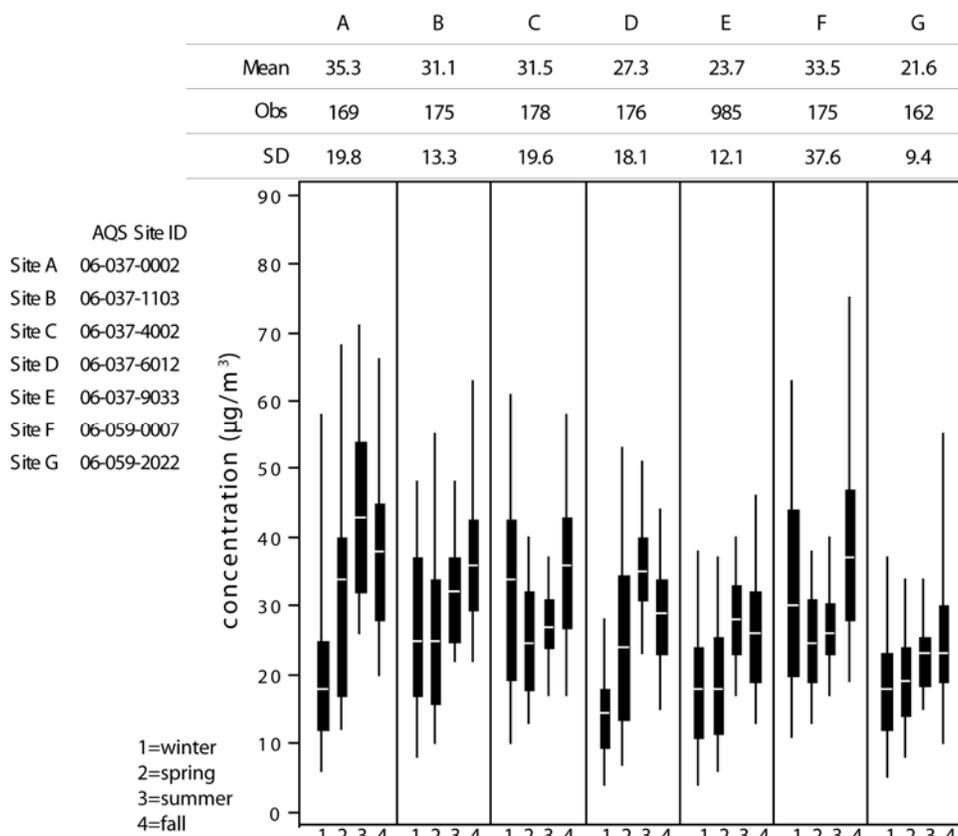
**Figure 3-24.** Box plots illustrating the seasonal distribution of 24-h average PM₁₀ concentrations for Los Angeles, CA.

**Table 3-16.** Inter-sampler correlation statistics for each pair of PM₁₀ AQS data for Los Angeles, CA.

| Site | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|
| A | 1.00 | 0.73 | 0.44 | 0.73 | 0.47 | 0.41 | 0.65 |
| | (0.0, 0.00) | (17.0, 0.17) | (27.0, 0.24) | (24.0, 0.22) | (28.0, 0.26) | (29.0, 0.24) | (30.0, 0.28) |
| | 169 | 153 | 154 | 157 | 169 | 155 | 143 |
| B | | 1.00 | 0.61 | 0.57 | 0.52 | 0.42 | 0.73 |
| | | (0.0, 0.00) | (14.0, 0.14) | (21.0, 0.24) | (23.0, 0.23) | (15.0, 0.16) | (20.0, 0.23) |
| | | 175 | 159 | 159 | 173 | 162 | 149 |
| C | | | 1.00 | 0.65 | 0.43 | 0.93 | 0.73 |
| | KEY Pearson R (90th Percentile, COD) n | | (0.0, 0.00) | (27.0, 0.28) | (22.0, 0.24) | (11.0, 0.11) | (21.0, 0.22) |
| | | | 178 | 158 | 176 | 159 | 148 |
| D | | | | 1.00 | 0.70 | 0.65 | 0.57 |
| | | | | (0.0, 0.00) | (16.0, 0.20) | (26.0, 0.28) | (19.5, 0.24) |
| | | | | 176 | 175 | 161 | 150 |
| E | | | | | 1.00 | 0.29 | 0.38 |
| | | | | | (0.0, 0.00) | (26.0, 0.25) | (20.0, 0.24) |
| | | | | | 985 | 173 | 159 |
| F | | | | | | 1.00 | 0.65 |
| | | | | | | (0.0, 0.00) | (21.5, 0.22) |
| | | | | | | 175 | 150 |
| G | | | | | | | 1.00 |

1   Figures 3-25 through 3-27 illustrate the relationship between inter-sampler correlation and distance

2 between sites for $PM_{10}$ measurements obtained in Boston, Pittsburgh and Los Angeles. These three cities

3 are characterized by different topography, climatology, sources and composition of PM. Plots are

4 provided for all fifteen urban areas of interest in Annex A. In each plot, a large amount of scatter can be

5 observed. This is consistent with the seasonal box plots of concentration shown in Figures 3-20, 3-22, and

6 3-24. The Boston data exhibit the strongest relationship between inter-sampler correlation and distance,

7 with average inter-sampler correlation remaining higher than 80% when samplers are 44 km apart

8 ($R^2 = 0.61$). The lowest correlations on this plot originate from comparisons between Site B (rural

9 Worcester, MA) and samplers located at Sites E (West Greenwich, RI) and G (Providence, RI). Boston is

10 subject to long range transport of sulfate, which is a regional pollutant and is a major component of $PM_{2.5}$

11 and $PM_{10}$ in the eastern U.S. The Pittsburgh data shows some lower inter-sampler correlations, with one

12 sampler pair having only 66% correlation within a distance of 2 km. On average, inter-sampler correlation

13 remained higher than 80% when samplers were also separated by 44 km, but in this case with much

14 greater scatter ($R^2 = 0.28$) than observed in the Boston data. As seen for the Pittsburgh $PM_{10}$ box plots in

15 Figure 3-22, sites D, H, I, and K have elevated means and high variability that is driving the observed

16 scatter. These four sites are all located in mountainous suburbs of Pittsburgh (North Braddock, PA,

17 Liberty, PA, Lincoln Boro, PA, and Beaver Falls, PA, respectively), where emissions from steel

18 manufacturing and frequent stable conditions in the planetary boundary layer cause localized events of

19 elevated concentration. When those four sites are removed, scatter decreases greatly ($R^2 = 0.56$). The Los

20 Angeles data exhibit a much steeper slope, with average inter-sampler correlation remaining higher than

21 80% when samplers are only 30 km apart ($R^2 = 0.56$). The lower inter-sampler correlations in part reflect

22 the fact that some of these monitoring sites are separated from each other by hills or, in the case of one

23 sited at Lancaster, CA, by the San Gabriel Mountains. The Los Angeles data exhibit greater scatter than

24 the Pittsburgh data. However, the smallest inter-sampler separation distance is 23 km, and there are

25 relatively fewer $PM_{10}$ samplers. It is not possible to judge how data would correlate on smaller spatial

26 scales.
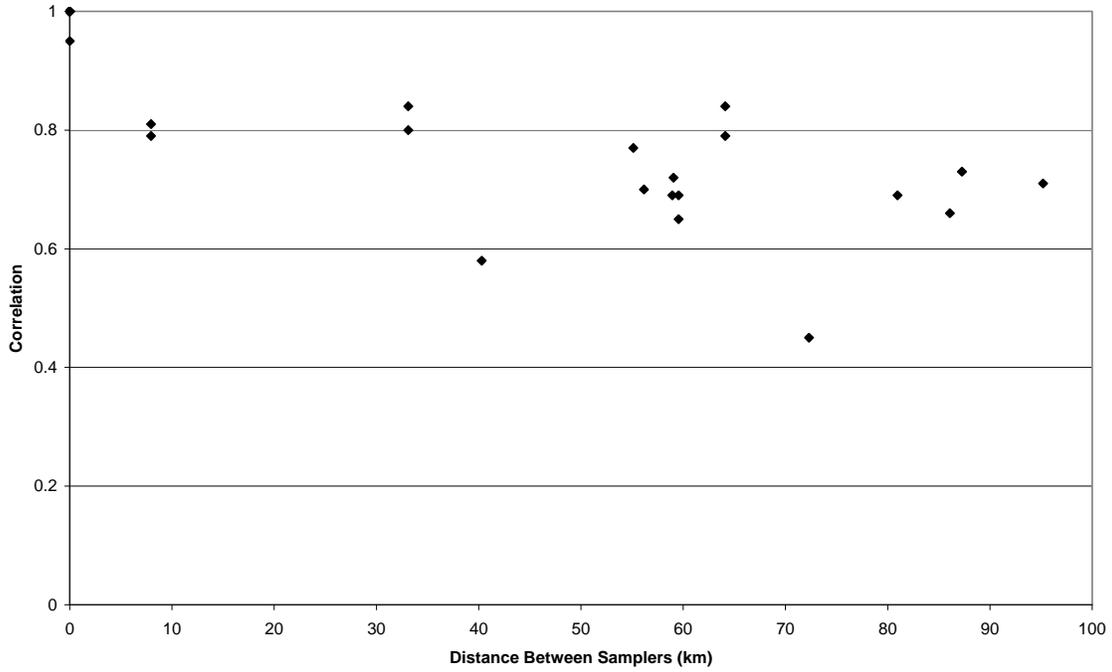
**Figure 3-25. PM$_{10}$ inter-sampler correlations as a function of distance between monitors for Boston.**
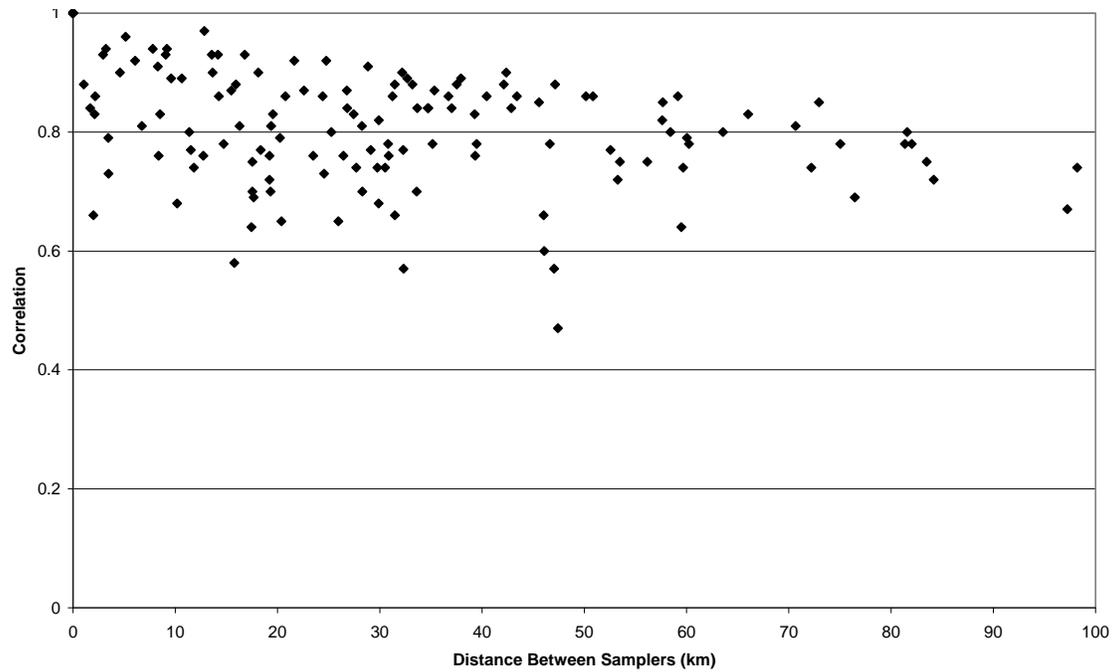


**Figure 3-26. PM$_{10}$ inter-sampler correlations as a function of distance between monitors for Pittsburgh.**
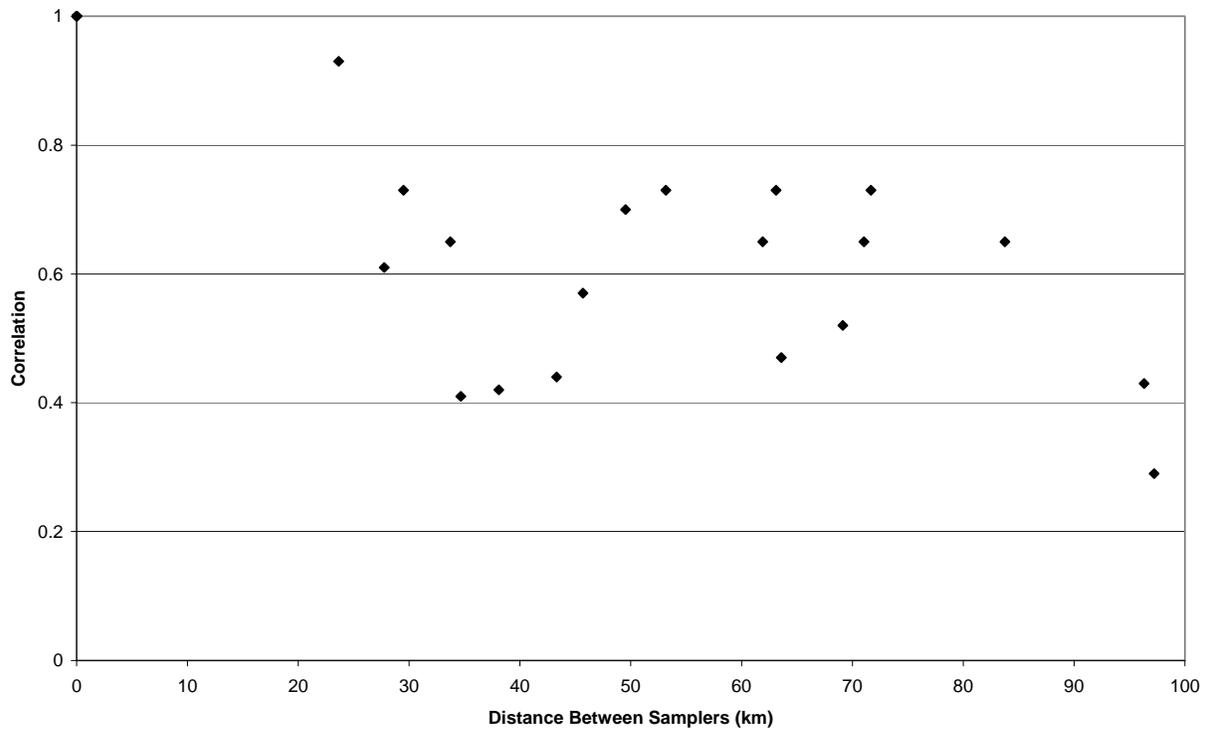
**Figure 3-27.  PM₁₀ inter-sampler correlations as a function of distance between monitors for Los Angeles.**

1    A table of complete pair wise, within-city comparisons for $PM_{10}$ measured at the available monitors

2    in each CSA/CBSA are included for Boston (Table 3-14), Pittsburgh (Table 3-15) and Los Angeles (Table

3    3-16); the complete set of tables for all 15 CSAs/CBSAs are shown in Annex A. Comparison statistics

4    include the Pearson correlation coefficient (R), the 90th percentile of the absolute difference in

5    concentrations (P90), the coefficient of divergence (COD) and the number of paired observations

6    (Wongphatarakul et al., 1998). The COD provides an indication of the variability across the monitoring

7    sites in each CSA/CBSA and is defined as follows:

$$COD_{jk} = \sqrt{\frac{1}{p}\sum_{i=1}^{p}\left(\frac{X_{ij}-X_{ik}}{X_{ij}+X_{ik}}\right)^{2}}$$

*Equation 3-1*

8    where $X_{ij}$ and $X_{ik}$ represent observed concentrations averaged over some measurement averaging period

9    (hourly, daily, etc.), for measurement period $i$ at sites $j$ and $k$, and $p$ is the number of paired observations.

10   A COD of 0 indicates there are no differences between concentrations at paired sites (spatial

11   homogeneity), while a COD approaching 1 indicates extreme spatial heterogeneity.
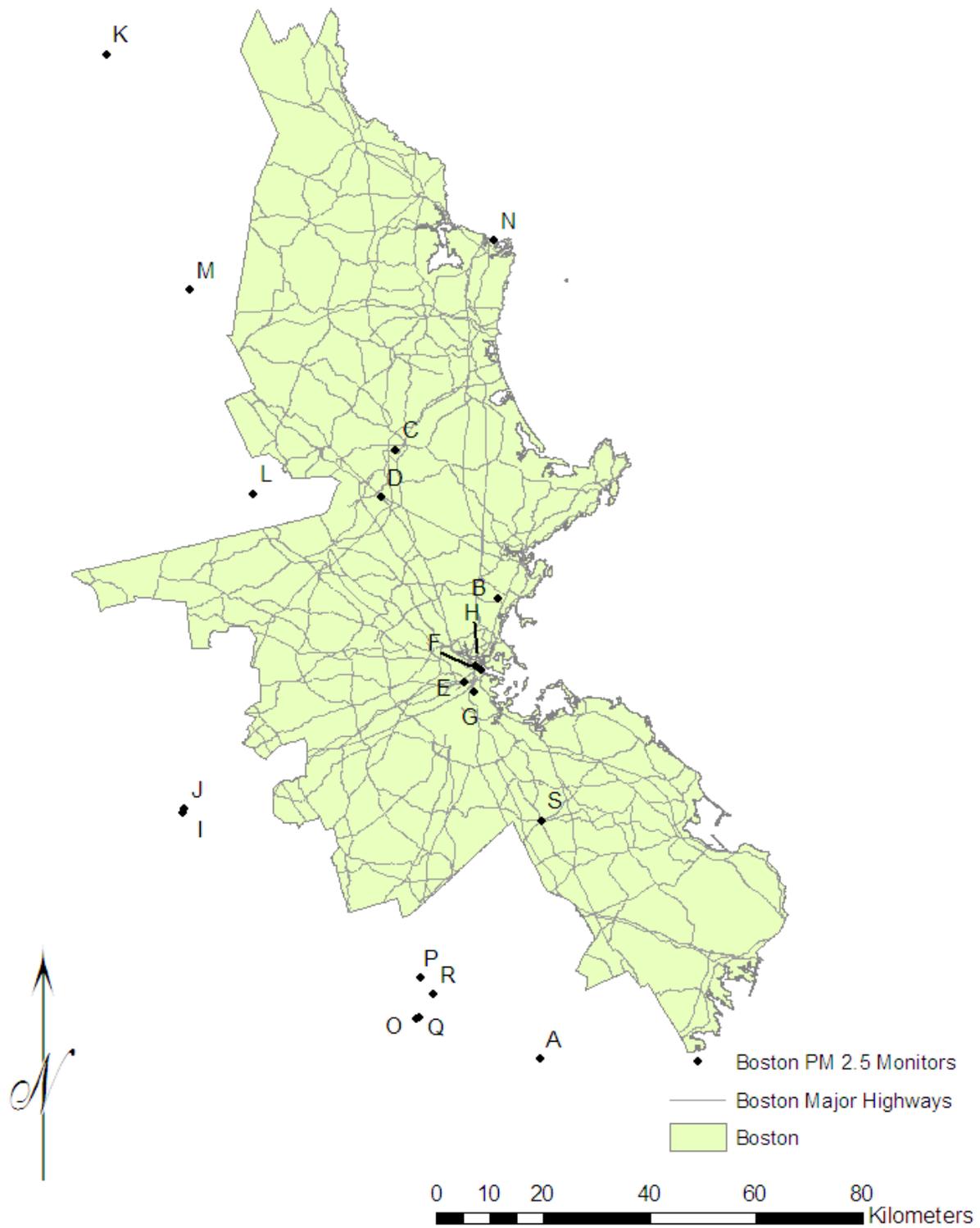
**Figure 3-28.** PM$_{2.5}$ monitor distribution in comparison with source distribution, Boston, MA.
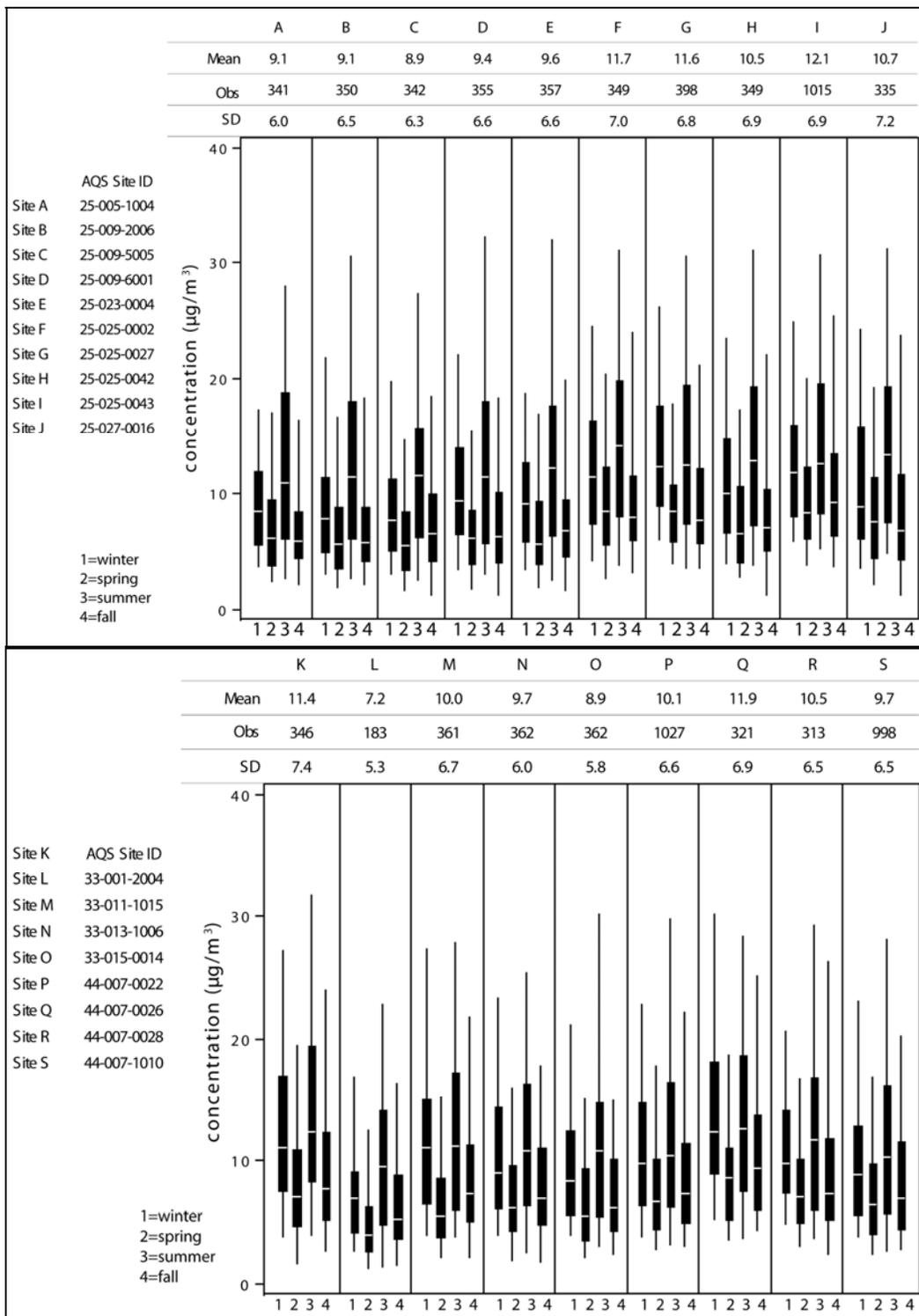
**Figure 3-29. Box plots illustrating the seasonal distribution of 24-h average PM$_{2.5}$ concentrations for Boston, MA.**

## Table 3-17. Inter-sampler correlation statistics for each pair of PM$_{2.5}$ AQS data for Boston, MA.

KEY
Pearson R
(90th Percentile, COD)
n

| Site | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 1.00 (0.0, 0.00) 341 | 0.80 (6.6, 0.21) 326 | 0.77 (6.2, 0.22) 318 | 0.71 (6.9, 0.23) 323 | 0.84 (4.8, 0.19) 329 | 0.79 (8.1, 0.23) 318 | 0.78 (7.7, 0.24) 319 | 0.79 (6.8, 0.22) 325 | 0.79 (7.9, 0.25) 338 | 0.77 (7.5, 0.24) 310 |
| B | | 1.00 (0.0, 0.00) 350 | 0.92 (4.1, 0.17) 328 | 0.87 (4.1, 0.18) 331 | 0.87 (4.7, 0.19) 339 | 0.90 (6.3, 0.21) 326 | 0.90 (6.2, 0.23) 323 | 0.90 (4.9, 0.19) 333 | 0.90 (7.1, 0.26) 343 | 0.85 (5.5, 0.21) 317 |
| C | | | 1.00 (0.0, 0.00) 342 | 0.90 (3.5, 0.17) 321 | 0.85 (5.3, 0.21) 331 | 0.90 (6.3, 0.24) 316 | 0.89 (6.3, 0.24) 318 | 0.90 (5.0, 0.20) 326 | 0.88 (6.8, 0.26) 336 | 0.86 (6.2, 0.21) 311 |
| D | | | | 1.00 (0.0, 0.00) 355 | 0.80 (5.6, 0.20) 336 | 0.88 (5.8, 0.21) 324 | 0.88 (5.8, 0.22) 329 | 0.86 (4.6, 0.19) 332 | 0.86 (7.0, 0.26) 345 | 0.87 (5.8, 0.19) 313 |
| E | | | | | 1.00 (0.0, 0.00) 357 | 0.90 (5.9, 0.19) 330 | 0.90 (5.8, 0.21) 333 | 0.89 (5.0, 0.19) 340 | 0.87 (6.9, 0.24) 350 | 0.87 (5.4, 0.20) 322 |
| F | | | | | | 1.00 (0.0, 0.00) 349 | 0.94 (3.8, 0.14) 324 | 0.94 (3.5, 0.15) 324 | 0.92 (4.5, 0.17) 339 | 0.92 (5.4, 0.18) 310 |
| G | | | | | | | 1.00 (0.0, 0.00) 398 | 0.94 (4.0, 0.16) 325 | 0.94 (4.3, 0.15) 338 | 0.89 (5.7, 0.20) 308 |
| H | | | | | | | | 1.00 (0.0, 0.00) 349 | 0.93 (4.7, 0.19) 342 | 0.89 (5.0, 0.17) 318 |
| I | | | | | | | | | 1.00 (0.0, 0.00) 1015 | 0.86 (6.9, 0.23) 330 |
| J | | | | | | | | | | 1.00 (0.0, 0.00) 335 |

| Site | K | L | M | N | O | P | Q | R | S |
|---|---|---|---|---|---|---|---|---|---|
| A | 0.77 (8.1, 0.23) 320 | 0.61 (8.3, 0.29) 173 | 0.71 (8.0, 0.23) 324 | 0.68 (7.9, 0.23) 334 | 0.73 (7.0, 0.22) 331 | 0.87 (5.3, 0.18) 326 | 0.81 (7.2, 0.23) 292 | 0.85 (5.6, 0.20) 285 | 0.86 (5.2, 0.18) 306 |
| B | 0.86 (6.6, 0.21) 329 | 0.80 (6.2, 0.23) 175 | 0.87 (5.3, 0.19) 331 | 0.83 (6.0, 0.21) 341 | 0.88 (4.7, 0.18) 336 | 0.86 (5.6, 0.19) 335 | 0.80 (7.9, 0.26) 300 | 0.85 (5.7, 0.21) 288 | 0.85 (6.0, 0.19) 314 |
| C | 0.86 (6.9, 0.21) 321 | 0.89 (4.8, 0.23) 173 | 0.93 (4.4, 0.17) 323 | 0.90 (4.6, 0.19) 335 | 0.93 (3.8, 0.18) 328 | 0.83 (5.9, 0.21) 329 | 0.79 (7.8, 0.26) 290 | 0.81 (6.2, 0.23) 281 | 0.82 (6.0, 0.21) 309 |
| D | 0.88 (6.4, 0.19) 325 | 0.79 (5.7, 0.25) 174 | 0.91 (3.5, 0.16) 329 | 0.85 (4.7, 0.19) 339 | 0.86 (4.2, 0.18) 334 | 0.80 (6.2, 0.20) 342 | 0.75 (7.8, 0.25) 300 | 0.79 (6.2, 0.21) 287 | 0.80 (5.8, 0.20) 321 |
| E | 0.87 (6.3, 0.20) 333 | 0.72 (8.3, 0.27) 179 | 0.83 (5.8, 0.17) 338 | 0.79 (6.3, 0.20) 347 | 0.84 (4.8, 0.18) 343 | 0.91 (4.5, 0.17) 343 | 0.86 (6.3, 0.22) 306 | 0.88 (4.9, 0.18) 295 | 0.91 (3.9, 0.17) 324 |
| F | 0.91 (4.7, 0.17) 323 | 0.78 (9.6, 0.33) 168 | 0.90 (5.3, 0.18) 323 | 0.85 (6.4, 0.20) 334 | 0.85 (7.5, 0.22) 330 | 0.89 (5.2, 0.16) 336 | 0.86 (6.0, 0.16) 295 | 0.88 (4.9, 0.16) 281 | 0.89 (5.5, 0.17) 316 |
| G | 0.90 (5.0, 0.19) 320 | 0.77 (9.0, 0.33) 172 | 0.90 (5.3, 0.19) 326 | 0.85 (6.3, 0.20) 335 | 0.87 (7.0, 0.22) 329 | 0.88 (5.5, 0.17) 383 | 0.86 (5.3, 0.17) 296 | 0.87 (5.2, 0.17) 282 | 0.88 (5.7, 0.19) 356 |
| H | 0.90 (4.4, 0.17) 327 | 0.75 (9.4, 0.30) 175 | 0.88 (4.9, 0.18) 332 | 0.83 (5.6, 0.21) 341 | 0.84 (6.8, 0.21) 336 | 0.89 (4.5, 0.16) 335 | 0.86 (6.0, 0.19) 299 | 0.87 (4.5, 0.16) 289 | 0.88 (5.1, 0.17) 314 |
| I | 0.87 (6.1, 0.20) 341 | 0.75 (10.0, 0.36) 181 | 0.86 (6.7, 0.22) 352 | 0.82 (7.2, 0.23) 356 | 0.83 (8.2, 0.25) 357 | 0.88 (6.1, 0.20) 957 | 0.84 (6.0, 0.16) 314 | 0.85 (6.0, 0.18) 306 | 0.87 (6.3, 0.21) 936 |
| J | 0.95 (3.0, 0.14) 316 | 0.73 (9.2, 0.28) 167 | 0.87 (5.2, 0.18) 314 | 0.84 (5.9, 0.20) 326 | 0.80 (7.5, 0.22) 323 | 0.90 (5.0, 0.17) 321 | 0.86 (5.9, 0.20) 283 | 0.87 (5.3, 0.17) 272 | 0.88 (5.2, 0.18) 302 |
| K | 1.00 (0.0, 0.00) 346 | 0.71 (10.3, 0.31) 170 | 0.88 (6.0, 0.16) 326 | 0.85 (6.5, 0.19) 337 | 0.81 (8.2, 0.22) 332 | 0.89 (5.2, 0.16) 331 | 0.86 (5.8, 0.18) 296 | 0.87 (5.5, 0.16) 286 | 0.88 (5.5, 0.18) 313 |
| L | | 1.00 (0.0, 0.00) 183 | 0.89 (6.7, 0.24) 176 | 0.91 (5.9, 0.23) 181 | 0.90 (4.8, 0.21) 177 | 0.68 (10.0, 0.29) 181 | 0.63 (12.1, 0.35) 153 | 0.72 (9.1, 0.30) 149 | 0.69 (9.8, 0.29) 164 |
| M | | | 1.00 (0.0, 0.00) 361 | 0.94 (3.8, 0.13) 341 | 0.90 (4.6, 0.16) 336 | 0.83 (5.5, 0.16) 345 | 0.81 (7.4, 0.20) 300 | 0.82 (5.8, 0.17) 288 | 0.84 (5.1, 0.16) 326 |
| N | | | | 1.00 (0.0, 0.00) 362 | 0.90 (4.4, 0.17) 346 | 0.77 (6.7, 0.19) 347 | 0.75 (8.1, 0.22) 309 | 0.78 (6.4, 0.20) 297 | 0.78 (6.2, 0.19) 327 |
| O | | | | | 1.00 (0.0, 0.00) 348 | 0.80 (5.8, 0.19) | 0.75 (8.8, 0.25) 304 | 0.79 (6.8, 0.21) 292 | 0.80 (6.0, 0.19) 330 |
| P | | | | | | 1.00 (0.0, 0.00) 1027 | 0.95 (3.6, 0.14) 307 | 0.97 (2.0, 0.09) 299 | 0.97 (2.1, 0.08) 943 |
| Q | | | | | | | 1.00 (0.0, 0.00) 321 | 0.92 (3.1, 0.13) 268 | 0.94 (4.0, 0.16) 290 |
| R | | | | | | | | 1.00 (0.0, 0.00) 313 | 0.94 (2.7, 0.12) 280 |
| S | | | | | | | | | 1.00 (0.0, 0.00) 998 |

**Figure 3-30. PM$_{2.5}$ monitor distribution in comparison with source distribution, Pittsburgh, PA.**
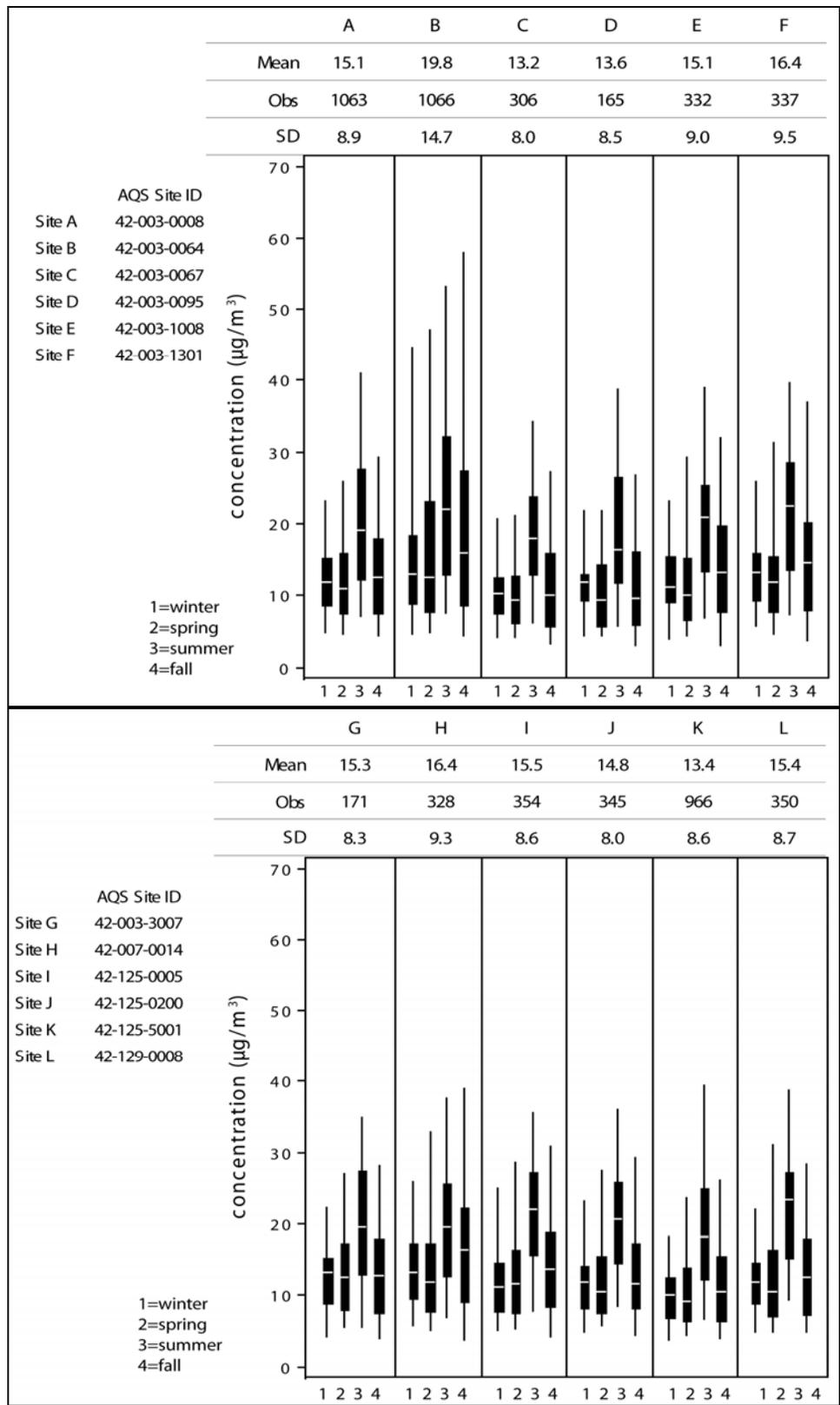
**Figure 3-31. Box plots illustrating the seasonal distribution of 24-h average PM$_{2.5}$ concentrations for Pittsburgh, PA.**

## Table 3-18. Inter-sampler correlation statistics for each pair of PM$_{2.5}$ AQS data for Pittsburgh, PA.

| | A | B | C | D | E | F | G | H | I | J | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 1.00 | 0.79 | 0.95 | 0.92 | 0.93 | 0.95 | 0.95 | 0.85 | 0.90 | 0.93 | 0.91 | 0.88 |
| | (0.0, 0.00) | (15.9, 0.19) | (5.6, 0.13) | (4.7, 0.11) | (4.7, 0.11) | (4.9, 0.10) | (3.8, 0.10) | (6.4, 0.13) | (6.4, 0.13) | (5.0, 0.12) | (6.0, 0.13) | (5.6, 0.12) |
| | 1063 | 1035 | 298 | 164 | 323 | 329 | 170 | 319 | 344 | 337 | 934 | 340 |
| B | | 1.00 | 0.71 | 0.65 | 0.80 | 0.85 | 0.76 | 0.69 | 0.71 | 0.68 | 0.68 | 0.67 |
| | | (0.0, 0.00) | (16.9, 0.24) | (17.4, 0.25) | (14.4, 0.19) | (12.5, 0.14) | (15.7, 0.20) | (17.0, 0.19) | (15.7, 0.21) | (17.8, 0.23) | (19.3, 0.25) | (15.9, 0.21) |
| | | 1066 | 303 | 165 | 329 | 335 | 171 | 324 | 350 | 341 | 938 | 346 |
| C | | | 1.00 | 0.93 | 0.90 | 0.91 | 0.94 | 0.80 | 0.93 | 0.96 | 0.95 | 0.91 |
| | | | (0.0, 0.00) | (2.8, 0.09) | (6.6, 0.16) | (8.7, 0.17) | (6.0, 0.14) | (9.4, 0.19) | (6.7, 0.15) | (4.6, 0.12) | (4.5, 0.10) | (6.5, 0.15) |
| | | | 306 | 144 | 282 | 282 | 148 | 268 | 290 | 286 | 270 | 286 |
| D | | | | 1.00 | 0.84 | 0.87 | 0.91 | 0.79 | 0.89 | 0.91 | 0.97 | 0.85 |
| | | | | (0.0, 0.00) | (6.4, 0.15) | (8.5, 0.16) | (5.8, 0.13) | (9.2, 0.17) | (5.9, 0.13) | (4.6, 0.11) | (3.1, 0.08) | (6.5, 0.15) |
| | | | | 165 | 153 | 161 | 158 | 156 | 158 | 155 | 146 | 157 |
| E | | | | | 1.00 | 0.90 | 0.90 | 0.85 | 0.86 | 0.88 | 0.88 | 0.83 |
| | | | | | (0.0, 0.00) | (6.4, 0.13) | (6.5, 0.13) | (6.8, 0.14) | (8.3, 0.16) | (7.7, 0.16) | (7.6, 0.15) | (7.3, 0.15) |
| | | | | | 332 | 313 | 157 | 295 | 320 | 315 | 290 | 318 |
| F | | | | | | 1.00 | 0.91 | 0.82 | 0.88 | 0.88 | 0.89 | 0.86 |
| | | | | | | (0.0, 0.00) | (6.7, 0.13) | (7.4, 0.14) | (7.1, 0.15) | (7.9, 0.15) | (8.8, 0.17) | (7.0, 0.14) |
| | | | | | | 337 | 167 | 302 | 327 | 319 | 296 | 322 |
| G | | | | | | | 1.00 | 0.78 | 0.94 | 0.93 | 0.90 | 0.91 |
| | | | | | | | (0.0, 0.00) | (7.3, 0.16) | (4.0, 0.10) | (5.0, 0.11) | (6.6, 0.15) | (5.0, 0.13) |
| | | | | | | | 171 | 159 | 163 | 159 | 149 | 161 |
| H | | | | | | | | 1.00 | 0.80 | 0.78 | 0.82 | 0.70 |
| | | | | | | | | (0.0, 0.00) | (8.4, 0.15) | (8.2, 0.17) | (9.0, 0.18) | (9.2, 0.18) |
| | | | | | | | | 328 | 317 | 309 | 288 | 314 |
| I | | | | | | | | | 1.00 | 0.93 | 0.89 | 0.88 |
| | | | | | | | | | (0.0, 0.00) | (5.0, 0.11) | (7.2, 0.16) | (6.0, 0.13) |
| | | | | | | | | | 354 | 334 | 310 | 339 |
| J | | | | | | | | | | 1.00 | 0.93 | 0.88 |
| | | | | | | | | | | (0.0, 0.00) | (5.5, 0.12) | (5.9, 0.13) |
| | | | | | | | | | | 345 | 302 | 331 |
| K | | | | | | | | | | | 1.00 | 0.86 |
| | | | | | | | | | | | (0.0, 0.00) | (6.9, 0.15) |
| | | | | | | | | | | | 966 | 306 |
| L | | | | | | | | | | | | 1.00 |
| | | | | | | | | | | | | (0.0, 0.00) |
| | | | | | | | | | | | | 350 |

KEY
Pearson R
(90th Percentile, COD)
n
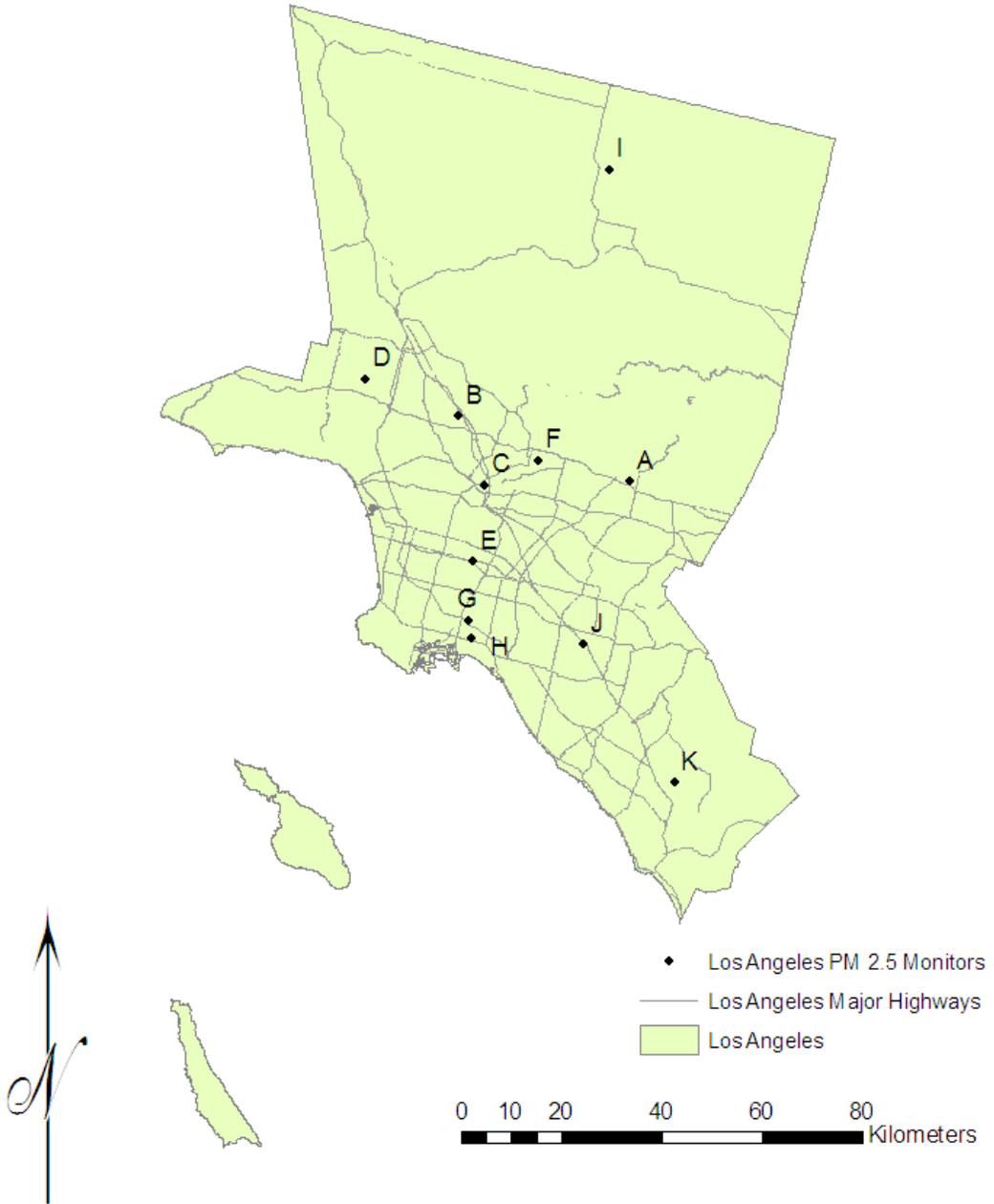
**Figure 3-32.   PM$_{2.5}$ monitor distribution in comparison with source distribution, Los Angeles, CA.**

| | A | B | C | D | E | F | G | H | I | J | K |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 16.1 | 17.0 | 16.7 | 13.3 | 16.7 | 14.3 | 14.7 | 14.2 | 8.2 | 14.4 | 10.9 |
| Obs | 862 | 308 | 1004 | 291 | 327 | 334 | 946 | 990 | 221 | 999 | 318 |
| SD | 10.8 | 10.2 | 9.8 | 7.5 | 9.3 | 8.9 | 8.4 | 7.7 | 3.8 | 8.5 | 6.4 |

| AQS Site ID | |
|---|---|
| Site A | 06-037-0002 |
| Site B | 06-037-1002 |
| Site C | 06-037-1103 |
| Site D | 06-037-1201 |
| Site E | 06-037-1301 |
| Site F | 06-037-2005 |
| Site G | 06-037-4002 |
| Site H | 06-037-4004 |
| Site I | 06-037-9033 |
| Site J | 06-059-0007 |
| Site K | 06-059-2022 |

concentration ($\mu g/m^3$)

1=winter
2=spring
3=summer
4=fall

**Figure 3-33.** Box plot illustrating the seasonal distribution of 24-h average PM$_{2.5}$ concentrations for Los Angeles, CA.

**Table 3-19.** Inter-sampler correlation statistics for each pair of PM$_{2.5}$ AQS data for Los Angeles, CA.

| | A | B | C | D | E | F | G | H | I | J | K |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 1.00 (0.0, 0.00) 862 | 0.86 (9.0, 0.18) 252 | 0.87 (7.7, 0.16) 803 | 0.81 (9.0, 0.19) 238 | 0.80 (9.7, 0.21) 262 | 0.88 (5.8, 0.14) 269 | 0.68 (11.5, 0.22) 761 | 0.64 (12.4, 0.23) 793 | 0.30 (18.0, 0.36) 179 | 0.70 (10.5, 0.21) 804 | 0.82 (11.4, 0.23) 259 |
| B | | 1.00 (0.0, 0.00) 308 | 0.92 (5.5, 0.11) 293 | 0.87 (9.1, 0.19) 250 | 0.83 (9.0, 0.15) 278 | 0.88 (7.6, 0.15) 279 | 0.77 (9.8, 0.17) 268 | 0.73 (11.6, 0.18) 282 | 0.31 (24.1, 0.38) 177 | 0.74 (11.9, 0.19) 292 | 0.71 (15.0, 0.27) 277 |
| C | | | 1.00 (0.0, 0.00) 1004 | 0.80 (9.6, 0.20) 274 | 0.89 (5.8, 0.11) 315 | 0.92 (6.4, 0.13) 319 | 0.84 (9.0, 0.15) 880 | 0.79 (10.0, 0.17) 913 | 0.29 (18.6, 0.38) 213 | 0.82 (9.4, 0.16) 920 | 0.78 (13.2, 0.25) 305 |
| D | | | | 1.00 (0.0, 0.00) 291 | 0.69 (10.9, 0.23) 263 | 0.77 (7.4, 0.18) 263 | 0.63 (11.3, 0.22) 256 | 0.60 (11.1, 0.22) 268 | 0.41 (14.8, 0.31) 164 | 0.64 (9.6, 0.21) 274 | 0.60 (11.6, 0.23) 261 |
| E | | | | | 1.00 (0.0, 0.00) 327 | 0.79 (9.1, 0.19) 301 | 0.95 (5.9, 0.11) 289 | 0.92 (7.6, 0.13) 301 | 0.34 (19.7, 0.39) 192 | 0.88 (8.2, 0.15) 307 | 0.76 (13.7, 0.27) 291 |
| F | | | | | | 1.00 (0.0, 0.00) 334 | 0.70 (10.5, 0.18) 290 | 0.70 (9.2, 0.19) 302 | 0.33 (14.8, 0.34) 184 | 0.69 (9.8, 0.19) 311 | 0.72 (9.9, 0.21) 293 |
| G | | | | | | | 1.00 (0.0, 0.00) 946 | 0.96 (4.0, 0.09) 859 | 0.23 (17.0, 0.35) 194 | 0.92 (5.4, 0.12) 882 | 0.78 (11.0, 0.21) 277 |
| H | | | | | | | | 1.00 (0.0, 0.00) 990 | 0.26 (15.3, 0.34) 208 | 0.91 (5.9, 0.12) 914 | 0.78 (9.5, 0.21) 294 |
| I | | | | | | | | | 1.00 (0.0, 0.00) 221 | 0.21 (18.3, 0.35) 205 | 0.31 (9.7, 0.28) 180 |
| J | | | | | | | | | | 1.00 (0.0, 0.00) 999 | 0.84 (9.8, 0.19) 298 |
| K | | | | | | | | | | | 1.00 (0.0, 0.00) 318 |

*PM$_{2.5}$*

1    PM$_{2.5}$ has a longer residence time in the atmosphere resulting from a slower settling velocity

2    compared to PM$_{10}$. As a result, increased spatial homogeneity is expected with less localized influence

3    from point sources. Maps of PM$_{2.5}$ monitor locations and box plots of seasonal PM$_{2.5}$ mass concentration

4    data are provided for Boston (Figures 3-28 and 3-29), Pittsburgh (Figures 3-30 and 3-31), and Los

5    Angeles (Figures 3-32 and 3-33) for direct comparison with the PM$_{10}$ maps and box plots provided in

6    Figures 3-19 through 3-24. Annex A shows the PM$_{2.5}$ monitor locations and box plots of seasonal PM$_{2.5}$

7    mass concentration for all 15 CSAs/CBSAs. With very few exceptions, the PM$_{2.5}$ is quite uniformly

8    distributed across the monitors. Boston, Los Angeles, New York and Phoenix all have one monitor that is

9    recording visually less PM$_{2.5}$ than the rest of the monitors within the respective CSAs/CBSAs; Riverside

10   has two such monitors. Unlike PM$_{10}$, PM$_{2.5}$ varies approximately the same magnitude between monitors

11   as it does between seasons for the 15 selected cities.

12       Figures 3-34 through 3-36 show the relationship between inter-sampler correlation and distance for

13   PM$_{2.5}$ measurements obtained in Boston, Pittsburgh, and Los Angeles to illustrate how this relationship

14   varies across urban areas with different topography, climatology, and sources in a way similar to that for

15   PM$_{10}$ as shown in Figures 3-25 through 3-27. Plots are provided for the fifteen CSAs/CBSAs

16   characterized here in Annex A. In each plot, substantially less scatter is observed in these plots when

17   compared with those for PM$_{10}$. This is consistent with the seasonal box plots of concentration shown in

18   Figures 3-29, 3-31, and 3-33. The Boston data exhibit the strongest relationship between inter-sampler

19   correlation and distance, with average inter-sampler correlation remaining higher than 80% when

20   samplers are 95 km apart ($R^2 = 0.55$). This small amount of variability is sensible given the consistency

21   between distributions shown in the box plots. The Pittsburgh data show some reductions in inter-sampler

22   correlations at short distances, with the samplers at Sites B (Liberty, PA, described above for PM$_{10}$) and G

23   (in the neighboring town of Clairton, PA located at a lower elevation on the bank of the opposite side of

24   the Monongahela River from Liberty) having only 76% correlation with a distance of less than 4 km. On

25   average, inter-sampler correlation remained higher than 80% when samplers were separated by 61 km,

26   but in this case with much greater scatter ($R^2 = 0.22$) than observed in the Boston data. This scatter is

27   driven by the measurements at Site B; Figure 3-31 shows an elevated mean and variability compared with

28   other monitors situated around the Pittsburgh CSA. When data from Site B are removed, the inter-sampler

29   correlation vs. distance plot for Pittsburgh PM$_{2.5}$ resembles the one from Boston (with $R^2$ increasing to

30   0.68). The Los Angeles data exhibit a much steeper slope, with average inter-sampler correlation

31   remaining higher than 80% when samplers are 29 km apart ($R^2 = 0.74$). This distance is similar to that for

1    the $PM_{10}$ data, which suggests that other factors, such as mountainous topography separating monitors,

2    the distribution of traffic and suspension of crustal components, and occurrence of stable boundary layers,

3    may cause more spatial variation in the PM concentration profile within the Los Angeles region when

4    compared with other parts of the country. The Site I monitor at Lancaster CA, separated from the rest of

5    the Los Angeles region by the San Gabriel Mountains, again provides the low correlations concentrated in

6    the lower right portion of Figure 3-36. Tables 3-17 through 3-18 contain the pair-wise statistics (R, PSO,

7    COD and N) for $PM_{2.5}$ in Boston, Pittsburgh, and Los Angeles, respectively. Annex A contains the

8    complete list of pair-wise statistics for $PM_{2.5}$ measured within the fifteen CSAs/CBSAs.
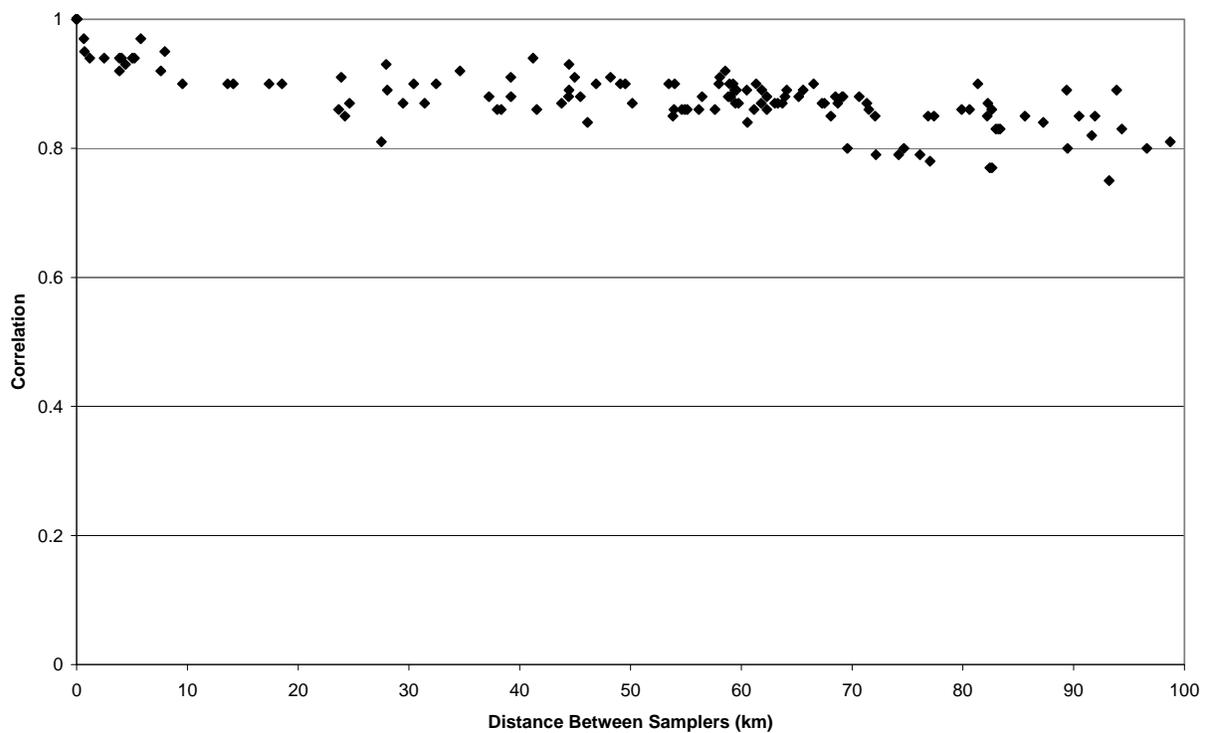


**Figure 3-34.  $PM_{2.5}$ inter-sampler correlations as a function of distance between monitors for Boston.**
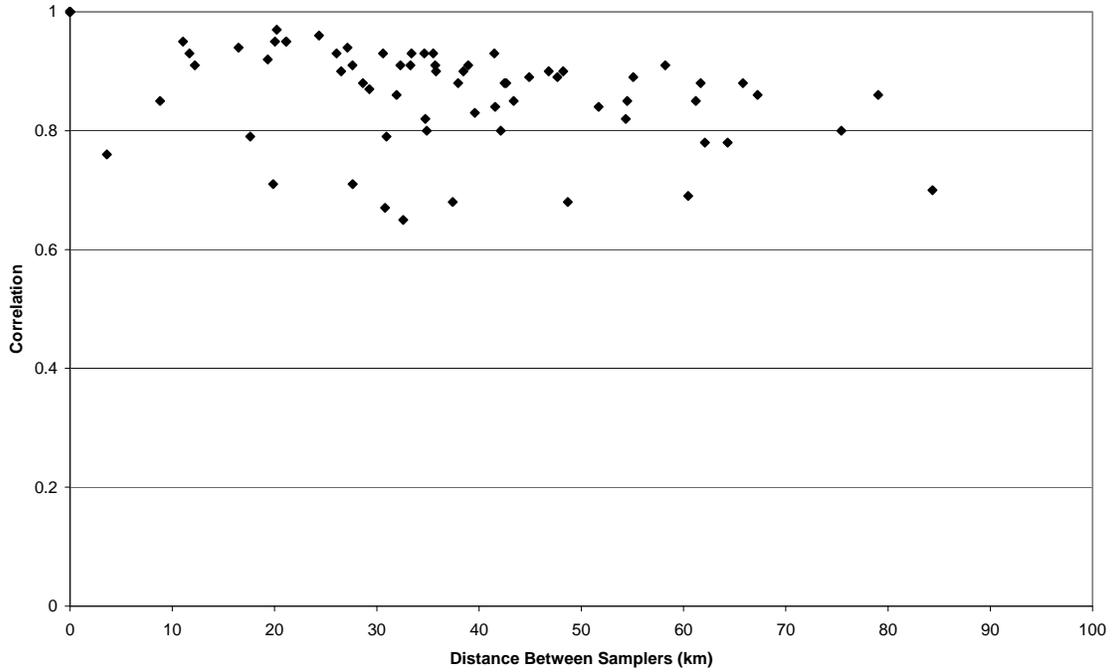
**Figure 3-35. PM$_{2.5}$ inter-sampler correlations as a function of distance between monitors for Pittsburgh.**
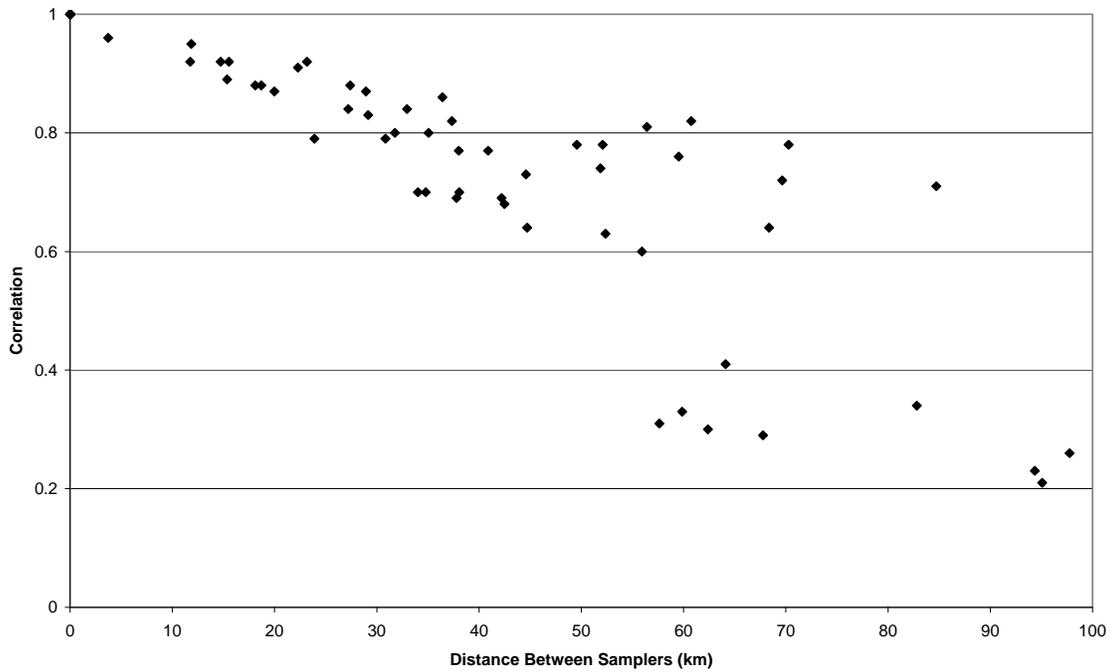


**Figure 3-36. PM$_{2.5}$ inter-sampler correlations as a function of distance between monitors for Los Angeles.**

**PM$_{10-2.5}$**

1    Given the limited number of co-located FRM PM$_{10}$ and FRM PM$_{2.5}$ monitors, only a very limited

2    investigation into the intra-urban spatial variability of PM$_{10-2.5}$ was possible. Of the 15 cities under

3    investigation, only six (Atlanta, Boston, Chicago, Denver, New York and Phoenix) contained co-located

4    FRM monitors adequate for generating PM$_{10-2.5}$. Of these six cities, only Boston and New York had more

5    than one qualifying location within the CSA to allow for calculation of comparison statistics similar to

6    those above for PM$_{10}$ and PM$_{2.5}$. Figure 3-37 contains box plots for all six CSAs/CBSAs and Annex A

7    contains the correlation tables for Boston and New York (two sites each). For Boston, the correlation

8    between the two sites for PM$_{10-2.5}$ was 0.45 compared with 0.84 for PM$_{10}$ alone and 0.73 for PM$_{2.5}$ alone

9    (using the same two monitoring sites). For New York, the correlation was slightly higher for the two sites:

10   0.74 for PM$_{10-2.5}$ compared with 0.82 for PM$_{10}$ alone and 0.93 for PM$_{2.5}$ alone. The COD for PM$_{10-2.5}$ also

11   increases in both cities compared with PM$_{10}$ and PM$_{2.5}$ alone, suggesting less spatial homogeneity. Some

12   of the disparity, however, could also be coming from the 2-monitor subtraction method used in calculating

13   PM$_{10-2.5}$.
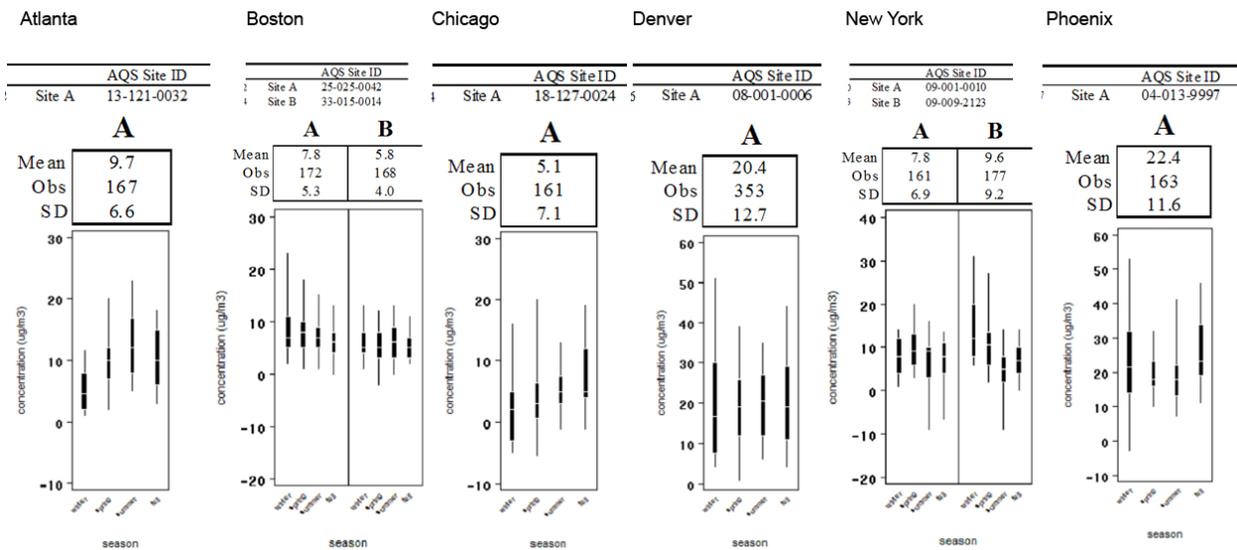


**Figure 3-37.   PM$_{10-2.5}$ generated from all available co-located FRM PM$_{10}$ and PM$_{2.5}$ monitors in Atlanta, Boston, Chicago, Denver, New York and Phoenix, 2005-2007.  Box plots show the median and interquartile range with whiskers extending to the 5th and 95th percentiles at each site during (1) winter (December-February), (2) spring (March-May), (3) summer (June-August) and (4) fall (September-November).**

### PM Constituents

1     The pie charts showing PM composition that were generated using the SANDWICH method for
2  the fifteen CSAs/CBSAs presented earlier in Figures 3-14 through 3-18 represent a spatial average across
3  each area. Similar pie charts for each individual monitor within the fifteen CSAs/CBSAs are contained in
4  Annex A. In general, these charts reveal spatial homogeneity in $PM_{2.5}$ bulk chemistry within each
5  metropolitan area. Some notable exceptions do exist, however. Birmingham and Detroit show variation in
6  the amount of crustal material, both spatially and seasonally. The Denver map reveals some spatial
7  variation in $NO_3^-$ during the winter, the season with the highest measured $PM_{2.5}$ mass. Several sites in the
8  New York and one in Pittsburgh have elevated percentages of EC relative to the other sites within the
9  respective cities. The excess EC at the Pittsburgh site is associated with higher $PM_{2.5}$ mass measured at
10  that site relative to others. In Phoenix, high winter $PM_{2.5}$ mass is site specific and appears to be associated
11  with high organic carbon; the crustal component also varies and is inversely proportional to total
12  measured mass.

### Ultrafine Particles

13     Only a handful of studies have performed direct comparisons of ultrafine measurements at multiple
14  locations within an urban center. An early study by Buzorius et al. (1999) suggested spatial homogeneity
15  in total particle number concentrations between multiple locations in Helsinki, Finland. They found
16  correlations in 10 min averages at three sites within the city as high as 0.84. The sites, however, were
17  relatively close together (2 km) and all near the same roadway. There was a high degree of correlation
18  between traffic intensity and total aerosol number concentrations, suggesting that traffic was the primary
19  source of the measured particles and the driving force behind the high correlations. Weekend correlations
20  (0.28-0.47) and correlations with a fourth monitor located 22 km outside the city (0.05-0.64) were much
21  lower.
22     Tuch et al. (2006) found more spatial heterogeneity in ultrafine particle concentrations measured
23  for an entire year at two locations 1.5 km apart in Leipzig, Germany. Figure 3-38 shows the correlation as
24  a function of particle size (mobility diameter) dropping off as the particle size decreases. Particles less
25  than 100 nm show correlations dropping from 0.5 down to 0.2. Annex A contains correlation coefficients
26  of hourly and daily average particle number, surface area and volume concentrations as a function of
27  particle diameter adapted from the Tuch et al. (2006) study. For all days (N = 5481 hourly observations),
28  the correlation between ultrafine particles (10-100 nm) measured at the two sites was 0.31.
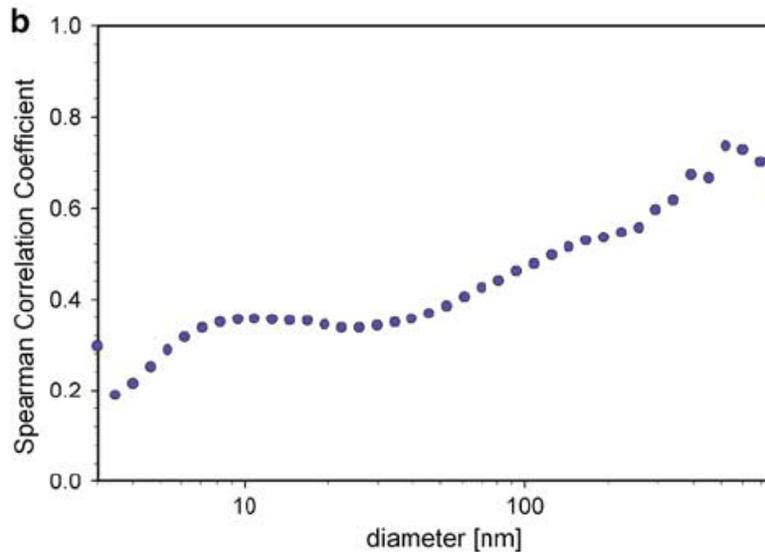
**Figure 3-38.  Bin-wise Spearman correlation coefficients in aerosol particle number concentrations between the lft (urban background) and the Eisenbahn-strasse (city/urban center) sites in Leipzig, Germany.**

1       The two sites represented in Figure 3-38 and Annex A were relatively close in proximity, but one

2     was located in a mixed semi-industrial region while the other was in a street canyon in a residential

3     neighborhood near busy roadways. This suggests a high degree of spatial heterogeneity in ultrafine

4     particles driven primarily by differences in traffic and industrial sources. Sioutas et al. (2005) reviewed

5     ultrafine studies and came to the similar conclusion that ultrafine particles are coming mostly from mobile

6     sources and therefore can exhibit substantial variability in space and time. This is to be expected since

7     ultrafine particle concentrations drop off much quicker with distance from roadways than larger particle

8     sizes (Levy et al., 2003; Reponen et al., 2003; Zhu et al., 2005 ). This is discussed further in the next

9     section.

## 3.5.1.3. Neighborhood-Scale Variability

10       Neighborhood density is an important determinant of the spatial distribution of PM concentration

11    because density impacts source prevalence, source magnitude, topographical-driven ventilation, and heat

12    island effect (e.g., Crist et al., 2008; Makar et al., 2006; Mfula et al., 2005; Rigby and Toumi, 2008).

13    These considerations are crucial to understanding variability in community monitoring data and for

14    monitor deployment planning. A number of computational and wind tunnel modeling street canyon

15    studies have demonstrated the potential variability in concentration within a canyon (e.g., Borrego et al.,

16    2006; Chang and Meroney, 2003; Kastner-Klein and Plate, 1999; So et al., 2005; Xiaomin et al., 2006).

1 Influential parameters include canyon height to width ratio (H/W), source positioning, wind speed and
2 direction, building shape and upstream configuration of buildings. Figure 3-39 shows concentrations
3 obtained from wind tunnel and computational fluid dynamics simulations of transport and dispersion in
4 an infinitely long street canyon with a line source centered at the bottom of the canyon (Xiaomin et al.,
5 2006). When the canyon height was equal to the street width (typical of moderate density suburban or
6 urban fringe residential neighborhoods) and lower background wind speed existed, concentrations on the
7 leeward canyon wall were four times those of the windward wall near ground level. When the canyon
8 height was twice the street width (typical of higher-density urban planning) and background winds were
9 somewhat higher, near ground-level concentrations on the windward canyon wall were roughly three
10 times higher than those measured at the leeward wall. These results suggest that micro- and
11 neighborhood-scale variation related to urban topography may have a significant impact on airborne PM
12 exposures.
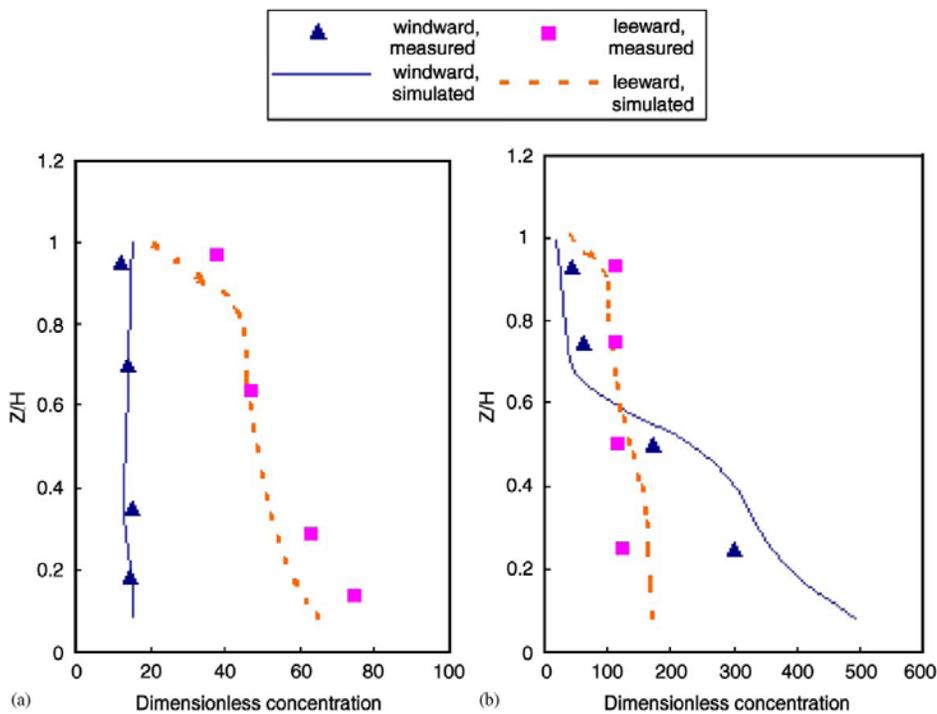


Source: Xiaomin et al. (2006)

**Figure 3-39.  Dimensionless concentration as a function of height at windward and leeward locations and street canyon aspect ratios (H/W).  (a) Dimensionless concentration on the windward and leeward sides of the canyon when H/W = 1 and wind speed = 3 m/s. (b) Dimensionless concentration on the windward and leeward sides of the canyon when H/W = 2 and wind speed = 5 m/s. Computational fluid dynamics modeling was performed, and measurements were obtained in wind tunnel simulations.**

1    The particle concentration profile is affected by land and building topography, meteorology,

2    particle size distribution, particle composition, and particle volatility. For instance, Viana et al. (2008)

3    observed higher concentrations of crustal elements in $PM_{10}$ and $PM_{2.5}$ samples in rural neighborhoods and

4    higher concentrations of combustion-derived $PM_{10}$ and $PM_{2.5}$, such as EC and $NO_3^-$, in higher density

5    urban areas. Gutiérrez-Dabán et al. (2005) examined the mass distribution of various PAHs under

6    different traffic and urban density conditions. Figure 3-40 displays the distributions for benz[a]pyrene

7    (BaP) at high and low traffic sites at the urban center, periphery, and industrial areas found in

8    Gutiérrez-Dabán et al. (2005). It can be seen that concentrations were nearly an order of magnitude lower

9    for the low traffic urban periphery location when compared with the high traffic or industrial locations.

10   Particles smaller than ~ 600 nm had roughly an order of magnitude higher concentration than those at

11   larger sizes and tended to have a larger spread in concentrations among sampling sites. Figure 3-41 shows

12   the distributions for sixteen PAHs at a high traffic location at the city center from Gutiérrez-Dabán et al.

13   (2005). PAH species varied in concentration by up to two orders of magnitude for each particle size bin,

14   and the highest concentrations of individual PAHs were generally found for particles smaller than ~ 600

15   nm.
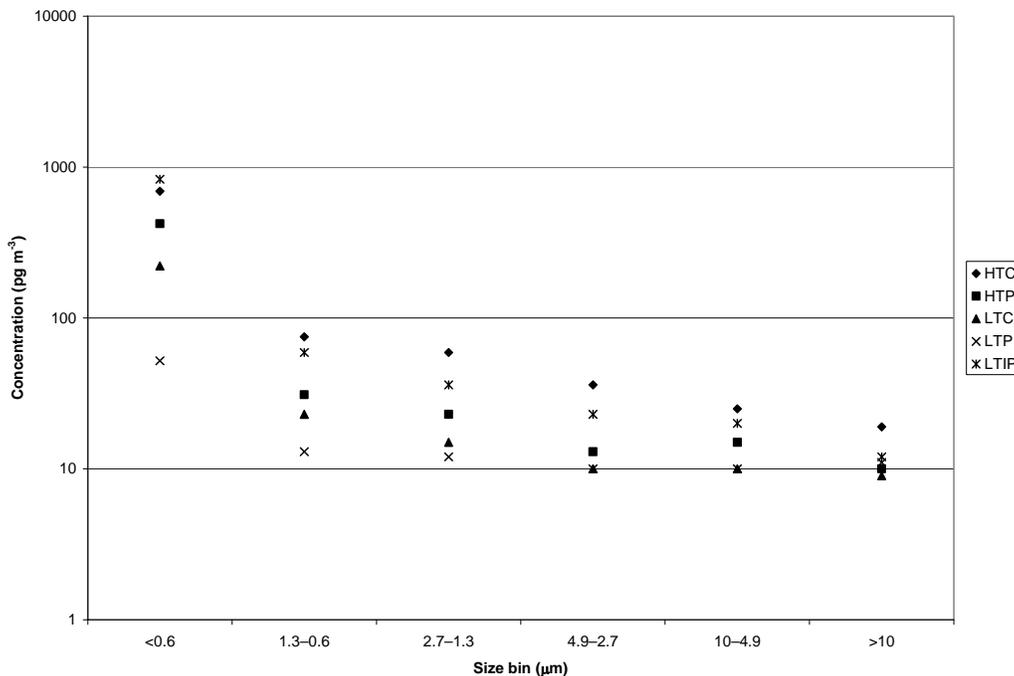


Source: Gutiérrez-Dabán et al. (2005).

**Figure 3-40.   Mass distributions for BaP at a high traffic urban center (HTC), high traffic urban periphery (HTP), low traffic urban center (LTC), low traffic urban periphery (LTP), and low traffic industrial urban periphery (LTIP) in Seville, Spain.**
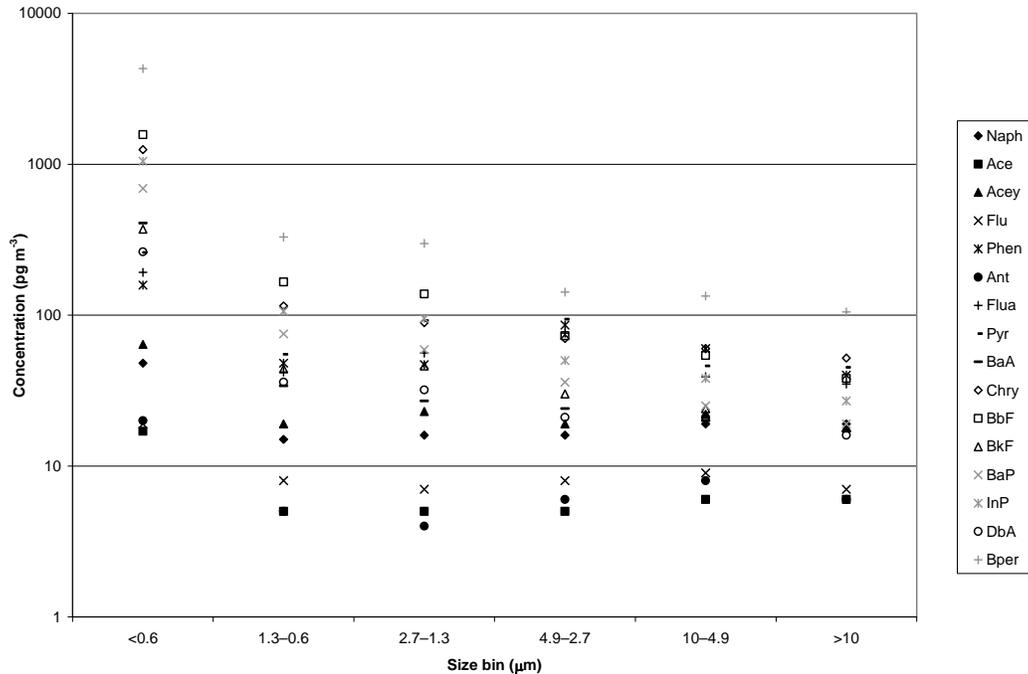
Source: Gutiérrez-Dabán et al. (2005).

**Figure 3-41. Mass distributions for sixteen PAHs at a high traffic city center in Seville, Spain.**

1      Near roadway environments can exhibit particularly high concentration gradients. After initial

2      emission from a motor vehicle, the evolution of the PM distribution within the plume is a function of:

3      (1) the turbulence that dilutes the plume; and (2) evaporation or condensation of the volatile portion of the

4      aerosol. Figure 3-42 shows the size distribution measured by Zhu et al. (2002b) at distances of 17-300 m

5      away from the roadway (in this case, highway 710 in Los Angeles) and at an upwind site. It can be seen

6      that a mode originally measured around 9 nm increases in diameter and decreases in magnitude as

7      distance from the highway increases. Smaller secondary modes appear around 30 m from the roadway

8      with multiple modes at some particle sizes. By 150 m away from the highway, the size distribution

9      flattens with a small mode around 50 nm. It is clear from the figure that the fine particle sizes are better

10     represented by one sampler than ultrafine particles because the fine PM mass concentration is fairly

11     constant with distance up to at least 300 m. Zhou and Levy (2007) performed a meta-analysis of

12     traffic-related air pollution literature and found that levels of background pollution and meteorology can

13     have important impacts on the size of the elevated concentration region around the highway. Zhu et al.

14     (2002b) noted that small particles can be lost due to evaporation or to coagulation during Brownian

15     diffusion to form bigger particles. Zhang et al. (2005a) also saw this upward shift in mode diameter with

16     distance from the roadway in field measurements of ultrafine PM. The count distribution in the upper

17     ultrafine and fine PM ranges does not change drastically because the agglomeration process results in loss

1    of particle number. Studies of particle sizes on roads (Kittelson et al., 2006b), in tunnels (Venkataraman et

2    al., 1994), and upwind and downwind of roads (Wilson and Suh, 1997; Zhu et al., 2002b) suggest that for

3    well-maintained spark-ignition vehicles most, and perhaps all, of the mass of particles emitted from the

4    vehicles are in the nuclei mode (i.e., smaller than accumulation mode). Traffic may also generate some

5    coarse mode particles (Wilson and Suh, 1997), presumably from material resuspended from the road. In

6    situations in which the dilution rates are lower than in a short tunnel or downwind of a road way,

7    condensation of condensable vapors can give rise to particles in the accumulation mode (Kittelson, 1998;

8    Wilson and Suh, 1997). Diesel engines, in particular, emit elemental (black) carbon in the lower end of

9    the accumulation mode, with number emissions dominated by semi-volatile material in the nuclei mode

10   (Kittelson, 1998; 2006a; 2006b). Sharp gradients in black carbon mass have been observed along

11   roadways with high diesel traffic (Zhu et al., 2002a). As the traffic pollution moves downwind, the

12   ultrafine particles may grow into the accumulation mode by coagulation or condensation. In addition to

13   Gaussian dispersion and wind eddies caused by the presence of natural and anthropogenic barriers,

14   Sahlodin et al. (2007) demonstrated that turbulence produced by vehicles can result in modification of the

15   plume emanating from the highway. Hence, on-road turbulence could potentially alter the aerosol size

16   distribution. This added turbulence could cause some evaporation of tiny nucleation particles that have

17   not absorbed or adsorbed onto soot nuclei.

18         Such knowledge of neighborhood-scale variability is important for interpreting data from $PM_{10}$ and

19   $PM_{2.5}$ community monitors. Figure 3-43 shows data derived from the fifteen CSAs/CBSAs for $PM_{10}$ and

20   $PM_{2.5}$ discussed in Section 3.5.1.2. This figure contains the inter-sampler correlations obtained for

21   sampler pairs located within a distance of 4 km (i.e. neighborhood scale). $PM_{2.5}$ data appear to have a

22   flatter slope, with average correlation maintained at 93% within 4 km ($R^2 = 0.22$). There is more scatter

23   and variability among the $PM_{10}$ data, with an average correlation of 70% within 4 km ($R^2 = 0.03$). The

24   level of variability in $PM_{10}$ compared with $PM_{2.5}$ relates to transport and dispersion of the $PM_{10-2.5}$

25   component of $PM_{10}$ compared with $PM_{2.5}$. However, differences in composition, source location,

26   topography, and monitor height—all of which could affect concentrations—could drive the relatively high

27   level of scatter for both size classes, considering the low computed $R^2$ values for each of these curves.
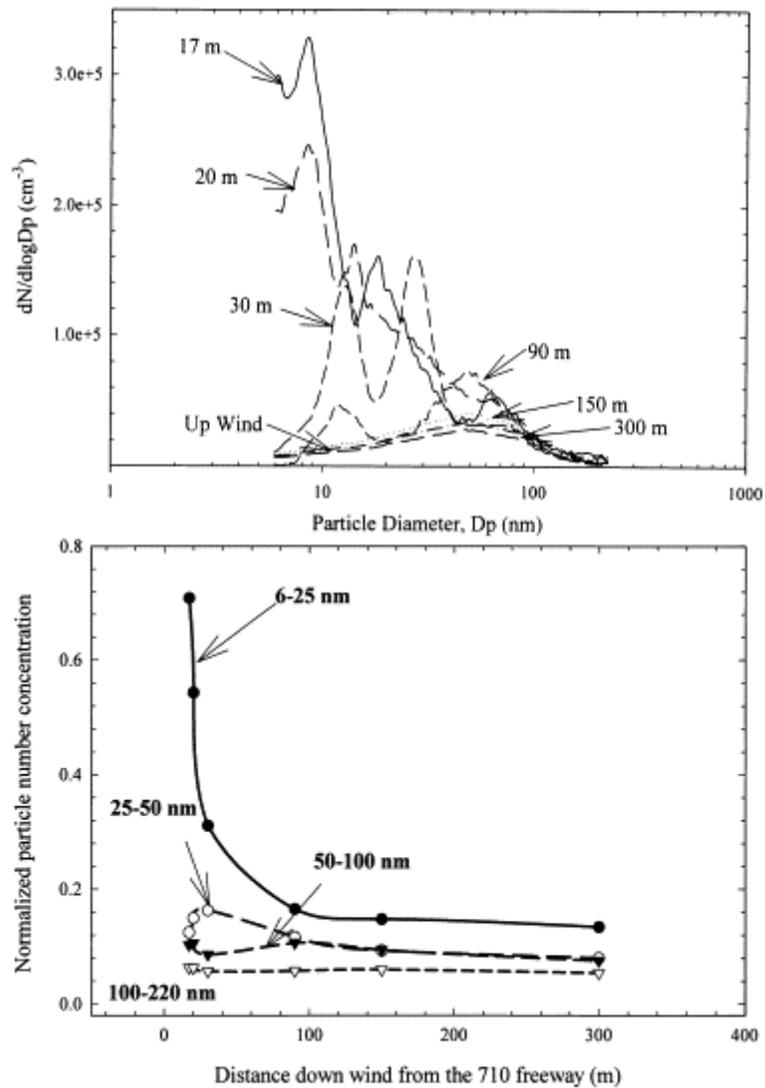
**Figure 3-42.   Figure to be replaced. Particle size distributions measured at various distances from the 710 freeway in Los Angeles (top), and particle number concentration as a function of distance from the 710 freeway (bottom).**
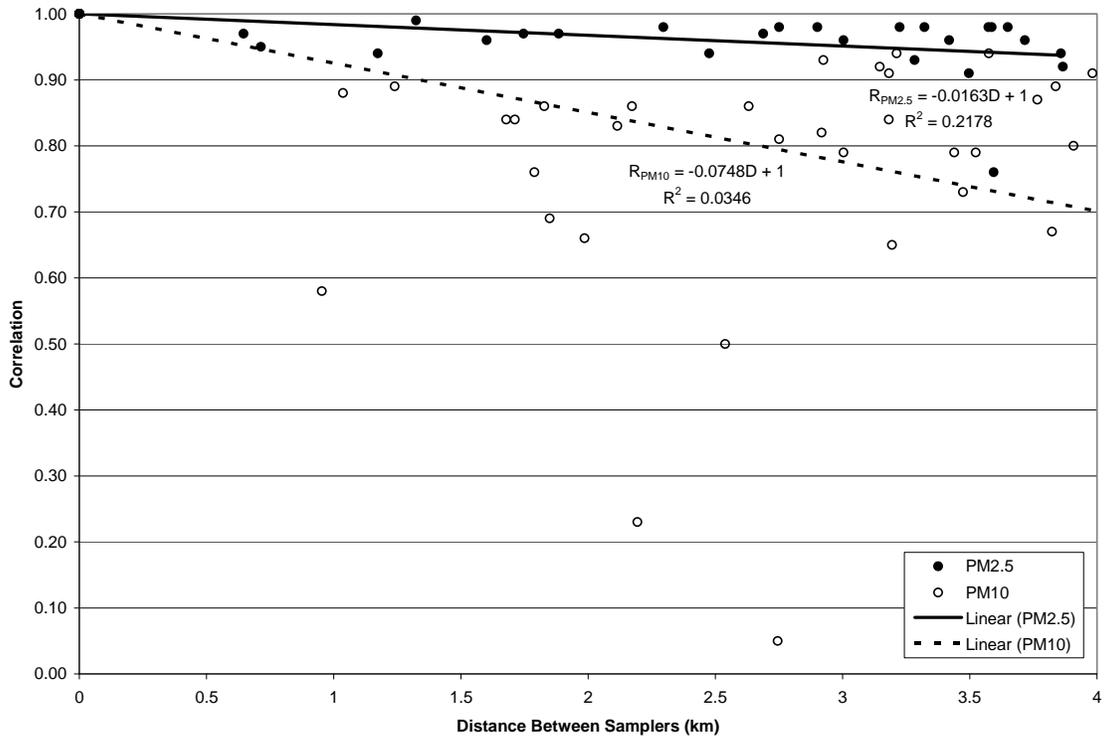
**Figure 3-43. Inter-sampler correlations as a function of distance between monitors for samplers located within 4 km (neighborhood scale) for $PM_{2.5}$ and $PM_{10}$.**

# 3.5.2. Temporal Variability

1    Temporal variability is another important factor in characterizing PM. This section addresses

2  trends, and seasonal and hourly variability. Trends in $PM_{10}$ and $PM_{2.5}$ are addressed in Section 3.5.2.1

3  based on AQS data. Seasonality is coupled with spatial variability and has been discussed in the regional

4  context above. Section 3.5.2.2 below briefly investigates the seasonality on a finer time scale, thereby

5  addressing issues relating to the seasonal definitions used earlier. Section 3.5.2.3 addresses hourly

6  patterns, an issue particularly important to understanding the behavior of PM concentrations in reference

7  to sources, human activity patterns and exposure. Hourly patterns are investigated using AQS data on a

8  national basis for $PM_{10}$ and $PM_{2.5}$. Data for ultrafine particles are presented where available.

## 3.5.2.1. Trends

### $PM_{10}$

9    Figure 3-44 shows the 20-year trend in U.S. ambient 24-h $PM_{10}$ concentrations from 1988 to 2007

10  along with the number of monitoring sites above the NAAQS. In 2007, the U.S. national average second

1     highest $PM_{10}$ concentration was 37 percent lower than in 1988 (see Figure 3-44a). Of 281 sites used in

2     this trend analysis, the number reporting concentrations above the level of the 24-h $PM_{10}$ NAAQS

3     (150 $\mu g/m^3$) fell from 23 in 1988 to 5 in 2007 with a max of 29 in 1989 (see Figure 3-44b). Figure 3-45

4     shows trends in the second highest 24-h $PM_{10}$ concentrations broken down by U.S. EPA region; all

5     regions saw an overall decrease from 1988 to 2007. Largest decreases occurred in EPA Region 10, which

6     incorporates Washington, Oregon, Idaho and Alaska. Most of the decrease occurred between 1988 and

7     1995.
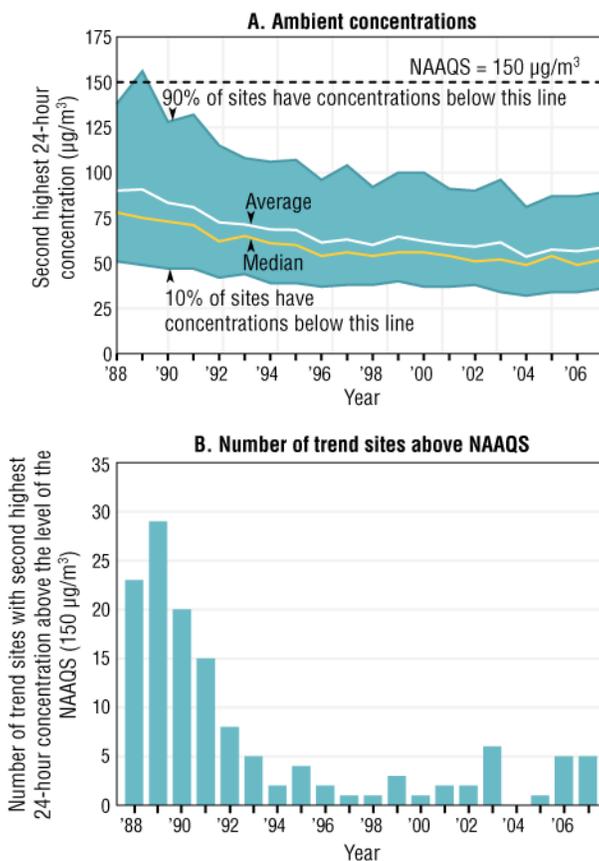


Source: U.S. EPA (2008a).

**Figure 3-44.  Ambient 24-h $PM_{10}$ concentrations in the U.S., 1988-2007, showing (A) ambient concentrations and (B) number of trends sites above the NAAQS.**
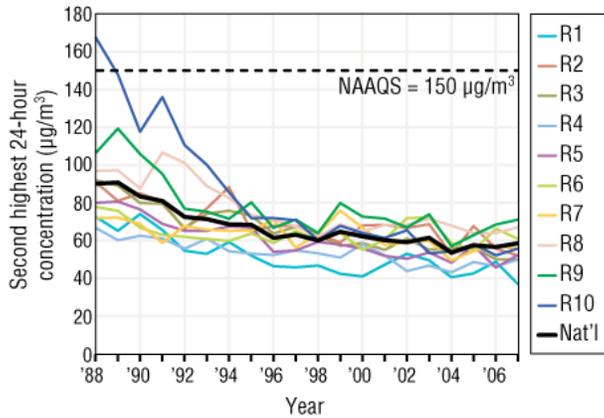
**Figure 3-45.   Ambient 24-h PM$_{10}$ concentrations in the contiguous U.S. by EPA region, 1988-2007.**

### PM$_{2.5}$

1    Figure 3-46 shows the trend in U.S. ambient 24-h PM$_{2.5}$ concentrations from 1999 to 2007 along

2    with the number of monitoring sites above the 24-h NAAQS. In the period 2005-2007, the three-year

3    average of the 98th percentile of 24-h PM$_{2.5}$ concentrations fell 10 percent from the 1999-2001 period

4    (see Figure 3-46a). The number of sites reporting values greater than the 24-h NAAQS declined 40

5    percent (see Figure 3-46b). Figure 3-47 illustrates the downward trend in the 98th percentile of 24-h PM$_{2.5}$

6    concentrations for three consecutive calendar years in all U.S. EPA regions. This trend is most

7    pronounced in Region 9 incorporating Arizona, California and Nevada where this value dropped 25%

8    from the 1999-2001 period to the 2005-2007 period.

**A. Ambient concentrations**

90% of sites have concentrations below this line

NAAQS = 35 µg/m³

Median

Average

10% of sites have concentrations below this line

98th percentile of 24-hour concentrations for three consecutive calendar years (µg/m³)

Averaging period

**B. Number of trend sites above NAAQS**

Number of trend sites with 98th percentile of 24-hour concentrations for three consecutive calendar years above the level of the NAAQS (35 µg/m³)

Averaging period

[a]**Coverage:** 718 monitoring sites in 489 counties nationwide (out of a total of 831 sites measuring $PM_{2.5}$ in 2007) that have sufficient data to assess $PM_{2.5}$ trends since 1999.

**Figure 3-46.   Ambient 24-h $PM_{2.5}$ concentrations in the U.S., 1999-2007, showing (A) ambient concentrations and (B) number of trends sites above the NAAQS.**

**Figure 3-47.  Ambient 24-h PM$_{2.5}$ concentrations in the contiguous U.S. by EPA region, 1999-2007.**

1    Figure 3-48 contains similar trend information for the annual PM$_{2.5}$ NAAQS. The seasonally

2    weighted 3-y average PM$_{2.5}$ concentrations for the years 2005 to 2007 were at the lowest since national

3    monitoring began in 1999 (see Figure 3-48a). The seasonally weighted 3-y average fell ten percent

4    between the 1999-2001 averaging period and the 2005-2007 averaging period. The number of sites

5    reporting concentrations above the annual average PM$_{2.5}$ NAAQS fell 56 percent over these same periods

6    (see Figure 3-48b). Figure 3-49 illustrates the annual trends in PM$_{2.5}$ by U.S. EPA region. Declines were

7    the greatest in Region 9 again where PM$_{2.5}$ concentrations fell 20 percent from the 1999-2001 averaging

8    period to the 2005-2007 averaging period.

**A. Ambient concentrations**

90% of sites have concentrations below this line

NAAQS = 15 µg/m³

Median

Average

10% of sites have concentrations below this line

Seasonally weighted annual average concentration for three consecutive calendar years (µg/m³)

Averaging period

**B. Number of trend sites above NAAQS**

Number of trend sites with seasonally weighted annual average concentration for three consecutive calendar years above the level of the NAAQS (15 µg/m³)

Averaging period

[a]**Coverage:** 718 monitoring sites in 489 counties nationwide (out of a total of 802 sites measuring $PM_{2.5}$ in 2007) that have sufficient data to assess $PM_{2.5}$ trends since 1999.

Source: U.S. EPA (2008a).

**Figure 3-48. Ambient annual $PM_{2.5}$ concentrations in the U.S., 1999-2007, showing (A) ambient concentrations and (B) number of trends sites above the NAAQS.**

Source: U.S. EPA (2008a).

**Figure 3-49.  Ambient annual PM$_{2.5}$ concentrations in the contiguous U.S. by EPA region, 1999-2007.**

1    Several monitoring sites were excluded from the above trend analyses to provide a consistent basis

2    for comparison over the years of monitoring. This included exclusion of sites when there was no

3    corresponding site in later or earlier years.

## 3.5.2.2. Seasonal Variations

4    Many of the figures and tables presented in the preceding sections have included a seasonal

5    break-down based on the following climatological seasons: winter (December-February), spring

6    (March-May), summer (June-August) and fall (September-November). Annex A contains plots of PM$_{2.5}$

7    composition by individual month, illuminating intra-annual variability on a finer time scale. The same 15

8    CSAs/CBSAs are investigated and included in these plots; they are generated from the same data used in

9    the seasonal and annual pie charts based on the SANDWICH method shown earlier in Figures 3-14

10   through 3-18.

11   Monthly plots for most of the areas reveal heterogeneity in PM composition within the 3-month

12   long seasonal bins defined earlier. This is especially true in the spring and fall when concentrations are

13   changing rapidly with time. Many cities exhibit very rapid fluctuation in PM$_{2.5}$ composition on short

14   timescales. For example, the NO$_3^-$ mass in Los Angeles and Riverside can vary from a small fraction to

15   the most prevalent fraction of PM$_{2.5}$ mass in a month's time based on the 3-y aggregate data in Annex A.

1  Therefore, selecting a different delineation point for the seasons can have an influence on the seasonal

2  composition analysis, specifically for constituents that fluctuate rapidly (e.g., $NO_3^-$).

3      Relatively little is known about the seasonal variability in ultrafine particles. Kuhn et al. (2005a)

4  and Zhu et al. (2004) found that the concentrations in the ultrafine mode can be much higher during

5  winter, particularly during evenings, because atmospheric dilution is reduced in response to lower mixing

6  heights. This can be seen in Figure 3-50. Mathis et al. (2005) found that emissions of particles in the

7  range of 45-900 nm are significantly higher with decreasing temperature and that cold-start conditions

8  produce roughly an order of magnitude greater PM number emissions in gasoline engines and more than

9  two orders of magnitude higher PM number emissions in diesel engines when compared with warm start

10 conditions.
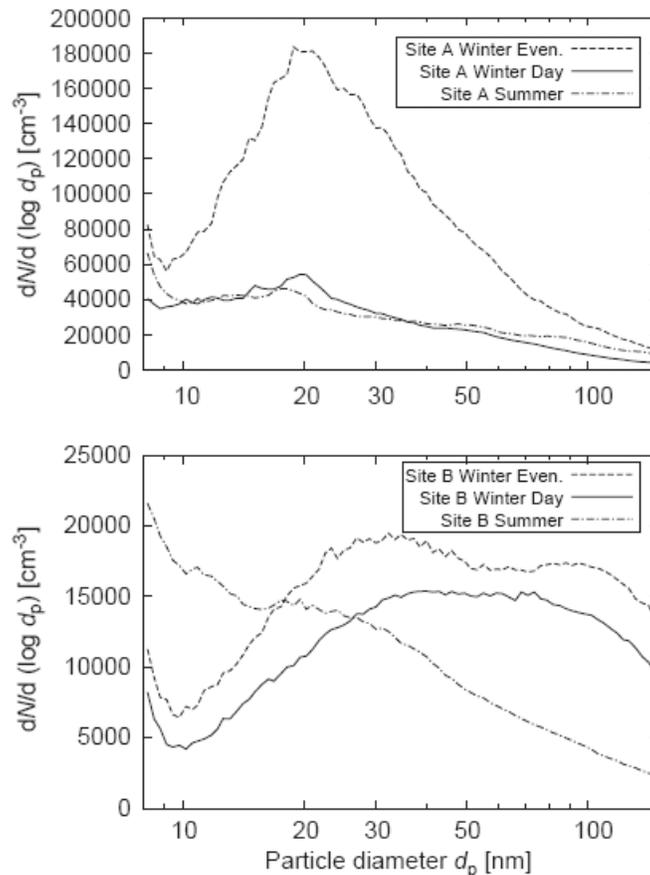


Source: Kuhn et al. (2005a).

**Figure 3-50. Ultrafine particle size distribution at highway (site A) and background (site B) sites in Los Angeles during summer and winter seasons, with winter broken into day and night distributions.**

## 3.5.2.3. Hourly Variability

1    Hourly $PM_{10}$ and $PM_{2.5}$ measurements are conducted at many sites using the beta gauge or TEOM.

2    Many of the hourly measurements for $PM_{10}$ have FRM or FEM status. All available hourly data from

3    FRM, FEM and FRM-like monitors in the fifteen CSAs/CBSAs discussed earlier were used to investigate

4    diel variation in PM. Of the fifteen CSAs/CBSAs, Atlanta, Chicago, Pittsburgh, Seattle and St. Louis had

5    qualifying hourly $PM_{10}$ and $PM_{2.5}$ data available. Denver, Detroit, Los Angeles, Philadelphia, Phoenix,

6    and Riverside had only qualifying hourly $PM_{10}$ data. Houston and New York had only qualifying $PM_{2.5}$

7    data. Birmingham and Boston had no qualifying hourly $PM_{10}$ or $PM_{2.5}$ data.

8    Annex A includes diel plots for $PM_{10}$ stratified by weekdays and weekends for eleven of the fifteen

9    CSAs/CBSAs with available data between 2005 and 2007. All cities show a gradual morning increase in

10    mean $PM_{10}$ starting at approximately 6:00 am on weekdays, corresponding with the start of the morning

11    rush hour before the break-up of overnight stagnation. The magnitude and duration of this peak, however,

12    varies considerably by area. Phoenix shows the most pronounced morning $PM_{10}$ peak concentration,

13    which drops off during the day and reappears in the evening. In contrast, Chicago shows a less

14    pronounced $PM_{10}$ peak concentration, which remains elevated throughout the day. Figure 3-51 shows the

15    diel plots of $PM_{10}$ for Chicago and Phoenix. In both instances, the weekend diel pattern is similar in shape

16    to the weekday pattern with less exaggerated peaks.

## Chicago

**Weekday (N = 1971)**

**Weekend (N = 793)**



Legend:
- —— Median
- ·—·— Mean
- - - - 90th & 10th
- ········ 95th & 5th

## Phoenix

**Weekday (N = 1532)**

**Weekend (N = 618)**
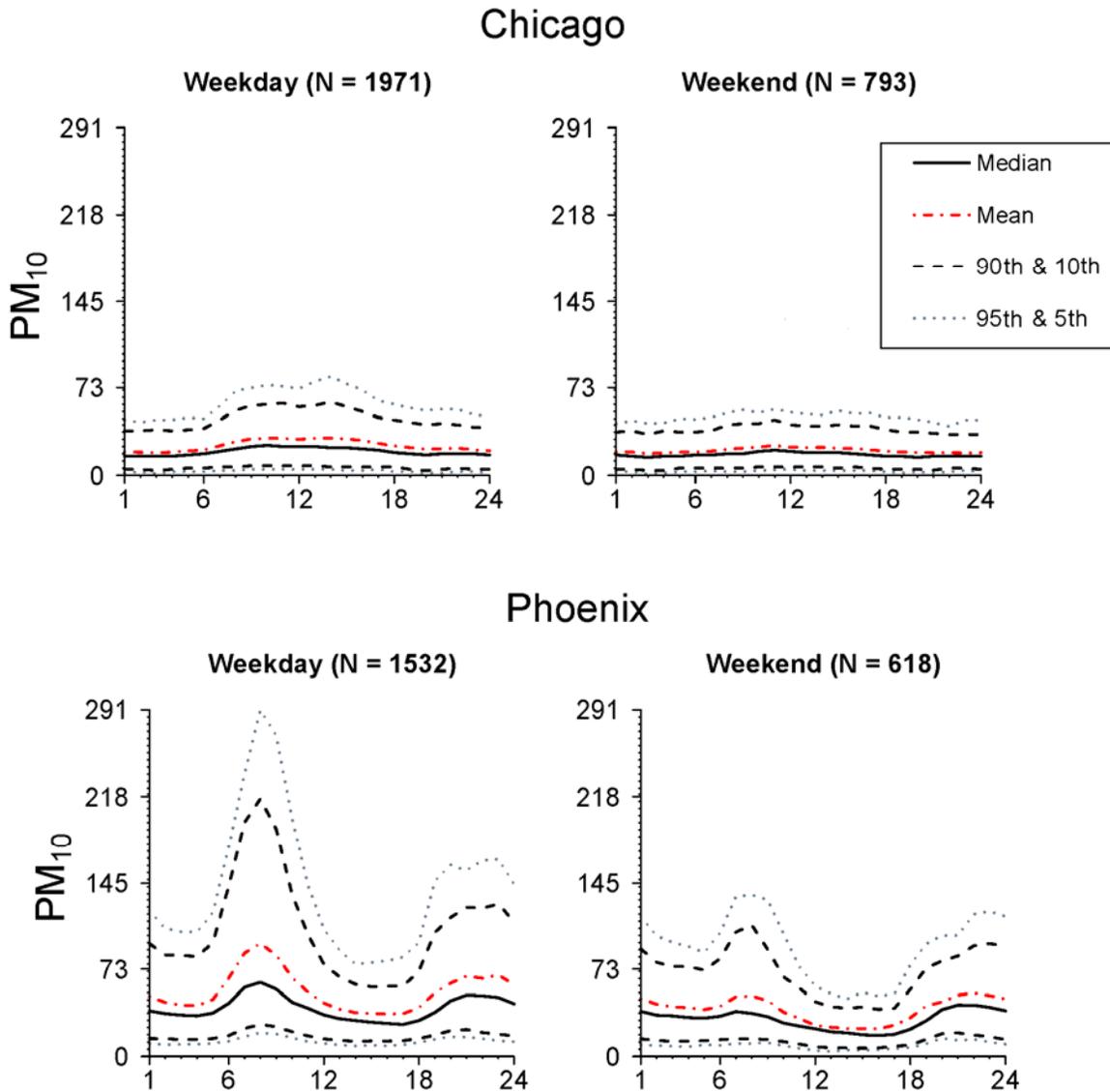


**Figure 3-51.** Diel plot generated from hourly FEM PM$_{10}$ data ($\mu$g/m$^3$) stratified by weekday (left) and weekend (right) for Chicago and Phoenix from 2005 to 2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles for each hour.

1      Annex A includes diel plots for PM$_{2.5}$ stratified by weekdays and weekends for seven of the fifteen

2      CSAs/CBSAs with available data between 2005 and 2007. A similar morning PM$_{2.5}$ peak starting at

3      approximately 6:00 am is present in all cities except Pittsburgh, where it appears that dispersion behavior

4      during the night results in elevated PM$_{2.5}$ levels throughout the night that blend in with any morning peak.

5      With the exception of Pittsburgh, all seven metropolitan areas show two distinct daily peaks on both the

6      weekdays and weekends. The evening PM$_{2.5}$ concentration peak is broader than the morning peak and

1    extends to overnight hours, reflecting the concentration increase caused by a drop in boundary layer

2    height at night. Figure 3-52 compares the 2-peak shape of the $PM_{2.5}$ diel distribution in Seattle with

3    Pittsburgh, where the overnight increase washes out the morning peak.
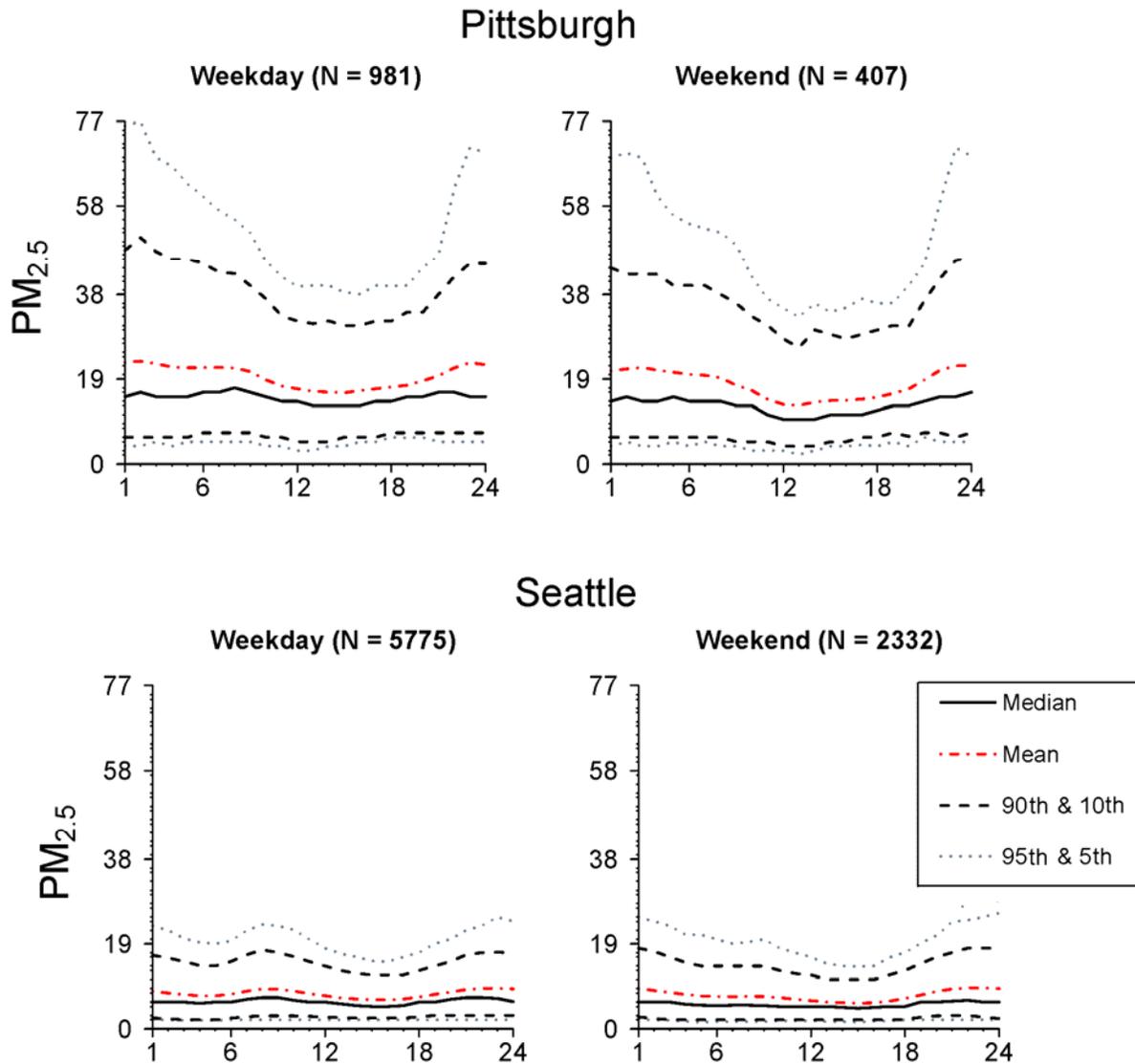


**Figure 3-52.   Diel plot generated from hourly FRM-like $PM_{2.5}$ data ($\mu g/m^3$) stratified by weekday (left) and weekend (right) for Pittsburgh and Seattle from 2005 to 2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles for each hour.**
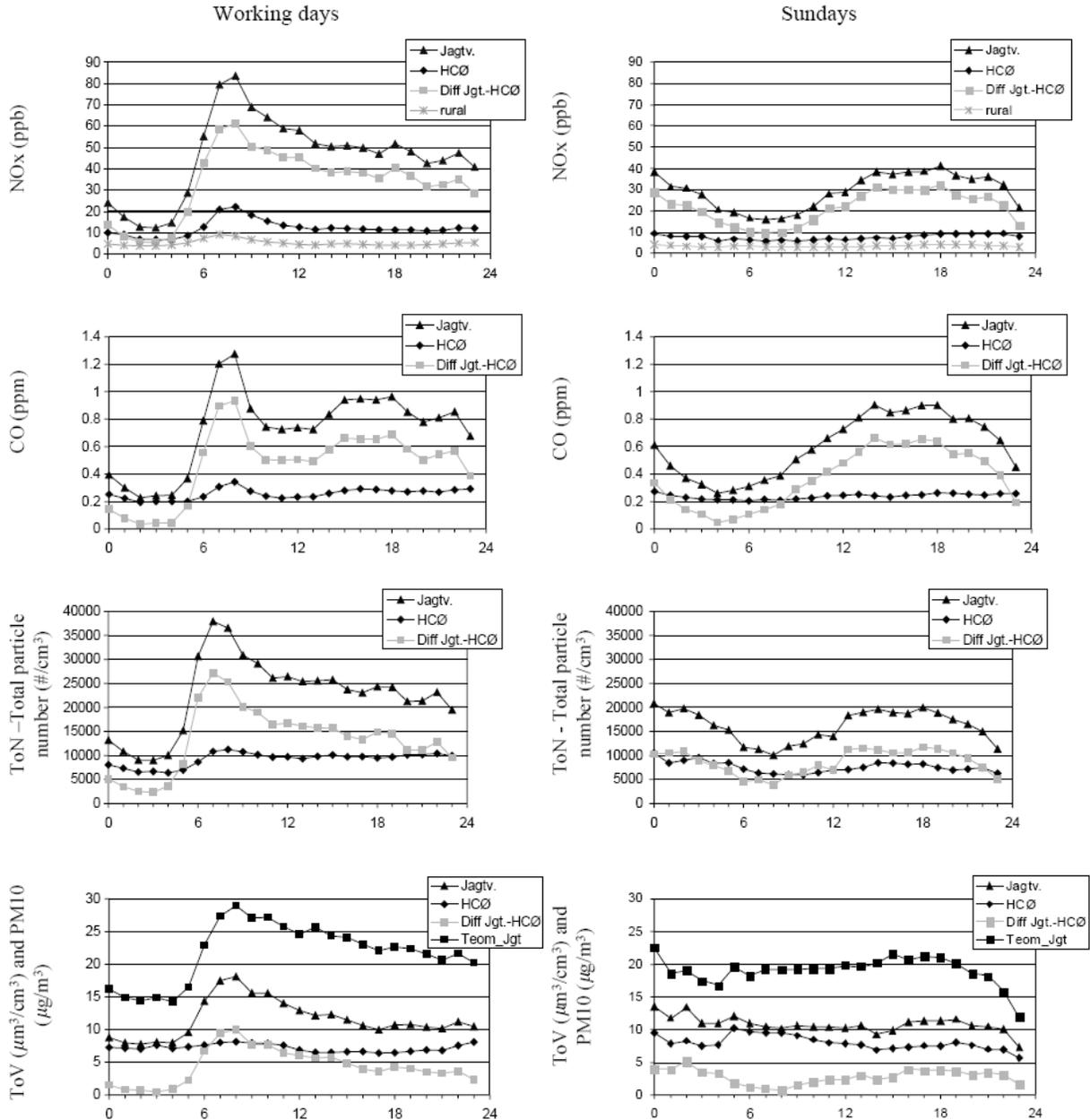
**Figure 3-53. Average diurnal variation of NO$_X$, CO, particle number and particle volume on weekdays (left) and Sundays (right).**

1    Ultrafine particles in urban environments have been shown to exhibit a similar two-peaked diel

2    pattern in Los Angeles (Moore et al., 2007; Sardar et al., 2005) and the San Joaquin Valley (Herner et al.,

3    2005) in California as well as in Kawasaki City, Japan (Hasegawa et al., 2005) and Copenhagen,

4    Denmark (Ketzel et al., 2003). Figure 3-53 from the Denmark study shows a large peak in total particle

5    number (dominated by ultrafine particles) corresponding with the morning rush hour. The morning peak

1    is absent on Sundays, however. Many studies also show a broad afternoon ultrafine concentration peak,

2    which likely originates from a combination of primary sources such as evening rush hour traffic and

3    secondary formation of ultrafine particles in the atmosphere. Secondary formation likely contributes a

4    substantial amount of ultrafine particles since the evening peak is present on weekends whereas the

5    morning traffic related peak essentially vanishes.
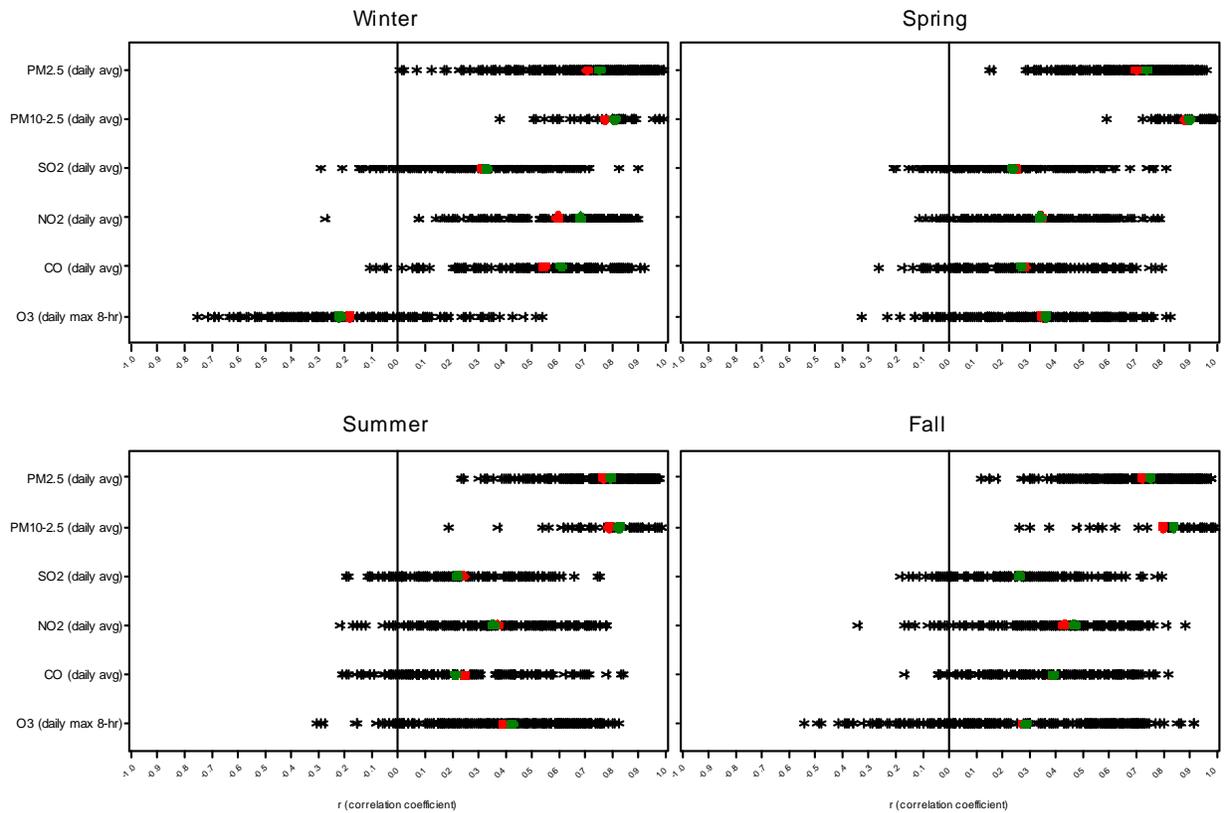


**Figure 3-54.   Correlations between 24-h PM$_{10}$ and co-located 24-h average PM$_{2.5}$, PM$_{10-2.5}$, SO$_2$, NO$_2$ and CO and daily max 8-h avg O$_3$ for the U.S. stratified by season (2005-2007). One point is included for each monitor pair with the mean (green stars) and median (red squares) of all correlations superimposed.**

## 3.5.3. Statistical Associations with Copollutants

6         Associations between PM and other copollutants including SO$_2$, NO$_2$, CO and O$_3$ are investigated

7    in this section. AQS data were obtained from all available co-located monitors across the U.S. after

8    application of an 11 or more observations per quarter completeness criteria. Pearson correlation

1 coefficients (R) were calculated using 2005-2007 data. The results are displayed graphically in Figure 3-

2 54 for correlations with $PM_{10}$ and Figure 3-55 for correlations with $PM_{2.5}$.
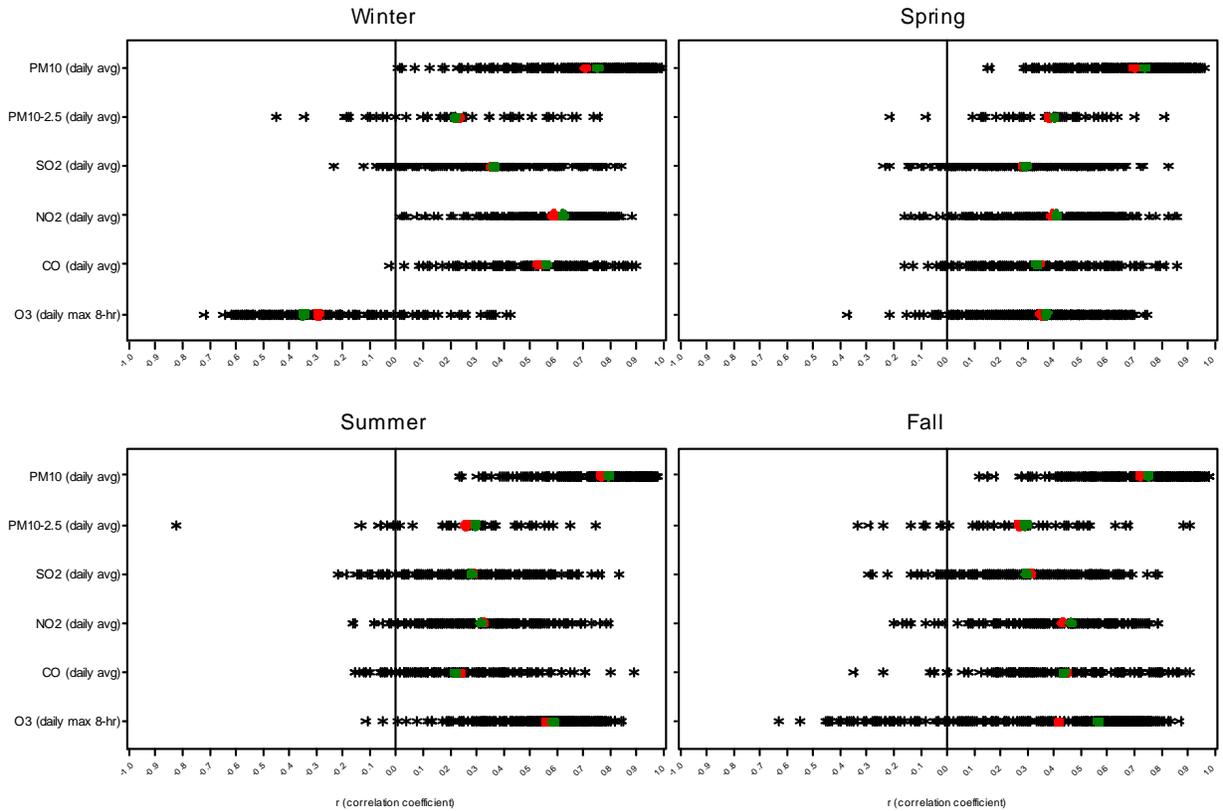


**Figure 3-55. Correlations between 24-h PM$_{2.5}$ and co-located 24-h average PM$_{10}$, PM$_{10-2.5}$, SO$_2$, NO$_2$ and CO and daily max 8-h avg O$_3$ for the U.S. stratified by season (2005-2007). One point is included for each monitor pair with the mean (green stars) and median (red squares) of all correlations superimposed.**

3 For both $PM_{10}$ and $PM_{2.5}$ national composite copollutant correlations, there is considerable spread

4 in the observed correlations in all four seasons. On average, $PM_{10}$ and $PM_{2.5}$ correlate with each other

5 better than with the gaseous copollutants. The correlations between $PM_{10}$ and $PM_{2.5}$ are all positive but

6 span the range from just above zero to near one. This illustrates the wide variability in correlation

7 between these two PM metrics. Fewer points are available for correlation with $PM_{10-2.5}$ because only data

8 from low-volume FRM/FRM-like samplers were used to calculate $PM_{10-2.5}$. The available data suggest a

9 stronger correlation between $PM_{10}$ and $PM_{10-2.5}$ than between $PM_{2.5}$ and $PM_{10-2.5}$ on a national basis.

10 The correlation between PM and the gaseous pollutants included in Figures 3-54 and 3-55 also

11 have a large range in values using the national composite data. There is little seasonal variability in the

1   mean correlation between PM and $SO_2$. $NO_2$ and CO, however, show higher correlations with PM on

2   average in the wintertime than in the other seasons. This is possibly driven by meteorology with increased

3   frequency of stagnation events in colder months. The correlation between daily max 8-h average $O_3$ and

4   PM shows high seasonal variability with positive correlations on average in the spring, summer and fall

5   and negative correlations on average in the winter. The highest positive correlations are in the summer,

6   likely driven by favorable photochemical formation conditions for both $O_3$ and secondary aerosols

7   (Joseph, 2008; Meng et al., 1997). The mean correlation drops below zero (-0.2 for $PM_{10}$ and -0.3 for

8   $PM_{2.5}$) in the wintertime. As discussed in chapter 3 of the last AQCD for Ozone and other Photochemical

9   Oxidants (U.S. EPA, 2006c), this situation arises because photochemical production of ozone in the

10  planetary boundary layer is much smaller during the winter than summer, while primary PM levels are

11  elevated in many areas as a product of heating emissions and lower mixing heights. Ozone in the

12  boundary layer is mainly associated with the subsidence from above the boundary layer following the

13  passage of cold fronts. This subsiding air has much lower PM concentrations than were present in the

14  boundary layer. Therefore, a negative association between $O_3$ and $PM_{2.5}$ is frequently observed in the

15  wintertime. Bell et al. (2007a) also observed a wintertime minima in same-day correlations between 24-h

16  average PM and $O_3$ using data from 98 U.S. urban communities over a 14-year period (1987-2000). The

17  average correlations were not negative in wintertime, however, as seen here. Furthermore, the highest

18  national average correlations were in spring and fall in the Bell et al. (2007a) analysis rather than summer

19  as observed here. This discrepancy could be a result of the different averaging times used for $O_3$ or the

20  selection of different monitoring networks and/or time periods.

21          Correlations among copollutants for individual CSAs/CBSAs are included in Annex A for $PM_{10}$

22  and Annex A for $PM_{2.5}$. The same fifteen CSAs/CBSAs were chosen for further investigation, but several

23  had an insufficient amount of co-located data to be included. As can be seen from the individual

24  CSAs/CBSAs in these figures with multiple pairs of co-located monitors per pollutant, there can be

25  considerable variation in the correlations even on an urban scale. Birmingham, Boston, and St. Louis all

26  show positive wintertime correlations between $PM_{10}$ and daily maximum 8-h average $O_3$; Denver, Detroit,

27  Houston, Los Angeles and Phoenix show negative wintertime correlations. The remaining seven

28  CSAs/CBSAs have insufficient data. For $PM_{2.5}$, all selected cities with sufficient data show negative

29  correlations in the wintertime with daily max 8-h average $O_3$ (including Birmingham, Boston, Chicago,

30  Denver, Houston, Los Angeles, Philadelphia, Phoenix, Pittsburgh, Riverside and St. Louis). The

31  remaining four CSAs/CBSAs have insufficient data. In Baltimore (not one of the fifteen CSAs/CBSAs

32  included in this investigation), Sarnat et al. (2001) found a significant (at the $p < 0.05$ level) positive (0.67)

33  and negative (-0.72) correlation between daily $PM_{2.5}$ and $O_3$ in the summer (June 19–August 23, 1998)

34  and winter (February 2–March 13, 1999), respectively. The negative correlation between $PM_{2.5}$ and $O_3$

1  observed in many cities across the U.S. in the wintertime illustrates the importance of considering

2  seasonality when assessing correlations between these air pollutants. While not as extreme, the other

3  pollutants can exhibit seasonal variation in correlations with PM as well.

# 3.5.4. Estimating Source Contributions to PM

4  Methods for analyzing the composition of ambient PM samples in terms of contributions from

5  different sources are reviewed in this section. Associations between exposures to ambient PM matter, as

6  represented by ambient monitors, and health outcomes have been extensively studied. Some health

7  studies, described in Section 6.6, have used source apportionment methods to evaluate relationships

8  between health outcomes and PM (mainly $PM_{2.5}$) from different sources. This section is intended to aid

9  interpretation of those study results. Understanding the contribution of different emissions sources to

10  ambient PM is also important in evaluating air quality data.

## 3.5.4.1. Receptor Models

11  Receptor models are diagnostic in their approach (i.e., they attempt to derive categories of source

12  contributions based either on ambient data alone or in combination with data on the chemical composition

13  of sources). Their formulation contrasts with that of other deterministic models (i.e., three-dimensional

14  chemistry and transport models) that are formulated in a prognostic, or predictive manner (i.e., they

15  attempt to predict species concentrations using a mass or species conservation equation that includes

16  terms based on emissions inventories, meteorology, atmospheric transport, chemical transformations, and

17  deposition). Receptor models have been primarily employed as part of the development of air quality

18  management plans. However, there have been several publications relating apportioned source types

19  based on receptor models to human health effects. Discussions in this section will focus mainly on those

20  methods that have been used to relate health outcomes to sources. More complete descriptions of a large

21  number of types of receptor models currently in use are given in Watson et al. (2008) who summarize the

22  properties of these methods, including the strengths and weaknesses. This compilation of receptor models,

23  broken down into different approaches (i.e., chemical mass balance, factor analysis, tracer-based,

24  meteorology based) is in Tables A-X through A-X.

25  Receptor models such as the chemical mass balance (CMB) model (Watson et al., 1990) relate

26  source category contributions to ambient PM concentrations based on analyses of the compositional

27  profiles of ambient and source emissions samples. It uses as its basis a mass balance equation that

28  represents all chemical species in an aerosol sample as linear combinations of contributions from a fixed

1    number of independent sources plus an error term representing the portion of the measurement that cannot

2    be fit by the model.

3          The compositional profiles used in receptor models can be extensive. As an example, several

4    studies have identified EC and over 100 organic carbon compounds in gasoline PM emissions, including

5    alkanes, PAHs, oxy-PAHs, steranes, hopanes, and organic acids (Schauer et al., 1999, 2002). This

6    breakdown in identifiable groups of organic compounds is illustrated in Figure 3-56 and Table 3-20.

7    Maricq (2007) noted that these 100+ compounds constituted less than 5% of total organic compounds in

8    the PM samples analyzed. Geller et al. (2006) noted that emissions factors for PAHs during steady-speed

9    operation were 40-60% lower in diesel vehicles and more than 90% lower in gasoline vehicles during

10   fluctuating speed operation. Riddle et al. (2007) found that low emissions gasoline vehicles emitted more

11   low molecular weight PAHs but fewer high molecular weight and large PAHs when compared with

12   gasoline vehicles employing three-way catalysts for hydrocarbon control. This was also observed by

13   Fraser et al. (1999) and Schauer et al. (2002). Additionally, several trace metals, including Al, Ca, Fe, K,

14   Mg, Na, Ba, Cr, Cu, Mn, Ni, Pb, S, Ti, V, and Zn have been identified in gasoline and diesel PM

15   emissions in significantly higher amounts for variable speed operation than under steady operation. Geller

16   et al. (2006) also tested the reduction-oxidation potential of ultrafine and accumulation mode PM

17   generated from diesel and gasoline under variable speed and steady speed conditions and found that diesel

18   PM under transient conditions was approximately 14% greater than gasoline PM under transient

19   conditions and 56% greater than diesel PM under steady driving conditions. Escribano et al. (2001) and

20   Sadezky et al. (2005) compared the diesel PM Raman spectroscopy curve with that of graphite and found

21   peaks at similar wave numbers. Data for the compositional profiles for several other important sources of

22   PM that could be used for CMB modeling are shown in Annex A.
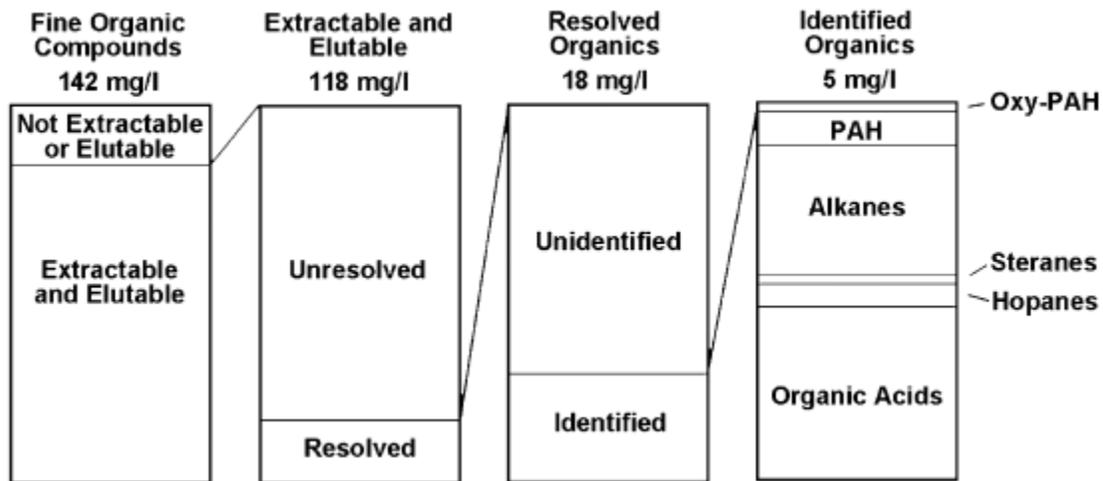
Source: Fraser et al. (1999).

**Figure 3-56.  Schematic of organic composition of particulate emissions from gasoline-fueled vehicles.**

1    In other methods, various forms of factor analysis are used that rely on the varying mix of species
2    present in ambient observations of compositional data to derive the source contributions. Standard factor
3    analytic approaches such as Principal Component Analysis (PCA) have been used but PCA alone can
4    apportion only the variance, not the mass, in an aerosol composition data set. Additional steps such as
5    those applied in Absolute Principal Components Scores (APCS) are required to apportion mass from PCA
6    (Miller et al., 2002; Thurston and Spengler, 1985). In Positive Matrix Factorization (PMF) (Paatero and
7    Tapper, 1994), which is becoming more widespread in its use, the ambient compositional data matrix is
8    decomposed into the product of a matrix representing the source contributions and one representing the
9    source profiles. Solutions are obtained by minimizing an object function with respect to these two
10   matrices, and solutions are subject to non-negativity constraints. PMF also allows for the treatment of
11   missing data and data near or below detection limits by weighting elements inversely according to their
12   uncertainties. The PMF approach can only be applied to time series data, whereas CMB can be applied to
13   one sample. Both the CMB and the PMF approaches find solutions based on least squares fitting and
14   minimization of an object function. Both methods provide error estimates for the solutions based on
15   estimates of the errors in the input parameters. It should be remembered, though, that the error estimates
16   for both methods often contain subjective judgments about the magnitude of the analytical and monitoring
17   errors.

**Table 3-20.** Emissions factors (ng/kg) for trace elements under variable speed and steady speed driving conditions for PM emitted by diesel and gasoline engines.

| Element | Diesel | | Gasoline | |
| --- | --- | --- | --- | --- |
| | Transient | Steady State | Transient | Steady State |
| Al | 9108 (5224) | 2706 | 2273 (545) | 252 |
| Ca | 69,443 (23,640) | 16,128 | 18,247 (3044) | 2324 |
| Fe | 22,910 (21,448) | 2036 | 10,266 (9928) | 138 |
| K | 4672 (752) | 1191 | 1935 (558) | 117 |
| Mg | 3087 (461 | 997 | 5183 (1706) | 183 |
| Na | 7736 (1751) | 1945 | 2237 (1125) | 321 |
| Ba | 583 (349) | 73 | 331 (55) | 4.8 |
| Be | 26 (12) | 23 | 6.7 (1.1) | 1.5 |
| Cr | 634 (354) | 93 | 138 (6.7) | 8.6 |
| Cu | 1944 (679) | 627 | 1745 (1803) | 16 |
| Li | 13 (0.2) | 7.9 | 3.0 (1.4) | 0.9 |
| Mn | 368 (183) | 76 | 152 (85) | 3.4 |
| Ni | 2310 (656) | 644 | 107 (0.7) | 21 |
| Pb | 793 (593) | 79 | 237 (2.3) | 11 |
| S | 23,750 (5295) | 6713 | 8705 (3375) | 349 |
| Ti | 2036 (320) | 345 | 118 (9.3) | 24 |
| V | 28 (9.4) | 11 | 15 (11) | 1.8 |
| Zn | 21,118 (4422) | 5620 | 4650 (1225) | 198 |

Source: Geller et al. (2006).

1

2    The nature of the solutions in terms of source categories is different in the CMB and PMF

3    approaches. In the CMB approach, the composition of the source emissions is assumed to be known

4    based on measurements. These assumptions may or may not reflect the composition of emissions

5    affecting a particular site at any given time or place. However, there may be variations in the composition

6    of individual source categories (e.g., soils, motor vehicle emissions) across a given airshed and even in

7    the composition of the same source with time. Source profiles can also be altered between emission and

8    receptor locations resulting from atmospheric reactions, depending on the source type and species under

9    analysis. The CMB technique was developed for apportioning source categories of primary PM and was

10    not formulated to include sources of secondary PM. All of the mass cannot be apportioned unless there is

11    information for the composition of all sources affecting a given site.

12    In PMF, the source solutions are more general in that they contain information about the

13    entrainment of emissions from additional sources during transport, the time dependence of the

14    composition of emissions from particular sources, the formation of secondary species and local

1     differences in source compositions. PMF differs from CMB because it derives the source mix from

2     measured data. However, the procedure used to find a solution results in some rotational ambiguity

3     (Paatero and Tapper, 1994). The assignment of sources and the factors modifying them depend largely on

4     past experience and judgments based on data for source profiles to identify the sources and their

5     modifying factors contained in the solution. These issues are alleviated to some degree by folding in

6     information about local wind fields and other physical parameters.

7         The UNMIX model takes a geometric approach that exploits the covariance of the ambient data to

8     determine the number of sources, the composition and contributions of the sources, and the uncertainties

9     (Henry, 1997). UNMIX uses PCA to find edges in m-dimensional space, where m is the number of

10     ambient species. Success of the UNMIX model hinges on the ability to find these "edges" in the ambient

11     data from which the number of source types and the source compositions are extracted. In simplest terms,

12     the approach can be seen to be similar to that for deriving ternary mixing diagrams, except there is

13     extension to higher dimensionality. Measurement errors in the ambient data "fuzz" the edges, making

14     them difficult to find. UNMIX employs an "edge-finding" algorithm to find the best edges in the presence

15     of error. UNMIX does not make explicit use of errors or uncertainties in the ambient concentrations,

16     unlike the methods outlined above. Rather they are implicitly incorporated into the analyses.

17         Partial least squares (PLS) is another mathematical model related to PCA which has been used in a

18     limited number of PM toxicology studies to establish a relationship between PM constituents and health

19     outcomes (McDonald et al., 2004; Seagrave et al., 2006; Veranth et al., 2006). Unlike PCA and other

20     receptor models discussed in this section, PLS incorporates both predictor variables (e.g., PM component

21     concentrations) and outcome variables (e.g., toxicological responses) into one coupled regression model

22     rather than relying on a stand-alone regression analysis after the fact. Like PCA, PLS groups the

23     observable variables into a reduced number of latent variables, thereby reducing the dimensionality of the

24     model (and, hence, PLS also stands for "projection to latent structures"). Typically, PM toxicology studies

25     have been limited to two-component models (two latent variables on the predictor side compared with

26     two on the outcome side), thereby producing a 2x2 loading plot revealing relationships between

27     predictors and outcomes. PLS is particularly useful when there are more predictor variables than

28     observations, which is a situation that other multivariate factor analysis approaches do not handle well.

29     However, since PLS is a variance based approach, it shares the same shortcomings discussed earlier for

30     PCA. PLS has also traditionally been limited to two-component applications even though this is not a

31     strict mathematical limitation.

*Results from Receptor Models*

1    Results of receptor modeling calculations indicate that $PM_{2.5}$ is most often produced mainly by

2    fossil fuel combustion. Fugitive dust, found mainly in the $PM_{10-2.5}$ size range, represents the largest source

3    of measured ambient $PM_{10}$ in many locations in the western U.S. Quoted uncertainties in the source

4    apportionment of constituents in ambient aerosol samples typically range from 10 to 50%. It is apparent

5    that a relatively small number of broadly defined source categories, compared to the total number of

6    chemical species that typically are measured in ambient monitoring-source receptor model studies, are

7    needed to account for the majority of the observed mass of PM in these studies. Compilations of source

8    attribution studies using CMB have appeared in the PM AQCD (U.S. EPA, 2004) for $PM_{10}$ and using

9    PMF in Engel-Cox and Weber (2007). Results of the compilation by Engel-Cox and Weber (2007) for the

10   eastern U.S. are shown in Figure 3-57. There are only three main source categories in the figure

11   constituting most of the $PM_{2.5}$ mass. Two of these are predominantly secondary and not identified by

12   sources of precursors. Tables listing results of other receptor modeling studies for $PM_{2.5}$ and $PM_{10}$, many

13   of which are in the western U.S., are given in Annex A.
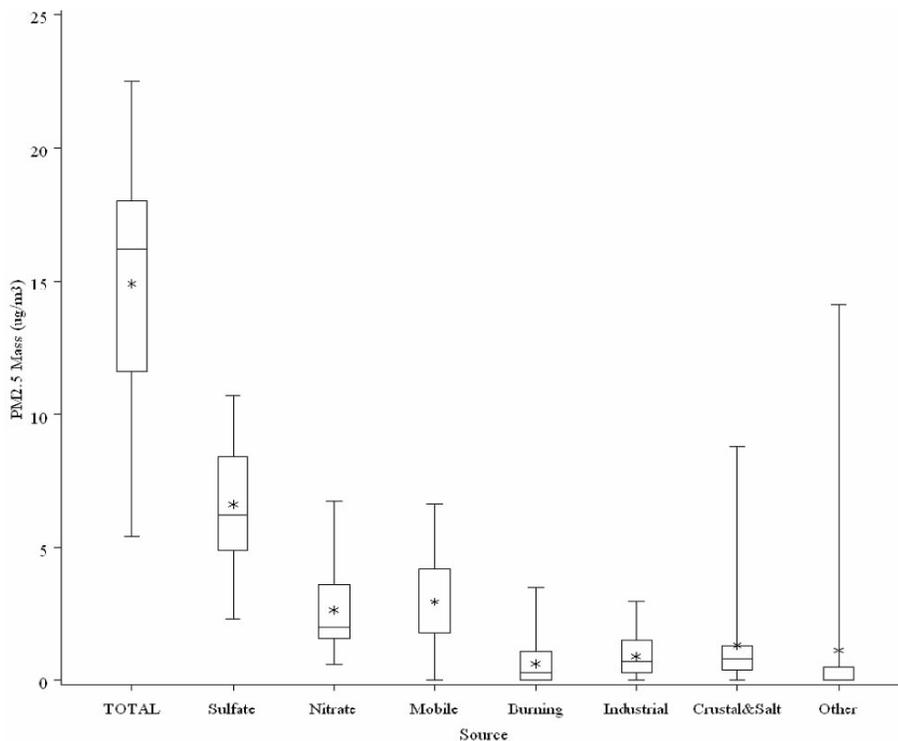


Source: Engel-Cox and Weber (2007)

**Figure 3-57    Source category contributions to PM$_{2.5}$ at a number of sites in the East derived using PMF.**

## Spatial Variability in Source Contributions to PM Based on Receptor Models

1    Spatial variability in source contributions across urban areas is an important consideration in

2    assessing the likelihood of exposure measurement error in epidemiologic studies relating health endpoints

3    to sources. Arguments similar to those for using ambient concentrations as surrogates for personal

4    exposures apply here. Studies for $PM_{2.5}$ (Kim et al., 2005b; Wongphatarakul et al., 1998) indicate that

5    intra-urban variability increases in the following order: regional (e.g., secondary $SO_4^{2-}$ from EGUs) < area

6    (on-road mobile sources) < point (stacks) sources. This point is illustrated in Figure 3-58. The only study

7    available for $PM_{10-2.5}$ (Hwang et al., 2008) indicates a similar ordering, but without a regional component

8    (resulting from the short lifetime of coarse PM compared to transport times on the regional scale) as

9    shown in Figure 3-59.
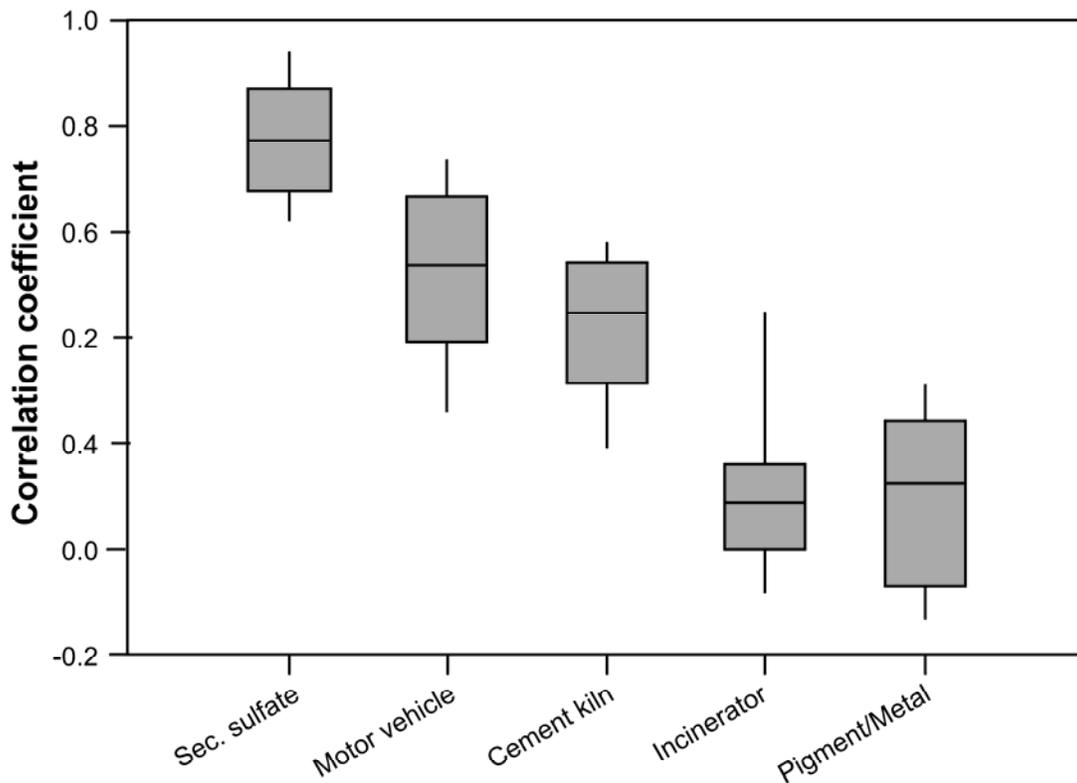


Source: Kim et al. (2005b)

Figure 3-58.  Pearson correlation coefficients for source category contributions to $PM_{2.5}$ at the ten Regional Air Pollution Study/Regional Air Monitoring System (RAPS/RAMS) monitoring sites in St. Louis.
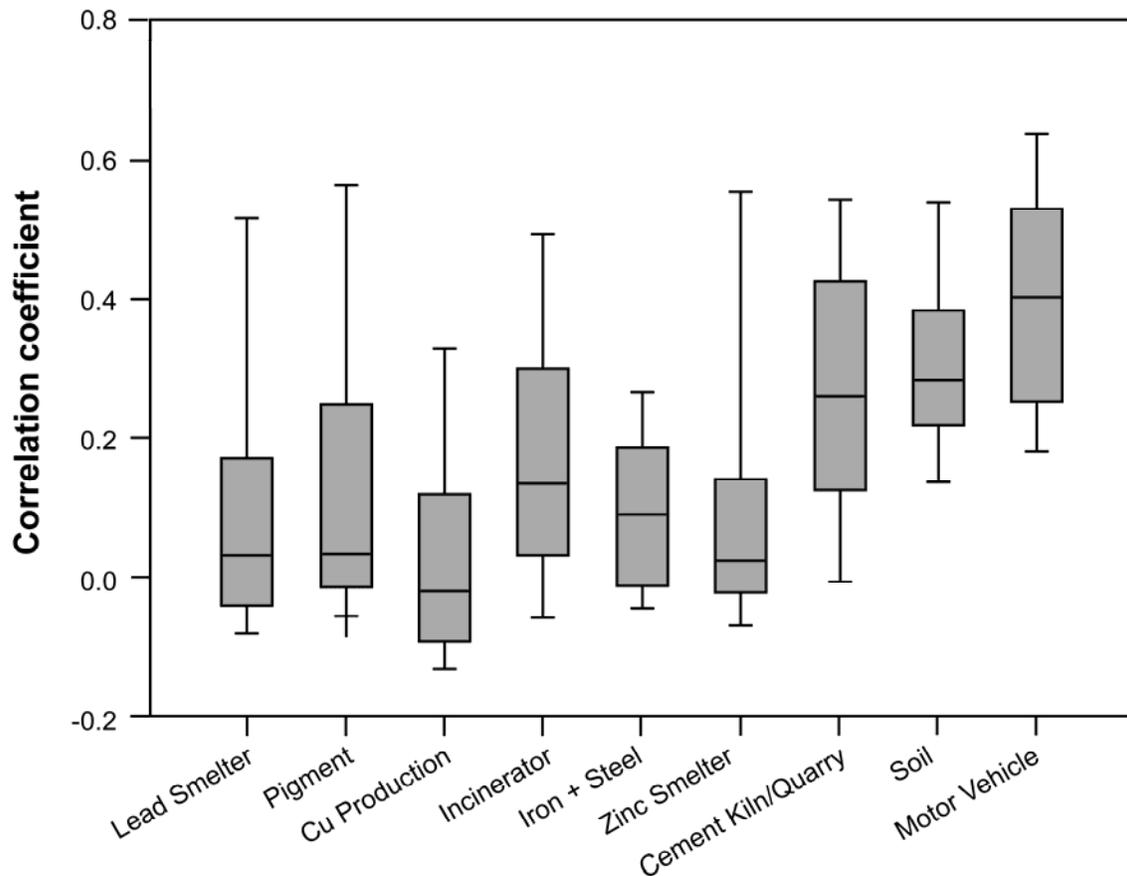
Figure 3-59. Pearson correlation coefficients for source contributions to $PM_{10-2.5}$ at the ten Regional Air Pollution Study/Regional Air Monitoring System (RAPS/RAMS) monitoring sites in St. Louis.

## Chemical Transport Models

1    CTMs are the prime tools used to compute the interactions among atmospheric pollutants and their

2    transformation products, the production of secondary aerosols, the evolution of particle size distribution,

3    and transport and deposition of pollutants. CTMs are driven by emissions inventories for primary species

4    such as $NO_X$, $SO_X$, $NH_3$, and primary PM, and by meteorological fields produced by other numerical

5    prediction models. Meteorological quantities such as winds and temperatures are taken from operational

6    analyses, reanalyses, or weather circulation models. In most cases, these are off-line meteorological

7    analyses, meaning that they are not modified by radiatively active species generated by the air quality

8    model (AQM), although new, integrated models of meteorology and chemistry are now available as well

9    (e.g., Binkowski et al., 2007).

10    Emissions of precursor compounds can be divided into anthropogenic and biogenic source

11    categories, and biogenic sources can be further divided into biotic (vegetation, microbes, animals) and

1   abiotic (biomass burning, lightning, geogenic) categories as presented above. However, the distinction

2   between biogenic sources and anthropogenic sources is often difficult to make, as human activities affect

3   directly or indirectly emissions from what would have been considered biogenic sources during the

4   preindustrial era. Thus, emissions from plants and animals used in agriculture have been referred to as

5   anthropogenic or biogenic in different applications. Wildfire emissions may be considered to be biogenic,

6   except that forest management practices may have led to the buildup of fuels on the forest floor, thereby

7   altering the frequency and severity of forest fires.

8       The initial conditions, or starting concentration fields of all species computed by a model, and the

9   boundary conditions, or concentrations of species along the horizontal and upper boundaries of the model

10  domain throughout the simulation, must be specified at the beginning of the simulation. Both initial and

11  boundary conditions can be estimated from models or data or, more generally, model + data hybrids.

12  Because data for vertical profiles of most species of interest are sparse, results of model simulations over

13  larger, usually global, domains are often used. As might be expected, the influence of boundary conditions

14  depends on the lifetime of the species under consideration and the time scales for transport from the

15  boundaries to the interior of the model.

16      Each of the model components described above has associated uncertainties and the relative

17  importance of these uncertainties varies with the modeling application. The largest errors in

18  photochemical modeling are still thought to arise from the meteorological and emissions inputs to the

19  model (Russell and Dennis, 2000). While the effects of poorly specified boundary conditions propagate

20  through the model's domain, the effects of these errors remain undetermined. Because many

21  meteorological processes occur on spatial scales smaller than the model grid spacing (either horizontally

22  or vertically) and thus are not calculated explicitly, parameterizations of these processes must be used.

23  These introduce additional uncertainty. Because the chemical production and loss terms in the continuity

24  equations for individual species are coupled, the chemical calculations must be performed iteratively until

25  calculated concentrations converge to within some preset criterion. The number of iterations and the

26  convergence criteria chosen also can introduce error.

27      CTMs have been developed for application over a wide range of spatial scales ranging up from

28  neighborhood to global. CTMs are used to: (1) obtain better understanding of the processes controlling

29  the formation, transport, and destruction of gas- and particle-phase criteria and hazardous air pollutants;

30  (2) understand the relations between concentrations of secondary pollutant products and concentrations of

31  their precursors; (3) understand relations among the concentration patterns of various pollutants that may

32  exert adverse effects; and (4) evaluate how changes in emissions propagate through the atmospheric

33  system to secondary products and deposition. More detailed discussion of CTM applications appears in

34  the 2008 ISA for $NO_X$ and $SO_X$ - Ecological Criteria (U.S. EPA, 2008e).

### Global Scale

1    Global-scale CTMs are used to address issues associated with climate change and stratospheric $O_3$
2    depletion, and to provide boundary conditions for the regional-scale models. The CTMs include
3    simplified mathematical descriptions of atmospheric transport, the transfer of solar radiation through the
4    atmosphere, chemical reactions, and removal to the surface by turbulent motions and precipitation for
5    pollutants emitted into the model domain. The upper boundaries of the CTMs extend anywhere from the
6    top of the mixed layer to the mesopause at ~80 km in order to obtain more realistic boundary conditions
7    for problems involving stratospheric dynamics.

8    Global simulations are typically conducted at a horizontal resolution of 200 $km^2$ or more.
9    Simulations of the effects of transport from long-range transport link multiple horizontal resolutions from
10   the global to the local scale. Finer resolution will only improve scientific understanding to the extent that
11   the governing processes are more accurately described at that scale. Consequently, there is a critical need
12   for observations at the appropriate scales to evaluate the scientific understanding represented by the
13   models.


### Regional Scale

14   Most major modeling efforts in the EPA center on the Community Multiscale Air Quality modeling
15   system (CMAQ) (2006; Byun and Ching, 1999). [A number of other modeling platforms using
16   Lagrangian and Eulerian frameworks were reviewed in the 2006 AQCD for $O_3$ (U.S. EPA, 2006c) and in
17   Russell and Dennis (2000)]. The capabilities of a number of CTMs designed to study local- and regional-
18   scale air pollution problems were summarized by Russell and Dennis (2000). Evaluations of the
19   performance of CMAQ are given in Arnold et al. (2003), Eder and Yu (2006), Appel et al. (2005), and
20   Fuentes and Raftery (2005). CMAQ's horizontal domain can extend from a few square kilometers to the
21   entire hemisphere. In addition, both of these classes of models allow resolution of the calculations over
22   specified areas to vary. CMAQ is most often driven by the MM5 mesoscale meteorological model
23   (Seaman, 2000), though it may be driven by other meteorological models including WRF and RAMS.
24   Simulations of pollution episodes over regional domains have been performed with a horizontal
25   resolution as low as 1 km, and smaller applications over limited domains have been performed at even
26   finer scales. However, simulations at such high resolutions require better parameterizations of
27   meteorological processes such as boundary layer fluxes, deep convection and clouds (Seaman, 2000), as
28   well as finer-scale emissions than are generally available at present. Finer spatial resolution is necessary
29   to resolve features such as urban heat island circulation; sea, bay, and land breezes; mountain and valley
30   breezes; and the nocturnal low-level jet, all of which can affect pollutant concentrations.

1    The vertical resolution of these CTMs is variable, and usually configured to have more layers in the

2    PBL and fewer higher up. Because the height of the boundary layer is of critical importance in

3    simulations of air quality, improved resolution of the boundary layer height would likely improve air

4    quality simulations. Additionally, current CTMs do not adequately resolve fine scale features such as the

5    nocturnal low-level jet in part because little is known about the nighttime boundary layer.

6    CTMs require time-dependent, three-dimensional wind fields for the period of simulation. The

7    winds may be generated either by a model using initial fields alone or with four-dimensional data

8    assimilation to improve the model's performance; i.e., model equations can be updated periodically to

9    bring results into agreement with observations. Modeling efforts typically focus on simulations of several

10   days' duration, the typical time scale for individual $O_3$ episodes. Longer term modeling series of several

11   months or multiple seasons of the year are now common. The current trend in modeling applications is

12   towards annual simulations. This trend is driven in part by the need to improve understanding of

13   observations of periods of high wintertime PM (e.g., Blanchard et al., 2002) and the need to simulate $O_3$

14   episodes occurring in spring, fall, and winter.

15   Chemical kinetics mechanisms (sets of chemical reactions) representing the important reactions

16   occurring in the atmosphere are used in CTMs to estimate the rates of chemical formation and destruction

17   of each pollutant simulated as a function of time. Unfortunately, chemical mechanisms that explicitly treat

18   the reactions of individual reactive species are too computationally demanding to be incorporated into

19   CTMs for regulatory use. So, for example, are very extensive "master mechanisms" (Derwent et al.,

20   2001) that include approximately 10,500 reactions involving 3603 chemical species (Derwent et al., 2001)

21   combined into mechanisms that group compounds of similar chemistry together.

22   CMAQ and other state-of-the-science CTMs incorporate processes and interactions of aerosol-

23   phase chemistry (Mebust et al., 2003). There have also been several attempts to study the feedbacks of

24   chemistry on atmospheric dynamics using meteorological models, like MM5 for example (Grell et al.,

25   2000; Liu et al., 2001; Lu et al., 1997; Park et al., 2001). This coupling is necessary to accurately simulate

26   feedbacks which may be caused by the heavy aerosol loading found in forest fire plumes (Lu et al., 1997;

27   Park et al., 2001) or in heavily polluted areas. Photolysis rates in CMAQ can now be calculated

28   interactively with model produced $O_3$, $NO_2$, and aerosol fields (Binkowski et al., 2007).

29   Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be

30   specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution

31   for many HCs, aldehydes, ketones, CO, $NH_3$, and $NO_X$. Emissions inventories for many species require

32   the application of algorithms for calculating the dependence of emissions on physical variables such as

33   temperature and to convert the inventories into formatted emission files which can be used by a CTM. For

34   example, preprocessing of emissions data for CMAQ is done by the Spare-Matrix Operator Kernel

1  Emissions (SMOKE) system (http://smoke-model.org). For many species, information concerning the

2  temporal variability of emissions is lacking, so long-term annual averages are used in short-term, episodic

3  simulations. Annual emissions estimates are often modified by the emissions model to produce emissions

4  more characteristic of the time of day and season. Significant errors in emissions can occur if

5  inappropriate time dependence is used. Additional complexity arises in model calculations because

6  different chemical mechanisms can include different species, and inventories constructed for use with

7  another mechanism must be adjusted to reflect these differences. This problem also complicates

8  comparisons of the outputs of these models because one chemical mechanism may produce some species

9  not present in another mechanism yet neither prediction may agree with the measurements.

### Sub-Regional Scale

10  The grid spacing in regional CTMs, usually between 1 and 12 $km^2$, is usually too coarse to resolve

11  spatial variations on the neighborhood scale. The interface between regional scale models and models of

12  smaller exposure scales described is provided by smaller scale dispersion models. Several models could

13  be used to simulate concentration fields near roads, each with its own set of strengths and weaknesses.

14  For example, AERMOD (http://www.epa.gov/scram001/dispersion_prefrec.htm) is a steady-state plume

15  model formulated as a replacement to the ISC3 dispersion model. In the stable boundary layer (SBL), it

16  assumes the concentration distribution to be Gaussian in both the vertical and horizontal dimensions. In

17  the convective boundary layer, the horizontal distribution is also assumed to be Gaussian, but the vertical

18  distribution is described with a bi-Gaussian probability density function (pdf). AERMOD has provisions

19  to be applied to flat and complex terrain and multiple source types (including, point, area and volume

20  sources) in both urban and rural areas. It incorporates air dispersion based on PBL turbulence structure

21  and scaling concepts and is meant to treat both surface and elevated sources and simple and complex

22  terrain in rural and urban areas. The dispersion of emissions from line sources like highways is treated as

23  the sum of emissions from a number of point sources placed side by side. However, emissions are usually

24  not in steady state and there are different functional relationships between buoyant plume rise in point and

25  line sources. However, AERMOD does not have provision for including secondary sources.

26  There are non-steady state models that incorporate plume rise explicitly from different types of

27  sources. For example, CALPUFF (http://www.src.com/calpuff/calpuff1.htm) is a non-steady-state puff

28  dispersion model that simulates the effects of time- and space-varying meteorological conditions on

29  pollution transport, transformation, and removal and has provisions for calculating dispersion from

30  surface sources. However, it should be noted that neither CALPUFF nor AERMOD was designed to treat

31  the dispersion of emissions from roads or to include secondary sources. In using either model, the user

32  would have to specify dispersion parameters that are specific to traffic. The distinction between a steady–

1    state and time varying model might not be important for long time scales; however for short time scales,

2    the temporal variability in traffic emissions could result in underestimation of peak concentration and

3    exposures.


# 3.6. Background PM

4    The background concentrations of PM useful for risk and policy assessments informing decisions

5    about NAAQS are referred to as Policy Relevant Background (PRB) concentrations and are those

6    concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental

7    North America (defined here as the U.S., Canada, and Mexico). PRB concentrations include contributions

8    from natural sources everywhere in the world and from anthropogenic sources outside these three

9    countries. Background levels so defined facilitate separation of pollution levels that can be controlled by

10   U.S. regulations (or through international agreements with neighboring countries) from levels that are

11   generally uncontrollable by the U.S. These levels can also be used in quantitative risk assessments of

12   human health and environmental effects. In this section, estimates are provided for daily average and

13   annual average PRB concentrations are needed, corresponding to averaging times for PM NAAQS.


## 3.6.1. Contributors to PRB levels of PM

14   Contributions to PRB levels of PM include both primary and secondary natural and anthropogenic

15   components. Natural sources include wind erosion of natural surfaces (Gillette and Hanson, 1989);

16   volcanic production of $SO_4^{2-}$, primary biological aerosol particles; wild fires producing EC, OC, and

17   inorganic and organic PM precursors; and SOA produced by oxidation of biogenic hydrocarbons such as

18   isoprene and terpenes. However, human intervention can be involved in the formation of SOA, as

19   production of natural SOA depends to a large extent on the presence of anthropogenic $NO_X$. As described

20   earlier in Section 3.3, prescribed fires are considered as part of PRB. In addition to emissions from forest

21   fires in the U.S., emissions from forest fires in other countries can be transported to the U.S. Boreal forest

22   fires in Canada (e.g., Mathur, 2008) and Siberia (Generoso et al., 2007) and tropical forest fires in the

23   Yucatan Peninsula and Central America (e.g., Wang et al., 2006a) have affected PM levels in the U.S.

24   PRB PM varies across the CONUS by region and season as a function of complex mechanism of

25   transport, dispersion, deposition, and reentrainment.

26   Dust from the Sahara desert and the Sahel in North Africa (e.g., Chiapello et al., 2005) affects

27   mainly the eastern U.S.; dust from the Gobi and Taklimikan deserts in Asia (e.g., VanCuren and Cahill,

28   2002; Yu et al., 2008) have the largest effects in the western U.S. but also affect air quality in the eastern

1    U.S. Husar et al. (2001) report that the average $PM_{10}$ level at over 150 reporting stations throughout the

2    northwestern U.S. was 65 $\mu g/m^3$ during an episode in the last week in April 1998, compared to an average

3    of about 20 $\mu g/m^3$ during the rest of April and May.

4          PRB contributions to $PM_{2.5}$, $PM_{10-2.5}$, and $PM_{10}$ can also be viewed as coming from two

5    conceptually separate components a reasonably consistent "baseline" component and an episodic

6    component. The baseline component consists of contributions that are generally well characterized by a

7    reasonably consistent distribution of daily values each year, although there is variability by region and

8    season. The episodic component consists of infrequent, sporadic contributions from natural

9    high-concentration events occurring over shorter periods of time (e.g. hours to several days) both within

10   North America (e.g. volcanic eruptions, large forest fires, dust storms) and outside North America (e.g.,

11   transport related to dust storms from deserts in North Africa and China and storms at sea). These episodic

12   natural events, as well as events like the uncontrolled biomass burning in Central America, are essentially

13   uncontrollable and do not necessarily occur in all years.

14         In-situ measurements provide evidence for the transport of anthropogenic PM from Asia on

15   Mt. Batchelor, OR by Jaffe et al. (2003). These data show sporadic but well correlated increases in CO,

16   $O_3$, total Hg, and aerosol backscatter associated with air coming from Asia. The ITCT-2K2 campaign also

17   found evidence for the oxidation of $SO_2$ to $H_2SO_4$ during trans-Pacific transport of Asian emissions. If

18   particulate $SO_4^{2-}$ were to be formed in the polluted boundary layer where it originated, it would likely be

19   deposited prior to transport across the Pacific Ocean (Brock et al., 2004). Thus primary species emitted

20   directly and secondary species formed during transport contribute to PRB levels. Satellite data have

21   provided images to track clouds of dust and pollution across the oceans. They have been used for some

22   quantitative estimation of the flux of material leaving continents. Yu et al. (2008) used optical thickness

23   data to estimate column loadings from the Mresolution Imaging Spectrometer (MODIS) along with

24   satellite assimilated wind fields to estimate the transport of PM from Asia. Three-dimensional,

25   global-scale, chemistry-transport models have also been used to estimate intercontinental transport of PM

26   pollution (UNCEC, 2007) and trans-Pacific transport of mineral dust from Asian deserts (Duncan Fairlie

27   et al., 2007) and the Sahara Desert (McKendry et al., 2007).

## 3.6.1.1. Estimating PRB Concentrations

28         Estimates of the distribution of daily average PRB concentrations in the 2004 PM AQCD

29   (U.S. EPA, 2004) were based on data obtained at IMPROVE monitoring sites in the West. Western sites

30   were chosen because they were thought to be among the least likely influenced by regional pollution

31   sources especially at the upper end of the concentration distribution. This conclusion was drawn from

32   back trajectory analyses and examination of the trace elemental composition. Estimates of PRB levels

1    reported in prior AQCDs for PM (U.S. EPA, 1996, 2004) were based in large measure on estimates by

2    Trijonis (1990) for the NAPAP as shown in Table 3-21.

**Table 3-21.    Estimates of annual average natural background concentrations of PM in different size fractions (μg/m³) from previous reviews.**

|        | $PM_{2.5}$ | $PM_{10}$ | $PM_{10-2.5}$ |
|--------|-----------|-----------|---------------|
| East   | 2-5       | 5-11      | ≤ 1-9         |
| West   | 1-4       | 4-8       | ≤ 1-7         |
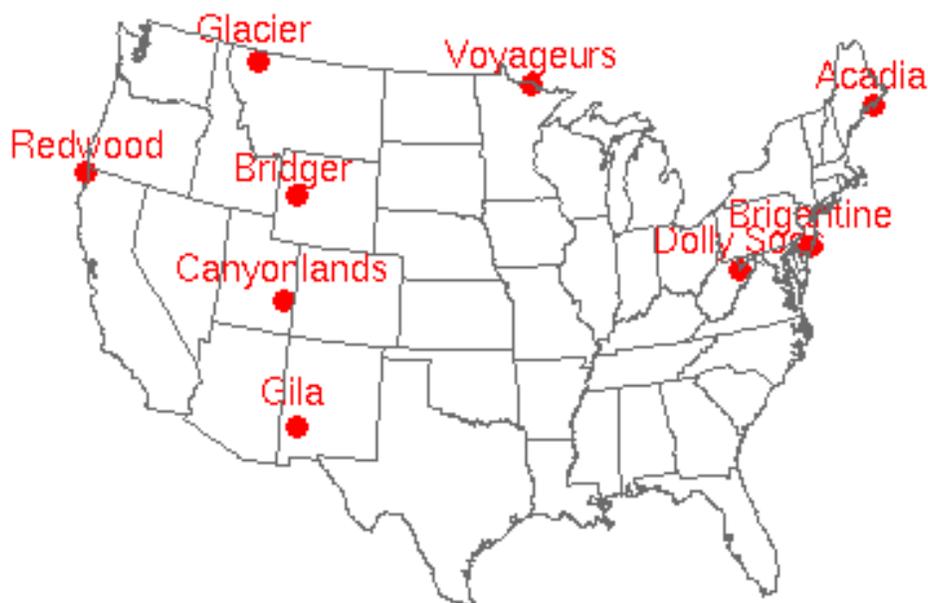


**Figure 3-60.   IMPROVE monitoring site locations.**

3         Table 3-22 shows annual and quarterly average $PM_{2.5}$ measurements from IMPROVE sites shown

4    in Figure 3-60 for 2004. Annual average concentrations tend to be higher in the East than in the Midwest

5    or West. However, when the data are broken down by season, more variability is notable. Highest values

6    in the East are found during the 3$^{rd}$ calendar quarter, whereas in the West highest quarterly averages can

7    occur during other quarters. As can also be seen from a comparison with values shown in Table 3-21,

8    values measured in the East are much higher than the estimated PRB levels.

**Table 3-22.    Annual and quarterly mean PM$_{2.5}$ concentrations (µg/m$^3$) measured at IMPROVE sites in 2004.**

|  | Mean | January-March | April-June | July-September | October-December |
|---|---|---|---|---|---|
| *EAST* | | | | | |
| Acadia | 4.5 | 3.9 | 4.6 | 6.0 | 3.5 |
| Brigantine | 9.5 | 8.1 | 11.3 | 11.6 | 7.3 |
| Dolly Sods | 9.5 | 6.7 | 9.8 | 15.5 | 5.7 |
| *MIDWEST* | | | | | |
| Voyageurs | 3.8 | 4.1 | 3.1 | 4.2 | 3.6 |
| *WEST* | | | | | |
| Bridger | 2.1 | 1.2 | 3.1 | 2.8 | 1.3 |
| Canyonlands | 2.6 | 2.2 | 3.2 | 2.9 | 2.1 |
| Gila | 2.9 | 2.0 | 4.0 | 3.8 | 1.8 |
| Glacier | 4.8 | 4.6 | 4.2 | 5.3 | 5.0 |
| Redwood | 3.5 | 2.7 | 3.6 | 3.7 | 3.9 |

1       Thus, estimating daily average PRB levels in the eastern U.S. using observations is highly

2   problematic because of the widespread mixing of precursors and anthropogenic PM generated in the East.

3   Two approaches were considered in the last NAAQS review. The first was to use the results of receptor

4   modeling studies to separate contributions from likely regional pollution sources from natural and

5   imported pollution. The second was to separate out components mainly thought to be emitted by regional

6   pollution sources such as $SO_4^{2-}$, which are obtained directly from observations at IMPROVE sites, and to

7   use the remaining PM components. Both of these approaches have limitations because receptor models

8   estimate the concentration profile but may suffer from inaccuracy of the assumptions used or limitations

9   in the grid approximations. Removal of regional pollutant sources involves assumptions about the

10   behavior of regional pollution that can lead to underestimation if all sources are not predicted.

## 3.6.1.2. CTM for Predicting PRB Concentrations

11       CTMs can be used to estimate the PRB concentrations of atmospheric components including PM

12   using a "zero-out" approach in which anthropogenic emissions inside the U.S., Canada, and Mexico are

13   set to zero and biogenic emissions remain, and both anthropogenic and biogenic emissions elsewhere in

14   the world remain. Numerical modeling can provide more precision in the estimate of PM PRB than

15   measurements since even the most remote measurement sites like some of those in the IMPROVE

16   network (see the discussion in Section 6.1.1. above) will necessarily be affected by non-local non-

17   biogenic pollution, thereby confusing the contributions from these sources.

1       For this assessment, we have coupled the global-scale circulation model GEOS-Chem with the

2 regional scale air quality model CMAQ (see the discussion of CMAQ in Section 3.5.4.) to simulate one

3 year of air quality data over the CONUS in two series of runs, the first with all anthropogenic and

4 biogenic emissions included and the second annual series with the zero-out approach described just

5 above. The models were set up in this way: GEOS-Chem version 7, with modifications to include

6 aromatic and biogenic secondary organic aerosol formation; emissions computed from a variety of

7 sources including the Global Emissions Inventory Activity (GEIA; Benkovitz et al., 1996), and Emissions

8 Database for Global Atmospheric Research, version 2 (EDGAR; Olivier et al., 1996; Olivier et al., 1999).

9 Particularized emissions in specific areas used the European Monitoring and Evaluation Program (EMEP;

10 (Auvray and Bey, 2005), BRAVO (Kuhns and Knipping, 2005) for Mexico, Streets et al. (2006) for Asia,

11 Martin et al. (2002) for additional $NO_X$ emissions from biofuels, lightning, and ship traffic, Bond et al.

12 (2004) for global primary organic aerosols, Cooke et al., (1999) and Park et al. (2003) for U.S. primary

13 organic aerosols. Biomass burning emissions are not climatological but were computed with GFEDv2

14 (Giglio et al., 2006; van der Werf et al., 2006) monthly values using active fire observations from

15 MODIS; global dust fields were computed off-line using GOCART (see emissions from DEAD

16 (http://dust.ess.uci.edu/dead/) to make annual adjustments to photolysis rates and heterogeneous-phase

17 chemistry.

18       The regional CTM was configured in this way: CMAQ version 4.7 (excluding the dynamic coarse

19 mode updates), using the SAPRC_99 chemical mechanism and AERO5 aerosol module; emissions

20 processed through SMOKE (http://smoke-model.org) version 2.4 based on the 2004 projections from the

21 NEI with specific CEM, biogenics, and fire updates; MM5 version 3.7.4 with the Asymmetric Convective

22 Mixing, version 2.2, PBL scheme; and data nudging to analyze fields for winds and temperature.

*Model Evaluation*

23       Details from evaluations of the performance of a number of CMAQ applications are given in

24 Arnold et al. (2003), Eder and Yu (2006), Appel et al. (2005), and Fuentes and Raftery (2005).

25       In an annual simulation series for 2002 using CMAQ v4.6.1 in two 12 km domains for the CONUS

26 (see Figure 3-61), predicted concentrations of summertime $pSO_4$, often a major determinant of surface-

27 layer PM concentrations, were well-predicted by CMAQ at 12 km grid spacings, to within a factor of 2 at

28 nearly every point of comparison and with $R^2 > 0.8$ across all three national networks (CASTNet,

29 IMPROVE and CSN); a more detailed description is included in the 2008 $NO_X$-$SO_X$ ISA (U.S. EPA,

30 2008e). This result for CMAQ v4.6.1 for 2002 tracks the generally well-predicted $SO_4^{2-}$ concentrations

31 found in most earlier CMAQ evaluations: see Mebust et al. (2003), Eder and Yu (2006), and Tesche et al.

32 (2006). Since $pSO_4^{2-}$ concentrations are strongly a function of precipitation, care must be taken to ensure

1   that the meteorological solution driving individual CMAQ chemical applications produces precipitation

2   fields with low bias as discussed by Appel et al. (2008).
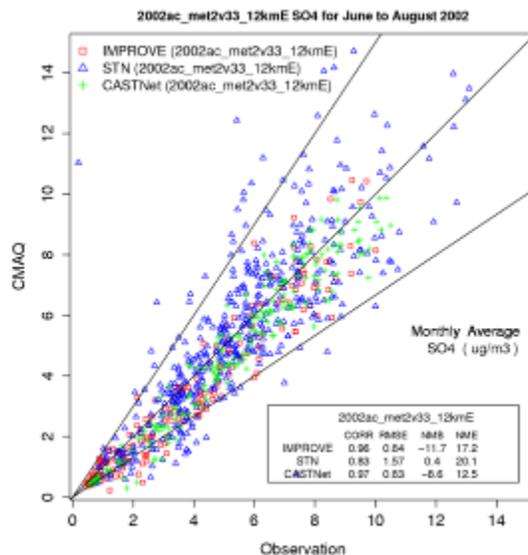


**Figure 3-61.   12-km EUS Summer SO$_4^{2-}$ PM each data point represents a paired monthly averaged (June/July/August) observation and CMAQ prediction at a particular IMPROVE, STN, and CASTNet site.  Solid lines indicate the factor of 2 around the 1:1 line shown between them.**

3           Wintertime pNO$_3$ (Figure 3-62) and total NO$_3$ (HNO$_3$ + pNO$_3$) (Figure 3-63) concentrations are

4   predicted as well by CMAQ; but NO$_3^-$ is a pervasively difficult species to measure and model. Still, at the

5   CASTNet nodes where the total NO$_3^-$ concentrations are higher than they are at all but a few of the

6   remote IMPROVE sites, CMAQ predicts concentrations for nearly every node to within a factor of 2 and

7   with an R$^2$ >0.8.
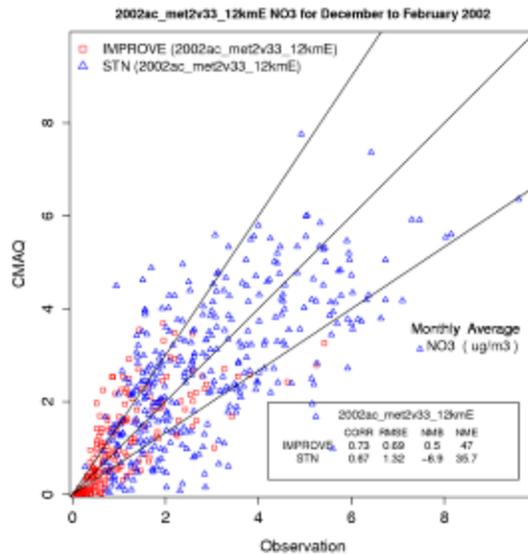
**Figure 3-62    12-km EUS Winter nitrate PM, each data point represents a paired monthly averaged (December/January/February) observation and CMAQ prediction at a particular IMPROVE and STN site.  Solid lines indicate the factor of 2 around the 1:1 line shown between them.**
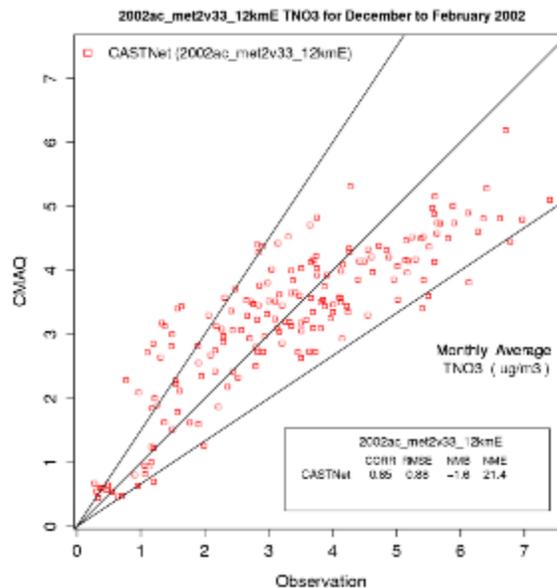


**Figure 3-63.   12-km EUS Winter total nitrate (HNO$_3$ + total pNO$_3$), each data point represents a paired monthly averaged (December/January/February) observation and CMAQ prediction at a particular CASTNet site.  Solid lines indicate the factor of 2 around the 1:1 line shown between them.**

1    A "base case" in which conditions for 2004 including all the anthropogenic and natural sources both

2    within and outside of the U.S., Canada and Mexico was run for comparison with measurements. A PRB

1    simulation was also run by shutting off the anthropogenic sources of primary PM and precursors to

2    secondary PM in the U.S., Canada and Mexico.
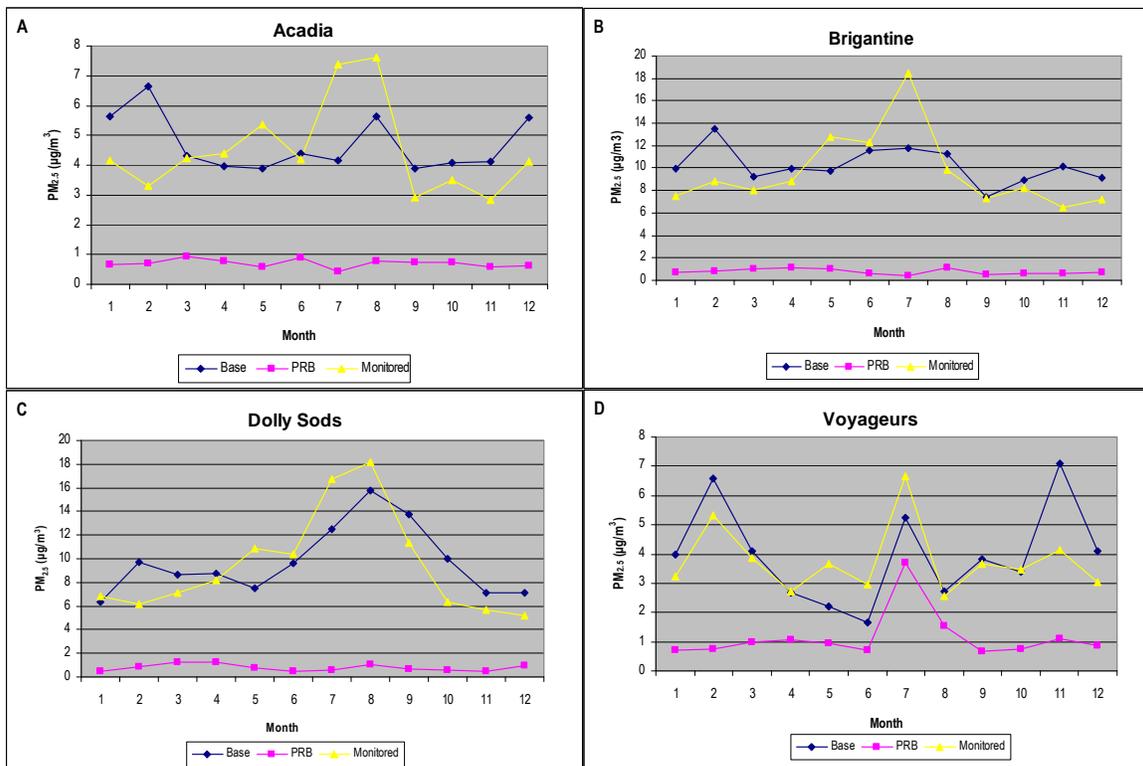


**Figure 3-64.   Monthly average of PM$_{2.5}$ concentrations measured at IMPROVE sites in the East and Midwest for 2004.  Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB.**

3          Figures 3-61 through 3-63 show monthly average concentrations, and Figures 3-64 through 3-66

4    show 24-h average concentration distributions for 2004 predicted by CMAQ for the base case and for

5    PRB and measurements at the IMPROVE sites shown in Figure 3-60. As can be seen from Figures 3-61

6    and 3-64 , CMAQ predicted base case concentrations are generally within 1 or 2 μg/m$^3$ across the entire

7    concentration distribution at Eastern and Midwestern sites. There is an indication that wild fires affected

8    the grid cell containing the Voyageurs site, but that the site itself was not affected. The "base case"

9    simulations tend to underestimate concentrations throughout the concentrations at most western sites as

10   shown in Figures 3-62 and 3-65. These underestimates are still within the range of a few μg/m$^3$. However,

11   the base case simulation also greatly over-predicts PM$_{2.5}$ concentrations at the upper end of the

12   distribution at the Redwoods site (Figure 3-66). This over-prediction results from emissions from wild

13   fires in northern California that are included in the grid cell containing the Redwoods site, but may not

1  have affected the site. However, wild fires indicated by MODIS would have affected other areas either

2  close to these sites or could have affected other locations in-between the IMPROVE sites.
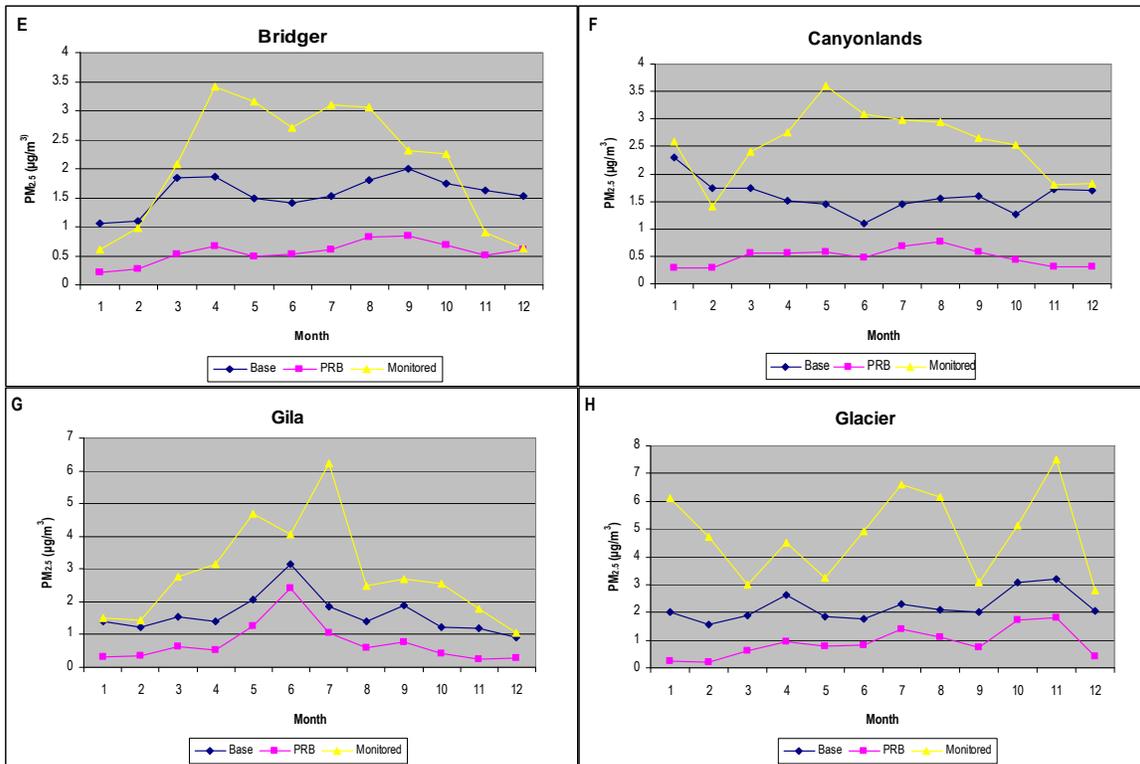


**Figure 3-65.** **Monthly average of PM$_{2.5}$ concentrations measured at IMPROVE sites in the West for 2004. Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB. Note the scale change from the preceding figures.**
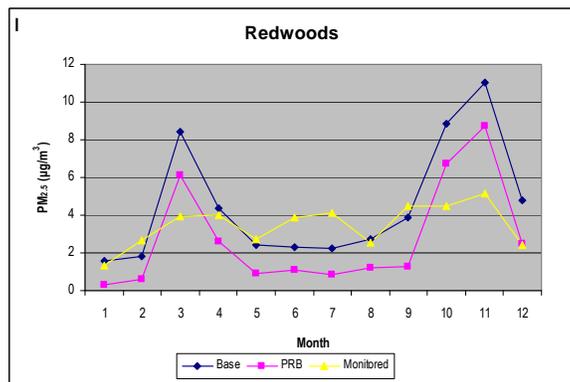


**Figure 3-66.** **Monthly average of PM$_{2.5}$ concentrations measured at the Redwoods National Park IMPROVE sites in California for 2004. Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB. Note the scale change from the preceding figures.**
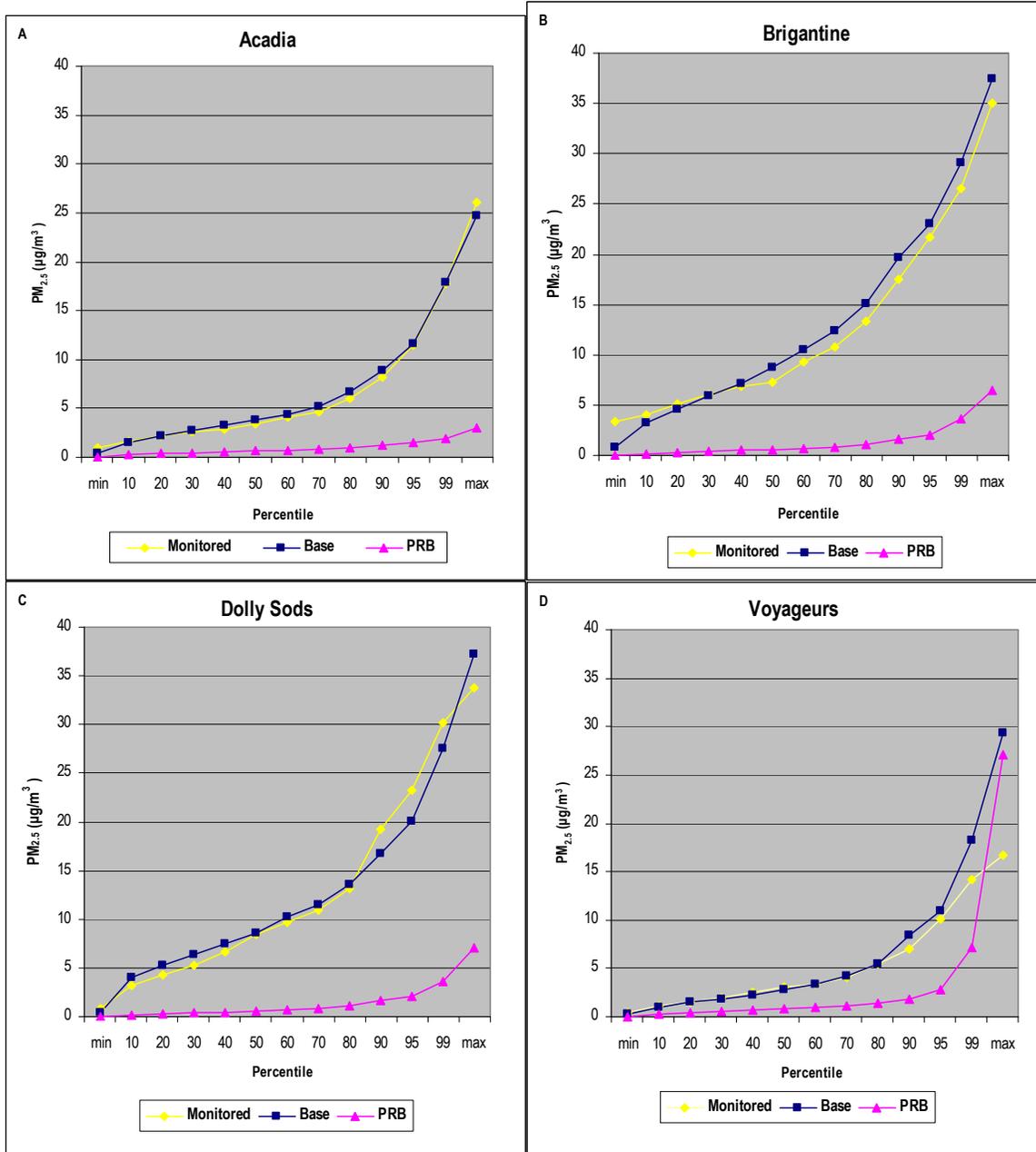
**Figure 3-67.** Distribution of PM$_{2.5}$ concentrations measured at IMPROVE sites in the East and Midwest for 2004. Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB.
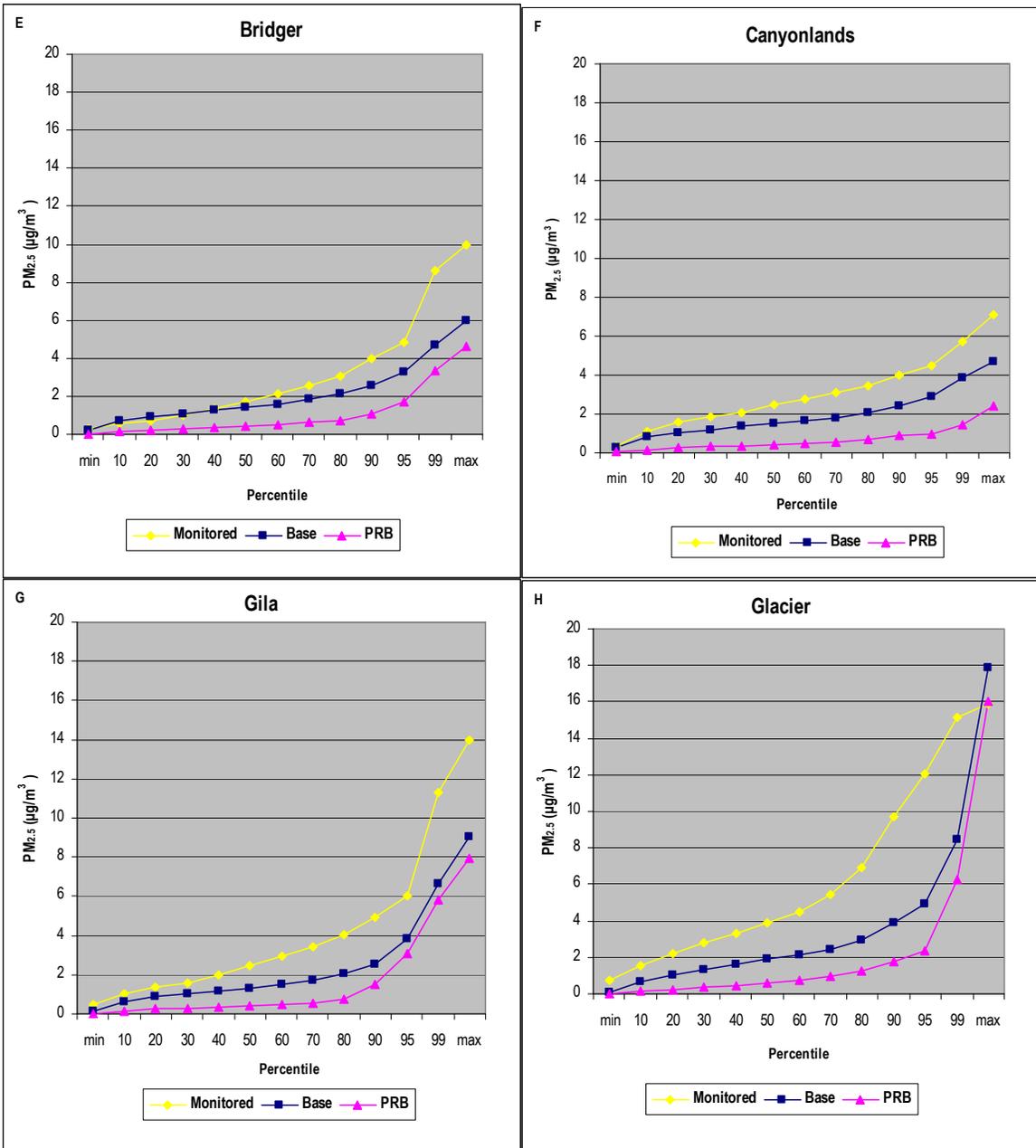
**Figure 3-68.** Distribution of PM$_{2.5}$ concentrations measured at IMPROVE sites in the West for 2004. Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB. Note the scale change from the preceding figures.
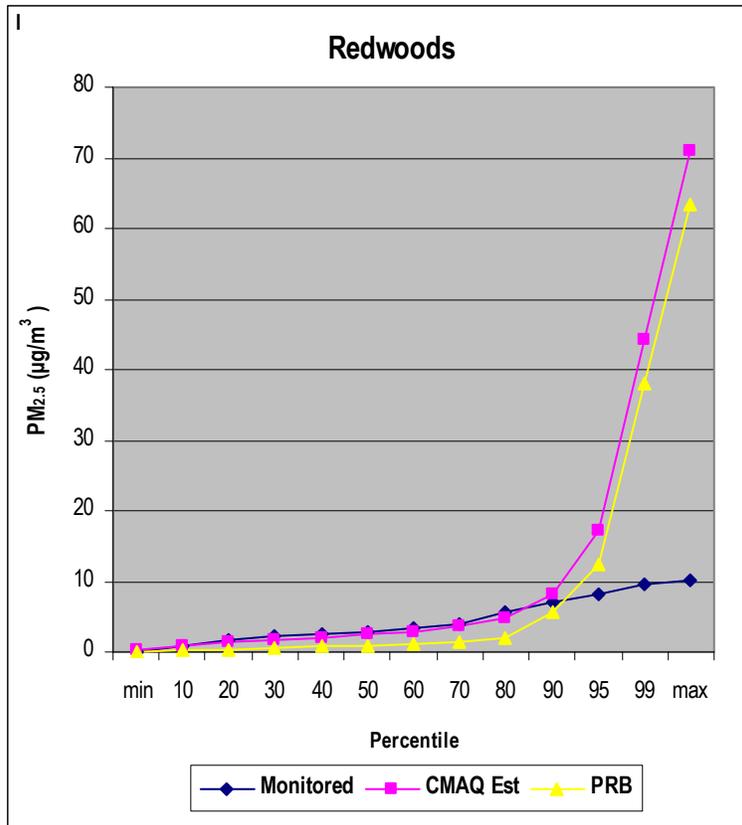
**Figure 3-69. Distribution of PM$_{2.5}$ concentrations measured at the Redwoods National Park IMPROVE sites in California for 2004. Also shown are distributions of PM$_{2.5}$ concentrations calculated by CMAQ for the base case and for PRB. Note the scale change from the preceding figures.**

1    Table 3-23 gives the annual and quarterly average CMAQ predictions at IMPROVE sites for the

2    "base case" and the ratio of CMAQ predictions to the measured concentrations at those sites in 2004.

3    CMAQ performance for the annual average concentrations and most of the seasonal averages is very

4    good in the East and Midwest, generally falling within 35%. In the West, CMAQ's prediction of PM2.5

5    mass averages at these remote sites is generally too low in all seasons, often by 50%. Air quality model

6    predictions in the mountainous West are often less-good than over the flatter terrain in the East and

7    Midwest because the model's grid spacing (36 km in this case) smoothes over significant variation at the

8    surface which results in differences at such remote sites. However, the model's trend relative to the

9    geospatial difference is correct: the predicted PM2.5 concentrations are lower at the western sites than

10   they are in the East, just as the measurements are. Table 3-24 shows corresponding PRB PM$_{2.5}$

11   concentrations at IMPROVE sites.

**Table 3-23. Annual and quarterly mean PM₂.₅ concentrations (µg/m³) for the CMAQ "base case" at IMPROVE sites in 2004.**

| | Annual; mod/obs | Jan-March; mod/obs | Apr-Jun; mod/obs | Jul-Sep; mod/obs | Oct-Dec; mod/obs |
|---|---|---|---|---|---|
| *EAST* | | | | | |
| Acadia | 4.7; 1.04 | 5.6; 1.44 | 4.0; 0.87 | 4.6; 0.77 | 4.6; 1.31 |
| Brigantine | 10.2; 1.07 | 10.9; 1.35 | 10.3; 0.91 | 10.2; 0.88 | 9.4; 1.29 |
| Dolly Sods | 9.8; 1.03 | 8.3; 1.24 | 8.6; 0.88 | 14.0; 0.90 | 8.0; 1.40 |
| *MIDWEST* | | | | | |
| Voyageurs | 4.0; 1.05 | 4.9; 1.19 | 2.2; 0.71 | 3.9; 0.93 | 4.9; 1.36 |
| *WEST* | | | | | |
| Bridger | 1.6; 0.76 | 1.3; 1.08 | 1.6; 0.52 | 1.8; 0.64 | 1.7; 1.30 |
| Canyonlands | 1.6; 0.62 | 1.9; 0.86 | 1.4; 0.44 | 1.5; 0.52 | 1.6; .76 |
| Gila | 1.6; 0.55 | 1.4; 0.70 | 2.2; 0.55 | 1.7; 0.45 | 1.1; 0.61 |
| Glacier | 2.2; 0.45 | 1.8; 0.39 | 2.1; 0.50 | 2.1; 0.40 | 2.8; 0.56 |
| Redwood | 4.6; 1.31 | 4.0; 1.48 | 3.0; 0.83 | 2.9; 0.78 | 8.4; 2.15 |

**Table 3-24. Annual and quarterly mean PM₂.₅ concentrations (µg/m³) for the CMAQ PRB simulations at IMPROVE sites in 2004.**

| | Annual | Jan-March | Apr-Jun | Jul-Sep | Oct-Dec |
|---|---|---|---|---|---|
| *EAST* | | | | | |
| Acadia | 0.70 | 0.76 | 0.76 | 0.65 | 0.65 |
| Brigantine | 0.77 | 0.86 | 0.91 | 0.70 | 0.63 |
| Dolly Sods | 0.79 | 0.88 | 0.83 | 0.75 | 0.66 |
| *MIDWEST* | | | | | |
| Voyageurs | 1.2 | 0.83 | 0.91 | 2.0 | 0.93 |
| *WEST* | | | | | |
| Bridger | 0.57 | 0.33 | 0.57 | 0.76 | 0.61 |
| Canyonlands | 0.49 | 0.38 | 0.54 | 0.68 | 0.35 |
| Gila | 0.74 | 0.42 | 1.4 | 0.80 | 0.32 |
| Glacier | 0.91 | 0.36 | 0.87 | 1.1 | 1.3 |
| Redwood | 2.8 | 2.4 | 1.5 | 1.1 | 6.1 |

1    Table 3-25 illustrates CMAQ predictions of seasonal variation in the base case PM₂.₅

2    concentrations across regions of the CONUS, while Table 3-26 shows CMAQ predictions of the seasonal

3    variation in regional PRB PM₂.₅ concentrations. Highest base case PM₂.₅ concentrations were observed for

1 the Northeast, Southeast, and Industrial Midwest with highest concentrations during the fall and winter

2 (and comparably high concentrations in the summer for the Industrial Midwest), while PRB PM$_{2.5}$

3 concentrations were highest annually in the Southeast, which has highest levels during the winter. In the

4 summer, PRB PM$_{2.5}$ is comparable for the Northwest and Southeast and elevated but slightly lower for the

5 Southwest. These observations also likely suggest the influence of wildfires in the west.

**Table 3-25.** Annual and quarterly mean of the CMAQ-predicted base case PM$_{2.5}$ concentrations (µg/m$^3$) in the U.S. EPA CONUS regions in 2004.

| | Annual | January-March | April-June | July-September | October-December |
|---|---|---|---|---|---|
| Northeast | 9.76 | 10.74 | 8.38 | 9.55 | 10.38 |
| Southeast | 10.05 | 12.28 | 7.72 | 9.78 | 10.42 |
| Industrial Midwest | 11.38 | 12.22 | 9.37 | 11.89 | 12.00 |
| Upper Midwest | 6.70 | 8.83 | 4.95 | 5.34 | 7.67 |
| Southwest | 3.30 | 4.08 | 2.77 | 3.31 | 3.03 |
| Northwest | 2.72 | 2.49 | 2.21 | 2.71 | 3.44 |
| Southern California | 4.43 | 4.64 | 3.93 | 4.34 | 4.82 |

**Table 3-26.** Annual and quarterly mean of the CMAQ-predicted PRB PM$_{2.5}$ concentrations (µg/m$^3$) in the U.S. EPA CONUS regions in 2004.

| | Annual | January-March | April-June | July-September | October-December |
|---|---|---|---|---|---|
| Northeast | 0.74 | 0.85 | 0.78 | 0.67 | 0.68 |
| Southeast | 1.72 | 2.43 | 1.41 | 1.41 | 1.64 |
| Industrial Midwest | 0.86 | 0.89 | 0.89 | 0.94 | 0.73 |
| Upper Midwest | 0.84 | 0.79 | 0.93 | 0.99 | 0.66 |
| Southwest | 0.62 | 0.61 | 0.76 | 0.70 | 0.40 |
| Northwest | 1.01 | 0.48 | 0.81 | 1.42 | 1.32 |
| Southern California | 0.84 | 0.54 | 0.92 | 1.21 | 0.67 |

# 3.7. Issues in Exposure Assessment for PM and its Components

## 3.7.1. Introduction and Key Concepts

1       The purpose of this section is to present the latest exposure assessment studies for the purpose of

2    aiding the interpretation of epidemiologic studies described in subsequent chapters of this Integrated

3    Science Assessment. A theoretical model of personal exposure is presented to highlight what is

4    measurable and what uncertainties exist in this framework.

5       An individual's daily exposure to airborne PM can be described based on a compartmentalization

6    of the person's activities throughout a day:

$$E = \int C_j \, dt$$

<div align="right">*Equation 3-2*</div>

7    where $E$ = 24-h exposure, $C_j$ = airborne PM concentration at location $j$, and $dt$ = portion of the day spent

8    in location $j$. This basic equation was broken down by Wu et al. (2005) into a microenvironmental model

9    that accounts for exposure to pollutants generated indoors and outdoors of the form:

$$E = f_o C_o + \sum f_i C_i$$

<div align="right">*Equation 3-3*</div>

10    where $f$ = fraction of a day, subscript $o$ = outdoor, and subscript $i$ = indoor. Note that $f_o + \Sigma f_i = 1$, and the

11    indoor term has a summation because it reflects various microenvironmental exposures. Here, "indoors"

12    refers to being inside any aspect of the built environment, e.g. home, office buildings, enclosed vehicles

13    (automobiles, trains, buses), and/or recreational facilities (movies, restaurants, bars). "Outdoor" exposure

14    can occur in parks, yards, sidewalks, and on bicycles or motorcycles. It is proportional to the ambient

15    concentration detected at monitoring sites. The complex human activity patterns across the population (all

16    ages) are illustrated in Figure 3-70 (Klepeis et al., 2001). This figure illustrates the diversity of daily

17    activities among the population as well as the proportion of time spent in each microenvironment.

**Figure 3-70. Distribution of time sample population spends in various environments, from the National Human Activity Pattern Survey.**
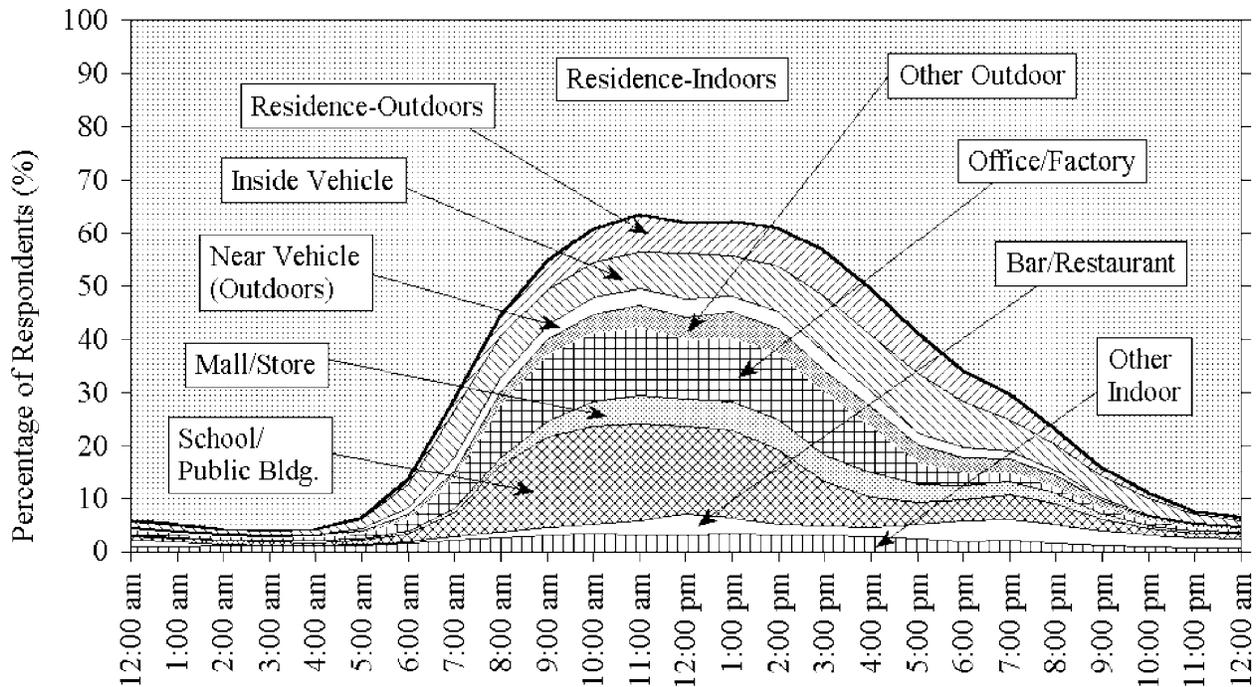
Source: Klepeis et al. (2001)

1    In general, the relationship between personal exposures and ambient concentrations is complex

2    because ambient pollutants can be lost through chemical and physical processes in microenvironments

3    and the composition of PM can be modified during infiltration of outdoor air into microenvironments

4    (Meng et al., 2007a; Sarnat et al., 2006b).

5    The infiltrated outdoor PM is a function of outdoor PM and infiltration factors specific to the

6    ventilation properties of the building or vehicle in which the person is exposed:

$$C_{o_{\text{inf}}} \;=\; F_{\text{inf}} \; C_o$$

*Equation 3-4*

8    where $F_{inf} = Pa/(a + k)$ = infiltration factor (assuming the indoor mass balance is at steady state),

9    $P$ = penetration coefficient, $a$ = air exchange rate and $k$ = particle loss rate. $F_{inf}$ quantifies the equilibrium

10   fraction of the PM concentration outside the microenvironment that penetrates inside the

11   microenvironment and remains suspended. It is a function of the building air exchange characteristics and

12   the particle properties. Properties of $F_{inf}$ and studies of infiltration are summarized in Section 3.7.3.

13   If there are no significant local, outdoor sources and sinks of PM, then $C_a$, the concentration

14   measured by an ambient monitor can be approximated by $C_o$. In this case, the ambient component of a

15   pollutant's microenvironmental concentration can be represented as the product of the ambient

1  concentration and the infiltration factor ($F_{inf}$ or α [if people spend 100% of their time indoors]). Alpha, α,

2  is the ratio of personal exposure from a pollutant of ambient origin to the pollutant's ambient

3  concentration (or the ambient exposure factor); α varies between 0 and 1. If local sources and sinks exist

4  and are significant, then the ambient component of outdoor air must be estimated using dispersion

5  models, land use regression models, receptor models, fine scale chemistry-transport models or some

6  combination of these techniques (cf. Section 3.7.2.3).

7      A variety of approaches can be used to estimate exposure to ambient PM. In some cases, individual

8  personal exposures are measured with personal exposure monitors (PEMs), where personal samples are

9  taken to estimate population exposure. In other cases, ambient concentrations are used as an exposure

10  surrogate. The ambient concentration may be based on measurements made at a single ambient monitor,

11  or as the average of several ambient monitors. If appropriate measurements are made, it is also possible to

12  estimate the ambient and non-ambient components of personal exposure. Two studies have used average

13  relationships for a panel to infer average relationships for a larger cohort (Dominici et al., 2000; Strand et

14  al., 2006), one study has used the average relationships for each member of a panel (Koenig et al., 2005),

15  and one study has estimated the unmeasured ambient and non-ambient components of personal exposure

16  for each panelist (Ebelt et al., 2005; Wilson and Brauer, 2006). Better associations are obtained between

17  health effects and ambient exposure than between health effects and total personal exposure. Wilson and

18  Brauer's (2006) results indicate that exposure error is introduced by: (1) using ambient concentrations

19  instead of ambient exposure (ambient concentrations showed an association with the effect but it was not

20  statistically significant): and (2) assuming ambient exposure and non-ambient exposure have the same

21  effects on health outcomes, i.e., identical toxicity, (there was essentially no association of the effect with

22  total personal exposure or the non-ambient component).

23      The use of personal exposure in population exposure assessment studies could cause various errors

24  in the health effect estimate because ambient and non-ambient particles differ in size distribution and

25  chemical composition (Ebelt et al., 2005; Long et al., 2001; Wilson and Suh, 1997), and the correlation

26  between personal exposure and ambient concentration may be different for each subject and may not be

27  statistically significant (Wilson et al., 2007b). Moreover, the use of ambient concentration could cause

28  error because the relationship between ambient concentration and personal exposure may be different for

29  each subject in the panel. The correlation between ambient concentration and personal exposure may be

30  high for some subjects, in which case the exposure error caused by using ambient concentration instead of

31  personal exposure may be small. In other subjects, the correlation may be low or negative (and not

32  statistically significant). In this case, the exposure error will be high and may obscure relationships

33  between ambient exposure and health effects. Table 3-27 shows the correlations between ambient

34  concentration and personal exposure and the t-statistic for the one panel (Ebelt et al., 2005; Wilson et al.,

1    2007b) (the relationship was statistically significant only for 5 of the 16 subjects). However, the

2    relationships between ambient concentration and the ambient component of personal exposure were

3    statistically significant for all subjects. These differences in correlation occur in part because the ambient

4    exposure factor, α, is different for each subject as shown in Table 3-27. Therefore, ambient concentration

5    will be better than total personal exposure as a surrogate for ambient exposure.

**Table 3-27.    Statistical parameters for the relationships between exposures and ambient concentrations for each subject separately (values of C based on average of five monitoring sites, E and A outliers included) sorted according to the correlation coefficient of E with C.**

| Subject | [1]R for E | [2]t for E | [3]r for A | [4]α |
|---------|------------|------------|------------|------|
| 13 | 0.83 | 3.35 | 0.92 | 0.71 |
| 2 | 0.82 | 3.15 | 0.95 | 0.78 |
| 4 | 0.74 | 2.47 | 0.75 | 1.04 |
| 15 | 0.74 | 2.17 | 0.89 | 0.82 |
| 1 | 0.72 | 2.33 | 0.90 | 0.64 |
| 11 | 0.68 | 1.85 | 0.99 | 0.96 |
| 3 | 0.66 | 1.98 | 0.96 | 0.83 |
| 5 | 0.51 | 1.20 | 0.86 | 0.70 |
| 8 | 0.44 | 1.09 | 0.87 | 0.95 |
| 14 | 0.40 | 0.96 | 0.56 | 0.39 |
| 7 | 0.20 | 0.45 | 0.87 | 0.72 |
| 10 | 0.08 | 0.18 | 0.90 | 0.54 |
| 12 | 0.02 | 0.04 | 0.98 | 0.64 |
| 9 | −0.19 | −0.42 | 0.97 | 0.94 |
| 6 | −0.28 | −0.65 | 0.90 | 0.73 |
| 16 | −0.68 | −1.59 | 0.77 | 0.62 |
| Average | 0.36 | | 0.88 | 0.75 |
| STD | 0.45 | | 0.11 | 0.18 |
| CV | 1.26 | | 0.13 | 0.24 |

[1]Pearson's correlation coefficient, R, for the correlation of the specified variable with the corresponding ambient concentration.
[2]The t-statistic for the slope of the regression of E against C (t >2 indicates statistical significance at the p <0.05 level).
[3]All values of r are statistically significant.
[4]Average, for each subject separately, of individual values of á ij estimated using $\alpha_{ij} = E_{ij}/C_i$ for $SO_4^{2-}$ data as an estimate of $\alpha_{ij}$.

Source: Wilson and Brauer (2006)

# 3.7.2. Methods for Estimating PM Exposures

1      The purpose of this section is to present new discoveries related to measuring and modeling aerosol

2    concentration and the error involved in these endeavors. A review of over 200 personal and

3    microenvironmental PM exposure studies published since 2002 (see Annex A) reveals that the majority of

4    the monitoring and modeling techniques in use were previously reviewed in the 2004 PM AQCD

5    (U.S. EPA, 2004) for PM. Detailed descriptions of these methodologies are provided in the 2004 PM

6    AQCD and therefore will not be repeated in this document. The following sections will include only

7    findings from 2002 or later regarding monitoring and modeling methodologies in common use and

8    significant advancements in understanding the capabilities and limitations of these methods for

9    assessment of PM exposure.

## 3.7.2.1. Exposure Monitoring and Associated Instrumental Measurement Errors

### *New Developments in Personal Exposure Monitoring Techniques*

10    Personal exposure sampling methodology consists largely of integrated filter sampling using a

11    cyclone or Personal Exposure Monitor (PEM) to achieve a cut-point at a desired particle size (e.g., Hopke

12    et al., 2003; Larson et al., 2004). This method of sampling facilitates speciation work because the filters

13    can be archived for chemical and gravimetric analysis. Additionally, light scattering aerosol detection

14    instruments, such as the personal DataRam (pDR) and SidePak personal aerosol monitor have seen some

15    usage in personal $PM_{10}$, $PM_{2.5}$, and $PM_1$ monitoring (e.g., Lewné et al., 2006). However, because these

16    technologies are not new, the reader is again referred to the 2004 PM AQCD for further information on

17    these techniques.

18    One area of further development is in personal sampling of the thoracic and respirable particle size

19    distribution. Variations of the cascade impactor have been developed for personal sampling and tested for

20    use in field studies (Case et al., 2008; Lee et al., 2006a; Singh et al., 2003). The models developed and/or

21    tested by (Lee et al., 2006a) and Case et al. (2008) operate with a 1 μm cut point and therefore can

22    characterize respirable particles well. The Personal Cascade Impactor Sampler (PCIS) has the capability

23    to sample down to a cutpoint of 250 nm (Singh et al., 2003). For $PM_{2.5}$, the difference between the PCIS

24    and MOUDI cascade impactor was 11%, while difference between the PCIS and SMPS-APS was only

25    2%. Difference in $PM_{2.5}$ species compared with the MOUDI was generally higher: 11% for $SO_4^{2-}$, 22%

26    for $NO_3^-$, 19% for EC, and 94% for OC. Mass was overestimated by 3%, 16%, and 31% for $PM_{1-0.5}$,

27    $PM_{0.5-0.25}$, and $PM_{0.25}$, respectively, when compared with the SMPS-APS. Similarly, Case et al. (2008)

28    found a difference ranging from -11 to +10% for $PM_{10-2.5}$ with the Personal Respirable Particulate

29    Sampler (PRPS), and Lee et al. (2006a) found a difference of -6 to 0% for $PM_{2.5}$ and -6 to -1% for $PM_{10}$

1    when comparing this device with the PEM. Leith et al. (2007) also tested a passive PM sampler for

2    detection of $PM_{10-2.5}$ and found the difference between a $PM_{10-2.5}$ FRM and the co-located passive sampler

3    was within 1σ of concentrations measured by the FRM samplers.

### New Developments in Microenvironmental Exposure Monitoring Techniques

4        The majority of developments since the 2004 PM AQCD regarding microenvironmental PM

5    characterization have involved real-time instrumentation in the ultrafine PM size range. Because these

6    methods are also used for ambient sampling, they are described in section 3.4.

7        New developments in microenvironmental sampling for exposure assessment have also included

8    construction, testing, and implementation of mobile environmental sampling laboratories for PM mass,

9    particle count, and composition, as well as other criteria pollutants (CO, $SO_X$, $NO_X$, $O_3$). These mobile

10   laboratories typically contain a suite of real-time equipment with short sampling intervals (e.g. 1-10

11   minutes), such as an SMPS with CPC, APS, laser photometers, and aethalometers for aerosols; FRMs for

12   the gaseous criteria pollutants; weather station for meteorological variables, and a Global Positioning

13   System (GPS) for position. Videotape or journal observations are sometimes logged simultaneously to

14   track local on-road sources of pollution in this way. One key application of mobile laboratory technology

15   is assessment of the outdoor microscale environments and in-vehicle microenvironments on roadways for

16   determining exposure during on-road transportation (Pirjola et al., 2004; Sabin et al., 2005; Weijers et al.,

17   2004; Westerdahl et al., 2005). For instance, Sabin et al. (2005) used videotape records to determine

18   whether BC detected on a school bus was the result of local outdoor sources from other vehicles or

19   "self-pollution" from the school bus's own engine exhaust. Westerdahl et al. (2005) used the GPS time

20   series to determine that minima in the ultrafine PM time series corresponded to passage through

21   residential areas of Long Beach and Pasadena, in contrast to the pollution spikes observed along

22   highways. Studies have also shown that detection of automobile and DE could be improved through use

23   of combined measurement results to improve statistical analysis (Ntziachristos and Samaras, 2006) and

24   identification of best tools for measurement (Kinsey et al., 2006).

### Measurement Error at Community-Based Ambient Monitors and Exposure Assessment

25       Section 3.4 discusses potential errors in measuring ambient PM in detail. Because there will likely

26   be some random component to instrumental measurement error, the correlation of the measured PM mass

27   with the true PM mass will likely be less than 1. Sheppard et al. (2005) indicate that instrument error in

28   the individual or daily average concentrations have "the effect of attenuating the estimate of α." However,

29   Zeger et al. (2000) state that the "instrument error in the ambient levels is close to the Berkson type" and

30   in order for this error to cause substantial bias in later estimation of the health outcome, the error term (the

1  difference between the true concentrations and the measured concentrations) must be strongly correlated

2  with the measured concentrations. Zeger et al. (2000) suggest that, "Further investigations of this

3  correlation in cities with many monitors are warranted."

### *Measurement Error for Personal Exposure Monitors*

4  PEMs are specialized monitors that, because people must carry them, have to be small, light, guiet,

5  and battery operated or passive. As a result, they may have lower flow rates and pressure drops for filter

6  measurements of PM or light scattering measurements that are not sensitive to ultrafine or smaller

7  accumulation mode particles. Thus, there may be considerable differences between the ambient

8  measurement and the PEM measurement of the same indicator. This is especially a problem for

9  semi-volatile components such as OC and $NH_4NO_3$. These errors are described in much greater detail in

10  the 2004 PM AQCD (U.S. EPA, 2004).

### *Exposure Error Associated with Community-Based Ambient Monitor Height*

11  Community-based ambient monitor height can affect estimates of exposure. Maletto et al. (2003)

12  measured vertical accumulation mode, fine, and coarse particle distributions for elevations up to 1000 m

13  with a suite of instruments and demonstrated substantial variability in the vertical profile. Their results

14  show significantly higher concentrations at ground level in the fine and coarse mode and substantially less

15  variation in the accumulation mode during daytime. In the case of community-based ambient monitoring,

16  variation closer to ground level is more relevant because monitors are not sited more than 14 m above

17  ground level (Watson et al., 1997). Wu et al. (2002) performed outdoor monitoring at heights of 2, 8, 19,

18  30, 59, and 79 m above ground level along a street with average traffic of 1485 vehicles per hour. When

19  moving from 2 m to 8 m above ground level, average measured concentration dropped by 26% for $PM_{10}$,

20  12% for $PM_{2.5}$, and 15% for $PM_1$. Over the measurement heights from 2 m to 79 m, averaged measured

21  concentration dropped by 40% for $PM_{10}$, 37% for $PM_{2.5}$, and 19% for $PM_1$. These findings suggest that

22  measurements from elevated community ambient monitors underestimate ground-level outdoor

23  exposures.

## 3.7.2.2. Uncertainties in PM Exposure Assessment

### *Relationship between Community-Based Ambient Measurements and Personal Exposure*

24  Intra-urban spatiotemporal variability (i.e. central site concentrations vs. concentrations outside a

25  subject's home), as well as infiltration properties related to particle size and composition, are important

26  factors in the relationship between ambient measurements and personal exposures. Filleul et al. (2005)

computed exposure based on varying contributions of community-based ambient monitors and proximal monitors (to represent a receptor) and found that increasing the weight of proximal monitors resulted in non-significant but increased mean concentrations. Meng et al. (2004) examined representation of the ambient contribution to personal exposure using four models with increasing detail regarding differential infiltration and residential ventilation properties. The authors found that both the contribution of ambient PM to indoor exposures and the variability in those estimates increased with increased model detail. In other studies comparing ambient concentrations with indoor concentrations and personal exposures, Liu et al. (2003) and Williams et al. (2008) both noted large differences between central site monitor data and data obtained from personal and indoor $PM_{10}$ and $PM_{2.5}$ samplers. Williams et al. also noted this for $PM_{10-2.5}$, as shown in Figure 3-71.

Spatial variability among various studies further suggests that use of a single or small number of ambient monitors introduces uncertainty in exposure assessment studies. Violante et al. (2006) studied personal exposures to traffic of parking police in Bologna, Italy to determine how personal exposure to outdoor $PM_{10}$ and benzene compares with that measured at a community-based monitor. This study found that personal exposures to $PM_{10}$ were significantly higher than at the community-based monitor, although the authors were not able to demonstrate significant effects of meteorology or traffic on those exposures. Spatial heterogeneity of personal exposures to metals in $PM_{10}$ and $PM_{2.5}$, with higher levels found near high-traffic and industrial areas, was observed by Nerriere et al. (2007). In a Bayesian hierarchical model analysis of personal exposure and ambient data from the pilot Baltimore Epidemiology-Exposure Panel Study of 16 subjects, McBride et al. (2007) showed that community monitors overestimated personal exposures, and that these results were not sensitive to model selection. Likewise, significant differences among personal, indoor, and outdoor community monitors in studies by Adgate et al. (2002; 2003) and Kim et al. (2005b) were also reported. The results of these studies are described further in Section 3.7.3, but they are important to mention here in the context of representativeness of community monitored ambient PM across an urban population.
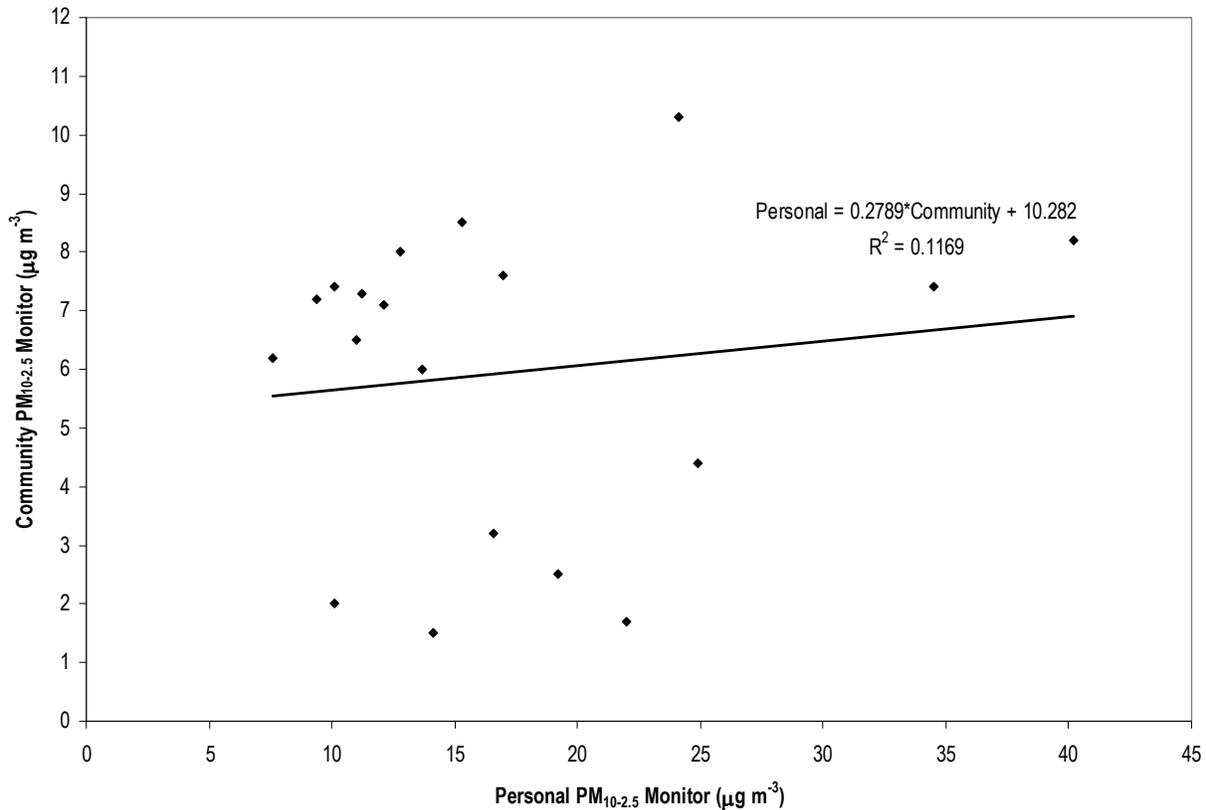
**Figure 3-71. Comparison of community dichot and personal exposure monitor for PM$_{10-2.5}$.**

### *Relationship between Community-Based Ambient Measurements and Community Averaged Concentrations*

#### Exposure Assessment for Community Time-Series Epidemiology

1    For community time-series epidemiology, the community averaged concentration, not the

2    concentration at each fixed monitoring site, is the concentration variable of concern (Zeger et al., 2000).

3    The correlation between the concentration at a central community ambient monitor and the community

4    averaged concentration depends on at least the following three factors:

5    ▪ Even distribution of the indicator across space: Regional pollutants such as $SO_4^{2-}$ will be

6        more evenly distributed than point source pollutants. Traffic emissions might show spatial

7        heterogeneity near sources but more homogeneous distribution farther downwind from

8        sources.

- Selection of the monitoring site chosen to represent the community average: If the site is selected to measure a "hot spot" or pollution from a nearby source, estimates across the community could be skewed upwards.

- Division of the community by terrain features or source locations into several sub-communities that differ in the temporal pattern of pollution: Intra-urban spatial heterogeneity is discussed in detail in Section 3.5. Community exposure may not be well-represented when monitors cover large areas with several sub-communities having different sources and topographies. This point is illustrated for Los Angeles in Figures 3-27 and 3-36.

In Phoenix, the use of ZIP-code classified mortality data enabled researchers to find high risk ratios in a small area near the monitoring site (Mar et al., 2003; Wilson et al., 2007b) while use of county-wide data produced non-significant associations (Moolgavkar, 2000; Smith et al., 2000). It seems likely that at least part of the heterogeneity found between cities in multicity studies is due to the use of a geographic area that is composed of several sub-communities that differ in the spatiotemporal distribution of air pollutants. For all metropolitan areas investigated in this assessment, the $PM_{10}$ data have significantly more scatter, which suggests that the uncertainty of the community average concentration would increase in the coarse PM range. Metrics have been developed and used to compare the spatial variability of air pollutants (Wongphatarakul et al., 1998). These metrics are useful in assessing the potential for exposure error in the epidemiologic studies, especially when different monitors are used on different days to construct city-wide averages.

### Long-Term Exposure Assessment for Epidemiology Studies

Epidemiologic studies of long-term exposure rely on differences among communities in long-term average ambient concentrations. If exposure errors are different in the different communities, the differences in long-term ambient concentrations among communities may not represent the differences in long-term average exposures. For example, there may be community to community differences in measurement error, in the average ambient exposure factor ($\alpha$) or the average non-ambient exposure. This could happen if exposure to fresh pollutants generated by vehicular traffic or pollutants from other localized sources differed among the spatial areas. Thus, in a regression of health effects against average concentration (as an indicator for average exposure) there could be a different amount of error (either positive or negative) in the exposure indicator for each spatial area. This could add error and bias the slope up or down. There is a general progression toward the use of concentration fields that account for spatial variations in concentration. However, it has not yet been possible to include individual or small-area variations in the personal exposure to ambient concentrations or variations in personal

1    exposures to indoor-generated pollutants in long-term studies of the associations of pollutants with health

2    effects.

### 3.7.2.3. PM Exposure Modeling

#### *Exposure Modeling Techniques*

**Stochastic Population Exposure Models**

3        Section 3.7.1 describes the conceptual model representing an individual's exposure to PM of

4    ambient and non-ambient origin. A number of techniques to describe these exposures at the individual and

5    population level have been published since 2002. Population-based methods, such as the Air Pollution

6    Exposure (APEX), Simulation of Human Exposure and Dose System (SHEDS), and EXPOLIS (exposure

7    in polis, or cities) models, involve stochastic treatment of the model input factors

8    (http://www.epa.gov/ttn/fera/human_apex.html (Burke et al., 2001; Kruize et al., 2003). Another approach

9    is to predict location-based exposures using a deterministic model such as the CMAQ model, California

10    Line Source Dispersion Model (CALINE), CALPUFF (long-range plume transport model), and

11    Operational Street Pollution Model (OSPM) for determination of street-level PM pollution coupled with

12    infiltration models to represent indoor exposure to ambient levels (Appel et al., 2008; Gilliam et al., 2005;

13    Hering, 2007; Mensink et al., 2008; Wilson and Zawar-Reza, 2006). Stochastic and deterministic methods

14    are often combined, as described below. Land use regression (LUR) models have also been developed to

15    describe pollution levels as a function of source behavior (Briggs et al., 1997; Gilliland et al., 2005; Ryan

16    and LeMasters, 2007). These are described in detail in Annex 3.7 of the 2008 $NO_X$ ISA (U.S. EPA,

17    2008c). Recent developments are described in this subsection, and relevant errors in these approaches are

18    described in the following sub-section.

19        Stochastic models, such as SHEDS, APEX, and EXPOLIS utilize a distribution of pollution and

20    individual-level variables, such as ambient and local PM concentration source contributions and breathing

21    rate respectively, to compute the probability of individual exposure. Recently, SHEDS has been linked

22    with the Modeling Environment for Total Risk Studies (MENTOR) model to expand population exposure

23    assessment to individual risk assessment (Georgopoulos et al., 2005). In this formulation, CMAQ was

24    used to predict initial concentrations at a coarse scale, and then a spatiotemporal random field method

25    (Vyas and Christakos, 1997) or Bayesian max entropy method (Serre and Christakos, 1999) was applied

26    to interpolate the concentration to census tract scale in which exposure estimates are made. Activity

27    diaries such as the Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000) are employed

28    to estimate the time basis of microenvironmental exposures, and then specific microenvironmental

29    exposures are assessed by utilizing distributions of parameters such as air exchange rate. Finally, within

1    MENTOR, the estimates of exposure are related to dose and metabolic distributions to estimate risk of

2    specific health impacts.

### Dispersion Models

3    Dispersion models have been used both for direct estimation of exposure and as inputs for

4    stochastic modeling systems, as described above. For instance, CALPUFF was used to model transport

5    and dispersion in lower Manhattan following the September 11, 2001 World Trade Center collapse

6    (Gilliam et al., 2005) to determine average location-based exposures, and Wilson and Zawar-Reza (2006)

7    used the MM5 model to assess $PM_{10}$ dispersion and potential for exposure in Christchurch, New Zealand.

8    In a method similar to that employed by Georgopoulos et al. (2005) with SHEDS, Wu et al. (2005) used

9    CALINE to predict street-level concentrations of pollutants and input the results of that dispersion model

10   into an individual exposure model that accounts for infiltration of specific building characteristics. Wu et

11   al. also employed CHAD to estimate the time-basis of exposures. With an individualized exposure

12   approach, the model is deterministic. However, population exposures can be estimated by performing

13   repeated simulations using various housing characteristics and then computing a posterior probability

14   distribution function for exposure.

### Land Use Regression Models

15   LUR models are also applied to individuals, primarily at the intra-urban scale (Ryan and

16   LeMasters, 2007). At the census tract level, an LUR is a multivariate description of pollution as a function

17   of traffic, land use, and topographic variables (Briggs et al., 1997). Originally, LUR was used for $NO_2$

18   dispersion, but it was adapted for $PM_{2.5}$ exposure estimation by Brauer et al. (2003) for Stockholm,

19   Sweden, Munich, Germany, and throughout The Netherlands. This study found a measure of traffic

20   density to be the most significant variable predicting $PM_{2.5}$ exposure. Ryan et al. (2008) reported on an

21   LUR model for childhood exposure to traffic-derived EC for the Cincinnati Allergy and Air Pollution

22   Study and also found traffic to be the most important determinant of pollution. In this case, wind direction

23   was also factored into the model as a determinant of EC mixing. Like deterministic dispersion models,

24   LUR can be performed over wide areas to develop a posterior probability distribution function of

25   exposure at the urban scale.

26   Source proximity is sometimes used as a surrogate for exposure. For instance, Baxter et al. (2007a)

27   predicted indoor exposure to $PM_{2.5}$, EC, and $NO_X$ based on distance to traffic sources, indoor source

28   characteristics, window opening, and ambient concentrations in the Boston metropolitan area. In this

29   effort, Baxter et al. examined a variety of factors obtained from GIS including roadway density, roadway

30   length, average daily traffic, and population density to determine which variables were significant

1     predictors. They found that $PM_{2.5}$ was largely influenced by ambient $PM_{2.5}$ while EC was more sensitive

2     to local traffic sources. In a different approach, Corburn (2007) tested two distinct metrics, the cumulative

3     air toxics surface (CATS) and the U.S. EPA's National Air Toxics Assessment (NATA) to determine how

4     these approaches can yield estimates of human exposure to diesel and 33 air toxics for environmental

5     impact assessment. The CATS approach included an exposure term incorporating source density and

6     distance to source, and the sources could include traffic as well as bus depots and transfer stations,

7     airports, and industrial point sources. Corburn's paper demonstrated that robust land use data can provide

8     an approximation for urban exposures, although he cautioned that such estimates should not supersede

9     environmental monitoring but be used in arguing for added monitoring. In using these approaches, Huang

10    and Batterman (2000) warn that geographic divisions must be sufficiently small to avoid inter-zone

11    variability in source and exposure characteristics.


### Model-Related Errors

12    Model-related errors are determined by four factors: accuracy of the mathematical model, accuracy

13    of model inputs, scale model resolution, and model sensitivity. If verification errors related to these four

14    factors are minimized, then the model can beevaluated against physical data to determine how well the

15    model truly captures a real situation (Roache). Detail of the model design and inputs can have significant

16    impact on validation, as demonstrated in Meng et al. (2005b) and Hering et al. (2007). Meng et al.

17    demonstrated how use of an increasingly more detailed mathematical model decreases the variability of

18    the results with respect to modeled indoor $PM_{2.5}$ concentration of outdoor origin and infiltration factor.

19    Hering et al. compared infiltration model results for PM-based EC, $NO_3^-$, and $SO_4^{2-}$. Model inputs were

20    from a central site monitor only, central site monitor with air exchange data, and detailed inputs related to

21    initial outdoor (outside test building) and indoor concentrations. Use of more detailed inputs resulted in

22    significant reductions in error for indoor EC concentration, smaller improvements for indoor $SO_4^{2-}$, and

23    negligible improvement in model results for indoor $NO_3^-$. Observed errors are consistent with

24    observations in the literature regarding adequacy of community based monitors for epidemiology studies

25    cited in Section 3.7.2.1 above. This distinction also illustrates the strong impact of differential infiltration

26    discussed in Section 3.7.3.
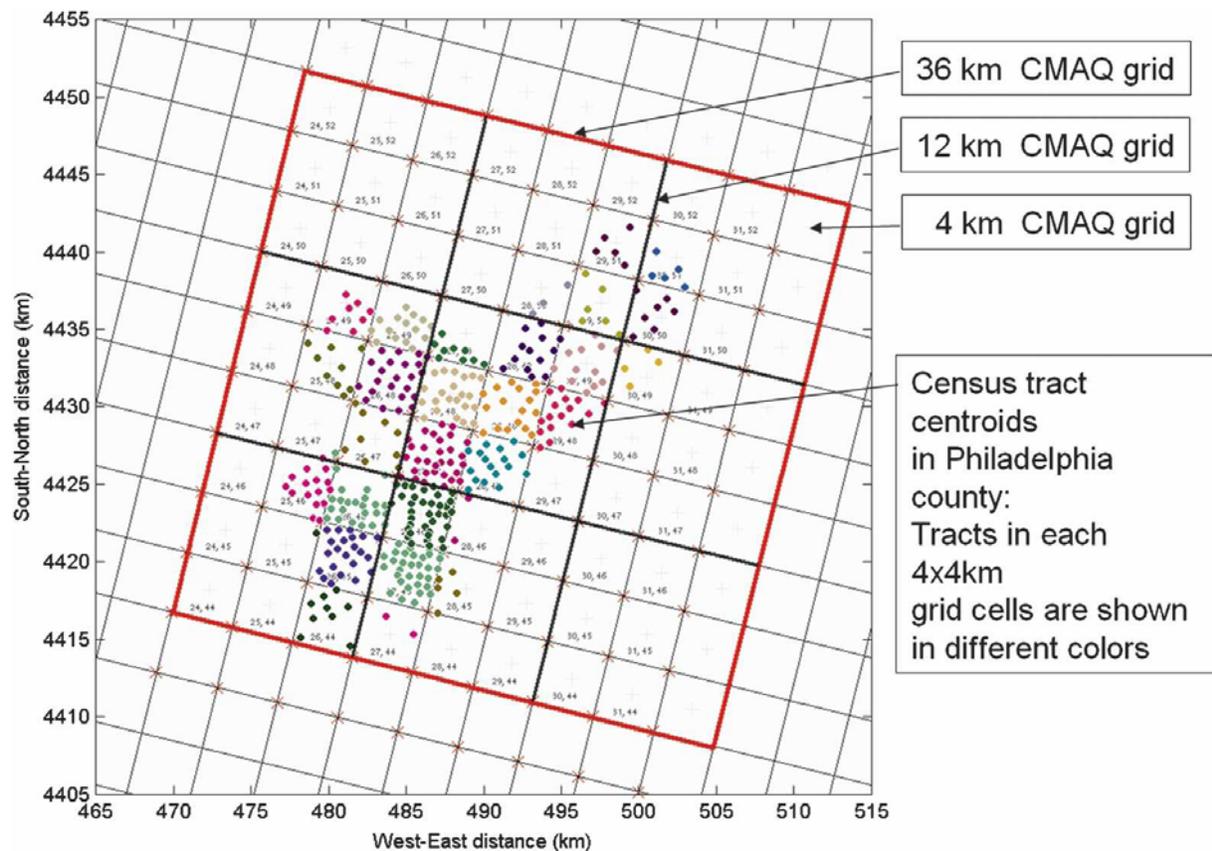
Source: Isakov et al. (2007).

**Figure 3-72. Grid resolution of the CMAQ model in Philadelphia compared with distribution of census tracts in which exposure assessment is performed.**

1    For any spatial interpolation models, grid resolution is another source of error addressed. Isakov et

2    al. (2007) linked CMAQ with the Hazardous Air Pollutant Exposure Model for exposure assessment in

3    Philadelphia. Their simulation was implemented on a 4 km nested grid within 12 km and 36 km grids to

4    bring the scale of their model from national to urban scale. However, the census tracts in which Isakov et

5    al. (2007) sought to describe exposure were distributed on a much finer scale (see Figure 3-72). They

6    were required to supplement the CMAQ model with an Industrial Source Complex Short Term (ISCST)

7    dispersion model to resolve the subgrid scale behavior. If concentrations were averaged across the cell

8    instead, Isakov et al. (2007) found that exposures were overestimated by a factor of two. Appel et al.

9    (2008) noted that their 36 km simulations provided a closer estimate of $SO_4^{2-}$ aerosol concentration than

10   did their 12 km nested simulation, which overestimated concentrations. Hogrefe et al. (2007) also noted

11   overestimation of the CMAQ model at the 12 km scale, where multiple point interpolation was used to

12   obtain subgrid estimates. Model convergence theory would suggest that the 36 km simulation is not

13   actually more accurate but coincidentally closer to the physical values (Roache, 1998). Likewise, use of

14   geospatial statistical methods for grid interpolation, as performed in the SHEDS/MENTOR simulation by

1    Georgopoulos et al. (2005), provides another methodology for grid interpolation. Similar to Isakov et al.

2    (2007), Georgopoulos et al. (2005) were linking CMAQ with an exposure model for estimation of

3    neighborhood-scale effects. The authors found that CMAQ underestimated $PM_{2.5}$ concentration at many

4    times during the simulation.


# 3.7.3. Findings from PM Exposure Studies

5          This section is intended to summarize current knowledge regarding exposures to ambient PM in

6    outdoor microscale environments including streets, sidewalks, and inside vehicles and in indoor

7    microenvironments such as office buildings and residences where the building's air exchange properties

8    in conjunction with the physical and chemical properties of the PM dictate levels of exposure to

9    ambient PM.


## 3.7.3.1. Outdoor Exposure to Ambient PM

10         Table 3-28 contains data from recent studies comparing outdoor personal exposure to fixed site

11   monitors. Only studies where samples were obtained outdoors and compared with a community-based

12   ambient monitoring site were included because indoor microenvironments have penetration losses that

13   impact the comparability of the results. Note that some of these studies included enclosed transportation

14   microenvironments (e.g. cars, buses, subways), but all studies examined personal exposure in the outdoor

15   microscale environment. Also note that studies must be reviewed cautiously because most used different

16   instrumentation for personal, microenvironmental, and ambient measurements so that the losses related to

17   each instrument may vary. The Violante et al. (2006), Kaur et al. (2005a; 2005b), and Adams et al. (2001)

18   studies showed that outdoor personal exposures to $PM_{10}$ and $PM_{2.5}$ near urban roads was significantly

19   higher than fixed community-based ambient monitoring site measurements. Curbside measurements

20   obtained at a fixed site in the Kaur et al. studies were typically lower than exposures during transit

21   (including during walking and cycling), but in the Adams et al. (2001) study exposures were higher than

22   curbside during the summer and lower than curbside during the winter. This suggests that particle

23   retention within the street canyon can lead to elevated local on-street concentrations through trapping of

24   sources and that this phenomenon may be modified by seasonal effects. Interestingly, Kinney et al. (2000)

25   showed that on-street $PM_{2.5}$ concentrations were not significantly different from ambient $PM_{2.5}$

26   measurements. However, in this study, EC was shown to increase linearly with increasing traffic counts

27   with large spatial variations where two sites had concentrations significantly higher than ambient

28   measurements. These observations suggests caution should be taken regarding the representativeness of

29   the community averaged monitoring data in Section 3.7.2, as well as hypotheses regarding the impact of

1    local sources (e.g. nearby traffic, resuspension from movement of vehicles and people) on personal

2    exposure.

**Table 3-28. Examples of studies comparing outdoor personal exposures with fixed site ambient concentrations.**

| Reference | Ambient monitors | Personal monitors | Microenvironment, other variables | Ambient v. Personal Association | Primary Findings |
|---|---|---|---|---|---|
| Violante et al. (2006)<br>Bologna, Italy | Fixed $PM_{10}$ and benzene monitoring station (method not specified). | Active pump with $PM_{10}$ PEM, passive sample for benzene desorbed and analyzed by GC-MS. | Localized traffic density (vehicles/h); Meteorology (wind speed, wind direction, visibility, relative humidity). | Personal: $185.10 \pm 38.52$ µg/m³<br>Fixed: $43.56 \pm 24.10$ µg/m³ (p<0.0001); small but significant correlation observed ($R^2 = 0.19$, p = 0.035) but disappeared after outlier removal ($R^2 = 0.09$, p = 0.165). | Fixed $PM_{10}$ correlated with multivariate model of traffic and meteorology but not personal $PM_{10}$; relationship between benzene and $PM_{10}$ not explored. |
| Kaur et al. (2005b)<br>London, UK | Fixed TEOM for $PM_{2.5}$ and fixed CO monitor at ambient and curbside sites. | High flow personal samplers for $PM_{2.5}$, P-Trak monitors for UFP, Langan T15 and T15v for CO. | Exposures stratified by mode of transport (walk, cycle, bus, car, taxi). | Average $PM_{2.5}$ at TEOMS was 3 times lower than average personal $PM_{2.5}$ sample, and 8 times lower than max personal $PM_{2.5}$ sample. | $PM_{2.5}$ exposures during walking significantly lower than during car and taxi rides, UFP exposures during walking significantly lower than bus and car rides, cycling exposures to $PM_{2.5}$ and UFP not significantly different from those on bus, car, or taxi. |
| Kaur et al. (2005a)<br>London, UK | Fixed TEOM for $PM_{2.5}$ and fixed CO monitor at ambient and curbside sites. | High flow personal samplers for $PM_{2.5}$ analyzed post-sample for reflectance for EC, P-Trak monitors for UFP, Langan T15 and T15v for CO. | Volunteers walking at set times and directions along Marylborne Rd in London. | Fixed vs. personal $PM_{2.5}$: slope = 0.29, R = 0.6; personal $PM_{2.5}$ measurements were >2 times background levels and more than 15 µg/m³ greater than curbside measurements. | Pedestrian exposures were significantly higher than fixed site curbside (or ambient measurements. Results indicate that exposure decline up to 10% from curb-side to building edge within a street canyon. |
| Adams (2001)<br>London, UK | Fixed TEOM for $PM_{2.5}$ and fixed CO monitor at ambient and curbside sites. | High flow personal samplers for $PM_{2.5}$. | Exposures stratified by mode of transport (cycle, bus, car, subway). | Median values: (µg/m³)<br><br>        Summer  Winter<br>Cycle  34.5     23.5<br>Bus    39.0     38.9<br>Car    37.7     33.7<br>Subway 247.2  157.3<br>Fixed  15       13<br>Curb   24       37 | Exposures were 2.3 – 16.5 times higher than ambient and 1.4-10.3 times higher than curbside during summer. During winter, only subway exposures were appreciably higher (4.3 times) than curbside. |
| Kinney et al. (2000)<br>New York City, NY (Harlem) | Ambient site filter in greased impactor with pump; absorbance testing on filter for EC. | Three high traffic sites filter in greased impactor with pump; absorbance testing on filter for EC. | Traffic counts per hour. | Mean values: (µg/m³)<br><br>          $PM_{2.5}$    EC<br>Site 1 (1.9)  45.7 (10.1)  6.2<br>Site 2 (0.6)  47.1 (16.4)  3.7<br>Site 3 (0.9)  36.6 (10.8)  2.3<br>Ambient (0.5)  38.7 (10.9)  1.5 | $PM_{2.5}$ at high traffic sites was not significantly higher than ambient; EC was significantly higher than ambient at 2 sites. EC increased linearly with traffic counts. |

*Outdoor Exposure to Local Sources*

**Industrial Sources**

1  Industrial sources of aerosols and characterization of their transport and dispersion among exposed
2  populations have been widely studied. $SO_4^{2-}$ and certain trace metals can largely be attributed to utilities
3  operations and industrial processes, while $NO_3^-$ and carbonaceous aerosols are derived from a variety of
4  sources. The 2004 PM AQCD discusses this knowledge extensively, and so the reader is referred there for
5  detailed information. Distinction of industrial sources from vehicular and indoor sources continues to
6  pose a challenge in the exposure assessment field (e.g., Nerriere et al., 2007).

**Short-Term Sources**

7  Short-term sources, such as time-limited biomass combustion (e.g. forest fire), or sources of rare
8  origin, such as demolition, can also contribute to acute, high exposures. In a study of air quality following
9  demolition of a hospital building, Hansen et al. (2008) showed increases of up to four times
10  pre-demolition concentrations for $PM_{5-1}$, $PM_{1-0.5}$, $PM_{0.5-0.3}$, and UFP concentrations immediately following
11  demolition. Likewise, Ng et al. (2005) published a time series of $PM_{2.5}$ concentration in New York City
12  from September to November, 2001, which includes the World Trade Center collapse. Significant spikes
13  in concentration were observed during that incident, as shown in Figure 3-73. The Ebelt et al. (2005)
14  study also illustrates the issue of non-representative PM events. On one day dust from the Gobi Desert
15  caused an increase in the concentration of fine and coarse PM. When this day was deleted from the
16  analysis, the relationships were changed and the associations, especially for coarse PM, became larger
17  and more significant. Forest fires, described in more detail for PRB in section 3.6, have shown spikes in
18  measured concentrations (Generoso et al., 2007; Mathur, 2008; Wang et al., 2006a) and signatures in
19  source apportionment exposure studies (Ogulei et al., 2006).
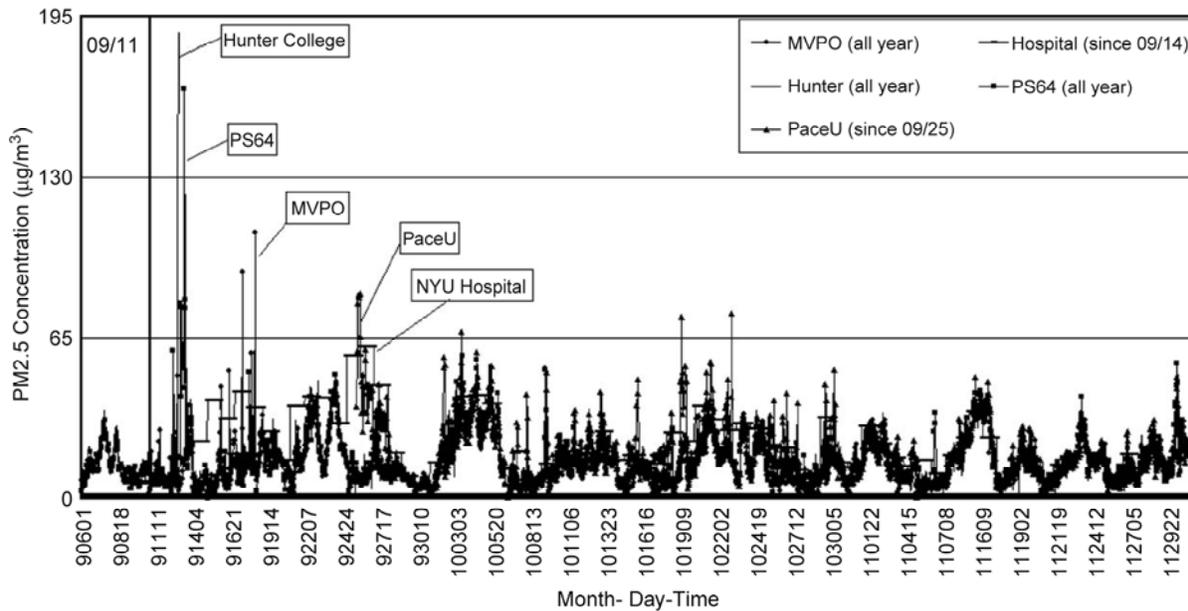
Figure 3-73. Time series plot of PM$_{2.5}$ concentration measured at various sites during September – November 2001. The Hunter College and PS 64 monitors operated near Lower Manhattan during the World Trade Center collapse, and the MVPO monitor operated in Upper Manhattan. The Pace and Hospital monitors began sampling several days to weeks after the collapse.

## The Near-Road Microscale Environment

1    Sections 3.3 and 3.5 describe the physical and chemical composition of traffic emissions as well as

2    evolution of the plume away from traffic sources. Particle chemistry is an important determinant of

3    human exposure because the chemical constituents dictate the toxicity and size-selective behavior of the

4    PM exposure, which then affect the mode and location of deposition of particles in the respiratory system.

5    The increased magnitude of the sources, turbulent transport, and physical and chemical transformation

6    processes described in Sections 3.3 and 3.5 in the near-road region complicate exposure assessment for

7    those living in the near-road environment (Zhang et al., 2005b; Zhou and Levy, 2007; Zhu et al., 2002b).

8    Farmer et al. (2003) found that exposure to particle-bound B[a]P and PAH can be 2-3 times higher among

9    those routinely exposed to outdoor traffic emissions (e.g. police, bus drivers) compared with control

10   subjects.

## In-Vehicle and In-Transit Exposures

11    In-vehicle pollution has been identified in various studies as a source of exposure to PM$_{10}$, PM$_{2.5}$,

12   and ultrafine PM (Briggs et al., 2008; Diapouli et al., 2007; Fruin et al., 2008; Gómez-Perales et al., 2004;

1    2007; Gulliver and Briggs, 2004, 2007; Rossner et al., 2008; Sabin et al., 2005). Results from recent

2    studies are provided in Annex A. In many of these studies, in-vehicle exposures are shown to be

3    comparable or less than that of walkers on the same route. Typically, in-vehicle exposures were still

4    higher than community-based ambient monitor concentrations for TSP and $PM_{10}$. However, as particle

5    size decreased to the fine and ultrafine range, less distinction between in-vehicle and ambient

6    concentrations were observed for PM mass or count, with the exception of the Diapouli et al. (Diapouli et

7    al., 2007) study where in-bus concentrations were several times higher than indoor or outdoor residential

8    and school concentrations. Fruin et al. (2008) and Westerdahl et al. (2005) observed that in-vehicle

9    concentrations increased for freeways in comparison with arterial roads. However, Sabin et al.

10   demonstrated for school buses that emissions control technologies had a significant impact on in-bus

11   concentrations. Although not tested here for other vehicle types with respect to PM, this finding suggests

12   that some in-vehicle emissions are due to self-pollution. Behrentz et al. (2004) tested self-pollution with

13   school buses using $SF_6$ tracer gas and demonstrated that as much as 0.3% of in-vehicle air comes from

14   self-pollution, and that this number was roughly ten times greater than in-vehicle concentrations related to

15   self-pollution on newer buses. The Behrenetz et al. study also measured EC and particle-bound PAH and

16   found that 25% of the variability in EC concentration was related to self-pollution, defined by Behrentz et

17   al. (2004) as the fraction of a vehicle's own exhaust entering the vehicle microenvironment. These

18   findings are important for partitioning local and ambient sources of pollution during transport in vehicles

19   for exposure estimation. Based on Fruin et al.'s (2008) estimation of 1.5 hours spent in vehicles each day

20   (for the Los Angeles area, but this value is typical for many other large metropolitan areas), cumulative

21   in-vehicle exposure can become important. Mixed findings from these studies suggests that in certain

22   limited cases, e.g., arterial road travel with low traffic, in-vehicle concentrations of fine particles can be

23   reasonably represented by community ambient monitors.

## 3.7.3.2. Indoor and Average Personal Exposure to Ambient and Non-Ambient PM

24          A number of exposure studies have been published since 2002. Annex A lists those studies

25   performed in the U.S. by region of the country with personal, microenvironmental, and ambient mass

26   concentrations presented (note that chemical speciation data where available are presented and discussed

27   below). The majority of these studies present $PM_{2.5}$ concentration data for personal exposure and ambient

28   concentrations. Some of these studies present ambient concentration as that measured outside the test

29   building, while others use a community site monitor. As would be expected, there is considerable

30   variability within and across regions of the country with respect to indoor exposures and ambient

31   concentrations. Furthermore, some regions are represented by only one or two studies, while some

32   regions have many studies. Among these regions, most are represented by only one or two metropolitan

areas. For this reason, the results presented may not be broadly representative. These differences highlight the uncertainties surrounding various estimates of the ambient contribution to personal exposure. This variation can be attributed to a number of factors, including scope and magnitude of microenvironmental sources, proximity to microenvironmental sources, ambient concentrations of PM, percentages of time spent in various microenvironments, the age and condition of indoor microenvironments, and outdoor meteorology. Findings related to source apportionment, infiltration, and differential infiltration studies are discussed further in the following subsections.

### Estimating the Ambient Component of Personal Exposure

In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrat88ions is more relevant than the association between personal total exposures (ambient component + nonambient component) and ambient concentrations. If there are no indoor or other non-ambient sources of a pollutant, the total personal exposure is equal to the ambient personal exposure. However, indoor or other non-ambient sources could significantly affect personal exposures to many pollutants. Strand et al. (2007) reviewed methods for estimating the ambient component of personal exposure and their limitations.

Wilson et al. (2000) first proposed that sulfate could be used as a tracer of the ambient PM infiltration rate. Sarnat et al. (2002) also noted that it is reasonable to assume that the size distribution of ambient $SO_4$ particles is sufficiently similar to the size distribution of ambient $PM_{2.5}$, and therefore that the ambient $SO_4$ to personal $SO_4$ ratio is an acceptable surrogate for the ratio of the ambient $PM_{2.5}$ exposure to the ambient $PM_{2.5}$ concentration. Sulfate has been used this way by, e.g., Ebelt et al. (2005), Wallace and Williams (2005), and Wilson and Brauer (2006). For this method to be successful, indoor or other non-ambient sources of the tracer must be small compared to ambient sources over the period of sampling. Wilson and Brauer (2006) noted that environmental tobacco smoke and tap water used in showers or humidifiers are indoor sources of sulfate. Other concerns in using sulfate as a tracer for $PM_{2.5}$ arise because sulfate tends to be concentrated in smaller particles and thus it might be a better tracer for fine mode particles than for all $PM_{2.5}$ particles. Strand et al. (2006) suggested that Fe be used as an additional tracer to correct for the infiltration of larger $PM_{2.5}$ particles. In their study, they noted that indoor sources of Fe were small. However, in other environments there could be more substantial contributions from tracking iron in soil indoors. The spatial variability of Fe is also larger than that of $PM_{2.5}$ across urban areas. Volatilization of nitrate or organic compounds after infiltration of $PM_{2.5}$ indoors could lead to bias in exposure estimates (Lunden et al., 2003a). This could be a large problem in areas in which PM contains a large semi-volatile component.

1        Figure 3-71 shows total exposure to $SO_4$ as a function of measured ambient $SO_4$ concentration.

2    Figure 3-75 shows estimated ambient exposure to $PM_{2.5}$ as a function of measured ambient $PM_{2.5}$

3    concentration, where ambient personal exposure is calculated from the ambient exposure factor for $SO_4$.

4    Close agreement between these figures can be observed. Figure 3-76 shows total exposure to $PM_{2.5}$ as a

5    function of measured ambient $PM_{2.5}$ concentration. However, the total exposure to $PM_{2.5}$ shows virtually

6    no association with ambient $PM_{2.5}$ because it contains non-ambient contributions to $PM_{2.5}$.
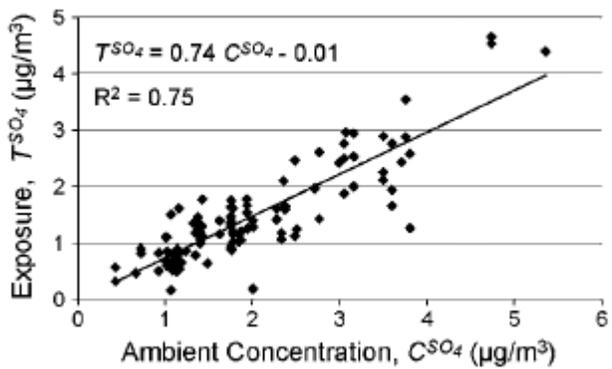


Source: Wilson and Brauer (2006).

**Figure 3-74. Total exposure to $SO_4$ as a function of measured ambient $SO_4$ concentration.**
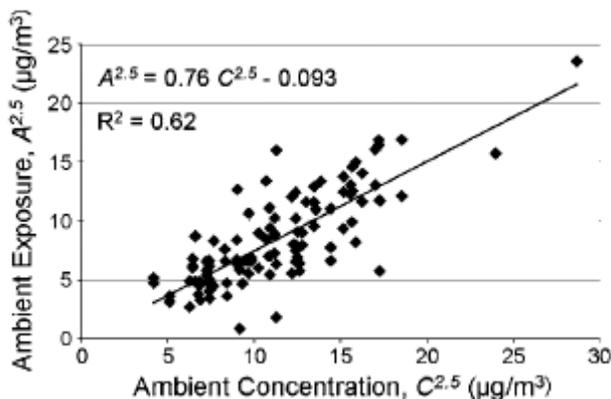


Source: Wilson and Brauer (2006).

**Figure 3-75.  Estimated ambient exposure to $PM_{2.5}$ as a function of measured ambient $PM_{2.5}$
                concentration.**

$$T^{2.5} = 0.77\, C^{2.5} + 8.24$$
$$R^{2.5} = 0.07$$
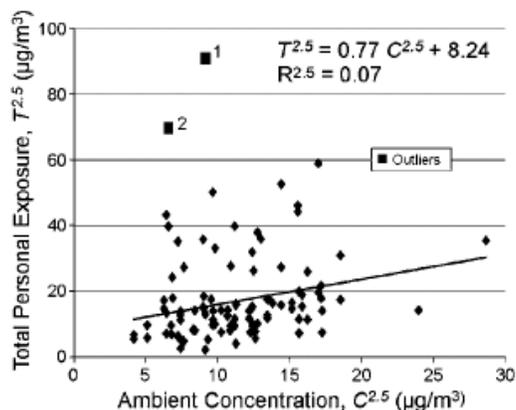
**Figure 3-76.  Total exposure to PM$_{2.5}$ as a function of measured ambient PM$_{2.5}$ concentration.**

1    The estimated ambient exposure to PM$_{2.5}$ is well correlated with measured ambient PM$_{2.5}$

2    concentration with zero intercept implying that non-ambient sources were unimportant. This technique

3    works well in areas where sulfate is a regional pollutant insuring that its spatial variations are small and it

4    is highly correlated with PM$_{2.5}$ (Kim et al., 2005a; U.S. EPA, 2004). The inferences drawn from this

5    method may still apply in areas where sulfate is a minor component of PM$_{2.5}$ or where there are

6    significant non-ambient sources of sulfate as long as the factors affecting a person's exposure are similar.

7    Source apportionment techniques could also be used, in principle, to derive ambient personal PM$_{2.5}$

8    concentrations. They would be especially useful in areas where the application of a tracer method might

9    be problematic. Hopke et al. (2003) used PMF to derive source contributions that affected community,

10    outdoor, indoor samples at a retirement facility in Towson, MD. Strand et al. (2007) noted that the four

11    outdoor factors (nitrate-sulfate, sulfate, OC, motor vehicle exhaust) would constitute an estimate of the

12    personal ambient PM$_{2.5}$ concentration. However, the data used in this portion of the analysis were

13    obtained only with fixed monitors and did not include measurements made by personal exposure monitors

14    (PEMs). They also used the Multilinear Engine (ME) to derive factors that were required to contribute

15    jointly to central indoor and outdoor, individual apartment and individual PEM samples of a panel of

16    residents. Hopke et al. (2003) found three sources (sulfate, unknown [perhaps combustion related] and

17    soil) jointly contributing 46%, 13% and 4% of PM$_{2.5}$ to the PEM samples. Further source resolution was

18    not possible because of a lack of data for a number of components in the PEM samples. The largest and

19    most clearly identified contribution to personal exposure was from the sulfate factor. This study also

20    determined that a few minor indoor and personal activity sources contributed < 10% of the ambient

21    sulfate source to personal exposures. Although this study did not directly attempt to determine the

22    ambient component of personal exposures, the sulfate factor could represent a lower limit on the ambient

1   personal concentration, as the study was conducted in an area where ambient sulfate concentrations are

2   fairly homogenous and where they are highly correlated to $PM_{2.5}$. This obviates the limitation from not

3   using data from the ambient monitors reporting to AQS.

4       The correlations between personal ambient PM exposures and ambient PM concentrations in

5   different types of exposure studies are relevant to different types of epidemiologic studies. There are three

6   types of correlations generated from the different study designs: longitudinal, "pooled," and daily-average

7   correlations as described in the 2004 PM AQCD and later in the 2008 $NO_X$ ISA (U.S. EPA, 2008c) and

8   the 2008 $SO_X$ ISA (U.S. EPA, 2008d). Generally, strong associations between personal exposures and

9   ambient concentrations were reported in the longitudinal studies. Wilson and Brauer (2006) and Ebelt et

10  al. (2005) reported that the Pearson correlation coefficients between personal ambient exposure

11  (estimated by the sulfate tracer method) and ambient concentration of $PM_{2.5}$ (for individual subjects)

12  ranged from 0.77 to 0.92, with a median of 0.88 in the Vancouver exposure study (16 COPD subjects, and

13  seven repeated measurements for each subject). Koutrakis et al. (2005) reported the median Spearman

14  correlation coefficients between personal sulfate exposure and ambient sulfate concentration were above

15  0.60 during both winter and summer in Boston and Baltimore (15 subjects with 12 consecutive

16  measurements during each season in both Boston and Baltimore). For another Baltimore cohort (15 senior

17  subjects with up to 23 consecutive measurements for each person), Hopke et al. (2003) reported that the

18  median Pearson correlation coefficient between personal exposure to sulfate factor and ambient sulfate

19  factor was 0.91 (ranging from 0.56 to 0.95 for different subjects), while the median Pearson correlation

20  coefficients were 0.34 for the crustal factor (ranging from -0.05 to 0.62), and 0.31 for an unnamed factor

21  (ranging from -0.01 to 0.88), respectively.

22      Wilson and Brauer (2006) reported that the pooled Pearson correlation coefficient was 0.79 for

23  personal ambient exposures (estimated by tracer element method) vs. ambient concentrations, and was

24  0.001 for personal nonambient exposure vs. ambient concentrations.

25      Strand et al. (2007) conducted an exposure study in Denver (from 2002 to 2004) for 6-12 year old

26  school children. Up to 10 personal exposure samples were collected on each day, and ambient

27  concentrations were measured simultaneously at a fixed site located at the school. The daily average

28  personal sulfate exposure was strongly associated with ambient sulfate concentration (r = 0.96, 120 > N >

29  100).

### Exposure to PM Species and Source Apportionment of Ambient and Non-Ambient Contributions to PM

30      Annex A presents exposure studies that include chemical speciation data. Some of these studies

31  focused on $SO_4^{2-}$, $NO_3^-$ or carbonaceous aerosols (EC, OC, particle-bound PAHs, B[a]P), while others

1  measured concentrations of trace metals from crustal (Ca, Fe, Mn, K, Al, S, Cl in salt), traffic (Al, Ca, Fe,

2  K, Mg, Na, Ba, Cr, Cu, Mn, Ni, Pb, S, Ti, V, and Zn; or industrial (particle-bound Hg, Cl, V, Zn, Ti, Cu,

3  Pb) sources. A number of source apportionment studies have been performed over the last five years to

4  determine the contribution of outdoor sources to indoor and personal PM constituents. These are listed in

5  Annex A.

6       A number of studies have examined exposure to $SO_4^{2-}$ (e.g., Brunekreef et al., 2005; Ebelt et al.,

7  2005; Kim et al., 2005b; Koutrakis et al., 2005; Noullett et al., 2006). Hopke et al. (2003) and Zhao et al.

8  (2006b) showed that secondary $SO_4^{2-}$ provides the largest ambient contribution to personal and indoor

9  exposures. These studies took place on the east coast in Baltimore and Raleigh/Chapel Hill, NC. In

10  Larson et al.'s (2004) source apportionment study in Seattle, vegetative burning was the most significant

11  source of outdoor origin. Zhao et al. (2007) performed a source apportionment study of personal exposure

12  to $PM_{2.5}$ among residents in Denver and also saw lower contributions from secondary $SO_4^{2-}$ in

13  comparison with motor vehicle emissions and secondary $NO_3^-$. This suggests that personal exposure to

14  $SO_4^{2-}$ in parts of the west is lower than in the mid-Atlantic.

15       Source apportionment for carbonaceous aerosols is complicated by the fact that they can be derived

16  from indoor and outdoor combustion sources. Carbonaceous aerosols are difficult to trace to specific

17  indoor and outdoor sources because combustion is widespread. Sørenson et al. (2005), Ho et al. (2004),

18  Larson et al. (2004), and Jansen et al. (2005) all found that personal and microenvironmental exposure to

19  total or BC was lower than that measured outdoors, while Sarnat et al. (2006a) showed significant

20  associations between personal and ambient measurements of EC for measurements taken during the fall

21  (slope = 0.66-0.73) and summer under high ventilation conditions (slope = 0.41). Wu et al. (Wu et al.,

22  2006), Delfino et al. (2006), and Turpin et al. (2007) all demonstrated much higher levels of OC

23  compared with EC in personal samples, possibly due to indoor sources of OC from cooking and home

24  heating. Reff et al. (2007) and Meng et al. (2007a) both reported findings from the RIOPA study in Los

25  Angeles, Houston, and Elizabeth, NJ. Results from Reff et al. (2007) are shown in Figure 3-77. These

26  reveal significantly higher detection of aliphatic C-H functional groups indoors and in personal samples

27  compared with outdoors. This information can be used to distinguish indoor and outdoor carbon in future

28  source apportionment studies. Little regional variation in the aliphatic, carbonyl, or $SO_4^{2-}$ groups tested

29  were reported in this study. In Meng et al., (2007a) indoor exposures were shown to decrease for

30  secondary formation aerosols including $SO_4^{2-}$ but excluding $NO_3^-$ (not tested) when compared with

31  outdoor concentrations, and indoor exposures to mechanically generated aerosols increased in comparison

32  with outdoors. Differences in infiltration based on constituents are shown in Figure 3-78.
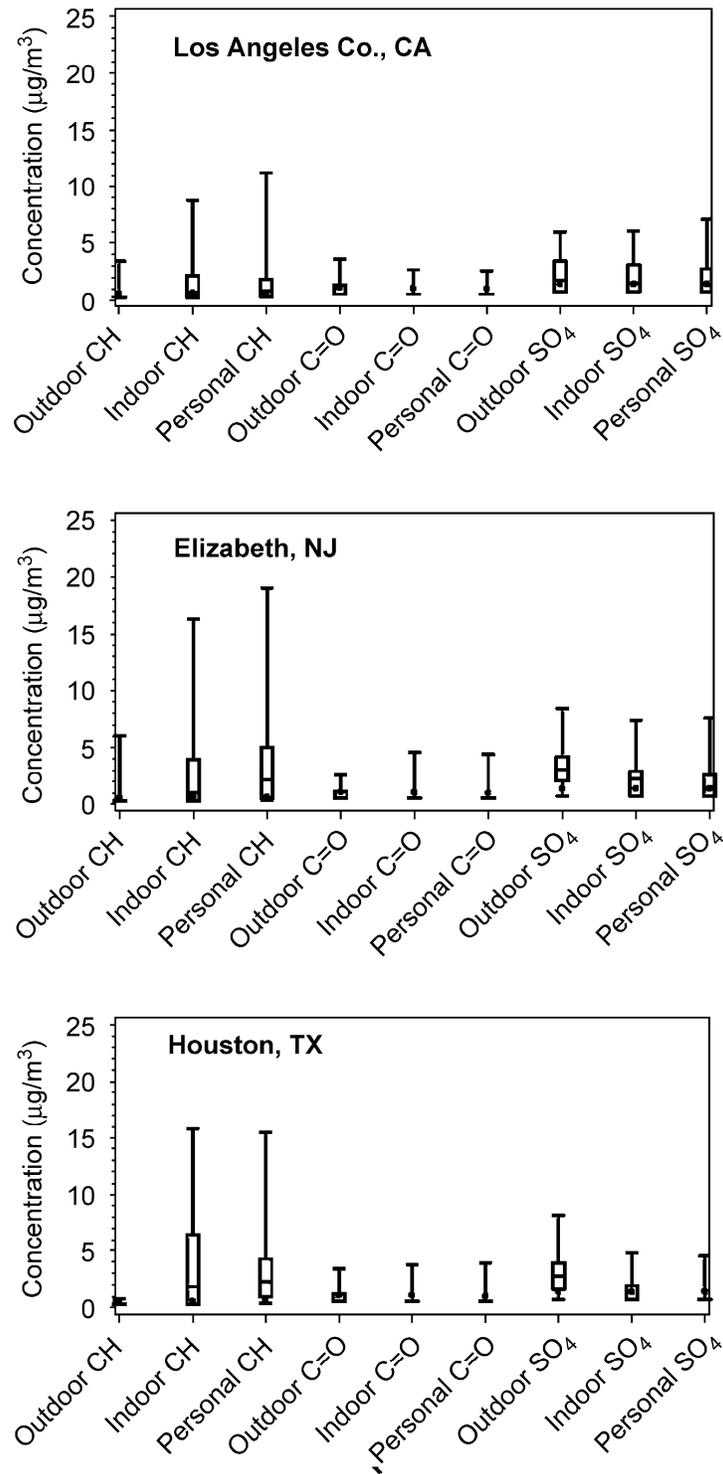
Source: Reff et al. (2007).

**Figure 3-77. Apportionment of aliphatic carbon, carbonyl, and SO₄⁻² components of outdoor, indoor, and personal PM₂.₅ samples, for Los Angeles (top), Elizabeth (center), and Houston (bottom).**
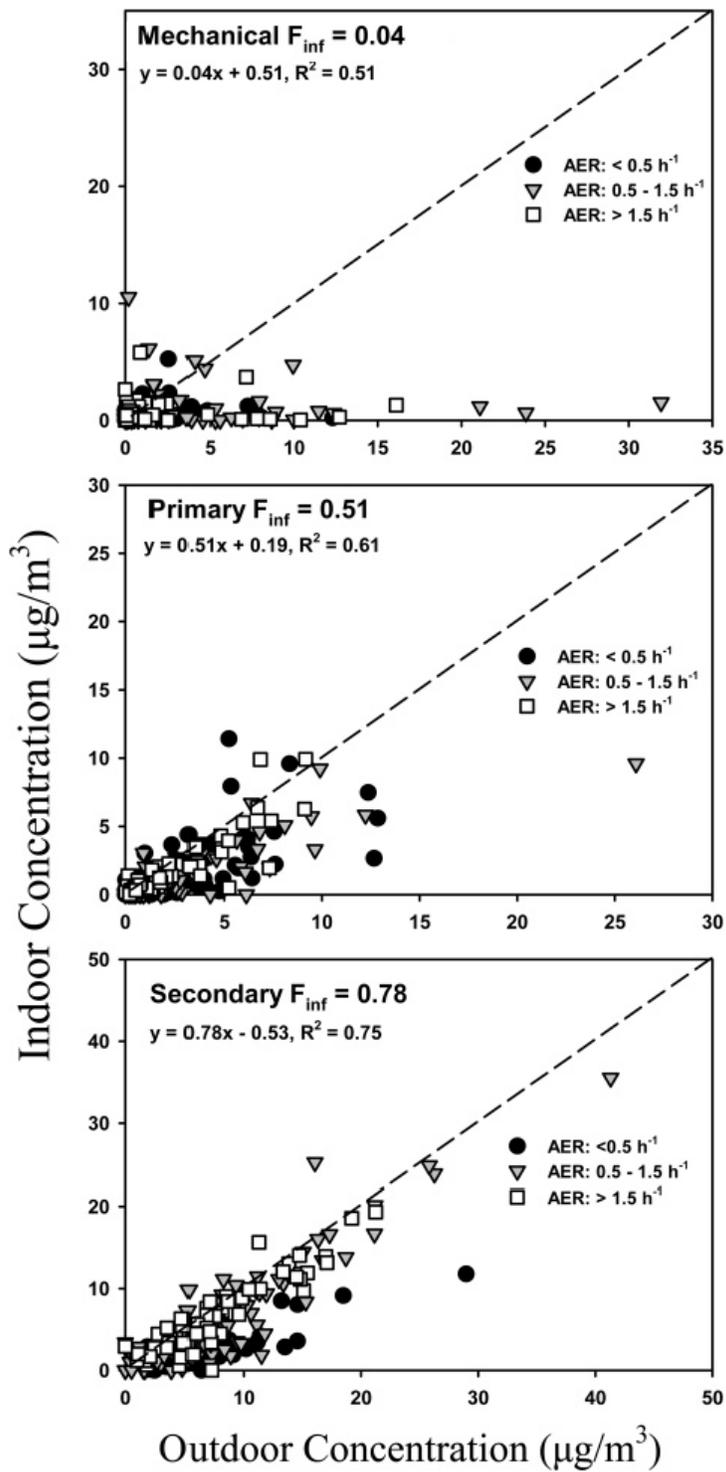
Source: Meng et al. (2007a).

**Figure 3-78. Apportionment of infiltrated mechanically-generated (top), primary combustion (center), and secondary combustion (bottom).**

1    Trace metal studies have shown variable results regarding personal exposure to ambient

2    constituents. For instance, Molnár et al. (2006) found that personal exposure was higher than outdoor and

3    ambient concentrations for mostly crustal Cl, K, Ca, Ti, Fe, and Cu. However, Adgate et al. (2007) found

4    that personal exposures were higher than ambient for Fe, Mg, K, Zn, Cu, Pb, and Mn but lower than

5    ambient for Al, Na, and Ti. Larson et al. (2004) found that personal exposure to Ca and Cl were higher

6    than concentrations measured at ambient (central site) and residential outdoor monitors, lower for Fe, K,

7    Mn, and As and the same for Al, Br, Cr, Cu. Source apportionment for trace metals can vary significantly

8    among cities and over seasons. For instance, in a Baltimore source apportionment study, exposure to Mn

9    could be attributed nearly equally to the Quebec wildfires, roadway wear, and soil, while Pb exposure was

10   largely found to be due to a local incinerator (Ogulei et al., 2006). In this case, the Quebec wildfires were

11   a transient episodic source while roadway wear and incineration were continuous. However, in Larson et

12   al. (2004), Mn and Pb exposures in Seattle were largely attributable to mobile source emissions, also

13   stationary sources. For this reason, source composition behavior cannot be assumed for characterizing

14   exposures and resulting health effects in specific locations or times.

## *Infiltration and Differential Infiltration*

15   $F_{inf}$ varies substantially given a vast array of conditions, and it can best be modeled dynamically

16   based on a distribution of air exchange and deposition or other ultrafine, accumulation mode, fine, and

17   coarse PM loss rates rather than a single value (Bennett and Koutrakis, 2006). Given that air exchange

18   rates within a building vary as a function of temperature and pressure, $F_{inf}$ is subject to seasonal and

19   regional changes (Meng et al., 2005a; Sarnat et al., 2006b). These factors make $F_{inf}$ a more accurate

20   descriptor of infiltration than a simple I/O ratio. This complex term becomes even more complicated

21   when one considers transformation of the size distribution and chemical composition of the PM through

22   site reactions, agglomeration, growth, and evaporation given that $F_{inf}$ depends on particle size (Keller and

23   Siegmann, 2001). $F_{inf}$ for PM is influenced by physical mechanisms, such as Brownian diffusion,

24   thermophoresis, and impaction, all of which are functions of particle size (Bennett and Koutrakis, 2006;

25   Tung et al., 1999). These differential effects are summarized below. Recent studies on infiltration are

26   summarized in Annex A. $F_{inf}$ and I/O are listed where available, although it is recognized that I/O is not as

27   meaningful a descriptor but provides a sense of the data where $F_{inf}$ has not been calculated.

28   A number of studies have examined the impact of season on PM infiltration. Season is important

29   because it impacts the ventilation practices used (e.g. open windows, air conditioning or heating use) and

30   the ambient temperature and humidity conditions affect the transport, dispersion, and size distribution of

31   the PM. Pandian et al. (1998) found that residential air exchange rates vary by season as: summer

32   > spring > winter > fall with summer air exchange roughly 1.5-2 times greater than average air exchange

1  rate for the entire year because they are driven by home air conditioning and heating usage. Allen et al.

2  (2003) gave information on the range and distribution of $F_{inf}$ at 44 residences in Seattle. The mean $F_{inf}$

3  (± SD) measured by light scattering for all sampling days was 0.65 ± 0.21. Differences in infiltration were

4  observed for the heating season (0.53 ± 0.16), when windows would be expected to be closed, versus

5  non-heating season (0.79 ± 0.18). Residences with open windows had a mean $F_{inf}$ of 0.69 vs. 0.58 for

6  residences with closed windows. The authors combined the light scattering results with indoor and

7  outdoor sulfur measurements to estimate that 79 ± 17% of indoor $PM_{2.5}$ was generated outdoors. This

8  study provides important data on the distribution of residential $F_{inf}$ values and illustrates the magnitude of

9  the effect of season and window position on infiltration rates. Barn et al. (2008) and Baxter et al. (2007a)

10  both also noted that window opening was an important variable. Barn et al. (2008) found $F_{inf}$ of

11  0.61 ± 0.27 for 13 homes during summer and 0.27 ± 0.18 for 19 homes during winter in Canada.

12  Likewise, location could impact residential ventilation practices and infiltration. Pandian et al. (1998)

13  observed that residential air exchange rates vary by region as: southwest > southeast > northeast

14  > northwest, which reflects regional use of air conditioning. Sarnat et al. (2006b) noted differences in

15  infiltration between coastal and inland residences, although variability in these datasets made the

16  differences not statistically significant.

17       Differential infiltration as a function of particle size has been observed to occur. Infiltration factors

18  for several particle diameters ranging from 20 nm to 10 μm were reported in Boston by Long et al. (2001)

19  during summer and fall for nighttime periods, when personal activity patterns would be less likely to

20  generate indoor PM. The maximum infiltration factor was reported for particles between 80 and 500 nm,

21  to range from 0.8-1.0. Summer values were uniformly higher than fall values, consistent with higher

22  observed air exchange rates. The infiltration factor decreased with size above 500 nm, reaching 0.1-0.2

23  for 6-10 μm diameter particles. Particles smaller than 80 nm also were reported to have lower infiltration

24  factors. This demonstrates the size dependence of PM infiltration, which has been further studied by

25  recent investigators. Sarnat et al. (2006b) examined infiltration as a function of particle size and found

26  that $F_{inf}$ does vary by particle diameter, as measured by a SPMS-APS system to estimate particle volume.

27  Figure 3-79 presents $F_{inf}$ values for size fractions ranging from 0.02-10 μm. The maximum infiltration

28  factors were observed around the accumulation mode (0.1-0.5 μm), with $F_{inf}$ = 0.7-0.8. Reduced

29  infiltration was observed for coarse-mode particles (0.1-0.2 for $D_p$ = 5-10 μm) and, to a lesser extent,

30  ultrafine particles (0.5-0.7 for $D_p$ = 0.02-0.1 μm). This is consistent with increased removal mechanisms

31  for those size fractions: settling for coarse-mode particles and diffusion for ultrafine particles.
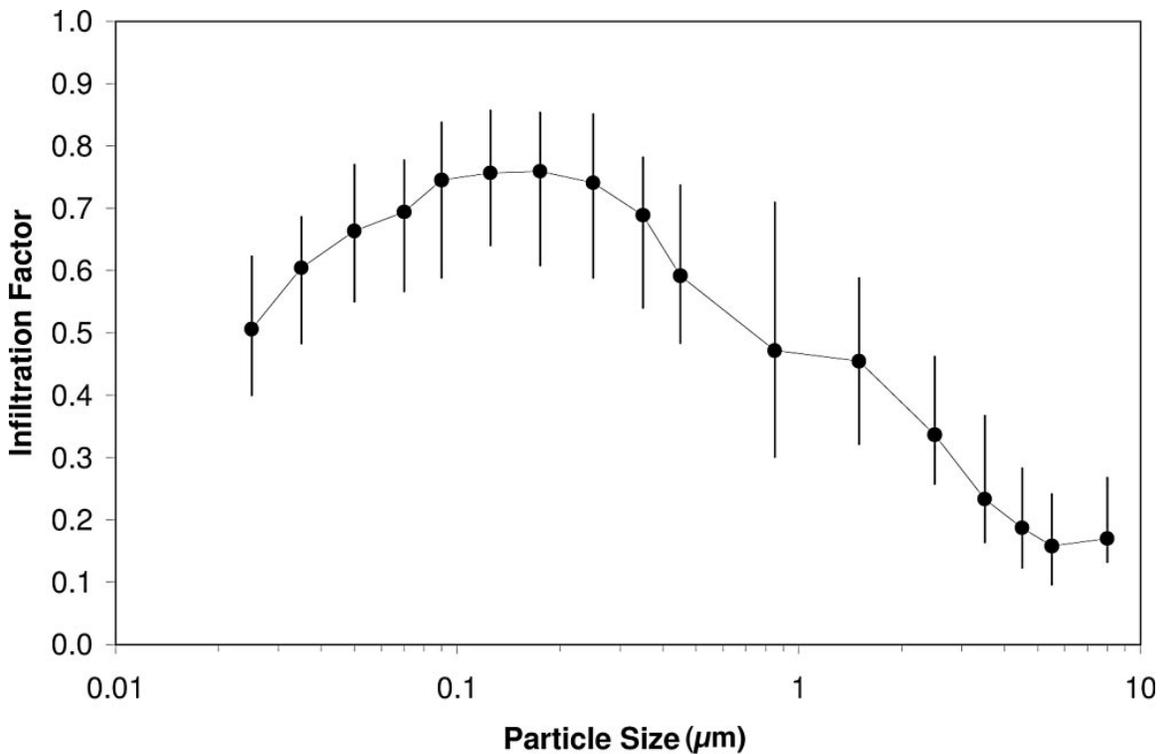
Source: Sarnat et al. (2006b).

**Figure 3-79.  F$_{inf}$ as a function of particle size.**

1    A number of chemical factors influence the tendency for differential infiltration in PM. Lunden et
2    al. (2003b) studied infiltration of BC and OC aerosols and found that F$_{inf}$ can also vary substantially as a
3    function of gas transport properties within differing air exchange rates. This study and Sarnat et al.
4    (2006b) also showed that BC aerosol infiltration is considerably higher than infiltration of OC, and that
5    carbonaceous aerosol infiltration differed substantially from $NO_3^-$ and $SO_4^{2-}$ aerosols under the same
6    building air exchange conditions. The evidence indicates that the ambient composition differs from the
7    indoor composition due to differences in penetration. As shown in Figure 3-80, the composition of indoor
8    PM that has infiltrated from outdoors is different from that of outdoor PM. In this case, the particles
9    containing photochemical products (probably mostly in the accumulation mode) have a higher infiltration
10   rate than the larger (probably mostly coarse mode) mechanically generated particles or the smaller
11   primary combustion particles (probably mostly ultrafine particles in the nucleation or Aitkin nuclei
12   mode). Hence there is a greater reduction in the concentration of the larger and smaller particles resulting
13   from losses during penetration and due to deposition within the home.
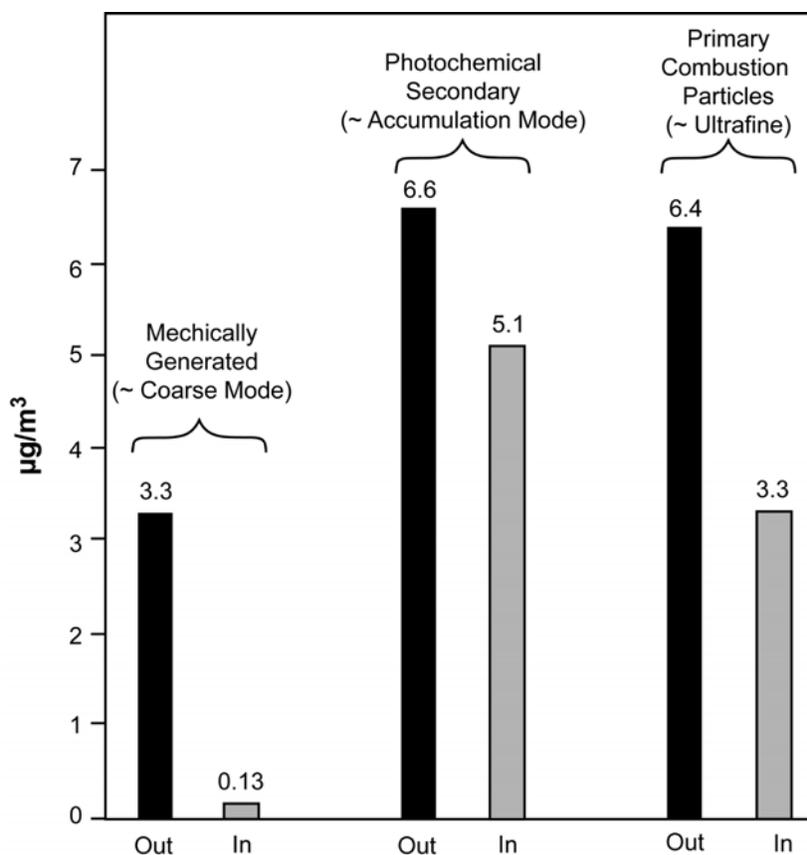
Source: Meng et al. (2007a).

**Figure 3-80. Results of the positive matrix factorization model showing differences in the composition of outdoor PM and PM that has infiltrated indoors.**

1    PM species enriched in the smaller end of the size distribution, such as $SO_4^{2-}$, will infiltrate more

2    efficiently than components with larger size distributions, such as iron (Strand et al., 2007). Lunden et al.

3    (2008) also compared I/O ratios for $PM_{2.5}$, total carbon, OC, and BC in an unoccupied house and found

4    the lowest ratio for $PM_{2.5}$ ($0.41 \pm 0.2$), the highest for BC ($0.61 \pm 0.2$), and intermediate values for total

5    carbon ($0.50 \pm 0.2$) and OC ($0.47 \pm 0.2$). The authors attributed the lower $PM_{2.5}$ ratio to indoor loss of

6    $NH_4NO_3$ aerosol. The authors note that their BC ratio of 0.6 is somewhat lower than BC ratios measured

7    in occupied spaces (Polidori et al., 2006). Conversely, indoor sources in occupied residences contribute to

8    observed OC I/O ratios greater than 1 in other studies (Polidori et al., 2006; Sawant et al., 2008).

9    Analytical results for $PM_{2.5}$ components from the Baxter (2007b) study found $F_{inf}$ of $0.95 \pm 0.07$ for S and

10   $0.60 \pm 0.04$ for V, the two components identified as having no indoor sources and which had I/O ratios

11   significantly less than 1 (Baxter et al., 2007b). The difference between these two values was not

12   addressed, although association of V with larger particles of lower penetration efficiency could contribute

1  to a lower infiltration rate. Meng et al. (2005a) also noted that the lack of indoor sources of S and V result

2  in much lower variability in penetration and loss rates.

3      The resulting composition differences between indoor-ambient PM and outdoor-ambient PM may

4  also result in differences in toxicity. $NO_3^-$, a more important PM component in the western U.S., has a

5  decreased $F_{inf}$ due to volatilization of $NO_3^-$ indoors. Sarnat et al. (2006b) calculated $F_{inf}$ values for $NO_3^-$,

6  $PM_{2.5}$, and BC, and found the values to increase in that order. $NO_3^-$ was low (median = 0.18,

7  IQR = 0.12-0.33), while BC was high (median = 0.84, IQR = 0.70-0.96); the intermediate value of $PM_{2.5}$

8  (median = 0.48, IQR = 0.39-0.57) reflected its composition as a mixture of those two components (among

9  others). Indoor volatilization of $NO_3^-$ enriches ambient PM in other components, creating differences in

10  toxicity between indoor ambient and outdoor ambient PM. The high infiltration of non-volatile BC

11  creates additional sorption sites for organics, including indoor-generated compounds. Meng et al. (2007a)

12  found that secondary formation accounts for 55% of indoor aerosols of outdoor origin, while primary

13  combustion accounts for 43% and mechanical generation for 2%. Meng et al. (2007a) noted that

14  secondary formation processes often result in slightly larger particles so that diffusion losses are not as

15  great as for primary combustion particles, composed primarily of nucleation and condensation modes.

16  Likewise, Polidori et al. (2007) suggest that similarities in the EC and OC size distributions and

17  infiltration factors indicate low vapor pressure secondary organic aerosols in the OC component.

18  Variations in the presence of outdoor PM indoors relates to the species composition and makeup of PM.

19  Differences in infiltration and in removal behavior once indoors tend to cause differences in the species

20  composition. The toxicological profile of outdoor and indoor-penetrated outdoor PM would therefore be

21  expected to be different. An example of these studies is Molnár et al. (2007), who reported indoor/outdoor

22  ratios of 0.4-0.7 for residences, schools, and preschools in Sweden, using sulfur and lead as tracers for

23  ambient PM. These ratios are consistent with those observed previously.

### Exposure to PM in Copollutant Mixtures

24      Analysis of personal exposure to multi-pollutant mixtures is an area of growing research. Several

25  multi-pollutant studies involving ultrafine, fine, and coarse PM are presented in Table A-91.

26  Understanding the health impacts of complex multi-pollutant mixtures, including multiple PM species,

27  can have a substantial impact on the interpretation of health effects data. Challenges are presented in

28  accurately estimating the components of a mixture, their concentrations, and personal exposure to those

29  species.

30      One question that has been raised is whether copollutants act as confounders in PM exposure

31  assessments. Sarnat et al. (2001) explored the relationship between PM and copollutant gases and

32  suggested that certain gases can serve as surrogates for describing exposure to other air pollutants. Sarnat

1    et al. (2001) found significant associations between personal exposure to $PM_{2.5}$ and ambient

2    concentrations of $O_3$, $NO_2$, CO (significant only for winter), and $SO_2$ in a panel study conducted in

3    Baltimore. Personal exposures to $PM_{2.5}$ and personal exposures to the gases were not correlated in this

4    study. This result may have arisen in part because personal exposures to the gases were often beneath

5    detection limits of the personal monitoring devices. Significant associations were found for ambient $PM_{2.5}$

6    and ambient $O_3$, $NO_2$, wintertime CO, and $SO_2$ concentrations. In both cases, ambient $O_3$ was positively

7    associated with $PM_{2.5}$ in summer and negatively associated with $PM_{2.5}$ in winter, which is consistent with

8    findings of Ito et al. (2005) for ambient PM (using $PM_{2.5}$ for New York and Philadelphia and $PM_{10}$ for

9    Houston, Minneapolis-St. Paul, Detroit, Cook County, IL (Chicago), St. Louis) and ambient $O_3$ for all

10   cities but Houston. Sarnat et al. (2001) suggested that relatively high correlations between ambient $PM_{2.5}$

11   and ambient $NO_2$ may be due to the emission of both substances by motor vehicles. Schwartz et al. (2007)

12   also used data from the Baltimore panel study to simulate distributions of personal exposures and ambient

13   concentrations of $PM_{2.5}$, $PM_{10}$, $SO_4^{2-}$, $NO_2$, and $O_3$. They found that personal $PM_{2.5}$ was significantly

14   associated with ambient $NO_2$ and ambient $O_3$ (in an inverse relationship) and personal $SO_4^{2-}$ was

15   significantly positively associated with ambient $O_3$. Brook et al. (2007) also noted the correlation between

16   ambient $PM_{2.5}$ and ambient $NO_2$ in a study of ten Canadian cities but suggested that $NO_2$ is a better

17   indicator of $PM_{2.5}$ exposure than ambient $PM_{2.5}$ because it is less variable. In a subset of this work, Brook

18   et al. (2007) also showed that the correlation between ambient $NO_2$ and ambient hopanes, indicative of

19   vehicle exhaust, was stronger than the correlation between ambient $PM_{2.5}$ and ambient hopanes (these

20   data were obtained for two weeks in Windsor, ON in March 2001).

21       Seasonality of the associations could be a result of seasonal variability in photochemistry, source

22   generation, and building ventilation. Sarnat et al. (2005) observed associations between personal $PM_{2.5}$

23   and ambient $O_3$, $NO_2$, and $SO_2$ exposure for a group of healthy senior citizens and school children in

24   Boston for summer but not for winter. In this study, correlations between personal exposure to ambient

25   $PM_{2.5}$ and personal $O_3$ exposures were observed, unlike the Baltimore study. In their study of personal

26   exposure to ambient air pollutants in Steubenville, OH, Sarnat et al. (2006a) found that, in the summer,

27   low but significant associations existed of ambient $O_3$ with personal $PM_{2.5}$, $SO_4^{2-}$, and EC. In the summer,

28   low but significant associations between ambient $SO_2$ and personal $PM_{2.5}$ and between ambient $NO_2$ and

29   personal EC were also observed. In the fall, ambient $O_3$ had a weak but significant association with

30   personal EC, and $SO_2$ had a weak but significant association with personal $SO_4^{2-}$. Ambient $NO_2$ was

31   significantly associated with personal $PM_{2.5}$, $SO_4^{2-}$, and EC with somewhat higher coefficient of

32   determination ($R^2 = 0.25\text{-}0.49$). In summary, the evidence is mixed that ambient gases can be considered

33   surrogates of $PM_{2.5}$ exposure. There is evidence that associations between ambient gases and personal

34   exposure to $PM_{2.5}$ of ambient origin exist but are complex and vary by season and region.

## 3.7.4. Exposure Assessment and Socioeconomic Status

1  The number and complexity of environmental equity studies have increased dramatically since the

2  First National People of Color Environmental Leadership Summit was held in 1991. The environmental

3  equity movement was borne from this conference and Executive Order 14898, in which President Clinton

4  declared that equity issues must be factored into the Environmental Impact Statement process. The

5  preponderance of environmental equity studies related to air quality has not examined the relationship

6  directly between airborne PM and SES because the scale of FRM networks for monitoring $PM_{10}$ and

7  $PM_{2.5}$ (or other criteria air pollutants) in many metropolitan areas is much larger than the spatial variations

8  in SES across neighborhoods. This point is illustrated in Figure 3-81, which shows the 15 km radius

9  around each $PM_{2.5}$ monitor within the Philadelphia CSA. (Note that maps of numbers below poverty level

10  per square mile and numbers with less than a high school diploma per square mile compared with $PM_{10}$

11  and $PM_{2.5}$ sampler density are provided for each of the fifteen CSAs/CBSAs in Annex A). Here, it can be

12  seen that for areas within 15 km of a $PM_{2.5}$ monitor in the Philadelphia CSA, significant variability in SES

13  exists. Tables 3-29 through 3-32 show percentages within the 1 km, 5 km, 10 km, and 15 km of the

14  monitor for populations below the poverty level and with less than high school, high school or more, and

15  college graduate education levels for the fifteen CSAs/CBSAs. These tables illustrate that the monitoring

16  stations do provide some coverage related to low SES groups. For $PM_{10}$, 27-94% of the population below

17  poverty level and 41-92% of the population with less than a high school education are within 15 km of a

18  monitor. 47-93% of the population below poverty level and 44-91% of the population with less than high

19  school education for those are within 15 km of a $PM_{2.5}$ monitor for the fifteen CSAs/CBSAs studied.

20  However, neighborhood scale SES issues are not shown to be well-represented, with 0.2-6% of the

21  population below poverty and 0.2-5% of the population with less than a high school education within 1

22  km of a $PM_{10}$ monitor. Likewise, 0.4-7% of the population below the poverty level and 0.4-5% of the

23  population with less than high school education are within 1 km of a $PM_{2.5}$ monitor.

24  Annex A lists 34 recent studies that specifically include the association between ultrafine,

25  accumulation, $PM_{2.5}$, or $PM_{10}$ and a health outcome as modified by one or more SES variables. The

26  effects of SES as an effect modifier in health effects studies are discussed in Section 8.2.4.

**Table 3-29.** Proximity to $PM_{10}$ and $PM_{2.5}$ monitors among adults older than 25 with less than a high school education by city. Percentages are given with respect to the total population per city provided.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| *PROXIMITY TO $PM_{10}$ MONITORS* | | | | | | | | | |
| Atlanta | 397037 | 5828 | 1.47 | 69214 | 17.43 | 157705 | 39.72 | 222027 | 55.92 |
| Birmingham | 139841 | 7135 | 5.10 | 60727 | 43.43 | 83681 | 59.84 | 93142 | 66.61 |
| Boston | 360791 | 5895 | 1.63 | 86575 | 24.00 | 156912 | 43.49 | 189101 | 52.41 |
| Chicago | 934491 | 8405 | 0.90 | 100953 | 10.80 | 278411 | 29.79 | 531905 | 56.92 |
| Denver | 170110 | 5094 | 2.99 | 53462 | 31.43 | 107939 | 63.45 | 143914 | 84.60 |
| Detroit | 464605 | 3428 | 0.74 | 53780 | 11.58 | 148470 | 31.96 | 253490 | 54.56 |
| Houston | 635036 | 6529 | 1.03 | 141564 | 22.29 | 367943 | 57.94 | 468206 | 73.73 |
| Los Angeles | 1963819 | 7114 | 0.36 | 265004 | 13.49 | 869291 | 44.27 | 1496953 | 76.23 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 598949 | 5045 | 0.84 | 46708 | 7.80 | 81712 | 13.64 | 163386 | 27.28 |
| Phoenix | 383484 | 23819 | 6.21 | 199483 | 52.02 | 316163 | 82.44 | 359337 | 93.70 |
| Pittsburgh | 256990 | 11379 | 4.43 | 100417 | 39.07 | 148283 | 57.70 | 174178 | 67.78 |
| Riverside | 477430 | 11257 | 2.36 | 151939 | 31.82 | 328305 | 68.77 | 381372 | 79.88 |
| Seattle | 254781 | 492 | 0.19 | 26330 | 10.33 | 73186 | 28.72 | 109413 | 42.94 |
| St. Louis | 264721 | 8756 | 3.31 | 86139 | 32.54 | 162996 | 61.57 | 186303 | 70.38 |
| *PROXIMITY TO $PM_{2.5}$ MONITORS* | | | | | | | | | |
| Atlanta | 397037 | 1816 | 0.46 | 44972 | 11.33 | 193590 | 48.76 | 280777 | 70.72 |
| Birmingham | 139841 | 2683 | 1.92 | 37608 | 26.89 | 95116 | 68.02 | 108593 | 77.65 |
| Boston | 360791 | 24546 | 6.80 | 184245 | 51.07 | 247784 | 68.68 | 294008 | 81.49 |
| Chicago | 934491 | 24519 | 2.62 | 400070 | 42.81 | 769226 | 82.32 | 869320 | 93.03 |
| Denver | 170110 | 4018 | 2.36 | 53903 | 31.69 | 120088 | 70.59 | 151516 | 89.07 |
| Detroit | 464605 | 10931 | 2.35 | 178094 | 38.33 | 352951 | 75.97 | 396954 | 85.44 |
| Houston | 635036 | 2581 | 0.41 | 47042 | 7.41 | 195735 | 30.82 | 301048 | 47.41 |
| Los Angeles | 1963819 | 23815 | 1.21 | 489939 | 24.95 | 1346707 | 68.58 | 1768102 | 90.03 |
| New York | 2450252 | 171684 | 7.01 | 1385259 | 56.54 | 1978746 | 80.76 | 2232024 | 91.09 |
| Philadelphia | 598949 | 26912 | 4.49 | 366191 | 61.14 | 493003 | 82.31 | 533423 | 89.06 |
| Phoenix | 383484 | 8294 | 2.16 | 100266 | 26.15 | 197412 | 51.48 | 246594 | 64.30 |
| Pittsburgh | 256990 | 8008 | 3.12 | 90904 | 35.37 | 161286 | 62.76 | 197209 | 76.74 |
| Riverside | 477430 | 9768 | 2.05 | 131733 | 27.59 | 276475 | 57.91 | 320506 | 67.13 |
| Seattle | 254781 | 1510 | 0.59 | 30561 | 12.00 | 87832 | 34.47 | 128641 | 50.49 |
| St. Louis | 264721 | 8550 | 3.23 | 87827 | 33.18 | 183985 | 69.50 | 210177 | 79.40 |

**Table 3-30.** Proximity to PM$_{10}$ and PM$_{2.5}$ monitors for the total population under poverty line by city. Percentages are given with respect to the total population per city provided.

| Region | Total CSA/CBSA N | ≤ 1 km N | ≤ 1 km % | ≤ 5 km N | ≤ 5 km % | ≤ 10 km N | ≤ 10 km % | ≤ 15 km N | ≤ 15 km % |
|---|---|---|---|---|---|---|---|---|---|
| *PROXIMITY TO PM$_{10}$ MONITORS* | | | | | | | | | |
| Atlanta | 448411 | 3745 | 0.84 | 55720 | 12.43 | 128942 | 28.76 | 191136 | 42.63 |
| Birmingham | 147103 | 5682 | 3.86 | 44522 | 30.27 | 66145 | 44.96 | 77685 | 52.81 |
| Boston | 392413 | 3581 | 0.91 | 53764 | 13.70 | 126432 | 32.22 | 170493 | 43.45 |
| Chicago | 1094372 | 9242 | 0.84 | 115912 | 10.59 | 333566 | 30.48 | 560160 | 51.19 |
| Denver | 189663 | 3342 | 1.76 | 55670 | 29.35 | 121772 | 64.20 | 161144 | 84.96 |
| Detroit | 514431 | 3228 | 0.63 | 60935 | 11.85 | 136051 | 26.45 | 223387 | 43.42 |
| Houston | 683428 | 7244 | 1.06 | 154230 | 22.57 | 378960 | 55.45 | 484010 | 70.82 |
| Los Angeles | 2142800 | 9433 | 0.44 | 281562 | 13.14 | 929477 | 43.38 | 1654985 | 77.23 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 657596 | 4484 | 0.68 | 51088 | 7.77 | 113232 | 17.22 | 215062 | 32.70 |
| Phoenix | 371104 | 19813 | 5.34 | 176270 | 47.50 | 288298 | 77.69 | 341603 | 92.05 |
| Pittsburgh | 255621 | 9344 | 3.66 | 77798 | 30.43 | 130064 | 50.88 | 163157 | 63.83 |
| Riverside | 488028 | 11292 | 2.31 | 150452 | 30.83 | 340809 | 69.83 | 394402 | 80.82 |
| Seattle | 215825 | 487 | 0.23 | 25714 | 11.91 | 63627 | 29.48 | 88950 | 41.21 |
| St. Louis | 296508 | 5359 | 1.81 | 63694 | 21.48 | 128961 | 43.49 | 162680 | 54.87 |
| *PROXIMITY TO PM$_{2.5}$ MONITORS* | | | | | | | | | |
| Atlanta | 448411 | 1687 | 0.38 | 44678 | 9.96 | 177700 | 39.63 | 261042 | 58.21 |
| Birmingham | 147103 | 1785 | 1.21 | 30719 | 20.88 | 80301 | 54.59 | 101233 | 68.82 |
| Boston | 392413 | 14787 | 3.77 | 155069 | 39.52 | 239226 | 60.96 | 302977 | 77.21 |
| Chicago | 1094372 | 32528 | 2.97 | 491859 | 44.94 | 869986 | 79.50 | 996601 | 91.07 |
| Denver | 189663 | 3365 | 1.77 | 54486 | 28.73 | 135353 | 71.37 | 168509 | 88.85 |
| Detroit | 514431 | 8814 | 1.71 | 159732 | 31.05 | 334534 | 65.03 | 410145 | 79.73 |
| Houston | 683428 | 2952 | 0.43 | 55174 | 8.07 | 216596 | 31.69 | 319934 | 46.81 |
| Los Angeles | 2142800 | 24354 | 1.14 | 507262 | 23.67 | 1431687 | 66.81 | 1957788 | 91.37 |
| New York | 2597288 | 128534 | 4.95 | 1269125 | 48.86 | 1954534 | 75.25 | 2251450 | 86.68 |
| Philadelphia | 657596 | 18770 | 2.85 | 321148 | 48.84 | 481617 | 73.24 | 544596 | 82.82 |
| Phoenix | 371104 | 7397 | 1.99 | 89820 | 24.20 | 179137 | 48.27 | 220683 | 59.47 |
| Pittsburgh | 255621 | 6458 | 2.53 | 67986 | 26.60 | 146525 | 57.32 | 192872 | 75.45 |
| Riverside | 488028 | 8415 | 1.72 | 128696 | 26.37 | 275673 | 56.49 | 322315 | 66.04 |
| Seattle | 215825 | 1357 | 0.63 | 24146 | 11.19 | 65529 | 30.36 | 95466 | 44.23 |
| St. Louis | 296508 | 6077 | 2.05 | 77103 | 26.00 | 167662 | 56.55 | 202379 | 68.25 |

**Table 3-31.** Proximity to PM$_{10}$ and PM$_{2.5}$ monitors for adults older than 25 with at least a high school degree by city. Percentages are given with respect to the total population per city provided.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| *PROXIMITY TO PM$_{10}$ MONITORS* | | | | | | | | | |
| Atlanta | 1417980 | 6269 | 0.44 | 102003 | 7.19 | 285569 | 20.14 | 508191 | 35.84 |
| Birmingham | 387984 | 8626 | 2.22 | 95125 | 24.52 | 171953 | 44.32 | 227554 | 58.65 |
| Boston | 1466291 | 6156 | 0.42 | 108181 | 7.38 | 295661 | 20.16 | 476645 | 32.51 |
| Chicago | 3024059 | 20451 | 0.68 | 321392 | 10.63 | 860819 | 28.47 | 1317793 | 43.58 |
| Denver | 733177 | 6235 | 0.85 | 91236 | 12.44 | 279592 | 38.13 | 468452 | 63.89 |
| Detroit | 1722217 | 4078 | 0.24 | 116031 | 6.74 | 283436 | 16.46 | 496870 | 28.85 |
| Houston | 1441713 | 9252 | 0.64 | 202238 | 14.03 | 545578 | 37.84 | 790301 | 54.82 |
| Los Angeles | 3531165 | 15995 | 0.45 | 367810 | 10.42 | 1291240 | 36.57 | 2405244 | 68.11 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 2046124 | 8425 | 0.41 | 143098 | 6.99 | 412022 | 20.14 | 810010 | 39.59 |
| Phoenix | 1167897 | 23332 | 2.00 | 345572 | 29.59 | 780607 | 66.84 | 1045509 | 89.52 |
| Pittsburgh | 1041150 | 26717 | 2.57 | 281423 | 27.03 | 528748 | 50.78 | 690759 | 66.35 |
| Riverside | 1118856 | 15916 | 1.42 | 237268 | 21.21 | 660137 | 59.00 | 837766 | 74.88 |
| Seattle | 1142988 | 1680 | 0.15 | 77015 | 6.74 | 244983 | 21.43 | 403001 | 35.26 |
| St. Louis | 1023482 | 10048 | 0.98 | 142311 | 13.90 | 331032 | 32.34 | 453422 | 44.30 |
| *PROXIMITY TO PM$_{2.5}$ MONITORS* | | | | | | | | | |
| Atlanta | 1417980 | 5392 | 0.38 | 146362 | 10.32 | 523634 | 36.93 | 855616 | 60.34 |
| Birmingham | 387984 | 4234 | 1.09 | 84724 | 21.84 | 235143 | 60.61 | 299384 | 77.16 |
| Boston | 1466291 | 27628 | 1.88 | 335506 | 22.88 | 675663 | 46.08 | 970310 | 66.17 |
| Chicago | 3024059 | 51344 | 1.70 | 976946 | 32.31 | 2008665 | 66.42 | 2540602 | 84.01 |
| Denver | 733177 | 4505 | 0.61 | 110496 | 15.07 | 365710 | 49.88 | 556030 | 75.84 |
| Detroit | 1722217 | 15101 | 0.88 | 364242 | 21.15 | 901878 | 52.37 | 1210638 | 70.30 |
| Houston | 1441713 | 2572 | 0.18 | 44544 | 3.09 | 207574 | 14.40 | 410350 | 28.46 |
| Los Angeles | 3531165 | 29011 | 0.82 | 660640 | 18.71 | 1979473 | 56.06 | 2875097 | 81.42 |
| New York | 5915247 | 184470 | 3.12 | 2034067 | 34.39 | 3596554 | 60.80 | 4409699 | 74.55 |
| Philadelphia | 2046124 | 34271 | 1.67 | 651790 | 31.85 | 1248293 | 61.01 | 1542036 | 75.36 |
| Phoenix | 1167897 | 8462 | 0.72 | 122557 | 10.49 | 296712 | 25.41 | 497653 | 42.61 |
| Pittsburgh | 1041150 | 18789 | 1.80 | 244276 | 23.46 | 578962 | 55.61 | 807780 | 77.59 |
| Riverside | 1118856 | 10547 | 0.94 | 184749 | 16.51 | 506166 | 45.24 | 658570 | 58.86 |
| Seattle | 1142988 | 5444 | 0.48 | 108082 | 9.46 | 343358 | 30.04 | 548899 | 48.02 |
| St. Louis | 1023482 | 13983 | 1.37 | 207288 | 20.25 | 493223 | 48.19 | 650270 | 63.54 |

**Table 3-32.** Proximity to $PM_{10}$ and $PM_{2.5}$ monitors for adults older than 25 with at least a college degree by city. Percentages are given with respect to the total population per city provided.

| Region | Total CSA/CBSA | ≤ 1 km | | ≤ 5 km | | ≤ 10 km | | ≤ 15 km | |
|---|---|---|---|---|---|---|---|---|---|
| | N | N | % | N | % | N | % | N | % |
| *PROXIMITY TO $PM_{10}$ MONITORS* | | | | | | | | | |
| Atlanta | 853073 | 6500 | 0.76 | 99524 | 11.67 | 250152 | 29.32 | 392639 | 46.03 |
| Birmingham | 157420 | 1344 | 0.85 | 24587 | 15.62 | 70055 | 44.50 | 108070 | 68.65 |
| Boston | 1090449 | 3003 | 0.28 | 132943 | 12.19 | 304776 | 27.95 | 447975 | 41.08 |
| Chicago | 1678748 | 4649 | 0.28 | 85800 | 5.11 | 269061 | 16.03 | 447794 | 26.67 |
| Denver | 479097 | 4347 | 0.91 | 56010 | 11.69 | 148519 | 31.00 | 257297 | 53.70 |
| Detroit | 676467 | 763 | 0.11 | 20620 | 3.05 | 59301 | 8.77 | 108423 | 16.03 |
| Houston | 761389 | 2340 | 0.31 | 89595 | 11.77 | 287098 | 37.71 | 434060 | 57.01 |
| Los Angeles | 2019245 | 6311 | 0.31 | 139325 | 6.90 | 566194 | 28.04 | 1150060 | 56.95 |
| New York | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Philadelphia | 1037440 | 1629 | 0.16 | 46973 | 4.53 | 190538 | 18.37 | 459073 | 44.25 |
| Phoenix | 515058 | 6626 | 1.29 | 134934 | 26.20 | 324835 | 63.07 | 447886 | 86.96 |
| Pittsburgh | 396981 | 6281 | 1.58 | 105147 | 26.49 | 215427 | 54.27 | 292152 | 73.59 |
| Riverside | 312236 | 3870 | 1.24 | 53356 | 17.09 | 180833 | 57.92 | 241193 | 77.25 |
| Seattle | 660973 | 544 | 0.08 | 39609 | 5.99 | 155878 | 23.58 | 295547 | 44.71 |
| St. Louis | 435940 | 1950 | 0.45 | 35179 | 8.07 | 105568 | 24.22 | 171505 | 39.34 |
| *PROXIMITY TO $PM_{2.5}$ MONITORS* | | | | | | | | | |
| Atlanta | 853073 | 5028 | 0.59 | 118328 | 13.87 | 382938 | 44.89 | 601057 | 70.46 |
| Birmingham | 157420 | 1848 | 1.17 | 36864 | 23.42 | 109871 | 69.79 | 140664 | 89.36 |
| Boston | 1090449 | 29378 | 2.69 | 248873 | 22.82 | 496229 | 45.51 | 708446 | 64.97 |
| Chicago | 1678748 | 15582 | 0.93 | 397700 | 23.69 | 1079947 | 64.33 | 1434516 | 85.45 |
| Denver | 479097 | 2566 | 0.54 | 73886 | 15.42 | 228579 | 47.71 | 356830 | 74.48 |
| Detroit | 676467 | 3403 | 0.50 | 105508 | 15.60 | 310644 | 45.92 | 451474 | 66.74 |
| Houston | 761389 | 436 | 0.06 | 6395 | 0.84 | 32141 | 4.22 | 110252 | 14.48 |
| Los Angeles | 2019245 | 12045 | 0.60 | 302402 | 14.98 | 950488 | 47.07 | 1424480 | 70.55 |
| New York | 3700528 | 157911 | 4.27 | 1364013 | 36.86 | 2223755 | 60.09 | 2767157 | 74.78 |
| Philadelphia | 1037440 | 21130 | 2.04 | 216512 | 20.87 | 537396 | 51.80 | 755892 | 72.86 |
| Phoenix | 515058 | 1977 | 0.38 | 32808 | 6.37 | 84812 | 16.47 | 191614 | 37.20 |
| Pittsburgh | 396981 | 3564 | 0.90 | 92830 | 23.38 | 214879 | 54.13 | 325673 | 82.04 |
| Riverside | 312236 | 1613 | 0.52 | 36761 | 11.77 | 136016 | 43.56 | 191453 | 61.32 |
| Seattle | 660973 | 1877 | 0.28 | 41826 | 6.33 | 178144 | 26.95 | 332915 | 50.37 |
| St. Louis | 435940 | 3719 | 0.85 | 83327 | 19.11 | 210846 | 48.37 | 288173 | 66.10 |
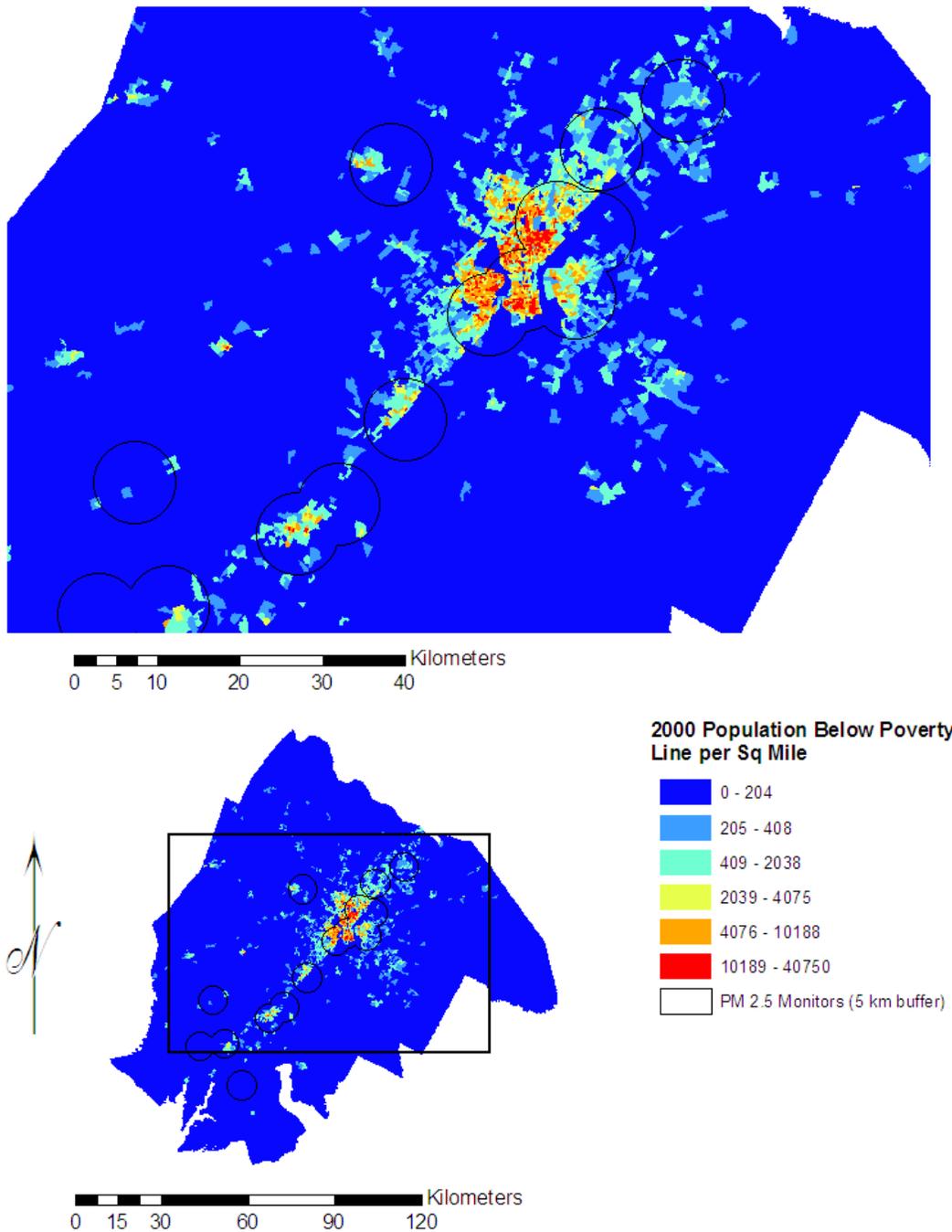
**Figure 3-81.** PM$_{2.5}$ sampler density compared with numbers in poverty per square mile in the Philadelphia CSA.

# 3.8. Summary and Conclusions

## 3.8.1. Concentrations and Sources of Atmospheric PM

### 3.8.1.1. Ambient PM Variability and Correlations

1    Advances in understanding the spatiotemporal distribution of PM mass and constituents have

2    recently been made, particularly with regard to $PM_{2.5}$ mass and chemical composition and ultrafine

3    concentrations. Emphasis in this ISA was on the period from 2005-2007 so that the most recent validated

4    EPA Air Quality System (AQS) data were used. Note, however, that a majority of U.S. counties were not

5    represented in AQS data, since their population densities fell below the regulatory monitoring threshold

6    for PM. Moreover, monitors reporting to AQS were not uniformly distributed across the U.S. or within

7    counties, and conclusions drawn from AQS data may not apply equally to all parts of a geographic region.

8    Furthermore, biases can exist for some PM constituents (and hence total mass) owing to volatilization

9    losses of nitrates and other semi-volatile compounds, and, conversely, to retention of particle-bound water

10   by hygroscopic species. The degree of spatial variability in PM was likely to be region-specific and

11   strongly influenced by region-specific sources and meteorological and topographic conditions.

### *Spatial Variability across the U.S.*

12   County-scale, 24-h average concentration data for $PM_{10}$ and $PM_{2.5}$ for 2005-–2007 showed

13   considerable variability across the U.S. Figures 3-6 and 3-7 show county-scale coverage and average

14   concentrations for $PM_{10}$ and $PM_{2.5}$. For $PM_{10}$, the highest reported annual average concentrations

15   ($>51$ $\mu g/m^3$) occurred in two counties in southern California and five counties in southern Arizona and

16   central New Mexico. The lowest reported annual average $PM_{10}$ concentrations ($\leq 20$ $\mu g/m^3$) were within

17   114 counties distributed fairly uniformly across the U.S. For $PM_{2.5}$, the highest reported annual average

18   concentration ($>20$ $\mu g/m^3$) were reported for six counties within the San Joaquin Valley and inland

19   southern California, as well as Jefferson County, AL (containing Birmingham) and Allegheny County, PA

20   (containing Pittsburgh). The lowest reported annual average $PM_{2.5}$ concentrations ($\leq 20$ $\mu g/m^3$) were

21   contained within 237 counties distributed throughout the west, northeast, Florida and the Carolinas.

22   The concentration of $PM_{2.5}$ relative to that of $PM_{10}$ varied substantially by location, with a larger

23   fraction of PM mass in the coarse mode in cities with dryer climates (e.g., Phoenix and Denver) and a

24   larger fraction in the fine mode in eastern U.S. cities (e.g., Pittsburgh and Philadelphia). Limiting the

25   differential calculation of $PM_{10-2.5}$ to low volume federal reference method (FRM) $PM_{10}$ and $PM_{2.5}$

26   monitors helps reduce sampling artifacts resulting from subtracting two independent mass measurements.

1    However, this results in poor geographic coverage since few sites have the appropriate co-located

2    monitors for computing this difference. Figure 3-8 contains all U.S. counties where co-located low

3    volume FRM data was available for this calculation. Although the general understanding of PM

4    differential settling leads to an expectation of greater spatial heterogeneity in the $PM_{10-2.5}$ fraction,

5    deposition of particles as a function of size depends strongly on local meteorological conditions. Current

6    data coverage is insufficient to draw any meaningful conclusions regarding the spatial distribution of

7    $PM_{10-2.5}$.

8        Spatial variability in $PM_{2.5}$ components obtained from the Chemical Speciation Network (CSN)

9    varied considerably by species, including OC, EC, $SO_4^{2-}$, $NO_3^-$ and $NH_4^+$ (see Section 3.5.1.1). The

10   highest annual average OC concentrations (>5 µg/m$^3$) were observed in the western and southeastern U.S.

11   Concentrations in the western U.S. peaked in the fall and winter, while concentrations in the Southeast

12   peaked anytime between spring and fall. EC exhibited less seasonality than OC and was particularly

13   stable in the eastern half of the U.S. Annual average EC concentrations greater than 1.5 µg/m$^3$ were

14   present in Los Angeles, Pittsburgh, New York and El Paso. Concentrations of $SO_4^{2-}$ were higher in the

15   eastern U.S. as a result of higher $SO_2$ emissions in the East, compared with the West. There is also

16   considerable seasonal variability with higher $SO_4^{2-}$ concentrations in the summer months when the

17   oxidation of $SO_2$ proceeds at a faster rate than during the winter. $NO_3^-$ concentrations were highest in

18   California, with annual averages >4 µg/m$^3$ at many monitoring locations. There were also elevated levels

19   of $NO_3^-$ in the Upper Midwest (>2 µg/m$^3$), particularly in the winter. In general, $NO_3^-$ was higher in the

20   winter across the country, in part as a result of temperature-driven partitioning and volatilization.

21   Exceptions existed in Los Angeles and Riverside, where high $NO_3^-$ readings appeared year round.

22   Concentrations of $NH_4^+$ were similar to concentrations of $NO_3^-$ or $SO_4^{2-}$ throughout the U.S. Clearly,

23   there is variation in both $PM_{2.5}$ mass and composition by city, some of which might be due to regional

24   differences; however, there are too many controlling variables (e.g. meteorology, sources, topography)

25   which are varied and too poorly characterized at this scale to allow conclusions to be drawn regarding

26   $PM_{2.5}$ composition across all cities within a given geographic region.

27        Variability in $PM_{2.5}$ components across the U.S. was examined by focusing on fifteen metropolitan

28   areas chosen based on their geographic distribution and coverage in recent health effects studies (see

29   Section 3.5.1.1). The urban areas selected were Atlanta, Birmingham, Boston, Chicago, Denver, Detroit,

30   Houston, Los Angeles, New York, Philadelphia, Phoenix, Pittsburgh, Riverside, Seattle and St. Louis. On

31   an annual average basis, sulfate was the dominant $PM_{2.5}$ component in the eastern cities, ranging from

32   42% of $PM_{2.5}$ mass in Chicago to 56% in Pittsburgh. Organic carbon mass (OCM) was the next largest

33   component. In the western cities, OCM was the largest constituent of $PM_{2.5}$ on an annual basis, ranging

34   from 34% in Los Angeles to 58% in Seattle. Sulfate, nitrate and crustal material were all important

1  components in the western cities analyzed. Sulfate ranged from 18% in Denver to 32% in Los Angeles.

2  Nitrate was particularly large in Riverside (22%), Los Angeles (19%) and Denver (15%); crustal material

3  constituted a substantial fraction of $PM_{2.5}$ year-round in Phoenix (28%) and Denver (16%), and during the

4  summer in Houston (26%), even though the annual average was much lower (11%).

### Spatial Variability on the Urban and Neighborhood Scales

5      In general, $PM_{10}$ has a shorter atmospheric lifetime than $PM_{2.5}$ because $PM_{10}$ contains larger

6  particles which have higher settling velocity. As a result, local emission sources often dominate $PM_{10}$

7  annual average mass concentrations at particular monitors, while $PM_{2.5}$ mass concentrations are more

8  homogeneously distributed (see Section 3.5.1.2). Therefore, as an example, using the 15 cities listed

9  above, there was considerably less decline in the correlation between monitors as a function of distance

10  for $PM_{2.5}$ than for $PM_{10}$. Furthermore, correlations between $PM_{2.5}$ concentrations exhibited substantially

11  less scatter. For $PM_{10}$, Atlanta, Boston, Denver, Los Angeles, New York City, Philadelphia, Phoenix,

12  Pittsburgh and Riverside all showed relatively high correlations as a function of distance (average

13  correlation of 0.75 at 40 km or greater monitor separation), while Birmingham, Chicago, Detroit, Houston

14  and St. Louis had correlations that dropped off much more quickly with distance (average correlation of

15  0.75 at 6 km or less monitor separation). The Seattle data only included two $PM_{10}$ monitoring sites, thus

16  providing insufficient information to draw any conclusions. For $PM_{2.5}$, most metropolitan areas exhibited

17  high correlations (generally >0.75) out to a distance of 100 km. Notable exceptions were Denver, Los

18  Angeles and Riverside, where correlations dropped below 0.75 somewhere between 20 and 50 km.

19  Insufficient data were available in the 15 metropolitan areas to perform similar analyses for $PM_{10-2.5}$ using

20  co-located, low volume FRM monitors.

21      Population density and associated building density are important determinants of the spatial

22  distribution of PM concentrations. Inter-sampler correlations as a function of distance between monitors

23  obtained for sampler pairs located less than 4 km apart (i.e., on a neighborhood scale) showed a shallower

24  slope for $PM_{2.5}$ than for $PM_{10}$. Average correlation was maintained at 0.93 for $PM_{2.5}$, while it dropped to

25  0.70 for $PM_{10}$ (see Section 3.5.1.3).

26      Few studies performed direct comparisons of ultrafine particle measurements at multiple locations

27  within an urban area. A decrease in the number of ultrafine particles was demonstrated with shifts from a

28  dominant mode at around 10 nm within 20 m of a freeway to a flattened dominant mode at around 50 nm

29  at a distance of roughly 100–150 m. At the same time, accumulation mode particle number concentration

30  remained relatively constant to within ~300 m from the freeway. These findings suggest a high degree of

31  spatial heterogeneity in ultrafine particles compared with accumulation mode particles on the urban scale.

## 3.8.1.2. Temporal Variability

1    Trends in $PM_{10}$ concentrations show a steady decline from 1988 to 2007 in all 10 EPA Regions. A

2    steady decrease in $PM_{2.5}$ concentrations from 1999 (the beginning of nationwide monitoring for $PM_{2.5}$) to

3    2007 was observed in all 10 EPA Regions, with the three-year average of the 98th percentile of 24-h

4    $PM_{2.5}$ concentrations dropping 10% over this time period.

5    Using hourly PM observations in the 15 metropolitan areas, diel variation showed peaks that differ

6    by pollutant and region. For $PM_{10}$, all areas showed a gradual morning increase in mean concentrations

7    starting at approximately 6:00 am on weekdays, corresponding with both the start of morning rush hour

8    and break-up of the overnight inversion layer. The magnitude and duration of this peak varied

9    considerably by metropolitan area. For $PM_{2.5}$, a similar morning peak was observed starting at

10    approximately 6:00 am in all cities except Pittsburgh, where elevated overnight $PM_{2.5}$ obscures any

11    morning peak. There was also an evening $PM_{2.5}$ concentration peak that was broader than the morning

12    peak and extended into the overnight period, reflecting the concentration increase caused by the usual

13    collapse of the mixed layer after sundown (see Section 3.5.2.3).

14    Studies indicate that ultrafine particles in urban environments exhibit similar two-peaked diel

15    patterns in Los Angeles and the San Joaquin Valley as well as in Kawasaki City, Japan and Copenhagen,

16    Denmark (see Section 3.5.2.3). The afternoon peak in ultrafine particles likely represents the combination

17    of primary source emissions such as evening rush hour traffic and photochemical formation of secondary

18    organic aerosol.

## 3.8.1.3. Correlations between Copollutants

19    Correlations between PM and gaseous copollutants including $SO_2$, $NO_2$, carbon monoxide (CO)

20    and $O_3$ varied both seasonally and spatially between and within metropolitan areas. On average, $PM_{10}$ and

21    $PM_{2.5}$ were correlated with each other better than with the gaseous copollutants. There was relatively little

22    seasonal variability in the mean correlation between PM in both size fractions and $SO_2$ and $NO_2$. CO,

23    however, showed higher correlations with $PM_{10}$ and $PM_{2.5}$ on average in the winter compared with the

24    other seasons. This seasonality results in part because a larger fraction of PM is primary in origin during

25    the winter. To the extent that this primary component of PM is associated with common sources of $NO_2$

26    and CO, then higher correlations with these gaseous co-pollutants are to be expected. Increased

27    atmospheric stability in colder months would also reinforce these associations.

28    The correlation between daily maximum 8-h average $O_3$ and PM showed the highest degree of

29    seasonal variability with positive correlations on average in the spring, summer and fall, and negative

30    correlations on average in the winter. This situation arises as the result of seasonal differences in sources

1  and photochemical production of secondary $PM_{2.5}$ and $O_3$. However, this relationship is not found in all

2  cities examined (e.g., Birmingham, Boston and St. Louis).

## 3.8.1.4. Measurement Techniques

3  Reliable methods have been developed to measure real-time PM mass concentrations (e.g., FDMS-

4  TEOM). Real-time (or continuous and semi-continuous) measurement techniques are also available for

5  PM species, such as PILS for multiple ions analysis and AMS for multiple components analysis.

6  Advances have also been achieved in PM organic speciation (e.g. TD-GC-MS). (For addition information

7  see Section 3.4.)

## 3.8.1.5. PM Source Characteristics

8  PM in the atmosphere contains both primary (i.e., emitted directly by sources) and secondary

9  components, which can be anthropogenic or natural in origin. Secondary components are produced by the

10  oxidation of precursor gases such as $SO_2$, $NO_X$ and ammonia ($NH_3$) and organic compounds. The largest

11  sources of primary $PM_{2.5}$ on a nationwide basis are wildfires, road dust, and electricity-generating units

12  (EGUs), with road dust being the largest single source of $PM_{10}$ according to the National Emissions

13  Inventory (NEI).

14  Developments in the chemistry of formation of secondary organic aerosol (SOA) indicate that

15  oligomers are likely a major component of OC in aerosol samples. Until a few years ago, the oxidation of

16  terpenes and aromatic compounds were considered as sources of SOA, but not the oxidation of isoprene.

17  However, recent observations suggest that small, but important quantities of SOA are formed from

18  isoprene oxidation. Gasoline engines have been found to emit a mix of OC, EC, and nucleation-mode

19  heavy and large polycyclic aromatic hydrocarbons on which unspent fuel and trace metals condense,

20  while diesel particles are composed of a soot nucleus on which $SO_4^{2-}$ and hydrocarbons condense.

21  Current inventories of emissions from combustion sources overestimate the primary component of

22  organic aerosol and underestimate the semi-volatile components in the emissions. This situation results

23  from the lack of capture of evaporated semi-volatile components upon dilution in standard emissions

24  tests. As a result, near-traffic sources of organic aerosol are underestimated, however, farther downwind

25  the overall formation rate of SOA increases as a result of the oxidation of these semi-volatile components.

## 3.8.1.6. Source Contributions to PM

26  Results of receptor modeling calculations indicate that $PM_{2.5}$ is produced mainly by combustion of

27  fossil fuel, either by stationary sources or by transportation. It is apparent that a relatively small number

1    of source categories, compared to the total number of chemical species that typically are measured in

2    ambient monitoring source receptor model studies, are needed to account for the majority of the observed

3    mass of PM in these studies. A compilation of study results shows that secondary sulfate (mainly from

4    EGUs), nitrate (from the oxidation of $NO_X$ emitted mainly from transportation and EGUs), and primary

5    mobile source categories constitute most of $PM_{2.5}$ (and $PM_{10}$) in the East. Fugitive dust, found mainly in

6    the $PM_{10-2.5}$ size range, represents the largest source of ambient $PM_{10}$ in many locations in the western

7    U.S. Quoted uncertainties in the source apportionment of constituents in ambient aerosol samples

8    typically range from 10 to 50%. An intercomparison of source apportionment techniques indicated that

9    the same major source categories of $PM_{2.5}$ were consistently identified by several independent groups

10   working with the same data sets. Soil-, sulfate-, residual oil-, and salt-associated mass were most clearly

11   identified by the groups. Other sources with more ambiguous signatures, such as vegetative burning and

12   traffic-related emissions were less consistently identified.

13        Spatial variability in source contributions across urban areas is an important consideration in

14   assessing the likelihood of exposure error in epidemiologic studies relating health endpoints to sources.

15   Concepts similar to those for using ambient concentrations as surrogates for personal exposures apply

16   here. Studies for $PM_{2.5}$ indicate that intra-urban variability increases in the following order: regional (e.g.

17   secondary $SO_4^{2-}$ from EGUs) < area (e.g. on road mobile sources) < point (e.g. stacks) sources. Only one

18   study was available for $PM_{10-2.5}$, indicating a similar ordering, but without a regional component (resulting

19   from the short lifetime of $PM_{10-2.5}$ compared to transport times on the regional scale).

## 3.8.1.7. Policy-Relevant Background

20        The background concentration of PM that is useful for risk and policy assessments informing

21   decisions about the NAAQS are referred to as policy-relevant background (PRB) concentrations. PRB

22   concentrations are those concentrations that would occur in the U.S. in the absence of anthropogenic

23   emissions in continental North America (defined here at the U.S., Canada and Mexico). PRB

24   concentrations include contributions from natural sources everywhere in the world and from

25   anthropogenic sources outside these three countries. Background levels so defined facilitate separation of

26   pollution levels that can be controlled by U.S. regulations (or through international agreements with

27   neighboring countries) from levels that are generally uncontrollable by the U.S. Contributions to policy-

28   relevant background (PRB) levels of PM include both primary and secondary natural and anthropogenic

29   components (see Section 3.6). PRB concentrations for the continental U.S. were estimated using a

30   deterministic, continental scale chemistry-transport model (CTM) using results from the GEOS-Chem

31   global scale CTM as boundary conditions. PRB concentrations of $PM_{2.5}$ were estimated to be less than 1

32   $\mu g/m^3$ on an annual basis and maximum daily average values generally range from about 3 to 20 $\mu g/m^3$

1    with a peak as high 63 µg/m$^3$ as at the nine national park sites across the U.S. that were used for model

2    evaluation.

# 3.8.2. Human Exposure

3        This section summarizes the findings from the recent exposure assessment literature, which include

4    the assessment of exposure to ambient PM, infiltration of ambient PM to indoor environments, and source

5    apportionment of exposure. This summary is intended to support the interpretation of the findings from

6    epidemiologic studies. For a more detailed explanation see Section 3.7.

### 3.8.2.1. Outdoor Exposure to Ambient PM

7        The correlation between the PM concentration measured at a central community ambient monitor

8    and the true community average concentration depends on the spatial distribution of the PM, selection of

9    the monitoring site chosen to represent the community average, and division of the community by terrain

10   features or source locations into several sub-communities that differ in the temporal pattern of pollution.

11   Some studies, conducted mainly in Europe, have found that personal $PM_{2.5}$ and $PM_{10}$ exposures for

12   pedestrians in street canyons could be much higher than ambient concentrations measured by urban

13   background ambient monitors. As a result, ambient monitors located at background, central urban, road

14   side, or near-residential sites might not reflect peak exposures to some individuals in a community.

15   Ambient monitor height also affects estimates of exposure because PM concentration varies as a function

16   of height. Within a street canyon, changes in wind direction and speed cause significant variability over a

17   small distance, with findings showing up to a two order of magnitude change in benzo[a]pyrene

18   concentrations across a street canyon. Wind tunnel studies have shown street canyon effects exist for

19   suburban and not just for downtown, heavily urbanized settings.

### 3.8.2.2. Indoor and Personal Exposure to Ambient PM

20       PM infiltration factors, $F_{inf}$, depend on particle size, chemical composition, season, and region of

21   the country. Infiltration can best be modeled dynamically based on a distribution of air exchange and

22   deposition PM loss rates rather than being represented by a single value. There is significant variability

23   within and across regions of the country with respect to indoor exposures to ambient PM. Infiltrated

24   ambient PM concentrations depend in part on the ventilation properties of the building or vehicle in which

25   the person is exposed. Season is important to PM infiltration because it affects the ventilation practices

26   used, and ambient temperature and humidity conditions affect the transport, dispersion, and size

1    distribution of PM. Residential air exchange rates have been observed to be higher in summer for regions

2    with low air conditioning usage, and regional differences in air exchange rates (Southwest < Southeast

3    < Northeast < Northwest) also reflect ventilation practices. Differential infiltration occurs as a function of

4    PM size and composition. PM infiltration is largest for accumulation mode particles, and decreases for

5    ultrafine PM lost to diffusion and for coarse particles lost through inertial impaction mechanisms.

6    Infiltration is also affected by variations in particle composition and volatility. For example, EC or black

7    carbon (BC) infiltrates more readily than OC. Differential infiltration can affect both exposure estimates

8    and PM toxicity.

9         Emission inventories and source apportionment studies suggest that sources of PM exposure vary

10   by region. Comparison of studies performed in the eastern U.S. with studies performed in the western

11   U.S. suggest that the contribution of $SO_4^{2-}$ to personal exposure is higher for the East (16-46%) compared

12   with the West (~4%) and that motor vehicle emissions and secondary $NO_3^-$ are larger sources of personal

13   exposure for the West (~9%) as compared with the East (~4%). Results of source apportionment studies

14   of personal exposure to $SO_4^{2-}$ indicate that personal $SO_4^{2-}$ exposures are mainly attributable to ambient

15   sources. Source apportionment for OC and EC is difficult because they originate from both indoor and

16   outdoor sources. Exposure to OC of indoor and outdoor origin can be distinguished by the presence of

17   aliphatic C-H groups generated indoors, since outdoor concentrations of aliphatic C-H are low. Trace

18   metal studies have shown variable results regarding personal exposure to ambient constituents with

19   significant variation among cities and over seasons that can be related to incinerator operation, fossil fuel

20   combustion, biomass combustion (wildfires), and presence of crustal materials in the built environment,

21   among other sources.

## 3.8.2.3. Implications for Epidemiologic Studies

22        Variations in PM and its components could lead to errors in using ambient PM measures as

23   surrogates for exposures to PM. $PM_{2.5}$ and $PM_{10}$ concentrations are relatively well-correlated across

24   monitors in the urban areas examined. Correlation coefficients tend to be lower, and concentration

25   differences tend to be higher between $PM_{10}$ monitoring sites than between $PM_{2.5}$ monitoring sites. Even if

26   $PM_{2.5}$ and $PM_{10}$ concentrations measured at sites within an urban area are highly correlated, significant

27   differences in their concentrations can occur on any given day. The degree of spatial uniformity in $PM_{10}$

28   and $PM_{2.5}$ concentrations in urban areas varies across the country. Current information suggests that

29   $PM_{10-2.5}$ and some PM components are more spatially variable than $PM_{2.5}$. These factors should be

30   considered in using data obtained from monitoring networks to estimate community-scale human

31   exposure to ambient PM, and caution should be exercised in extrapolating conclusions obtained from one

32   urban area to another.

Community, time-series epidemiologic studies use the average community PM concentration as a surrogate for the average personal exposure to ambient PM. The resulting health effect risk estimate, based on the average community ambient concentration, differs from the risk that would be estimated if the average community ambient exposure were used in the epidemiologic study. This difference is given by the average ambient exposure factor. However, the risk estimate based on the ambient concentration gives the change in health effects resulting from a change in ambient concentration of PM and is, therefore, an appropriate measure for risk assessment and risk management. Variations in ambient concentrations across a community, variations in individual ambient exposures around the community average, and seasonal or daily variation in the ambient exposure factor may increase standard errors of PM health effects estimates, making it more difficult to detect a true underlying association between the correct exposure metric and the health outcome studied. The use of the community average ambient PM concentration as a surrogate for the community average personal exposure to ambient PM is not expected to change the principal conclusions from PM epidemiologic studies that use community average health and pollution data (U.S. EPA, 2004). Several recent studies support this by showing how the ambient component of personal exposure to $PM_{2.5}$ could be estimated using various tracer and source apportionment techniques and that is highly correlated with ambient concentrations of $PM_{2.5}$. These studies also show that the non-ambient component of personal exposure to $PM_{2.5}$ is basically uncorrelated with ambient $PM_{2.5}$ concentrations. For long-term studies that use differences in long-term community average ambient PM concentrations as an exposure metric, the effect of possible community-to-community differences in the average ambient exposure factor or in the average non-ambient exposure are less understood. For panel epidemiologic studies, the most appropriate exposure metric may depend on the health outcome measured. However, sufficient information should be obtained to enable determining the association of the health outcome with ambient concentration, ambient exposure, non-ambient exposure, and total personal exposure.

A number of studies have examined whether gaseous copollutants could act as surrogates for exposure to ambient PM. Several studies have concluded that ambient concentrations of $O_3$, $NO_2$, and $SO_2$ are associated with the ambient component of personal exposure to total $PM_{2.5}$ as opposed to the ambient component of personal exposures to the gases. However, in some studies this result may have arisen in part because personal exposure to the gases was often beneath the detection limits of the personal monitoring devices. Thus, the evidence that ambient gases can be considered surrogates of $PM_{2.5}$ exposure is mixed. It is likely that associations between ambient gases and personal exposure to $PM_{2.5}$ of ambient origin exist, but they are complex and vary by season and location.

# Chapter 4. Dosimetry

## 4.1. Introduction

1        Particle dosimetry refers to the characterization of deposition, translocation, clearance, and

2   retention of particles and their constituents within the respiratory tract and extrapulmonary tissues. This

3   chapter summarizes basic concepts presented in dosimetry chapters of the 1996 and 2004 PM AQCDs

4   (U.S. EPA, 1996, 2004), and updates the state of the science based upon new literature appearing since

5   publication of these PM AQCDS. Although our basic understanding of the mechanisms governing

6   deposition and clearance of inhaled particles has not changed, there has been significant additional

7   information on the role of certain biological determinants such as gender, age and lung disease on

8   deposition and clearance. Additionally, new studies have further characterized the retention and

9   translocation of ultrafine particles (also commonly referred to as nanoparticles) following deposition in

10   the respiratory tract.

11        The dose from inhaled particles deposited and retained in the respiratory tract is governed by a

12   number of factors. These include exposure concentration and duration, activity and ventilatory

13   parameters, and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and

14   cellular components). The basic characteristics of particles as they relate to deposition and retention, as

15   well as anatomical and physiological factors influencing particle deposition and retention, were discussed

16   in depth in Chapter 10 of 1996 PM AQCD and updated in Chapter 6 of the 2004 PM AQCD. Species

17   differences between humans and rats in particle exposures, deposition patterns, and pulmonary retention

18   were also reviewed in Brown et al. (2005). The current review of PM dosimetry focuses mainly on issues

19   that may affect the susceptibility of an individual to adverse effects as well as issues that affect our ability

20   to extrapolate findings between studies (e.g., in vitro to in vivo) and between species.

### 4.1.1. Size Characterization of Inhaled Particles

21        Particle size is a major determinant of the fraction of inhaled particles depositing in and cleared

22   from various regions of the respiratory tract. The distribution of particle sizes in an aerosol is typically

23   described by the lognormal distribution (i.e., the situation in which the logarithms of particle diameter are

24   distributed normally). The geometric mean is the median of the distribution, and the variability around the

25   median is the geometric standard deviation (GSD or $\sigma_g$) and is given by:

$$GSD = \sigma_g = \frac{d_{84\%}}{d_{50\%}} = \frac{d_{50\%}}{d_{16\%}}$$

<div align="right"><em>Equation 4-1</em></div>

1  where: $d_{16\%}$, $d_{50\%}$, $d_{84\%}$ are the particle diameters associated with the 16th, 50th (i.e. the median), and the

2  84th percentiles from the cumulative frequency distribution of particle sizes. Note that the GSD is always

3  greater than one. The particle size associated with any percentile of the distribution, $d_i$, is given by:

$$d_i = d_{50\%}\, \sigma_g^{z(P)}$$

<div align="right"><em>Equation 4-2</em></div>

4  where: $z(P)$ is the normal standard deviate for a given probability. In most cases, the aerosols to which

5  people are naturally exposed are polydisperse. By contrast, most experimental studies of particle

6  deposition and clearance in the lung use monodisperse particles (GSD < 1.15). Ambient aerosols may also

7  be composed of multiple size modes, each mode should be described by its specific median diameter and

8  GSD.

9  Aerosol size distributions may be measured and described in various ways. When a distribution is

10  described by counting particles, the median is called the count median diameter (CMD). On the other

11  hand, the median of a distribution based on particle mass in an aerosol is the mass median diameter

12  (MMD). Impaction and sedimentation of particles in the respiratory tract depend on a particle's

13  aerodynamic diameter ($d_{ae}$), which is the size of a sphere of unit density that has the same terminal

14  settling velocity as the particle of interest. The size distribution is frequently described in terms of $d_{ae}$ as

15  the mass median aerodynamic diameter (MMAD), which is the median of the distribution of mass with

16  respect to aerodynamic equivalent diameter. Alternative descriptions should be used for particles with

17  actual physical sizes below $\approx 0.5$ µm because, for these sized particles, aerodynamic properties become

18  less important and diffusion becomes ever more important. For these smaller particles, their physical

19  diameter or CMD are typically used since diffusivity is not a function of particle density. For aggregates,

20  a thermodynamic-equivalent size, i.e., the diameter of a spherical particle that has the same diffusion

21  coefficient in air as the aggregate, is appropriate.

## 4.1.2. Structure of the Respiratory Tract

22  The basic structure of the human respiratory tract is illustrated in Figure 4-1. A recent review of

23  interspecies similarities and differences in the structure and function of the respiratory tract is provided by

24  Phalen et al. (2008). Although the structure varies, the illustrated anatomic regions are common to all

25  mammalian species with the exception of the respiratory bronchioles. Respiratory bronchioles, the

1 transition region between ciliated and fully alveolated airways, are found in humans, dogs, ferrets, cats,

2 and monkeys. Respiratory bronchioles are absent in rats and mice and abbreviated in hamsters, guinea

3 pigs, oxen, sheep, and pigs. The branching structure of the ciliated bronchi and bronchioles also differs

4 between species from being a rather symmetric and dichotomous branching network of airways in

5 humans to a more monopodial branching network in other mammals.
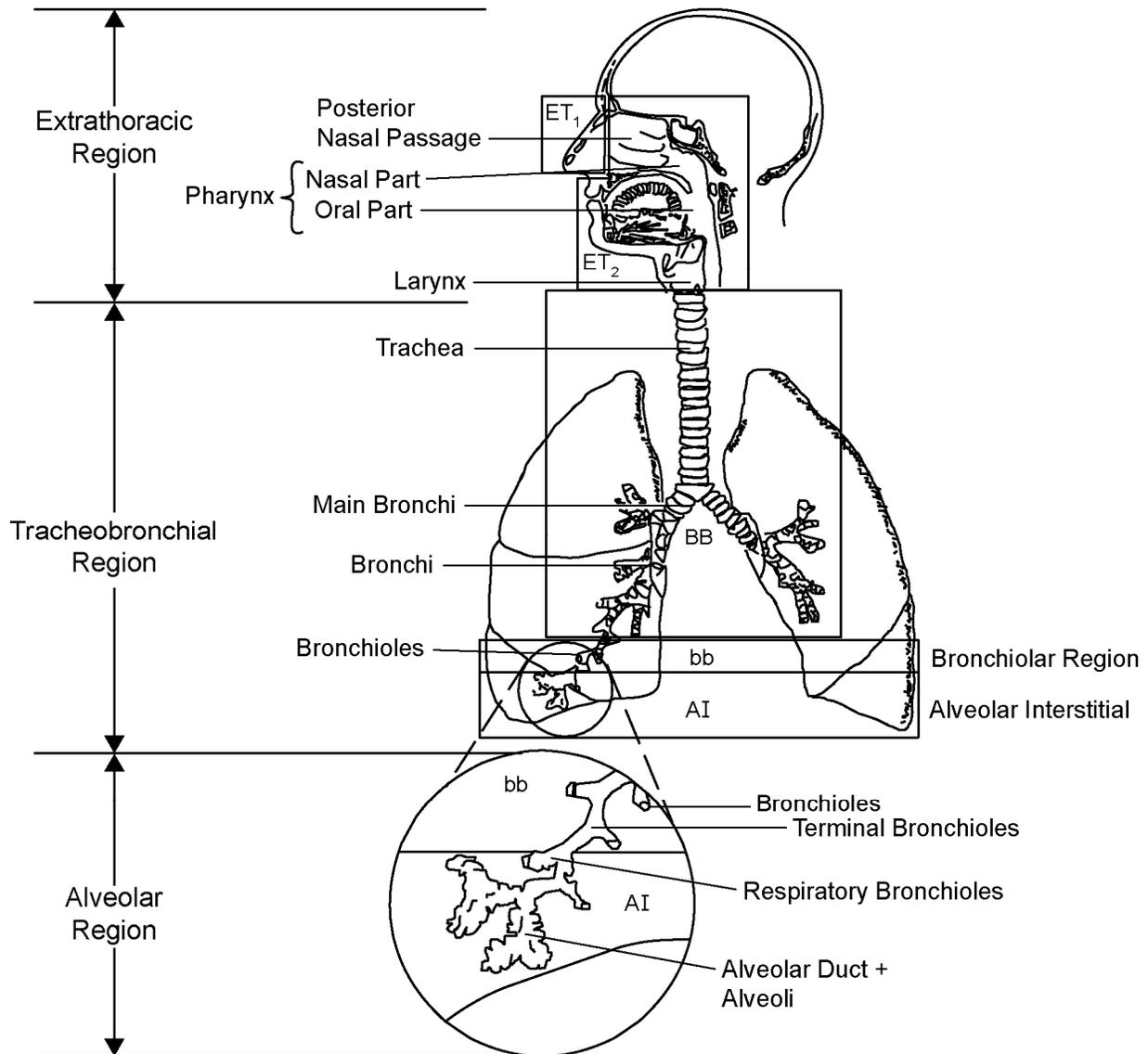


Source: Based on ICRP (1994).

**Figure 4-1.    Diagrammatic representation of respiratory tract regions in humans.  Structures are anterior nasal passages, ET$_1$; oral airway and posterior nasal passages, ET$_2$; bronchial airways, BB; bronchioles, bb; and alveolar interstitial, AI.**

1    Another species difference relevant to particle dosimetry is the route of breathing. For instance, rats

2    are obligate nose breathers, whereas most humans are oronasal breathers who breathe through the nose

3    when at rest and increasingly through the mouth with increasing activity level. There is inter-individual

4    variability in the route by which people breathe. Most people, 87% (26 of 30) in the Niinimaa et al.

5    (1981) study, breathed through their nose until an activity level was reached where they switched to oro-

6    nasal breathing. Thirteen percent (4 of 30) of the subjects, however, were oronasal breathers even at rest.

7    These two subject groups are commonly referred to in the literature (e.g., (ICRP, 1994) as "normal aug-

8    menters" and "mouth breathers," respectively. In contrast to healthy subjects, Chadha et al. (1987) found

9    that the majority (11 of 12) of patients with asthma or allergic rhinitis breathe oronasally even at rest.
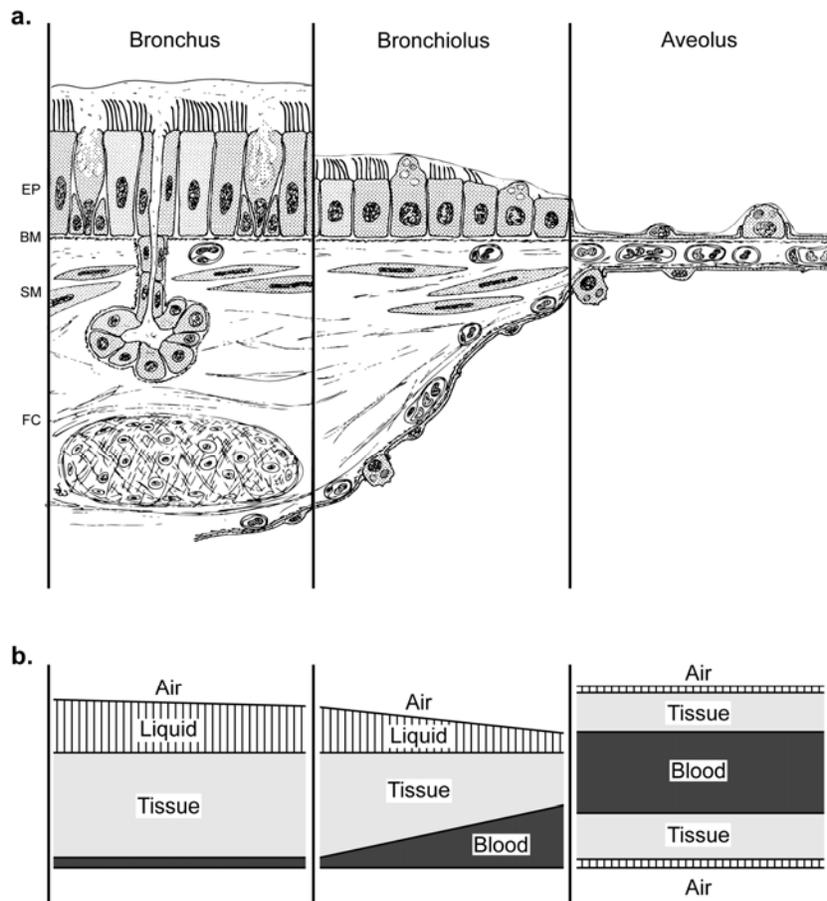


Source: Panel (a) reproduced with permission (ER Weibel, Design and structure of the human lung,
In: Pulmonary Diseases and Disorders, ed. AP Fishman, McGraw-Hill, New York, 1980, p. 231)(Fishman and Elias, 1980).

**Figure 4-2.    Structure of lower airways with progression from the large airways to the alveolus. Panel (a) illustrates basic airway anatomy. Structures are epithelial cells, EP; basement membrane, BM; smooth muscle cells, SM; and fibrocartilaginous coat, FC. Panel (b) illustrates the relative amounts of liquid, tissue, and blood with distal progression.**

1    The site of particle deposition within the respiratory tract has implications related to lung retention

2    and surface dose of particles as well as potential systemic distribution of particles or their constituents.

3    Figure 4-2 illustrates the progressive change in airway anatomy with distal progression into the lower

4    respiratory tract. In the bronchi there is a thick liquid lining and mucociliary clearance rapidly moves

5    deposited particles toward the mouth. In general, in the bronchi, only highly soluble materials moving

6    from the air into the liquid layer will have systemic access via the blood. With distal progression, the

7    protective liquid lining diminishes and clearance rates slow. Soluble compounds and some poorly soluble

8    ultrafine particles may cross the air-liquid interface to enter the tissues and the blood especially in the

9    alveolar region.

## 4.2. Particle Deposition

10    Inhaled particles may be either exhaled or deposited in the extrathoracic (ET), tracheobronchial

11    (TB), or alveolar (A) region. A particle becomes deposited when it moves from the airway lumen to the

12    wall of an airway. The deposition of particles in the respiratory tract depends primarily on inhaled particle

13    size, route of breathing (through the nasal or oronasal), tidal volume ($V_T$), breathing frequency ($f$), and

14    respiratory tract morphology. The distinction between air passing through the nose versus the mouth is

15    important since the nasal passages more effectively remove inhaled particulate than the oral passage.

16    Respiratory tract morphology, which affects particle transport and deposition, varies between species, the

17    size of an animal or human, and health status.

18    The fraction of inhaled aerosol becoming deposited in the human respiratory tract has been

19    measured experimentally. Studies, using light scattering or particle counting techniques to quantify the

20    amount of aerosol in inspired and expired breaths, have characterized total particle deposition for varied

21    breathing conditions and particle sizes. The vast majority of in vivo data on the regional particle

22    deposition has been obtained by scintigraphic methods. These data have shown highly variable regional

23    deposition with sites of highly localized deposition or "hot spots" in the obstructed lung relative to the

24    healthy lung. Even in the healthy lung, "hot spots" occur in the region of airway bifurcations.

25    Mathematical models aid in predicting the mixed effects of particle size, breathing conditions, and lung

26    volume on total and regional deposition.

27    In order to potentially become deposited in the respiratory tract, particles must first be inhaled. The

28    inspirable particulate mass fraction of an aerosol is that fraction of the ambient airborne particles that can

29    enter the uppermost respiratory tract compartment, the head (Soderholm, 1985). The American

30    Conference of Governmental Industrial Hygienists (ACGIH) and the International Commission on

31    Radiological Protection (ICRP) have established inhalability criteria for humans (ACGIH, 2005; ICRP,

1 1994). These criteria are indifferent to route of breathing and assume random orientation with respect to

2 wind direction. They are based on experimental inhalability data for $d_{ae} \leq 100$ μm at wind speeds of

3 between 1 and 8 m/s. For ACGIH criterion, inhalability is 97% for an $d_{ae} = 1$ μm, 87% for an $d_{ae} = 5$ μm,

4 77% for an $d_{ae} = 10$ μm, and plateaus at 50% $d_{ae}$ above ~40 μm. The ICRP criterion, which also plateaus

5 at 50% for very large $d_{ae}$, does not become of real importance until an $d_{ae} = 5$ μm where inhalability is

6 97%. Dai et al. (2006) reported slightly lower nasal particle inhalability in humans during moderate

7 exercise than rest (e.g., 89.2 vs. 98.1% for 13 μm particles, respectively). Nasal particle inhalability is

8 similar between an adult and 7-year-old child (Hsu and Swift, 1999). Inhalability into the mouth from

9 calm air in humans also becomes important for $d_{ae} >10$ μm (Anthony and Flynn, 2006; Brown, 2005).

10 Unlike the inhalability from high wind speeds which plateaus at 50% for $d_{ae}$ greater than ~40 μm, particle

11 inhalability from calm air continues to decrease toward zero with increasing $d_{ae}$.

12 Inhalability data in laboratory animals, such as rats, are only available for breathing from relatively

13 calm air (velocity $\leq 0.3$ m/s). For nasal breathing, inhalability becomes an important consideration for $d_{ae}$

14 of above 1 μm in rodents and 10 μm in humans (Ménache et al., 1995). The inhalability of particles

15 having $d_{ae}$ of 2.5, 5, and 10 μm is 80, 65, and 44% in rats, respectively, whereas it only decreases to 96%

16 for a $d_{ae}$ of 10 μm in humans during nasal breathing (Ménache et al., 1995). Asgharian et al. (2003)

17 suggested that an even more rapid decrease in inhalability with increasing $d_{ae}$ may occur in rats.

18 Inhalability is a particularly important consideration for rodent exposures to coarse particles. Section 4.2.3

19 provides additional discussion of interspecies patterns of particle deposition.

## 4.2.1. Mechanisms of Deposition

20 Particle deposition in the lung is predominantly governed by diffusion, impaction, and

21 sedimentation. Most discussion herein focuses on these three dominant mechanisms of deposition. Simple

22 interception, which is an important mechanism of fiber deposition, is not discussed in this chapter.

23 Electrostatic and thermophoretic forces as mechanisms of deposition have not been thoroughly evaluated

24 and receive limited discussion. Some generalizations with regard to deposition by these mechanisms

25 follows, but should not be viewed as absolute rules. Both experimental studies and mathematical models

26 have demonstrated that breathing patterns can dramatically alter regional and total deposition for all sized

27 particles. The combined processes of aerodynamic and diffusive (or thermodynamic) deposition are

28 important for particles in the range of 0.1 μm to 1 μm. Aerodynamic processes predominate above and

29 thermodynamic processes predominate below this range.

30 Diffusive deposition, by the process of Brownian diffusion, is the primary mechanism of deposition

31 for particles having physical diameters of less than 0.1 μm. For particles having physical diameters of

1    roughly between 0.05 and 0.1 μm, diffusive deposition occurs mainly in the small distal bronchioles and

2    the pulmonary region of the lung. However, with further decreases in particle diameter below ~0.05 μm,

3    increases in particle diffusivity shift more deposition to the proximally to the bronchi and ET regions.

4         Governed by inertial or aerodynamic properties, impaction and sedimentation increase with $d_{ae}$.

5    When a particle has sufficient inertia, it is unable to follow changes in flow direction and strikes a surface

6    thus depositing by the process of impaction. Impaction occurs predominately at bifurcations in the

7    proximal airways, where linear velocities and secondary eddies are at their highest. Sedimentation, caused

8    by the gravitational settling of a particle, is most important in the distal airways and pulmonary region of

9    the lung. In these regions, residence time is the greatest and the distances that a particle must travel to

10   reach the wall of an airway are minimal.

11        The electrical charge on some particles may result in an enhanced deposition over what would be

12   expected from size alone. With an estimated charge of 10-50 negative ions per 0.5 μm particle, Scheuch et

13   al. (1990) found deposition in humans ($V_T$ = 500 ml, $f$ = 15 $min^{-1}$) to increase from 13.4% (no charge) to

14   17.8% (charged). This increase in deposition is thought to result from image charges induced on the

15   surface of the airway by charged particles. Yu (1985) estimated a charge threshold level above which

16   deposition fractions would be increased of about 12, 30, and 54 for 0.3, 0.6, and 1.0 μm diameter

17   particles, respectively. Electrostatic deposition is generally considered negligible for particles below

18   0.01 μm because so few of these particles carry a charge at Boltzmann equilibrium. This mechanism is

19   also thought to be a minor contributor to overall particle deposition, but it may be important in some

20   laboratory studies due to specific aerosol generation techniques such as nebulization. Laboratory methods

21   such as passage of the aerosols through a Kr-85 charge neutralizer prior to inhalation are commonly used

22   to mitigate this effect.

23        The National Radiological Protection Board (NRPB) recently evaluated the potential for corona

24   discharges from high voltage power lines to charge particles and enhance particulate doses (NRPB, 2004).

25   They concluded that electrostatic effects would be the most important for particles in the size range from

26   about 0.1-1 μm, where deposition may theoretically increase by a factor of three to ten. However, given

27   that the small fraction of ambient particles would pass through the corona to become charged, the small

28   range of relevant particle sizes (0.1-1 μm), and the subsequent required transport of charged particles to

29   expose individuals; the NRPB concluded that effects, if any, of electric fields on particle deposition in the

30   human respiratory tract would likely be minimal.

31        Thermophoretic forces on particles occur due to temperature differences between respired air and

32   respiratory tract surfaces. Temperature gradients of around 20°C are thought to produce sufficient

33   thermophoretic force to oppose diffusive and electrostatic deposition during inspiration and to perhaps

34   augment deposition by these mechanisms during expiration (Jeffers, 2005). Thermophoresis is only

1 relevant in the extrathoracic and large bronchi airways and reduces to zero as the temperature gradient

2 decreases deeper in the lung. Theoretical analysis of thermophoresis has been done for smooth walled

3 tubes and is important over distances that are several orders of magnitude smaller than the diameter of the

4 trachea. The alteration of the flow patterns by airway surface features such as cartilaginous rings may

5 affect particle transport and deposition over far greater distances than thermophoretic force.

## 4.2.2. Deposition Patterns

6     Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount

7 of deposition therein is necessary for understanding and interpreting the health effects associated with

8 exposure to particles. Particles deposited in the various respiratory tract regions are subjected to large

9 differences in clearance mechanisms and pathways and, consequently, retention times. Deposition

10 patterns in the human respiratory tract were described in considerable detail in dosimetry chapters of prior

11 PM AQCD (U.S. EPA, 1996, 2004); as such, they are only briefly described here.
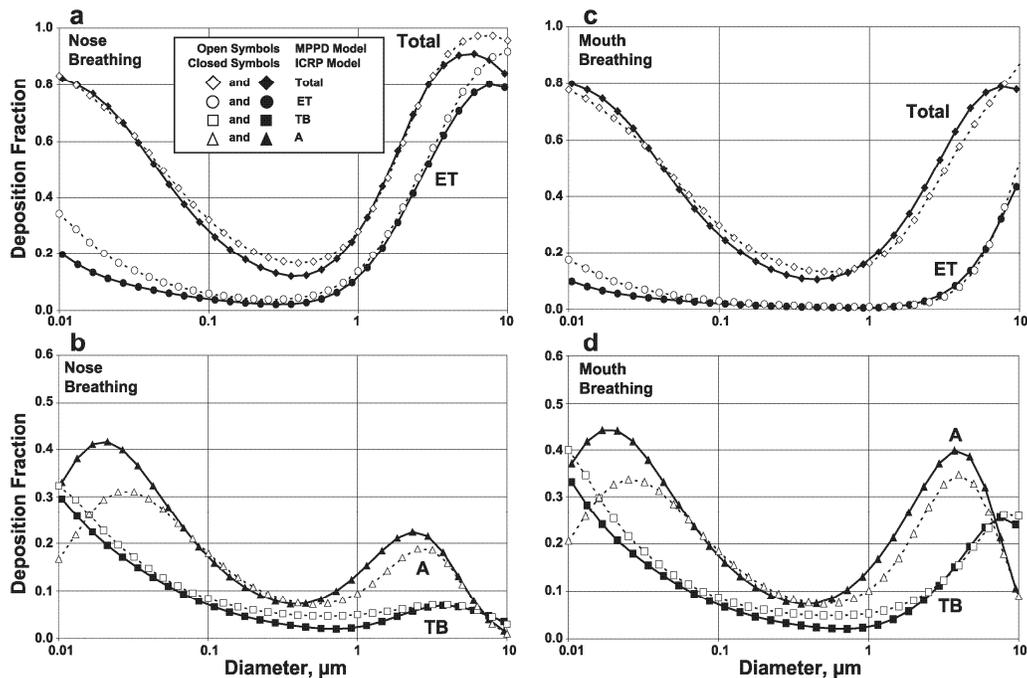


**Figure 4-3**     **Comparison of total and regional deposition results from the ICRP and the MPPD models for a resting breathing pattern ($V_T$ = 625 ml, $f$ = 12 min$^{-1}$). Panels a-b are for nose breathing. Panels c-d are for mouth breathing.**
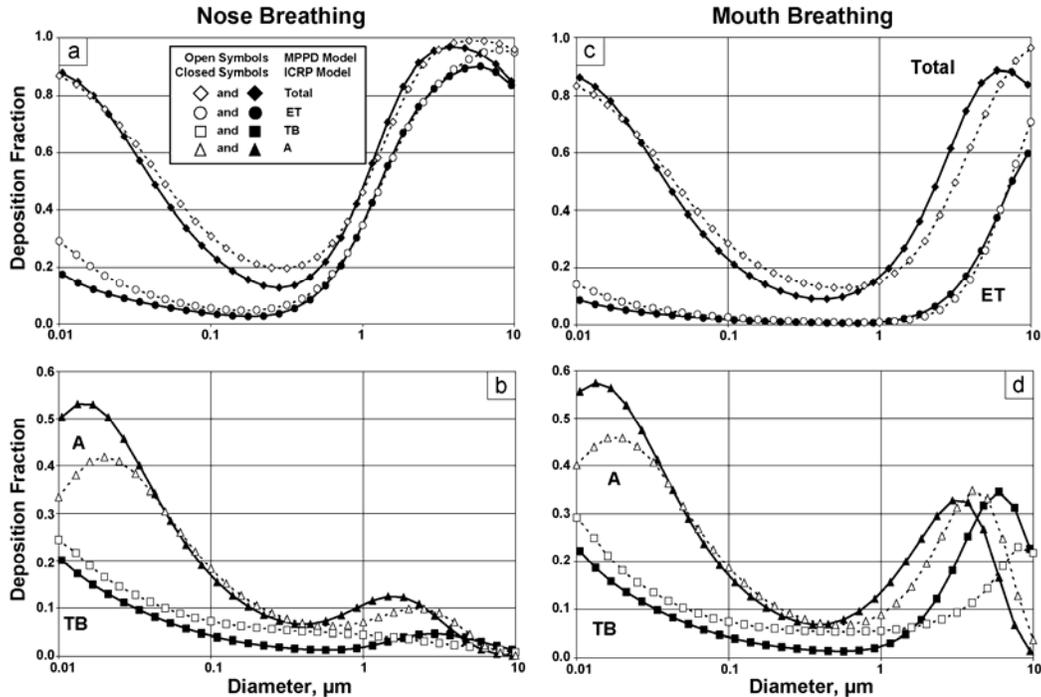
**Figure 4-4** **Comparison of total and regional deposition results from the ICRP and the MPPD models for a light exercise breathing pattern ($V_T$ = 1250 ml, $f$ = 20 min$^{-1}$). Panels a-b are for nose breathing. Panels c-d are for mouth breathing.**

1    Predicted total and regional deposition for an adult male during rest and light exercise are

2    illustrated in Figures 4-3 and 4-4, respectively. Although these figures were provided in Chapter 6 of the

3    2004 PM AQCD, they are reproduced here to illustrate changes in deposition as a function of particle size

4    and breathing conditions. The predictions were based on two publicly available particle deposition

5    models, the ICRP (1994) and the MPPD model (Version 1.0, ©2002). The ICRP (1994) model was

6    implemented by LUDEP (Version 2.07, June 2000). The MPPD model was developed by the CIIT

7    Centers for Health Research with support from the Dutch National Institute of Public Health and the

8    Environment. The MPPD model (Version 2) is currently available from The Hamner Institutes for Health

9    Sciences, RTP, NC.

## 4.2.2.1. Total Respiratory Tract Deposition

10    The efficiency of deposition in the respiratory tract may generally be described as a "U-shaped"

11    curve on a plot of deposition efficiency versus the of log particle diameter. Total deposition shows a

12    minimum for particle diameters in the range of 0.1 to 1.0 μm, where particles are small enough to have

13    minimal sedimentation or impaction and sufficiently large so as to have minimal diffusive deposition.

14    Total deposition does not decrease to zero for any sized particle because of mixing between particle laden

1    tidal air and residual lung air. The particles mixed into residual air remain in the lung following a breath

2    and are removed on subsequent breaths or gradually deposited. Total deposition approaches 100% for

3    particles of roughly 0.01 μm (physical diameter) due to diffusive deposition and for particles of around

4    10 μm (aerodynamic diameter) due to the efficiency of sedimentation and impaction.

5    Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 4-5.

6    These experimental data were obtained by using monodisperse spherical test particles in healthy adults

7    during controlled breathing on a mouthpiece. Despite the control of inhaled particle size and breathing

8    conditions, there is variability in deposition efficiencies due to inter-individual differences in lung size

9    and anatomical variability in airway dimensions and branching patterns.
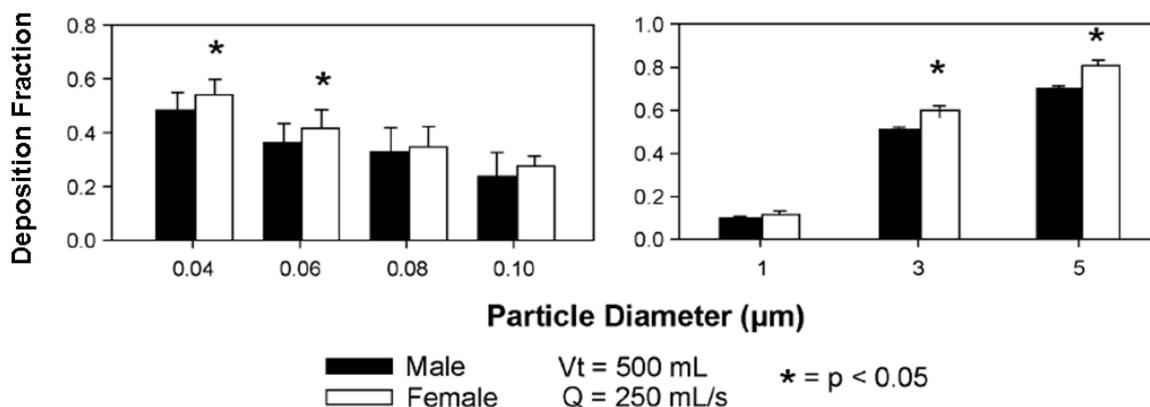


Source: Data from Kim and Hu (1998) and Kim and Jaques (2000).

**Figure 4-5.    Total lung deposition measured in healthy adults (ultrafine, 11 M, 11 F, 31 ± 4 years; fine and coarse, 11 M, 11 F, 25 ± 4 years) during controlled breathing on a mouthpiece. Deposition calculated from aerosol bolus measurements between 50 and 500 mL into a breath with 50 mL increments. Illustrated data are means and standard errors.**

## 4.2.2.2. Extrathoracic Region

10    The first line of defense for protecting the lower respiratory tract from inhaled particles is the nose

11    and mouth. The 2004 PM AQCD (U.S. EPA, 2004) concluded that the ET region, especially the nasal

12    passages, acts as an efficient filter for small ultrafine particles (< 0.01 μm) and larger particles

13    (>2 μm $d_{ae}$), reducing the amount of particles within a wide size range that are available for deposition in

14    the TB and A regions. Newer studies have become available, but are generally limited to computational

15    fluid dynamics (CFD) modeling and experimental measurements in casts. As most of these studies do not

16    substantially improve our understanding of deposition in the ET region they are not reviewed here.

17    For particles >1 μm $d_{ae}$, deposition efficiency in the oral and nasal passages has been generally

18    described as a function of an impaction parameter (Stokes number) with the addition of a flow regime

parameter (Reynolds number) for the oral passages (Finlay and Martin; Grgic et al., 2004; Kelly et al., 2005; Schroeter et al., 2006). For an adult male, the CFD simulations of Schroeter et al. (2006) predicted nasal deposition of 10 μm $d_{ae}$ particles was 90%, and 100% for a Ve of 7.5 L/min (rest) and 15 L/min (light activity), respectively. Thus, relatively few large coarse particles will pass through the nasal passages into the lungs.

Since the nasal passages are more efficient at removing inhaled particles than the oral passage, an individual's mode of breathing (i.e., oral vs. nasal) influences the quantity of particles penetrating to the lung. In limited studies, it has been shown that children tend to have more oral breathing both at rest and during exercise and also displayed more variability than adults (Becquemin et al., 1999; Bennett et al., 2008; James et al., 1997). In contrast to adults, there is little data on the uptake of particles for oral or nasal breathing in children. Theoretical calculations by Xu and Yu (1986) predict enhanced deposition of particles (greater than 2 μm) in the head region for children when compared to adults. Studies of fine particle deposition in physical models of the nose, scaled to adult vs. children sizes, predict that deposition efficiency in the nose is a function of pressure drop across the nose (Phalen et al., 1989). Consequently, these model analyses suggest that, when properly scaled physiological flows are used in the calculation of nasal deposition, children, who have higher nasal resistance than adults, should have higher nasal deposition compared to adults. Surprisingly, the few studies reporting measures of nasal deposition in children, found lower nasal deposition efficiencies for fine particles (1-3 μm $d_{ae}$) as compared to adults, despite their higher nasal resistances (Becquemin et al., 1991; Bennett et al., 2008). These findings of lesser nasal vs oral breathing and less efficient nasal deposition suggest that children's lower respiratory tract may receive a higher dose of ambient PM compared to adults.

### 4.2.2.3. Tracheobronchial and Alveolar Region

Inhaled particles passing the ET region enter and may become deposited in the lungs. For any given particle size, the pattern of particle deposition influences clearance by partitioning deposited material between lung regions. Deposition in the tracheobronchial airways and alveolar region cannot be directly measured in vivo. Much of the available deposition data for the TB and A regions have been obtained from experiments with radioactively labeled, poorly soluble particles (U.S. EPA, 1996) or by use of aerosol bolus techniques (U.S. EPA, 2004). In general, the ability of these experimental data to define specific sites of particle deposition is limited to anatomically large regions of the respiratory tract such as the head, larynx, bronchi, bronchioles, and alveolar region. Mathematical modeling can provide more refined predictions of deposition sites. Comparisons of the modeling results obtained with two publicly available models were provided in Figures 4-3 and 4-4. Highly localized sites of deposition within the bronchi are described in Section 4.2.2.4. Both experimental and modeling techniques are based on many

1  assumptions that may be relatively good for the healthy lung but not for the diseased lung. For discussion

2  of these issues, the reader is referred to Sections 4.2.4.3 and 4.2.4.4.

### 4.2.2.4. Localized Deposition Sites

3      From a toxicological perspective, it is important to realize that not all epithelial cells in an airway

4  will receive the same dose of deposited particles. Localized deposition in the vicinity of airway

5  bifurcations has been analyzed using experimental and mathematical modeling techniques. In the 1996

6  PM AQCD, experimental data were available illustrating the peak deposition of coarse particles (3, 5, and

7  7 μm $d_{ae}$) in daughter airways during inspiration and the parent airway during expiration, but always near

8  the carinal ridge (Kim and Iglesias, 1989; Kim et al., 1989). In the 2004 PM AQCD, mathematical models

9  predicted distinct "hot spots" of deposition in the vicinity of the carinal ridge for both coarse (10 μm) and

10  ultrafine (0.01 μm) particles (Heistracher and Hofmann, 1997; Hofmann et al., 1996). In a model of

11  generations 4-5 during inspiration, hot spots occurred at the carinal ridge for 10 μm $d_{ae}$ particles due to

12  inertial impaction and for 0.01 μm particles due secondary flow patterns formed at the bifurcation. During

13  expiration, preferential sites of deposition for both particle sizes occurred 1) approaching the juncture of

14  daughter airways on the walls forming and across the lumen from the carinal ridge and 2) the top and

15  bottom (visualizing the Y-shaped geometry laying horizontal) of the parent airway downstream of the

16  bifurcation.

17      Recent studies further support these findings (Balásházy et al., 2003; Farkas et al., 2006; 2008;

18  Isaacs et al., 2006). Most of these studies quantified localized deposition in terms of an enhancement

19  factor. Typically, the enhancement factor is the ratio of the deposition in a pre-specified surface area (e.g.,

20  100 × 100 μm which corresponds to ~ 10 × 10 epithelial cells) to the average deposition density for the

21  whole airway geometry. These enhancement factors are very sensitive to the size of the surface

22  considered (Balásházy et al., 1999). The studies by Farkas et al. (2006; 2008) investigated the phenomena

23  of localized deposition down to 0.001 μm particles. The deposition of 0.001 μm was rather uniform,

24  however, the deposition pattern became increasingly less uniform with increasing particle size. These

25  studies indicate that, for particles greater than ~0.01 μm, some cells located near the carinal ridge of

26  bronchial bifurcations may receive hundreds to thousands times the average dose (particles per unit

27  surface area) of the parent and daughter airways. Furthermore, the inertial impaction of particles ≥ 1 μm

28  $d_{ae}$ at the carinal ridge of large bronchi will increase with increasing inspiratory flows. In a comparison of

29  constricted versus healthy airways, Farkas et al. (2006) also reported that the overall deposition efficiency

30  of 10 μm $d_{ae}$ particles at bifurcations downstream of a constriction may be increased by 18 times. Given

31  these considerations, Phalen and Oldham (2006) noted that substantial doses of particles (≥ 1 μm $d_{ae}$) may

32  be justified for in vitro studies using tracheobronchial epithelial cell cultures.

## 4.2.3. Interspecies Patterns of Deposition

1    The primary purpose of this document is to assess the health effects of particles in humans. As
2    such, human dosimetry studies have been stressed in this chapter. Such studies avoid the uncertainties
3    associated with the extrapolation of dosimetric data from laboratory animals to humans. However, animal
4    models have been and continue to be used in evaluating PM health effects because of ethical
5    considerations regarding the types of studies that can be performed with human subjects. Thus, there is a
6    considerable need to understand dosimetry in animals and dosimetric differences between animals and
7    humans. Limited new data are becoming available. Similar deposition efficiencies have been reported in
8    nasal casts of human and rhesus monkey for 1 to 10 μm $d_{ae}$ for inspiratory flows mimicking resting
9    breathing patterns (Kelly et al., 2005). Oldham and Robinson (2007) recently provided morphologic data
10   and predicted particle deposition in an asthma mouse model.

11   Interspecies similarities and differences in deposition were described in detail in the last two PM
12   AQCDs (U.S. EPA, 1996, 2004). It was concluded that the general pattern of total particle deposition
13   efficiency was similar between laboratory animals and humans: deposition increases on both sides of a
14   minimum that occurs for particles of 0.2 to 1 μm. There are, however, marked interspecies differences in
15   uptake into the respiratory tract and regional deposition. For instance, the nasal inhalability of 10 μm $d_{ae}$
16   particles is predicted to be 96% in humans, whereas it is only 44% in rats (Ménache et al., 1995). In most
17   laboratory animal species (rat, mouse, hamster, guinea pig, and dogs), deposition in the ET region is near
18   100% percent for particles greater than 5 μm $d_{ae}$ (Raabe et al., 1985), indicating greater efficiency than
19   that seen in humans. Detailed presentation of dosimetric difference between rats and humans are available
20   elsewhere (Brown et al., 2005; Jarabek et al., 2005).

21   Brown et al. (2005) conducted a thorough evaluation of extrapolations between rats and humans in
22   relation to particulate exposures. One of many factors they considered was the choice of a dose metric
23   appropriate for comparison between species. For example, deposited mass may be an appropriate PM
24   indicator for health effects associated with soluble PM constituents. For health effects associated with
25   insoluble PM, the particle number, surface area, or mass may be appropriate indicators. Given
26   interspecies differences in deposition patterns and clearance rates, the question of retained versus
27   deposited dose was also discussed. It was concluded that for acute effects, the maximum deposited
28   incremental dose may be the appropriate type of dose metric. For chronic effects, long-term burden may
29   be more appropriate. For various dose metrics, estimates of particle concentration and exposure duration
30   required for a rat to receive the same dose as received by a human were obtained with consideration of
31   activity levels and particle size distributions. It was noted that high PM exposures over the period of
32   months can lead to particle overload in rats (see Section 4.3.4.4). Exposure regimes were derived as a

1 function of particle size and exposure duration that should avoid overwhelming macrophage mediated

2 clearance achieving particle overload in rats (see Table 12, Brown et al., 2005). Their dosimetric

3 calculations indicated that to achieve nominally similar acute doses per surface area in rats, relative to

4 humans undergoing moderate to high exertion, PM exposure concentrations for rats would need to be

5 somewhat higher than for humans. Since particle clearance from the lungs of rats is faster than humans,

6 much higher exposure concentrations are required for the rat to simulate retained burdens of humans.

7 Illustrating the complexity of such analyses, in some cases, rats were found to require lower exposures

8 than humans to have comparable doses.

# 4.2.4. Biological Factors Modulating Deposition

9     Evaluation of factors affecting particle deposition is important to help understand potentially

10 susceptible subpopulations. Differences in biological response following pollutant exposure may be

11 caused by dosimetry differences as well as by differences in innate sensitivity. The effects of different

12 biological factors on deposition were discussed in the 2004 PM AQCD (U.S. EPA, 2004) and are

13 summarized briefly here.

## 4.2.4.1. Age

14     Airway structure and respiratory conditions vary with age, and these variations may alter the

15 amount and site of particle deposition in the respiratory tract. It was concluded in the 2004 PM AQCD

16 (U.S. EPA, 2004) that significant differences between adults and children had been predicted by

17 mathematical models and observed in experimental studies. Studies generally indicated that ET and TB

18 deposition was greater in children and that children received greater doses of particles per lung surface

19 area than adults. Deposition studies in the elderly are still quite limited.

20     Breathing patterns are well recognized to change with increasing age, i.e., tidal volumes increase

21 and respiratory rates decrease (Tabachnik et al., 1981; Tobin, 1983). Bennett and Zeman (1998) measured

22 deposition fraction of inhaled, fine particles in children as they breathed the aerosol with their natural,

23 resting breathing pattern. Among the children, variation in deposition fraction, measured by photometry at

24 the mouth, was highly dependent on intersubject variation in tidal volume. On the other hand, they found

25 no difference in deposition fraction for the children vs. adults for these fine particles. This finding and the

26 modeling predictions (Hofmann et al., 1989) are explained in part by the smaller tidal volume and faster

27 breathing rate of children relative to adults for natural breathing conditions. Bennett et al. (2008) also

28 recently reported measures of fine particle deposition fraction for ventilation associated with light

29 exercise in children and adults and showed that, like with resting breathing, deposition fraction was

1    predicted by breathing pattern and was not different or tended to be less in children compared to adults.

2    On the other hand, because children breathe at higher minute ventilations relative to their lung volumes,

3    the rate of deposition of fine particles normalized to lung surface area may be greater in children vs.

4    adults (Bennett and Zeman, 1998).

5    Bennett and Zeman (2004) expanded their measures of fine particle deposition during resting

6    breathing to a larger group of healthy children (6–13 yr; 20 boys, 16 girls) and found again that the

7    variation in total deposition, was best predicted by tidal volume (r = 0.79, p < 0.001). But both tidal

8    volume and resting minute ventilation increased with both height and body mass index of the children.

9    Interestingly, these data suggest that for a given height and age, children with higher body mass index

10   (BMI) have larger minute ventilations and tidal volumes at rest than those with lower BMI. These

11   differences in breathing patterns as a function of BMI translated into increased deposition of fine particles

12   in the heaviest children, the rate of deposition (i.e., particles depositing/time) in the overweight children

13   was 2.8 times that of the leanest children (p < 0.02). Among all children, the rate of deposition was

14   significantly correlated with BMI (r = 0.46, p < 0.004). Some of the increased deposition fraction in

15   heavier children may be due to their elevated tidal volume, which was well correlated with BMI (r = 0.72,

16   p < 0.001).

17   In 62 healthy adults with normal lung function aged 18–80, Bennett et al. (1996) showed there was

18   no effect of age on the whole lung deposition fraction of 2-μm particles under natural breathing

19   conditions. Across all subjects, the deposition fraction was found to be independent of age, depending on

20   breathing period (r = 0.58, p < 0.001) and airway resistance (r = 0.46, p < 0.001). In the same adults

21   breathing with a fixed pattern (360 mL tidal volume, 3.4 sec breathing period), there was a mild decrease

22   in deposition with increasing age, which could be attributed to increased peripheral airspace dimensions

23   in the elderly.

## 4.2.4.2. Gender

24   Males and females differ in body size, conductive airway size, and ventilatory parameters;

25   therefore, gender differences in deposition might be expected. In some of the controlled studies, however,

26   the men and women were constrained to breathe at the same tidal volume and frequency. Since women

27   are generally smaller than the men, the increased minute ventilation compared to their normal ventilation

28   could affect deposition patterns. This may help explain why gender related effects on deposition have

29   been observed in some studies.

30   Kim and Hu (1998) assessed the regional deposition patterns of 1-, 3-, and 5-μm MMAD particles

31   in healthy adult males and females using controlled breathing. The total fractional deposition in the lungs

32   was similar for both genders with the 1-μm particle size, but was greater in women for the 3- and 5-μm

1  particles. Deposition also appeared to be more localized in the lungs of females compared to those of

2  males. Kim and Jaques (2000) measured deposition in healthy adults using sizes in the ultrafine mode

3  (0.04 to 0.1 μm). Total fractional lung deposition was greater in females than in males for 0.04- and 0.06-

4  μm particles. The region of peak fractional deposition was shifted closer to the mouth and peak height

5  was slightly greater for women than for men for all exposure conditions. The total and regional deposition

6  data from these studies are illustrated in Figure 4-5. These differences were generally attributed to the

7  smaller size of the upper airways, particularly of the laryngeal structure, in females.

8       In another study (Bennett et al., 1996), the total respiratory tract deposition of 2-μm particles was

9  examined in adult males and females aged 18 to 80 years who breathed with a normal resting pattern.

10  There was a tendency for a greater deposition fraction in females compared to males. However, since

11  males had greater minute ventilation, the deposition rate (i.e., deposition per unit time) was greater in

12  males than in females. More recently, Bennett and Zeman (2004) found no difference in the deposition of

13  2-μm particles in boys versus girls aged 6–13 yr (n = 36).

## 4.2.4.3. Anatomical Variability

14       Anatomical variability, even in the absence of respiratory disease, can affect deposition throughout

15  the respiratory tract. The ET region is the first exposed to inhaled particles and, therefore, deposition

16  within this region would reduce the amount of particles available for deposition in the lungs. Variations in

17  relative deposition within the ET region will, therefore, propagate through the rest of the respiratory tract,

18  creating differences in calculated doses from individual to individual.

19       The influence of variations in nasal airway geometry on particle deposition has been investigated.

20  Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size

21  from 0.004 to 0.15 μm and at two constant inspiratory flow rates, 167 and 333 mL/s. Inter-individual

22  variability in deposition was correlated with the wide variation of nasal dimensions, in that greater surface

23  area, smaller cross-sectional area, and increasing complexity of airway shape were all associated with

24  enhanced deposition. Bennett and Zeman (2005) have also shown that nasal anatomy influences the

25  efficiency of particle uptake in the noses of adults. For light exercise breathing conditions in adults, their

26  study demonstrated that nasal deposition efficiencies for both 1- and 2-μm monodisperse particles were

27  significantly less in African Americans versus Caucasians. The lesser nasal efficiencies in African-

28  Americans were associated with both lower nasal resistance and less elliptical nostrils compared to

29  Caucasians.

30       Within the lungs, the branching structure of the airways may also differ between individuals. Zhao

31  et al. (2008) recently examined the bronchial anatomy of the left lung in patients (132 M, 84 W; mean age

32  47 years). At the level of the segmental bronchus in the upper and lower lobes, a bifurcation occurred in

the majority of patients. A trifurcation, however, was observed in 23% of the upper and 18% of the lower lobes. Other more unusual findings were also reported such as four bronchi arising from the left upper lobe bronchus. As described in Section 4.2.2.4, deposition can be highly localized near the carinal ridge of bifurcations. The effect of a bifurcation versus other branching patterns on airflow patterns and particle deposition has not been described in the literature. Martonen et al. (1994) showed that a wide blunt carinal ridge shape dramatically affected the flow stream lines relative to a narrower and more rounded ridge shape. Specifically, there were high flow velocities across the entire area of the blunt carinal ridge versus a smoother division of the airstream in the case of the narrow rounded ridge shape. The implication may be that localized particle deposition on the carinal ridge would increase with ridge width. A similar situation might be expected for a trifurcation versus a bifurcation. These differences in branching patterns provide a clear example of anatomical variability between individuals that might affect both air flow patterns and sites of particle deposition.

## 4.2.4.4. Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that occurring in healthy individuals. The effect of airway diseases on deposition has been studied extensively, as described in the 1996 and 2004 PM AQCD (U.S. EPA, 1996, 2004). Studies described therein showed that people with COPD had very heterogeneous deposition patterns and differences in regional deposition compared to healthy individuals. People with obstructive pulmonary diseases tended to have greater deposition in the TB region than did healthy people. Furthermore, there tended to be an inverse relationship between bronchoconstriction and the extent of deposition in the A region, whereas total respiratory tract deposition generally increased with increasing degrees of airway obstruction.

The vast majority of deposition studies in individuals with respiratory disease have been performed during controlled breathing, i.e., all subjects breathed with the same tidal volume and respiratory rate. However, although resting tidal volume is similar or elevated in people with COPD compared to healthy individuals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, given that breathing patterns differ between healthy and obstructed individuals, particle deposition data for controlled breathing may not be appropriate for estimating respiratory doses from ambient PM exposures.

Bennett et al. (1997) measured the fractional deposition of insoluble 2-μm particles in moderate-to-severe COPD patients (n = 13; mean age 62 years) and healthy older adults (n = 11; mean age 67 years) during natural resting breathing. COPD patients had about a 50% greater deposition fraction and a 50% increase in resting minute ventilation relative to the healthy adults. As a result, the patients had an average

1   deposition rate of about 2.5 times that of healthy adults. Similar to previously reviewed studies

2   (U.S. EPA, 1996, 2004), these investigators observed an increase in deposition with an increase in airway

3   resistance, suggesting that deposition increased with the severity of airway disease.

4       Brown et al. (2002) measured the deposition of an ultrafine aerosol (CMD = 0.033 μm) during

5   natural resting breathing in 10 patients with moderate-to-severe COPD (mean age 61 years) and 9 healthy

6   adults (mean age 53 years). The COPD group consisted of 7 patients with chronic bronchitis and 3

7   patients with emphysema. The aerosol deposition fraction in the bronchitic patients (0.67) was

8   significantly ($p < 0.02$) greater than in either the patients with emphysema (0.48) or the healthy subjects

9   (0.54). Minute ventilation increased with disease severity (healthy, 5.8 L/min; chronic bronchitic, 6.9

10  L/min; emphysema, 11 L/min). Relative to the healthy subjects, the average dose rate was significantly ($p$

11  $< 0.05$) increased by 1.5 times in the COPD patients, whereas the average deposition fraction only tended

12  to be increased by 1.1 times. These data further demonstrate the need to consider dose rates (which

13  depend on minute ventilation) rather than just deposition fractions when evaluating the effect of

14  respiratory disease on particle deposition and dose.
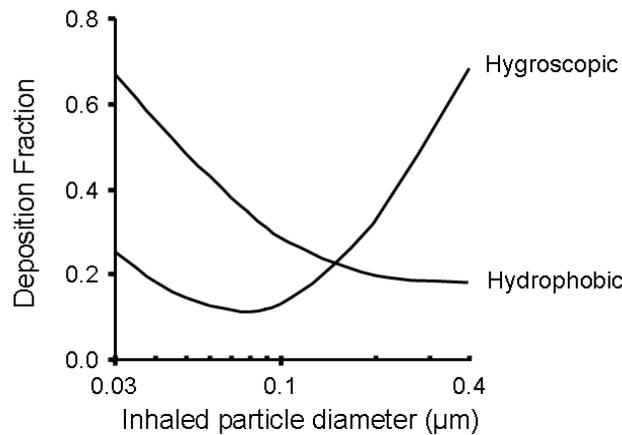


Source: Adapted from Tu and Knutson (1984).

**Figure 4-6.   Total deposition of hygroscopic sodium chloride and hydrophobic aluminosilicate aerosols during oral breathing ($V_T$ = 1.0 L, f = 15 min$^{-1}$).**

## 4.2.4.5. Hygroscopicity of Aerosols

15      Experimental and modeling studies of hygroscopic aerosol growth and deposition in the lung were

16  extensively discussed in Section 10.4.3.1 of the 1996 PM AQCD. Hygroscopic ambient aerosols include

17  sulfates, nitrates, some organics, and aerosols laden with sodium or potassium. The high relative humidity

18  in the lungs contributes to rapid growth of hygroscopic particles and dramatically alters the deposition

1 characteristics of ambient hygroscopic aerosols relative to nonhygroscopic aerosols. Nonhygroscopic

2 particles in the range of 0.3 μm have minimal intrinsic mobility and low total deposition in the lungs.

3 However, a 0.3 μm salt particle (dry) will grow in vivo to nearly 2 μm and deposit to a far greater extent

4 (Anselm et al., 1990). The hygroscopic growth of particles in the respiratory tract decreases diffusive

5 deposition and increases aerodynamic deposition as illustrated in Figure 4-6.

## 4.2.5. Summary

6       Particle deposition in the respiratory tract occurs predominantly by diffusion, impaction, and

7 sedimentation. Deposition is minimal for particle diameters in the range of 0.1 to 1.0 μm, where particles

8 are small enough to have minimal sedimentation or impaction and sufficiently large so as to have minimal

9 diffusive deposition. In humans, total respiratory tract deposition approaches 100% for particles of

10 roughly 0.01 μm (physical diameter) due to diffusive deposition and for particles of around 10 μm $d_{ae}$ due

11 to the efficiency of sedimentation and impaction.

12       The first line of defense for protecting the lower respiratory tract from inhaled particles is the

13 nose and mouth. Nasal deposition approaches 100% in humans for 10 μm $d_{ae}$ particles. Experimental

14 studies show lower nasal particle deposition in children than adults. Relative to adults, children also tend

15 to breathe more through their mouth which is less efficient for removing inhaled particles than the nose.

16 These findings suggest that the lower respiratory tract of children may receive a higher dose of ambient

17 PM compared to adults. Since children breathe at higher minute ventilations relative to their lung

18 volumes, the rate of particle deposition normalized to lung surface area may be further increased relative

19 to adults.

20       People with chronic obstructive pulmonary disease (COPD) generally have greater total

21 deposition and more heterogeneous deposition patterns compared to healthy individuals. The observed an

22 increase in deposition correlates with increases in airway resistance, suggesting that deposition increases

23 with the severity of airway disease. COPD patients also have an increased resting minute ventilation

24 relative to the healthy adults. This demonstrates the need to consider dose rates (which depend on minute

25 ventilation) rather than just deposition fractions when evaluating the effect of respiratory disease on

26 particle deposition and dose.

27       Modeling studies indicate that, for particles greater than ~0.01 μm, some cells located near the

28 carinal ridge of bronchial bifurcations may receive hundreds to thousands times the average dose

29 (particles per unit surface area) of the parent and daughter airways. The inertial impaction of particles $\geq 1$

30 μm $d_{ae}$ at the carinal ridge of large bronchi increases with increasing inspiratory flows. Airway

31 constriction can further augment the overall deposition efficiency of coarse particles at downstream

1    bifurcations. These findings suggest that substantial doses of particles ($\geq$ 1 μm $d_{ae}$) may be justified for in

2    vitro studies using tracheobronchial epithelial cell cultures.

3         Our ability to extrapolate between species has not generally changed since the 2004 PM AQCD.

4    However, some considerations related to coarse particles warrant comment. The inhalability of particles

5    having $d_{ae}$ of 2.5, 5, and 10 μm is 80, 65, and 44% in rats, respectively, whereas it remains near 100% for

6    a $d_{ae}$ of 10 μm in humans. In most laboratory animal species (rat, mouse, hamster, guinea pig, and dogs),

7    deposition in the extrathoracic region is near 100% percent for particles greater than 5 μm $d_{ae}$. By

8    contrast, in humans nasal deposition approaches 100% for 10 μm $d_{ae}$. Oronasal breathing versus obligate

9    nasal breathing further contributes to greater penetration of coarse particles into the lower respiratory tract

10   of humans than rodents.

# 4.3. Clearance of Poorly Soluble Particles

11       This section discusses the clearance and translocation of poorly soluble particles that have

12   deposited in the respiratory tract. The term "clearance" is used here to refer to the processes by which

13   deposited particles are removed by mucociliary action or phagocytosis from the respiratory tract.

14   "Translocation" is used here mainly to refer to the movement of free particles across cell membranes and

15   to extrapulmonary sites. In the literature, translocation may also refer to the extra- and intracellular

16   dissolution of particles and the subsequent transfer of dissociated material to the blood through extra- and

17   intracellular fluids and across the various cell membranes and lung tissues. The clearance and distribution

18   of soluble particles and soluble constituents of particles are discussed in Section 4.4.

19       A basic overview of biological mechanisms and clearance pathways from various regions of the

20   respiratory tract are presented in the following sections. Then regional kinetics of particle clearance are

21   addressed. Subsequently, an update on interspecies patterns and rates of particle clearance is provided.

22   The translocation of ultrafine particles is also discussed. Finally, information on biological factors that

23   may modulate clearance is presented.

## 4.3.1. Clearance Mechanisms and Kinetics

24       For any given particle size, the deposition pattern of poorly soluble particles influences clearance

25   by partitioning deposited material between lung regions. Tracheobronchial clearance of poorly soluble

26   particles in humans, with some exceptions, is thought (in general) to be complete within 24 to 34 h

27   through the action of the mucociliary escalator. Clearance of poorly soluble particles from the alveolar

28   region is a much slower process which may continue from months to years.

### 4.3.1.1. Extrathoracic Region

1    Particles deposited in either the nasal or oral passages are cleared by several mechanisms. Particles
2    depositing in the mouth may generally be assumed to be swallowed or removed by expectoration.
3    Particles deposited in the posterior portions of the nasal passages are moved via mucociliary transport
4    towards the nasopharynx and swallowed. Mucus flow in the most anterior portion of the nasal passages is
5    forward, toward the vestibular region where removal occurs by sneezing, wiping, or nose blowing.

### 4.3.1.2. Tracheobronchial Region

6    Mucociliary clearance in the tracheobronchial region has generally been considered to be a rapid
7    process that is relatively complete by 24 to 48 h post-inhalation in humans. Mucociliary clearance is
8    frequently modeled as a series of "escalators" moving material proximally from one generation to the
9    next. As such, the removal of particles from an airway generation increases with increasing tracheal
10   mucus velocity. Assuming continuity in the amount of mucus between airway generations, mucus
11   velocities decrease and transit times within an airway generation increase with distal progression.
12   Although clearance from the TB region is generally rapid, experimental evidence discussed in the
13   1996 and 2004 PM AQCD, showed that a fraction of material deposited in the TB region is retained much
14   longer. The slow cleared fraction from the TB region was thought to increase with decreasing particle
15   size. For instance, Roth et al. (1993) showed approximately 93% retention of ultrafine particles (30 nm
16   median diameter) thought to be deposited in the tracheobronchial region at 24 h post inhalation. The slow
17   phase clearance of these ultrafine particles continued with an estimated half-time ($t_{1/2}$) of around 40 days.
18   Using a technique to target inhaled particles (monodisperse 4.2 μm MMAD) to the conducting airways,
19   Möller et al. (2004) observed that $49 \pm 9\%$ of particles cleared rapidly ($t_{1/2}$ of $3.0 \pm 1.6$ h), whereas the
20   remaining fraction cleared considerably slower ($t_{1/2}$ of $109 \pm 78$ days). A portion of the slow cleared
21   fraction from the TB region appears to be associated with small bronchioles. For large particles
22   ($d_{ae} = 6.2$ μm) inhaled at very slow rate to theoretical deposit mainly in small ciliated airways, 50% had
23   cleared by 24-h post-inhalation. Of the remaining particles, 20% of cleared with a $t_{1/2}$ of 2.0 days and 80%
24   with a $t_{1/2}$ of 50 days (Falk et al., 1997). Using the same techniques, Svartengren et al. (2005) also
25   reported the existence of long-term clearance in humans from the small airways. It should be noted that
26   the clearance rates for the slow cleared TB fraction still exceeds the clearance rate of the alveolar region
27   in humans. The underlying sites and mechanisms of long-term TB retention in the smaller airways were
28   not known and remain unknown.

### 4.3.1.3. Alveolar Region

1    The primary alveolar clearance mechanism is macrophage phagocytosis and migration to terminal

2    bronchioles where the cells are cleared by the mucociliary escalator. Alveolar macrophages originate from

3    bone marrow, circulate briefly as monocytes in the blood, and then become pulmonary interstitial

4    macrophages before migrating to the luminal surfaces. Under normal conditions, a small fraction of

5    ingested particles may also be cleared through the lymphatic system. This may occur by transepithelial

6    migration of alveolar macrophage following particle ingestion or free particle translocation with

7    subsequent uptake by interstitial macrophages. Snipes et al. (1997) have also demonstrated the

8    importance of neutrophils in clearance of particles from the alveolar region. Rates of alveolar clearance of

9    poorly soluble particles vary between species and are briefly discussed in Section 4.3.2. The translocation

10   of particles from their site of deposition is discussed in Section 4.3.3.

11   On the basis of in vitro studies, the efficiency of macrophage phagocytosis is thought to be greatest

12   for particles between 1.5 and 3 μm (Oberdörster, 1988). The decreased efficiency of alveolar macrophage

13   for engulfing ultrafines increases the time available for these particles to be taken up by epithelial cells

14   and moved into the interstitium (Ferin et al., 1992). Consistent with this supposition (i.e., translocation

15   increases with time), an increase in $TiO_2$ transport to lymph nodes has been reported following inhalation

16   of a cytotoxin to macrophages (Greenspan et al., 1988). Interestingly, the long-term clearance kinetics of

17   the poorly soluble ultrafine (15-20 nm CMD) iridium (Ir) particles were found to be similar to the kinetics

18   reported in the literature for micrometer-sized particles (Semmler-Behnke et al., 2007; Semmler et al.,

19   2004). Semmler-Behnke et al. (2007) concluded that ultrafine Ir particles are less phagocytized by

20   alveolar macrophage than larger particles, but are effectively removed from the airway surface into the

21   interstitium. Particles are then engulfed by interstitial macrophages which then migrate to the airway

22   lumen and are removed by mucociliary clearance to the larynx. The major role of macrophage-mediated

23   clearance was supported by lavage of relatively few free particles versus predominantly phagocytized

24   particles at time-points of up to 6-months. It is also possible that some free particles as well as particle-

25   laden macrophage were carried from interstitial sites via the lymph flow to bronchial and bronchiolar

26   sites, including bronchial-associated lymphatic tissue, where they were excreted again into the airway

27   lumen.


## 4.3.2. Interspecies Patterns of Clearance and Retention

28   There are differences between species in both the rates of particle clearance from the lung and

29   manner in which particles are retained in the lung. For instance, based of models of mucociliary clearance

30   from un-diseased airways, >95% of particles deposited in the tracheobronchial airways of rats are

1   predicted to be cleared by 5 h post deposition, whereas it takes nearly 40 h for comparable clearance in

2   humans (Hofmann and Asgharian, 2003). As noted in Section 4.3.1.2, however, there is considerable

3   evidence that a sizeable fraction of particle deposited in the ciliated airways of humans (as well as

4   canines) are cleared at a far slower rate. In contrast, studies of mice and rats show negligible long-term

5   retention of particles in the ciliated airways (Kreyling et al., 2006).
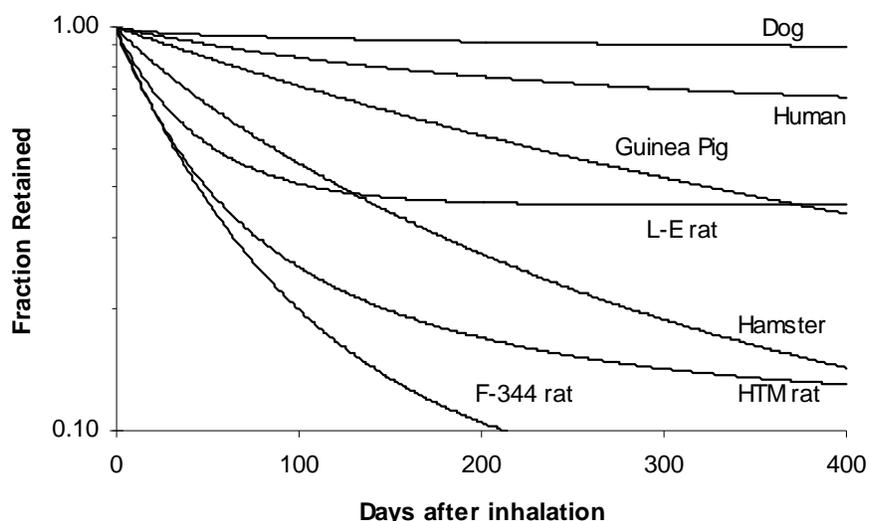


Source: Adapted from Kreyling and Scheuch (2000).

**Figure 4-7.    Retention of poorly soluble particles (0.5-5 μm) in the alveolar region of the lung over various mammalian species.**

6        Figure 4-7 illustrates rates of alveolar clearance for 0.5-5 μm particles in various mammalian

7   species. The alveolar clearance rate of particles smaller than 0.1 μm and larger than 5 μm is slower than

8   that of particles in the 0.5 to 5 μm range. From interspecies comparisons of alveolar clearance, the path

9   length from alveoli to ciliated terminal bronchioles may affect the particle transport rate (Kreyling and

10  Scheuch, 2000). The path length from alveoli to ciliated terminal bronchioli is longer in humans,

11  monkeys, and dogs, than in sheep, rats, hamsters, and mice. Transport time and hence retention times may

12  increase with path length. This hypothesis fits with all species in this comparison, except guinea pigs,

13  which have a short path length yet particle retention that is nearly as long as in humans, monkeys, and

14  dogs. However, sheep have a short path length and particle transport as fast as rodents. Thus, despite the

15  exception of guinea pigs, there is evidence of a large mammal species confirming the hypothesis.

16        There are also distinct differences in the sites of particle retention between species. Large mammals

17  retain particles in interstitial tissues under normal conditions, whereas rats retain particles in alveolar

18  macrophages (Snipes, 1996). In rats, with chronic high doses there is a shift in the pattern of dust

19  accumulation and response from that observed at lower doses in the lungs (Snipes, 1996; Vincent and

1    Donaldson, 1990). Rats chronically exposed to high concentrations of insoluble particles experience a

2    reduction in their alveolar clearance rates and an accumulation of interstitial particle burden (Bermudez et

3    al., 2002; 2004; Ferin et al., 1992; Oberdörster et al., 1994a; 1994b; Warheit et al., 1997). The influence

4    of exposure concentration on the pattern of particle retention in rats (exposed to diesel soot) and humans

5    (exposed to coal dust) was examined by (Nikula et al., 2001). In rats, the DE particles were found to be

6    primarily in the lumens of the alveolar duct and alveoli; whereas in humans, retained dust was found

7    primarily in the interstitial tissue within the respiratory acini.

## 4.3.3. Particle Translocation

8    Mucociliary and macrophage mediated clearance of poorly soluble particles from the respiratory

9    tract was discussed in Section 4.3.1. and Section 4.3.2. There is evidence that particles may cross cell

10   membranes and move from their site of deposition by other mechanisms. The following subsections

11   discuss the movement of particles from the luminal surfaces of the alveolar region and from the olfactory

12   region to the brain.

### 4.3.3.1. Alveolar Region

13   Numerous studies have examined the translocation of ultrafine particles from their site of

14   deposition in the lung. Traditionally viewed as a relatively inert particle type, ultrafine $TiO_2$ has received

15   the most study. At the time the 2004 PM AQCD was released, there were conflicting results regarding the

16   rate and magnitude of ultrafine carbon translocation from the human lung. Since that time, it has become

17   well-established that the transport of ultrafine carbon particles from the lung is far slower than that of

18   soluble materials. However, it has also been shown that ultrafine particles cross cell membranes by

19   mechanisms different from larger (~1 μm) particles and that a fraction of these particles enter capillaries

20   and may distribute systemically. Details of selected new studies investigating the disposition of poorly

21   soluble particles are provided in Annex B.

22   There has been some contention regarding ability of ultrafine carbon particles to rapidly diffuse

23   from the lungs into the systemic circul ation. Based on their study of 5 healthy volunteers, Nemmar et al.

24   (2002) suggested that ultrafine carbon particles (< 100 nm) pass rapidly into the systemic circulation.

25   However, Brown et al. (2002) found that the majority of ultrafine carbon particles (CMD, $33 \pm 2$ nm)

26   were still in the lungs of healthy human adult volunteers (n = 9; aged 40 to 67 years) and COPD patients

27   (n = 10; 45 to 70 years) at 24-h post inhalation. Brown et al. (2002) and Burch (2002) contended that the

28   findings reported by Nemmar et al. (2002) were consistent with soluble pertechnetate clearance, but not

29   insoluble ultrafine carbon particles. Highly soluble in normal saline, pertechnetate clears rapidly from the

1    lung with a half-time of ~10 mins and accumulates most notably in the bladder, stomach, thyroid, and

2    salivary glands. Three recent studies have confirmed that the majority (>95%) of ultrafine carbon

3    particles deposited in the lungs of human volunteers are retained at 24 h post inhalation (Mills et al.,

4    2006; Wiebert et al., 2006a; 2006b). Wiebert et al. (2006b) modified their aerosol generation system to

5    reduce leaching of the $^{99m}$Tc radiolabel from carbon particles. Except for a small amount of radiotracer

6    leaching from particles (1.0 ± 0.6% of initially deposited activity in urine by 24 h), these investigators

7    found negligible radiolabel and associated particle clearance from the lungs by 70 h. The available data

8    show that there is not a rapid or significant amount of ultrafine carbon particle migration into circulation

9    (2002; 2002; Mills et al., 2006; Möller et al., 2008; Wiebert et al., 2006a; 2006b).

10    Although human studies show that the vast majority of ultrafine carbon particles are retained in the

11    lungs until at least 24 h post inhalation, both in vitro and in vivo studies support the rapid [≤ 1 h]

12    translocation of free ultrafine TiO$_2$ particles across pulmonary cell membranes (Churg et al., 1998; Ferin

13    et al., 1992; Geiser et al., 2005). Peculiar to TiO$_2$ aerosols, there is evidence that particle aggregates may

14    disassociate once deposited in the lungs. This disassociation makes inhaled aggregate size the determinant

15    of deposition amount and site, but primary particle size the determinant of subsequent clearance

16    (Bermudez et al., 2002; Ferin et al., 1992; Takenaka et al., 1986). Following disaggregation, the ultrafine

17    TiO$_2$ particles are cleared more slowly and cause a greater inflammatory response (PMN influx) than fine

18    TiO$_2$ particles (Bermudez et al., 2002; Ferin et al., 1992; Oberdörster et al., 1994a; 1994b; 2000). The

19    differences in inflammatory effects and possibly lymph burdens between fine and ultrafine TiO$_2$ in many

20    studies appear related to lung burden in terms of particle surface area and not particle mass or number

21    (Oberdörster et al., 1992; 1996; 2000; Tran et al., 2000). More recently, others have noted that particle

22    surface area is not an appropriate metric across all particle types (Warheit et al., 2006). Surface

23    characteristics such as roughness can also affect protein binding and potentially clearance kinetics, with

24    smoother TiO$_2$ surfaces being more hydrophobic (Sousa et al., 2004).

25    Geiser et al. (2005) conducted a detailed examination of the disposition of inhaled ultrafine TiO$_2$ in

26    20 healthy adult rats. They found that distributions of particles among lung tissue compartments appeared

27    to follow the volume fraction of the tissues and did not significantly differ between 1 and 24 h post-

28    inhalation. Averaging 1- and 24-h data, 79.3 ± 7.6% of particles were on the luminal side of the airway

29    surfaces, 4.6 ± 2.6% were in epithelial or endothelial cells, 4.8 ± 4.5% were in connective tissues, and

30    11.3 ± 3.9% were within capillaries. Particles within cells were not membrane bound. It is not clear why

31    the fraction of particles identified in compartments such as the capillaries did not differ between 1 and 24

32    h post-inhalation. These findings were consistent with the smaller study of 5 rats by Kapp et al. (2004)

33    who reported identifying TiO$_2$ aggregates in a type II pneumocyte, a capillary close to the endothelial

34    cells, within the surface-lining layer close to the alveolar epithelium immediately following a 1-h

1   exposure. These studies effectively demonstrate that some inhaled ultrafine $TiO_2$ particles once deposited

2   on the pulmonary surfaces can rapidly [$\leq$ 1 h] translocate beyond the epithelium and even into the

3   vasculature.

4          Extrapulmonary translocation has also been described for poorly soluble ultrafine gold and iridium

5   particles. In male Wistar-Kyoto rats exposed to ultrafine gold particles (5-8 nm), Takenaka et al. (2006)

6   reported a low but significant fraction (0.03 to 0.06% of lung concentration) of gold in the blood from 1

7   to 7 days post inhalation. Semmler et al. (2004) also found small but detectable amounts of poorly soluble

8   Ir particle (15 and 20 nm CMD) translocation from the lungs of male Wistar-Kyoto rats to secondary

9   target organs like the liver, spleen, brain, and kidneys. Each of these organs contained about 0.2% of

10  deposited Ir. The peak levels in these organs were found 7 days post inhalation. The translocated particles

11  were largely cleared from extrapulmonary organs by 20 days and Ir levels were near background at 60

12  days post inhalation. Particles may have been distributed systemically via the gastrointestinal tract.

13  Immediately after the 6 h inhalation, $18 \pm 5$ of the deposited Ir particles had already cleared into the

14  gastrointestinal tract. After 3 wk, $31 \pm 5\%$ of the deposited particles were retained in the lung. By 2 and 6

15  months post inhalation, lung retention was $17 \pm 3$ and $7 \pm 1\%$, respectively. The particles appeared to be

16  cleared predominantly from the peripheral lung via the mucociliary escalator into the GI tract and were

17  found in feces.

18         A few recent studies have characterized differences in the behavior of fine and ultrafine particles in

19  vitro. Geiser et al. (2005) found that both ultrafine and fine (0.025 µm gold, 0.078 µm $TiO_2$, and 0.2 µm

20  $TiO_2$) particles cross cellular membranes by non-endocytic (i.e. involving vesicle formation) mechanisms

21  such as adhesive interactions and diffusion, whereas the phagocytosis of larger 1 µm $TiO_2$ particles is

22  ligand-receptor mediated. Edetsberger et al. (2005) found that ultrafine particles (0.020 µm polystyrene)

23  translocated into cells by first measurement (~1 min after particle application). Intracellular agglomerates

24  of 88-117 nm were seen by 15-20 mins and of 253-675 nm by 50-60 mins after particle application. These

25  intracellular aggregates were thought to be result from particle incorporation into endosomes or similar

26  structures since Genistein or Cytochalasin treatment generally blocked aggregate formation. Interestingly,

27  particles did not translocate into dead cells, rather they attached to the outside of the cell membrane.

28  Amine- or carboxyl-modified surfaces (46 nm polystyrene) did not affect translocation across cultures of

29  human bronchial epithelial cells with about 6% regardless of the surface characteristics (Geys et al.,

30  2006).

## 4.3.3.2. Olfactory Region

31         Numerous studies have demonstrated the translocation of soluble and poorly soluble particles from

32  the olfactory mucosa via the axons to the olfactory bulb of the brain. The vast majority of these studies

were conducted in rodents. However, DeLorenzo (1970) observed the rapid (within 30-60 mins) movement of 50 nm silver-coated colloidal gold particles instilled on the olfactory mucosa into the olfactory bulb of squirrel monkeys. The specifics of this and other key studies that have investigated the translocation of particles to the olfactory bulb are provided in Annex B.

Two recent studies reported the movement of ultrafine particles deposited in the olfactory region of the nose along the olfactory nerve and into the olfactory bulb of the brain in rats. Oberdörster et al. (2004) exposed rats to ultrafine carbon particles (36 nm CMD, 1.7 $\sigma_g$) containing $^{13}C$ in a whole-body chamber for 6 h. The distribution of $^{13}C$ was followed for seven days postexposure. There was a significant increase in $^{13}C$ in the olfactory bulb on Day 1 with persistent and continued increased through Day 7. Elder et al. (2006) exposed rats to Mn oxide (~30 nm equivalent sphere with 3-8 nm primary particles) via body inhalation exposure for 12 d (6 h/d, 5 d/wk) with both nares open or Mn oxide for 2 d (6 h/d) with right nostril blocked. After the 12 d exposure via both nostrils, Mn in the olfactory bulb increased 3.5-fold, whereas in the lung Mn concentrations only doubled. After the 2 d exposure with the right nostril blocked, Mn was found mainly in the left olfactory bulb (2.4-fold increase). These studies suggest the neuronal uptake and translocation of ultrafine particles without particle dissolution and in the absence of mucosal injury.

Elder et al. (2006) also addressed the issue of whether solubilization of particles was requisite for translocation along the olfactory nerve and into the brain. Similar amounts of soluble $MnCl_2$ and poorly soluble Mn oxide were instilled onto the left naris of anesthetized rats. At 24 h post instillation, similar amounts of Mn were found in the left olfactory bulb of rats instilled with $MnCl_2$ (8.2 ± 3.6% of instilled) and Mn oxide (8.2 ± 0.7% of instilled). If solubilization were required for translocation, then a lower amount of Mn oxide than $MnCl_2$ should have reached the olfactory bulb. Following 14 consecutive days of aerosol exposure, Dorman et al. (2001) demonstrated that more soluble Mn sulfate reaches the olfactory bulb and striatum of rat brains than the poorly soluble form of Mn tetroxide. Nonetheless, the Mn levels were statistically increased in both the olfactory bulb and striatum following exposure to Mn tetroxide relative to filter air. In a subsequent 13-wk exposure study, Dorman et al. (2004) also demonstrated that more soluble $MnSO_4$ reached the olfactory bulb than was observed for the less soluble Mn form (hureaulite). Both the soluble and less soluble forms of Mn resulted in statistically increased levels of Mn in the olfactory bulb relative to air exposed controls. The soluble $MnSO_4$ was also observed to reach the striatum and cerebellum. In addition, Yu et al. (2003) demonstrated increased Mn levels in the brains of rats exposed to welding-fumes for 60 days, however, the role of transport via the blood is less clear in this study.

The translocation of zinc and titanium dioxide to the olfactory bulb has also been reported in the literature. Persson et al. (2003) observed the translocation of Zn to the olfactory bulbs following

1    instillation in both rats and freshwater pike. Wang et al. (2007) reported the translocation of both fine (155

2    nm) and ultrafine (21 and 71 nm) $TiO_2$ particles. These particles are readily characterized in the literature

3    as poorly soluble. Interestingly, a qualitative analysis of the data showed that more of the fine $TiO_2$ than

4    ultrafine $TiO_2$ reached the olfactory bulb. Wang et al. (2007) suggested that a strong hydrophilic character

5    and propensity for aggregation reduced the translocation of the ultrafine $TiO_2$.

6        The importance of particle translocation to the brain is not yet understood. Translocation via the

7    axon to the olfactory bulb has been observed for numerous compounds of varying composition, particle

8    size, and solubility. Although the rate of translocation is rapid, perhaps less than an hour, the magnitude of

9    transport remains poorly characterized. With regard to the magnitude of transport, Elder et al. (2006)

10   found that as much as 8% of both soluble and insoluble forms of Mn were translocated to the olfactory

11   bulb in rats following intranasal instillation. It is also still unclear to what extent translocation to the

12   olfactory bulb and other brain regions may vary between species. The olfactory mucosa covers

13   approximately 50% of the nasal epithelium in rodents versus only about 5% in primates (Aschner et al.,

14   2005). Additionally, a greater portion of inhaled air passes through the olfactory region of rats relative to

15   primates (Kimbell, 2006). These differences may predispose rats, more so than humans, to deposition of

16   particles in the olfactory region with subsequent particle translocation to the olfactory bulb.

# 4.3.4. Factors Modulating Clearance

## 4.3.4.1. Age

17       It was previously concluded that there appeared to be no clear evidence for any age-related

18   differences in clearance from the lung or total respiratory tract, either from child to adult, or young adult

19   to elderly (U.S. EPA, 1996, 2006d). Studies showed either no change or some slowing in mucus clearance

20   with age after maturity. Although some differences in alveolar macrophage function were reported

21   between mature and senescent mice, no age-related decline in macrophage function had been observed in

22   humans. A comprehensive review of the recent and older literature supports a decrease in mucociliary

23   clearance with increasing age beyond adulthood in humans and animals. Limited animal data also suggest

24   macrophage-mediated alveolar clearance may also decrease with age.

25       Studies addressing the effects of age on respiratory tract clearance are provided in Annex  B. Ho et

26   al. (2001) demonstrated that nasal mucociliary clearance rates were about 40% lower in old versus young

27   men and women. Tracheal mucus velocities in elderly (or aged) humans and beagle dogs are about 50%

28   that of young adults (Goodman et al., 1978; Whaley et al., 1987). Several human studies have

29   demonstrated decreasing rates of mucociliary particle clearance from the large and small bronchial

airways with increasing age (Puchelle et al., 1979; Svartengren et al., 2005; Vastag et al., 1985). Linear

fits to the data show that rapid clearance (within 1 h) from large bronchi and prolonged clearance

(between 1-21 days) from the small bronchioles in an 80 year-old is only about 50% of that in 20 year-old

(Svartengren et al., 2005; Vastag et al., 1985). One study reported that alveolar particle clearance rates

decreased by nearly 40% in old versus young rats (Muhle et al., 1990). Another study has reported that

older rats have an increased susceptibility to pulmonary infection due to altered alveolar macrophage

function and slowed bacterial clearance (Antonini et al., 2001). Although data are somewhat limited, they

consistently show a depression of clearance throughout the respiratory tract with increasing age from

young adulthood in humans and laboratory animals.

## 4.3.4.2. Gender

Gender was not found to affect clearance rates in prior reviews (U.S. EPA, 1996, 2004). Studies not

included in those reviews also show that human males and females have similar nasal mucus clearance

rates (Ho et al., 2001), tracheal mucus velocities (Yeates et al., 1981), and large bronchial airway

clearance rates (Vastag et al., 1985).

## 4.3.4.3. Respiratory Tract Disease

At the time of the last two reviews (U.S. EPA, 1996, 2004), it was well recognized that obstructive

airways disease may influence both the site of initial deposition and the rate of mucociliary clearance

from the airways. When deposition patterns are matched, mucociliary clearance rates are reduced in

patients with COPD relative to healthy controls.

Using a bolus technique to target specific lung regions, Möller et al. (2008) examined particle

clearance from the ciliated airways and alveolar region of healthy subjects, smokers, and patients with

COPD. Airway retention after 1.5 h was significantly lower in healthy subjects ($89 \pm 6\%$) than smokers

($97 \pm 3\%$) or COPD patients ($96 \pm 6\%$). At 24 and 48 h, retention remained significantly higher in COPD

patients ($86 \pm 6\%$ and $82 \pm 6\%$, respectively) than healthy subjects ($75 \pm 10\%$ and $70 \pm 9\%$, respectively).

However, these findings are confounded by the more central pattern of deposition in the healthy subjects

than in the smokers and COPD patients. Alveolar retention of particles was similar between the groups at

48 h post-inhalation.

Chen et al. (2006b) investigated the effect of endotoxin on the disposition of particles. Healthy rats

and those pretreated with endotoxin (12 h before particle instillation) were instilled with ultrafine (56.4

nm) or fine (202 nm) particles. In healthy rats, there were no marked differences in lung retention or

systemic distribution between the ultrafine and fine particles. In healthy animals, ultrafine particles were

1    primarily retained in lungs (72 ± 10% at 0.5-2 h; 65 ± 1% at 1 d; 62 ± 5% at 5 d). Initially, there was rapid

2    particle movement into the blood (2 ± 1% at 0.5-2 h; 0.1 ± 0.1% at 5 d) and liver (3 ± 2% at 0.5-2 h;

3    1 ± 0.1% at 5 d). At 1 d post-instillation, about 13% of the particles were in the urine or feces. In rats

4    pretreated with endotoxin, by 2 h post-instillation, the ultrafine particles accessed the blood (5 vs. 2%)

5    and liver (11 vs. 4%) to a significantly greater extent than fine particles. The endotoxin treated rats also

6    had significantly greater amounts of ultrafine particles in the blood (5 vs. 2%) and liver (11 vs. 3%)

7    relative to the healthy rats. This study demonstrates that acute lung injury caused by endotoxin increases

8    the migration of ultrafine particles into systemic circulation.

## 4.3.4.4. Particle Overload

9    Unlike other laboratory animals, rats appear susceptible to "particle overload" effects due to

10   impaired macrophage-mediated alveolar clearance. Numerous reviews have discussed this phenomenon

11   and the difficulties it poses for the extrapolation of chronic effects in rats to humans (ILSI, 2000; Miller,

12   2000; Morrow, 1994; Oberdörster, 1995, 2002). Large mammals have slow pulmonary particle clearance

13   and retain particles in interstitial tissues under normal conditions, whereas rats have rapid pulmonary

14   clearance and retain particles in alveolar macrophages (Snipes, 1996). With chronic high doses of

15   particulate there is a shift in the pattern of dust accumulation and response from that observed at lower

16   particulate doses in rat lungs (Snipes, 1996; Vincent and Donaldson, 1990). Rats chronically exposed to

17   high concentrations of insoluble particles experience a reduction in their alveolar clearance rates and an

18   accumulation of interstitial particle burden (Bermudez et al., 2002; 2004; Ferin et al., 1992; Oberdörster

19   et al., 1994a; 1994b; Warheit et al., 1997). With continued exposure, some rats eventually develop

20   pulmonary fibrosis and both benign and malignant tumors (Lee et al., 1985a, b; 1986; Warheit et al.,

21   1997). Oberdörster (1996, 2002) proposed that high-dose effects observed in rats may be associated with

22   two thresholds. The first threshold is the pulmonary dose that results in a reduction in macrophage-

23   mediated clearance. The second threshold, occurring at a higher dose than the first, is the dose at which

24   antioxidant defenses are overwhelmed and pulmonary tumors develop. Intrapulmonary tumors following

25   $TiO_2$ exposures are exclusive to rats and are not found in mice or hamsters (Mauderly, 1997). Moreover,

26   Lee et al. (1985b) noted that the squamous cell carcinomas observed with prolonged high concentration

27   $TiO_2$ exposures developed from the alveolar lining cells adjacent to the alveolar ducts, whereas squamous

28   cell carcinomas in humans are generally linked with cigarette smoking are thought to arise from basal

29   cells of the bronchial epithelium. Quoting Lee et al. (1986), "Since the lung tumors were a unique type of

30   experimentally induced tumor under exaggerated exposure conditions and have not usually been seen in

31   man or animals, their relevance to man in questionable."

## 4.3.5. Summary

1    For any given particle size, the pattern of poorly soluble particle deposition influences clearance by
2    partitioning deposited material between regions of the respiratory tract. Particles depositing in the mouth
3    may generally be assumed to be swallowed or removed by expectoration. Particles deposited in the
4    posterior portions of the nasal passages or the tracheobronchial airways are moved via mucociliary
5    transport towards the nasopharynx and swallowed. Although clearance from the tracheobronchial region
6    is generally rapid, there appears to be fraction of material deposited in the tracheobronchial region of
7    humans that is retained much longer. The underlying sites and mechanisms of long-term tracheobronchial
8    retention are not known. In contrast to humans, mice and rats appear to have negligible long-term
9    retention of particles in tracheobronchial airways. The primary alveolar clearance mechanism is
10   macrophage phagocytosis and migration to terminal bronchioles where the cells are cleared by the
11   mucociliary escalator. Clearance from both the tracheobronchial and alveolar region is more rapid in
12   rodents than humans. Mucociliary and macrophage-mediated clearance decreases with age beyond
13   adulthood.

14   Human data show that there is not a rapid or significant amount of ultrafine carbon particle
15   migration into circulation. However, both in vitro and in vivo studies support the rapid [$\leq 1$ hr]
16   translocation of free ultrafine $TiO_2$ particles across pulmonary cell membranes. Extrapulmonary
17   translocation has also been described in rats for poorly soluble ultrafine gold and iridium particles. A low,
18   but statistically significant, fraction (0.03 to 0.06% of lung concentration) of ultrafine gold particles has
19   been observed in the blood of rats from 1 to 7 days post inhalation. The translocation in detectable
20   amounts (< 1% of deposited material) of poorly soluble Ir particles (15 and 20 nm CMD) from the lungs
21   of rats to secondary target organs like the liver, spleen, brain, and kidneys has also been reported.
22   However, the systemic distribution of particles may have occurred via normal clearance from the lungs to
23   the gastrointestinal tract.

24   Although the importance of particle translocation to the brain is not yet understood, translocation
25   from the olfactory mucosa via the axon to the olfactory bulb has been reported in primates, rodents, and
26   freshwater pike for numerous compounds of varying composition, particle size, and solubility. The rate of
27   translocation is rapid, perhaps less than an hour. In rats, as much as 8% of material may become
28   translocated to the olfactory bulb following intranasal instillation. It is unclear to what extent
29   translocation to the olfactory bulb and other brain regions may vary between species. Interspecies
30   differences may predispose rats, more so than humans, to the deposition of particles in the olfactory
31   region with subsequent translocation to the olfactory bulb.

# 4.4. Clearance of Soluble Materials

1        Soluble particles and soluble constituents of particles may be absorbed through the epithelium and

2    distributed systemically or retained in the lung. The rate of dissolution depends on a number of factors,

3    including particle surface area and chemical structure. Some dissolved materials bind to proteins or other

4    components in the airway surface liquid layer. In the ciliated airways, solutes are cleared by mucociliary

5    transport and diffuse into underlining tissues and the blood. In the alveolar regions, the thin barrier

6    between the air and blood allows for rapid transport of solutes into the blood. The movement of soluble

7    materials depends on the site of deposition in the lung, the rate of material dissolution from particles, and

8    the molecular weight of the solute. The rate of soluble material clearance from the lungs depends on

9    epithelial permeability which may be affected by age, respiratory disease, and concurrent exposures.

10   While enhanced clearance of insoluble particles acts to reduce dose to airway tissue, increased transport

11   of soluble matter into the blood stream may enhance effects on extra-pulmonary organs.

## 4.4.1. Clearance Mechanisms and Kinetics

12        The rate of absorption across the epithelium for materials that dissolve in the airway or alveolar

13   lining fluid is fairly rapid (minutes to hours) and is a function of their molecular size and their water or

14   lipid solubility (Enna and Schanker, 1972; Huchon et al., 1987; Oberdörster, 1988; Schanker et al., 1986).

15   Huchon et al. (1987) studied the clearance of a variety of aerosolized solutes from the lungs of dogs.

16   Solute clearance was inversely related to molecular weight. Negligible clearance of the largest molecular

17   weight solute (transferrin; mol wt ~76,000 daltons) in their study was found over a 30-min observation

18   period. At the other extreme, free pertechnetate (mol wt ~163 daltons) had a clearance rate of 6% per min.

19   Clearance of hydrophilic solutes is diffusion limited by pore sizes associated with intercellular tight

20   junctions (estimated at 0.6 to 1.5 nm). Absorption of lipophilic compounds that pass easily through cell

21   membranes is perfusion limited and thus generally occurs very rapidly. However, if lipophilic materials

22   are adsorbed onto insoluble particles their retention in the lung may be prolonged (Creasia et al., 1976). In

23   addition to diffusion through intercellular junctions, transcellular transport of large solutes by pinocytosis

24   in epithelial cells has also been observed (Chinard, 1980). Once a particle is phagocytosed by an alveolar

25   macrophage it may slowly dissolve and be released from the cell to move across the epithelium into the

26   bloodstream. The dissolution rate is inversely related to particle size and directly related to specific

27   surface area (Kreyling and Scheuch, 2000) and facilitated by the acidic (pH of 4.3 to 5.3) environment of

28   the phagolysosome (Kreyling, 1992).

1       There is considerable evidence as well that soluble particles depositing in the bronchial airways are

2 also cleared by mucociliary transport (Bennett and Ilowite, 1989; Lay et al., 2003; Matsui et al., 1998;

3 Sakagami et al., 2002; Wagner and Foster, 2001). The relative contribution of their removal by

4 transepithelial absorption vs. mucociliary clearance is likely a function of both the molecular size and

5 water or lipid solubility of the material (Enna and Schanker, 1972; Huchon et al., 1987; Oberdörster,

6 1988; Sakagami et al., 2002). Furthermore, the rate of mucociliary transport for soluble particles may be

7 less than that of insoluble particles (Lay et al., 2003). Consequently, non-permeating hydrophilic solutes

8 may remain in contact with the airway epithelium for a longer period than insoluble particles. This may

9 be due to diffusion of a greater portion of the solute into the periciliary sol layer which may be

10 transported less efficiently than the mucus layer during mucociliary clearance. Bronchial blood flow has

11 also been shown to modulate airway retention of soluble particles (Wagner and Foster, 2001), i.e.

12 decreasing blood flow increases airway retention of soluble particles.

13       As an example of how transport of soluble components of PM may clear the lung by transepithelial

14 absorption, Wallenborn et al. (2007) measured elemental content of lungs, plasma, heart, and liver of

15 healthy male WKY rats (12-15 weeks old) 4 or 24 h following a single intratracheal (IT) instillation of

16 saline or 8.33 mg/kg of oil combustion PM containing a variety of transition metals with differing water

17 and acid solubility. Metals with high water solubility and relatively high concentration in oil combustion

18 PM were increased in extrapulmonary organs. Elements with low water or acid solubility, like silicon and

19 aluminum, were not detected in extrapulmonary tissues despite decreased levels in the lung suggesting

20 they cleared the lung primarily by mucociliary clearance. Thus, PM-associated metals deposited in the

21 lung may be released into systemic circulation at different rates depending on their water/acid solubility,

22 thereby providing a means by which metals may elicit direct extrapulmonary effects.

## 4.4.2. Factors Modulating Clearance

23       A number of studies have evaluated the epithelial permeability by measuring the clearance of

24 ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), a small hydrophilic solute (492 daltons, 0.57

25 nm). These studies are the basis for much of the discussion in this section.

### 4.4.2.1. Age

26       In humans, the clearance of water-soluble particles (^{99m}Tc-DTPA) from the alveolar epithelium

27 generally slows with increasing age (Braga et al., 1996; Pigorini et al., 1988). However, Tankersley et al.

28 (2003) recently showed enhanced permeability of soluble particles (^{99m}Tc-DTPA) in terminally senescent

1   mice just before death, suggesting that a disintegration of the epithelial barrier may be a feature of lung

2   homeostatic loss during this period of terminal senescence.

## 4.4.2.2. Exercise

3       The transepithelial transport rates of soluble particles, $^{99m}$Tc-DTPA, have also been found to

4   increase during exercise (Hanel et al., 2003; Lorino et al., 1989; Meignan et al., 1986). This enhancement

5   was linked to increases in tidal volume associated with exercise (Lorino et al., 1989). Regionally, this

6   effect was dominated by increased apical lung clearance and attributed to an increase in apical blood flow

7   (Meignan et al., 1986). The increased permeability with exercise appears to resolve to baseline after a

8   short period post exercise, i.e. within a couple hours (Hanel et al., 2003).

## 4.4.2.3. Disease

9       Because the integrity of the epithelial surface lining of the lungs may be damaged from lung

10  disease, particles (either insoluble or soluble) may gain greater access to the interstitium, lymph, and

11  blood stream. Damage to the epithelial barrier is most likely to acutely affect transepithelial transport

12  rates of soluble particles. From bronchial biopsies, Laitinen et al. (1985) found various degrees of

13  epithelial damage, from loosening of tight junctions to complete denudation of the airway epithelium, in

14  asthmatics. Consistent with these findings, Ilowite et al. (1989) found that asthmatics had increased

15  permeability of the bronchial mucosa to the hydrophilic solute $^{99m}$Tc-DTPA. On the other hand, a more

16  recent study in a sheep model showed that the presence of bronchial edema could slow the uptake of

17  soluble DTPA into the blood and enhanced retention in the airways, likely within the expanded interstitial

18  barrier (Foster and Wagner, 2001). Both a leaky epithelial barrier and expanded interstitial barrier

19  associated with asthma may result in enhanced exposure of submucosal immune and smooth muscle cells

20  to xenobiotic substances.

21      Alveolar epithelial permeability was also shown affected by the presence of lung inflammation.

22  The most common finding has been a clear increase in alveolar permeability induced by cigarette

23  smoking (Jones et al., 1980). This effect appears to be dependent the recent cigarette smoke exposure as

24  indexed by carboxyhaemoglobin (Jones et al., 1983) and is rapidly reversible within a week smoking

25  cessation (Mason et al., 1983). In fact, Huchon et al. (1984) demonstrated that COPD patients who have

26  stopped smoking have normal clearance of $^{99m}$Tc-DTPA.

27      In general, increased alveolar permeability to $^{99m}$Tc-DTPA has been found to be associated with any

28  lung syndrome characterized by pulmonary edema. While the trans-alveolar transport of a small solute

29  like DTPA is very sensitive to even mild acute lung injury (such as that associated with even mild

1 cigarette smoking), increased transport rates of larger molecules (>100K daltons) across the alveolar

2 epithelium require more severe damage like that seen in adult respiratory distress syndrome (ARDS)

3 (Braude et al., 1986; Peterson et al., 1989). Interstitial lung disease and pulmonary fibrosis are also

4 characterized by increased alveolar permeability (Antoniou et al., 2006; Bodolay et al., 2005; Watanabe et

5 al., 2007). Interestingly, these recent studies have also shown that the increased permeability in these

6 patients could be corrected with immunosuppressive/steroid treatments (Bodolay et al., 2005; Watanabe et

7 al., 2007). Furthermore, studies of DTPA clearance in bleomycin injured dogs, a model of pulmonary

8 fibrosis, suggest that the enhanced permeability is associated with the initial acute phase of the lung

9 damage, with clearance rates returning to normal as chronic fibrosis developed over time (Suga et al.,

10 2003).

11     Finally, as evidence of lung complications associated with non-insulin dependent diabetes (type 2)

12 patients, Lin et al. (2002a) found impairment of alveolar integrity as shown by increased transport rates of

13 both hydophilic and lipophilic solutes from the lungs in these patients. By contrast, a number of other

14 studies have found epithelial permeability reduced, i.e. slower transport rates, in diabetes (Caner, 1994;

15 Mousa et al., 2000; Özsahin et al., 2006) that may be related to disease duration and metabolic control

16 (Özsahin et al., 2006). These findings are consistent with thickening of alveolar basement membrane

17 detected in autopsies of diabetes patients (Weynand et al., 1999).

## 4.4.2.4. Concurrent Exposures

18     The integrity of the alveolar epithelium may be disrupted by copollutants such that soluble

19 components of inhaled particles can more easily enter the interstitium and blood stream. Like active

20 cigarette smoking discussed previously, Beadsmoore et al. (2007) showed clearance half-times in healthy

21 passive smokers to be shorter compared with healthy non-smokers but still longer than in healthy

22 smokers. These findings show a progressive increase in epithelial permeability with exposure to cigarette

23 smoke. Similarly, acute exposure of humans to 0.4 ppm ozone for 2 h with intermittent exercise has been

24 shown to alter epithelial integrity and increase clearance of soluble hydrophilic particles from the alveolar

25 surfaces of the lung (Kehrl et al., 1987). This effect persists to at least 24 h post-exposure to even low

26 concentrations (0.24 ppm average for 130 minutes) of ozone (Foster and Stetkiewicz, 1996). Similarly,

27 0.8 ppm $O_3$ exposure for 2 h in rats shows increased permeability to macromolecules at all levels of the

28 respiratory tract (Bhalla et al., 1986) that persisted in the alveolar region beyond 24-h post-exposure.

29 Chang et al. (2005a) recently showed that ultrafine carbon black acts through a reactive oxygen species

30 (ROS) dependent pathway to increase epithelial permeability in mice.

31     But chronic exposure to other particulate or gaseous pollutants has not always led to increased

32 epithelial permeability. Studying subjects with a variety of occupational exposures, Kaya et al. (2006)

showed that nonsmoking welders actually have decreased epithelial permeability relative to nonsmoking control subjects, and occupational exposure of painters to isocyanates has no effect on bronchoalveolar epithelial permeability (Kaya et al., 2003).

## 4.4.3. Summary

The healthy airway and alveolar epithelium is generally impermeable to very large insoluble macromolecules and particles. Water and acid soluble particles may more rapidly move through the epithelium as they dissolve on the airway surface or within the phagolysomes of macrophages. The presence of airway inflammation in a variety of airway diseases (e.g. asthma, fibrosis, ARDS, pulmonary edema, inflammation from smoking) alters epithelial integrity to allow more rapid movement of these solutes into the bloodstream. While diabetics are another group recently shown to have increased susceptibility to particulate air pollution (Zanobetti and Schwartz, 2002), it is unclear whether transport of soluble particles across the epithelium is affected in these patients. In general, it appears that co-exposure to irritant pollutants results in a disruption of epithelial integrity and macrophage function which, on the one hand, retards mucociliary and alveolar clearance, but also allows for a more rapid movement of soluble constituents across the epithelial surface into the interstitium and blood stream. Cohen et al. , e1997 #9299} may have best illustrated the competing effects of mucociliary and transepithelial transport by showing that co-exposure to ozone affected the retention of inhaled chromium in rats differently depending on its solubility. In its soluble potassium chromate form, ozone decreased the retention of chromium, but when chromium was inhaled as insoluble barium chromate, its retention in the lung was increased by ozone co-exposure. Similarly, a study that showed decreased clearance of insoluble cesium oxide particles following influenza infection also showed a virus induced enhancement of clearance for a soluble cesium chloride (Lundgren et al., 1978). These alterations in epithelial permeability by disease, pollutant exposure, or infection may partially explain increased susceptibility to PM associated with these co-conditions.

# Chapter 5. Possible Pathways/
# Modes of Action

1    The mechanisms underlying pulmonary effects of inhaled PM have been well-studied and there is
2    general agreement regarding the key roles played by cellular injury and inflammation. These pathways
3    are initiated following the inhalation of particles and their deposition on respiratory tract surfaces. Since
4    most of these studies were conducted at concentrations of PM higher than ambient levels, there is some
5    question regarding the relevance of these responses and mechanisms to ambient exposures.

6    Interestingly, inhaled PM may also affect the cardiovascular, hematopoietic and other systems.
7    Mechanisms underlying these extra-pulmonary effects are incompletely understood. However, pulmonary
8    inflammation can lead to systemic inflammation and pulmonary reflexes can activate the autonomic
9    nervous system. These latter responses may mediate cardiovascular and other systemic effects, as will be
10   discussed below. In addition, it has been proposed that PM or soluble components of PM reach the
11   circulation by translocating across the epithelial barrier of the respiratory tract. In this way PM or its
12   components may interact directly with cells in the vasculature, blood, heart and other organs. At this time,
13   evidence clearly supports the translocation of soluble components following some high dose exposures
14   involving intratracheal instillation; however there is insufficient evidence to support translocation of
15   soluble components or intact particles following inhalation exposures at lower concentrations (see
16   Chapter 4). Future studies will be required to resolve these issues.

17   The following sections discuss biological pathways which comprise proposed modes of action for
18   the pulmonary and extra-pulmonary effects of inhaled PM. Overall themes are emphasized and supportive
19   evidence from new in vitro and in vivo animal studies is cited. The characterization of evidence here is
20   for PM in general, since most of the potential pathways or modes of action described below do not appear
21   to be specific to a particular size class of PM. Finally, a compilation of results from new inhalation studies
22   which are relevant to ambient PM exposures and which confirm and extend these proposed mechanisms
23   is found at the end of this chapter. Detailed descriptions of these key new studies are found in Chapters 6
24   and 7.

# 5.1. Pulmonary Effects

## 5.1.1. Reactive Oxygen Species

1    A great deal of research interest has focused on the role of ROS in the initiation of pulmonary

2    injury and inflammation following exposure to PM. Numerous studies have demonstrated PM oxidative

3    potential in in vitro assay systems (Ayres et al., 2008; Cho et al., 2005a; Shi et al., 2003; Tao et al., 2003).

4    Both redox active surface components such as metals and organic species and the surface characteristics

5    of crystal structures have been shown to contribute to oxidative potential (Jiang et al., 2008; Tao et al.,

6    2003; Warheit et al., 2007). In this way, PM may be a direct source of ROS in the respiratory tract (Figure

7    5-1).
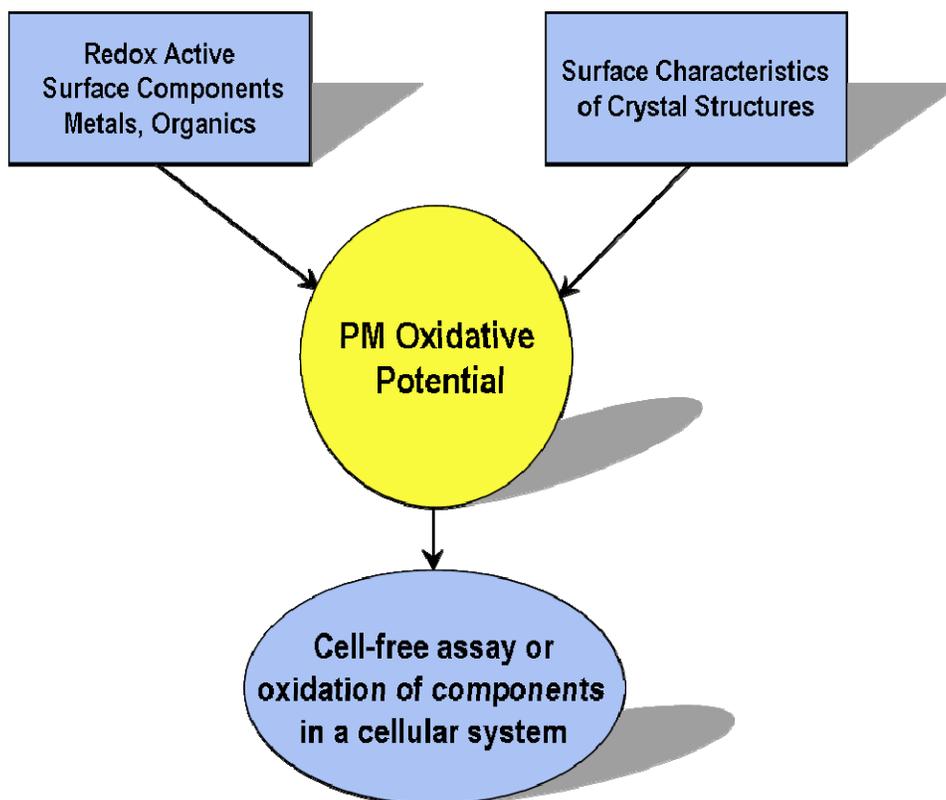


**Figure 5-1.    PM oxidative potential.**

8    PM may also act as an indirect source of ROS in the respiratory tract by stimulating cells to

9    produce ROS (Ayres et al., 2008; Tao et al., 2003) (Figure 5-2). This may explain the observation that PM

10    oxidative potential does not always correlate with cellular or tissue oxidative stress. Numerous studies

1 have demonstrated that exposure to PM increases intracellular production of ROS by a variety of

2 mechanisms. For example, PM interaction with cell surfaces results in stimulation of NADPH oxidase in

3 macrophages (i.e. the respiratory burst) (Dostert et al., 2008) and in epithelial cells (Amara et al., 2007;

4 Becher et al., 2007; Tamaoki et al., 2004). Absorption of PM soluble components by respiratory tract cells

5 can occur (Penn et al., 2005) and be followed by microsomal transformation of polycyclic aromatic

6 hydrocarbons to quinones or by redox cycling of soluble metals with the resulting production of

7 intracellular ROS (Molinelli et al., 2002; Xia et al., 2004). Disruption of intracellular iron homeostasis

8 with the subsequent generation of ROS has also been demonstrated following PM exposure (Ghio and

9 Cohen, 2005). In some cases, mitochondria serve as the source of ROS in response to PM (Huang et al.,

10 2003b; Risom et al., 2005; Soberanes et al., 2006). Furthermore, PM interaction with cells can lead to the

11 induction of nitric oxide synthase (Becher et al., 2007; Lindbom et al., 2007; Xiao et al., 2005; Zhao et

12 al., 2006a) and the production of nitric oxide and other reactive nitrogen species (RNS).
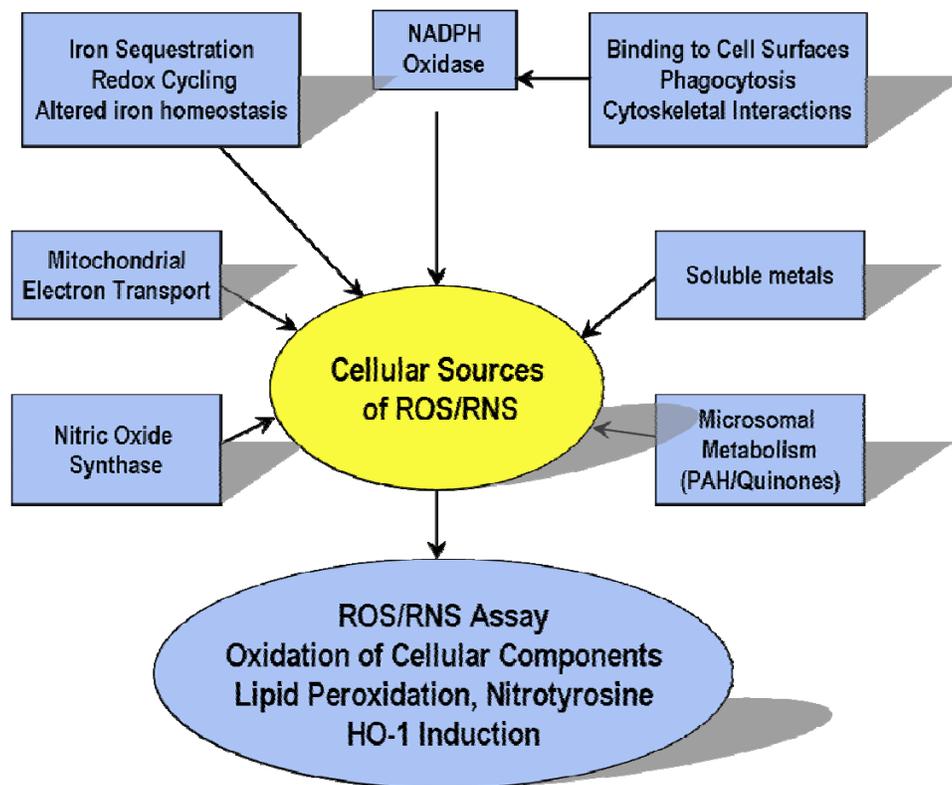


**Figure 5-2.    PM stimulates pulmonary cells to produce ROS/RNS.**

13 High levels of intracellular ROS/RNS can lead to irreversible protein modifications, loss of cellular

14 membrane integrity and cellular toxicity. Lower levels of ROS/RNS may involve reversible protein

15 modifications which trigger intracellular signaling pathways and/or adaptive responses.

## 5.1.2. Activation of Cell Signaling Pathways

1    Activation of cell signaling pathways by ROS/RNS has received increasing attention in recent
2    years. An early example was provided by Kaul and Forman (1996) who demonstrated that respiratory
3    burst-derived $H_2O_2$ activates the transcription factor $NF_KB$. Numerous studies since then have
4    demonstrated that PM, which serves as both a direct and indirect source of ROS/RNS, activates cell
5    signaling pathways by this mechanism.

6    PM exposure results in activation of cell signaling by other mechanisms as well. For example, PM
7    delivers water-soluble components such as endotoxin and zinc to cell surfaces. Endotoxin binds to toll-
8    like receptors on alveolar macrophages and results in the upregulation of cytokines (Becker et al., 2002).
9    Zinc, a transition metal which does not redox cycle, inhibits protein tyrosine phophatases in airway
10   epithelial cells resulting in a cascade of cell signaling events (Tal et al., 2006). Similarly, PM-mediated
11   delivery of lipid soluble components such as PAH in mice results in binding and activation of the
12   arylhydrocarbon receptor (AhR) in mice. AhR is a transcription factor responsible for the upregulation of
13   CYP1A1, a cytochrome oxidase involved in PAH metabolism (Rouse et al., 2008). In addition, interaction
14   of PM with cell surfaces by perturbation of the cytoskeleton, adherence, internalization, or
15   receptor-mediated pathways has been demonstrated to activate cell signaling pathways.
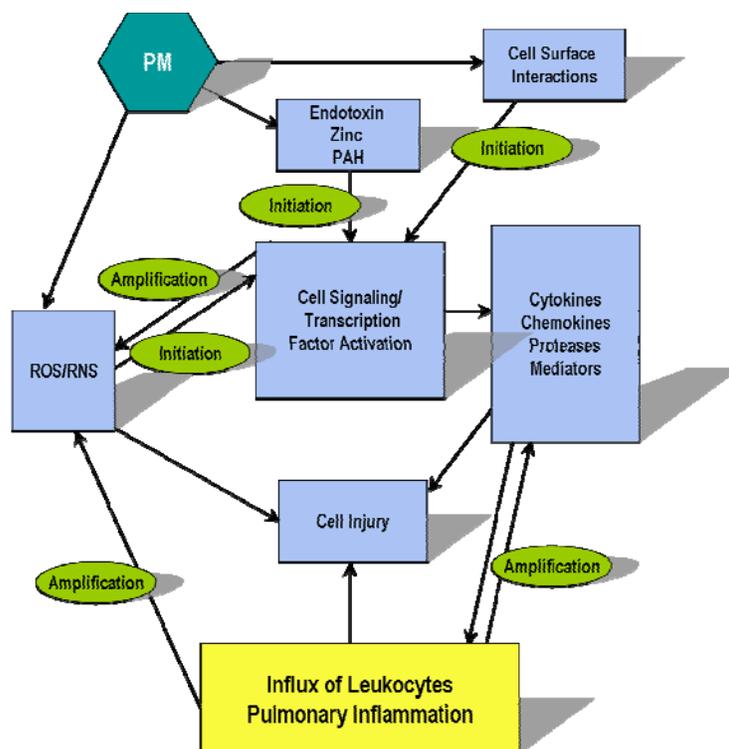


**Figure 5-3.    PM activates cell signaling pathways leading to pulmonary inflammation.**

1　　　　Recent studies involving PM exposures have focused on intracellular pathways involving protein

2　　kinases such as: MAPK (Aam and Fonnum, 2007; Bayram et al., 2006; Lee et al., 2005a; Roberts et al.,

3　　2003), AKT (Ahsan et al., 2005), src (Cao et al., 2007) and epidermal growth factor receptor (Blanchet et

4　　al., 2004; Cao et al., 2007; Tamaoki et al., 2004); and ras (Tamaoki et al., 2004), toll-like receptors

5　　(Becker et al., 2005a; 2005b), protein tyrosine phosphatases (Tal et al., 2006), phospholipases $A_2$ (Lee et

6　　al., 2003c), calcium (Agopyan et al., 2003; Brown et al., 2004a; 2004b; Geng et al., 2005, 2006;

7　　Sakamoto et al., 2007), caspases (Soberanes et al., 2006; Zhang et al., 2007a), PARP-1 (Zhang et al.,

8　　2007a) and histone acetylation (Gilmour et al., 2003). The transcription factors regulated by these

9　　pathways, including NFκB (Bayram et al., 2006; Lee et al., 2005a; Takizawa et al., 2003), AP-1

10　　(Donaldson et al., 2003), STAT (Cao et al., 2007), ARE (Li and Nel, 2006) and AhR (Rouse et al., 2008),

11　　have also been studied following PM exposures. Activation of these intracellular pathways and

12　　transcription factors leads to the upregulation of genes responsible for inflammatory, immune and acute

13　　phase responses as well as genes responsible for antioxidant defense and xenobiotic metabolism.

## 5.1.3. Inflammation

14　　　　Transcription factor activation in macrophages and epithelial cells stimulates the synthesis and

15　　release of proteins involved in inflammatory and immune responses including cytokines, chemokines,

16　　proteases and eicosanoids (Figure 5-3). These soluble mediators play a role in recruiting inflammatory

17　　cells such as neutrophils, monocytes, mast cells and eosinophils to the lung. Interactions between

18　　macrophages and epithelial cells enhance these responses (Tao and Kobzik, 2002).

19　　　　Inflammatory cells can also serve as a source of extracellular ROS which, along with soluble

20　　mediators derived from the inflammatory cells, can amplify the inflammatory response. Unchecked

21　　inflammation may cause cellular and tissue injury through the generation of ROS and soluble mediators.

22　　In some cases the oxidative potential of PM is well-correlated with the degree of inflammation (Dick et

23　　al., 2003b), suggesting that the inflammation is a direct consequence of PM-associated ROS. However, in

24　　other cases the oxidative potential of PM is not well-correlated with the degree of inflammation (Beck-

25　　Speier et al., 2005), suggesting that the inflammation is a consequence of the other mechanisms by which

26　　PM activates intracellular signaling pathways.

## 5.1.4. Epithelial Barrier Function

27　　　　Epithelial injury can lead to an increase in permeability across the airway epithelial and

28　　alveolar-capillary barriers. Airway and alveolar edema may occur subsequently. Enhanced transport of

soluble and insoluble PM components into the circulation may occur under these conditions. Increased epithelial permeability is also associated with enhanced immune responses to proteins, including allergens, on the epithelial surface, presumably due to the greater availability of antigens to underlying immune cells. Soluble mediators derived from inflammatory and lung cells (Chang et al., 2005a) and peptides released by some nerve cells (Widdicombe and Lee, 2001) can also increase permeability across epithelial barriers. Edema resulting from nerve cell stimulation is one component of neurogenic inflammation.

## 5.1.5. Antioxidant Defenses and Adaptive Responses

Antioxidant defenses and adaptive responses are important modulators of oxidative stress and other cellular stresses resulting from PM exposure. Antioxidants are present in the epithelial lining fluid at all levels of the respiratory tract. In addition, they are present in cells of the lung parenchyma and inflammatory cells found in airways and alveoli. Some antioxidants act directly against oxidant species (e.g. glutathione, ascorbate, superoxide dismutase) while others act indirectly (e.g. $\gamma$GCS, glutathione reductase). Furthermore, some antioxidants (e.g. Phase 2 enzymes HO-1, NQO1 GST) are inducible via activation of the Nrf2-ARE pathway which occurs as an adaptive response to stress (Cho et al., 2006; Li and Nel, 2006). Antioxidants play an important role in reducing the oxidative potential of those PM species which directly generate ROS. They also inhibit responses due to generation of intracellular ROS.

Recently a three-tier response to oxidative stress was proposed (Li and Nel, 2006). In this scheme, mild oxidative stress enhances antioxidant defenses by upregulating Phase 2 and other antioxidant enzymes (Tier 1). Further increase in oxidative stress induces inflammation (Tier 2) and cell death (Tier 3). Experimental evidence is supportive of this scheme. Numerous studies have demonstrated that enhancement of lung and cellular antioxidant defenses inhibits inflammation, cytotoxicity and other responses following exposure to PM (Ahsan et al., 2005; Bachoual et al., 2007; Bayram et al., 2006; Chang et al., 2005a; Imrich et al., 2007; Koike et al., 2004; Koike and Kobayashi, 2005; Li et al., 2007; Liu et al., 2005a; Ramage and Guy, 2004; Rhoden et al., 2004; Steerenberg et al., 2004b; Takizawa et al., 2003; Tao et al., 2003; Upadhyay et al., 2003; Wan and Diaz-Sanchez, 2006, 2007; Yin et al., 2004b).

Cellular and tissue exposure to xenobiotics carried by PM can lead to induction of Phase 1 and Phase 2 detoxifying enzymes subsequent to the activation of cell signaling pathways and transcription factors AhR and ARE, respectively (Rengasamy et al., 2003; Rouse et al., 2008; Zhao et al., 2006a).

# 5.1.6. Pulmonary Function

1        PM exposure may alter pulmonary function by a variety of different mechanisms (Figure 5-4). In

2    the short term, AHR may ensue due to the influence of inflammatory mediators. In the long-term,

3    morphological changes may occur, in some cases leading to mucus hypersecretion and airway

4    remodeling. Activation of irritant receptors and stimulation of the autonomic nervous system (ANS) in the

5    respiratory tract is another mechanism by which PM exposure may alter pulmonary function

6    (Section 5.3).
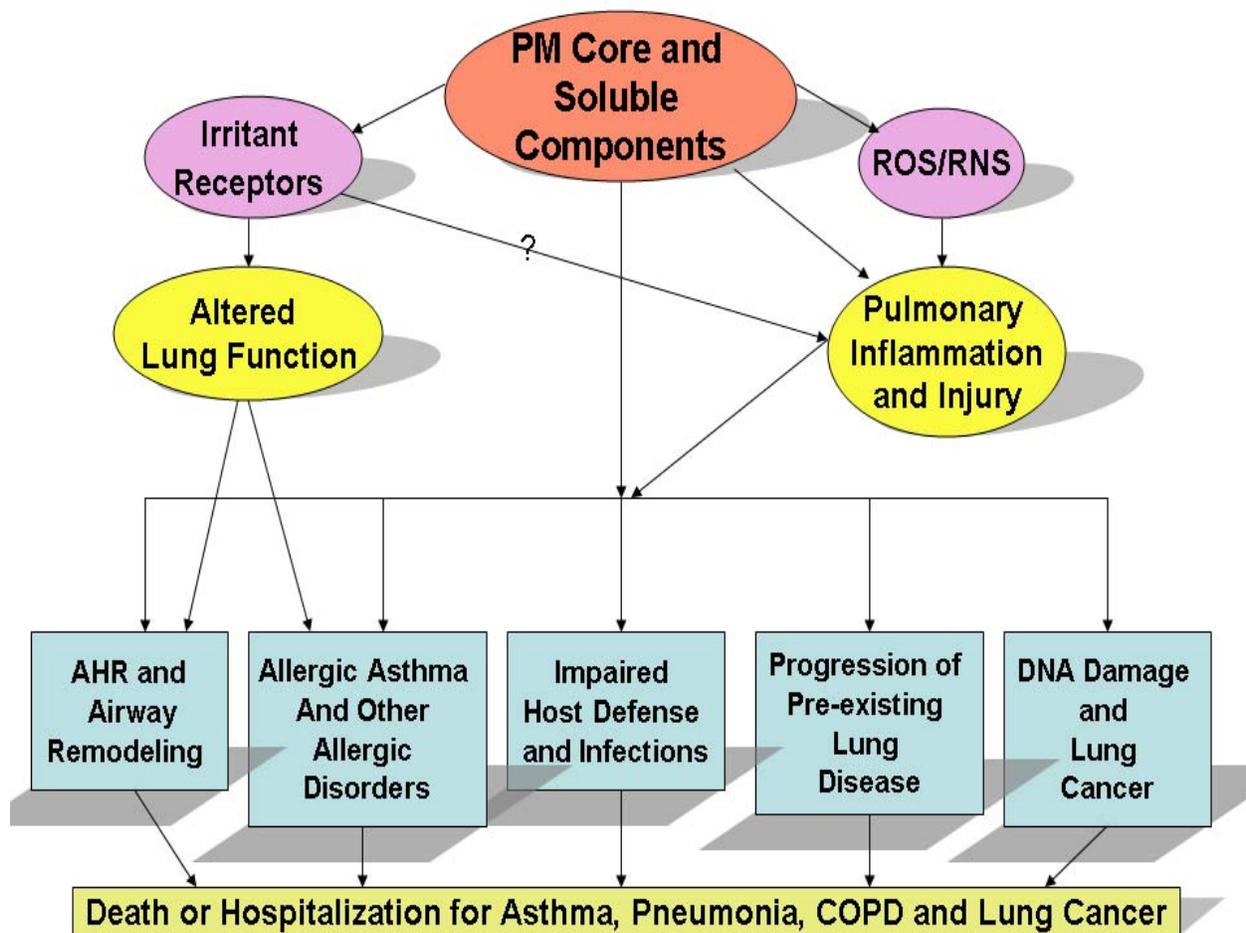


**Figure 5-4.**    **Potential pathways for the effects of PM on the respiratory system.**

## 5.1.7. Allergic Disorders

1    PM exposure sometimes leads to the development of allergic immune responses (Figure 5-4).

2    These responses are mediated by T helper cells, which fall along a continuum from T helper type 1 (Th1)

3    to T helper type 2 (Th2). Th1 responses, characterized by IFN-γ, are inflammatory, and in excess can lead

4    to tissue damage. Alternatively, Th2 responses are characterized by IL-4, IL-5, IL-13, eosinophils, and

5    IgE, and are associated with allergy and asthma. PM exposure can also lead to the exacerbation of allergic

6    responses, such as antigen-specific IgE production and AHR.

7    Due to soluble mediators and immune cell trafficking, pulmonary exposure may result in systemic

8    immune alterations. Not only do macrophages ingest PM, but they are also antigen presenting cells whose

9    level of activation dictates costimulation and thus subsequent T cell responses. These cells are highly

10   mobile, and can transport PM to other sites such as lymph nodes. Dendritic cells (DC) also play a key role

11   as antigen presenting cells and in modulating T and B cell activity. A cell culture model of the human

12   epithelial airway wall was used to demonstrate that DC extend processes between epithelial cells through

13   the tight junctions to collect particles in the lumenal space and to transport them through cytoplasmic

14   processes between epithelial cells across the epithelium or to transmigrate through the epithelium to take

15   up particles on the epithelial surface. Furthermore, DC interacted with particle-loaded macrophages on

16   top of the epithelium and with other DC within or beneath the epithelium to transfer particles (Blank et

17   al., 2007). In vitro studies also demonstrate that the adjuvant activity of DEP may involve stimulation of

18   immature monocyte-derived dendritic cells (iMDDC) to undergo maturation by an altered airway

19   epithelial cell-derived microenvironment (Bleck et al., 2006). Additionally, DEP directly influences the

20   profile of cytokines secreted by DC and causes a predisposition toward Th2-mediated or allergic

21   responses (Chan et al., 2006b). Thus PM can negatively affect both innate immunity through effects on

22   macrophage pathogen handling (see Section 5.1.8) as well as adaptive immunity by altering macrophage

23   or dendritic cell antigen presenting activity and subsequent T cell responses.

## 5.1.8. Impaired Lung Defense Mechanisms

24   PM exposure may impair lung defense mechanisms and result in frequent or persistent infections

25   (Figure 5-4). Potential targets include mucociliary transport, surfactant function and pathogen clearance.

26   Pathogen clearance is dependent on the integrity of macrophages and their migration, phagocytosis and

27   respiratory burst functions. PM-mediated cytotoxicity of macrophages with the concomitant release of

28   lysosomal contents may affect pathogen clearance and cause damage to nearby cells and tissues.

29   Intratracheal instillation and cell culture experiments have demonstrated PM-dependent impairment of

lung defense mechanisms (Jaspers et al., 2005; Kaan and Hegele, 2003; Long et al., 2005; Moller et al., 2005; Monn et al.; Roberts et al., 2007; Yin et al., 2004a).

## 5.1.9. Resolution of Inflammation/Progression of Disease

Resolution of pulmonary inflammation and injury has been demonstrated in many experimental models using higher than ambient concentrations of PM. Factors contributing to this complex process are likely to include the uptake and clearance of PM by macrophages, the retention of PM in parenchymal cells and tissues, pro- and anti-inflammatory soluble mediators, the balance of oxidants/antioxidants and the presence of pre-existing disease. These factors may also influence the resolution of pulmonary responses to ambient PM exposures (Figure 5-4). A recent study suggests an important role for retained particles in the progression of disease. Complexation of endogenous iron by retained particles resulted in retained particles growing larger over time. The authors suggested that redox cycling of complexed iron may be responsible for disease progression (Ghio et al., 2004; Ghio and Cohen, 2005).

## 5.1.10. Pulmonary DNA Damage

Pulmonary DNA damage can occur primarily or secondarily to PM exposure. Primary effects include oxidative DNA injury or DNA adduct formation due directly to PM while secondary effects occur due to PM-mediated inflammation (de Kok et al., 2005; Gábelová et al., 2007b; Gallagher et al., 2003; Schins and Knaapen, 2007). These responses may lead to chromosomal aberrations or DNA strand breaks. PM effects on cell cycle arrest, proliferation, apoptosis, and DNA repair mechanisms may also influence the genotoxic, mutagenic or carcinogenic potential of DNA damage.

# 5.2. Systemic Inflammation

Pulmonary inflammation can trigger systemic inflammation through the action of cytokines and other soluble mediators which leave the lung and enter the circulation (Figure 5-5). Cytokines released by alveolar macrophages can stimulate bone marrow production of leukocytes resulting in an increased number of total and immature leukocytes in the circulation (van Eeden et al., 2001; van Eeden and Hogg, 2002). They also activate neutrophils and promote their sequestration in microvascular beds (van Eeden et al., 2001). The time course of these responses varies according to the acute or chronic nature of the PM exposure (van Eeden et al., 2005).
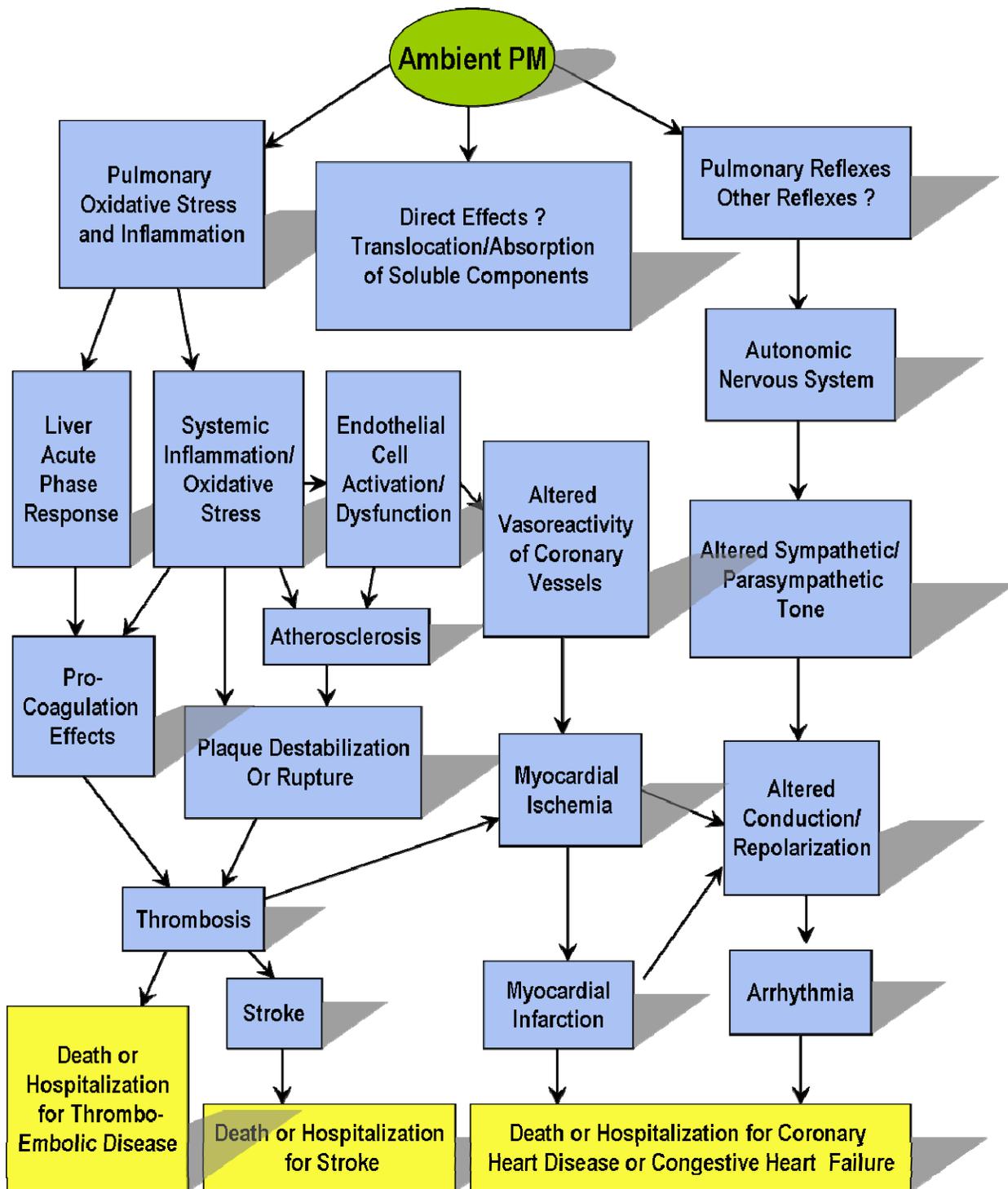
**Figure 5-5.** Potential pathways for the effects of PM on the cardiovascular system.

1    Systemic inflammation is seen under conditions of mild pulmonary inflammation – and sometimes

2    under conditions of no measurable pulmonary inflammation – following PM exposure. The time-

3    dependent nature of pulmonary and systemic inflammatory responses may in part explain these findings

1  since biomarkers of inflammation are frequently measured only at one time point. Furthermore, chronic

2  exposures may lead to adaptive responses. Systemic inflammation is associated with changes in

3  circulating white blood cells, the acute phase response, pro-coagulation effects, endothelial dysfunction

4  and the development of atherosclerosis (Figure 5-5). Adverse effects on the cardiovascular and

5  cerebrovascular systems such as thrombosis, plaque rupture, MI and stroke may result. Systemic

6  inflammation may affect other organ systems such as the liver or the central nervous systerm.

7      One recent study demonstrates that alveolar macrophage-derived IL-6 mediated pro-coagulation

8  effects in mice exposed by intratracheal instillation to 10 µg $PM_{10}$ (Mutlu et al., 2007). This study

9  provides a definitive link between lung cytokines and systemic responses in one model system. Whether

10  this mechanism or others account for the majority of extrapulmonary effects following PM exposure is

11  not yet clear.


## 5.2.1. Endothelial Dysfunction and Altered Vasoreactivity

12      The lumenal surface of blood vessels is lined by endothelial cells which, in addition to providing a

13  barrier function, are key regulators of vascular homeostasis. Endothelial cells synthesize and release

14  vasodilators such as nitric oxide and prostacyclin and vasoconstrictors such as endothelin which act on

15  neighboring smooth muscle cells. Endothelin also stimulates endothelial nitric oxide synthesis through a

16  feedback mechanism. Inhalation of high concentrations of PM has been reported to increase endothelin

17  levels in the circulation (Thomson et al., 2005). Endothelin has also been proposed to play a role in

18  hypoxia-induced MI (Caligiuri et al., 1999). However the role of endothelin in mediating cardiovascular

19  effects following ambient PM exposures is unclear.

20      Endothelial dysfunction can arise under conditions of systemic inflammation and/or oxidative

21  stress. Cytokines activate endothelial cells and upregulate endothelial cell adhesion molecules. They also

22  promote the sequestration of neutrophils in microvascular beds. Neutrophil sequestration is sometimes

23  associated with the deposition of myeloperoxidase on endothelial cell surfaces (Nurkiewicz et al., 2006).

24  ROS-derived from neutrophils, myeloperoxidase, other adhered inflammatory cells and/or other sources

25  can perturb the balance of vasodilator and vasoconstrictor species produced by endothelial cells.

26  Oxidative stress can result in decreased synthesis of nitric oxide due to limitation of the redox-sensitive

27  cofactor tetrahydrobiopterin and in decreased bioavailability of nitric oxide due to reaction with

28  superoxide. Prostacyclin synthesis is also decreased by oxidative stress. These processes can affect

29  vasoreactivity, in that blood vessels may be unable to respond to vasoconstrictor stimuli with

30  compensatory vasodilation.

1     Loss of nitric oxide and prostacyclin synthesis due to oxidative stress may have other consequences

2     since both exert negative influences on platelet and neutrophil activation. While endothelial surfaces

3     normally are antithrombotic, endothelial dysfunction can contribute to thrombus formation. Furthermore

4     inflammation and oxidative stress associated with endothelial dysfunction can contribute to the

5     development or progression of atherosclerosis (van Eeden et al., 2005).


## 5.2.2. Activation of Coagulation and Acute Phase Response

6     The primary function of the coagulation cascade is to stop the loss of blood after vascular injury by

7     forming a fibrin clot. However in some cases, activation of coagulation can promote intravascular

8     thrombosis (Karoly et al., 2007). It has been proposed that PM air pollution can activate clotting pathways

9     and enhance the likelihood of an obstructive cardiac ischemic event (e.g. myocardial infarction) or

10    cerebral event (e.g. stroke) (Seaton et al., 1995).

11    Coagulation is regulated by intrinsic and extrinsic pathways. The intrinsic pathway occurs

12    following activation of Factor XII and does not require the addition of an exogenous agent (Mackman,

13    2005). On the other hand, the extrinsic pathway is an inducible signaling cascade that can be activated by

14    tissue factor produced in response to inflammation or endothelial injury (Karoly et al., 2007).

15    In general, platelets, RBC s and endothelial cells are effector cells for inducing a procoagulant state

16    in the vasculature. Circulating factors may enhance coagulation or promote activation of platelets.

17    Cytokines formed during tissue damage and inflammation lead to tissue factor induction. Tissue factor is

18    the initiating stimulus for coagulation following vascular injury or plaque erosion. Complexes of tissue

19    factor: Factor VIIa form on endothelial cell surfaces and play a key role in thrombin generation by

20    initiating the extrinsic blood coagulation pathway (Gilmour et al., 2005). Thrombin generates fibrin from

21    fibrinogen and amplifies the intrinsic pathway (Karoly et al., 2007). Tissue factor and thrombin also have

22    pro-inflammatory actions independent of coagulation functions (Chu, 2005); thus activation of

23    coagulation may lead to or potentiate inflammation.

24    The fibrinolytic system opposes these processes by facilitating the removal of a clot. The

25    fibrinolytic pathway is regulated by the ratio of tissue plasminogen activator (tPA) and plasminogen

26    activator inhibitor (PAI). Furthermore, the endothelial cell surface has antithrombotic properties due to the

27    expression of tissue factor pathway inhibitor (TFPI) and thrombomodulin (Mackman, 2005).

28    Inhibition of the fibrinolytic pathway, along with increased plasma viscosity, plasma fibrinogen and

29    Factor VII concentrations, contributes to a pro-thrombotic state (Gilmour et al., 2005). In acute lung

30    injury, vascular cells have enhanced procoagulant activity and impaired fibrinolytic activity (Gilmour et

1  al., 2005). In arterial atherosclerosis, tissue factor expression is increased within plaques. As a result,

2  spontaneous plaque rupture may trigger intravascular clotting (Karoly et al., 2007).

3  Acute phase responses also play a role in hemostasis by exerting procoagulant effects. Cytokines

4  such as IL-6 stimulate the liver to produce acute phase proteins including C-reactive protein (CRP),

5  fibrinogen and antiproteases (van Eeden et al., 2001).


# 5.3. Activation of the Autonomic Nervous System by Pulmonary Reflexes

6  Chemosensitive receptors, including rapidly activating receptors (RARs) and sensory C-fiber

7  receptors, are found at all levels of the respiratory tract and are sensitive to irritant particles as well as to

8  irritant gases (Coleridge and Coleridge, 1994; Widdicombe, 2006). Activation of these vagal afferents

9  cause central nervous system reflexes resulting in bronchoconstriction, mucus secretion, mucosal

10  vasodilation, cough, apnea followed by rapid shallow breathing and effects on the cardiovascular system

11  such as bradycardia and hypotension or hypertension (Coleridge and Coleridge, 1994; Widdicombe and

12  Lee, 2001; 2006; 2003). Some evidence suggests that cardiovascular responses may be mediated

13  primarily by the C-fiber receptors (Coleridge and Coleridge, 1994) and that irritants in the lower

14  respiratory tract cause more pronounced cardiovascular responses than irritants in the upper respiratory

15  tract (Widdicombe and Lee, 2001).

16  Early experiments demonstrated that reflexes were mediated by cholinergic parasympathetic

17  pathways involving the vagus nerve and inhibited by atropine (Grunstein et al., 1977; Nadel et al., 1965a;

18  Nadel et al., 1965b). However more recent experiments have shown that noncholinergic mechanisms may

19  also be involved. For example, stimulation of C-fiber receptors can activate local nervous system reflexes.

20  These local axon pathways are responsible for secretion of neuropeptides and the development of

21  neurogenic inflammation (Widdicombe and Lee, 2001). It has been proposed that, in some cases,

22  neurogenic pulmonary responses can switch from their normally protective function to one that

23  perpetuates pulmonary inflammation (Wong et al., 2003). Differences in respiratory tract innervation

24  between rodents and humans suggest that C-fiber mediated neurogenic inflammation may be more

25  important in rodents than in humans (Groneberg et al., 2004; Widdicombe and Lee, 2001; 2003).

26  However the role of neurogenic inflammation in mediating pulmonary responses in humans is an active

27  area of investigation.

28  VR1 receptors represent a subset of neuropeptide and acid-sensitive irritant receptors which are

29  located on the sensory C-fibers which lie underneath and between lung epithelial cells. In addition, these

receptors are found on immune and non-immune airway cells. Recent research interest has focused on the role played by these receptors in mediating inflammation following exposure to PM (Veronesi and Oortgiesen, 2001). Exposure to PM has been shown to result in an immediate increase in intracellular calcium followed by the release of neuropeptides and inflammatory cytokines (Veronesi et al., 1999; 2000). In one study this response was found to be due to an intrinsic property of the particle core and was not metal-dependent (Oortgiesen et al., 2000), while in another study electrostatic charge was found to activate VR1 receptors (Veronesi et al., 2003). A recent study demonstrated PM-mediated activation of VR1 receptors which results in increases in intracellular calcium and apoptosis in epithelial cells (Agopyan et al., 2003).

At this time, it is not clear how activation of the autonomic nervous system by pulmonary reflexes may contribute to the kinds of altered conduction and/or repolarization properties of the heart which may be linked to arrhythmias (Figure 5-5). Pulmonary reflexes, as they are currently understood, initially lead to increases in parasympathetic tone. However decreased heart rate variability appears to be reflective of decreased parasympathetic tone and/or increased sympathetic tone. Thus activation of the autonomic nervous system by mechanisms other than pulmonary reflexes seems likely in response to PM. Very little is known about these putative alternative mechanisms although some new studies have focused on the role of CNS centers in regulating pulmonary and cardiovascular functions. Furthermore the effects of pre-existing alterations in the autonomic nervous system on PM responses are not understood.

# 5.4. Translocation of Ultrafine PM or Soluble PM Components

Ultrafine PM is small enough to be taken up by cells through endocytosis and transcytosis. Localization of ultrafine PM in macrophage mitochondria has been demonstrated by electron microscopy (Li et al., 2003). Whether particles are capable of crossing the epithelial barrier and reaching capillary endothelial cells or the circulation is in question (Figure 5-5). To date, the evidence for ultrafine or other PM size fractions accessing the circulation by traversing this barrier is not convincing (see Chapter 4). However, macrophage-associated particles may be transported to the lymph nodes and gastrointestinal system and gain access to the circulation by an alternate mechanism.

Soluble components from all size fractions of PM have the potential to translocate across the alveolar-capillary barrier into the circulation (Figure 5-5). Possible mechanisms involved in translocation include paracellular pathways and metal transporters. Wallenborn et al. (2007) demonstrated the rapid appearance of water-soluble metals in the blood, heart and liver following intratracheal instillation of oil

combustion PM in rats (see Chapter 4). Similarly, Gilmour et al. (2006b) demonstrated the rapid appearance of zinc in the plasma of rats intratracheally instilled with zinc sulfate. Soluble zinc was also associated with cardiac effects following intratracheal instillation of rats with zinc-containing PM (Kodavanti et al., 2008). Inhalation studies involving concentrations of PM relevant to ambient exposures have not yet demonstrated the translocation of soluble components.

Interaction of circulating PM or soluble PM components with vascular endothelial cells, platelets, and other leukocytes is a potential mechanism underlying the cardiovascular effects of inhaled PM. A role for PM-derived ROS and/or cellular-derived ROS has been proposed. Furthermore, soluble metals which do not redox-cycle may activate cell signaling pathways without the generation of ROS. In this way PM may promote adverse cardiovascular effects such as endothelial dysfunction, atherosclerosis and thrombosis. Circulating PM or soluble PM components also have the potential to impact other organ systems.

## 5.5. Disease of the Cardiovascular and Other Organ Systems

As discussed above, deposition of PM in the lung may lead not only to pulmonary disease but also to diseases of other systems (Figure 5-5). In the cardiovascular system, myocardial ischemia and MI may occur as a result of the above proposed effects on atherosclerosis, plaque instability, thrombosis, plaque rupture and/or altered vasoreactivity of coronary vessels. Myocardial ischemia and MI may alter the conduction and depolarization properties of the heart and lead to arrhythmic events. In addition, thrombosis may lead to stroke and/or thromboembolic disease. At this point, it seems that many of these processes are interlinked and that responses to ambient PM exposures may involve multiple mechanisms simultaneously with some variability depending on PM composition.

## 5.6. Results of New Inhalation Studies which Contribute to Modes of Action

Prior to this review, much of the evidence for the proposed modes of action was obtained from animal studies involving intratracheal instillation or inhalation of high concentrations of PM and from cell culture experiments. In many cases, the types of PM used were of questionable relevance to ambient exposures (i.e. ROFA, metals, ambient PM collected on filters). Since then, many inhalation studies have been conducted using CAPs, combustion-derived PM and BC, generally using concentrations of PM

1    lower than 1 mg/m$^3$. Much of this research has been conducted in animal models of disease. These key

2    new studies, described in detail in Chapters 6 and 7, add to the understanding of modes of action which

3    are relevant to ambient PM exposure. A compilation of pertinent results is found below.

4    ▪    Mild pulmonary inflammation in response to short-term exposures to CAPs and combustion-
5         derived PM.

6    ▪    Pulmonary, cardiovascular and systemic oxidative stress in response to CAPs, combustion-
7         derived PM and "inert particles."

8    ▪    Antioxidant intervention which ameliorates PM effects on oxidative stress, allergic responses,
9         and airway hyperresponsiveness.

10   ▪    Altered lung function including respiratory frequency and airway responsiveness following
11        short-term exposures to CAPs and combustion-derived PM.

12   ▪    Allergic sensitization and exacerbation of allergic responses, in response to CAPs and
13        combustion-derived PM.

14   ▪    Increased susceptibility to respiratory infection following exposure to diesel PM.

15   ▪    Effects on nasal epithelial mucosubstances, airway morphology and airway mucosubstances
16        in chronic studies using roadside air and woodsmoke.

17   ▪    Effects on lung development in chronic studies using roadside air.

18   ▪    A role for irritant receptors in activating local neural and CNS reflexes through
19        parasympathetic pathways following short term exposure to CAPs and diesel PM.

20   ▪    A role for TRPV1 irritant receptors in mediating lung and heart oxidative stress through
21        increased parasympathetic and sympathetic activity in response to CAPs.

22   ▪    Altered heart rate variability in response to CAPs and combustion-derived PM.

23   ▪    Arrhymthmic events in response to CAPs.

24   ▪    Decreased cardiac contractility following short-term exposure to PM

25   ▪    Enhanced myocardial ischemia in response to CAPs.

26   ▪    Endothelial dysfunction and altered vascular reactivity in response to short- and long-term
27        exposure to CAPs.

28   ▪    Increased levels of blood coagulation factors following short-term PM exposures.

- Progression of atherosclerosis and induction of tissue factor in aortic plaques following long-term exposure to CAPs.

- CNS responses following short- and long-term exposures to CAPs.

- DNA adducts in lung and liver and heritable DNA mutations in germ line cells in long-term studies involving roadside air.

However new studies do not provide a complete picture of the biological pathways involved in mediating PM effects. In fact, there is a lack of information regarding the time-dependence of many of the responses which makes it difficult to understand the underlying biological mechanisms. Other existing gaps in knowledge include:

- Effects of ambient PM exposures on epithelial barrier function in the lung.

- The putative modulation of neural reflexes involving vagal parasympathetic pathways by pre-existing disease or other factors.

- The putative role of other neural reflexes besides vagal parasympathetic pathways.

- The putative role of endothelin in altering vasomotor tone following PM exposure.

- The putative translocation of PM or soluble components across the epithelial barrier of the lung into the circulation.

- The putative translocation of PM from olfactory epithelium to the olfactory bulb and other brain regions.

# Chapter 6. Integrated Health Effects of Short-Term PM Exposure

## 6.1. Introduction

1    This chapter summarizes, reviews and integrates the evidence of relationships between short-term

2    exposures to PM and a variety of health-related endpoints. Cardiovascular and respiratory health effects

3    of short-term exposure to various size fractions and sources of PM have been examined in an expansive

4    number of epidemiologic, human clinical and toxicological studies. In addition, there is a large body of

5    literature evaluating the relationship between mortality and short-term exposure to PM. The association

6    between PM exposure and central nervous system function has also been assessed, although far fewer

7    studies are available. The research approaches used to evaluate health effects of PM exposure are

8    described in Section 1.5 along with advantages and limitations of the various study types. Chapter 5

9    provides an overview of the potential pathophysiological pathways and modes of action underlying the

10   PM-induced health effects observed in animal and human studies. Evidence from the scientific literature

11   of specific cardiovascular and systemic effects, respiratory effects, and central nervous system effects

12   associated with exposure to PM are presented in Sections 6.2, 6.3, and 6.4, respectively. More detailed

13   descriptions of each study evaluated for this assessment are presented in Annexes C, D, and E. Evidence

14   of associations between short-term exposure to PM and mortality are described in Section 6.5, along with

15   causal determinations of mortality by PM metric (Section 6.5.3). The chapter concludes with a

16   preliminary evaluation of PM-induced health effects attributable to specific constituents or sources

17   (Section 6.6).

18   Findings for cardiovascular and respiratory effects are presented by specific endpoint or measure of

19   effect, leading from more subtle health outcome measures (e.g., heart rate variability [HRV]) to the more

20   severe, such as hospitalization for cardiovascular disease. Conclusions from the 2004 PM AQCD are

21   briefly summarized at the beginning of each section, and the evaluation of evidence from recent studies

22   builds upon what was available during the previous review. For each health outcome, results are

23   summarized for studies from the specific scientific discipline, i.e., epidemiologic, human clinical, and

24   toxicological studies. The sections conclude with summaries of the evidence on the various health

25   outcomes and integration of the findings that leads to conclusions regarding causality based upon the

26   framework described in Chapter 1. Determination of causality is made for the overall health effect

27   category, such as cardiovascular effects, with coherence, consistency and plausibility being based upon

the evidence from across disciplines and also across the suite of related health outcomes. In these summary sections for cardiovascular and respiratory morbidity, the evidence is summarized and independent conclusions drawn for relationships with $PM_{10}$, $PM_{10-2.5}$, $PM_{2.5}$, and ultrafine particles (Sections 6.2.11 and 6.3.9, respectively). Evidence of central nervous system effects is also divided by scientific discipline (Section 6.4), however, the lack of data does not allow for informative summaries of effect by PM metric.

# 6.1.1. Methodological Considerations

## 6.1.1.1. Epidemiologic Studies

Although the multicity studies analyzed in the 2004 PM AQCD reported an association between short-term exposure to $PM_{10}$ and mortality, these studies also found large spatial heterogeneity in city-specific excess risk estimates. Similar results have also been observed for studies that analyzed other health outcomes (e.g., respiratory and cardiovascular hospital admissions and mortality associated with long-term exposure). The reasons for such variation in effects estimates were not well understood, but factors likely contributing to the apparent heterogeneity between cities have been identified, including, but not limited to geographic differences in: (1) air pollution mixtures; (2) composition and sources of ambient PM; and (3) personal and sociodemographic factors potentially affecting PM exposure (e.g., air conditioning use). Overall, studies published at that time provided insufficient information to adequately examine the factors that contribute to the heterogeneity observed in effect estimates.

Copollutants have generally been considered as potential confounders or effect modifiers of the health effect attributed to a specific air pollutant. The 2004 PM AQCD conducted a detailed examination of confounding and effect modification of mortality and morbidity effect estimates due to copollutants. The overall evidence tended to support the conclusion that short-term exposure to ambient $PM_{10}$ and $PM_{2.5}$ is most clearly associated with mortality and morbidity effects, acting either alone or in combination with other covarying gaseous pollutants, with more limited support for $PM_{10-2.5}$. The results from multicity studies suggested that PM-mortality/morbidity associations were generally robust to the inclusion of copollutants. This draft ISA presents results from epidemiologic studies that report multipollutant model results.

Epidemiologic studies have used a variety of approaches to control for weather effects (i.e., meteorological variables) to disentangle the true effect due to PM. Various studies were identified that appear to demonstrate increased PM-related mortality/morbidity risks beyond those attributed to weather influences alone. However, similar to the issues surrounding models developed to control for

1    potential confounding, a clear consensus was not reached as to what constitutes an appropriate or

2    adequate model to control for possible weather contributions to the mortality/morbidity effects attributed

3    to PM exposure. In addition, it was unclear on how best to characterize possible joint (interactive) effects

4    of weather and ambient PM or other air pollutants on mortality.

5         To date, epidemiologic studies have used various lag structures to examine the association between

6    air pollution and health effects. The maximum effect sizes for mortality due to short-term exposure to PM

7    have often been reported for 0-1 day lags, but evidence is beginning to suggest that more consideration

8    should be given to lags of several days (e.g., distributed lags). It has also been hypothesized that different

9    PM size or chemical components may produce effects by different mechanisms manifested at different

10   lags, but limited data was available to substantiate these claims.

11        The majority of studies analyzed in the 2004 PM AQCD that examined the association between

12   short-term exposure to PM and mortality/morbidity used time-series analyses. Although the time-series

13   study design allows for a detailed analysis of the affect of daily fluctuations in PM levels on

14   mortality/morbidity, complex modeling is required to control for seasonal variation, time trends, and slow

15   time varying confounders. To date, a clear consensus as to the extent of modeling required to accurately

16   measure PM-mortality/morbidity effects has not been reached. The case-crossover study design was

17   developed as an alternative to using complex models to control for confounders. Some of the control

18   selection procedures that have been used in case-crossover studies include 'unidirectional' control

19   selection (i.e., control periods all before the case/hazard period), 'bi-directional' control selection

20   (i.e., control periods equally spaced before and after the case period [e.g. 7 days]), and 'time-stratified'

21   control selection (i.e., control periods in the same calendar month). Although the 2004 PM AQCD did not

22   conclude, which control/referent selection procedure should be used, a recent comprehensive review by

23   Janes et al. (2005) examined each of the control/referent selection strategies used in case-crossover

24   studies of air pollution, and recommended the use of the time-stratified control selection procedure for use

25   in all future case-crossover air pollution studies (Janes et al., 2007).

26        Although the majority of studies only analyzed the association between short-term exposure to

27   ambient levels of PM and mortality, some multi- and single-city studies also conducted analyses to

28   examine the presence of a threshold. Overall, the results from large multicity studies suggest that strong

29   evidence does not exist for a clear threshold for PM mortality/morbidity effects. However, some

30   single-city studies suggest a hint of a threshold, but not in a statistically clear manner. As a result, the PM

31   AQCD concluded that more data is needed to answer the question of whether a threshold exists, but the

32   use of linear PM effect models appears to be appropriate.

33        Lastly, the 2004 PM AQCD examined the role of measurement error in time-series epidemiologic

34   studies using a simulation study and mathematical analyses. The simulation study indicated that "transfer

of effects" (i.e., the effects of one pollutant are inappropriately attributed to another in multi-pollutant

models) occurred when the correlation between the true predictor and the confounder was very high (r $\geq$

0.90) with the true predictor having moderate error ($\sigma > 0.5$) and the confounder having no error, but

transfer of effects lessened as the confounder became subject to error (U.S. EPA, 2006b). The

mathematical analyses found that only under unusual circumstances (i.e., true predictors having high

positive or negative correlation; substantial measurement error; or extremely negatively correlated

measurement errors) did weak predictors appear stronger than true predictors. It was concluded that some

of the conditions reported that could potentially lead to the transfer of effects have not been observed in

actual air pollution data.

With regard to issues surrounding the design of air pollution epidemiologic studies the 2004 PM

AQCD concluded: (1) heterogeneity exists between cities, which can primarily be attributed to personal

and sociodemographic factors, and PM sources/composition; (2) although evidence supports the

conclusion that short-term exposure to $PM_{10}$ and $PM_{2.5}$ (and to a lesser extent $PM_{10-2.5}$) alone or in

combination with gaseous copollutants are associated with mortality/morbidity, it still remains unclear

which statistical methods should be used to identify potential confounding, and insufficient information is

available to examine the effect modification of PM by copollutants; (3) a consensus has not been reached

as to the best approach to control for meteorological effects or the joint (interactive effects) of weather

and air pollutants on mortality/morbidity; (4) although the previous review did not conclude which

control/referent selection procedure should be used in the case-crossover study design, the time referent

approach has gained increasing credibility; (5) the maximum mortality/morbidity effect size attributed to

PM has been observed for 0-1 day lags with lags of multiple days possibly showing the greatest effects,

and limited data exists to examine the lags associated with PM size and chemical components; (6) the

results from single- and multicity studies suggest that it seems appropriate to use a linear threshold during

the examination of mortality effects attributed to PM exposure; and (7) measurement error, specifically

the "transfer of effects," has only been observed in simulations and mathematical analyses under unusual

circumstances, which some have not been reported in real world scenarios.

## 6.1.1.2. Experimental Studies

### CAPs

The Methodological Considerations Section of Chapter 7 in the 2004 PM AQCD provides a brief

discussion of particle concentrators used in concentrated ambient particles (CAPs) studies. Particle

concentrators enable human subjects, animals, or cell culture systems to be exposed to atmospheric PM at

concentrations much greater than that observed under ambient conditions. As ambient PM is just one

1   component of a complex mixture that interacts with gases and other aerosols, CAPs systems provide a

2   method of exposing subjects to the particle phase. Gases (such as $O_3$ and $SO_2$) are not concentrated nor

3   are thoracic coarse particles (except for the coarse particle concentrator) and only certain systems are

4   capable of concentrating ultrafine PM. In ultrafine CAPs systems, increased number fraction of organic

5   carbon and PAHs, along with decreased relative percentage of EC particles have been reported in

6   concentrated PM compared to ambient PM (Su et al., 2006). These data suggest that for ultrafine

7   concentrators, the CAPs do not accurately reflect atmospheric ultrafine composition. There are several

8   instrument systems used to concentrate ambient PM in controlled human or animal exposure studies

9   (Gordon et al., 1999; Maciejczyk et al., 2005; Sioutas et al., 1995; Sioutas et al., 1997; Sioutas et al.,

10   1999).

11       The system developed by Sioutas et al. (1995) and Sioutas et al. (1997) was based on a series of

12   three virtual impactors, and concentrates ambient particles in the aerodynamic size range from 0.15 μm to

13   2.5 μm by a factor of 25-30. Ultrafine PM cannot be effectively concentrated by the system. Sioutas et al.

14   (1997) evaluated the system and reported that the concentration factors for particles in different size

15   ranges were different (23.3 ± 0.7 for 0.15-0.25 μm, and 26.9 ± 1.0 for 1.0-2.5 μm) as a result of the

16   different collection efficiencies for particles with different sizes. In addition, Sioutas et al. (1997)

17   observed a similar concentration factor for nitrate, which is similar to sulfate and fine PM mass. However,

18   the sampling artifact of nitrate on Teflon filters was not examined during the evaluation study, and

19   therefore, the loss of semi-volatile PM components during concentration was not clear. Furthermore, the

20   increase in PM concentration could potentially increase particle losses through coagulation and therefore

21   change particle size distribution; and the large pressure drop through the virtual impactors might change

22   the surface properties of a particle constituent without changing its bulk profile.

23       The method developed by Gordon et al. (1999) are based on a cyclone, and can concentrate

24   ambient PM in the aerodynamic size range of 0.5-2.5 μm by a factor of 10. Similar to Sioutas et al.

25   (1995), the system can not effectively concentrate ultra-fine PM. Concentration factors for PM with

26   different sizes, and therefore the particle size distribution for CAPs, were observed to be a function of the

27   system tuning conditions. Cautions need to be exercised when comparing CAPs produced under different

28   instrument conditions.

29       An ultrafine PM concentrating system was developed by Sioutas et al. (1999) and Maciejczyk et al.

30   (2005). The system was based on the Condensation Particle Counter (CPC) theory to let a particle grow

31   until the inertia force could effectively function on the particle, so that the grown particles could be

32   concentrated by the two systems mentioned above. After concentration, excess water on particles was

33   removed and particles shrunk to their original sizes. Sioutas et al. (1999) reported that the system could

34   effectively concentrate ultrafine particles, and no coagulation and nitrate evaporation was observed.

1  However, the results presented by Sioutas et al. (1999) suggested that the particle size distribution of

2  ultrafine PM could be changed after concentration under ambient conditions. Sioutas et al. (1999) also

3  suggested that the PM toxicity might be modified by the system due to the re-distribution of water soluble

4  components within a particle. In addition, it is possible that some of the physical properties, such as PM

5  surface properties and particle shape, could also be modified by the system.

6  A coarse particle concentrator has recently been developed by the civil engineering department of

7  the University of Southern California that consists of virtual impactors in parallel and can enrich ambient

8  $PM_{10-2.5}$ concentrations by a factor of 8–30 (Chang et al., 2002).

## *Human Clinical Study Advantages and Limitations*

9  Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants in a

10  highly controlled laboratory setting. Also referred to as human clinical studies, these experiments allow

11  investigators to expose subjects to fixed concentrations of air pollutants under carefully regulated

12  environmental conditions and activity levels. Controlled human   exposures to particulate matter typically

13  involve exposing subjects either at rest or while engaged in intermittent exercise in a whole-body

14  exposure chamber, although mouthpiece and facemask systems can also be used. A variety of different

15  types of particles are used in these studies including ambient outdoor particles, concentrated ambient

16  particles (CAPs), diesel exhaust from a diesel engine, wood smoke generated in a wood stove, laboratory

17  generated surrogate particles (e.g., elemental carbon or zinc oxide), or particles collected on a filter,

18  resuspended in saline, and administered either through instillation or inhalation (aerosolized and delivered

19  using a nebulizer). The recovery of particles on filters is variable and some components, such as organics,

20  may be too volatile to be collected. Exposures to processed emission artificially generated particles may

21  provide important information on the health effects of particulate matter, but are not truly representative

22  of ambient air pollution particles. The direct exposure of humans to ambient air pollution particles may be

23  complicated by factors that cannot be controlled such as co-exposures to other air pollutants (e.g., $O_3$,

24  $SO_2$, and $NO_2$). In concentrating ambient particulates, gaseous co-pollutants are not proportionately

25  concentrated and interactions between PM and the co-pollutants cannot be investigated unless the latter

26  are re-introduced. These limitations as well as daily variability in concentration and composition can

27  make it difficult to compare the results of human clinical studies employing particles from different

28  sources.

29  Human clinical studies are valuable in characterizing the associations observed in epidemiologic

30  studies between exposure to particulate matter and a given health endpoint. In some instances, these

31  studies can also be used to characterize concentration-response relationships at pollutant concentrations

32  relevant to ambient conditions. Controlled human exposures are typically conducted using a randomized

crossover design with subjects exposed both to PM and a clean air control. In this way, subjects serve as their own controls, effectively controlling for many potential confounders. However, human clinical studies are limited by a number of factors including a small sample size and short exposure time. The repetitive nature of ambient PM exposures may lead to cumulative health effects, but this type of exposure is not practical to replicate in a laboratory setting. In addition, although subjects do serve as their own controls, personal exposure to pollutants in the hours and days preceding the controlled exposures may vary significantly between and within individuals. Finally, human clinical studies require investigators to adhere to stringent health criteria for a subject to be included in the study, and therefore the results cannot necessarily be generalized to an entire population. Although some human clinical studies have included health comprised individuals such as asthmatics or individuals with COPD or coronary artery disease, these individuals must also be relatively healthy and do not represent the most sensitive individuals in the population.

## Selection Criteria for Key Toxicological Studies

The majority of toxicological studies highlighted in the text were selected if the exposure route was inhalation and the exposure concentration was within 3 orders of magnitude of ambient PM concentrations. Most of these studies utilized ambient particles (including CAPs, PM collected on filters, or PM obtained from soil or road surfaces) or diesel exhaust; the remainder of studies utilized gasoline emissions, wood smoke, residual oil fly ash, carbon black, or titanium dioxide ($TiO_2$). A few studies were included that employed intratracheal instillation techniques, mainly for thoracic coarse PM studies in rodents, new emerging areas of investigation (e.g., vasoreactivity, relative toxicity of different size fractions, etc.), or in attempts of elucidating specific pathways or mechanisms of response. Only a select number of in vitro studies that examined pulmonary toxicity were included and studies that looked at direct particle effects on cardiac or vascular cells were excluded, as their relevance based on the current state of knowledge regarding particle translocation is unclear. All toxicological studies examined for inclusion in the PM ISA are included in Appendix D.

## Apolipoprotein E knockout mouse

Atherosclerosis and related pathways has been studied primarily in the Apolipoprotein E (ApoE) knockout mouse. Developed by Nobuyo Maeda's group in 1992 (Piedrahita et al., 1992; Zhang et al., 1992), the ApoE$^{-/-}$ mouse and related models have become the workhorse of atherosclerosis research over the past 15 years. The ApoE molecule is involved in the clearance of fats and cholesterol. When ApoE (or the LDL receptor) is deleted from the genome, mice develop severely elevated lipid and cholesterol profiles; ApoE$^{-/-}$ mice on a high-fat ("Western") diet exhibit cholesterol levels exceeding 1000 mg/dl

1    (normal is ~150 mg/dl) (Huber et al., 1999; Moore et al., 2005). As a result, the lipid uptake into the

2    vasculature is increased and the atherosclerotic process is dramatically hastened. Furthermore, the LDLs

3    in ApoE$^{-/-}$ mice are highly susceptible to oxidation (Hayek et al., 1994), which may be a crucial event in

4    the air pollution-mediated vascular changes.


# 6.2. Cardiovascular and Systemic Effects

## 6.2.1. Heart Rate and Heart Rate Variability

5    Heart rate (HR), HRV, and BP are all regulated, in part, by the sympathetic and parasympathetic

6    nervous systems. Changes in one or more may increase the risk of cardiovascular events (e.g.

7    arrhythmias, myocardial infarction, etc.). Decreases in HRV have been associated with cardiovascular

8    mortality/morbidity in older adults and those with significant heart disease (TFESCNASPE, 1996).

9    HRV is measured using electrocardiograms (ECG) and can be analyzed in the time domain (e.g.

10   standard deviation of all NN intervals [SDNN], square root of the mean squared successive NN interval

11   differences [r-MSSD]), and/or the frequency domain measured by power spectral analysis (e.g. high

12   frequency [HF], low frequency [LF], ratio of LF to HF [LFHFR]). SDNN generally reflects the overall

13   modulation of HR by the autonomic nervous system, whereas r-MSSD generally reflects parasympathetic

14   activity and high frequency variations in HR. Thus, r-MSSD is generally well correlated with HF, which

15   also reflects the parasympathetic modulation of HR. LF primarily reflects sympathetic modulation of HR,

16   but may also estimate the contribution of both sympathetic and parasympathetic influences on HRV. Thus

17   LFHFR is thought to estimate the ratio of sympathetic influences on HR to parasympathetic influences.

18   While HRV is commonly described as being a reflection of vagal and adrenergic input to the heart,

19   there is clearly a more complex phenomenon reflected in HRV parameters. Rowan et al. (2007) provide a

20   review of HRV and its use and interpretation with respect to air pollution studies. To summarize, HRV

21   indices are excellent measures of extrapulmonary effects from inhaled pollutants, but the characterization

22   of the acute, reversible responses as being either parasympathetic or sympathetic in origin, much less

23   predictive of some adverse outcomes such as ventricular arrhythmia, is relatively unsupported by the

24   clinical literature. This is consistent with the 2004 PM AQCD which stated that there is inherent

25   variability in the minute-to-minute spectral measurements, but long-term HRV measures demonstrate

26   excellent day-to-day reproducibility (U.S. EPA, 2004).

27   The 2004 PM AQCD presented limited evidence of PM-induced changes in HRV. However,

28   findings from epidemiologic, human clinical and toxicological studies were seemingly contradictory, with

1 reports of both decreases and increases in HRV following PM exposure. Recent epidemiologic studies

2 have demonstrated a more consistent decrease in HRV (SDNN and r-MSSD), which is supported by

3 several human clinical studies published since 2003. In these studies, decreases in HRV were observed in

4 HRV among healthy adults following short-term exposures to $PM_{2.5}$ and $PM_{10-2.5}$ CAPs. It is interesting to

5 note that these effects were not observed in adults with asthma or COPD. The effect of PM on HRV

6 observed in animal toxicological studies continues to vary greatly, which may be due in part to strain

7 differences in baseline HRV.

### 6.2.1.1. Epidemiologic Studies

8 The 2004 PM AQCD reviewed several studies of PM exposure and HR or HRV and decribed

9 discrepant findings across studies (U.S. EPA, 2004). Several studies have investigated the association

10 between acute changes in multiple HRV parameters and ambient air pollutant concentrations in the U.S.,

11 Canada, Europe, Mexico, and Asia. Features and results of these studies are presented in Table 6-1, and

12 are summarized below.

13 In a multicity study, Liao and colleagues (2004) used data from the fourth cohort evaluation of the

14 Atherosclerosis Risk in Communities (ARIC) Study (1996-1998) (Liao et al., 2004). The 6784 subjects

15 were 45-64 years of age and lived in either Washington County, MD, Forsyth County, NC, or the suburbs

16 of Minneapolis, MN. The mean $PM_{10}$ concentration during the study is shown in Table 6-1. At each HRV

17 measurement session, each subject rested comfortably for 15 mins in the supine position in a quiet,

18 semi-dark room, with a constant temperature of 24°C. Then, resting, supine, 5-min beat-to-beat RR-

19 interval data were collected. All measurements were made between 8:30 a.m. and 12:30 p.m. Liao et al.

20 (2004) used linear regression models, adjusting for multiple covariates (i.e. age, ethnicity, gender,

21 education, smoking, body mass index, cardiovascular medications, presence of coronary heart disease,

22 diabetes, hypertension, HR, humidity, temperature, and season), to examine the change in HRV associated

23 with $PM_{10}$, $O_3$, $SO_2$, CO, and $NO_2$ concentrations in the 1-3 days prior to ECG measurement. Among all

24 subjects, each 11.5 μg/m$^3$ increase in mean daily $PM_{10}$ concentration 1 day before the ECG measurement

25 was associated with a 0.06 ms$^2$ decrease in log-transformed HF (95% CI: -0.10 to -0.02) and a 1.03 ms

26 decrease in SDNN (95% CI: -1.64 to -0.42). A smaller non-significant decrease was also observed for log

27 transformed LF. These HRV changes were larger among hypertensive subjects (Liao et al., 2004)

28 suggesting this may be a group particularly susceptible to the autonomic effects of PM.

29 Timonen et al. (2006) conducted a multicity panel study of n = 131 elderly subjects with stable

30 coronary heart disease who lived in 3 European cities (Amsterdam, Netherlands; Erfurt, Germany; or

31 Helsinki, Finland) (Timonen et al., 2006). They collected ECGs biweekly for six months in each subject.

32 This analysis, done as part of the ULTRA Study, examined changes in HRV (resting, paced breathing,

| 1 | supine, and five min beat-to-beat NN intervals) associated with changes in fixed monitor particulate |
| 2 | concentrations ($PM_{2.5}$, $PM_{10-2.5}$) with an emphasis on ultrafine particle counts (UFP; 0.01-0.1 μm |
| 3 | particles) and counts of accumulation mode particles (ACP; 0.1-1.0 μm particles). The mean city-specific |
| 4 | particulate concentrations are shown in Table 6-1. Mixed models adjusting for time trend, weekday, |
| 5 | humidity, barometric pressure, and temperature were first fit to estimate the change in HRV associated |
| 6 | with particulate (UFP, ACP, $PM_{2.5}$, and $PM_{10-2.5}$) concentrations on the same and previous four days in |
| 7 | each city. Then, in pooled analyses, the most consistent results were for LFHFR. During paced breathing, |
| 8 | each 10,000 particles/$cm^3$ increase in two day lagged UFP was associated with a 13.5% decrease in |
| 9 | LFHFR (95% CI: -20.1 to -7.1). Each 1000 particles/$cm^3$ increase in 1 day lagged ACP was associated |
| 10 | with a 7.8% decrease in LFHFR (95% CI: -13.0 to -0.2). Although not statistically significant, each |
| 11 | 10 μg/$m^3$ increase in 2 day lagged mean $PM_{10-2.5}$ concentration was associated with a 3.3% decrease in |
| 12 | LFHFR (95% CI: -12.7 to 6.1). For $PM_{2.5}$, however, results were not consistent across cities, and thus a |
| 13 | pooled estimate was not appropriate. $PM_{2.5}$ was associated with decreased HF power and increased |
| 14 | LFHFR in Helsinki, increased HF power and decreased LFHFR in Erfurt, and not associated with any |
| 15 | HRV metric in Amsterdam. The authors state that these contrasting city-specific $PM_{2.5}$ findings do not |
| 16 | clearly support a PM/HRV association, but suggest that effects may be dependent on PM sources and |
| 17 | subject characteristics in each city (Timonen et al., 2006). |
| 18 |     The association between HRV and short-term increases in PM was also examined in single-city |
| 19 | studies (Table 6-1). Among U.S. and Canadian cities, increases in $PM_{2.5}$ were generally associated with |
| 20 | decreased SDNN (Adar et al., 2007a; Chahine et al., 2007; Park et al., 2005b; Pope et al., 2004a; |
| 21 | Schwartz et al., 2005b) and/or decreased HF power (Adar et al., 2007a; Chahine et al., 2007; Park et al., |
| 22 | 2005b; Park et al., 2006b; Park et al., 2008a; Schwartz et al., 2005a), but not in all studies. Two studies |
| 23 | reported increased SDNN associated with $PM_{2.5}$ concentrations (Riediker et al., 2004b; Wheeler et al., |
| 24 | 2006a). Yeatts et al. (2007) also reported increased r-MSSD, SDANN5 (standard deviation of the average |
| 25 | of normal to normal intervals in all 5-min intervals in a 24-h period), and SDNN24HR (standard deviation |
| 26 | of the average of all normal to normal intervals in a 24-h period), and HF power associated with increased |
| 27 | $PM_{2.5}$ concentrations (Yeatts et al., 2007). |
| 28 |     Lipsett et al. (2006) reported significantly decreased SDNN associated with increases in 2- and 6-h |
| 29 | mean $PM_{10}$ and $PM_{10-2.5}$ concentrations (Lipsett et al., 2006). Similarly, Yeatts et al. (2007) reported |
| 30 | decreased r-MSSD, SDNN24HR, SDANN5, ASDNN5 (mean of the standard deviation in all 5-min |
| 31 | segments of a 24 h recording), proportion of NN intervals < 50 ms apart (pNN50; 7-min and 24-h), and |
| 32 | HF power ssociated with increased $PM_{10-2.5}$ concentration. |
| 33 |     Of those studies examining HRV associations with particle counts (Adar et al., 2007a; Park et al., |
| 34 | 2005b), only Adar et al. (2007a) found clear evidence of such effects. Decreased HRV was also associated |

1    with increases in ambient mean sulfate concentration (Luttmann-Gibson et al., 2006; Park et al., 2008a)

2    ambient mean BC concentration, (Park et al., 2005b; Park et al., 2008a; Schwartz et al., 2005b), and

3    traffic generated particles/pollution (Adar et al., 2007a). Riediker et al. (2004b) reported increased HRV

4    associated with traffic generated pollution (2004a; Riediker et al., 2004b).

5        Studies in Asia and Mexico have also reported decreased HRV associated with increases in PM

6    concentration (Chan et al., 2004; Chuang et al., 2005a; 2007b; Holguin et al., 2003; Romieu et al., 2005;

7    Vallejo et al., 2006). However, Riojas-Rodriguez et al. (2006) reported significantly decreased LF and HF

8    power associated with each 1 ppm increase in CO concentration, but only small non-significant decreases

9    associated with $PM_{2.5}$.

10       HRV studies investigated lagged pollutant concentrations from 2 h to 5 days before ECG

11   measurement, reporting effects associated with mean pollutant concentrations lagged as short as 1-2 h,

12   and more consistently lagged 24-48 h. Taken together, these international and U.S./Canadian studies show

13   decreases in HRV associated with PM in most studies that use SDNN (14 of 17), and most (12 of 19)

14   studies that use r-MSSD or HF power. However, these proportions may be inflated by publication bias

15   (i.e., studies showing little or no effects are not submitted for publication). Studies of HRV and PM

16   concentration are summarized in Table 6-1.

## HRV Studies Investigating Specific Mechanisms

17       Panel studies investigating PM/HRV associations have also been useful in investigating potential

18   mechanistic pathways by which PM may elicit a cardiovascular response. Romieu et al. (2005)

19   hypothesized that the omega-3 fatty acids in fish oil supplements would mitigate the adverse effects of

20   acute PM exposure on HRV. In a randomized controlled trial of n = 50 residents of a Mexico City nursing

21   home (aged >60 years), subjects were randomized to either 2 g/day of fish oil or 2 g/day of soy oil. They

22   used random-effects regression models to estimate the change in HRV associated with mean $PM_{2.5}$

23   concentration in the pre-supplementation and supplementation phases. In the group receiving the fish oil

24   supplement, each 8 $\mu g/m^3$ increase in 24-h mean total $PM_{2.5}$ exposure (weighted average of indoor and

25   outdoor $PM_{2.5}$ based on time activity diaries) was associated with a 54% reduction (95% CI: -72% to

26   -24%) in log transformed HF in the pre-supplementation phase. However, in the supplementation phase of

27   the trial, each 8 $\mu g/m^3$ increase in 24-h mean total $PM_{2.5}$ concentration was associated with only a 7%

28   reduction in log transformed HF (95% CI: -20% to 7%). Decreases in other HRV parameters associated

29   with $PM_{2.5}$ were also muted in the supplementation phase. In the group receiving the soy oil supplement,

30   the reduction in HF was also smaller in magnitude during the supplementation phase. However, among

31   those receiving the soy oil supplement, the differences between the pre-supplementation $PM_{2.5}$/HF change

32   and the supplementation $PM_{2.5}$/HF change were smaller compared to those receiving the fish oil, and were

1    not statistically significant (Romieu et al., 2005). Romieu et al. (2008) also report that omega-3

2    polyunsaturated fatty acids appear to modulate the adverse effect of $PM_{2.5}$ based on measured biomarkers

3    of oxidative response (see Section 6.2.9.1.).

4        By studying effect modification of the PM/HRV association by genetic polymorphisms, subject

5    characteristics, and chronic lead exposure, a series of analyses using data from the Normative Aging

6    Study has also provided mechanistic insights into the PM/HRV association (Chahine et al., 2007; Park et

7    al., 2005b; 2006b; 2008a; Schwartz et al., 2005a). Park et al. (2005b) studied the association between

8    short-term increases in ambient air pollution and changes in HRV using n = 497 males from the

9    Normative Aging Study (mean age 72.7 years) living in the Boston metropolitan area. Subjects had ECG

10   measurements made during a 4-min rest period between 8:00 a.m. and 1:00 p.m. Using linear regression

11   models, adjusted for age, BMI, fasting blood glucose, smoking, cardiac medications, room temperature,

12   and season. Park et al. (2005b) examined the association between HRV metrics and $PM_{2.5}$, $O_3$, $NO_2$, $SO_2$,

13   CO, BC, and particle number count moving averages in the previous 4, 24, and 48 h. They also estimated

14   the modifying effects of hypertension, diabetes, ischemic heart disease, and use of hypertensive

15   medications. Of the pollutants examined, only $PM_{2.5}$ and $O_3$ were associated with reductions in HRV, and

16   each pollutant's effect appeared independent of the other. Each 8 µg/m$^3$ increase in mean $PM_{2.5}$

17   concentration in the previous 48 h was associated with a 20.8% decrease in the component of HRV HF

18   (95% CI: -34.2% to -4.6%), with larger effects among subjects with hypertension, ischemic heart disease

19   (IHD), and diabetes. Ozone effects were strongest with the 4 h moving average. The authors state that

20   since BC concentrations were also associated with adverse changes in HRV, this suggests that traffic

21   pollution may be particularly toxic (Park et al. (2005b).

22       In further analyses of the Normative Aging Study cohort, Schwartz et al. (2005b) examined the

23   hypothesis that adverse changes in HRV due to PM are mediated by an oxidative stress response

24   (Schwartz et al., 2005a). They examined whether the change in the HF component of HRV associated

25   with each 10 µg/m$^3$ increase in 48 h mean $PM_{2.5}$ was modified by the presence or absence of the allele for

26   glutathione S-transferase M1 (GSTM1), use of statins, obesity, high neutrophil counts, higher BP, and/or

27   older age. In subjects without the GSTM1 allele and its protection against oxidative stress, each 10 µg/m$^3$

28   increase in 48 h mean $PM_{2.5}$ concentration was associated with a 34% decrease in HF (95% CI: -52% to

29   -9%). There was no association among those with at least one copy of the allele. Obesity and high

30   neutrophil counts also worsened the effect of PM on HRV regardless of allele (Schwartz et al., 2005a).

31       Park et al. (2006b) hypothesized that transition metals may be responsible for PM/cardiorespiratory

32   effects (Park et al., 2006b). Again using the Normative Aging Study cohort, they investigated whether

33   subjects with two hemochromatosis (HFE) polymorphisms associated with increased iron uptake had a

34   smaller decrease in HF HRV associated with PM than those subjects without either variant. Each

1    10 μg/m$^3$ increase in 48 h mean PM$_{2.5}$ was associated with a 31.7% decrease in HF (95% CI: -48.1 to

2    -10.3%) among subjects without either polymorphism, but not among those with the two protective HFE

3    alleles (Park et al., 2006b).

4          Again using the Normative Aging Study cohort, Chahine et al. (2007) reported a 10.5% reduction

5    in SDNN (95% CI: -18.2% to -2.2%) associated with each 10 μg/m$^3$ increase in the mean 48 h PM$_{2.5}$

6    concentration among those without the GSTM1 allele, but only a 2.0% SDNN decrease (95% CI: -11.3%,

7    8.3%) in those with the allele. This confirmed the PM/HF HRV findings of Schwartz et al. (2005a).

8    Further, subjects with the long repeat polymorphism in the heme oxygenase-1 (HO-1) promoter had a

9    greater decline in SDNN associated with each 10 μg/m$^3$ increase in the mean 48-h PM$_{2.5}$ concentration

10   (-8.5%; 95% CI: -14.8% to -1.8%) than those with the short repeat polymorphism in HO-1 (7.4 %

11   increase; 95% CI: -8.7%, 26.2%). Again, this suggests that PM-HRV changes are mediated, in part, by

12   oxidative stress (Chahine et al., 2007).

13         Among those Normative Aging Study subjects with high chronic lead exposure as measured using

14   X-ray fluorescence of the tibia, each 7 μg/m$^3$ increase in mean PM$_{2.5}$ concentration in the previous 48 h

15   was associated with a 22% decrease in HF HRV (95% CI: -37.4% to -1.7%). Decreases in HF HRV were

16   also associated with each 2.5 μg/m$^3$ increase in mean sulfate concentration in the previous 48 h

17   (22% decrease; 95% CI: -40.4%, 1.6%) and each 16 ppb increase in mean ozone concentration in the

18   previous 48 h (38% decrease; 95% CI: -54.6% to -14.9%). The authors suggest that these findings are

19   consistent with an oxidative stress response (Park et al., 2008a). Although this series of studies suggest a

20   role of oxidative stress in these acute PM/HRV associations, replication by other investigators in other

21   cities and in other populations will aid interpretations of these findings.

### *Summary*

22         Omega-3 fatty acid was found to modulate the effect of PM on HRV in a randomized trial

23   conducted in Mexico City (Romieu et al., 2005). In addition, several analyses of data from the Normative

24   Aging Study have provided evidence that HRV is modulated by genetic polymorphisms related to

25   oxidative stress (Chahine et al., 2007; Park et al., 2006b; Schwartz et al., 2005b) or preexisting conditions

26   such as diabetes, IHD, and hypertension (Park et al., 2005b). Another analysis reports that the HRV-PM

27   association is more pronounced among those with chronic lead exposure (Park et al., 2008a).

**Table 6-1. Characteristics of epidemiologic/panel studies investigating associations between PM and changes in HRV.**

| | PM Type, Exposure Lag | Study Subjects | Ambient Concentration Mean (SD) ** | Recording Length | SDNN | LF | HF, r-MSSD | LFHFR |
|---|---|---|---|---|---|---|---|---|
| *U.S. AND CANADIAN STUDIES* | | | | | | | | |
| Park et al. (2005b) | $PM_{2.5}$, 48-h avg | 497 men (mean age = 73[7] years), Normative Aging Study Boston MA | 24-h: 11.4 (8.0) $\mu g/m^3$ | 4-min | ↓ | ↓ | ↓ | ↑ |
| | PN, 48-h avg | | 24-h: 28,942 (13,527) particles/$cm^3$ | | → | ↓ | ↓ | ↓ |
| | BC, 48-h avg | | 24-h: 0.92 (0.47) $\mu g/m^3$ | | ↓ | ↓ | ↓ | ↑ |
| Liao et al. (2004) | 24-h $PM_{10}$, lag 1-d | 6784 (mean age = 62[6] years), ARIC study: MD, NC, MN | 24.3 $\mu g/m^3$ | 5-min | ↓ | ↓ | ↓ | |
| Riedeker et al. (2004b) | In-vehicle $PM_{2.5}$ (mass) 9-h avg | 9 state troopers, NC | 9-h in-vehicle avg. 23 $\mu g/m^3$ | 10-min | ↓ | ↑ | → | ↑ |
| Schwartz et al. (2005b) | BC, 24-h | 28 (61-89 y), 12 wk follow-up, Boston, MA | 24-h Median: 1.0 $\mu g/m^3$ | 23-min | ↓ | | ↓ | ↑ |
| | $PM_{2.5}$, 24-h | | 24-h Median: 10 $\mu g/m^3$ | | ↓ | | ↓ | ↑ |
| | Secondary PM (estimated), 24-h | | 1-h Median: -1.7 $\mu g/m^3$ | | ↓ | | ↓ | ↑ |
| Yeatts et al. (2007) | 24-h $PM_{10-2.5}$ | 12 adult asthmatics, Chapel Hill, NC | 5.3 (2.8) $\mu g/m^3$ | 5-min | ↓ | ↓ | ↓ | |
| | 24-h $PM_{2.5}$ | | 12.5 (6.0) $\mu g/m^3$ | | ↑ | ↓ | ↑ | |
| Wheeler et al. (2006a) | $PM_{2.5}$, 4-h avg | 18 COPD, Atlanta, GA | 17.8 $\mu g/m^3$ | 20-min | ↑ | ↑ | ↑ | ↑ |
| | $PM_{2.5}$, 4-h avg | 12 MI, Atlanta, GA | | | ↓ | ↑ | ↓ | ↓ |
| | EC, 4 –h avg | 18 COPD, Atlanta, GA | 2.3 $\mu g/m^3$ | | ↑ | Not presented | Not presented | Not presented |
| | EC, 4 –h avg | 12 MI, Atlanta, GA | | | ↓ | Not presented | Not presented | Not presented |
| Dales (2004) | $PM_{2.5}$ 24-h avg (personal) | 36 CAD patients, Toronto, Canada | 19.9 (13.8) $\mu g/m^3$ | Not described | → | → | → | → |
| Luttmann-Gibson et al. (2006) | $PM_{2.5}$, lag 1-d | 32 (65+ y), Steubenville OH | 24-h: 19.7 $\mu g/m^3$ | ~30-min. | ↓ | ↓ | ↓ | |
| | Sulfate, lag 1-d | | 24-h: 6.9 $\mu g/m^3$ | | ↓ | ↓ | ↓ | |
| | Nonsulfate PM, lag 1-d | | 24-h: 10.0 $\mu g/m^3$ | | ↓ | ↓ | ↓ | |
| | EC, lag 1-d | | 24-h: 1.1 $\mu g/m^3$ | | ↑ | ↓ | → | |
| Adar et al. (2007b) | $PM_{2.5}$, 24-h avg | 44 (60+ y), diesel bus riders, St. Louis, MO | 7.7 $\mu g/m^3$ | 5-min. | ↓ | ↓ | ↓ | ↑ |
| | BC, 24-h avg | | 330 $ng/m^3$ | | ↓ | ↓ | ↓ | ↑ |
| | PC fine | | 42 particles/$cm^3$ | | ↓ | ↓ | ↓ | ↑ |
| | PC course | | 0.02 particles/$cm^3$ | | ↑ | ↑ | ↑ | ↓ |

| | PM Type, Exposure Lag | Study Subjects | Ambient Concentration Mean (SD) ** | Recording Length | SDNN | LF | HF, r-MSSD | LFHFR |
|---|---|---|---|---|---|---|---|---|
| Pope et al. (2004a) | 24-h PM$_{2.5}$ (FRM), lag 1-d | 88 subjects (65+ years of age; 250 p-days), Utah Valley | 23.7 (20.2) µg/m$^3$ | 24-h | ↓ | | ↓ | |
| Sullivan et al. (2005b) | PM$_{2.5}$, 1, 2, 24-h averages | 21 subjects (65+ years) with CVD, Seattle WA | Median:10.7 µg/m$^3$ | 20-min | → | | → | |
| | | 13 subjects (65+ years) w/out CVD, Seattle WA | | | → | | → | |
| Lipsett (2006) | PM$_{10}$, lag * | 19 CAD patients (65+ y), 12 wk fu, Coachella Valley, CA | 31.0 and 46.1 µg/m$^3$ | 5-min F domain; 2-h, 24-h T domain | ↓ | ↓ | ↓ | |
| | PM$_{10-2.5}$, lag* | | None given | | ↓ | ↓ | → | |
| | PM$_{2.5}$, lag* | | 14 & 23.2 µg/m$^3$ | | ↓ | ↓ | ↑ | |
| Ebelt et al. (2005) | PM$_{10}$ – 24 h | 16 subjects with COPD in Vancouver, Canada | 17 (6) µg/m$^3$ | 24-h | ↓ | | ↓ | |
| | PM$_{10-2.5}$ (calculated from PM$_{10}$ and PM$_{2.5}$ values) | | 5.6 (3.0) µg/m$^3$ | | ↑ | | → | |
| | PM$_{2.5}$ – 24-h | | 11.4 (4.6) µg/m$^3$ | | ↓ | | ↓ | |
| | PM$_{2.5}$ Sulfate – 24-h outdoor | | 2.0 (1.1) µg/m$^3$ | | ↓ | | → | |

*INTERNATIONAL STUDIES*

| | PM Type, Exposure Lag | Study Subjects | Ambient Concentration Mean (SD) ** | Recording Length | SDNN | LF | HF, r-MSSD | LFHFR |
|---|---|---|---|---|---|---|---|---|
| Timonen et al. (2006) | UF, lags 0-2 days | Stable CHD patients (65 years of age and older) n = 37: Amsterdam n = 47: Erfurt n = 47: Helsinki | Amsterdam: 17,300 particles/cm$^3$ Erfurt: 21,100 particles/cm$^3$ Helsinki: 17,000 particles/cm$^3$ | 5-min (Pooled estimates during paced breathing presented to the right) | ↓ | | ↑ | ↓ |
| | AC, lags 0-2 days | | Amsterdam: 2100 particles/cm$^3$ Erfurt: 1800 particles/cm$^3$ Helsinki: 1400 particles/cm$^3$ | | ↓ | | ↑ | ↓ |
| | PM$_{2.5}$, lags 0-2 days | | Amsterdam: 20.0 µg/m$^3$ Erfurt: 23.1 µg/m$^3$ Helsinki: 12.7 µg/m$^3$ | | ↓ | | ↑ | ↓ |
| | PM$_{10-2.5}$, 2-day lag | | Amsterdam: 15.3 µg/m$^3$ Erfurt: 3.7 µg/m$^3$ Helsinki: 6.7 µg/m$^3$ | | → | | → | ↓ |

| | PM Type, Exposure Lag | Study Subjects | Ambient Concentration Mean (SD) ** | Recording Length | SDNN | LF | HF, r-MSSD | LFHFR |
|---|---|---|---|---|---|---|---|---|
| Chan et al. (2004) | $NC_{0.02-1}$ 1-4 h | 9 adults (19-29) with lung function impairment Taipei, Taiwan | 23,407 (19,836) particles/cm³ | 5 min | ↓ | ↓ | ↓ | ↓ |
| | | 10 adults (42-79) with lung function impairment Taipei, Taiwan | 25,529 (20,783) particles/cm³ | | ↓ | ↓ | ↓ | ↓ |
| Chuang et al. (2005b) | $PM_{1.0-0.3}$ 1-4 h | 16 CHD hypertensive patients, Taipei Taiwan | 37.2 (25.8) µg/m³ | 5-min | ↓ | ↓ | ↓ | ↑ |
| | $PM_{2.5-1.0}$ 1-4 h | | 12.6 (7.8) µg/m³ | | ↓ | ↓ | ↓ | ↑ |
| | $PM_{10-2.5}$ 1-4 h | | 14.0 (11.1) µg/m³ | | ↓ | ↓ | ↓ | ↑ |
| | $PM_{1.0-0.3}$ 1-4 h | 10 CHD patients, Taipei Taiwan | 26.8 (25.9) µg/m³ | | ↓ | ↓ | ↓ | → |
| | $PM_{2.5-1.0}$ 1-4 h | | 10.9 (8.5) µg/m³ | | ↓ | ↓ | ↓ | ↓ |
| | $PM_{10-2.5}$ 1-4 h | | 16.4 (10.7) µg/m³ | | ↓ | ↓ | ↓ | ↑ |
| Holguin et al. (2003) | 24-h $PM_{2.5}$ | 21 without hypertension (60-96 years), Mexico City | 37.2 (13.5) µg/m³ | 5-min | | ↓ | ↓ | ↑ |
| | | 13 with hypertension (60-88 years), Mexico City | | | | ↓ | ↓ | ↑ |
| Romieu et al. (2005) | 24-h $PM_{2.5}$ (outdoor and indoor) | 50 nursing home residents 65+ y, Mexico City | Outdoor: 19.4 (5.7) µg/m³ Indoor: 18.3 (5.8) µg/m³ | 6-min (Indoor $PM_{2.5}$, pre-supplement phase presented) | ↓ | ↓ | ↓ | |
| Riojas-Rodriguez et al. (2006) | Personal $PM_{2.5}$ | 30 IHD patients, Mexico City | Geometric mean: 46.8 µg/m³ | 5-min | | ↓ | ↓ | |

Notes: Increases ('), decreases (") and no effects (') in HRV associated with PM concentration are indicated. Statistical significance was not necessary to categorize an effect as an increase or decrease.
For time domain measures moving average lags up to 24-h were explored. For frequency domain measures lags of 2-h, 4-h and 24-h were explored.
** All concentrations are means, unless otherwise noted.

## 6.2.1.2. Human Clinical Studies

1    The 2004 PM AQCD cited one study in which parasympathetic stimulation of HRV increased

2    relative to filtered air control following a 2-h exposure with intermittent exercise to fine concentrated

3    ambient particles (CAPs) (average concentration 174 µg/m³) in both healthy and asthmatic volunteers

4    (Gong et al., 2003a). This effect was observed immediately following the exposure and at 2-days

5    post-exposure, but not at 4-h post-exposure. Although not statistically significant, HRV (total power)

6    increased following exposure to filtered air and decreased following exposure to CAPs. Two new studies

7    have evaluated the effect of $PM_{2.5}$ CAPs (2-h exposures to concentrations of 20-200 µg/m³) on HRV in

8    elderly subjects (Devlin et al., 2003; Gong et al., 2004a). In both studies, subjects experienced significant

9    decreases in HRV following exposure to CAPs relative to filtered air exposures. Interestingly, Gong et al.

10    (2004a) found that decreases in HRV were more pronounced in healthy older adults than in those with

COPD. In another study, healthy and asthmatic adults were exposed to thoracic coarse CAPs (average concentration 157 $\mu g/m^3$) for 2 h with intermittent exercise (Gong et al., 2004b). HRV was not affected immediately following the exposure, but decreased in both groups at 4- and 22-h after the end of the exposure, with greater responses observed in non-asthmatics.

Several additional new human clinical studies have evaluated the effect of PM on HRV in healthy and health-compromised individuals. Beckett et al. (2005) exposed twelve resting, healthy adults for 2-h to filtered air and 500 $\mu g/m^3$ zinc oxide in the ultrafine (40.4 ± 2.7 nm) and fine (291.2 ± 20.2 nm) modes. Time and frequency domain parameters of HRV were analyzed immediately following exposure as well as at 3-, 6-, 11-, and 23-h post-exposure. Neither ultrafine nor fine zinc oxide produced a significant change in any measure of HRV when compared to filtered air. However, the relevance of zinc oxide to ambient pollutant particles is unclear.

In a random order crossover human clinical study, Routledge et al. (2006) examined the effects of ultrafine carbon particles (50 $\mu g/m^3$) alone and in combination with 200 ppb $SO_2$ on HRV among 20 healthy older adults (age 56-75), as well as 20 older adults with coronary artery disease (age 52-74). Five minute recordings of HRV data were obtained prior to and immediately following the 1-h exposure, as well as 3 h post-exposure. In healthy subjects, exposure to carbon particles resulted in small increases in RR-interval, SDNN, rMSSD, and LF power immediately following exposure compared to filtered air control. At 3 h post-exposure, there were no significant differences in HRV measures between carbon particle and filtered air exposures. Conversely, $SO_2$-induced decreases in HRV were observed at 3 h, but not immediately following exposure. Concomitant exposure to carbon particles and $SO_2$ followed a pattern similar to that observed with $SO_2$ alone, but did not reach statistical significance. Subjects with coronary artery disease did not experience any significant changes in HRV following exposure to either pollutant. The authors postulated that this lack of effect may be due to differences in medication between the two groups, as 70% of subjects with stable angina reported using beta blockers, which are known to increase cardiac vagal control. In this study, subjects were exposed to pollutants at concentrations similar to those experienced in urban areas and to which have been associated with mortality and hospital admissions. The lack of any significant reductions in HRV following exposure to carbon particles is an important finding, as it provides evidence to suggest that the health effects observed following exposure to PM may be due to particle constituents other than carbon.

Samet et al. (2007) recently compared the effects of 2-h exposures with intermittent exercise to ultrafine (average concentration 47 $\mu g/m^3$; mean size 0.049 $\mu m$), fine (average concentration 120 $\mu g/m^3$; mean size 0.65 $\mu m$), and thoracic coarse (average concentration 89 $\mu g/m^3$; mean size 3.59 $\mu m$) CAPs among healthy subjects between the ages of 18 and 35 years in Chapel Hill, North Carolina. In both the ultrafine and thoracic coarse studies, a crossover design was used in which each subject was exposed to

1    both PM and filtered air. In the case of the fine PM study, subjects did not serve as their own control, but

2    were exposed to either PM or filtered air (Ghio et al., 2000). Thoracic coarse fraction CAPs produced a

3    statistically significant decrease in SDNN 20 h after exposure compared with filtered air exposure. No

4    statistically significant effects on HRV were observed following exposure to ultrafine PM as measured

5    during controlled 5-min intervals. However, the authors did observe a significant decrease in SDNN

6    following exposure to ultrafine PM based on an analysis of the 24-h ambulatory measurements. No

7    differences were reported in HRV between fine PM exposures and exposures to filtered air. While the

8    methodologies, exposure criteria, and results have been published separately on the fine PM exposures

9    included in this investigation (Ghio et al., 2000), only a general summary of the results from the thoracic

10   coarse and ultrafine exposures are presented in Samet et al. (2007).

11       In a double-blind, crossover, controlled-exposure study, Peretz et al. (2008b) exposed three healthy

12   adult volunteers and 13 adults with metabolic syndrome while at rest to filtered air and two levels of DE

13   (fine PM concentrations of 100 and 200 $\mu g/m^3$) in 2-h sessions. HRV parameters were assessed prior to

14   exposure, as well as at 1-, 3-, 6- and 22-h following the start of exposure, and included both time domain

15   (SDNN and RMSSD) and frequency domain parameters (HF power, LF power, and the LFHFR ratio).

16   The authors observed an increase in HF power and a decrease in LFHFR 3 h after the start of exposure to

17   200 $\mu g/m^3$ relative to filtered air. Although these changes were statistically significant ($p < 0.05$) the

18   effects were not consistent among the study subjects. No other significant effect of DE on HRV was

19   observed at either concentration or time point. The authors attributed the lack of consistent effects to the

20   small and non-homogeneous population and the timing of measurement. There was no difference in either

21   baseline or diesel-induced changes in HRV parameters between normal individuals and patients with

22   metabolic syndrome, although the number of normal individuals was quite small (n = 3). It is unclear if

23   patients with metabolic syndrome were taking any medications. Gong et al. (2008) exposed healthy

24   (n = 17) and asthmatic (n = 14) adult volunteers to ultrafine CAPs (Los Angeles) for 2 h with intermittent

25   exercise. Relative to control (filtered air) exposures, UFP exposures (average mass = 100 $\mu g/m^3$, average

26   particle count = 145,000/$cm^3$) among healthy and asthmatic subjects were associated with a transient

27   decrease in LF power ($p < 0.05$) 2 h post-exposure.

28       The results of several new controlled human exposure studies provide limited evidence to suggest

29   that acute exposure to near ambient levels of PM may be associated with small changes in HRV. Changes

30   in HRV parameters, however, are inconsistent with some showing increased parasympathetic activity

31   relative to sympathetic activity and others showing the opposite. Although a direct comparison between

32   younger and older adults has not been made, PM exposure appears to result in a decrease in HRV more

33   consistently in healthy older adults (Devlin et al., 2003; Gong et al., 2004a).

## 6.2.1.3. Toxicological Studies

1    Toxicological studies that examined HR and HRV are presented in the 2004 PM AQCD and overall
2  demonstrated differing responses, which were collectively characterized as providing limited evidence for
3  PM-related cardiovascular effects (U.S. EPA, 2004). The studies described that reported HR or HRV
4  effects following PM exposure were conducted with a variety of particle types (CAPs, diesel, ROFA,
5  metals), exposure methods (inhalation and IT), and doses (100–3000 $\mu g/m^3$ for inhalation; up to 8.3
6  mg/kg for IT).

7    SH rats exposed to CAPs in Tuxedo, NY for 4 h (mean $PM_{2.5}$ concentration 73 $\mu g/m^3$; single-day
8  concentrations 80 and 66 $\mu g/m^3$; February and May, 2001, respectively) demonstrated decreased HR
9  when exposure groups were combined that returned to baseline values when exposure ceased (Nadziejko
10  et al., 2002). Fine or ultrafine sulfuric acid exposure (mean concentration 225 and 468 $\mu g/m^3$,
11  concentration range 119–299 and 140–750 $\mu g/m^3$, respectively) did not induce any HR effects. Another
12  study demonstrated a trend toward increased HR following a 1- or 4-day $PM_{2.5}$ CAPs exposure (Wistar
13  Kyoto rats; 4.5 h/day; Yokohama City, Japan; 5/2004, 11/2004, 9/2005) but the correlation between
14  change in HR and cumulative PM mass collected over the exposure period was not significant (Ito et al.,
15  2008).

16    Decreased SDNN was observed in SH rats exposed via nose-only inhalation to ultrafine CAPs for
17  two 5-h periods separated by 24 h in the spring (mean mass concentration 202 $\mu g/m^3$; $30 \times 10^5$
18  particles/$cm^3$; number concentration range $7.12 \times 10^3$–$8.26 \times 10^5$ particles/$cm^3$), but not the summer (mean
19  mass concentration 141 $\mu g/m^3$; mean number concentration $2.78 \times 10^5$ particles/$cm^3$; number concentration
20  range $7.76 \times 10^3$–$8.87 \times 10^5$ particles/$cm^3$) (Chang et al., 2005b). Each of the four animals served as their
21  own control and mixed effects models were used to determine statistical significance. The estimated mean
22  PM effects for the SDNN decreases from the start to the end of exposure were 85 to 60% of baseline,
23  respectively. CAPs effects on rMSSD were less remarkable.

24    Anselme et al. (2007) used a myocardial infarction model of CHF where the left descending
25  coronary artery of Wistar rats was occluded to induce ischemia. After 3 months of recovery, rats were
26  exposed to diesel emissions for 3 h (PM concentration 500 $\mu g/m^3$; $NO_2$ 1.1 ppm; CO 4.3 ppm) and
27  decreases in rMSSD were observed during the first 2-h of a 3-h diesel exposure, which returned to
28  baseline values for the last 1-h of exposure. Healthy rats also demonstrated decreased rMSSD when
29  measured over the entire exposure period. The duration of ventricular premature beat (VPB) attributable
30  to diesel exposure in CHF rats lasted much longer than the rMSSD change (>5 h post-exposure),
31  indicating that the HRV response was not driving the increased arrhythmia incidence.

1    A model of premature senescence has been developed by Tankersley et al. (2003), using aged AKR

2    mice whose body weight abruptly declines ~5 wk prior to death and is accompanied by deficiencies in

3    other vital physiological function including HR and temperature regulation. When exposed to carbon

4    black by inhalation (mean concentration 160 $\mu g/m^3$; 3 h/day × 3 day), terminal senescent mice responded

5    with robust cardiovascular effects, including bradycardia and increased HRV indices (rMSSD and SDNN)

6    (Tankersley et al., 2004). SDNN was also increased in healthy senescent mice exposed to carbon black.

7    Another measure of HRV, the LFHFR, was similarly elevated in healthy mice with carbon black exposure

8    compared to the near-terminal mice. These studies indicate that HR regulatory mechanisms are altered in

9    susceptible mice exposed to PM (sympathetic and parasympathetic changes in healthy senescent mice and

10   increased parasympathetic influence in terminally senescent mice), which may translate into lowered

11   homeostatic competence in these animals. Results from the near-terminal group should be interpreted

12   with caution, as only 3 mice were in this group.

13   Subsequent research with similar exposure protocols (mean carbon black concentration 159 $\mu g/m^3$;

14   3 h) as the above study used C57BL/6J and C3H/HeJ mice to determine whether an acute PM challenge

15   can modify HR regulation in two mice strains with differing baseline HR (Tankersley et al., 2007).

16   Besides the higher HR and lower SDNN and rMSSD in C3H/HeJ compared to C57BL/6J, there were no

17   carbon black-related changes in HR or HRV. When the C57BL/6J mice (average HR ~80 bpm lower than

18   C3H/HeJ) were given propanolol (a sympathetic antagonist), carbon black exposure caused an increase in

19   HR and decrease in rMSSD compared to air during the last 2-h of exposure, indicating withdrawal of

20   parasympathetic tone. The authors recognize that there may be differences in regional particle deposition

21   based on strain-specific breathing patterns, which may partially explain the variable HR with carbon

22   black exposure. Despite this potential shortcoming, this study revealed that inherent autonomic tone,

23   which is genetically varied between these mouse strains, may affect cardiovascular responses following

24   PM exposure. In extrapolating these results to humans, individual variation in genetic factors likely plays

25   some role in PM-induced adjustments in HR control via the ANS.

26   A recent study in mice (C3H/HeJ, C57BL/6J, and C3H/HeOuJ) examined the effects of a 2-h ozone

27   (mean concentration 0.584 ppm) pretreatment followed by a 3 h exposure to carbon black (mean

28   concentration 536 $\mu g/m^3$) on HR and HRV measures (Hamade et al., 2008). Data from the both C3H

29   strains were combined because there were no statistically detectable differences in responses. HR

30   decreased to the greatest extent during ozone pre-exposure for C3H and C57BL/6J mice that were then

31   exposed to carbon black. The percent change in SDNN and rMSSD were increased in C3H mice during

32   ozone pre-exposure and carbon black exposure compared to the filtered air group; however, these HRV

33   parameters gradually decreased over the duration of the experiment and appeared to be ozone dependent.

34   Together, these findings led to the conclusion that increases in parasympathetic tone and/or decreases in

1 sympathetic input may explain the observed bradycardia. In a subset of all mice pre-exposed to ozone,

2 rMSSD remained significantly elevated during the carbon black exposure compared to filtered air. The

3 results from this study confirm what was observed in Tankersly et al. (2007) in that genetic determinants

4 affect HR regulation in mice with exposure to air pollutants.

5      In summary, both increases and decreases in HR have been observed in rats or mice following PM

6 exposure. Fine or ultrafine sulfuric acid did not result in HR changes in SH rats. Similarly, decreased

7 SDNN was reported for ultrafine CAPs exposure, but only in the spring and lowered rMSSD was

8 observed with diesel exposure. In near-terminal senescent mice, HRV responses were robust following

9 carbon black exposure and represented increased parasympathetic influence. Strain differences in baseline

10 HR and HRV likely contribute to PM responses. HRV changes with preexposure to ozone and carbon

11 black appeared to be ozone dependent, although rMSSD remained elevated during PM exposure.

## Source Apportionment and PM Components

12      An additional analysis of CAPs data (Chen and Hwang, 2005; Hwang et al., 2005) was conducted

13 to link short-term HR and HRV effects to major PM source categories using source apportionment

14 methodology (Lippmann et al., 2005a). The source categories were: (1) regional secondary sulfate

15 comprised of high S, Si, and OC (mean 63.41 $\mu g/m^3$); (2) resuspended soil characterized by high

16 concentrations of Ca, Fe, Al, and Si (mean concentration 5.88 $\mu g/m^3$); (3) residual oil derived from

17 power-plant emissions in the Eastern U.S. and containing high levels of V, Ni, and Se (mean

18 concentration 1.53 $\mu g/m^3$); and (4) motor vehicle traffic and other unknown sources (34.92 $\mu g/m^3$)

19 (Lippmann et al., 2005a). Exposures occurred from 9:00 a.m. to 3:00 p.m., 5 days/wk and the daily time

20 periods considered in the analysis were 11:00 a.m. to 1:00 p.m., 4:00 to 6:00 p.m., and 1:30 to 4:30 a.m.

21 $PM_{2.5}$ mass was associated with a daily interquartile change (difference between third and first quartile of

22 measured concentrations) of -4.1 beat/min HR during exposure in $ApoE^{-/-}$ mice and a similar magnitude

23 of effect was observed with resuspended soil (-4.5 beat/min). Resuspended soil was also associated with a

24 HR increase in the afternoon post-exposure (2.6 beat/min); the secondary sulfate factor was linked to

25 lowered HR in the afternoon post-exposure (-2.5 beat/min). A 6.2% increase in rMSSD collected in the

26 afternoon post-exposure was associated with the residual oil factor, compared to a 5.6% and 2.4%

27 decrease in rMSSD at night for secondary sulfate and $PM_{2.5}$ mass, respectively. Resuspended soil was

28 associated with a 4.3% increase in rMSSD the night following CAPs exposure. Compared to rMSSD, the

29 residual oil and secondary sulfate categories showed similar statistically significant parameter estimates

30 for SDNN.

31      Recent studies of ECG alterations in mice have indicated a role for PM-associated Ni in driving the

32 cardiovascular effects. Lippman et al. (2006) presented a posthoc analysis of daily variations in $PM_{2.5}$ and

1  changes in cardiac dynamics in ApoE$^{-/-}$ mice (average exposure: 85.6 μg/m$^3$; 7/21/ 2004–1/12/2005;

2  Tuxedo, NY). On the 14 days that the exposed mice had unusually elevated HR, Ni, Cr, and Fe comprised

3  12.4% of the PM mass, compared to only 1.5% on the other 89 days. Back trajectory analyses indicated

4  high-altitude winds from the northwest that did not traverse population centers and industrial areas except

5  the Sudbury Ni smelter in Ontario, Canada. On the 14 days that high HR was observed, the HR elevation

6  lasted for two days, but only the current day CAPs concentration was statistically significant. SDNN

7  decreases were statistically significant for all 3 lags (0, 1, 2 days). The GAM regression analysis showed

8  that only Ni produced a statistically significant effect for HR and SDNN.

## 6.2.2. Arrhythmia

9  Epidemiologic and toxicological studies presented in the 2004 PM AQCD provided some evidence

10  of arrhythmia following exposure to PM. However, a positive association between PM and ventricular

11  arrhythmias among patients with implantable cardioverter defibrillators was only observed in one study

12  conducted in Boston, MA, while toxicological studies reported arrhythmogenesis in rodents only

13  following exposure to ROFA, diesel exhaust, or metals. Recent epidemiologic studies have confirmed the

14  findings of PM-induced ventricular arrhythmias in Boston, MA, and have also reported increases in

15  ectopic beats in studies conducted in the Midwest and Pacific Northwest regions of the U.S. In addition,

16  two studies from Germany have demonstrated positive associations between traffic and combustion

17  particles and changes in repolarization parameters among patients with ischemic heart disease. Findings

18  of recent toxicological studies are mixed, with both demonstrated decreases and increases in frequency of

19  arrhythmia following exposure to CAPs.

### 6.2.2.1. Epidemiologic Studies

*Studies of Arrhythmias Using Implantable Cardioverter Defibrillators*

20  One study reviewed in the 2004 PM AQCD (described below) assessed the effect of short-term

21  fluctuations in PM on ventricular arrhythmias. Ventricular arrhythmias (i.e. ventricular tachycardia and

22  ventricular fibrillation), potentially lethal disturbances of the cardiac autonomic nervous system, are

23  common precursors to sudden cardiac death, and have been examined in several recent studies, described

24  below.

25  Previously, Peters et al. (2000) conducted a pilot study in Boston, MA to examine the association

26  between short-term changes in ambient air pollutant concentrations and increased risk of ventricular

27  arrhythmias, among a cohort of patients with implantable cardioverter defibrillators (ICD) (Peters et al.,

1    2000). ICDs continuously monitor subject's HR and rhythm and upon detection of an abnormal rhythm

2    (i.e. rapid HR), they can be programmed to deliver pacing and/or shock therapy to restore normal sinus

3    rhythm. Those abnormal rhythms that are most severe or rapid are assumed to be due to ventricular

4    tachycardia or ventricular fibrillation (i.e. life-threatening arrhythmias), and are thus treated with electric

5    shock. These ICD devices also store information on each abnormal rhythm detected, including the date,

6    time, and therapy given. Thus, using the date and time of those arrhythmias resulting in electric shock,

7    Peters et al. (2000) reported an increased risk of ICD shock associated with mean nitrogen dioxide

8    concentration in the previous two days. Among subjects with frequent events (10 or more during three

9    years of follow-up) an increased risk of ICD shock was also associated with interquartile range increases

10   in CO, $NO_2$, $PM_{2.5}$, and BC in the previous 2 days (Peters et al., 2000). Based on these findings, several

11   studies were conducted to confirm these findings. The study characteristics, as well as the reported effect

12   estimates and 95% CI associated with each PM metric, are shown in Table 6-2.

13       Dockery et al. (2005a; 2005b) conducted a follow-up study of n = 203 ICD patients living in

14   eastern Massachusetts and followed subjects for a longer period of time (up to 7 years) (2005a; 2005b).

15   They reviewed the ECG for each ICD-detected arrhythmia and included only ventricular arrhythmias

16   (ventricular fibrillation or ventricular tachycardia). In single pollutant models (generalized estimating

17   equations), adjusted for season, temperature, relative humidity, day of the week, patient, and a recent prior

18   arrhythmia, Dockery et al. (2005a; 2005b) reported increased risks of confirmed ventricular arrhythmias

19   associated with interquartile range increases in every pollutant ($PM_{2.5}$, BC, sulfate, $NO_2$, $SO_2$, $O_3$, and

20   particle number count). None were statistically significant. Among those with a prior ventricular

21   arrhythmia in the past three days, interquartile range increases in 2 calendar day mean $PM_{2.5}$, $NO_2$, $SO_2$,

22   CO, $O_3$, sulfate, and BC concentrations were all associated with significant and markedly higher risks of

23   ventricular arrhythmia than among those without a prior arrhythmia. Last, the authors suggested that the

24   pollutants associated with increased risk of ventricular arrhythmia implicate traffic pollution (Dockery et

25   al., 2005a; 2005b).

26       Rich et al. (2005) conducted a case-crossover analysis of these same data to investigate moving

27   average pollutant concentrations lagged <48 h (Rich et al., 2005). After adjusting for temperature, dew

28   point temperature, and barometric pressure, they reported significantly increased risk of ventricular

29   arrhythmia associated with mean $PM_{2.5}$ and ozone concentrations in the 24 h before the arrhythmia. Each

30   pollutant effect appeared independent in two pollutant models. In single pollutant models, $NO_2$ and $SO_2$

31   also were significantly associated with increased risk, but when included in two pollutant models with

32   $PM_{2.5}$, only $PM_{2.5}$ remained associated with increased risk. They did not, however, find evidence of a

33   more acute arrhythmic response to pollution (i.e., larger risk estimates associated with moving averages

34   < 24-h before arrhythmia detection) (Rich et al., 2005).

1    Rich et al. (2006b) conducted another case-crossover study in the St. Louis, MO metropolitan area.

2    Using the same methods as in Boston, they reported increased risk of ventricular arrhythmia associated

3    mean $SO_2$ concentration in the 24-h before the arrhythmia, but not $PM_{2.5}$ (in single-pollutant models).

4    Again, they found no evidence of an arrhythmic response with moving average pollutant concentrations

5    < 24-h before the arrhythmia (Rich et al., 2006a).

6    In Vancouver, Canada, Vedal et al. (2004) did not find increased risk of ICD shocks associated with

7    increases in any pollutant concentration ($PM_{10}$, Ozone, $SO_2$, $NO_2$, and CO), after adjusting for temporal

8    trends, temperature, relative humidity, wind speed, barometric pressure, and proportion of hours with rain.

9    Secondary analyses among those subjects with two or more discharges per year, and analyses stratified by

10   season were also null for $PM_{10}$, although an association with $SO_2$ (lag 2 d) was observed (Vedal et al.,

11   2004). A case crossover of these dame data examining additional particulate pollutant concentrations

12   available for a shorter time frome (e.g., $PM_{2.5}$, sulfate, EC, and OC) also found no increased risk of ICD

13   shock associated with any pollutant. Rich et al. (2004) did not use the time-stratified control selection

14   procedure. They used an ambi-directional approach, taking control periods 7 days before and after the

15   case day when pollution data was available.

16   The largest ICD study to date examined the risk of ventricular arrhythmias associated with

17   increases in the daily concentration of numerous particulate and gaseous pollutants in Atlanta, GA

18   (Metzger et al., 2007). However, they also did not find significant or consistently increased risk of a

19   ventricular arrhythmia associated with any interquartile range increase in mean daily particulate or

20   gaseous pollutant concentration at any lag examined (Metzger et al., 2007).

21   Albert et al. (2007), although not investigating associations with ambient pollution, conducted a

22   case-crossover study of the association between ventricular arrhythmia and traffic exposure in the hours

23   before the arrhythmia. They reported an increased risk of ventricular arrhythmia associated with traffic

24   exposure or driving in the previous hour. They hypothesized that this increased risk was due to either a

25   stress response from being in a car in heavy traffic, or from traffic-generated air pollution, or a

26   combination of both (Albert et al., 2007).

27   Although ICDs detect and treat potentially life-threatening ventricular arrhythmias, other

28   arrhythmias including episodes of paroxysmal atrial fibrillation (AF) may also be detected. AF is a

29   common sustained arrhythmia in clinical practice (Go et al., 2001) and a risk factor for stroke

30   (Prystowsky et al., 1996) and premature mortality (Kannel et al., 1983). In another case-crossover

31   analysis of data from the Boston ICD study described above, Rich et al. (2006a) identified 91 confirmed

32   episodes of paroxysmal AF among 29 subjects. In single pollutant models, they reported an increased risk

33   of AF associated with each 21.7 ppb increase in mean ozone concentration in the hour before the

1    arrhythmia, each 9.4 µg/m$^3$ increase in $PM_{2.5}$ in the hour before the arrhythmia, and each 0.83 µg/m$^3$

2    increase in BC concentration in the 24 h before the arrhythmia (Table 6-2) (Rich et al., 2006a).

3            Since 2004, only one study (in Boston), reported adverse associations between PM and ICD

4    detected ventricular arrhythmias (Berger et al., 2006; Dockery et al., 2005a; 2005b; Dusek et al., 2006;

5    Ebelt et al., 2005; Peters et al., 2000; Rich et al., 2005; Sarnat et al., 2006c), while other studies done

6    elsewhere did not (Dusek et al., 2006; Metzger et al., 2007; Rich et al., 2004; Vedal et al., 2004). A wide

7    range in exposure lags has been reported in the Boston study (3 h to 3 days) (Dockery et al., 2005a;

8    Dockery et al., 2005b; Rich et al., 2005). It is not clear why these findings are inconsistent. Rich et al.

9    (2005) reported that use of the mean pollutant concentration from the specific 24 h before the arrhythmia

10   rather than just the day of the arrhythmia, resulted in less exposure misclassification and less bias towards

11   the null, possibly explaining the lack of association when using just the day of ICD discharge and daily

12   PM concentrations (Rich et al., 2005). Other reasons for the inconsistent findings may include differing

13   degrees of exposure misclassification within each study or city due to differences in PM composition and

14   pollutant mixes (e.g., less transition metals and sulfates in the Pacific Northwest than the Northeast U.S.),

15   and differences in the size of study areas (Boston: within 40 km of $PM_{2.5}$ monitoring site; Vancouver:

16   Lower Mainland of British Columbia 90 km east of Vancouver). Studies of ventricular arrhythmia and

17   PM concentration in patients with ICDs are summarized in Table 6-2.

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**Table 6-2.** **Studies of ventricular arrhythmia and ambient PM concentration, in patients with implantable cardioverter defibrillators.**

| Reference | Outcome and Sample Size | Study Design and Analytic Method | Copollutants | PM Metric | Ambient Concentration | Lag and its Increment Units | OR | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| Dockery (2005a; 2005b) Eastern MA | N = 670 days with ≥ 1 EGM confirmed ventricular arrhythmias among n = 84 subjects | Generalized estimating equations Lags Evaluated: 2 calendar day means | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{2.5}$ | Daily Median: 10.3 µg/m$^3$ | 2 day 6.9 µg/m$^3$ | 1.08 | 0.96, 1.22 |
| | | | | BC | Daily Median: 0.98 µg/m$^3$ | 2 day 0.74 µg/m$^3$ | 1.11 | 0.95, 1.28 |
| | | | | Sulfate | Daily Median: 2.55 µg/m$^3$ | 2 day 2.04 µg/m$^3$ | 1.05 | 0.92, 1.20 |
| | | | | Particle Number | Daily Median: 29,300 particles/cm$^3$ | 2 day 19,120 particles/cm$^3$ | 1.14 | 0.87, 1.50 |
| Rich et al. (2005) Eastern MA | N = 798 EGM confirmed ventricular arrhythmias among n = 84 subjects | Time-stratified case-crossover study. Conditional logistic regression Lags Evaluated: 3, 6, 24, 48 h moving averages | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{2.5}$ | Daily Median: 9.8 µg/m$^3$ | 24-h moving average 7.8 µg/m$^3$ | 1.19 | 1.02, 1.38 |
| | | | | BC | Daily Median: 0.94 µg/m$^3$ | 24-h moving average 0.83 µg/m$^3$ | 0.93 | 0.74, 1.18 |

| Reference | Outcome and Sample Size | Study Design and Analytic Method | Copollutants | PM Metric | Ambient Concentration | Lag and its Increment Units | OR | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| Rich et al. (2006b) St. Louis metro area | N = 139 EGM confirmed ventricular arrhythmias among n = 56 subjects | Time-stratified case-crossover study. Conditional logistic regression Lags Evaluated: 6, 12, 24, 48 h moving averages | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{2.5}$ | Daily Median: 16.2 μg/m³ | 24-h moving average 9.7 μg/m³ | 0.95 | 0.72, 1.27 |
| | | | | EC | Daily Median: 0.6 μg/m³ | 24-h moving average 0.5 μg/m³ | 1.18 | 0.93, 1.50 |
| | | | | Organic Carbon | Daily Median: 4.0 μg/m³ | 24-h moving average 2.3 μg/m³ | 1.08 | 0.81, 1.43 |
| Vedal et al. (2004) Vancouver, BC, CA | N = 257 days with ≥ 1 ICD shock among n = 50 subjects | Generalized estimating equations Lags Evaluated: 0, 1, 2, 3 daily moving average | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{10}$ | Daily Median: 11.6 μg/m³ | Lag Day 0 5.6 μg/m³ | 1.00* | 0.82, 1.19* |
| Rich et al. (2004) Vancouver, BC, CA | N = 77 to 98 days with with ≥ 1 ICD shock among n = 34 subjects | Ambi-directional case-crossover study. Conditional logistic regression Lags Evaluated: 0, 1, 2, and 3 day moving averages | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{2.5}$ | Daily Mean: 8.2 μg/m³ | Lag Day 0 5.2 μg/m³ | 1.0† | 0.9, 1.1† |
| | | | | $PM_{10}$ | Daily Mean: 13.3 μg/m³ | Lag Day 0 7.4 μg/m³ | 0.9† | 0.5, 1.5† |
| | | | | EC | Daily Mean: 0.8 μg/m³ | Lag Day 0 0.4 μg/m³ | 1.1† | 0.9, 1.3† |
| | | | | Organic Carbon | Daily Mean: 4.5 μg/m³ | Lag Day 0 2.2 μg/m³ | 1.1† | 0.9, 1.3† |
| | | | | Sulfate | Daily Mean: 1.3 μg/m³ | Lag Day 0 0.9 μg/m³ | 0.9† | 0.7, 1.2† |
| Metzger et al. (2007) Atlanta, GA | N = 6287 EGM confirmed ventricular arrhythmias among n = 518 subjects | Generalized estimating equations Lags Evaluated: 0, 1, and 2 day moving averages | $NO_2$, CO, $SO_2$, $O_3$ | $PM_{2.5}$ | Daily Median: 16.2 μg/m³ | 24-h moving average 10 μg/m³ | 1.00 | 0.95, 1.04 |
| | | | | $PM_{10}$ | Daily Median: 26.4 μg/m³ | 24-h moving average 10 μg/m³ | 1.00 | 0.97, 1.03 |
| | | | | $PM_{10-2.5}$ | Daily Median: 8.7 μg/m³ | 24-h moving average 5 μg/m³ | 1.03 | 1.00, 1.07 |
| | | | | $PM_{2.5}$ EC | Daily Median: 1.4 μg/m³ | 24-h moving average 1 μg/m³ | 1.01 | 0.98, 105 |
| | | | | $PM_{2.5}$ Organic Carbon | Daily Median: 3.9 μg/m³ | 24-h moving average 2 μg/m³ | 1.01 | 0.98, 1.03 |
| | | | | $PM_{2.5}$ Sulfate | Daily Median: 4.1 μg/m³ | 24-h moving average 5 μg/m³ | 0.99 | 0.93, 1.06 |
| | | | | $PM_{2.5}$ water soluble elements | Daily Median: 0.022 μg/m³ | 24-h moving average 0.03 μg/m³ | 0.95 | 0.90, 1.00 |

Estimated from Figure 3 (Vedal et al., 2004)
† Estimated from Figure 3 (Rich et al., 2004)


## *Ectopy Studies Using ECG Measurements*

1    A few panel studies have used ECG recordings to evaluate associations between ectopic beats

2    (ventricular or supraventricular) and mean particulate concentrations in the previous hours and/or days

1    (Berger et al., 2006; Ebelt et al., 2005; Sarnat et al., 2006c). Ectopic beats are defined as extra cardiac

2    depolarizations and are the most common disturbance in heart rhythm. Ectopic beats are usually benign,

3    and may present with or without symptoms, such as palpitations or dizziness. When three or more occur

4    in succession, this is called a non-sustained ventricular tachycardia. Sustained ventricular tachycardias are

5    the arrhythmias investigated in the ICD studies described above. Sarnat et al. (2006c) conducted a panel

6    study among 32 nonsmoking older adults residing in Steubenville, OH (Sarnat et al., 2006c). In this study,

7    the median daily $PM_{2.5}$ concentration was 17.7 $\mu g/m^3$. The median daily sulfate concentration was

8    5.7 $\mu g/m^3$, and the median daily EC concentration was 1.0 $\mu g/m^3$. They used logistic regression models to

9    examine lagged effects of 1-10 day moving average concentrations of $PM_{2.5}$, sulfate, EC, $O_3$, $NO_2$, and

10   $SO_2$. In single pollutant models, each 10.0 $\mu g/m^3$ increase in 5-day mean $PM_{2.5}$ concentration was

11   associated with increased risk of supraventricular ectopy (OR = 1.42; 95% CI: 0.99, 2.04), but not

12   ventricular ectopy (OR = 1.02; 95% CI: 0.63–1.65). Similarly, increased risk of supraventricular ectopy,

13   but not ventricular ectopy, was associated with each interquartile range increase in 5-day mean sulfate and

14   ozone concentration (Sarnat et al., 2006c).

15       Ebelt et al. (2005) conducted a repeated measures panel study of 16 patients with COPD in the

16   summer of 1998 in Vancouver, British Columbia (Ebelt et al., 2005). Their goal was to evaluate the

17   relative impact of ambient and non-ambient exposures to $PM_{2.5}$, $PM_{10}$, and $PM_{10-2.5}$ on several health

18   measures. The mean $PM_{2.5}$ concentration during this study was 11.4 $\mu g/m^3$. Using mixed models with

19   random subjects effects to investigate only same day PM concentrations, Ebelt et al. (2005) reported an

20   increase in supraventricular ectopic beats associated with same day ambient exposures to each PM size

21   fraction (Ebelt et al., 2005); however, results were presented in figures only.

22       Berger and colleagues (2006) conducted a panel study of 57 men with coronary heart disease living

23   in Erfurt, Germany (Berger et al., 2006). Using 24-h ECG measurements made once every 4 weeks, they

24   studied associations between runs of supraventricular and ventricular tachycardia and lagged

25   concentrations of $PM_{2.5}$, UFP (0.01-0.1 $\mu m$), ACP (0.1-1.0 $\mu m$), $SO_2$, $NO_2$, CO, and NO. Using

26   generalized additive models, as well as poisson and linear regression models, they reported increases in

27   supraventricular tachycardia and the number of runs of ventricular tachycardia associated with 5-day

28   mean $PM_{2.5}$, UFP counts (0.01-0.1 $\mu m$), and ACP counts (0.1-1.0 $\mu m$), after controlling for long-term time

29   trend, weekday, air temperature, relative humidity, and barometric pressure. They found these associations

30   at all lags evaluated (during ECG recording, 0-23 h before, 24-47 h before, 48-71-h before, 72-95 h

31   before, and 5 day mean), but the largest effect estimates were generally associated with the 24-47 h mean

32   and the 5 day mean (Berger et al., 2006).

33       These studies of ectopic beats and runs of supraventricular and ventricular tachycardia, captured

34   using ECG measurements, all report positive associations. They are consistent with the Boston ICD

1    studies described above, although they report findings in other regions (Midwest U.S., Pacific Northwest,

2    and Erfurt Germany). A range of lags were investigated (0-10 days) with the strongest effects observed

3    for either the 5-day mean or same day PM concentrations. Taken together, these ICD studies and ectopy

4    studies provide some evidence of an arrhythmic response to PM, although further study is needed to

5    understand the discrepancy in ICD study findings.

### ECG Abnormalities Indicating Arrhythmia

6    No investigations of the relationship of PM concentration and ECG abnormalities indicating

7    arrhythmia were conducted prior to 2002 and thus were not included in the 2004 PM AQCD.

8    Abnormalities in the myocardial substrate, myocardial vulnerability, and resulting repolarization

9    abnormalities are believed to be key factors contributing to the development of arrhythmogenic

10   conditions such as those discussed above. These abnormalities include ECG measures of repolarization

11   such as QT duration (time for depolarization and repolarization of the ventricles), T-wave complexity (a

12   measure of repolarization morphology), and T-wave amplitude (height of the T-wave). Abnormalities in

13   repolarization may also identify subjects potentially at risk of more serious events such as sudden cardiac

14   death (Atiga et al., 1998; Berger et al., 1997; Chevalier et al., 2003; Okin et al., 2000; Zabel et al., 1998).

15   Recent studies of changes in these measures following acute increases in air pollution are described

16   below.

17   Two studies conducted in Erfurt, Germany (Henneberger, 2005; Yue et al., 2007) examined the

18   association between measures of repolarization (QT duration, T-wave complexity, T-wave amplitude,

19   T-wave amplitude variability) and particulate air pollution. Henneberger et al. (2005) conducted a panel

20   study of 56 males with ischemic heart disease (Henneberger, 2005). Each subject was measured every 2

21   weeks for 6 months. During the study, the median daily $PM_{2.5}$ concentration was 14.9 $\mu g/m^3$. The median

22   EC concentration was 1.8 $\mu g/m^3$, while the median OC concentration was 1.4 $\mu g/m^3$. The median count of

23   UFP counts (0.01-0.1 $\mu m$) was 11,444 particles/$cm^3$, while the median count of ACP (0.1-1.0 $\mu m$) was

24   1238 particles/$cm^3$. Using generalized additive models adjusted for subject, long-term time trend,

25   temperature, relative humidity, barometric pressure, and weekday, they examined the change in these

26   ECG parameters associated with the mean pollutant (UFP, ACP, $PM_{2.5}$, OC, and EC) concentrations 0-5,

27   6-11, 12-17, 18-23, and 0-23 h before, and 2-5 days before the ECG measurement. Significant decreases

28   in T-wave amplitude were associated with $PM_{2.5}$ mass, UFP, and ACP. Each 16.4 $\mu g/m^3$ increase in the

29   mean $PM_{2.5}$ concentration in the previous 5 h was associated with a 6.46 $\mu V$ decrease in T-wave

30   amplitude (95% CI: -10.88 to -2.04). Each 0.7 $\mu g/m^3$ increase in the mean OC concentration in the

31   previous 5 h was associated with a 4.15 ms increase in QT interval (95% CI: 0.22, 8.09). There was a

1   similar sized effect for 24-h mean OC concentration. Significant increases in the variability of T-wave

2   complexity were also associated with acute increases in EC and OC concentration (Henneberger, 2005).

3       Yue et al. (2007) then used positive matrix factorization to identify 5 sources of ambient PM

4   (airborne soil, local traffic-related UFP, combustion generated aerosols, diesel traffic-related particles, and

5   secondary aerosols). Using similar statistical models, they examined the association between these same

6   repolarization changes and incremental increases in the mean concentration of each particle source in the

7   24-h before the ECG measurement. They also examined associations with CRP and vWF concentrations

8   in the blood. Both UF from local traffic and diesel particles from traffic had the strongest associations

9   with repolarization parameters (Yue et al., 2007).

10      These two analyses demonstrate associations between PM pollution and repolarization changes, at

11  lags of 5 h to 2 days. Moreover, the findings from the Yue et al. (2007) study demonstrate a potential role

12  of traffic particles/pollution.

## 6.2.2.2. Toxicological Studies

13      The ECG of animal research models frequently exhibit different characteristics than that of

14  humans. Mice and rats are notable in this regard, as they do not have an isoelectric ST-segment typical of

15  larger species, likely owing to their rapid heart rates (~600 and ~350 bpm, respectively). However, the

16  ultimate function of the pumping heart is conserved and reflected by the ECG in a remarkably consistent

17  manner across species. Thus, atrial depolarization causes an electrical inflection represented by the

18  P-wave, ventricular depolarization elicits the QRS complex, and the biopotential recovery of the

19  ventricles is reflected by the T-wave.

20      The earliest indication that there may be cardiovascular system effects of PM came from ECG

21  studies in susceptible animal models (rats with pulmonary hyptertension (Watkinson et al., 1998) and

22  dogs with coronary occlusion (Godleski et al., 2000), which were summarized in the 2004 PM AQCD.

23  However, a study of dogs exposed to ROFA did not demonstrate ECG changes, perhaps due to differences

24  in disease state, as these were the oldest dogs in the colony with clinical signs of preexisting, naturally

25  occurring heart disease (Muggenburg et al., 2000). Much of the research conducted since the release of

26  the last PM AQCD has been focused on exploring susceptibility or varying exposure methodologies, with

27  little new evidence into the mechanisms for ECG changes of inhaled PM.

28      Wellenius et al. (2004) used a susceptible model that was previously shown to produce significant

29  results with exposures to ROFA (Wellenius et al., 2002) to examine ECG-related PM effects. Using an

30  anesthetized model of post-infarction myocardium sensitivity, Wellenius and colleagues tested the effects

31  of concentrated $PM_{2.5}$ on the induction of spontaneous arrhythmias in rats (Sprague Dawley; 1-h

32  exposure; Boston, MA; July 2000 to January 2003; mean mass concentration 523.11 $\mu g/m^3$; range of mass

concentration 60.3–2202 μg/m$^3$). CAPs caused a statistically significant decrease (67.1%) in ventricular premature beat (VPB) frequency during the post-exposure period in rats with a high number of pre-exposure VPB. No interaction was observed with co-exposure to carbon monoxide (35 ppm), which reduced VPB frequency during the exposure period when administered alone. When further analyses were conducted to determine whether the CAPs number concentration or the mass concentration of any single element was a predictor of VPB frequency, no significant results were found. In a follow-up publication, results from the analysis of supraventricular ectopic beats (SVEB) were provided (Wellenius et al., 2006b). A decrease in the number of SVEB was observed with CAPs (mean mass concentration 645.7 μg/m$^3$; range of mass concentration 78.0–2202.5 μg/m$^3$) or CO (average concentration 37.9 ppm) compared to filtered air. Furthermore, an increase in CAPs number concentration of 1000 particles/cm$^3$ was associated with a 3.3% decrease in SVEB frequency. The findings of decreased ventricular arrhythmia differ from those observed following ROFA exposure in the same animal model in that an increased frequency of premature ventricular complexes was observed with ROFA, albeit the exposure concentration was >3000 μg/m$^3$ (Wellenius et al., 2002). It is difficult to directly compare the result of these studies due to differences in exposure concentrations and the nature of CAPs exposures (i.e., varying daily PM composition), but collectively they may suggest an important role for the soluble components of PM, including transition metals, as only ROFA induced increases in ventricular arrhythmia occurrence.

Anselme and colleagues (2007) exposed rats with and without induced CHF to diesel emissions for 3 h (PM concentration 500 μg/m$^3$; NO$_2$ 1.1 ppm; CO 4.3 ppm). While no dramatic change was noted in HR, prominent increases in the incidence of VPB were observed in CHF rats, which lasted at least 4–5 h after the exposure ceased. It is interesting to contrast the work of Anselme with the studies by Wellenius et al. (2002; 2004; 2006a), as the arrhythmia incidence in the acute infarction model was greatest with ROFA, while the CHF model demonstrated sensitivity to diesel exposure. However, several differences in the research designs preclude strong comparisons.

In older rats (Fisher 344; ~18 mo) exposed to PM$_{2.5}$ CAPs in Tuxedo, NY (4 h; mean concentration 180 μg/m$^3$; single-day concentrations 161 and 200 μg/m$^3$; August 2000), the frequency of delayed beats was greater than in rats exposed to air (Nadziejko et al., 2004). The majority of these beats were characterized as pauses (a delay of 2.5 times the adjacent interbeat intervals) rather than premature beats. When the same animals were exposed to generated ultrafine carbon (mean concentration 890 μg/m$^3$; single-day concentrations 500 and 1280 μg/m$^3$; 30–50 nm MMAD) or SO$_2$ (1.2 ppm), no significant differences were observed in arrhythmia frequency between air controls and exposed animals. The authors also report using the same protocol for young Wistar rats (concentration 215 μg/m$^3$) and very few arrhythmias were observed, thus precluding statistical analysis. The results of this study indicate 1)

1    involvement of the sino-atrial node, as the observed arrhythmias were mostly of a delayed nature and 2)

2    particle size and $PM_{2.5}$ constituents may play a role in these effects.

3          Using $ApoE^{-/-}$ mice on a high-fat diet as a model of pre-existing coronary insufficiency (Caligiuri et

4    al., 1999), Campen and colleagues studied the impact of inhaled diesel and gasoline emissions and road

5    dust (6 h/day × 3 day) on ECG morphology (2005; Campen et al., 2006). Moreover, the investigators used

6    a high efficiency particle filter to compare the whole exhaust with an atmosphere containing only the

7    gaseous components. For gasoline emissions, the PM-containing atmosphere (PM mean concentration

8    61 $\mu g/m^3$; $NO_X$ mean concentration 18.8 ppm; CO mean concentration 80 ppm) induced T-wave

9    morphological alterations, while the PM-filtered atmosphere did not (Campen et al., 2006). Moreover,

10   resuspended road dust ($PM_{2.5}$), at up to 3500 $\mu g/m^3$ had no impact on ECG. For diesel emissions at higher

11   concentrations (PM mean concentration 512, 770, or 3634 $\mu g/m^3$; $NO_X$ mean concentration 19, 105, 102

12   ppm for low whole exhaust, high PM filtered, and high whole exhaust, respectively; CO levels not

13   provided), dramatic bradycardia, decreased T-wave area, and arrhythmia (atrioventricular-node block and

14   VPB) were only observed in $ApoE^{-/-}$ mice exposed to the high filtered and high whole exhaust groups

15   (Campen et al., 2005). These effects remained after filtration of PM, suggesting that the gaseous

16   components of the whole DE drove the cardiovascular findings. These results contrast, in that the gasoline

17   emissions required particles to induce T-wave changes, whereas the PM-filtered diesel emissions

18   produced altered ECG responses. However, the diesel emissions contained much greater PM

19   concentrations compared to the gasoline emissions.

20         The above studies demonstrate mixed results for arrhythmias. Wellenius et al. (2004; 2006b)

21   showed decreased frequency of VPB and SVEB following CAPs exposure in rats with induced MI (>12-h

22   prior to exposure). In contrast, rats with a MI model of chronic heart failure (3-month recovery) had

23   increased incidence of VPB with diesel exposure (Anselme et al., 2007). One study reported increased

24   frequency of premature beats in older rats exposed to CAPs, which were not observed with ultrafine

25   carbon particles (Nadziejko et al., 2004). As for ECG morphology changes, T-wave alterations were

26   reported for gasoline emissions that were absent when the PM was filtered (Campen et al., 2006).

27   However, for DE, increased atrioventricular-node block, VPB, and decreased T-wave area were observed

28   with whole exhaust and remained after filtration of PM, indicating that the gases were responsible for the

29   effects (Campen et al., 2005).

## 6.2.3. Ischemia

30         Although no evidence from epidemiologic or human clinical studies of PM-induced myocardial

31   ischemia was included in the 2004 PM AQCD, one toxicological study was cited that observed ST-

1   segment changes in dogs following a 3 day exposure to CAPs. In epidemiologic studies published since

2   the 2004 PM AQCD, associations have been demonstrated between PM and ST-segment depression, and

3   one new human clinical study reported significant increases in exercise-induced ST-segment depression

4   among men with prior MI following a controlled exposure to diesel exhaust. Results from recent

5   toxicological studies confirm the findings presented in the 2004 PM AQCD and provide coherence and

6   biological plausibility for the effects observed in epidemiologic and human clinical studies.

## 6.2.3.1. Epidemiologic Studies

### ECG Abnormalities Indicating Ischemia

7   There were no studies of ECG abnormalities indicating ischemia reviewed in the 2004 PM AQCD.

8   The ST-segment duration is typically in the range of 0.08 to 0.12 sec (80 to 120 ms). A depression in the

9   ST-segment may indicate coronary ischemia, while an elevation may indicate MI. Several short-term

10  exposure studies of air pollution investigated the association of ST-segment depression with PM

11  concentration.

12  Gold et al. (2005) studied 24 elderly residents of Boston, MA (aged 61-88 years) residing at or near

13  an apartment complex that was ~ 0.5 km from an air pollution monitoring station. A protocol of

14  continuous Holter monitoring including 5 mins of rest, 5 mins of standing, 5 mins of outdoor exercise, 5

15  mins of rest, and then 20 cycles of paced breathing was done up to 12 times for each subject (n = 269

16  ECG measurements for analysis). From these ECG measurements, they identified occurrences of ST-

17  segment depression and examined whether mean BC, CO, and $PM_{2.5}$ concentrations in the previous 5 and

18  12-h were associated with ST-segment depression. The median 5 h mean BC concentration was

19  1.28 $\mu g/m^3$ and the median 12-h mean BC concentration was 1.14 $\mu g/m^3$. The median 5 h mean $PM_{2.5}$

20  concentration was 9.5 $\mu g/m^3$, and the median 12 hour mean $PM_{2.5}$ concentration was 9.8 $\mu g/m^3$. Using

21  single pollutant, conditional linear mixed regression models, including a cubic term for current hourly

22  temperature and a linear trend of time, Gold et al. (2005) reported that the mean BC concentrations in the

23  5 and 12 h before testing predicted ST-segment depression in most portions of the protocol. However,

24  these effects were strongest in the post-exercise periods. For example, during the post-exercise rest

25  period, each 10th-90th percentile increase (1.59 $\mu g/m^3$) in the mean 5 hour BC concentration was

26  associated with a -0.11 mm ST-segment depression (95% CI: -0.18 to -0.05). In two pollutant models, CO

27  did not appear to confound this association. These findings suggest traffic-generated particulate pollution

28  may be associated with ST-segment depression (Gold et al., 2005).

29  Previously, Pekkanen et al. (2002) conducted a panel study of 45 subjects with stable coronary

30  heart disease living in Helsinki, Finland. Each subject had biweekly sub-maximal exercise testing for 6

1    months (n = 342 exercise tests with 72 exercise-induced ST-segment depressions). During this study, the

2    median daily $PM_{2.5}$ concentration was 10.6 $\mu g/m^3$, and the median daily count of ACP (ACP: 0.1–1.0 $\mu m$)

3    was 1200 particles/$cm^3$. Using logistic regression and generalized additive models adjusting for time

4    trend, temperature, relative humidity, and HR change during testing, they examined the risk of ST-

5    segment depression associated with mean pollutant concentrations (UFP, ACP, $PM_1$, $PM_{2.5}$, $PM_{2.5-10}$, $NO_2$,

6    CO) in the previous 24-h, and the 3 previous lagged 24-h periods. Each 7.9 $\mu g/m^3$ increase in mean $PM_{2.5}$

7    concentration, lagged 2 days, was associated with significantly increased risk of ST-segment depression

8    >0.1 mV (OR: 2.84 [95% CI: 1.42–5.66]). Each 760 particles/$cm^3$ increase in the count of ACP, lagged 2

9    days, was also associated with significantly increased risk of ST-segment depression >0.1 mV (OR: 3.29

10   [95% CI: 1.57–6.92]). Similarly sized increased risks of ST-segment depression were also found for other

11   particulate pollutants, including $PM_{10-2.5}$, $PM_1$, and the counts of UFP (0.01–0.1 $\mu m$).

12       This same research group, then conducted a principal components analysis to identify five $PM_{2.5}$

13   sources (crustal, long range transport, oil combustion, salt, and local traffic) (Lanki et al., 2006b). Using

14   similar statistical models, each 1 $\mu g/m^3$ increase in "local traffic" particle concentration, lagged 2 days,

15   was associated with increased risk of ST-segment depression (OR: 1.53 [95% CI: 1.19–1.97]). Similarly,

16   each 1 $\mu g/m^3$ increase in "long range transport" particle concentration was also associated with increased

17   risk of ST-segment depression (OR: 1.11 [95% CI: 1.02–1.20]). No significant associations for other

18   sources were reported for any lag time. These studies demonstrate associations between PM pollution and

19   ST-segment depression at lags of 5 hours to 2 days. Morever, these findings demonstrate a potential role

20   for traffic (Gold et al., 2005) and long-range transported PM (Lanki et al., 2006a).

## 6.2.3.2. Human Clinical Studies

21       Among a group of 20 men with prior MI, Mills et al. (2007) found that DE (300 $\mu g/m^3$ PM)

22   significantly increased exercise-induced ischemic burden during exposure, calculated as the product of

23   exercise duration and change in ST-segment amplitude. The mechanism by which DE induced the

24   exacerbation of ischemic burden remains unclear, and appears to be unrelated to impaired vasodilation.

25   However, the authors suggest that this discrepancy may be due to the timing of the vascular assessment,

26   as measures of blood-flow were taken 5 hours after the observed increase in ischemic burden.

## 6.2.3.3. Toxicological Studies

27       There were no toxicological studies cited in the 2004 PM AQCD that directly examined myocardial

28   ischemia. One study was reviewed in the 2004 PM AQCD that evaluated ST-segment changes in dogs

1    during occlusion and following a 3-day exposure to Boston CAPs reported increased magnitude and

2    decreased time to ST-segment elevation (Godleski et al., 2000).

3        In the first study of its kind, Cozzi et al. (2006) exposed ICR mice to ultrafine PM (100 μg via

4    intratracheal instillation), followed by ischemia/reperfusion injury to the left anterior coronary artery.

5    Both the area-at-risk (the region of tissue perfused by the left anterior descending coronary artery) and the

6    infarct size were measured 2 h following reperfusion and while the area-at-risk was not affected by PM

7    exposure, the infarct size was nearly doubled in mice who received ultrafine PM. Increases in infarct size

8    were associated with increased myocardial neutrophil density in the infarct zone and lipid peroxidation in

9    the myocardium.

10       A more recent study in dogs (female mixed-breed canines, 14–18 kg) evaluated myocardial blood

11    flow during myocardial ischemia following 5-h $PM_{2.5}$ CAPs exposures in Boston (daily mass

12    concentration range 94.1–1556.8 μg/m$^3$; particle number concentration range 3000–69300 particles/cm$^3$;

13    BC concentration range 1.3–32.0 μg/m$^3$) (Bartoli et al., 2008). Similar methods were used for the

14    coronary occlusion and exposure method as those described in Wellenius et al. (2003). In addition,

15    silicone catheters were chronically implanted in the left atrium and descending aorta for fluorescent

16    microsphere injection and blood flow measurements, respectively. Using a crossover design, 4 animals

17    were exposed to alternating CAPs and filtered air two times (8 total CAPs exposures). Immediately after

18    exposure, dogs underwent two 5-min occlusions of the left anterior descending coronary artery with

19    injection of microspheres (15 μm diameter) after 3 min of ischemia during the second occlusion. Blood

20    was sampled from the descending aorta to determine the absolute flow to tissue samples. Post-mortem

21    analysis of cardiac tissue and blood samples allowed for quantification of microspheres using flow

22    cytometry. CAPs-exposed dogs had decreased total myocardial blood flow and increased coronary

23    vascular resistance during coronary artery occlusion that was greatest in tissue within or near the ischemic

24    zone. The rate-pressure product (product of HR and systolic BP) was unchanged in animals exposed to

25    CAPs during occlusion, indicating that cardiac metabolic demand was not altered. The multi-level linear

26    mixed models demonstrated that myocardial blood flow and coronary vascular resistance during

27    occlusion were inversely and significantly associated with CAPs mass concentration, particle number

28    concentration, and BC concentration, with the strongest effects observed with particle number

29    concentration. The results of this study provide evidence that exacerbation of myocardial ischemia

30    following PM exposure is due to reduced myocardial blood flow.

31       The two studies described above provide evidence that PM can induce greater myocardial

32    responses following ischemic events, as demonstrated by increased infarct size, decreased myocardial

33    blood flow and increased coronary vascular resistance. The results indicate that collateral vessels may be

34    dysfunctional following PM exposure.

1    A study that examined ECG changes in dogs (female; retired mongrel breeder dogs) following

2    CAPs exposure (mean mass concentration 345 μg/m$^3$; mass concentration range 161–957 μg/m$^3$;

3    September 2000 to March 2001; Boston, MA) and left anterior descending coronary artery occlusion as

4    an indicator of myocardial ischemia reported changes in ST-segment (Wellenius et al., 2003). The

5    experimental protocol was a 6-h exposure to CAPs or filtered air via tracheostomy, followed by a

6    preconditioning occlusion (5 min), rest interval (20 min), and the experimental occlusion (5 min).

7    Increased ST-segment elevation (estimated as the area under the response curve) was observed following

8    PM$_{2.5}$ during the experimental occlusion period compared to filtered air. Furthermore, peak ST-segment

9    elevation attributable to CAPs was reported with the experimental occlusion, which remained elevated

10   24-h post-exposure. Ventricular arrhythmias were rarely observed during occlusion and when observed,

11   were unrelated to CAPs exposure. The results from this study support those observed previously

12   (Godleski et al., 2000) and provides greater support that enhanced myocardial ischemia occurs relatively

13   quickly following PM exposure (within hours).

### PM Components

14   The Wellenius et al. (2003) study employing dogs also attempted to link ST-segment changes with

15   four CAPs elements (Si, Ni, S, and BC) as tracers of PM$_{2.5}$ sources in Boston. In the multivariate

16   regression analyses, peak ST-segment elevation and integrated ST-segment change were significantly

17   associated with only the mass concentration of Si (Si mean concentration 8.17 μg/m$^3$; Si concentration

18   range 2.31–13.93 μg/m$^3$). In the univariate regression analyses, Pb also demonstrated a significant

19   association for both ST-segment measures, although the p-value was greater than that observed with Si.

## 6.2.4. Vasomotor Function

20   Perhaps the most noteworthy new health-related revelation in the past six years with regards to PM

21   exposure is that the systemic vasculature may be a target organ. The vasculature of all tissues is lined with

22   endothelial cells that will naturally encounter any systemically absorbed toxin. The endothelium

23   (1) maintains barrier integrity to ensure fluid compartmentalization, (2) communicates dilatory and

24   constrictive stimuli to vascular smooth muscle cells, and (3) recruits inflammatory cells to injured

25   regions. Smooth muscle cells lie within the layer of endothelium and are crucial to the regulation of blood

26   flow and pressure. In states of injury and disease, both cell types can exhibit dysfunction and even

27   pathological responses.

28   Endothelial dysfunction is a factor in many diseases and may contribute to the origin and/or

29   exacerbation of perfusion-limited diseases, such as MI or IHD, as well as hypertension. Endothelial

1 dysfunction is also a characteristic feature of early and advanced atherosclerosis. A primary outcome of

2 endothelial dysfunction is impaired vasodilatation, frequently due to uncoupling of NOS. It is this

3 uncoupling that appears central to impaired vasodilation and thus endothelial dysfunction.

4       One human clinical study cited in the 2004 PM AQCD reported a decrease in bronchial artery

5 diameter (BAD) among healthy adults following exposure to CAPs in combination with ozone.

6 Conclusions based on this finding were limited due to the concomitant exposure to ozone as well as a lack

7 of published results from epidemiologic and toxicological studies. Recent human clinical studies have

8 provided support to the findings described in the 2004 PM AQCD, with changes in vasomotor function

9 observed following controlled exposures to diesel exhaust, elemental carbon particles, and indoor air

10 particles. In addition, epidemiologic studies have observed associations between PM and decreases in

11 BAD and flow mediated dilatation in healthy adults and diabetics. These findings are further supported by

12 a large body of new toxicological evidence of impaired vasodilation following exposure to PM.

## 6.2.4.1. Epidemiologic Studies

13       O'Neill et al. (2005a) examined the association between 2 measures of vascular reactivity

14 (nitroglycerin mediated reactivity and flow-mediated reactivity) and ambient mean particulate pollutant

15 concentration ($PM_{2.5}$, sulfates, BC, particle number count [PNC]) on the same and previous few days

16 (O'Neill et al., 2005a). They studied a panel of 270 subjects with diabetes or at risk for diabetes, who

17 lived in the greater Boston metropolitan area. The mean $PM_{2.5}$ concentration during this study was

18 11.5 $\mu g/m^3$. Using linear regression models adjusted individually for age, gender, body mass index, and

19 race, O'Neill et al. (2005a) estimated the change in vascular reactivity associated with moving average

20 pollutant concentrations across the same and previous 5 days. Interquartile range (values not reported)

21 increases in the mean $PM_{2.5}$ concentration, BC concentration, and PNC over the previous 6 days were

22 associated with decreased vascular reactivity among diabetics, but not among subjects at risk for diabetes.

23 For sulfates, the mean concentration on lag day 0, lag day 1, and the 3-day, 4-day, and 5-day moving

24 averages all were associated with similarly sized reductions in both metrics of vascular reactivity. Among

25 diabetics, each interquartile range increase in the mean sulfate concentration over the previous 6 days was

26 associated with a 5.4% decrease in nitroglycerin-mediated reactivity (95% CI: -10.5 to -0.1) and flow-

27 mediated reactivity (-10.7% [95% CI: -17.3 to -3.5]). Also among diabetics, each interquartile range

28 increase in the mean $PM_{2.5}$ concentration over the previous 6 days was associated with a significant 7.6%

29 decrease in nitroglycerin-mediated reactivity (95% CI: -12.8 to -2.1) and a non-significant 7.6% decrease

30 in flow-mediated reactivity (95% CI: -14.9 to 0.4). Each interquartile range increase in the mean BC

31 concentration over the previous 6 days was associated with a 12.6% decrease in flow mediated reactivity

32 (95% CI: -21.7 to -2.4), but not nitroglycerin-mediated reactivity. PNC was associated with

1    non-significant decreases in both. Effect estimates were larger for type II diabetics than type 1 diabetics

2    (O'Neill et al., 2005a).

3         Dales et al. (2007) conducted a panel study of 39 healthy volunteers who sat at 1 of 2 bus stops in

4    Ottawa, Canada for 2 h (Dales et al., 2007). Flow-mediated vasodilation of the brachial artery was

5    measured immediately after the bus stop exposure, but not before. The mean $PM_{2.5}$ concentrations,

6    measured at the 2 bus stops, were 40 and 10 $\mu g/m^3$. Using mixed effects models with random slopes,

7    adjusting for location, time of the day, and temperature, Dales et al. (2007) examined the association

8    between flow-mediated vasodilation and 2-h mean $PM_{2.5}$, $PM_1$, $NO_2$, and traffic density at the bus stop

9    (vehicles/h). The authors report that each 30 $\mu g/m^3$ increase in 2-h mean $PM_{2.5}$ concentration was

10    associated with a significant 0.48% reduction in flow-mediated dilation (FMD) ($p = 0.05$). This

11    represented a 5% relative change in the maximum ability to dilate (Dales et al., 2007).

12         This same research group conducted a panel study of 25 type I or II diabetic subjects living in

13    Windsor, Ontario (aged 18-65) (Liu et al., 2007b). For each subject, personal $PM_{10}$ concentrations were

14    measured for 24 h before measurements of BAD, FMD, and other biomarkers. The mean 24-h mean $PM_{10}$

15    concentration, measured with personal monitors, was 25.5 $\mu g/m^3$. Each 10 $\mu g/m^3$ increase in 24-h mean

16    $PM_{10}$ concentration was associated with a 0.20% increase in end-diastolic FMD (95% CI: 0.04 to 0.36)

17    and a 0.38% increase in end-systolic FMD (95% CI: 0.03 - 0.73), but decreases in end-diastolic basal

18    diameter (-2.52 $\mu m$ [95% CI: -8.93 to 3.89]) and end-systolic basal diameter (-9.02 $\mu m$ [95% CI: -16.04

19    to -2.00]) (Liu et al., 2007b).

20         Rundell et al. (2007) examined the change in FMD associated with high and low $PM_1$

21    (0.02-1.0 $\mu m$) pollution in a panel of 16 young intercollegiate athletes (mean age = 20.5 ± 2.4 years), who

22    were non-smokers, non-asthmatics, and free of cardiovascular disease (Rundell, 2007). Each subject had

23    FMD of the brachial artery measured 10-20 mins before and 20-30 mins after each of two 30 min exercise

24    tests (85-90% of maximal HR). The exercise tests were done outside either on an inner campus location

25    free of automobile and truck traffic (low $PM_1$; mean = 5309 ± 1942 particles/$cm^3$) or on a soccer field

26    adjacent to a major highway (high $PM_1$; mean = 143,501 ± 58,565 particles/$cm^3$). The order of the

27    exercise test locations was chosen randomly. Using paired t-tests for analysis, they reported FMD was

28    impaired after high $PM_1$ exposure (pre-exercise: 6.8% ± 3.58%; post-exercise: 0.30% ± 2.74%;

29    $p = 0.0001$ for the change) but not low $PM_1$ exposure (pre-exercise: 6.6% ± 4.04%; Post-exercise:

30    4.89% ± 4.42%; p-value for the change not given). Further, they found basal brachial artery

31    vasoconstriction (4%; pre-exercise BAD: 4.66 ± 0.61 mm; post-exercise BAD: 4.47 ± 0.63 mm;

32    $p = 0.0002$ for the change) after the 'high $PM_1$' exposure, but not the 'low $PM_1$' exposure (-0.3%

33    pre-exercise BAD: 4.66 ± 0.63 mm; post-exercise BAD: 4.68 ± 0.61 mm; p-value for the change not

34    given) (Rundell, 2007).

1    Each study demonstrated an acute association between measures of vascular function and ambient

2    PM concentrations (Dales et al., 2007; Liu et al., 2007b; O'Neill et al., 2005a; Rundell, 2007). Two

3    studied a panel of diabetics (Liu et al., 2007b; O'Neill et al., 2005a), and two a panel of young healthy

4    subjects (Dales et al., 2007; Rundell, 2007). Only one study investigated multiple lags (lag days 0 to 6)

5    and reported the strongest association with the 6 day mean PM concentration (O'Neill et al., 2005a). In

6    other studies, responses were observed in as short as 30 mins after the exposure (Rundell, 2007). The

7    Rundell et al. (2007) findings are consistent with other studies showing an adverse response to ambient

8    particulate pollution emitted from vehicular traffic (2007a; Adar et al., 2007b; Riediker et al., 2004a;

9    Riediker et al., 2004b).

## 6.2.4.2. Human Clinical Studies

10    Some evidence of a PM-induced increase in brachial artery vasoconstriction is presented in the

11    2004 PM AQCD. Brook et al. (2002) exposed 24 healthy adults to $PM_{2.5}$ CAPs (150 $\mu g/m^3$) along with

12    120 ppm $O_3$ for a period of 2 hours. A significant decrease in BAD was observed immediately following

13    exposure compared with filtered air control. No significant changes were observed in either

14    endothelial-dependent or endothelial-independent vasomotor function, as determined by FMD and

15    nitroglycerin-mediated dilatation, respectively. However, the lack of any FMD in these subjects suggests

16    that there may have been a technical problem with the measurement of FMD in this study. A subsequent

17    analysis of the CAPs constituents revealed a significant negative association between the post-exposure

18    change in BAD and both the organic and EC concentrations of CAPs (Urch et al., 2004). However, the

19    observed vasomotor effects cannot conclusively be attributed to $PM_{2.5}$, as subjects were exposed

20    concurrently to $PM_{2.5}$ and $O_3$.

21    In a more recent randomized cross-over controlled human exposure study, Mills et al. (2005)

22    exposed 30 healthy men (20–38 years old) to both diluted DE (300 $\mu g/m^3$) and filtered air control for 1-h

23    with intermittent exercise. Half of the subjects underwent vascular assessments at 6 to 8 hours following

24    exposure to diesel or filtered air, while in the other 15 subjects, vascular assessments were performed at 2

25    to 4 hours post-exposure. DE attenuated forearm blood flow increase induced by bradykinin,

26    acetylcholine, and sodium nitroprusside infusion measured 2 and 6 hours after exposure. The authors

27    postulated that the effect of diesel on vasomotor function may be the result of reduced NO bioavailability

28    in the vasculature stemming from oxidative stress induced by the nanoparticulate fraction of DE. A

29    diesel-induced decrease in the release of t-PA was also observed at 6 hour post-exposure, which may

30    provide additional mechanistic evidence supporting the observed association between air pollution and

31    MI.

1    To further investigate the effects of DE on vasomotor function, Mills et al. (2007) exposed 20 men

2    (average age 60 years) with previous MI on two separate occasions to dilute DE (300 μg/m$^3$; mean

3    particle size 54 nm) or filtered air for 1 h with intermittent exercise. Contrary to previous findings in

4    younger, healthy adults (Mills et al., 2005), DE was found not to affect vasomotor function in peripheral

5    resistance vessels at 6 h post-exposure as measured by endothelium-dependent (acetylcholine) and

6    endothelium-independent (sodium nitroprusside) vasodilation (forearm blood flow). However, similarly

7    to younger adults, bradykinin-induced release of t-PA was observed to decrease 6 hours following

8    exposure to DE in older adults with stable coronary artery disease. In a subsequent randomized crossover

9    study, Mills et al. (2008) evaluated the effect of fine and ultrafine CAPs on vasomotor function in a group

10   of 12 males with stable coronary heart disease (mean age = 59 years), as well as in 12 healthy males

11   (mean age = 54 years). Relative to filtered air exposure, exposure to PM (average

12   concentration = 190 μg/m$^3$) did not significantly affect vascular function in either group. The authors

13   attributed the lack of response in endothelial function to the composition of the CAPs used in the study,

14   which were low in combustion-derived particles and consisted largely of sea salt.

15   Peretz et al. (2008b) exposed both healthy adults (n = 10) and adults with metabolic syndrome

16   (n = 27) for 2 h to filtered air and two concentrations of diluted DE (fine PM concentrations of 100 and

17   200 μg/m$^3$). Compared with filtered air, DE at 200 μg/m$^3$ elicited a statistically significant decrease in

18   BAD (0.11 mm; 95% confidence interval, 0.02–0.18 mm) immediately following exposure. A smaller

19   diesel-induced decrease in BAD (0.05 mm) was observed following exposure to 100 μg/m$^3$. Plasma levels

20   of endothelin-1 (ET-1) were observed to increase relative to filtered air exposure approximately 1 h after

21   exposure to 200 μg/m$^3$ DE (p = 0.01). Exposure to DE was not shown to significantly affect

22   endothelium-dependent flow-mediated dilatation. The results of this study provide evidence of an acute

23   endothelial response and arterial vasoconstriction resulting from short-term exposure to DE.

24   Diesel-induced changes in vasoconstriction and ET-1 release were more pronounced in the healthy

25   subjects than in the subjects with metabolic syndrome. The authors attributed this to small number of

26   normal individuals, and also postulated that subjects with metabolic syndrome may have stiffer vessels

27   that are not as responsive to vasoconstrictor stimuli.

28   Tornqvist et al. (2007) evaluated diesel-induced changes in vascular function 24 h following a 1-h

29   exposure with intermittent exercise in a group of 15 healthy male subjects (18–38 years old). Subjects

30   were exposed to DE at a particle concentration of 300 μg/m$^3$, as well as filtered air in a randomized

31   cross-over study design. Compared with filtered air, exposure to DE significantly reduced

32   endothelium-dependent (acetylcholine) vasodilation (p = 0.01) at 24-h post exposure. Bradykinin-induced

33   vasodilation was marginally attenuated by DE (p = 0.08), while no effects of diesel on

34   endothelium-independent vasodilation (sodium nitroprusside) were observed. Although the release of t-PA

1    was not affected by DE 24 h following exposure, the authors suggest that the persistent association

2    between diesel exposure and vasomotor function observed in this study provides supporting mechanistic

3    evidence of the observation of an increase in cardiovascular events occurring 24 h after a peak in PM

4    concentration.

5        In the previously described studies by Mills et al. (2005; 2007), Peretz et al. (2008b) and Tornqvist

6    et al. (2007), subjects were exposed to DE, which, in addition to PM, includes DE gases such as nitrogen

7    oxides and carbon monoxide. Therefore, it is possible that the observed effects may be due in part to

8    exposure to non-particle components of DE. However, Brauner et al. (2008) found that using high

9    efficiency particle air (HEPA) filters in the homes of 21 healthy older couples (60-75 years old)

10   significantly improved microvascular function (assessed by digital peripheral artery tone after arm

11   ischemia) at the end of a 48-h period when compared against a 48 hour period in the same group without

12   filtration. In this study, the HEPA filter reduced average $PM_{2.5}$ concentration from 12.6 to 4.7 $\mu g/m^3$; no

13   difference in $NO_2$ concentration was observed between the two exposure periods. The effect of particulate

14   exposure on microvascular function demonstrated in this study can most likely be attributed to changes in

15   autonomic function as no changes in inflammatory mediators, oxidative stress parameters, or coagulation

16   markers were observed.

17       A recent study evaluated the effect of EC UFP on vascular function in a group of sixteen healthy

18   subjects (18-40 years old) (Shah et al., 2008). Subjects were exposed via mouthpiece to 50 $\mu g/m^3$ UFP for

19   2 h with intermittent exercise. Venous occlusion plethysmography was used to measure reactive

20   hyperemia of the forearm prior to exposure, immediately following exposure, and 3.5 h, 21 h, and 45 h

21   post-exposure. Peak forearm blood flow was observed to increase with air at 3.5 hours post-exposure, but

22   not following exposure to UFP (p = 0.03). Venous nitrate levels were significantly lower at 21 h following

23   exposure to UFP compared with air (p = 0.038). Based on these findings the authors concluded that UFP

24   may induce vasomotor dysfunction and reduce NO bioavailability.

25       Taken together, the two studies by Mills et al. (2005; 2007) along with the studies by Peretz et al.

26   (2008a) and Tornqvist et al. (2007) suggest that, in healthy subjects, DE exposure inhibits

27   endothelium-dependent and endothelium-independent vasodilation acutely (within 2–6 h), and that the

28   suppression of endothelium-dependent vasodilation may remain up to 24 h following exposure. In

29   patients with coronary artery disease, vasodilator function does not appear to be affected 6–8 h following

30   exposure; however, vascular assessments were not performed at earlier time points. In addition, the use of

31   medications in these patients may have blunted the response to PM. The findings of Shah et al. (2008)

32   suggest that UFP carbon core may be sufficient to produce small changes in systemic vascular function,

33   but the mechanisms remain obscure. The authors demonstrated a decrease in nitrate levels following

1   exposure to EC UFP; however, venous nitrite level, which more closely reflects NO production, was

2   unchanged.

## 6.2.4.3. Toxicological Studies

3   Vascular dysfunction is a function of altered production of vasoconstrictors and vasodilators. In the

4   2004 PM AQCD, studies examining ET as an activator of vasoconstriction were limited to those

5   conducted by Bouthiller et al. (1998) and Vincent et al. (2001), in which increased plasma ET levels were

6   observed in rats exposed to high concentrations (40 or 5 mg/m$^3$) of resuspended Ottawa (EHC-93) or

7   diesel PM, respectively. The authors postulated that PM altered vasoconstriction via elevated ET. No

8   studies were cited in the 2004 PM AQCD that looked at direct measures of vasoreactivity.

9   As this area is newly emerging, numerous studies are included below that utilize intratracheal

10  instillation and/or high exposure levels; the studies that expose vessels directly to particles ex vivo are

11  included in the annex only, as their relevance is questionable. There is clearly a need for more

12  toxicological research examining the relationship between vascular measurements and PM exposures

13  using ambient particles at lower concentrations. Furthermore, no new studies have advanced the

14  knowledge in regards to ET as a biomarker of PM-induced vasoconstriction since the last PM review.

15  Nurkiewicz et al. (2004; 2006) have shown a relationship between the impairment of

16  endothelium-dependent dilation in the systemic microvasculature following intratracheal instilled PM.

17  Using a model of instilled residual oil fly ash (ROFA; partially soluble) or TiO$_2$ (insoluble) particles (0.1

18  or 0.25 mg/rat), the authors studied the systemic microvascular effects (right spinotrapezius muscle) in

19  healthy Sprague Dawley rats 24 h after exposure. The authors found comparable dose-dependent

20  impairment of calcium ionophore NO dependent-induced dilation in the arteriole, regardless of the

21  particle type (Nurkiewicz et al., 2004). NO-independent arteriolar dilation (measured by inhibiting local

22  NO synthesis with NG-monomethyl-L-arginine) was also impaired by ROFA, but a NO donor (sodium

23  nitroprusside) did not affect dilation when directly applied to the exterior arteriolar wall; this indicates

24  that arteriolar smooth muscle responsiveness was unaltered with ROFA exposure. Arteriole adrenergic

25  sensitivity to phenylephrine was not affected by 0.25 mg ROFA, indicating that contractile activity was

26  unchanged (Nurkiewicz et al., 2006).

27  Identification of increased adherence and "rolling" of leukocytes in the systemic vasculature was

28  further characterized in a follow-up intratracheal instillation study, indicative of an activated endothelium,

29  which was induced similarly for both ROFA and TiO$_2$ (Nurkiewicz et al., 2006). Vascular deposition of

30  myleoperoxidase (MPO) was observed in the spinotrapezius muscle and the authors suggested that the

31  adherent leukocytes may have deposited the MPO to be taken up by endothelial cells (Nurkiewicz et al.,

32  2006). However, this is in contrast to another study (Cozzi et al., 2006) that did not find changes in blood

1  neutrophil MPO release in mice exposed to ultrafine PM via intratracheal instillation (100 μg; Chapel

2  Hill, NC; ICR mice; assessed 24-h post-exposure), although this finding may be a reflection of differing

3  analysis approaches. Lastly, increased oxidative stress in the arteriolar wall was increased following 0.25

4  mg ROFA, as measured by the tetranitroblue tetrazolium reduction method. $TiO_2$ and ROFA induced

5  varying degrees of pulmonary inflammation in these animals, but elicited very similar vascular effects,

6  indicating that the vascular responses may be due to PM presence in the lung rather than its intrinsic

7  pulmonary toxicity. Furthermore, the microvasculature responses do not appear dependent upon the

8  soluble PM components.

9       A subsequent study by Nurkiewicz et al. (2008) compared the arteriole dilation responses with

10  inhalation exposure to fine or ultrafine $TiO_2$ (1 μm and 21 nm, respectively; mean mass concentration

11  range 3–16 and 1.5–12 mg/m$^3$, respectively) for durations ranging from 4 to 12-h in Sprague Dawley rats.

12  Similar to what was observed in the previous studies, both size fractions of $TiO_2$ induced impaired

13  dilation with calcium ionophore infusion in a dose-dependent manner. When ultrafine and fine $TiO_2$ were

14  compared at similar mass doses, the systemic microvascular dysfunction was greater with the ultrafine

15  particles. Furthermore, two exposures of differing durations and concentrations that produced equal

16  calculated pulmonary deposition of ultrafine $TiO_2$ (30 μg) demonstrated similar dilation responses,

17  indicating that impairment is dependent upon the time × concentration product.

18       Tamagawa et al. (2008) reported reduced acetylcholine (ACh)-stimulated relaxation in carotid

19  arteries from rabbits (New Zealand Whites) exposed to PM (EHC-93) for 1 or 4 weeks (2.6 mg/kg on 1st,

20  3rd, and 5th days or 2 mg/kg twice weekly, respectively) via intrapharyngeal instillation.

21  Endothelium-dependent NO-mediated vasorelaxation correlated with increased serum IL-6 levels in the

22  acute study and during weeks 1 and 2 of the 4-week exposure, which may indicate a role for systemic

23  inflammation in the response. Maximal SNP-induced dilation was not affected by PM exposure,

24  indicating that the dilatory response was not acting via endothelium-independent NO-mediated

25  mechanisms. This finding is consistent with that by Nurkiewicz et al. (2004) and suggests that the

26  arteriolar smooth muscle is not involved in the PM-impaired dilatation response.

27       Cozzi et al. (2006) used ICR mice to examine the effects of ultrafine PM exposure on vascular

28  reactivity following PM exposure and ischemia/reperfusion injury. Mice received 100 μg of ultrafine PM

29  collected from Chapel Hill, NC via intratracheal instillation. At 24-h following exposure, mice were given

30  an experimental ischemia/reperfusion injury by temporarily occluding the left anterior descending artery

31  for 20 mins. Reperfusion of the left anterior descending artery lasted 2-h and aortic rings were evaluated

32  for their contractile and dilatory responses. Maximum ACh-induced relaxation was impaired in

33  PM-exposed vessels, as well as a rightward shift in sensitivity to ACh. There was no difference in

34  constriction to phenylephrine between aortic rings from control and PM-exposed mice. The reduced

1    ACh-induced relaxation may be important for reperfusion of critical vascular beds following occlusion,

2    potentially leading to a greater area of infarction (as in this study). A new study in dogs supports the

3    results observed in the above study and provides evidence of reduced myocardial blood flow following

4    PM exposure (Bartoli et al., 2008), and is discussed in more detail in Section 6.2.3.3.

5        Vasoreactivity of aortic rings was measured 4 and 24-h following intratracheal instillation exposure

6    to 10 mg/kg PM (EHC-93; SH rats), with an increase in ACh-induced vasorelaxation observed with PM

7    exposure (Bagate et al., 2004a). This endothelium-dependent response was greatest at 4 h and was still

8    significantly different from the control group at 24 h. Similarly, vasorelaxation induced by SNP

9    (endothelium-independent) 4-h post-PM exposure was enhanced. Furthermore, the vasorelaxation

10   response was attenuated after denudation of the aortic rings, suggesting that the effect is

11   endothelium-dependent. The findings of enhanced dilation with PM exposure contrast with those reported

12   by Nurkiewicz et al. (2004; 2006), Tamagawa et al. (2008), and Cozzi et al. (2006) and may be

13   attributable to differences in PM type, animal species, or disease models. The authors attribute their

14   findings to the SH rat as a well-documented model of sympathetic hyperactivity (increased affinity of

15   aortic smooth muscle α-adrenergic receptors) that demonstrates upregulation of NO formation and/or

16   release (Safar et al., 2001). No change in vasoconstriction was observed with PM with either

17   phenylephrine or potassium chloride.

18       Consistent with the impaired vasodilatory responses observed in the microvasculature and aortic

19   rings following PM exposure, Courtois et al. (2008) demonstrated less relaxation to ACh in

20   intrapulmonary arteries of Wistar rats exposed via intratracheal instillation to a very high dose (5 mg) of

21   ambient PM (SRM1648). This response was only observed 12-h after PM exposure and not at shorter (6

22   h) or longer (24 or 72 h) time points. Interestingly, fine $TiO_2$ did not alter ACh-induced relaxation.

23       Sprague Dawley rats were exposed to $PM_{2.5}$ CAPs (5 h/day × 3 day; mean mass concentration

24   range 73.5–733 μg/m$^3$; mean mass concentration range for 3-day exposure 126.1–481.0 μg/m$^3$; Boston,

25   MA; March 1997 to June 1998) then the pulmonary arterial vasculature was evaluated (Batalha et al.,

26   2002). Some animals were repeatedly exposed to $SO_2$ (5 h/day × 5 day/wk × 6 wk) to induce chronic

27   bronchitis (CB). Morphometric measurements indicated that the pulmonary artery lumen-to-wall (L/W)

28   ratio was decreased for the both CAPs groups compared to the normal/air group. Furthermore, decreased

29   L/W ratio in CAPs-exposed animals (regardless of pre-treatment) was significantly associated with

30   particle mass and composition when the mean concentrations from the second and third exposure days

31   were used in a univariate linear regression. These results indicate a change in vascular tone following

32   acute exposure to PM.

33       The venous circulation plays a prominent role in heart failure exacerbation (Gehlbach and Geppert,

34   2004). In heart failure, patients are often volume overloaded and are subsequently placed on diuretics to

1     alleviate symptoms of pulmonary congestion and chest pain. Knuckles et al. (2008) hypothesized that if

2     veins constrict in a manner similar to arteries, then patients with severe heart failure may have temporary

3     shunting of fluid to the pulmonary circulation, which may elicit signs and symptoms of heart failure.

4     Using mesenteric vessels from mice (C57BL/6) exposed to whole diesel emissions (350 $\mu g/m^3 \times 4$ h), the

5     authors reported a significant enhancement of ET-1-induced vasoconstriction in veins with a much weaker

6     responses in arteries. In an ex vivo experiment, venous constriction was blocked by the arginine analog,

7     L-NAME, which eliminates the feedback NOS activation via endothelial $ET_B$ receptors; this is indicative

8     of impaired or uncoupled eNOS. The authors hypothesized that volatile organic compounds might be

9     responsible these effects, but no significant effects were observed for acetaldehyde, formaldehyde,

10     acetone, hexadecane, or pristane.

11        In addition to studies that look at vascular reactivity, three recent studies have examined plasma ET

12     levels following exposure to vehicle emissions. Circulating levels of ET-1 (measured 18 h post-exposure)

13     were elevated in animals exposed to gasoline emissions and filtration of particles did not reduce this

14     effect (see study details in Section 6.2.2.2.) (Campen et al., 2006). The results of Campen et al. (2006) are

15     consistent with those observed by Bouthillier et al. (1998) following a very high exposure to EHC-93, but

16     it is difficult to attribute the effects to PM alone, as Campen et al. (2006) showed that the gaseous

17     gasoline emissions were required for the ET-1 increase. In contrast, a study of old rats (21 month; Fischer

18     344) exposed to on-road highway aerosols (number concentration range 0.95–3.13$\times 10^5$ particles/cm$^3$;

19     Interstate 90 between Rochester and Buffalo, NY) for 6 h demonstrated decreased plasma ET-2 (18 h

20     post-exposure) and unchanged levels of ET-1 and ET-3 (Elder et al., 2004a).

21        One study examined the mRNA expression of ET-1 and the $ET_A$ receptor in hearts of Wistar Kyoto

22     rats exposed to CAPs (1 or 4 days; 4.5 h/day; mean mass concentration range 1000–1900 $\mu g/m^3$; May

23     2004, November 2004, September 2005; Yokohoma City, Japan) and reported correlations between

24     mRNA upregulation and increasing PM cumulative mass collected on chamber filters (Ito et al., 2008).

25     Furthermore, relative cardiac mRNA expressions of ET-1 and $ET_A$ receptor were significantly correlated

26     with CYP1B1 and HO-1 expression, indicating a possible relationship between ET-1 metabolism or

27     oxidative stress.

28        Another plasma indicator of vasomotor tone is asymmetric dimethylarginine (ADMA), which is an

29     endogenous inhibitor of NOS. Dvonch et al. (2004) assessed levels of ADMA in Brown Norway rats 24-h

30     following a 3-day $PM_{2.5}$ CAPs exposure (8 h/day; southwest Detroit, MI; July 2002). CAPs (mean mass

31     concentration 354 $\mu g/m^3$) resulted in increased plasma ADMA compared to air controls, although the

32     levels reported were well below the 2 $\mu M/L$ range associated with increased CVD risk in humans in

33     chronic studies. Therefore, the preliminary results identified a new potential biomarker of vascular tone

34     that had not previously been used in air pollution toxicological studies.

1   The toxicological findings with respect to vascular reactivity are generally in agreement and
2   demonstrate impaired dilation following PM exposure that is likely endothelium dependent. These effects
3   have been demonstrated in varying vessels (right spinotrapezius muscle, carotid arteries, and aortic rings)
4   and in response to different PM types (ROFA, $TiO_2$, EHC-93, ultrafine ambient PM). Only one study
5   showed enhanced dilation with PM exposure, but the authors attributed the conflicting results to the SH
6   rat. No constriction changes in response to phenylephrine were observed following PM exposure. The
7   responses observed in the pulmonary circulation after PM exposure include pulmonary vasoconstriction,
8   decreased L/W ratio, and impaired vasodilation in intrapulmonary arteries. These results are consistent
9   and indicate altered vascular tone. Enhancement of vasoconstriction in mesenteric veins following DE is
10  the first study of its kind to report on venous circulatory effects.

11  The ET responses were mixed, with one study demonstrating ET-1 increases after exposure to
12  gasoline emissions that were particle independent and another reported decreased ET-2, but no change in
13  ET-1 or ET-3 with on-road highway exposure. Elevated levels of ET-1 and $ET_A$ receptor mRNA were
14  noted in hearts of rats exposed to CAPs. A relatively novel marker, ADMA, was used to evaluate
15  vasomotor tone in rats and was found to be elevated following exposure to CAPs, although the results are
16  preliminary and have not been confirmed.

### PM Components

17  In the Batalha et al. (2002) study described above, univariate analyses were conducted that
18  regressed log L/W on differential exposure concentrations of tracer elements determined using principal
19  components analysis with verimax rotation. For CAPs exposure (regardless of pre-treatment), CAPs
20  mass, Si, Pb, sulfate, EC, and OC were all negatively correlated with L/W ratio. Si and sulfate were
21  negatively correlated with L/W ratio in normal rats and Si and OC were negatively correlated with L/W
22  ratio in CB rats. When a multivariate analysis was conducted using normal and CB animals, only the
23  association with Si remained significant. V was not associated with L/W ratio in any analysis.

## 6.2.5. Blood Pressure

24  One of the potential outcomes of air pollution-mediated alterations in vascular tone is its impact on
25  variable BP or hypertension. BP is tightly regulated by autonomic (central and local), cardiac, renal, and
26  regional vascular homeostatic mechanisms with changes in arterial tone being countered by changes in
27  cardiac contractility, HR, or fluid volume. The evidence of PM-induced changes in BP presented in the
28  2004 PM AQCD is limited and inconsistent. Recent epidemiologic, human clinical, and toxicological
29  studies have similarly reported conflicting results regarding the effect of PM on BP. However, the

1   majority of these studies have evaluated changes in BP at some point following exposure to PM. A

2   significant increase in diastolic BP was observed in the only human clinical study that evaluated BP

3   during exposure (concomitant exposure to CAPs and ozone). In addition, evidence from toxicological

4   studies suggests that the effect of PM on BP may be modified by health status, as PM-induced increases

5   in BP have been more consistently observed in SH rats.

## 6.2.5.1. Epidemiologic Studies

6       Increased BP was associated with PM concentration in two of three studies reviewed in the 2004

7   PM AQCD. Increases in left ventricular BP (systolic and diastolic) are well established risk factors for

8   cardiovascular mortality/morbidity (Welin et al., 1993). Changes in HR and BP both reflect changes in

9   autonomic tone, and have been examined following short-term increases in PM pollution in several recent

10   studies.

11       Ibald-Mulli et al. (2004) examined associations between BP (systolic [SBP], diastolic [DBP]) and

12   ambient $PM_{2.5}$ concentrations, UFP counts, and ACP counts in a multicity panel study (Amsterdam,

13   Netherlands; Helsinki, Finland; Erfurt, Germany) of 131 adults with coronary heart disease (Ibald-Mulli

14   et al., 2004). Although based on the same ULTRA Study (Timonen et al., 2006) with study methods as

15   described previously in Section 6.2.1.1., the study period was different. They investigated changes in BP

16   (SBP and DBP) associated with mean $PM_{2.5}$, UFP, and ACP concentration/counts (lag days 0, 1, and 2, as

17   well as the 5 day mean) in each city and then generated a pooled estimate across the cities. The median

18   $PM_{2.5}$ concentration, median UFP count, and median ACP count for each city are given below in Table 6-

19   3. Pooled analyses across all 3 cities showed small, but statistically significant decreases in SBP and DBP

20   associated with different lagged concentrations/counts of each particulate pollutant.

**Table 6-3.      Median particulate concentration.**

| City | Median daily $PM_{2.5}$ concentration (µg/m³) | Median daily UFP concentration (0.01-0.1 µm; particles/cm³) | Median daily ACP concentration (0.1-1.0 µm; particles/cm³) |
|---|---|---|---|
| Amsterdam, Netherlands | 16.9 | 17,147 | 1,874 |
| Erfurt, Germany | 16.3 | 19,198 | 1,492 |
| Helsinki, Finland | 10.6 | 14,886 | 1,200 |

21       Each 10 µg/m³ increase in the mean $PM_{2.5}$ concentration over the previous 5 days was associated

22   with a 0.36 mmHg decrease in SBP (95% CI: -0.99, 0.27) and a 0.39 mmHg decrease in DBP (95%

23   CI: -0.75 to -0.03). Each 10,000 particles/cm³ increase in UFP was associated with a 0.72 mmHg decrease

1  in SBP (95% CI: -1.92, 0.49), and a 0.70 mmHg decrease in DBP (95% CI: -1.38 to -0.02). Each 1000

2  particles/cm$^3$ increase in 5 day average ACP was associated with a 1.11 mmHg decrease in SBP (95%

3  CI: -2.12 to -0.09) and a 0.95 mmHg decrease in DBP (95% CI: -1.53 to -0.37). The authors concluded

4  that these findings do not support previous findings of an increase in BP associated with increases in

5  particulate pollutant concentrations (Ibald-Mulli et al., 2004).

6       Single city studies examining the association between BP and particulate air pollution have been

7  done in several U.S. and Canadian cities. Dales et al. (2007) conducted a panel study of 39 healthy

8  volunteers who sat outside at two different bus stops for 2-h in Ottawa, Canada (Dales et al., 2007). The

9  median $PM_{2.5}$ concentrations measured at the bus stops during each 2-h exposure session were 40 and

10  10 µg/m$^3$. Post exposure SBP and DBP were not associated with the mean $PM_{2.5}$ concentration measured

11  at the bus stops during the 2 hour exposure session. The change in BP (post-exposure – pre-exposure)

12  could not be evaluated, as health measurements were only made after the 2-h exposure session (Dales et

13  al., 2007).

14       Jansen et al. (2005) studied changes in BP among 16 older subjects (aged 60-86 years) with asthma

15  or COPD in Seattle Washington, associated with indoor, outdoor, and personal $PM_{10}$, $PM_{2.5}$, and BC

16  measurements (levels within the health measurement session) on 12 consecutive days. The mean daily

17  outdoor $PM_{10}$ and $PM_{2.5}$ concentrations were 13.47 and 10.47 µg/m$^3$, respectively. The mean daily

18  outdoor BC concentration was 2.01 µg/m$^3$. The study authors reported that no associations were observed

19  between BP and daily mean $PM_{10}$, $PM_{2.5}$, or BC concentrations, but did not present any of these results in

20  the paper (Jansen et al., 2005).

21       Zanobetti et al. (2004) examined the association between BP (SBP, DBP, and mean arterial BP) and

22  mean $PM_{2.5}$ concentrations in the previous 24, 48, 72, 96, and 120 h in 62 elderly, cardiac rehabilitation

23  patients in Boston, MA (Zanobetti et al., 2004). The median $PM_{2.5}$ concentration during the study was

24  8.8 µg/m$^3$. Each 10.4 µg/m$^3$ increase in mean $PM_{2.5}$ concentration in the previous 120 hours was

25  associated with significant increases in resting DBP (2.82 mmHg, 95% CI: 1.26, 4.41), SBP (2.68 mmHg,

26  95% CI: 0.04, 5.38), and mean arterial BP (2.76 mmHg, 95% CI: 1.07, 4.48) (Zanobetti et al., 2004).

27       Mar et al. (2005b) studied this same $PM_{2.5}$-BP association in 88 subjects aged >57 years in Seattle,

28  WA. Among healthy subjects taking medications (bronchodilators, inhale corticosteroids,

29  anti-hypertensives, beta-blockers, calcium channel blockers, and/or cardiac glycosides), each 10 µg/m$^3$

30  increase in mean outdoor $PM_{2.5}$ concentration on the same day as the BP measurement was made was

31  associated with small increases in SBP and DBP (the results for these analyses were presented in figures

32  only). However, among all subjects, each 10 µg/m$^3$ increase in same day mean $PM_{2.5}$ concentration was

33  associated with non-significant decreases in SBP (-0.81 mmHg, 95% CI: -2.34, 0.73) and DBP (-0.46

34  mmHg, 95% CI: -1.49, 0.57) (Mar et al., 2005b).

As described earlier, Ebelt et al. (2005) conducted a repeated measures panel study of 16 patients with COPD in the summer of 1998 in Vancouver, British Columbia to evaluate the relative impact of ambient and non-ambient exposures to $PM_{2.5}$, $PM_{10}$, and $PM_{10-2.5}$ on multiple health outcomes including ectopy and BP. Using the same analytic methods, pollutant concentrations, and lags, they reported decreased systolic BP associated with same day ambient exposures to each PM size fraction (results were presented in figures only) (Ebelt et al., 2005).

Two similar studies were done in Incheon, South Korea (Choi et al., 2007) and Taipei, Taiwan (Chuang et al., 2005b). Both reported significant increases in BP associated with acute increases in ambient PM. Choi et al. (2007) reported significantly increased SBP and DBP associated with the mean $PM_{10}$ concentration over the same and previous 2 days in the warm season only (July to September). Chuang et al. (2005a) reported significant increases in SBP and DBP associated with the mean UFP count (0.01 to 0.1 µm particles) 1 to 3 hours before the BP measurement (Chuang et al., 2005b).

These studies (Choi et al., 2007; Chuang et al., 2005a; Dales et al., 2007; Ibald-Mulli et al., 2004; Mar et al., 2005b; Zanobetti et al., 2004) are not entirely consistent with regard to their BP-PM associations. Most have reported increases in SBP and DBP associated with increases in either $PM_{2.5}$, $PM_{10}$, or UFP (Choi et al., 2007; Chuang et al., 2005a; Mar et al., 2005b; Zanobetti et al., 2004). However, two studies reported small decreases in BP associated with multiple particulate pollutants (Ibald-Mulli et al., 2004); Mar et al., 2005), Dale et al. (2007) reported no change in BP associated with a 2 hour exposure to bus stop $PM_{2.5}$ and Jansen at al. (2005) reported null findings among older adults in Seattle, WA. Exposure lags ranging from 1-3 hours (Chuang et al., 2005a), to the same day (Ebelt et al., 2005; Mar et al., 2005b; Rich et al., 2008), to the mean across the previous 5 days (Zanobetti et al., 2004) were reported as having the strongest associations with BP.

### *Right Ventricular Pressure*

Several recent studies, summarized in the section on hospital admissions and ED visits for CVD causes, have reported increased risk of hospital admissions for congestive heart failure associated with increased PM concentration on the same day (Wellenius et al., 2005b; 2006b). As a possible mechanism for these reported associations, Rich et al. (2008) hypothesized that these hospital admissions for decompensation of heart failure would be preceded by more subtle increases in pulmonary arterial (PA) and right ventricular (RV) diastolic pressures. They used passively monitored PA and RV pressures on 5807 person-days, among 11 subjects implanted with the Chronicle Implantable Hemodynamic Monitor [Medtronic, Inc. Medtronic, MN]). Using a two-stage modeling process (generalized additive model and mixed effects model adjusted for time trend, weekday, calendar month, apparent temperature, and barometric pressure), they examined the change in daily mean right heart pressures associated with mean

PM$_{2.5}$ concentration on the same and previous 6 days. Each 11.62 µg/m$^3$ increase in same day mean PM$_{2.5}$ concentration was associated with small but statistically significant increases in estimated PA diastolic pressure (0.19 mmHg; 95% CI: 0.05, 0.33) and RV diastolic pressure (0.23 mmHg; 95% CI: 0.11, 0.34). These effects were not attenuated when controlling for all lags simultaneously. Thus, PM induced right heart pressure increases may mark another potential pathway between PM exposure and incidence of cardiovascular events, but further studies on this same hypothesis are needed for confirmation.

Wellenius et al. (2007) conducted a panel study of 28 subjects living in the greater Boston metropolitan area, each with chronic stable heart failure and impaired systolic function. They hypothesized that circulating levels of B-type natriuretic peptide (BNP), measured in whole blood at 0, 6, and 12 weeks, were associated with acute changes in ambient air pollution, as a possible mechanistic explanation for the observed association between hospital admissions for heart failure and ambient PM concentration (2005b; Wellenius et al., 2006b). During the study, the mean PM$_{2.5}$ concentration was 10.9 µg/m$^3$, while the mean BC concentration was 0.73 µg/m$^3$. Using linear mixed models, they reported no association between any pollutant (PM$_{2.5}$, CO, SO$_2$, NO$_2$, O$_3$, and BC) and BNP at any lag (e.g., each 10 µg/m$^3$ increase in mean daily PM$_{2.5}$ concentration [0.8% increase in BNP; 95% CI: -16.4, 21.5]) (Wellenius et al., 2007).

## 6.2.5.2. Human Clinical Studies

Only one controlled human exposure study cited in the 2004 PM AQCD reported any PM-induced changes in BP. Gong et al. (2003a) found that exposure to PM$_{2.5}$ (174 µg/m$^3$) decreased systolic BP in asthmatics, but increased systolic BP in healthy subjects. Among healthy adults, BP was not affected following 2-h exposures to 200 µg/m$^3$ diesel PM (Nightingale et al., 2000), 150 µg/m$^3$ PM$_{2.5}$ CAPs with 120 ppb O$_3$ (Brook et al., 2002), or 10 µg/m$^3$ ultrafine carbon particles (Frampton, 2001). One recent study demonstrated a significant increase (9.3%) in diastolic BP among healthy adults immediately prior to the end of a 2-h exposure to 150 µg/m$^3$ PM$_{2.5}$ CAPs in combination with 120 ppb O$_3$ (Urch et al., 2005). The authors also found that the magnitude of change in BP was significantly associated with PM$_{2.5}$ carbon content, but not total PM$_{2.5}$ mass. It was postulated that the disparity between these finding and those of a similar study by the same group (Brook et al., 2002) could be due to differences in experimental methods. The Brook et al. (2002) study measured post-exposure BP approximately 10 mins following exposure, while the study by Urch et al. (2005) measured BP during exposure.

The effect of PM on BP has been further investigated in several recent controlled human exposure studies. Routledge et al. (2006) did not observe any changes in BP among healthy older adults and older adults with stable angina following a 1-h exposure to UF EC (50 µg/m$^3$), with or without co-exposure to 200 ppb SO$_2$. Similarly, Shah et al. (2008) reported no changes in BP among younger healthy adults

1  following exposure to UF EC. Beckett et al. (2005) found no effect of either fine or ultrafine zinc oxide

2  (500 μg/m$^3$) on BP in a group of healthy adults. Two new studies have assessed BP changes following a

3  1-h exposure to DE with a particle concentration of 300 μg/m$^3$. Tornqvist et al. (2007) reported no

4  changes in BP following exposure to DE compared with filtered air control; however, post-exposure BP

5  was only measured 24-h following exposure. In a similar study, Mills et al. (2005) evaluated changes in

6  BP 2 h following exposure to DE and found a 6 mmHg increase in diastolic BP of marginal statistical

7  significance (p = 0.08) compared to filtered air control. At lower particle concentrations in dilute DE

8  (100-200 μg/m$^3$ fine PM), Peretz et al. (2008a) did not observe any changes in systolic or diastolic BP in

9  either healthy adults or adults with metabolic syndrome following a 2-hour exposure. The findings of

10  these new studies do not provide conclusive evidence of an association between PM exposure and an

11  increase in BP; however, they do suggest that there is a need for additional investigations of PM-induced

12  changes in BP at various time points following exposure.

## 6.2.5.3. Toxicological Studies

13  In healthy animal models, little evidence exists for significant BP changes following inhalation

14  exposure to environmentally-relevant concentrations of PM. Only one animal toxicological study is

15  mentioned in the 2004 PM AQCD that examined BP with PM exposure and no effect was observed

16  (Vincent et al., 2001).

17  In a recent study of dogs, exposure to PM$_{2.5}$ CAPs from Boston (mean concentration 358.1 μg/m$^3$;

18  concentration range 94.1–1557 μg/m$^3$) for 5 h resulted in increased systolic BP (2.7 mmHg), diastolic BP

19  (4.1 mmHg), mean arterial pressure (3.7 mmHg), and lowered pulse pressure (1.7 mmHg) when measured

20  upstream of the femoral artery (Bartoli et al., 2008). Administration of an α-adrenergic antagonist

21  (prazosin) prior to CAPs attenuated the BP responses. These findings indicate that CAPs exposure may

22  have activated α-adrenergic receptors and increased peripheral vascular resistance. Baroreflex sensitivity

23  was measured immediately before and after exposure during a transient elevation of arterial pressure that

24  was induced by phenylephrine; increased baroreflex sensitivity was observed in subgroup of dogs

25  exposed to CAPs, which is consistent with an upregulation of vagal reflexes.

26  Chang et al. (2004) noted slight increases in SH rat BP (5–10 mmHg) when exposed to ultrafine

27  CAPs (mean mass concentration 202 μg/m$^3$) during spring months. However, during summer months,

28  when the CAPs exposure level was less (140 μg/m$^3$), this effect was not observed. It was unclear,

29  therefore, whether the effects were seasonal or dose-related. In a preliminary study of SH rats exposed to

30  CAPs during a dust storm event, mean BP was elevated the third and fourth h of a 6-h exposure, although

31  interpretation of this finding is difficult due to few animals in the exposure group (n = 2; details provided

32  above) (Chang et al., 2007b). In another study, the increased change in mean BP measured using the tail

cuff method following CAPs exposure weakly correlated with PM mass accumulated on chamber filters over the entire exposure duration (see Section 6.2.4.3. for details) (Ito et al., 2008). Furthermore, $ET_A$ receptor mRNA expression in cardiac tissue was positively correlated with the change in mean BP.

Limited toxicological evidence provides support for elevated BP in dogs or rats with CAPs, ultrafine CAPs, or CAPs during a dust storm event. However, most of the studies reviewed above were conducted outside of the U.S.

# 6.2.6. Cardiac Contractility

The 2004 PM AQCD did not include any toxicological studies that evaluated cardiac contractility either directly or indirectly following exposure to PM. Two recent animal toxicological studies have demonstrated reductions in cardiac fractional shortening, diminished ejection shortening, or changes in the QA interval following PM exposure. The results of these studies provide some evidence of PM-induced changes in cardiac contractility in animal models.

## 6.2.6.1. Toxicological Studies

The strength of the contracting heart is reflected by its contractility. In heart failure, contractility wanes significantly and the heart can not compensate during periods of increased physical activity. Measuring true contractility in a whole animal is difficult, requiring extensive surgical instrumentation and monitoring. There were no toxicological studies that examined cardiac contractility in the last PM AQCD.

A recent study using old (18 to 28-mo-old) mice (C57BL/6, C3H/HeJ, and B6C3F1) demonstrated significant reductions in cardiac fractional shortening (due to increased left ventricular end-diastolic and end-systolic diameters) following a 4-day (3 h/day) exposure to carbon black ($PM_{2.5}$ mean concentration 401 μg/m$^3$; $PM_{10}$ mean concentration 553 μg/m$^3$) using echocardiography (Tankersley et al., 2008). Hemodynamic measurements of diminished ejection fraction and maximum change in pressure over time further supported lowered myocardial contractility. Furthermore, increased right ventricular pressure associated with elevated right atrial and pulmonary vascular pressures and resistance, was indicative of pulmonary vasoconstriction in carbon black exposed mice. Heart tissue and isolated cardiomyocytes from exposed animals demonstrated enhanced ROS that was partially attributable to NOS3-uncoupling and elevated MMP2 and MMP9 levels, which may implicate myocardial remodeling. The combined results from this study suggest that cellular mechanisms involving NOS-uncoupled ROS generation likely mediate PM-induced cardiac effects. Furthermore, mRNA expression for atrial and brain natriuretic peptides (ANP and BNP, respectively) was increased in hearts from exposed mice compared to control,

1    which is consistent with pulmonary congestion. There were no reported strain-related differences in any

2    response.

3        In a less invasive procedure employing radiotelemetry, SH rats were repeatedly and alternately

4    exposed to ultrafine CAPs in Taiwan on separate days in spring or summer (details provided in Section

5    6.2.5.3.) (Chang et al., 2004). The QA interval was used as an indirect measure of cardiac contractility

6    and was calculated as the time duration between the Q wave in the ECG and point A (upstroke in aortic

7    pressure) in the pressure trace. During the spring exposure, QA interval decreased by 1.6 ms as

8    demonstrated by fixed effects in linear mixed-effects modeling, which indicates an increase in cardiac

9    contractility. There were no changes in QA interval observed for the summer months, which may be

10   attributable to lower ultrafine PM concentrations (mean mass concentration 140 $\mu g/m^3$) or differing PM

11   compositions.

12       All of the studies above provide some evidence that cardiac contractility may be altered

13   immediately following PM exposure in animal models. Results from the Tanksersley (2008) study

14   provide the strongest support for PM-induced contractility changes, as echocardiography and

15   hemodynamic measurements are well-established for examining cardiac function.

# 6.2.7. Systemic Inflammation

16       The evidence presented in the 2004 PM AQCD of increases in markers of systemic inflammation

17   associated with PM was limited and not sufficient to formulate a definitive conclusion. Recent human

18   clinical and toxicological studies continue to provide mixed results for an effect of PM on markers of

19   systemic inflammation including cytokine levels, C-reactive protein, and white blood cell count. While

20   results from recent epidemiologic studies have also been inconsistent across studies, there is some

21   evidence to suggest that PM levels may have a greater effect on inflammatory markers among populations

22   with preexisting diseases.

## 6.2.7.1. Epidemiologic Studies

23       Several studies reviewed in the 2004 PM AQCD investigated the association of short-term

24   fluctuations in PM concentration with markers of inflammation (e.g. oxygen saturation, CRP and white

25   blood cells). These preliminary studies were found to offer limited support for mechanistic explanations

26   of the associations between PM concentration and heart disease outcomes. Recent studies, published since

27   2002, are reviewed below.

28       Diez-Roux et al. (2006) used the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to examine

29   the whether C-reactive protein (CRP) increased in response to changes in the mean ambient $PM_{2.5}$

1  concentrations in the prior day, prior 2 days, prior week, prior 30 days, and prior 60 days (Diez Roux et

2  al., 2006). Subjects (n = 5,634) lived in either Baltimore City or County, MD, Chicago, IL, Forsyth

3  County, NC, Los Angeles County, CA, Northern Manhattan and the Bronx, NY, or St. Paul, MN. Each

4  10 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentrations over the previous 30 days was weakly associated

5  with a 3% increase in CRP (95% CI: -2% to 10%). Similarly, each 10 $\mu g/m^3$ increase in the mean $PM_{2.5}$

6  concentrations over the previous 60 days was weakly associated with a 4% increase in CRP (95%

7  CI: -3%, 11%). However, there was no association between CRP level and the mean $PM_{2.5}$ concentrations

8  on the prior day, prior 2 days, or prior week. The authors state that the $PM_{2.5}$ averaging process for longer

9  periods of time (i.e. mean for 30 or 60 days vs. the mean for 1 day) reduces exposure error and hence

10  increases the ability to detect association with 30 and 60 day means, but not 1 and 2 day means (Diez

11  Roux et al., 2006).

12  Ruckerl et al. (2007b) conducted a multi-city longitudinal study to examine whether changes in

13  markers of inflammation were associated with short-term increases in particulate concentrations ($PM_{10}$,

14  $PM_{2.5}$, particle number concentration [PNC]) and gaseous pollutant ($NO_2$, $SO_2$, CO, $O_3$). Study subjects

15  were MI survivors (n= 1003) living in either Athens, Greece; Augsburg, Germany; Barcelona, Spain;

16  Helsinki, Finland; Rome, Italy; or Stockholm, Sweden. Repeated measurements of IL-6 and CRP were

17  made during the study. Fibrinogen was also measured in this study and results are discussed in Section

18  6.2.8.1. The mean city-specific pollutant concentrations during the study are shown below in Table 6-4.

**Table 6-4.    Ambient concentrations in six European cities.**

| Pollutant | Helsinki | Stockholm | Augsburg | Rome | Barcelona | Athens |
|---|---|---|---|---|---|---|
| PNC (particles/cm$^3$) | 8,534 | 9,748 | 11,876 | 34,450 | 18,133 | 20,589 |
| $PM_{2.5}$ ($\mu g/m^3$) | 8.2 | 8.8 | 17.4 | 24.5 | 24.2 | 23.0 |
| $PM_{10}$ ($\mu g/m^3$) | 17.1 | 17.8 | 33.1 | 42.1 | 40.7 | 38.5 |

Source: Ruckerl et al. (2007b)

19  In pooled analyses, each interquartile range (not provided) increase in PNC in the 12 to 17 hours

20  before the health measurement was associated with a 2.7% increase in the geometric mean IL-6 (95%

21  CI: 1.0, 4.6). None of the pollutants, at any lag, were associated with CRP levels in these subjects. There

22  did not appear to be effect modification of these results by smoking, diabetes, or heart failure (Ruckerl et

23  al., 2007b). Two smaller studies conducted by the same group of investigators among 57 male patients

24  with coronary heart disease in Efurt, Germany found associations of UFP, ACP and $PM_{10}$ with CRP

25  (Ruckerl et al., 2006) and UFP and ACP with sCD40L, a marker for platelet activation (Ruckerl et al.,

26  2007b).

1    Single city studies of several markers of inflammation have also been conducted in the U.S. and

2    Canada. To examine changes in inflammation related to short-term fluctuations in air pollution, Delfino et

3    al. (2008) measured CRP, IL-6, TNF-α, sP-selectin, sVCAM-1 and sICAM-1 in blood during a period of

4    12 weeks. Associations of these markers with average PM concentration (quasi-ultrafine [$PM_{0.25}$],

5    $PM_{0.25-2.5}$, $PM_{10-2.5}$, EC, OC, BC, primary OC, secondary OC, PN) 24-h to 9 days prior to the blood draw

6    were examined. Subjects included residents of two downtown Los Angeles nursing homes who were 65+

7    years old with a history of coronary artery disease. Both 24-h average and multiday average

8    concentrations of quasi-ultrafine, EC, primary OC, BC, PN and gaseous pollutants were associated with

9    CRP, IL-6 and sP-selectin in this study.

10    Pope et al. (2004a) conducted a panel study of 88 non-smoking, elderly subjects residing in the Salt

11    Lake City, Ogden, and Provo metropolitan area of Utah (Pope et al., 2004a). The mean $PM_{2.5}$

12    concentration during the study was 18.9 µg/m$^3$. Each 100 µg/m$^3$ increase in same day mean $PM_{2.5}$

13    concentration was associated with a 0.81 mg/dL increase in CRP (95% CI: 0.48, 1.14), but not white

14    blood cells (WBC). However, when excluding 1 influential subject, each 100 µg/m$^3$ increase in same day

15    mean $PM_{2.5}$ concentration was associated with only a 0.19 mg/dL increase in CRP (95% CI: -0.01, 0.39)

16    (Pope et al., 2004a). Several markers of coagulation were examined in this study and are discussed in

17    Section 6.2.8.1.

18    Zeka et al. (2006b) studied 710 elderly members of the VA Normative Aging Study to examine

19    changes in systemic markers of inflammation and acute changes in particulate pollutant concentrations in

20    the previous 48 hours, 1 week, and 2 weeks (Zeka et al., 2006b). The median 48-h PNC was 24,200

21    particles/cm$^3$, while the median 48-h $PM_{2.5}$ concentration was 9.39 µg/m$^3$. The median 48 hour BC

22    concentration was 0.61 µg/m$^3$, while the median 48 sulfate concentration was 1.84 µg/m$^3$. They did not

23    find consistent or significant associations with any pollutant and CRP. The authors state that the largest

24    effects were observed for the mean PNC and BC concentration in the previous 4 weeks, but there were no

25    consistent findings for lagged $PM_{2.5}$ or sulfates (Zeka et al., 2006b).

26    O'Neill et al. (2007) conducted a cross-sectional study of 92 Boston residents with type 2 diabetes,

27    to examine the association between plasma levels of intercellular adhesion molecule (ICAM-1), vascular

28    adhesion molecule (VCAM-1) and PM concentrations (O'Neill et al., 2007). Results for markers of

29    coagulation measured in this study are discussed in Section 6.2.8.1. $PM_{2.5}$, BC, and sulfate concentrations

30    were measured 0.5 km from the patient exam site. The mean $PM_{2.5}$ concentration during the study was

31    11.4 µg/m$^3$. The mean BC concentration was 1.1 µg/m$^3$, and the mean sulfate concentration was

32    3.0 µg/m$^3$. For all moving averages examined (1-6 days), increases in mean $PM_{2.5}$ and BC concentration

33    were associated with increased ICAM-1 and VCAM-1 concentrations. Each 7.6 µg/m$^3$ increase in the

34    mean $PM_{2.5}$ concentration over the previous 6 days was associated with a 11.76 ng/mL increase in

1    VCAM-1 (95% CI: 3.48-20.70), and each 0.6 µg/m$^3$ increase in the mean BC concentration over the

2    previous 6 days was associated with a 27.51 ng/mL increase in VCAM-1 (95% CI: 11.96, 45.21).

3    However, there were no consistent associations between the mean sulfate concentration at any lag and any

4    marker (O'Neill et al., 2007).

5        Sullivan et al. (2007) conducted a panel study of n = 47 subjects (aged >55 years) either with

6    COPD (n = 23) or without COPD (n = 24) in Seattle, WA (Sullivan et al., 2007). They examined the

7    association between levels of CRP and mean daily PM$_{2.5}$ concentration. Results for fibrinogen and

8    d-Dimer are discussed in Section 6.2.8.1. The median PM$_{2.5}$ concentration during the study was

9    7.7 µg/m$^3$. They did not find any associations between 24-h mean PM$_{2.5}$ concentrations and levels of CRP

10   in individuals with or without COPD. Similarly, in the study by Liu et al. (2007b), conducted in Toronto

11   Ontario, neither CRP (0.11 µg/mL; 95% CI: -0.03–0.25) nor TNF-α (0.03 pg/mL; 95% CI: -0.07–0.13)

12   was associated with 24-h mean PM$_{10}$ concentration. However, significant positive associations with

13   markers of oxidative stress, FMD and BP were found (Liu et al., 2007b) are discussed in Sections 6.2.9.1.,

14   6.2.4.1., and 6.2.5.1., respectively.

15       In the St. Louis Bus Study, each 5.4 µg/m$^3$ increase in the mean PM$_{2.5}$ concentration over the

16   previous week was associated with 5.5% increase in WBC (95% CI: 0.10–11) (Dubowsky et al., 2006).

17   Each 6.1 µg/m$^3$ increase in the mean PM$_{2.5}$ concentration over the previous 5 days was associated with a

18   14% increase in CRP among all subjects (95% CI: -5.4–37), but an 81% increase in CRP (95% CI: 21–

19   172) among subjects with diabetes, obesity, and/or hypertension. Associations between PM$_{2.5}$ and IL-6

20   were only observed among those with diabetes, obesity, and/or or hypertension (Dubowsky et al., 2006).

21   In another study of in-vehicle PM, each 10 µg/m$^3$increase in PM$_{2.5}$ concentration during a work-shift was

22   associated with decreased lymphocytes, increased mean corpuscular volume, neutrophils, and CRP over

23   the next 10-14 hours among 9 healthy North Carolina state troopers (Riediker et al., 2004b).

24       Using another marker of inflammation, DeMeo et al. (2004) estimated the change in oxygen

25   saturation and mean PM$_{2.5}$ concentration in the previous 24 h (DeMeo et al., 2004) in a panel of elderly

26   subjects. They used the same panel of elderly Boston residents (n = 28) and study protocol and analytic

27   methods (12 weeks of repeated oxygen saturation measurements) as Gold et al. (2005) and Schwartz et al.

28   (2005b) in studies of ST-segment depression and HRV, respectively. At each clinic visit, subjects had 5

29   mins each of rest, standing, post-exercise rest, and 20 cycles of paced breathing. The median PM$_{2.5}$

30   concentration during the study period was 10.0 µg/m$^3$ (Schwartz et al., 2005b). DeMeo et al. (2004)

31   reported that each 13.4 µg/m$^3$ increase in the mean PM$_{2.5}$ concentration in the previous 6 hours was

32   associated with a 0.2% decrease in oxygen saturation (95% CI: -0.3–0.0) during the baseline rest period.

33   Each 13.4 µg/m$^3$increase in mean 6 hour PM$_{2.5}$ concentration was also associated with a decline in oxygen

34   saturation during the post-exercise period (-0.2%; 95% CI: -0.3–0.0), and post-exercise paced breathing

1   period (-0.1%; 95% CI: -0.3–0.0), but not during the exercise period. The authors suggest that these

2   oxygen saturation reductions may result from pulmonary vascular and inflammatory changes (DeMeo et

3   al., 2004).

4        International studies of the effect of air pollution on markers of inflammation have been conducted.

5   In a large cross-sectional study of healthy subjects in Tel Aviv, Steinvil et al. (2008) examined biological

6   markers of inflammation (CRP and WBC) collected as part of routine health examinations for 3,659

7   individuals. Associations with air pollutants (including $PM_{10}$) measured at local monitoring sites for the

8   day of the examination and up to 7 days prior were examined. No significant associations were found

9   between pollutant levels and indications of enhanced inflammation. By contrast, both $PM_{10}$ and $PM_{2.5}$

10  were associated with increases in hs-CRP in healthy students in Taiwan (Chuang et al., 2007a).

### Summary

11       The most commonly measured marker of inflammation in the studies reviewed was CRP. CRP was

12  adversely associated with PM in some (Chuang et al., 2008; Delfino et al., 2008; Diez Roux et al., 2006;

13  Dubowsky et al., 2006; Riediker et al., 2004b) but not all studies (Liu et al., 2007b; Ruckerl et al., 2007a;

14  Steinvil et al., 2008; Sullivan et al., 2007; Zeka et al., 2006b). A multi-city study of MI survivors in

15  Europe failed to provide evidence of an effect of PM on CRP (Ruckerl et al., 2007a). However, IL-6 was

16  associated with PNC 12-17 h prior to the health measurement in this population (Ruckerl et al., 2007a).

17  Two studies reported an adverse associations with markers of inflammation among diabetics or those with

18  hypertension (Dubowsky et al., 2006; O'Neill et al., 2007). Several other markers of inflammation have

19  been examined in relation to PM (e.g. VCAM, ICAM, sP-selectin, oxygen saturation) but the number of

20  studies examining the same marker is too few to allow results to be compared across studies.

## 6.2.7.2. Human Clinical Studies

21       Several human clinical studies were included in the 2004 PM AQCD which evaluated markers of

22  systemic inflammation following exposure to PM. Salvi et al. (1999) exposed 15 healthy volunteers

23  (21-28 years old) for 1 h to DE (300 $\mu g/m^3$ particle concentration) and observed a significant increase in

24  neutrophils in peripheral blood 6 hours post-exposure compared with filtered air control. Gong et al.

25  (2003a) did not observe any effect of $PM_{2.5}$ CAPs (174 $\mu g/m^3$) on serum amyloid A, while Frampton

26  (2001) reported no change in leukocyte activation following exposure to a low concentration (10 $\mu g/m^3$)

27  of UF carbon. In a more recent study, Frampton et al. (2006) evaluated the effect of varying

28  concentrations (10-50 $\mu g/m^3$) of UF carbon on blood leukocyte expression of adhesion molecules in

29  healthy and asthmatic adults. Healthy subjects (n = 40) were exposed for 2-h to filtered air and UF carbon

30  under three separate protocols: 10 $\mu g/m^3$ at rest (n = 12), 10 and 25 $\mu g/m^3$ with intermittent exercise

1    (n = 12), and 50 μg/m$^3$ with intermittent exercise (n = 16). Asthmatics (n = 16) were exposed at a single

2    concentration (10 μg/m$^3$) for 2 h with intermittent exercise. Leukocyte expression of surface markers were

3    quantified using flow cytometry on peripheral venous blood samples collected prior to and immediately

4    following exposure, as well as at 3.5 and 21 hours post-exposure. Among healthy resting adults, UFP

5    exposure at a concentration of 10 μg/m$^3$ had no effect on blood leukocytes. The expression of adhesion

6    molecules CD54 and CD18 on monocytes, and CD18 on PMNs was shown to decrease with UFP

7    exposure in healthy exercising adults. In exercising asthmatics, expression of CD11b on monocytes and

8    eosinophils, as well as CD54 on PMNs were reduced following exposure to UFP. In both asthmatics and

9    healthy adults, a UFP-induced decrease in eosinophils and basophils was observed. Although the clinical

10   significance of these findings is unclear, the authors concluded that their findings of UFP-induced

11   changes in leukocyte distribution and expression were consistent with increased retention of leukocytes in

12   the pulmonary vasculature, which may be due to an increase in pulmonary vasoconstriction.

13        In an effort to better understand the inflammatory response of exposure to PM, Peretz et al. (2007)

14   conducted a pilot study in which gene expression in peripheral blood mononuclear cells (PBMCs) of

15   healthy human volunteers was evaluated following a 2 hour controlled exposure to DE (200 μg/m$^3$ PM$_{2.5}$).

16   Adequate RNA samples for microarray analysis (Affymetrix U133 Plus 2.0) from both pre- and 4 hour

17   post-exposure to filtered air and DE were available in 4 of the 11 subjects enrolled. The authors found

18   differential expression of 10 genes involved in the inflammatory response when comparing DE exposure

19   (8 upregulated, 2 downregulated) and exposure to filtered air. Two participants had available samples

20   from 20 h post-exposure. At this time point, DE was associated with 4 differentially expressed genes (1

21   upregulated, 3 downregulated). However, this study is limited by a small sample size with limited

22   statistical power.

## *Cytokines*

23        Changes in plasma cytokine levels (e.g., IL-6 and TNF-α) have not been observed in human

24   clinical studies of exposures to CAPs (Ghio et al., 2003) or zinc oxide (Beckett et al., 2005). Similarly,

25   Mills et al. (2005) found no effect of DE (300 μg/m$^3$) on serum IL-6 or TNF-α among healthy adult

26   volunteers 6 hours after exposure. However, at the same PM concentration of DE, Tornqvist et al. (2007)

27   observed a significant increase in plasma IL-6 and TNF-α in a group of healthy adults 24 h following

28   exposure. Although the physiological significance of this finding is unclear, this study does provide

29   evidence of a mild systemic inflammatory response induced by exposure to DE.

### *Cell counts*

Two studies have observed increased peripheral basophils in healthy older adults 4 hours following a 2 hour exposure to $PM_{2.5}$ CAPs (200 $\mu g/m^3$) (Gong et al., 2004b), and increased white blood cell counts in healthy young adults 24-h after a 2 hour exposure to $PM_{2.5}$ CAPs (120 $\mu g/m^3$) (Ghio et al., 2003). Frampton et al. (2006) reported decreases in blood monocytes, basophils, and eosinophils 0-21-h following exposure to ultrafine carbon (10-50 $\mu g/m^3$) among exercising asthmatics and healthy adults. However, other recent human clinical studies have found no association between peripheral blood cell counts and exposure to fine or ultrafine zinc oxide (Beckett et al., 2005), ultrafine carbon (Routledge et al., 2006), or DE (Mills et al., 2005; Mills et al., 2007; Tornqvist et al., 2007).

### *C-reactive Protein*

Several controlled human exposure studies have measured CRP to evaluate systemic inflammation following exposure to PM. In these studies, no statistically significant changes in CRP concentrations have been observed 0–24 h following controlled exposures to ultrafine, fine, or thoracic coarse CAPs (Ghio et al., 2003; 2007), ultrafine carbon (Routledge et al., 2006), or DE (Carlsten et al., 2007; Mills et al., 2005; Mills et al., 2007; Tornqvist et al., 2007).

## 6.2.7.3. Toxicological Studies

There has been limited evidence that hematopoiesis may occur in animals exposed to PM. Two studies in the 2004 PM AQCD provided support for this effect, with one study measured stimulated release of PMNs from bone marrow and another examined peripheral blood PMN and blood cell counts; however, one study did not find associations between CAPs and peripheral blood counts. Thus, it was concluded that consistent evidence of PM-induced hematopoiesis remained to be demonstrated. However, in a study of humans exposed to biomass burning during the 1997 Southeast Asian smoke-haze episodes, $PM_{10}$ demonstrated the best relationship with blood PMN band cell counts expressed as a percentage of total PMN at lag 0 and 1, indicating a relatively quick response (Tan et al., 2000).

In a study of fine and ultrafine carbon black particles (Wistar rats; 7 h; mean mass concentration 1400 and 1660 $\mu g/m^3$ for fine and ultrafine CB, respectively; mean number concentration $3.8 \times 10^3$ and $5.2 \times 10^4$ particles/$cm^3$, respectively), only ultrafine CB induced elevated blood leukocytes at 0 and 48 h post-exposure compared to the control rats and no effect was observed at 16 h (Gilmour et al., 2004c). Smith et al. (2006) examined the hematology parameters in Sprague Dawley rats following a 3-day inhalation exposure (4 h/day) to coal fly ash (mean mass concentration 1400 $\mu g/m^3$) and reported increased blood neutrophils and reduced blood lymphocytes at 36 h but not 18 h post-exposure.

1    Consistent with the studies above, other studies that measure complete blood counts at 18–24-h

2    after PM exposure do not report increases in WBC or blood neutrophils. A 2-day CAPs study employing

3    SH rats did not report increased WBC 18–20 h post-exposure (see details above) (Kodavanti et al., 2005).

4    A study utilizing fine and/or ultrafine CAPs demonstrated decreased WBC in SH rats 18 h after a 2-day (6

5    h/day) nose-only exposure (details provided in Section 6.2.8.3.) (Kooter et al., 2006). The decrease was

6    largely attributable to lowered neutrophils in the fine CAPs-exposed rats and reduced lymphocytes in the

7    ultrafine+fine CAPs animals. In another study, blood neutrophils were decreased in SH rats exposed to

8    ultrafine carbon black for 6 h and no effects were observed in old Fischer 344 rats (details provided

9    above) (Elder et al., 2004b).

10    Elevated systemic IL-6 and TNF-α cytokine levels were observed following $PM_{10}$ instillation in

11    mice (details provided in Section 6.2.8.3.) (Mutlu et al., 2007). IL-6 was decreased with PM exposure in

12    macrophage-depleted mice, indicating that some of the IL-6 release originated in macrophages. For mice

13    (male C57Bl/6J) exposed to $PM_{10-2.5}$ derived from coal fly ash via intratracheal instillation (200 μg),

14    increased plasma IL-6 levels were only observed in animals that also received 100 μg of LPS (Finnerty et

15    al., 2007); this response was not observed with LPS alone, indicating a role for $PM_{10-2.5}$. In contrast, an

16    inhalation study of carbon black in rats did not demonstrate any change in plasma IL-6 levels (details

17    provided in Section 6.2.4.3.) (Elder et al., 2004b).

18    Overall, these studies provide evidence of time-dependent responses of systemic inflammation

19    induced by PM exposure. Alterations in WBC have been reported generally as elevations immediately (0

20    h) or < 36 h post-exposure and no change or reductions are noted from 18–24 h.


## 6.2.8. Blood Coagulation

21    The 2004 PM AQCD presented limited and inconsistent evidence from epidemiologic, human

22    clinical, and toxicological studies of PM-induced changes in blood coagulation markers. The body of

23    scientific literature investigating hemostatic effects of PM has grown significantly since the publication of

24    the 2004 PM AQCD, with epidemiologic studies demonstrating consistent increases in von Willebrand

25    factor (vWf) associated with PM. Recent human clinical and toxicological studies have also observed

26    changes in blood coagulation markers (e.g., fibrinogen, vWf, factor VII, t-PA) following exposure to PM.

27    However, the findings of these studies are somewhat inconsistent, which may be due in part to differences

28    in the post-exposure timing of the assessment.

## 6.2.8.1. Epidemiologic Studies

1       Several studies investigating the association of short-term fluctuations in PM concentration with

2 markers of coagulation (e.g. blood viscosity and fibrinogen) were included in the 2004 PM AQCD. These

3 preliminary studies were found to offer limited support for mechanistic explanations of the associations of

4 PM concentration with heart disease outcomes. New studies, published since 2002, are reviewed in this

5 section.

6       Liao et al. (2005) used a cross-sectional study to examine the association between short-term

7 increases in air pollutant concentrations (mean $PM_{10}$, $NO_2$, CO, $SO_2$, and $O_3$ over the previous 3 days) and

8 several plasma hemostatic markers (fibrinogen, factor VIII-C, vWF, albumin). Study subjects were middle

9 aged participants in the ARIC (Atherosclerosis Risk in Communities) study (n = 10,208), and were

10 residents of Washington County, MD, Forsyth County, NC, selected suburbs of Minneapolis, MN, or

11 Jackson, MS. The mean $PM_{10}$ concentration during the study was 29.9 $\mu g/m^3$. Liao et al. (2005) found

12 that each 12.8 $\mu g/m^3$ increase in the mean $PM_{10}$ concentration 1 day before the health measurements were

13 made was associated with a 3.93% increase in vWF (95% CI: 0.40–7.46) among diabetics, but not among

14 non-diabetics (-0.54%, 95% CI: -1.68–0.60). Each 12.8 $\mu g/m^3$ increase in the mean $PM_{10}$ concentration 1

15 day before the health measurements were made was also associated with a 0.006 g/dL decrease in serum

16 albumin (95% CI: -0.012 to 0.000) among those with CVD, but not among those without CVD (0.029

17 g/dL increase, 95% CI: -0.004 to 0.062). The mean CO concentration on the previous day was also

18 associated with a significant decrease in serum albumin. The authors reported significant curvilinear

19 associations between $PM_{10}$ and factor VIII-C, and suggest that this may indicate a threshold effect.

20 Similar curvilinear associations were observed between $O_3$ with fibrinogen, and vWF, and $SO_2$ with factor

21 VIII-C, WBC, and serum albumin (Liao et al., 2005). Liao et al. (2005) did not observe a significant

22 association with fibrinogen. However, in the European multicity study described in Section 6.2.7.1.,

23 Ruckerl et al. (2007b), found that each 13.5 $\mu g/m^3$ increase in the mean $PM_{10}$ concentration over the

24 previous 5 days was associated with a 0.6% increase in the arithmetic mean fibrinogen level (95%

25 CI: 0.1–1.1.

26       Similar studies have been done in other U.S. and Canadian cities. To examine changes in

27 inflammation related to short-term fluctuations in air pollution, Delfino et al. (2008) measured fibrinogen

28 and D-dimer in blood of subjects who resided at two downtown Los Angeles nursing homes. As described

29 in Section 6.2.7.1., measurements were made over a period of 12 weeks and subjects were 65+ years old

30 with a history of coronary artery disease. These markers were not associated with the broad array PM

31 metrics studied (e.g. quasi-ultrafine, $PM_{0.25-2.5}$, $PM_{10-2.5}$, EC, OC, primary OC, BC). In the study of 92

32 Boston residents with type 2 diabetes described previously, O'Neill et al. (2007) found that increases in

33 mean $PM_{2.5}$ and BC concentration were associated with vWF concentrations for all moving averages

1    examined (1-6 days). Reidiker et al. (2004b) also reports that in-vehicle $PM_{2.5}$ was associated with

2    decreased vWF over the next 10-14 hours among 9 police troopers. However, in the panel study described

3    previously in Section 6.3.7.1, Sullivan et al. (2007) did not observe associations with fibrinogen, or

4    D-dimer in individuals with or without COPD (Sullivan et al., 2007). However, neither RBC, platelets nor

5    blood viscosity were associated with $PM_{2.5}$ concentration in a panel study of 88 non-smoking elderly

6    subjects residing in the Salt Lake City, Ogden and Provo metropolitan area of Utah (Pope et al., 2004a).

7    Although Zeka et al. (2006b) did not observe an association with CRP in the analysis of the NAS

8    population in Boston (Section 6.3.7.1), increased fibrinogen level was associated with increases in the the

9    number of particles/$cm^3$ over the previous 48 hours and 1 week, and an incremental increase in BC

10   concentration over the previous 4 weeks (Zeka et al., 2006b). There were no consistent findings for

11   lagged $PM_{2.5}$ or sulfates (Zeka et al., 2006b).

12       Three studies of coagulation markers were conducted outside the U.S. and Canada. In a study of

13   healthy individuals in Taiwan, adverse associations were also observed between between $PM_{2.5}$, $PM_{10}$,

14   nitrate, and sulfate concentrations, fibrinogen and plasminogen activator fibrinogen inhibitor-1 (PAI-1)

15   (Chuang et al., 2007a). A large cross-sectional study of healthy subjects in Tel-Aviv, Steinvil et al. (2008)

16   examined fibrinogen collected as part of routine health examinations for 3,659 individuals. No significant

17   associations were found between pollutant levels (lagged 1-7 days) and fibrinogen. Finally, Baccarelli and

18   colleagues reported adverse associations between $PM_{10}$ and prothrombin time (Baccarelli et al., 2007a).

### *Summary*

19       The most commonly measured markers of coagulation in the studies reviewed were fibrinogen and

20   vWF. Most studies reported effects of PM on vWF (Liao et al., 2005; 2007; 2004b). Results for fibrinogen

21   were less consistent (2008; Liao et al., 2005; Ruckerl et al., 2006; Sullivan et al., 2007; Zeka et al.,

22   2006b) Positive associations with fibrinogen were reported in older adults residing in Boston (Zeka et al.,

23   2006b) and in the multicity European study of MI survivors. Several other markers have been examined

24   (e.g. D-dimer, prothrombin time) but not in adequate numbers of studies to allow comparisons across

25   studies.

## 6.2.8.2. Human Clinical Studies

26       In two separate studies conducted by Ghio and colleagues, controlled exposures (2 hours) to fine

27   CAPs (Chapel Hill, NC) at concentrations between 15 and 350 $\mu g/m^3$ have been shown to increase blood

28   fibrinogen 18- to 24-h following exposure among healthy adults (Ghio et al., 2000; 2003). Increases in

29   blood fibrinogen or factor VII would suggest an increase in blood coagulability, which could result in an

30   increased risk of coronary thrombosis. However, a similar study conducted in Los Angeles observed a

1    $PM_{2.5}$ CAPs-induced decrease in factor VII blood levels in healthy subjects and found no association

2    between $PM_{2.5}$ CAPs and blood fibrinogen among healthy and asthmatic volunteers (Gong et al., 2003a).

3         Since the publication of the 2004 PM AQCD, several new controlled human exposure studies have

4    evaluated the effects of PM on blood coagulation markers. Routledge et al. (2006) did not observe any

5    changes in fibrinogen or D-dimers following a 1-h exposure to ultrafine carbon among a group of resting

6    healthy older adults and older adults with stable angina. Similarly, Beckett et al. (2005) found no changes

7    in hemostatic markers (e.g., factor VII, fibrinogen, and von Willebrand factor) following exposure to

8    ultrafine and fine zinc oxide. Mills and colleagues have recently demonstrated a significant effect of DE

9    (300 $\mu g/m^3$) on fibrinolytic function both in healthy men and in men with coronary heart disease (Mills et

10   al., 2005; 2007). In both groups of volunteers, bradykinin-induced release of tissue plasminogen activator

11   (tPA) was observed to decrease 6 hours following exposure to DE compared to filtered air exposure. The

12   same group did not observe an attenuation of t-PA release 24-h after a 1-h exposure (300 $\mu g/m^3$) to DE in

13   a group of health adults (Tornqvist et al., 2007). Carlsten et al. (2007) conducted a similar study involving

14   exposure of healthy adults to DE with a particulate concentration of 200 $\mu g/m^3$. Although the authors

15   observed an increase in D-dimer, von Willebrand factor, and platelet count 6 hours following exposure to

16   DE, these increases did not reach statistical significance. In a subsequent study with a similar study

17   design, the same researchers found no effect of a 2-h exposure to DE (100 and 200 $\mu g/m^3$ $PM_{2.5}$) on

18   prothrombotic markers in a group (n = 16) of adults with metabolic syndrome (Carlsten et al., 2008). The

19   authors postulated that the lack of significant findings could be due to a relatively small sample size. In

20   addition, Carlsten et al. (2007; 2008) exposed subjects at rest while Mills et al. (2005) exposed subjects to

21   a higher concentration (300 $\mu g/m^3$) with intermittent exercise.

22       Barregard et al. (2006) recently evaluated the effect of WS on markers of coagulation,

23   inflammation, and lipid peroxidation. Subjects (n = 13) were healthy males and females (20-56 years old)

24   and were exposed for 4 hours to $PM_{2.5}$ concentrations of 240-280 $\mu g/m^3$. The authors reported an increase

25   in serum amyloid A at 0, 3, and 20 h following exposure to WS, as well as an WS-induced increase in the

26   ratio of factor VIII/von Willebrand factor, which is an indicator of an increased risk of venous

27   thromboembolism. Samet et al. (2007) reported an association between various coagulation markers and

28   exposure to ultrafine, fine, and thoracic coarse CAPs among healthy adults (18-40 years old). Results

29   from exposures to ultrafine and thoracic coarse CAPs are presented in summary form, while the

30   relationship between fine CAPs and an increase in blood fibrinogen has been described in detail in Ghio

31   et al. (2000). Exposure to thoracic coarse CAPs did not result in a statistically significant change in

32   prothrombin, fibrinogen, factor VII, t-PA, D-dimer, or von Willebrand factor. However, the authors

33   observed a trend in CAPs-induced levels of several coagulation factors which they suggested could be

34   viewed as "pro-clotting." Exposure to ultrafine CAPs was associated with a significant increase (17%) in

the concentration of D-dimer. Whereas many coagulation markers provide evidence of an increased potential to form clots (e.g., an increase in fibrinogen or a decrease in t-PA), D-dimer is actually a degradation product of a blood clot that has formed. Therefore, the preliminary finding of an association between ultrafine CAPs and elevated levels of D-dimer is potentially very important to our understanding of the relationship between elevated concentrations of PM and cardiovascular morbidity and mortality observed in epidemiologic studies. Taken together, these new studies have provided additional evidence that short-term exposure to PM at near ambient levels may have small, yet statistically significant effects on hemostatic markers in healthy subjects or patients with coronary artery disease.

### 6.2.8.3. Toxicological Studies

In general, the limited toxicological studies reviewed in the 2004 PM AQCD reported positive and negative findings for plasma fibrinogen levels or other factors involved in the coagulation cascade. Rats exposed to New York City CAPs did not have any exposure-related effects on any measured coagulation markers (Nadziejko et al., 2002), whereas rats exposed to a high concentration of ROFA did demonstrate increased plasma fibrinogen (Kodavanti et al., 2002).

The coagulation effects of inhaled ultrafine carbon black (count median diameter = 36 nm) at a concentration of 150 $\mu g/m^3$ for 6 h were evaluated 24-h post-exposure in two rat models (11–14 mo. SH and 23 mo. Fischer 344), some of which received LPS via intraperitoneal injection prior to particle exposure (Elder et al., 2004b). LPS has been shown to induce the expression of molecules involved in coagulation, inflammation, oxidative stress, and the acute-phase response. In those animals only exposed to carbon black, SH rats demonstrated increased thrombin-anti-thrombin complexes (TAT) and decreased fibrinogen. For F344 rats, TAT complexes and fibrinogen were elevated only in those that received LPS and carbon black. Whole-blood viscosity was not altered in either rat strain with particle exposure.

Mutlu et al. (2007) used a $PM_{10}$ sample collected from Dusseldorf, Germany in mice (C57BL/6) with and without the gene coding for IL-6. The authors report using a moderate intratracheal instillation dose (10 $\mu g$/mouse; roughly equivalent to 400–500 $\mu g$/kg); the PM sample had previously been characterized as having significant Fe, Ni, and V content (Upadhyay et al., 2003). In C57BL/6 mice, the Dusseldorf PM shortened bleeding (32%), prothrombin (13%), and activated partial thromboplastin (16%) times and increased platelet count, fibrinogen, and Factors II, VIII, and X activities 24-h following exposure. The authors further demonstrated accelerated coagulation by a reduction in the left carotid artery occlusion time (experimentally-derived by direct application of $FeCl_3$). Additional experiments demonstrated that IL-6$^{-/-}$ or macrophage-depleted mice showed dramatically attenuated effects of $PM_{10}$ on hemostatic indices, thrombin generation, and occlusion time. In IL-6$^{-/-}$ mice, there was no change in total cell counts or differentials in BAL fluid compared to the wild-type mice, despite the lack of IL-6. In

1    contrast, the model of macrophage depletion had reduced levels of macrophages and IL-6 in BAL fluid,

2    following PM exposure. These studies suggest that instillation of Dusseldorf $PM_{10}$ activates clotting

3    through an alveolar macrophage-dependent release of IL-6; however, other factors may also be involved

4    in the prothrombotic response (i.e., activation of neutrophils, other inflammatory cells, or alterations in

5    the levels of other cytokines).

6       Plasma fibrinogen levels were elevated 18 h following a single (6 h) exposure to on-road highway

7    aerosols when groups of rats pretreated with saline or influenza virus were combined (i.e., there was a

8    significant effect of particles) (Elder et al., 2004a). A $PM_{2.5}$ CAPs exposure conducted for 2 days (4 h/day;

9    mean mass concentration range 144–2758 μg/m$^3$; August to October 2001; Research Triangle Park, NC)

10    in SH rats induced plasma fibrinogen increases (measured 18–20 h post-exposure) in 5 of 7 separate

11    studies (Kodavanti et al., 2005). Fibrinogen was not different from the air control group on the two days

12    with the highest CAPs concentrations (1129 and 2758 μg/m$^3$), indicating that the response was likely not

13    attributable to mass. In SH rats exposed via nose-only inhalation to $PM_{2.5}$ CAPs for 6 h in one of three

14    locations in the Netherlands (Bilthoven–background location, Utrecht–industrial location, or a site near a

15    freeway tunnel and river with substantial shipping activity; mean mass concentration range 270–2400,

16    335–3720, and 655–3660 μg/m$^3$, respectively), plasma fibrinogen was increased 48-h post-exposure

17    (Cassee et al., 2005). A similar study conducted by the same group (Kooter et al., 2006) reported no

18    changes in plasma fibrinogen measured 18 h after a 2-day exposure (6 h/day) to fine or fine+ultrafine

19    CAPs (mean mass concentration range 399.0–1067.5 and 269.0–555.8 μg/m$^3$, respectively; fine CAPs site

20    in Bilthoven and ultrafine+fine site in freeway tunnel in Hendrik Ido Ambacht; 1/2003–4/2004).

21    However, elevated vWF was observed in SH rats exposed to the highest concentration of fine CAPs. In a

22    study employing $PM_{10-2.5}$ collected from six European locations with contrasting traffic profiles,

23    intratracheal instillation resulted in fibrinogen increases only in SH rats in the 10 mg/kg dose group at

24    24-h post-exposure; similar responses were observed in rats exposed to $PM_{2.5}$ (Gerlofs-Nijland et al.,

25    2007).

26       A few studies have evaluated red blood cell (RBC) measurements following PM exposure. In

27    Wistar rats pre-exposed to ozone (1600 μg/m$^3$; 8-h) then CAPs for 6 h, increases in RBC, hemoglobin,

28    and hematocrit were observed 2 days after CAPs exposure (Cassee et al., 2005). For SH rats exposed to

29    CAPs only, decreased mean corpuscular hemoglobin concentration were reported (Cassee et al., 2005).

30    Decreases in mean corpuscular volume (MCV), and elevations in mean platelet volume (MPV) and mean

31    platelet component (MPC) were reported in SH rats 18 h following a 2-day exposure to ultrafine+fine

32    CAPs in a freeway tunnel (details provided above) (Kooter et al., 2006). In another study that employed

33    coal fly ash (mean mass concentration 1400 μg/m$^3$; 4 h/day×3 day) Sprague Dawley rats demonstrated

1    increases in hematocrit and MCV in Sprague Dawley rats at 36 h but not 16-h post-exposure (Smith et al.,

2    2006).

3        Increases in coagulation and thrombotic markers were observed in some studies of rats or mice

4    exposed to PM. Plasma TAT complexes were increased in carbon black-exposed SH rats and shortened

5    bleeding, prothrombin, and activated partial thromboplastin times were observed in mice 24-h

6    post-exposure. Furthermore, the latter study also reported increased levels of Factors II, VIII, and X

7    activities in mice. Another study demonstrated increased vWF in response to $PM_{2.5}$ CAPs. As for plasma

8    fibrinogen, these studies provide some evidence that increased plasma fibrinogen levels are observed

9    18 h to 48 h post-exposure to PM, although one study reported no change and another reported a decrease

10   in this biomarker. Alterations in platelet measurements have also been observed with PM exposure,

11   including increased platelet number, mean platelet volume, and mean platelet component. The

12   toxicological results of RBC-related measurements are limited and inconsistent following PM exposure,

13   which may be attributable to different exposure protocols, time of analysis, or rat strain.

# 6.2.9. Systemic and Cardiac Oxidative Stress

14   Very little information on systemic oxidative stress associated with PM was available for inclusion

15   in the 2004 PM AQCD. However, recent epidemiologic studies have provided consistent evidence of

16   PM-induced increases in markers of systemic oxidative stress including plasma TBARS, CuZn-SOD,

17   8-oxodG, and total homocysteine. This is supported by a limited number of human clinical studies that

18   observed PM-induced increases in free-radical mediated lipid peroxidation as well as upregulation of the

19   DNA repair gene hOGG1. In addition, recent toxicological studies have demonstrated an increase in

20   cardiac oxidative stress following PM exposure in rats.

## 6.2.9.1. Epidemiologic Studies

21   Although studies of markers of inflammation and coagulation were considered, no studies of

22   markers of oxidative stress were reviewed in the 2004 PM AQCD. Since 2002, numerous studies have

23   examined whether short-term increases in mean PM concentrations are associated with adverse changes

24   in systemic markers of oxidative stress.

25   In a separate analysis of the randomized trial evaluating the effect of omega-3 fatty acid

26   supplementation on HRV among nursing home residents living in Mexico city, Romieu et al. (2008)

27   investigated the effect of this intervention on markers of systemic oxidative stress (Cu/Zn SOD activity,

28   LPO in plasma and GSH in plasma). Supplementation with both fish oil and soy oil was related to an

29   increase in Cu/Zn SOD activity and GSH plasma levels. A significant decrease of Cu/Zn SOD was

1    associated with a 10 μg/m$^3$ increase of PM$_{2.5}$ in both groups [Fish oil: β = -0.17 (SE = 0.05), p = 0.002;

2    Soy oil: β = -0.06 (SE = 0.02) p = < 0.001]. A decrease in GSH was associated with a 10 μg/m$^3$ increase

3    in PM$_{2.5}$ in the fish oil group (β = -0.09 (SE = 0.04, p = 0.017).

4         Two studies evaluated plasma homocysteine levels in relation to PM (Baccarelli et al., 2007a).

5    Baccarelli et al. (2007a) investigated fasting and postmethionine-load total homocysteine (tHcy) among

6    1,213 normal subjects in Lombardia, Italy. Plasma homocysteine is a risk factor for CVD and a marker for

7    oxidative stress. Among smokers, average PM$_{10}$ level during the 24-h preceding the measurement was

8    associated with 6.3% (95% CI: 1.3_11.6) and 4.9% (95% CI: 0.5–9.6) increases in fasting and

9    postmethionine-load tHcy, respectively. No associations were observed among non-smokers. Park et al.

10   (2008b) investigated the association of BC, OC, sulfate and PM$_{2.5}$ with tHcy among 960 male participants

11   of the NAS. Effect modification by folate and vitamins B6 and B12 was also examined. BC and OC were

12   associated with increases in tHcy and associations were more pronounced in those with lower plasma

13   folate and vitamin B12.

14        In smaller studies with 25 to 50 healthy or diseased participants, several markers of oxidative stress

15   have been associated with PM size fractions or components. These associations include thiobarbituric

16   acid reactive substances (TBARS) with 24-h PM$_{10}$ (Liu et al., 2007b); several PM metrics (e.g. ultrafine,

17   coarse, EC, OC, BC and PN) with Cu/Zn-SOD (Delfino et al., 2008); PM$_{2.5}$, BC, vanadium and chromium

18   with plasma proteins (Sorensen et al., 2003); DNA damage assessed by 7-hydro-8-oxo-2-deoxyguanosine

19   (8-oxodG) in lymphocytes (Sørenson et al., 2005) and, 8-OHdG with sulfates (Chuang et al., 2007b).

### *Summary*

20        Oxidative stress responses measured by plasma tHcy, CuZn-SOD, TBARS, 8-oxodG have been

21   consistently observed (Baccarelli et al., 2007a; Chuang et al., 2007b; Delfino et al., 2008; Liu et al.,

22   2007b; Romieu et al., 2008; Sorensen et al., 2003; Sørenson et al., 2005).

## 6.2.9.2. Human Clinical Studies

23        Brauner et al. (2007) recently investigated the effect of urban traffic particles on oxidative

24   stress-induced damage to DNA. Healthy adults (20-40 years old) were exposed to low concentrations of

25   urban traffic particles as well as filtered air for periods of 24 h, which included two 90-min periods of

26   exercise. Exposures took place in an exposure chamber above a busy road with high traffic density in

27   Copenhagen. Non-filtered air was pumped into the chamber from above the street, with average PM$_{2.5}$ and

28   PM$_{2.5-10}$ mass concentrations of 9.7 μg/m$^3$ and 12.6 μg/m$^3$, respectively. The ultrafine/fine (6-700 nm)

29   particle number concentration was continuously monitored throughout the exposure. The PM$_{2.5}$ fraction

30   was rich in sulfur, vanadium, chromium, iron, and copper. PBMCs were isolated from blood samples

1    collected at 6 and 24-h. DNA damage, as measured by strand breaks (SB) and

2    formamidopyrimidine-DNA glycosylase (FPG) sites, was evaluated using the Comet assay. The activity

3    and mRNA levels of the DNA repair enzyme 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1) were

4    also measured. The authors observed increased levels of DNA strand breaks and FPG sites following

5    6 and 24 h of exposure to PM. Using a mixed-effects regression model, the particle concentration at the

6    57 nm mode was found to be the major contributor of these measures of DNA damage. The results of this

7    study suggest that short-term (6–24 h) exposure to ambient levels of ultrafine particles cause systemic

8    oxidative stress resulting in damage to DNA.

9        In a human clinical study of controlled exposure to WS, Barregard et al. (2006) found an increase

10    in urinary excretion of free 8-iso-prostaglandin2α among healthy adults (n = 9) approximately 20 h

11    following a 4 hour exposure to $PM_{2.5}$ (mass concentration of 240-280 μg/m[3)]. This finding provides

12    evidence of a PM-induced increase in free-radical mediated lipid peroxidation. From the same study,

13    Danielsen et al. (2008b) reported an increase in the mRNA levels of the DNA repair gene hOGG1 in

14    peripheral mononuclear cells 20 h after exposure to WS relative to filtered air. Potential evidence of

15    systemic oxidative stress has also been observed following controlled human exposures to DE. Tornqvist

16    et al. (2007) reported an increase in plasma antioxidant capacity in a group of healthy volunteers 24-h

17    after a 1-h exposure to DE with a particle concentration of 300 μg/m^{3}. The investigators suggested that

18    systemic oxidative stress occurring following exposure may have caused this up-regulation in antioxidant

19    defense. Peretz et al. (2007) observed some significant differences in expression of genes involved in

20    oxidative stress pathways between exposure to DE (200 μg/m^{3} $PM_{2.5}$) and filtered air. However, the

21    conclusions of this investigation are limited by a small number of subjects.

22        Based on the results of these studies, it appears that exposure to PM at or near ambient levels may

23    increase systemic oxidative stress in human subjects.


## 6.2.9.3. Toxicological Studies

24        Very little information was available for inclusion in the 2004 PM AQCD on oxidative stress in the

25    cardiovascular system. A few new studies have evaluated ROS in blood or the heart following PM

26    exposure. Some studies have used chemiluminescence (CL), which is measured using the decay of

27    excited states of molecular oxygen, and may also be prone to artifact.

28        Gurgueira et al. (2002) measured oxidative stress in Sprague Dawley rats immediately following a

29    5-h CAPs exposure ($PM_{2.5}$; mean mass concentration range 99.6–957.5 μg/m^{3}; Boston, MA; July 2000 to

30    February 2001) and reported increased in situ CL in hearts of CAPs-exposed animals. CL evaluated after

31    CAPs exposure durations of 1 and 3 h did not demonstrate changes from the filtered air group, although a

32    5-h exposure resulted in increased CL in hearts. When animals were allowed to recover for 24-h prior to

1    CL evaluation, oxidative stress returned to control values. To compare potential particle-induced

2    differences in in situ CL, rats were exposed to ROFA (1.7 mg/m$^3$ for 30 min) or carbon black (170 μg/m$^3$

3    for 5 h) and only the ROFA-treated animals exhibited increased CL in cardiac tissue. Additionally, levels

4    of antioxidant enzymes in the heart (Cu/Zn superoxide dismutase (SOD) and MnSOD) were increased

5    (100% and ~40%, respectively) in CAPs-exposed rats.

6    Recently, Rhoden et al. (2005) tested the role of the ANS in driving CAPs-induced cardiac

7    oxidative stress in heart tissues of Sprague Dawley rats. At mass concentrations of 700 μg/m$^3$ (Boston,

8    MA), pretreatment with N-acetylcysteine (an antioxidant; NAC), atenolol (a β$_1$-receptor antagonist), or

9    glycopyrrolate (a muscarinic receptor antagonist) attenuated the CL and TBARS effects observed in the

10    heart following a 5-h PM$_{2.5}$ exposure. The wet/dry ratio (edema) of cardiac tissue also returned to control

11    values in animals treated with NAC prior to CAPs. These combined results indicate involvement of both

12    the sympathetic and parasympathetic pathways in the cardiac oxidative stress response observed

13    following PM exposure.

14    More recently, a type of irritant receptor, the Transient Receptor Potential Vanilloid Receptor 1

15    (TRPV1), was identified as central to the inhaled CAPS-mediated induction of cardiac tissue CL and

16    TBARS (Ghelfi et al., 2008). In these studies (Sprague Dawley rats; mean CAPs concentration

17    218 μg/m$^3$; mean CAPs concentration range 100–550 μg/m$^3$; Boston, MA), capsazapine (a TRPV1

18    inhibitor) abrogated cardiac CL, TBARS, edema, and QT-interval shortening when measured at the end of

19    the 5-h exposure. These studies provide some evidence that the ANS may be involved in producing

20    cardiac oxidative stress following exposure to CAPs. Furthermore, this response could be acting, at least

21    in part, via TRPV receptors.

22    In Wistar Kyoto rats exposed to CAPs in Japan, relative mRNA expression of HO-1 was increased

23    in cardiac tissue and was also significantly correlated with the cumulative mass of PM collected on

24    chamber filters throughout the exposure (Ito et al., 2008). Other studies presented in earlier sections also

25    demonstrated ROS (via CL) and nitrotyrosine expression (via ELISA) in the left ventricle with carbon

26    black exposure (Tankersley et al., 2008) and oxidative stress in the systemic microcirculation (via

27    tetranitroblue tetrazolium reduction method) following ROFA intratracheal instillation exposure

28    (Nurkiewicz et al., 2006).

29    When considered together, the above studies provide some evidence that PM exposure results in

30    oxidative stress as measured in cardiac tissue by CL, TBARS, HO-1 mRNA expression, and nitrotyrosine

31    expression. Cardiac oxidative stress may have resulted from PM stimulation of the ANS, although these

32    studies have only been conducted in one laboratory. A single study provided support for vascular

33    oxidative stress as demonstrated in the microcirculation following ROFA exposure.

*PM Components*

1    Individual PM component concentrations were linked to CL levels in rat heart tissue using separate

2    univariate linear regression models, with total PM mass, Al, Si, Ti, and Fe having p-values $\leq 0.007$

3    (Gurgueira et al., 2002). The highest $R^2$ value in the regression analyses was for Al (0.67) and its

4    concentration ranged from 0.000 to 8.938 $\mu g/m^3$.


# 6.2.10. Hospital Admissions and ED Visits

5    The 1996 PM AQCD (1996) considered just two time-series studies regarding the association

6    between daily variations in PM levels and the risk of cardiovascular disease (CVD) morbidity as

7    measured by the number of daily hospitalizations with primary discharge diagnoses related to CVD

8    (Burnett et al., 1995; Schwartz and Morris, 1995). In contrast, the 2004 PM AQCD (U.S. EPA, 2004)

9    reviewed more than 25 publications relating PM and risk of CVD hospitalizations. Results from a handful

10   of larger multicity studies were emphasized, with the greatest emphasis placed on findings from the U.S.

11   National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al., 2000) and a subsequent

12   reanalysis (Zanobetti and Schwartz, 2003). The NMMAPS study evaluated the effect of daily changes in

13   ambient PM levels on total CVD hospitalizations among elderly Medicare beneficiaries in 14 U.S. cities

14   and found a ~1% excess risk per 10 $\mu g/m^3$ increase in $PM_{10}$. The 2004 PM AQCD concluded that these

15   results, along with those of the other single- and multicity studies reviewed "generally appear to confirm

16   likely excess risk of CVD-related hospital admissions for U.S. cities in the range of [0.6 to 1.7% per

17   10 $\mu g/m^3$] $PM_{10}$, especially among the elderly" (U.S. EPA, 2004). The 2004 PM AQCD also concluded

18   that there was some evidence from single city studies suggesting an excess risk specifically for

19   hospitalizations related to ischemic heart disease and heart failure. Furthermore, the 2004 PM AQCD

20   found that "insufficient data exist from the time-series CVD admissions studies […] to provide clear

21   guidance as to which ambient PM components, defined on the basis of size or composition, determine

22   ambient PM CVD effect potency" (U.S. EPA, 2004). The key studies reviewed in the 2004 PM AQCD on

23   this topic included those by Burnett and colleagues (1997; 1999), Lippman and colleagues (2000), Ito

24   (2003), and Peters et al. (2001).

25   Recent large studies conducted in the U.S., Europe, and Australia and New Zealand have confirmed

26   these findings for $PM_{10}$, and have also observed consistent associations between $PM_{2.5}$ and cardiovascular

27   hospitalizations. However, findings from single city studies have demonstrated regional heterogeneity in

28   effect estimates. It is apparent from these recent studies that the observed increases in cardiovascular

29   hospitalizations are largely due to admissions for ischemic heart disease and congestive heart failure

30   rather than cerebrovascular diseases. The new literature on hospitalizations and ED visits for

1    cardiovascular causes published since 2002 is reviewed in the following sections. First, the specific CVD

2    outcomes captured using ICD codes from hospital admissions databases are discussed. Second, the

3    methods used in the large and multicity studies are described. The remainder of the chapter is organized

4    as follows: (1) evidence PM effects by outcome (e.g. all CVD, cardiac diseases, IHD, MI, CHF,

5    arrhythmias, cerebrovascular diseases, ischemic and hemorrhagic stroke, peripheral vascular disease); (2)

6    evidence of PM effects in susceptible populations; and (3) overall summary. Within each section,

7    evidence from large/multi-city studies is emphasized and results from U.S. and Canadian single city

8    studies are also discussed. Although the single city studies may lack statistical power needed to evaluate

9    interactions and detect some of the subtle effects of air pollution, they inform our interpretation of the

10   heterogeneous effect estimates that have been observed across North America.

### Cardiovascular Disease ICD Codes

11   When the 2004 PM AQCD was written, few studies had evaluated the link between ambient PM

12   and specific CVD outcomes such as congestive heart failure, ischemic heart disease or ischemic stroke. In

13   contrast, the majority of recent studies have focused on specific CVD outcomes. This trend is justified by

14   the fact that the short-term exposure effects of PM may be very different for different cardiovascular

15   outcomes. For example, given the current putative biological pathways involved in the acute response to

16   PM exposure, there is no a priori reason why short-term fluctuations in PM levels would have similar

17   effects on the risk of acute MI, chronic atherosclerosis of the coronary arteries, and hemorrhagic stroke.

18   Almost all of the published time-series studies of cardiovascular hospitalizations and emergency

19   department visits identified cases based on administrative discharge diagnosis codes as defined by the

20   International Classification of Disease 9th revision (ICD-9) or 10th revision (ICD-10) (NCHS, 2007). A

21   complicating factor in interpreting the results of these studies is the lack of consistency in both defining

22   specific health outcomes and in the nomenclature used.

23   Table 6-5 shows major groups of diagnostic codes used in air pollution studies for diseases of the

24   circulatory system. The codes ICD-9: 390-459 are frequently used to identify all CVD morbidity. Note

25   that this definition of CVD includes diseases of the heart and coronary circulation, cerebrovascular

26   disease, and peripheral vascular disease. In contrast, the term cardiac disease specifically excludes

27   diseases not involving the heart or coronary circulation. While this distinction is conceptually

28   straightforward, the implementation of the definition of cardiac disease in terms of ICD-9 or ICD-10

29   codes varies among authors. Even greater heterogeneity can be found among studies in the

30   implementation of definitions related to cerebrovascular disease.

**Table 6-5.    Description of ICD-9 and ICD-10 codes for diseases of the circulatory system.**

| Description | ICD-9 Codes | ICD-10 Codes |
|---|---|---|
| All Cardiovascular Disease | 390-459 | I00-I99 |
| Ischemic Heart Disease | 410-414 | I20-I25 |
| Acute Myocardial Infarction | 410 | I21 |
| Diseases Of Pulmonary Circulation | 415-417 | I26-I28 |
| Heart Failure | 428 | I50 |
| Arrhythmia | 427 | I47, I48, I49 |
| Cerebrovascular Disease | 430-438 | I60-I69 |
| Ischemic Stroke And Transient Ischemic Attack (TIA) | 430-432 | I63 |
| Hemorrhagic Stroke | 433-435 | I60-I62 |
| Peripheral Vascular Disease (PVD) | 440-448 | I70-I79 |

## *Design and Methods of Large and Multicity Hospital Admission and Emergency Department Visit Studies*

1    Recently, multiple research groups in the U.S., Europe, and Australia have created large datasets to

2    evaluate specific CVD and respiratory endpoints using more detailed and relevant measures of PM

3    concentration. In the U.S., the MCAPS analyses of Dominici et al. (2006), Bell et al. (2008a) and Peng et

4    al. (2008) are large, comprehensive and informative studies based on Medicare hospitalization data.

5    Likewise, the Atlanta-based SOPHIA study (Metzger et al., 2004; Peel et al., 2005) is the largest and most

6    comprehensive study of U.S. cardiovascular and respiratory ED visits. In Europe, the APHEA initiative

7    (Le Tertre et al., 2002a; 2003), the more recent HEAPSS study (von Klot et al., 2005), and the French

8    PSAS program (Host et al., 2008; Larrieu et al., 2007) are similarly noteworthy for their large sample

9    size, geographic diversity, and consideration of specific CVD and/or respiratory endpoints. These studies

10    contain adequate data to examine interactions by season and region; the effects of different size fractions,

11    components and sources of PM; or the effect of PM on susceptible subpopulations. The following section

12    provides a detailed review of the study design and methods used by each of the large studies. A discussion

13    of the results of each study can be found in later sections of the ISA.

### MCAPS: Medicare Air Pollution Study

14    Dominici et al. (2006) created a database of daily time-series for 1999 through 2002 of hospital

15    admission rates for a range of cardiovascular and respiratory outcomes among Medicare beneficiaries

16    aged $\geq$ 65 years, ambient $PM_{2.5}$ levels, and meteorological variables for 204 U.S. urban counties. The

17    specific CVD outcomes considered were: cerebrovascular disease (ICD-9: 430-438), peripheral vascular

1   disease (440-448), ischemic heart diseases (410-414, 429), heart rhythm disturbances (426, 427), and

2   heart failure (428). Injuries (800-849) were evaluated as a control outcome. Gaseous and other particulate

3   pollutant size fractions were not considered.

4   Data on $PM_{2.5}$ were obtained from the AQS database of the U.S. EPA. Within each county,

5   associations between cause-specific hospitalization rates and same-day $PM_{2.5}$ levels were evaluated using

6   Poisson regression models controlling for long-term temporal trends and meteorologic conditions with

7   natural cubic splines. County-specific results were subsequently averaged using Bayesian hierarchical

8   models. In addition to evaluating single day lags, three-day distributed lag models (lags 0, 1, and 2 days)

9   were also considered in a subset of 90 U.S. counties with daily $PM_{2.5}$ data available during the study time

10   period.

11   Subsequently, Peng et al. (2008) and Bell et al. (2008a) extended the database of daily time-series

12   of hospital admissions, $PM_{2.5}$, and other covariates for 202 U.S. counties through 2005. Importantly, Peng

13   et al. (2008) added data on $PM_{10-2.5}$ to this database for 108 U.S. counties with one or more co-located

14   $PM_{2.5}$ and $PM_{10}$ monitors. Analyses with $PM_{10-2.5}$ were carried out using similar methods to those of

15   Dominici et al. (2006). Peng et al. (2008) evaluated the robustness of $PM_{2.5}$ associations to adjustment for

16   thoracic coarse PM (Peng et al., 2008). Gaseous pollutants were not considered in these analyses.


### SOPHIA: Study of Particulates and Health in Atlanta

17   SOPHIA investigators (Metzger et al., 2004; Peel et al., 2005; 2007; Tolbert et al., 2000) compiled

18   data on 4,407,535 emergency department (ED) visits between 1993 and 2000 to 31 hospitals in the

19   Atlanta metropolitan statistical area (20 counties). Specific cardiovascular outcomes considered were:

20   ischemic heart disease (ICD-9: 410–414), acute myocardial infarction (410), cardiac dysrhythmias (427),

21   cardiac arrest (427.5), congestive heart failure (428), peripheral vascular and cerebrovascular disease

22   (433–437, 440, 443–444, 451–453), atherosclerosis (440), and stroke (436). Finger wounds (883.0) were

23   evaluated as a control outcome.

24   The air quality data included measurements of criteria pollutants (PM and gaseous pollutants) for

25   the entire study period, as well as detailed measurements of mass concentrations for the fine ($PM_{2.5}$) and

26   thoracic coarse fractions ($PM_{10-2.5}$) of PM and several physical and chemical characteristics of $PM_{2.5}$ for

27   the final 25 months of the study using data from the ARIES monitoring station. Rates of ED visits for

28   specific causes were assessed in relation to the 3-day moving average (lags 0-2 days) of daily measures of

29   air pollutants using Poisson generalized linear models controlling for long-term temporal trends and

30   meteorologic conditions with cubic splines. Tolbert et al. (2007) published interim results of this study in

31   relation to both cardiovascular and respiratory disease visits, Metzger et al. (2004) published the main

32   results for CVD visits, and Peel et al. (2005) published the main results for respiratory conditions. An

1   analysis of co-morbid conditions that may make individuals more susceptible to PM-related

2   cardiovascular risk was carried out by Peel et al. (2007). Tolbert et al. (2007) extended the available data

3   through 2002 and compared results from single and multipollutant models while Sarnat et al. (2008)

4   evaluated the risk of ED visits for cardiovascular and respiratory diseases in relation to specific sources of

5   ambient PM using the extended dataset.

### APHEA and APHEA-2: Air pollution and Health: a European Approach

6   APHEA-2 investigators compiled daily data on cardiovascular (Le Tertre et al., 2002b, 2003) and

7   respiratory (Atkinson et al., 2001; 2004) disease hospital admissions in the following 8 European cities:

8   Barcelona, Birmingham, London, Milan, the Netherlands, Paris, Rome, and Stockholm. (The publications

9   on respiratory diseases were reviewed in the 2004 PM AQCD.) The specific CVD outcomes considered in

10  each city were: cardiac diseases (ICD-9: 390-429), ischemic heart disease (410-413) and cerebrovascular

11  diseases (430-438). Routine registers in all cities provided daily data on hospitalizations. Only emergency

12  hospitalizations were considered, except in Milan, Paris, and Rome where only general admissions data

13  were available.

14  Ambient $PM_{10}$ levels were available in all cities except Paris ($PM_{13}$ used), and Milan and Rome

15  (total suspended particulates [TSP] used). Data on gaseous pollutants ($NO_2$, $SO_2$, CO, and $O_3$) were also

16  available in most cities. Five of the eight cities provided data on black smoke (BS). The length of the

17  available time-series varied by city but generally spanned from the early to mid 1990s.

18  Within each city, associations between cause-specific hospitalization rates and same-day $PM_{2.5}$

19  levels were evaluated using Poisson generalized additive models (GAMs) controlling for long-term

20  temporal trends and meteorologic conditions. City-specific results were subsequently averaged using

21  standard meta-analytic methods. The original analyses (Atkinson et al., 2001; Le Tertre et al., 2002a)

22  were carried out using GAMs and LOESS smoothers. Following reports of problems associated with

23  using the default convergence criteria in the standard S-plus GAM procedure (Dominici et al., 2002),

24  study authors reanalyzed the data on cardiac admissions using GAMs and stricter convergence criteria,

25  and generalized linear models (GLMs) with natural splines and penalized splines (Atkinson, 2004; Le

26  Tertre et al., 2003). The authors found that the results of the original analyses were insensitive to the

27  choice of convergence criteria and that the use of GLMs with penalized splines yielded very similar

28  results.

### HEAPSS: Health Effects of Air Pollution among Susceptible Subpopulations

29  HEAPSS investigators collected data on patients hospitalized for a first myocardial infarction (MI)

30  in five European cities between 1992 and 2000. Patients were identified from MI registers in Augsburg

1    and Barcelona, and from hospital discharge registers in Helsinki, Rome and Stockholm. Data on daily

2    levels of $PM_{10}$, were measured at central monitoring sites in each city. Particle number concentration, a

3    proxy for ultrafine particles, was measured for a year in each city and then modeled retrospectively for the

4    whole study period. Associations of outcomes with gaseous criteria pollutants were also evaluated.

5         Von Klot et al. (2005) identified 22,006 survivors of a first MI in the five participating European

6    cities and collected data on subsequent first cardiac re-hospitalizations between 1992 and 2001.

7    Readmissions of interest were those with primary diagnoses of acute MI, angina pectoris, or cardiac

8    disease (which additionally includes dysrhythmias and heart failure). Within each city, associations

9    between cause-specific hospitalization rates and same-day levels of $PM_{10}$ were evaluated using Poisson

10   GAMs controlling for long-term temporal trends and meteorologic conditions using penalized splines.

11   City-specific results were combined using standard meta-analytic methods. Subsequently, Lanki et al.

12   (2006a) used HEAPSS data from 26,854 patients to evaluate the association between daily $PM_{10}$ and

13   particle number concentrations and the risk of hospitalization for first MI.


### PSAS: The French National Program on Air Pollution Health Effects

14        Larrieu et al. (2007) evaluated the association between $PM_{10}$ and the risk of hospitalization in 8

15   French cities between 1998 and 2003. The cities examined were: Bordeaux, Le Havre, Lille, Lyon,

16   Marseille, Paris, Rouen and Toulouse. The specific CVD outcomes considered in each city included: total

17   CVD (ICD-10: I00-I99), cardiac disease (I00-I52), ischemic heart diseases (I20-I25) and stroke (I60-I64,

18   G45-G46). The available data did not differentiate between emergency and non-emergency

19   hospitalizations. Daily mean $PM_{10}$ and $NO_2$ levels as well as 8-h maximum ozone levels were obtained

20   from a network of monitors in each city.

21        Within each city, associations between cause-specific hospitalization rates and 2-day moving

22   average (lag 0-1 days) levels of $PM_{10}$ were evaluated using Poisson GAMs controlling for long-term

23   temporal trends and meteorologic conditions using penalized splines. City-specific results were combined

24   using standard meta-analytic methods. Host et al. (2008) used a subset of these data (6 cities, 2000-2003)

25   to compare the effects of the fine ($PM_{2.5}$) and course fractions ($PM_{10-2.5}$) of ambient particles on the risk of

26   cardiovascular and respiratory admissions. CVD outcomes assessed in this analysis were all CVD

27   (ICD-10 I00-I99), cardiac (I00-I52) and IHD (I20-I25). $PM_{2.5}$ levels were obtained from the same

28   network of background monitors described above. $PM_{10-2.5}$ was calculated by subtracting $PM_{2.5}$ levels

29   from $PM_{10}$ levels. Gaseous pollutants and hospital admissions for stroke were not considered in this

30   analysis.

**Multicity Studies in Australia and New Zealand**

1   Barnett et al. (2006) collected data on daily CVD emergency hospital admissions and pollution data

2   between 1998 and 2001 in five Australian cities (Brisbane, Canberra, Melbourne, Perth, Sydney) and two

3   cities in New Zealand (Auckland, Christchurch). In 2001, these cities covered 53% of the Australian

4   population and 44% of the New Zealand population. The specific outcomes considered in each city were:

5   all circulatory diseases (ICD-9 390-429, ICD-10 I00-I99 with exclusions); heart failure (ICD-9 428,

6   ICD-10 I50); arrhythmia (ICD-9 427 ICD-10 I46-49); cardiac disease (ICD-9 390-429, ICD-10 I00-I52,

7   I97.0, I97.1, I98.1); ischemic heart disease (ICD-9 410-413, ICD-10 I20-24, I25.2); acute MI (ICD-9 410,

8   ICD-10 I21-22); and stroke (ICD-9 430-438, ICD-10 I60-66, I67, I68, I69, G45-46 with exclusions).

9   Air pollutants considered were 24-h average $PM_{10}$, 24-h average $PM_{2.5}$, BSP and gaseous

10   pollutants. Within each city, associations between cause-specific hospitalization rates and 2-day moving

11   average (lags 0-1 days) of $PM_{10}$ were evaluated using the time-stratified case-crossover approach which

12   controls for long-term and seasonal time trends by design rather than analytically. City-specific results

13   were combined using random effects meta-analytic methods.

**EMECAS: Spanish Multicentric Study on the Relation between Air Pollution and Health**

14   Ballester et al. (2006) collected data on daily cardiovascular emergency hospital admission and air

15   pollution data between approximately 1995 and 1999 in 14 cities in Spain. The specific outcomes

16   considered in each city were: total CVD (ICD-9: 390-459) and heart diseases (410-414, 427, 428). Air

17   pollutants considered were $PM_{10}$, TSP, BS, $SO_2$, $NO_2$ (24-h averages), CO and ozone (8-h maximums).

18   Within each city, associations between cause-specific hospitalization rates and daily levels of each

19   pollutant metric were evaluated using Poisson GAMs with strict convergence criteria. In all models,

20   pollutants were entered as linear continuous variables and included control for confounding by

21   meteorological variables, influenza rates, long-term time trends, and unusual events. The authors

22   considered both distributed lag models (lags 0-3 days) and the 2-day moving average of pollution (lags

23   0-1 days). City-specific results were combined using standard meta-analytic methods.

## 6.2.10.1. All Cardiovascular Disease

24   The 2004 PM AQCD incorporated the results of a large number of time-series studies in the U.S.

25   and elsewhere relating ambient PM levels and risk of hospitalization for CVD. The 2004 PM AQCD

26   noted that the strongest evidence for this association came from the NMMAPS study (Samet et al., 2000)

27   and the subsequent reanalysis by Zanobetti and Schwartz (2003).

28   Since then, the U.S. MCAPS study evaluated the association between $PM_{2.5}$ and risk of CVD

29   hospitalization in 202 U.S. counties between 1999 and 2005 and found a 0.7% (95% posterior interval

1    (PI): 0.5, 1.0) increase in risk per 10 μg/m$^3$ increase in PM$_{2.5}$ on the same day (Peng et al., 2008). In 108

2    U.S. counties with co-located PM$_{10}$ and PM$_{10-2.5}$ monitors, the authors found a 0.4% (95% PI, 0.1 to 0.7,

3    lag 0) increase in risk per 10 μg/m$^3$ PM$_{10-2.5}$ (Peng et al., 2008). In a 2-pollutant model adjusted for PM$_{2.5}$,

4    the association between PM$_{10-2.5}$ and CVD hospitalization lost precision (0.3% [95% PI: −0.1 to 0.6])

5    (Peng et al., 2008). Bell et al. (2008a) found evidence of substantial and statistically significant variability

6    in the effects of PM$_{2.5}$ on cardiovascular hospitalizations by season and region, with the highest national

7    average estimates occurring in the winter and the highest regional estimates in the Northeastern U.S.

8    (1.08% 95%PI: 0.79, 1.37, lag 0, per 10 μg/m$^3$ increase in PM$_{2.5}$). Estimates for the nation (1.49%

9    (95%PI: 1.09, 1.89, lag 0) and northeast (2.01% 95%PI 1.39, 2.63, lag 0) were highest in the winter.

10    Additional evidence is provided by several large multicity studies conducted outside of the U.S.

11    The European APHEA2 study (Le Tertre et al., 2002a) looked at admissions for CVD (defined as ICD-9

12    390-429) among those aged ≥ 65 and found a 0.7% (95% CI: 0.4, 1.0, lag 0-1 day average) increase in

13    risk per 10 μg/m$^3$ PM$_{10}$. The Spanish EMECAS study (Ballester et al., 2006) looked at admissions for

14    CVD (defined as ICD-9 390-459) and found a 0.9% (95% CI: 0.4, 1.5, lag 0-1 day average) increase in

15    risk per 10 μg/m$^3$ PM$_{10}$. The French PSAS program looked at CVD hospitalizations (defined as ICD-10

16    I00-I99) among the elderly and found a 1.1% (0.5, 1.7%) increase in risk with PM$_{10}$ and a 1.9% (95% CI:

17    0.9, 3.0, lag 0-1 day average) increase in risk with a 10 μg/m$^3$ increase in PM$_{2.5}$ (Host et al., 2007; Larrieu

18    et al., 2007). Non-significant increases in association with PM$_{10-2.5}$ were reported (1.0% [95% CI: -1.0 to

19    3.0]) (Host et al., 2008). In multiple cities across New Zealand and Australia, Barnett et al. (2006) looked

20    among the elderly (CVD defined as ICD-9 390-459 and found a 1.3% (95% CI: 0.6–2.0, lag 0-1 day

21    average) increase in risk per 10 μg/m$^3$ increase in PM$_{2.5}$.

22    The Atlanta-based SOPHIA study found a 0.9% (95% CI: -0.2 to 1.9, lag 0-2 d average) and a 3.3%

23    (95% CI: 1.0–5.6, lag 0-2 d average) increase in risk with a 10 μg/m$^3$ increase in PM$_{10}$ and PM$_{2.5}$,

24    respectively (Metzger et al., 2004). In a more recent analysis from this study with an additional 4 years of

25    data, ED visits for CVD were not significantly associated with PM$_{10}$ or PM$_{2.5}$, but were significantly

26    associated with total carbon (1.6% [95% CI: 0.5–2.6, per IQR increase]), EC (1.5% [95% CI: 0.5–2.5, per

27    IQR increase]) and organic carbon (1.5% [95% CI: 0.5–2.6, per IQR increase]) components of PM$_{2.5}$

28    (Tolbert et al., 2007). More recently, Sarnat et al. (2008) used multiple source-apportionment methods to

29    evaluate the association between all CVD ED visits and specific PM$_{2.5}$ sources and found consistent

30    positive associations with sources related to motor vehicles and biomass combustion. These results were

31    insensitive to the source-apportionment technique used. It is noteworthy that other traffic-related gaseous

32    pollutants were associated with CVD ED visits in the SOPHIA study (Metzger et al., 2004).

33    Using meta-regression techniques and the reported association between PM$_{10}$ and CVD

34    hospitalizations from the 14 cities included in the NMMAPS analysis, Janssen et al. (2002) examined

1 whether the between-city variability in relative risk estimates were related to the local contribution of a

2 number of PM sources. The authors found that in multivariate analyses $PM_{10}$ coefficients increased

3 significantly with increasing percentage of $PM_{10}$ emissions from highway vehicles/diesels and oil

4 combustion.

5      A small number of additional single-city studies have been published showing positive associations

6 between hospital admissions and ambient PM in Copenhagen, Denmark (Andersen et al., 2007b), and

7 weak nonsignificant associations in Spokane, WA (Schreuder et al., 2006; Slaughter et al., 2005) and two

8 small counties in Idaho (Ulirsch et al., 2007). Schreuder et al. (2006) performed a source apportionment

9 analysis using seven years of daily speciation data from the same residential monitor in Spokane, WA

10 used by Slaughter et al. (2005). These authors related daily levels of four sources (woodsmoke, an As-rich

11 source, motor vehicle emissions, and airborne soil) to the excess risk of cardiovascular ED visits. During

12 the heating season the only notable association for CVD-related ED visits was with woodsmoke, while in

13 the non-heating season the only notable association was with airborne soil. While neither of these

14 associations reached statistical significance, the study likely lacked the statistical power to find effects of

15 the expected magnitude. In fact, it is doubtful that studies conducted outside of large metropolitan areas

16 have sufficient statistical power to detect associations of the expected magnitude.

17      Studies in several cities in Australia have investigated the association of cardiovascular disease

18 admissions with PM concentration and sources. A study from Sydney, Australia found a 0.3% (95% CI:

19 -0.8 to 1.4) and 1.8% (95% CI: 0.4–3.2) excess risk per 10 $\mu g/m^3$ increase in the 2-day moving average

20 (lags 0-1 days) in $PM_{10}$ and $PM_{2.5}$, respectively (Jalaludin et al., 2006) Johnston et al. (2007) and Hanigan

21 et al. (2008) studied the association between $PM_{10}$ and cardiovascular and respiratory hospitalizations in

22 Darwin, Australia, where the predominant source of PM is from biomass combustion. The authors found

23 little or no evidence of an association between $PM_{10}$ and cardiovascular disease hospital admissions in the

24 general population.

25      Crustal material has also been investigated in an effort to explain associations of PM concentration

26 with cardiovascular disease admissions. Studies of a dust storm in the Gobi desert that transported PM

27 across the Pacific Ocean reaching the western U.S. in the spring of 1998 have been conducted. An

28 analysis of the health impacts of this event on the population of British Columbia's (Canada) Lower

29 Fraser Valley found no excess risk of cardiac or respiratory hospital admissions despite hourly $PM_{10}$

30 levels >100 $\mu g/m^3$ (Bennett et al., 2006). On the other hand, a number of studies in Asia and Eastern

31 Europe have identified some adverse health effects associated with dust storm events. Middleton et al.

32 (2008) found that dust storms in Cyprus were associated with a 4.7% (95% CI: 0.7–9.0) and 10.4% (95%

33 CI: -4.7 to 27.9) increase in risk of hospitalization for all causes and cardiovascular diseases, respectively.

34 Chan et al. (2008) studied the effects of Asian dust storms on cardiovascular hospital admissions in

1    Taipei, Taiwan and also found significant adverse effects during 39 Asian dust events with high $PM_{10}$

2    levels (daily $PM_{10}$ >90 $\mu g/m^3$). Bell et al. (2008) analyzed these data independently and concluded that

3    Asian dust storms were positively associated with risk of hospitalization for ischemic heart disease.

4        The effect estimates from multicity studies and single city studies conducted in the U.S. and

5    Canada are included in Figure 6-1. Information on PM concentrations during the relevant study period is

6    presented in Table 6-6. In summary, large studies from the U.S., Europe, and Australia/New Zealand

7    published since the 2004 PM AQCD provide support for an association between short-term increases in

8    ambient levels of $PM_{10}$ and $PM_{2.5}$ and increased risk of hospitalization for total CVD. The average excess

9    risk among the U.S. elderly is likely in the range of 0.5 to 1.0% per 10 $\mu g/m^3$ increase in $PM_{2.5}$, although

10   substantial variability by region of the country and season has been demonstrated. An excess risk of ED

11   visits for CVD of a similar magnitude appears likely. The excess risk of CVD hospitalization may be

12   somewhat greater in Europe and Australia/New Zealand than in the U.S. Sources including wood burning,

13   oil burning, traffic and crustal material have been associated with increases in cardiovascular

14   hospitalization or ED visits.
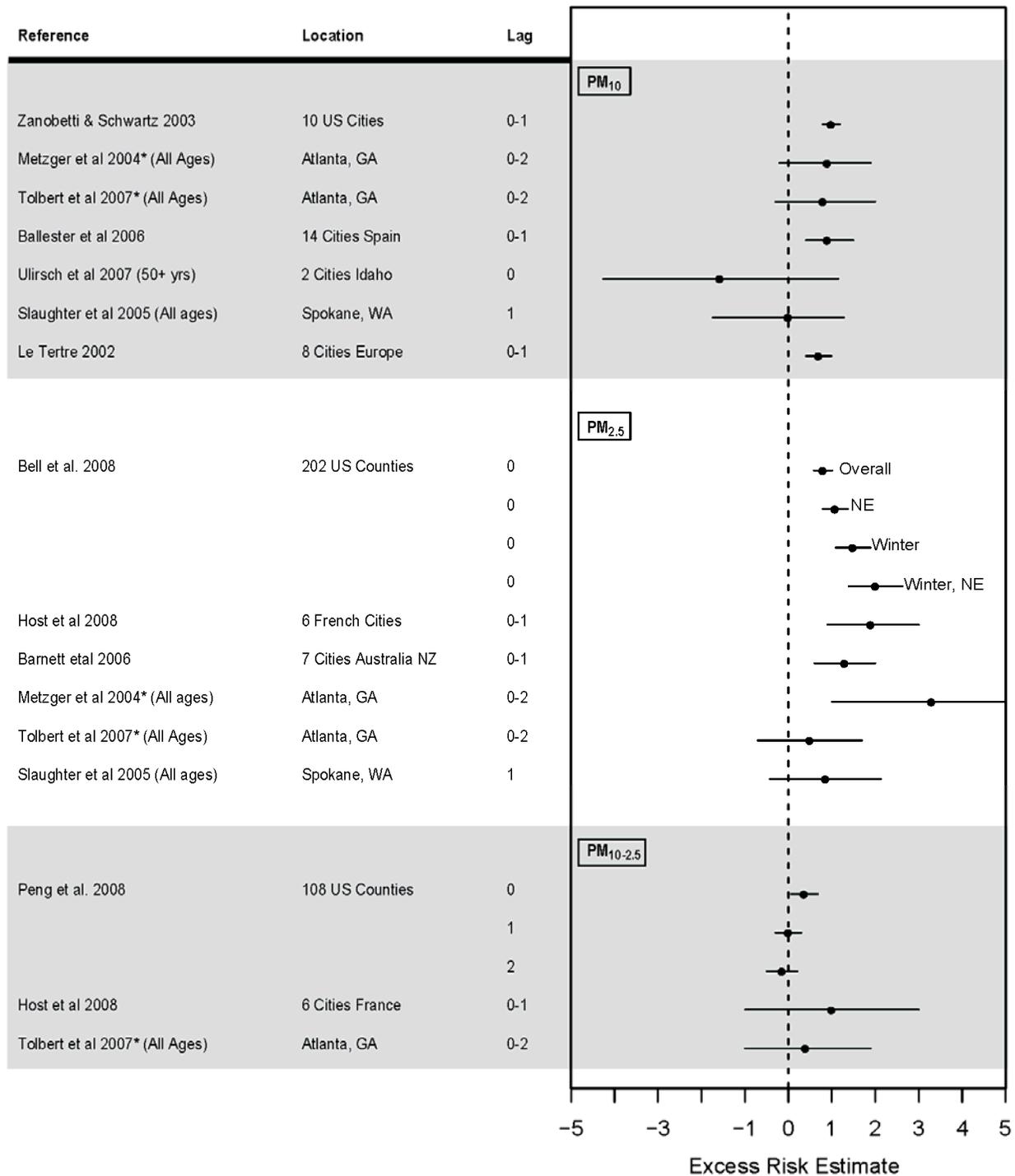
**Figure 6-1.** Excess risk estimates per 10 μg/m³ increase in $PM_{10}$, $PM_{2.5}$ and $PM_{10}$ 2.5 for studies of CVD ED visits * and hospitalizations. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. or Canada are also included.

**Table 6-6.** Characterization of ambient PM concentrations in studies of hospital admission and ED visits for cardiovascular diseases.

| Pollutant | Author | Location | Mean Concentration ($\mu g/m^3$) | Upper Percentile Concentration ($\mu g/m^3$) |
|---|---|---|---|---|
| *PM₁₀* | | | | |
| | Ballester et al. (2006) | 14 cities in Spain | NR | NR |
| | Barnett et al. (2006) | 5 cities in Australia and New Zealand | NR | NR |
| | Burnett et al. (1999) | Toronto, Canada | 30.2 | |
| | Ito et al. (2003); Lippmann (2000) | Detroit, MI | 31 | |
| | Jalaludin et al. (2006) | Sydney, Australia | 16.8 | 75th: 19.9 Max: 103.9 |
| | Larrieu et al. (2007) | 8 cities in France | | |
| | Le Tertre et al. (2002a) | 8 cities in Europe | Range: 15.5-55.7 | Range 75th: 19.9-66 |
| | Linn et al. (2000) | Los Angeles, California | 45 | 78 (summer) -132 (autumn) |
| | Metzger et al. (2004) | Atlanta, GA | 26.3 | 90th: 44.7 |
| | Morris et al. (1998) | Chicago, Illinois | 41 | 75th: 51 Max: 117 |
| | Peters et al. (2001) | Boston, MA | | |
| | Schwartz et al. (1995) | Detroit, MI | 48 | 90th: 82 |
| | Slaughter et al. (2005) | Spokane, WA | NR | 90th: 41.9 |
| | Tolbert et al. (2007) | Atlanta, GA | | |
| | Ulirsch et al. (2007)* | 2 cities in southeast Idaho | 24.2/23.2 | 90th: 40.7/37.4 |
| | Wellenius et al. (2005b) | Pittsburgh, PA | 31.1 | 95th: 70.5 |
| | Wellenius et al. (2006b) | 7 cities in the U.S. | 28.3 (median) | 90th: 57 |
| | Zanobetti and Schwartz (2005) | Boston, MA | 28.4 (median) | 90th: 53.6 |
| | Wellenius et al. (2005b) | 9 cities in the U.S. | 28.4 (median) | 90th: 57.9 |
| *PM₂.₅* | | | | |
| | Bell et al. (2008a) | 202 counties in the U.S. | NR | NR |
| | Host et al. (2008) | 6 cities in France | 13.8-18.8 | NR |
| | Barnett et al. (2006) | 7 cities in Australia | | |
| | Metzger et al. (2004) | Atlanta, GA | 17.8 | 90th: 32.3 |
| | Tolbert et al. (2007) | Atlanta, GA | 17.1 | |
| | Slaughter et al. (2005) | Spokane, WA | NR | 90th: 20.2 |
| | Dominici et al. (2006) | 204 counties in the U.S. | NR | NR |
| | Burnett et al. (1999) | Toronto Canada | 18 | |
| | Ito et al. (2003); Lippmann (2000) | Detroit, MI | 18 | |
| | Pope et al. (2006) | Wasatch Front, Utah | | |
| | Symons et al. (2006) | Baltimore, MD | 16 | 69.2 |
| | Villenueve et al. (2006) | Edmonton, Canada | 8.5 | 75th: 11 |
| *PM₁₀-₂.₅* | | | | |
| | Burnett et al. (1999) | Toronto, Canada | 12.2 | |
| | Peng et al. (2008) | 204 cities in the U.S. | NR | NR |

| | | | |
|---|---|---|---|
| Le Tertre et al. (2002a) | 8 cities in Europe | NR | NR |
| Tolbert et al. (2007) | Atlanta, GA | 9 | |
| Host et al. (2008) | 6 cities in France | 7-11 | NR |
| Peters et al. (2001) | Boston, MA | 7.4 | |
| Ito et al. (2003); Lippmann (2000) | Detroit, MI | 13 | |
| Metzger et al. (2004) | Atlanta, GA | 9.1 | 90th: 16.2 |
| Slaughter et al. (2005) | Spokane, WA | NR | NR |

\* Results presented separately for 2 separate time series

## 6.2.10.2. Cardiac Diseases

1  Cardiac disease represents a subset of CVD which specifically excludes hospitalizations for

2  cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart

3  or coronary circulation. Only a small number of studies published since the 2004 PM AQCD have

4  evaluated the association between ambient PM and hospitalizations for cardiac diseases, as most

5  investigators have focused instead on more narrowly defined outcomes.

6  The French PSAS program found a 1.5% (95% CI: 0.5, 2.2, lag 0-2) and 2.4% (95% CI: 1.2, 3.7,

7  lag 0-2) excess risk among the elderly per 10 $\mu g/m^3$ increase in $PM_{10}$ and $PM_{2.5}$, respectively (Host et al.,

8  2007). The European HEAPSS study looked at cardiac readmissions among survivors of a first MI and

9  found a 2.1% (95% CI: 0.4, 3.9, lag 0) excess risk per 10 $\mu g/m^3$ increase in $PM_{10}$ (von Klot et al., 2005).

10  A 1.9% (95% CI: 1.0, 2.7, lag 0-1) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ was observed in several

11  cities in Australia and New Zealand (Barnett et al., 2006). Single-city studies of hospital admissions from

12  Kaohsiung and Taipei, Taiwan, and an ED visit study from Sydney, Australia also reported statistically

13  significant positive associations (Chang et al., 2005c; Jalaludin et al., 2006; Yang et al., 2004a).

14  In summary, large studies from Europe and Australia/New Zealand published since the 2004 PM

15  AQCD provide support for an association between short-term increases in ambient levels of $PM_{10}$ and

16  $PM_{2.5}$ and increased risk of hospitalization for cardiac disease. The excess risk for cardiac hospitalizations

17  may be somewhat larger than for total CVD hospitalizations.

## 6.2.10.3. Ischemic Heart Disease

18  IHD represents a subset of all cardiac disease hospitalizations and typically includes acute MI (ICD

19  9: 410), other acute and subacute forms of ischemic heart disease (411), old MI (412), angina pectoris

20  (413), and other forms of chronic ischemic heart disease (414). Some authors term this category coronary

21  heart disease. Published studies evaluating IHD as a single outcome are considered first, followed by

22  consideration of studies looking at acute MI, a specific form of IHD.

1    In 1995 Schwartz and Morris (1995) reported a 0.6% (95% CI: 0.2, 1.0%) excess risk of

2    hospitalization for IHD per 10 $\mu g/m^3$ increase in mean $PM_{10}$ levels over the past two days among elderly

3    Medicare beneficiaries living in Detroit between 1986 and 1989. As reviewed in the 2004 PM AQCD,

4    similar associations were subsequently observed in many single-city studies including: London, England

5    (Atkinson et al., 1999), Toronto, Canada (Burnett et al., 1999), and Seoul, Korea (Lee et al., 2003).

6    Studies in Hong Kong (Wong et al., 1999; 2002b), Birmingham, England (Anderson et al., 2001), and

7    London, England (Wong et al., 2002a) yielded positive point estimates of a similar magnitude, but did not

8    reached statistical significance.

9        The positive associations between short-term changes in PM and IHD hospitalizations observed in

10   the early single-city studies have been confirmed in several large multicity studies. The U.S. MCAPS

11   study (Dominici et al., 2006) found a 0.4% (95% CI: 0.0, 0.8) excess risk of hospitalization for IHD per

12   10 $\mu g/m^3$ increase in $PM_{2.5}$ two days earlier. The European APHEA-2 study (Le Tertre et al., 2002b)

13   considered $PM_{10}$ and found a 0.8% (95% CI: 0.3–1.2, lag 0-1) excess risk among those aged $\geq$ 65 years.

14   Among the elderly in 5 cities in Australia and New Zealand (Barnett et al., 2006) there was a 4.3% (95%

15   CI: 1.9–6.4, lag 0-1) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Among the elderly in several French

16   cities there was a 4.5% (95% CI: 2.3–6.8, lag 0-1) and 2.9% (95% CI: 1.5, 4.3, lag 0-1) excess risk per

17   10 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10}$, respectively (Host et al., 2007).

18       With regard to ED visits, the Atlanta-based SOPHIA study (Metzger et al., 2004) found positive

19   associations with $PM_{10}$ and $PM_{2.5}$ (ranging from 1.1 to 2.3%), but the effect estimates did not reach

20   statistical significance. In Sydney, Australia, Jalaludin et al. (2006) found a 0.8% (95% CI: -1.2 to 2.8%)

21   and 2.6% (95% CI: 0.1–5.2) excess risk of ED visits for IHD per 10 $\mu g/m^3$ increase in 2-day moving

22   average of $PM_{10}$ and $PM_{2.5}$, respectively.

23       To explore this link further, Pope et al. (2006) used data from an ongoing registry of patients

24   undergoing coronary angiography at a single referral center in Salt Lake City, UT, between 1994 and

25   2004. The authors found a 4.8% (95% CI: 1.0–8.8, lag 0) excess risk of acute myocardial infarction or

26   unstable angina per 10 $\mu g/m^3$ increase in $PM_{2.5}$ among 4818 patients. These results were robust to changes

27   in the definition of the outcome. The results of this study are particularly noteworthy given the high

28   specificity of the outcome definition.

29       In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the

30   2004 PM AQCD provide support for an association between short-term increases in ambient levels of

31   $PM_{10}$ and $PM_{2.5}$ and increased risk of hospitalization or ED visits for ischemic heart diseases. Estimates of

32   the excess risk vary considerably between studies, but as was the case for total CVD hospitalizations, the

33   excess risk appears to somewhat greater in Europe and Australia/New Zealand. Results from multicity

34   studies and U.S. and Canadian single city studies are presented in Figure 6-2.

Reference | Location | Lag

**Ischemic Heart Disease**

PM₁₀

Ito 2003, Lippmann et al. 2000 — Detroit, MI — 1
Le Tertre et al. 2002 — Europe 8 Cities — 0-1
Metzger et al. 2004* (All Ages) — Atlanta, GA — 0-2
Larrieu et al. 2007 (All Ages) — 8 French Cities — 0-1
Burnett et al. 1999 (All Ages) — Toronto, Canada — 0-2
Le Tertre et al. 2002 — 8 European Cities — 0-1
Jalaludin et al. 2006* — Sydney, Australia — 0-1
Larrieu et al. 2007 — 8 French Cities — 0-1

PM₂.₅

Ito 2003, Lippmann et al. 2000 — Detroit, MI — 1
Pope et al. 2006 (All Ages) — Wasatch Front, UT — 0
Host et al. 2007 (All Ages) — 6 French Cities — 0-1
Metzger et al. 2004* (All Ages) — Atlanta, GA — 0-3
Barnett et al. 2006, (15-64 years) — 5 Cities Australia/NZ — 0-1
Dominici et al. 2006 — 204 US Counties — 0
— 1
— 2
— 0-2 DL
Barnett et al. 2006 — 5 Cities Australia/NZ — 0-1
Host et al. 2007 — 6 French Cities — 0-1
Burnett et al. 1999 (All Ages) — Toronto, Canada — 0-1

PM₁₀₋₂.₅

Ito 2003, Lippmann et al. 2000 — Detroit, MI — 1
Metzger et al. 2004* (All Ages) — Atlanta, GA — 0-3
Host et al. 2007 (All Ages) — 6 French Cities — 0-1
Host et al. 2007 (65+ years) — 6 French Cities — 0-1
Burnett et al. 1999 (All Ages) — Toronto, Canada — 0

**Myocardial Infarction**

PM₁₀

Linn et al. 2000 (>30 yrs) — Los Angeles, CA — 0
Peters et al. 2001 (All Ages) — Boston, MA — 2 h
Peters et al. 2001 (All Ages) — Boston, MA — 24 h
Zanobetti & Schwartz (2005), 21 — 0

PM₂.₅

Peters et al. 2001 (All Ages) — Boston, MA — 2 h
— 24 h
Sullivan et al. 2005 (21-98 y) — King County WA — 1 h
— 2 h
— 4 h
— 24 h
Zanobetti & Schwartz 2005 — Boston, MA — 0

PM₁₀₋₂.₅

Peters et al. 2001 (All Ages) — Boston, MA — 2 h
— 24 h

Excess Risk Estimate
-5   -1   2   5   8   11   15   19   23   27

**Figure 6-2.** Excess risk estimates per 10 µg/m³ increase in PM₁₀, PM₂.₅, PM₁₀₋₂.₅ for studies of ED visits * and hospitalizations for IHD and MI. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. and Canada are also included.

## 6.2.10.4. Acute Myocardial Infarction

1    Because even IHD refers to a heterogeneous collection of diseases and syndromes, several authors

2    have evaluated the association between short-term fluctuations in ambient PM and acute MI, a specific

3    form of ischemic heart disease.

4    In 2001, Peters et al. (2001) published their landmark study evaluating the effects of PM on the risk

5    of MI among 772 Boston-area participants in the Determinants of Myocardial Infarction Onset Study. The

6    authors found that a 10 $\mu g/m^3$ increase in the 2-h or 24-h average levels of $PM_{2.5}$ was associated with a

7    17% (95% CI: 4–32) and 27% (95% CI: 6–53) excess risk of MI, respectively. In contrast, a similar study

8    among 5793 patients in King County, WA, found no association with $PM_{2.5}$ with lag times of 1, 2, 4, or

9    24 h (Sullivan et al., 2005a). Among 852 hospitalized patients in Augsburg, Germany, Peters et al. (2005)

10   also found no association between $PM_{2.5}$ and MI risk within this time frame, although they did find a

11   positive and statistically significant association with time spent in traffic (Peters et al., 2004).

12   These three studies are particularly important because in each one: (1) cases were prospectively

13   identified based on clinical criteria rather than retrospectively based on discharge diagnoses, and (2) time

14   of MI symptom onset was used for exposure assessment rather than date of hospital admission. Whether

15   the discrepant results among these studies are due to regional differences in population characteristics

16   and/or air pollution sources remains unclear. The King County study suggests that differences in statistical

17   approaches are unlikely to account for the discrepant results (Sullivan et al., 2005a). Analyses from the

18   U.S. MCAPS study suggest that substantial heterogeneity of effects are to be expected across regions of

19   the country (Bell et al., 2008a).

20   Several studies have assessed the association between acute exposure to ambient PM and MI using

21   administrative databases. In the U.S., MI was not one of the specific endpoints evaluated in the MCAPS

22   study (Dominici et al., 2006) or in the Atlanta-based SOPHIA study of ED visits (Metzger et al., 2004).

23   However, Zanobetti and Schwartz (2005) found a 0.7% (95% CI: 0.3–1.0) excess risk of MI per 10 $\mu g/m^3$

24   increase in same-day $PM_{10}$ among elderly Medicare beneficiaries in 21 cities. Subsequently, the same

25   authors found that among elderly Medicare beneficiaries living in the Boston metropolitan region a

26   10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 4.9% (95% CI: 1.1, 8.2) excess risk on the same day

27   (Zanobetti and Schwartz, 2006).

28   This body of evidence may implicate traffic-related pollution generally as a risk factor for

29   myocardial infarction (MI). In the study described above, Peters et al. (2001) found positive associations

30   between risk of hospitalization for MI and potential markers of traffic-related pollution measured at a

31   central monitor including BC, CO and $NO_2$. However, none of these associations were statistically

32   significant in models adjusting for season, meteorological variables, and day of week. Zanobetti and

33   Schwartz (2006) examined the association between traffic-related pollution and risk of hospitalization for

1    MI among Medicare beneficiaries in the Boston area and found that MI risk was positively and

2    significantly associated with measures of $PM_{2.5}$, BC, $NO_2$, and CO, but not with levels of

3    non-traffic-related $PM_{2.5}$. Peters et al. (2004) interviewed 691 subjects with MI who survived at least 24-h

4    after the event and found a strong positive association between self-reported exposure to traffic and the

5    onset of MI within one hour (OR: 2.9; 95% CI: 2.2, 3.8; P< 0.001). The association was somewhat

6    stronger among subjects traveling by bicycle or public transportation in the hour prior to the event. Of

7    note, however, this study did not directly measure traffic-related pollution.

8    Similar studies with administrative databases have been conducted in Europe, Australia, and New

9    Zealand. In Rome, D'Ippoliti et al. (2003) carried out a case-crossover study and found a statistically

10   significant positive association between total suspended particles (TSP) and the risk of hospitalization for

11   MI. Barnett et al. (2006) observed that in 5 cities in Australia and New Zealand, a 10 μg/m$^3$ increase in

12   $PM_{2.5}$ was associated with a 7.3% (95% CI: 3.5, 11.4, lag 0-1 day) excess risk. In contrast, the HEAPSS

13   study found no evidence of an association between $PM_{10}$ and risk of hospitalization for a first MI in 5

14   European cities (2006a), although there is some indication that among survivors of a first myocardial

15   infarction, risk of re-hospitalization for MI may be related to transient elevations in $PM_{10}$ (von Klot et al.,

16   2005).

17   In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the

18   2004 PM AQCD provide support for an association between short-term increases in ambient levels of

19   $PM_{10}$ and $PM_{2.5}$ and increased risk of hospitalization for MI, but the results have not been consistent.

20   These results need to be interpreted together with those studies evaluating hospitalization for IHD since

21   myocardial infarctions make up the majority of ischemic heart diseases. U.S. studies of MI are included in

22   Figure 6-2.

## 6.2.10.5. Congestive Heart Failure

23   Perhaps the first suggestion of an association between ambient PM and hospitalization for

24   congestive heart failure (CHF) was provided by the study of Schwartz and Morris (1995). These authors

25   reported that among elderly Medicare beneficiaries living in Detroit between 1986 and 1989, a 10 μg/m$^3$

26   increase in mean $PM_{10}$ levels over the past two days was associated with a 1.0% (95% CI: 0.4, 1.6%)

27   increase in risk of hospitalization for CHF. As reviewed in the 2004 PM AQCD, using similar approaches,

28   statistically significant positive associations with $PM_{10}$ or $PM_{2.5}$ were subsequently reported in single-city

29   studies looking at hospitalizations for CHF in Toronto (Burnett et al., 1999), Hong Kong (Wong et al.,

30   1999), and Detroit (Lippmann et al., 2000), but not Los Angeles (Linn et al., 2000) or Denver (Koken et

31   al., 2003).

1    Subsequent multicity studies support the presence of a positive association. In the U.S., Wellenius

2    et al. (2006) reported a 0.7% (95% CI: 0.4, 1.1) excess risk of hospitalization for CHF per 10 μg/m$^3$

3    increase in same-day $PM_{10}$ among elderly Medicare beneficiaries in 7 cities. The larger MCAPS study

4    found a 1.3% (95%: 0.8, 1.8) excess risk per 10 μg/m$^3$ increase in same-day $PM_{2.5}$ (Dominici et al., 2006).

5    In Australia and New Zealand, Barnett et al. (2006) found a 9.8% (95% CI: 4.8, 14.8, lag 0-1 day) and

6    4.6% (95% CI: 2.8, 6.3, lag 0-1 days) excess risk of hospitalization for CHF associated with a 10 μg/m$^3$

7    increase in $PM_{2.5}$ and $PM_{10}$, respectively. Results from more recent single-city studies in Pittsburgh

8    (Wellenius et al., 2005b) and Taipei, Taiwan (Yang, 2008) have also reported positive associations.

9    Findings from the Atlanta-based SOPHIA study (Metzger et al., 2004) also support the presence of

10   a positive association. Specifically, the SOPHIA study found a 5.5% (95% CI: 0.6, 10.5, lag 0-2 days)

11   excess risk of emergency department visits for CHF per 10 μg/m$^3$ increase in the 3-day moving average of

12   $PM_{2.5}$. Positive associations were also observed for CHF and EC and organic carbon components of

13   $PM_{2.5}$. No associations were observed with $PM_{10}$.

14   Only one published study has attempted to evaluate the effects of ambient particles on CHF

15   symptom exacerbation using data which was not derived from administrative databases. Symons et al.

16   (2006) interviewed 135 patients with prevalent CHF hospitalized for symptom exacerbation in Baltimore,

17   MD. The authors found a 7.4% (95% CI: -7.5 to 24.2) excess risk of hospitalization per 10 μg/m$^3$ increase

18   in $PM_{2.5}$ two days prior to symptom onset. Although the authors' findings did not reach statistical

19   significance, the study was ill-powered to find an effect of the expected magnitude.

20   In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the

21   2004 PM AQCD provide support for an association between short-term increases in ambient levels of

22   $PM_{10}$ and $PM_{2.5}$ and increased risk of hospitalization and ED visits for heart failure. The excess risk

23   associate with heart failure hospitalizations and ED visits are consistently greater than those observed for

24   other CVD endpoints. The results of multicity studies and U.S. and Canadian single city studies are

25   summarized in Figure 6-3.

| Reference | Location | Lag |
|---|---|---|
| Burnett et al. 1999 | Toronto, Canada | 0-2 |
| Linn et al. 2000 (>30) | Los Angeles, CA | 0 |
| Ito 2003/Lippmann et al. 2000 | Detroit, MI | 0 |
| Metzger et al. 2004* (All Ages) | Atlanta, GA | 0-2 |
| Barnett et al. 2006 (15-64) | 5 Cities Australia/NZ | 0-1 |
| Schwartz et al. 1995 | Detroit, MI | 0-1 |
| Morris et al. 1998 | Chicago, IL | 0 |
| Wellenius et al. 2005 | Pittsburgh, PA | 0 |
| Wellenius et al. 2006 | 7 US Cities | 0 |
| Barnett et al. 2006 | 5 Cities Australia/NZ | 0-1 |
| Burnett et al. 1999 (All Ages) | Toronto, Canada | 0-2 |
| Ito 2003/Lippmann et al. 2000 | Detroit, MI | 1 |
| Metzger et al. 2004* (All Ages) | Atlanta, GA | 0-2 |
| Barnett et al. 2006 (15-64 y) | 5 Cities Australia/NZ | 0-1 |
| Symons et al. 2006 (All Ages) | Baltimore, MD | 2 |
| Dominici et al. 2006 | 204 US Counties | 0 |
| Barnett et al. 2006 | 5 Cities Australia/NZ | 0-1 |
| Burnett et al. 1999 (All Ages) | Toronto, Canada | 0-2 |
| Ito 2003/Lippmann et al. 2000 | Detroit, MI | 0 |
| Metzger et al. 2004* (All Ages) | Atlanta, GA | 0-2 |

**Figure 6-3.** Excess risk estimates per 10 µg/m³ increase in $PM_{10}$, $PM_{10\text{-}2.5}$ and $PM_{10\text{-}2.5}$ for studies of CHF ED visits * and hospitalizations. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. and Canada are also included.

## 6.2.10.6. Cardiac Arrhythmias

1  A number of studies based on administrative databases have sought to evaluate the association

2  between short-term fluctuations in ambient PM levels and the risk of hospitalization for cardiac

3  arrhythmias (also known as dysrhythmias). Typically in these studies a primary discharge diagnosis of

4  ICD-9 427 has been used to identify hospitalized patients. However, ICD-9 427includes a heterogeneous

5  group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation

6  and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoarterial node

7  dysfunction. One study in the Netherlands found that the positive predictive value of ICD-9 codes related

1   to ventricular arrhythmias and sudden cardiac death was 82% (De Bruin et al., 2005). The positive

2   predictive value of other codes related to cardiac arrhythmias is unknown but likely to be lower.

3      The results from early studies of arrhythmia-related hospitalizations have been inconsistent with

4   positive findings in Toronto (Burnett et al., 1999) and null findings in Detroit (Schwartz and Morris,

5   1995), Los Angeles (Linn et al., 2000), and Denver (Koken et al., 2003). The U.S. MCAPS study found a

6   statistically significant 0.6% (95% CI: 0.0, 1.2%) excess risk of hospitalization for the combined end

7   point of cardiac arrhythmias and conduction disorders (ICD-9: 426, 427) per 10 $\mu g/m^3$ increase in

8   same-day $PM_{2.5}$ (Dominici et al., 2006). A multicity study in Australia and New Zealand found no

9   evidence of an association between arrhythmia hospitalizations and either $PM_{10}$ or $PM_{2.5}$ (Barnett et al.,

10  2006). Similarly, the Atlanta-based SOPHIA study found no evidence of an association between any

11  measure of ambient PM and the rate of ED visits for cardiac arrhythmias (Metzger et al., 2004).

12     A number of studies in patients with implanted cardioverter defibrillators have been more

13  successful at evaluating the link between ambient air pollution and the risk of atrial and ventricular

14  arrhythmias (Berger et al., 2006; Dockery et al., 2005a; Dockery et al., 2005b; Peters et al., 2000; Rich et

15  al., 2004; Vedal et al., 2004). An important strength of these studies is the ability to examine recordings of

16  arrhythmic episodes, thereby reducing misclassification of the outcome. These studies are reviewed in

17  detail in Section 6.2.2.1.

18     In summary, the current evidence does not support the presence of a consistent association between

19  short-term increases in ambient levels of $PM_{10}$ and $PM_{2.5}$ and increased risk of hospitalization for cardiac

20  arrhythmias. However, it should be noted that studies of hospital admissions or ED visits are ill-suited to

21  the study of cardiac arrhythmias. Studies in patients with implanted defibrillators, human panel studies

22  with ambulatory ECG recordings, and animal toxicological studies provide a more appropriate setting for

23  evaluating this endpoint.

## 6.2.10.7. Cerebrovascular Disease

24     Time-series studies evaluating the hypothesis that short-term increases in ambient PM levels are

25  associated with increased risk of hospitalization for cerebrovascular disease have been inconsistent with a

26  minority of studies reporting statistically significant positive associations (Chan et al., 2006a; Dominici et

27  al., 2006; Metzger et al., 2004; Wordley et al., 1997), and several studies reporting null or negative

28  associations (Anderson et al., 2001; Barnett et al., 2006; Burnett et al., 1999; Jalaludin et al., 2006;

29  Larrieu et al., 2007; Le Tertre et al., 2002b; Peel et al., 2007; Villeneuve et al., 2006; Wong et al., 1999).

30     The U.S. MCAPS study found a 0.8% (95% CI: 0.3, 1.4) excess risk of hospitalization for

31  cerebrovascular disease per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$ (Dominici et al., 2006). Interestingly,

32  the association showed regional variability with the strongest associations observed in the Eastern U.S.

1     The Atlanta-based SOPHIA study found a 2.0% (95% CI: -0.1, 4.3, lag 0-2 days) excess risk of ED visits

2     for a combined endpoint of cerebrovascular and peripheral vascular disease excluding hemorrhagic

3     strokes per 10 $\mu g/m^3$ increase in $PM_{10}$ and a 5.0% (95% CI: 0.8, 9.3, lag 0-2 days) excess risk for $PM_{2.5}$

4     (Metzger et al., 2004).

5         In contrast, large multicity studies outside of North America have failed to observe an association.

6     The APHEA study, found a 0.0% (95% CI: -0.3, 0.3) excess risk of hospitalization for cerebrovascular

7     disease per 10 $\mu g/m^3$ increase in the 2-day moving average of $PM_{10}$ in 8 European cities (Le Tertre et al.,

8     2002b). Investigators from the French PSAS program reported a 0.8% (95% CI: -0.9, 2.5, lag 0-1 days)

9     excess risk per 10 $\mu g/m^3$ increase in $PM_{10}$ among patients aged $\geq$ 65 years and a 0.2% (95% CI: -1.6, 1.9,

10     lag 0-1 days) excess risk among all patients (Larrieu et al., 2007). Although neither estimate was

11     statistically significant, the estimated excess risk among the elderly is very similar to that observed in the

12     U.S. MCAPS study. Barnett et al. (2006) examined this hypothesis in New Zealand and Australia and

13     found no association, but the authors did not report point estimates or confidence intervals.

14         All of the above studies have identified cases of cerebrovascular disease based on ICD-9 or ICD-10

15     codes (most commonly ICD-9 430-438). However, the range of ICD codes commonly used in these

16     studies includes ischemic strokes, hemorrhagic strokes, transient ischemic attacks (TIAs) and several

17     poorly defined forms of acute neurological events (e.g. seizures from a vascular cause) (see Table 6-5). It

18     is plausible that ambient PM has different effects on each of these disparate outcomes.

## 6.2.10.8. Ischemic Strokes and Transient Ischemic Attacks

19         An increasing number of studies have specifically evaluated the association between PM and the

20     risk of ischemic stroke (Chan et al., 2006a; Henrotin et al., 2007; Linn et al., 2000; Lisabeth et al., 2008;

21     Tsai et al., 2003b; Villeneuve et al., 2006; Wellenius et al., 2005a). Linn et al. (2000) found a 1.3% (95%

22     CI: 1.0, 1.6 per 10 $\mu g/m^3$, lag 0) excess risk of hospitalization for ischemic stroke in the Los Angeles

23     metropolitan area. Wellenius et al. (2005a) reported a statistically significant 0.4% (95% CI: 0.0, 0.9)

24     excess risk per 10 $\mu g/m^3$ increase in same-day $PM_{10}$ among elderly Medicare beneficiaries in 9 U.S.

25     cities. In Kaohsiung, Taiwan, Tsai et al. (2003b) found a 5.9% (95% CI: 4.3, 7.4, lag 0-2 days) excess risk

26     of hospitalization for ischemic stroke per 10 $\mu g/m^3$ increase in $PM_{10}$ after excluding days with mean daily

27     temperature < 20°C. Meanwhile, in Taipei, Taiwan, Chan et al. (2006a) found a 1.6% (95% CI: -0.8, 3.9,

28     lag 3) and 3.0% (95% CI: -0.8, 6.6, lag 3) excess risk per 10 $\mu g/m^3$ increase in $PM_{10}$ and $PM_{2.5}$,

29     respectively. Villeneuve et al. (2006) found no association between either $PM_{2.5}$ or $PM_{10}$ and emergency

30     department visits for acute ischemic stroke in Edmonton, Canada.

31         Two recent studies are particularly noteworthy given the high specificity of the outcome definition.

32     Henrotin et al. (2007) used data on 1432 confirmed cases of ischemic stroke from the French Dijon Stroke

1    Register and found 0.9% (-7.0, 9.4%) excess risk of ischemic stroke per 10 μg/m$^3$ increase in PM$_{10}$ on the

2    same day and a 1.1% (-0.2, 9.4%) excess risk on the previous day (lag 1 day). Lisabeth et al. (2008) used

3    data on 2350 confirmed cases of ischemic stroke and 1158 cases of TIA from the Brain Attack

4    Surveillance in Corpus Christi Project (BASIC), a population-based stroke surveillance project designed

5    to capture all strokes in Nueces County, Texas. The authors found a 6.0% (95% CI: -0.8, 13.2) and 6.0%

6    (95% CI: -1.8, 14.4) excess risk of ischemic stroke/TIA per 10 μg/m$^3$ increase in PM$_{2.5}$ on the previous

7    day and the same day, respectively.

8        Only the study by Villeneuve et al. (2006) specifically evaluated the association between ambient

9    PM and the risk of TIAs. This study failed to find any evidence of an association with either PM$_{2.5}$ or

10   PM$_{10}$.

## Hemorrhagic Strokes

11       Most of the studies in the preceding section also evaluated the association between ambient PM

12   and the risk of hemorrhagic stroke (Chan et al., 2006; Henrotin et al., 2007; Tsai et al., 2003; Villeneuve

13   et al., 2006; Wellenius et al., 2005). In Kaohsiung, Taiwan, Tsai et al. (2003) noted a 6.7% (95% CI: 4.2,

14   9.4, lag 0-2 days) excess risk of hospitalization for hemorrhagic stroke per 10 μg/m$^3$ increase in PM$_{10}$,

15   after excluding days where the mean temperature was < 20°C. However, in the U.S., Wellenius et al.

16   (2005) failed to find any association between ambient PM$_{10}$ levels and risk of hemorrhagic stroke among

17   Medicare beneficiaries in 9 U.S. cities. Similarly, Villeneuve et al. (2006) found no evidence of an

18   association between emergency department visits for hemorrhagic stroke and either PM$_{10}$ or PM$_{2.5}$ levels

19   in Edmonton, Canada. Henrotin et al. (2007) found no evidence of an association between risk of

20   hospitalization and PM$_{10}$ levels in Dijon, France, and Chan et al. (2006) found no evidence of an

21   association between risk of hospitalization and either PM$_{10}$ or PM$_{2.5}$ levels in Taipei, Taiwan.

22       In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the

23   2004 PM AQCD provide inconsistent support for an association between short-term increases in ambient

24   levels of PM$_{10}$ and PM$_{2.5}$ and risk of hospitalization and ED visits for cerebrovascular disease (Figure

25   6-4). The heterogeneity in results is likely partly attributed to differences in the sensitivity and specificity

26   of the various outcome definitions used in the relevant studies. Effect estimates from multicity studies and

27   single city U.S. and Canadian studies are included in Figure 6-4.
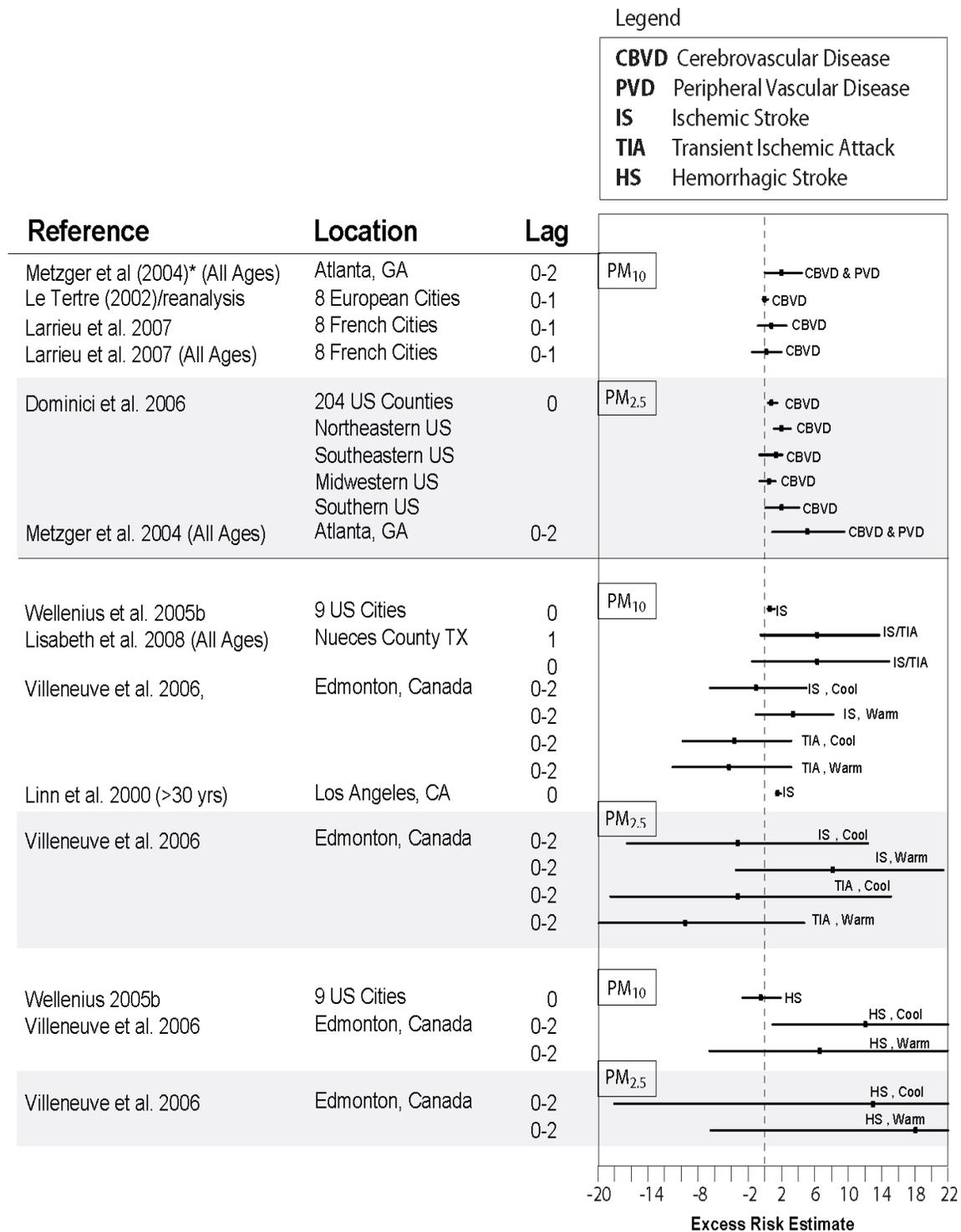
**Figure 6-4.** Excess risks estimates per 10 μg/m³ increase in PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ for studies of ED visits* and hospitalizations for cerebrovascular diseases. Studies represented in the figure included all multicity studies. Single city studies conducted in the U.S. and Canada are also included.

## Peripheral Vascular Disease

1   In the U.S., the large MCAPS study (Dominici et al., 2006) evaluated the association between

2   mean daily $PM_{2.5}$ levels and the risk of hospitalization among elderly Medicare beneficiaries in 204 urban

3   counties and found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was not significantly associated with risk of

4   hospitalization for peripheral vascular disease 0-2 days later. An earlier study in Toronto (Burnett et al.,

5   1999) found a negative association with $PM_{2.5}$ (point estimate and confidence intervals not reported), a

6   positive non-significant association with $PM_{10}$ (0.5%; 95% CI: -0.5, 1.6%), and a positive statistically

7   significant association with $PM_{10-2.5}$ (2.2%; 95% CI: 0.1, 4.3%). The Atlanta-based SOPHIA study

8   (Metzger et al., 2004) of emergency department visits grouped visits for PVD with those for

9   cerebrovascular disease, making interpretation of these results challenging.

10   In summary, there is insufficient published data to determine whether or not there may be an

11   association between short-term increases in ambient levels of $PM_{10}$ and $PM_{2.5}$ and increased risk of

12   hospitalization and ED visits for peripheral vascular disease.

## PM and Out of Hospital Cardiovascular Deaths

13   One study of out of hospital cardiac death conducted in Seattle, WA (Checkoway et al., 2000),

14   which reported no association with PM was included in the 2004 PM AQCD. In the U.S., the survival rate

15   of sudden cardiac arrest is less than 5%. In addition, as discussed above, Zeka et al. (2006a) found that the

16   estimated mortality risk due to short-term exposure to $PM_{10}$ was much higher for out-of-hospital

17   cardiovascular deaths than for in-hospital cardiovascular deaths. The analysis of studies that examine the

18   association between PM and cardiac arrest could provide evidence for an important link between the

19   morbidity and mortality effects attributed to PM.

20   Sullivan et al. (2003) examined the association between the incidence of primary cardiac arrest and

21   daily measures of $PM_{2.5}$ (measured by nephelometry) using a case-crossover analysis of 1,206

22   Washington State out-of-hospital cardiac arrests (1985–1994) among persons with (n = 774) and without

23   (n = 432) clinically recognized heart disease. The authors examined PM associations at 0- through 2-day

24   lags using the time-stratified referent sampling scheme (i.e., the same day of the week and month of the

25   same year). The estimated relative risk for a 13.8-$\mu g/m^3$ increase in 1-day lag $PM_{2.5}$ (nephelometry: 0.54 ×

26   10–1 km–1 bsp) was 0.94 (95% CI: 0.88–1.02), or 0.96 (0.91, 1.0) per 10 $\mu g/m^3$ increase. Similar

27   estimates were reported for 0- or 2-day lags. The presence or absence of clinically recognized heart

28   disease did not alter the result. This finding is consistent with the previous study of cardiac arrest in

29   Seattle (Levy et al., 2001) that reported no PM association. It is also consistent with the Sullivan et al.

30   (2005a) analysis of PM and onset of MI, and the Sullivan et al. (2007) analysis of PM and blood markers

31   of inflammation in the elderly population, both of which were conducted in Seattle. Note also that the

1    analysis of the NMMAPS data for the years 1987-1994 also found no $PM_{10}$ association for all-cause

2    mortality in Seattle. Overall, the results of studies conducted in Seattle consistently found no association

3    between PM and cardiovascular outcomes or all-cause mortality.

4        Rosenthal et al. (2008) examined associations between $PM_{2.5}$ and out-of-hospital cardiac arrests in

5    Indianapolis, Indiana for the years 2002-2006 using a case-crossover design with time-stratified referent

6    sampling. Using all the cases (n = 1,374), they found no associations between $PM_{2.5}$ and cardiac arrest in

7    any of the 0 through 3-day lags or multi-day averages thereof (e.g., for 0-day lag, OR = 1.02 [CI: 0.94,

8    1.11] per 10 $\mu g/m^3$ increase in $PM_{2.5}$). However, for cardiac arrests witnessed by bystanders (n = 511),

9    they found a significant association with $PM_{2.5}$ exposure (by TEOM, corrected with FRM measurements)

10   during the hour of the arrest (OR = 1.12 [CI: 1.01, 1.25] per 10 $\mu g/m^3$ increase in $PM_{2.5}$), and even larger

11   risk estimates for older adults (age 60-75) or those that presented with asystole. There have been very few

12   PM studies that used hourly PM measurements, and further studies are needed to confirm associations at

13   such time scales.

14       In Rome, Forastiere et al. (2005) examined associations between air pollution (particle number

15   concentration, or PNC, $PM_{10}$, CO, $NO_2$, and $O_3$) and out-of-hospital coronary deaths (n = 5,144) for the

16   study period of 1998-2000. A case-crossover design with the time-stratified referent sampling was used to

17   examine the pollution indices at lag 0 through 3 days and the average of 0-1 lags. They found associations

18   between deaths and PNC (lag 0 and 0-1), $PM_{10}$ (lag 0, 1, and 0-1), and CO (lag 0 and 0-1) but not with

19   $NO_2$ or $O_3$. The risk estimate for 0-day lag $PM_{10}$ was 1.59% (CI: 0.03, 3.18) per 10 $\mu g/m^3$ increase. The

20   older adults (65–74 and 75+ age groups) showed higher risk estimates than the younger (35–64) age

21   group. Because PNC is considered to be associated with ultrafine particles, and CO was also associated

22   with out-of-hospital cardiac arrests, combustion sources were implicated.

23       In summary, only a few studies have examined out-of-hospital cardiac arrest or deaths. The two

24   studies from Seattle, WA consistently found no association (also consistent with other cardiac effects and

25   mortality studies conducted in that locale); a study in Indianapolis, IN found an association with hourly

26   $PM_{2.5}$ but not daily $PM_{2.5}$; and a study in Rome found an association with $PM_{10}$ but also with particle

27   numbers and CO. Because multicity mortality studies examining this association found heterogeneity in

28   PM risk estimates across regions, future studies of out-of-hospital cardiac arrest will need to consider

29   location and the air pollution mixture during their design.

# 6.2.11. Summary of Causal Determinations by PM Metric

## 6.2.11.1. PM$_{10}$

### *Causal Determination*

The bulk of recent evidence for PM$_{10}$ health effects is derived from epidemiologic studies of hospital admissions and ED visits. Although some regional heterogeneity is evident in the single city effect estimates, consistent increases in hospital admission or ED visits for cardiovascular diseases have been observed. Further, multicity analyses indicate a significant increase in CVD admissions that are consistent with those reported in the 2004 PM AQCD. The recent literature also implicates IHD and CHF as largely responsible for these CVD admissions rather than cerebrovascular diseases. However, a large multicity U.S. study provides evidence of an association of PM$_{10}$ with ischemic stroke. The results of these studies provide support of associations between short-term PM$_{10}$ exposure and increased risk of cardiovascular admissions in areas with mean concentrations from 16.8 to 48 μg/m$^3$ (Figure 6-1).

No human clinical studies have evaluated the effect of PM$_{10}$ on measures of cardiovascular function. However, animal toxicological studies have been published since the 2004 PM AQCD that employ PM$_{10}$, demonstrating impacts on the cardiovascular system. A recent inhalation study found lowered myocardial contractility upon exposure to PM$_{10}$, while several intratracheal instillation studies observed altered vasoreactivity and elevated levels of systemic inflammatory and blood coagulation markers, thus providing coherence with the epidemiologic findings of increases in hospital admissions and ED visits. Several epidemiologic studies of HRV, systemic markers of inflammation and coagulation as well as oxidative stress demonstrated PM$_{10}$-related effects in areas with mean concentrations ranging from 14 to 42 μg/m$^3$. Coherence of specific endpoints across epidemiologic and toxicological studies is strongest for vasomotor function and coagulation markers.

Overall, recent evidence supports the conclusion of the 2004 PM AQCD that short-term exposure to PM$_{10}$ is associated with an increased risk of cardiovascular morbidity. Furthermore, findings of altered systemic inflammation, autonomic function, coagulation, and vasoreactivity provide biological plausibility that exposure to PM$_{10}$ could lead to more severe effects, including hospital admissions or ED visits for IHD, CHF, or ischemic stroke. Collectively, **the evidence is sufficient to conclude that a causal relationship is likely to exist between PM$_{10}$ exposures and cardiovascular morbidity**.

### *Heart Rate Variability*

**Epidemiologic Studies:** Discrepant findings across six epidemiologic studies of HRV were described in the 2004 PM AQCD. Although approximately 20 new studies of HRV have been conducted

1     only three included ambient $PM_{10}$ concentration (Ebelt et al., 2005; Liao et al., 2005; Lipsett et al., 2006).

2     Findings from these studies were consistent, with each reporting decreases in time and frequency domain

3     measures of HRV.

### Arrhythmia

4     **Epidemiologic Studies:** Recent studies of $PM_{10}$ and ventricular arrhythmias report no associations

5     (Metzger et al., 2004; Rich et al., 2004; Vedal et al., 2004). However, Ebelt et al. (2005) reported an

6     increase in supraventricular ectopic beats with same day $PM_{10}$ concentration.

### Vasomotor Function

7     **Epidemiologic Studies:** One recent study investigating the association of $PM_{10}$ with vasomotor

8     function reported increased FMD, but decreased basal diameter in healthy volunteers (Liu et al., 2007b).

9     **Toxicological Studies:** There were no studies that directly measured vasomotor function in the

10     2004 PM AQCD. Endothelin, an activator of vasoconstriction, was evaluated in two studies that reported

11     increased plasma ET-1 and ET-3 levels in rats following extremely high exposure concentrations to $PM_{10}$

12     (EHC-93). There are two intratracheal instillation studies that employed $PM_{10}$ (EHC-93) to evaluate

13     vasoreactivity, although over 99% of the particles were < 3 μm. One study in carotid arteries of rabbits

14     exposed to $PM_{10}$ reported reduced ACh-stimulated relaxation, whereas the other study in aortic rings of

15     SH rats found enhanced ACh-induced relaxation. No change in vasoconstriction was observed in the latter

16     study and it was not measured in the former study.

### Blood Pressure

17     **Epidemiologic Studies:** Findings from the previous AQCD were inconsistent regarding the

18     association of $PM_{10}$ (or TSP) with BP. No increases in BP were reported in recent studies examining $PM_{10}$

19     (Ebelt et al., 2005; Jansen et al., 2005).

20     **Toxicological Studies:** Only one animal toxicological study reviewed in the 2004 PM AQCD

21     measured BP and did not report any effect following exposure to diesel soot ($PM_{10}$). There are no new

22     studies that evaluated BP responses and exposure to $PM_{10}$ at reasonable concentrations.

### Cardiac Contractility

23     **Toxicological Studies:** A recent inhalation study conducted in mice used echocardiography and

24     demonstrated reductions in cardiac fractional shortening, diminished ejection fraction, and maximum

25     change in pressure over time with carbon black exposure. These results support lowered myocardial

26     contractility.

### Systemic Inflammation

**Epidemiologic Studies:** Several studies of $PM_{10}$ (and TSP) reviewed in the 2004 PM AQCD provided limited support for mechanisms related to CVD development or progression. Newer studies have focused on $PM_{2.5}$. Findings in the few new studies examining $PM_{10}$ have been inconsistent (Ruckerl et al., 2006; 2007b; 2008; Sullivan et al., 2007).

**Toxicological Studies:** There were mixed results reported in the 2004 PM AQCD in regard to systemic inflammation. Only one toxicological study conducted in rabbits demonstrated increased circulating PMN band cell counts following $PM_{10}$ exposure (EHC-93). The one recent study that employed intratracheal instillation of $PM_{10}$ reported elevated systemic IL-6 and TNF-α levels.

### Blood Coagulation

**Epidemiologic Studies:** Studies reviewed in the 2004 PM AQCD reported associations of $PM_{10}$ with blood viscosity and fibrinogen. Newer studies have focused on $PM_{2.5}$; however, $PM_{10}$ was associated with an increase in vWF, but not fibrinogen in a U.S. multicity study (Liao et al., 2005), fibrinogen in a European multicity study (Ruckerl et al., 2007b) and prothrombin time (Baccarelli et al., 2007a).

**Toxicological Studies:** A recent study reported numerous blood coagulation measures that were altered in mice exposed to $PM_{10}$ from Dusseldorf, Germany, which indicated accelerated coagulation.

### Cardiac or Systemic Oxidative Stress

**Epidemiologic Studies:** Two new studies demonstrated associations between $PM_{10}$ and oxidative stress measurements of TBARS and tHcy (Baccarelli et al., 2007a; Liu et al., 2007b).

### Clinical Outcomes in Epidemiologic Studies

An increase in CVD admissions with $PM_{10}$ concentration between 0.6% and 1.7%, per 10 μg/m$^3$ was estimated based on studies reviewed in the 2004 PM AQCD. Pooled estimates from MCAPS and other multicity analyses indicate a significant increase in admissions within this range (Barnett et al., 2006; Larrieu et al., 2007; Le Tertre et al., 2002b; Zanobetti and Schwartz, 2003). Heterogeneity in effect estimates is evident across single city studies. Newer studies have indicated that IHD and CHF rather than cerebrovascular diseases appear to drive these associations observed between $PM_{10}$ and cardiovascular disease admissions and ED visits. Out-of-hospital cardiac arrest was associated with $PM_{10}$ in one study conducted in Rome.

### 6.2.11.2. $PM_{10-2.5}$

*Causal Determination*

1    Several recent epidemiologic studies of the effect of ambient $PM_{10-2.5}$ concentration on hospital

2    admissions and ED visits for cardiovascular diseases have been conducted. Of particular note, a study of

3    Medicare patients in 108 counties across the U.S. reports that $PM_{10-2.5}$ is not associated with

4    cardiovascular disease admissions after adjustment for $PM_{2.5}$. There is a small body of evidence from

5    single city studies and a 6-city study in France that may provide evidence to the contrary, but the U.S.

6    study of Medicare patients is the only study to adjust $PM_{10-2.5}$ for $PM_{2.5}$.

7    There are very few studies that examined the effect of exposure to $PM_{10-2.5}$ on cardiovascular

8    endpoints or biomarkers in humans or animals. Two human clinical studies found decreases in HRV in

9    healthy subjects following exposure, and a trend toward an increase in blood coagulation factors was also

10   demonstrated in one of these studies. The only $PM_{10-2.5}$ toxicological studies that evaluated cardiovascular

11   responses were comparative studies of various size fractions and only blood or plasma parameters were

12   measured. Both studies used non-inhalation methodologies and relatively high doses of PM. Therefore,

13   evidence of biological plausibility for cardiovascular morbidity effects following $PM_{10-2.5}$ exposure is

14   sparse.

15   Limited evidence exists for short-term $PM_{10-2.5}$ exposures and cardiovascular morbidity. In its

16   entirety, the literature shows that **evidence is inadequate to determine if a causal relationship exists**

17   **between $PM_{10-2.5}$ exposures and cardiovascular morbidity**.

*Heart Rate Variability*

18   **Epidemiologic Studies:** Findings from five recent studies of the effect of $PM_{10-2.5}$ on HRV were

19   inconsistent (Adar et al., 2007a; Ebelt et al., 2005; Lipsett et al., 2006; Timonen et al., 2006; Yeatts et al.,

20   2007). Study populations yielding these discrepant results included bus riders, asthmatics, COPD and

21   heart disease patients.

22   **Human Clinical Studies:** Two new studies have observed decreases in HRV (SDNN) among

23   healthy adults, but not asthmatics, following exposure to $PM_{10-2.5}$ (Gong et al., 2004b; Samet et al., 2007).

*Arrhythmia*

24   **Epidemiologic Studies:** The only recent study that examined the effect of $PM_{10-2.5}$ on ICD

25   recorded arrhythmias (Metzger et al., 2007) reported null findings. However, an association of $PM_{10-2.5}$

26   was observed with supraventricular ectopic beats (Sarnat et al., 2006c).

### Ischemia and ECG Abnormalities Indicating Ischemia

**Epidemiologic Studies:** One recent study examined $PM_{10-2.5}$ in relation to ST-segment depression and found an association that was comparable to those observed with other PM metrics (e.g. $PM_{2.5}$, UFP and ACP) (Pekkanen et al., 2002).

### Blood Pressure

**Epidemiologic Studies:** In the only study of $PM_{10-2.5}$ and BP, decreases were reported (Ebelt et al., 2005).

### Blood Coagulation

**Human Clinical Studies:** One new study reported a trend toward elevated levels of pro-clotting factors following exposure to thoracic coarse CAPs in a group of healthy adults (Samet et al., 2007).

### Clinical Outcomes in Epidemiologic Studies

Two studies of the association of $PM_{10-2.5}$ with cardiovascular admissions were reviewed in the 2004 PM AQCD. The recent study by Peng et al. (2008) provides new insights regarding the relative toxicity of $PM_{10-2.5}$ versus $PM_{2.5}$. After adjustment for $PM_{2.5}$, there was no association between $PM_{10-2.5}$ and risk of CVD hospitalizations. In the SOPHIA study associations of cardiovascular outcomes with $PM_{10-2.5}$ were weak and not statistically significant compared to associations with levels of $PM_{2.5}$. Similarly the French PSAS program reported substantially weaker associations for $PM_{10-2.5}$ and total CVD and cardiac hospitalizations. However, these investigators reported similar effect sizes per IQR increases in $PM_{2.5}$ and $PM_{10-2.5}$ for the outcome of IHD. Results from single city studies are heterogenous and imprecise.

## 6.2.11.3. PM<sub>2.5</sub>

### Causal Determination

A large body of evidence from studies of the effect of $PM_{2.5}$ on hospital admissions and ED visits for cardiovascular diseases has been published since the 2004 PM AQCD. Associations with $PM_{2.5}$ are consistently positive with the majority of studies reporting increases in hospital admissions or ED visits ranging from a 0.5 to 3.4% per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The largest U.S.-based multicity study, Medicare Air Pollution Study (MCAPS) reported excess risks in the range of approximately 0.7% with the largest excess risks in the North East (1.08%) and in the winter (1.49%). These $PM_{2.5}$ effects appear to be driven by IHD and CHF rather than cerebrovascular diseases. Several recent studies have examined associations of specific $PM_{2.5}$ components or sources. Positive associations have been observed with

1    several components produced by traffic or combustion and source apportionments have linked these

2    sources to cardiovascular hospital admissions and ED visits. However, no single component has been

3    identified to explain the toxicity of $PM_{2.5}$. Overall, the results of these studies provide support of

4    associations between short-term $PM_{2.5}$ exposure and increased risk of cardiovascular admissions in areas

5    with mean concentrations ranging from 13.8 to 18.8 $\mu g/m^3$. Numerous epidemiologic studies of HRV,

6    ECG abnormalities, vasomotor function, systemic inflammation, coagulation and oxidative stress support

7    the biological plausibility of these effects at ambient levels.

8       Changes in various measures of cardiovascular function have been consistenly demonstrated

9    following controlled human exposures to $PM_{2.5}$. The majority of the new studies described have been

10   conducted using DE or CAPs, and provide strong evidence of $PM_{2.}$-induced decreases in HRV and

11   vasomotor function, as well as increases in markers of systemic oxidative stress. One new study also

12   observed a decrease in ST-segment depression following exposure to DE in a group of older adults with

13   prior MI. Although not consistently observed across studies, some investigators have reported

14   $PM_{2.5}$-induced changes in BP, blood coagulation markers, and markers of systemic inflammation. These

15   findings from human clinical studies provide coherence and biological plausibility for the associations

16   observed in epidemiologic studies.

17      A number of toxicological studies have been conducted that demonstrate findings with $PM_{2.5}$ and

18   cardiovascular endpoints. Consistent with evidence from human clinical studies, the most significant

19   contributions from the current toxicological literature for acute $PM_{2.5}$-induced cardiovascular effects are

20   decreased myocardial blood flow following ischemia, changes in vascular reactivity and morphology, and

21   increased cardiac oxidative stress. Results for HRV, arrhythmia, systemic inflammation, and blood

22   coagulation are mixed. For BP and cardiac contractility, very few studies were evaluated or the study

23   design was weak.

24      Together, the collective **evidence is sufficient to conclude that there is a causal relationship**

25   **between relevant $PM_{2.5}$ exposures and cardiovascular morbidity**.

### *Heart Rate Variability*

26      **Epidemiologic Studies:** Discrepant findings across six epidemiologic studies of HRV were

27   described in the 2004 PM AQCD. Overall, the majority of recent studies have observed decreases in time

28   and frequency domain measures of HRV with $PM_{2.5}$ (findings for LFHFR were not consistent across

29   studies). However, heterogeneity in effects was observed within the U.S. and between 3 European cities

30   studies (Timonen et al., 2006). Several studies included $PM_{2.5}$ components including BC, EC, sulfate and

31   secondary PM in their analyses (Adar and Kaufman, 2007; Ebelt et al., 2005; Luttmann-Gibson et al.,

32   2006; Park et al., 2005b; Schwartz et al., 2005b; Wheeler et al., 2006a). Although some studies showed

1    decreases in time or frequency domain HRV measures associated with these components, results were not

2    consistent. Finally, several analyses from the Normative Aging Study in Boston as well as a randomized

3    trial of omega-3 fatty acid in Mexico City have indicated a role for oxidative stress in the relationship

4    between the $PM_{2.5}$ and HRV (Chahine et al., 2007; Romieu et al., 2005)Park et al. 2005; Park et al. 2008;

5    Park et al. 2006; Schwartz et al. 2005b).

6    **Human Clinical Studies:** Two pilot studies cited in the 2004 PM AQCD found no effect of $PM_{2.5}$

7    CAPs on HRV in healthy adults (Gong et al., 2000; Petrovic et al., 2000). However, a larger study

8    reported a significant decrease in the ratio of LF/HF power in healthy and asthmatic adults immediately

9    following a 2-h exposure to fine CAPs (Gong et al., 2003a). Two more recent human clinical studies have

10    demonstrated a decrease in HRV (SDNN and PNN50) among healthy older adults, but not older adults

11    with COPD, following exposure to $PM_{2.5}$ CAPs (Devlin et al., 2003; Gong et al., 2004a). Another new

12    human clinical study reported some evidence of a decrease in LF/HF power ratio 1-h following exposure

13    to DE in healthy subjects and subjects with metabolic syndrome (Peretz et al., 2008b).

14    **Toxicological Studies:** There were two animal toxicological studies in the 2004 PM AQCD that

15    examined HRV. Dogs exposed to CAPs had decreased HR and increased HRV and rats with induced MI

16    had lowered SDNN compared to those exposed to air or carbon black. In the latest $PM_{2.5}$ CAPs studies,

17    increase and decreases in H were observed. For the carbon black studies that examined H, bradycardia

18    was reported. Fine sulfuric acid did not induce any H effect, but DE induced lowered H in ApoE$^{-/-}$ mice.

19    Increased HRV measures (SDNN, LF/HF ratio, and rMSSD) were observed with carbon black exposure.

20    Diesel exposure resulted in decreased rMSSD in rats with congestive heart failure. Using source

21    apportionment methodologies, H and HRV changes were associated with resuspended soil, secondary

22    sulfate, residual oil, and motor vehicle/other sources. In a separate research article from this study, Ni was

23    implicated in elevated H and lowered SDNN.

*Arrhythmia*

24    **Epidemiologic Studies:** The initial study indicating a possible association of $PM_{2.5}$ and BC with

25    ventricular arrhythmias among a cohort of patients with ICDs in Boston was reviewed in the 2004 PM

26    AQCD (Peters et al., 2000). Several additional analyses of this same cohort that examined different lags

27    and pollutants have also reported increased risk of arrhythmia with $PM_{2.5}$, BC and sulfate exposure

28    (Dockery et al., 2005a; 2005b). Studies conducted in other regions (e.g. St. Louis, Vancouver, Atlanta)

29    have not supported these findings (Dusek et al., 2006; Metzger et al., 2004; Rich et al., 2004; Vedal et al.,

30    2004). However, three studies of supraventricular ectopic beats or supraventricular tachycardia conducted

31    in regions outside of the North East have all shown positive associations with $PM_{2.5}$ (Berger et al., 2006;

32    Ebelt et al., 2005; Sarnat et al., 2006) and sulfate in one study (Sarnat et al., 2006). $PM_{2.5}$, ACP (0.1-1 μm)

EC and OC, traffic and combustion particles were associated with repolarization parameters in two analyses of IHD patients in Erfurt Germany (Henneberger, 2005; Yue et al., 2007).

**Toxicological Studies:** Arrhythmogenesis was reported for studies reviewed in the 2004 PM AQCD. Generally these results were observed in animal models of disease (SH rat, MI, pulmonary hypertension) exposed to non-atmospheric $PM_{2.5}$ (i.e., ROFA, DE, metals). One recent study employing $PM_{2.5}$ CAPs demonstrated decreased arrhythmia frequency in a rodent model of MI. In contrast, older rats had elevated frequency of delayed beats with $PM_{2.5}$ CAPs exposure. Increased incidence of VPB was reported with DE in a rat model of CHF and in $ApoE^{-/-}$ mice, although for the latter study, it appeared that the gases were responsible for the effect. For a study employing gasoline exhaust, the particle fraction was required to induce T-wave changes in $ApoE^{-/-}$ mice.

## Ischemia

**Epidemiologic Studies:** Two recent studies of ST-segment depression and $PM_{2.5}$ report adverse associations (Gold et al., 2005; Pekkanen et al., 2002). Gold et al. (2005) also reported an association with BC and Pekkanan et al. (2002) reported an association with ACP (0.1-1 μm).

**Human Clinical Studies:** One recent study observed an increase in exercise-induced ST-segment depression during exposure to DE in a group of subjects with prior MI (Mills et al., 2007).

**Toxicological Studies:** In the 2004 PM AQCD, one study reported increased ST-segment magnitude in response to $PM_{2.5}$ CAPs in dogs with experimentally-induced ischemia. However, in dogs with signs of naturally occurring heart disease, ROFA did not induce any change in ST-segment or the T-wave. A recent study of dogs with induced ischemia reported increased ST-segment elevation with $PM_{2.5}$ CAPs exposure that was linked to the mass concentration of Si as a tracer of source. Myocardial blood flow during myocardial ischemia was decreased and coronary vascular resistance was increased in dogs following $PM_{2.5}$ CAPs exposure.

## Vasomotor Function

**Epidemiologic Studies:** Studies of fine PM (e.g. $PM_{2.5}$, $PM_1$) (Dales et al., 2007; O'Neill et al., 2005b; Rundell, 2007) and components (e.g. $PM_{2.5}$, $PM_1$, sulfate, BC) (O'Neill et al., 2005b) have been conducted since the 2004 PM AQCD. Decreases in FMD and BAD were observed with fine PM and BC in healthy and diabetic populations.

**Human Clinical Studies:** The 2004 PM AQCD presented the results of one study that observed a decrease in BAD following exposure to fine CAPs in combination with ozone (Brook et al., 2002). A subsequent study found that this effect on vasoreactivity was associated with both the organic and EC fraction of the fine CAPs (Urch et al., 2004). One additional recent study found no effect of fine CAPs,

composed largely of sea salt, on vasomotor function in healthy adults (Mills et al., 2008). However, several new human studies have observed decreases in forearm blood flow and BAD following exposure to DE or fine indoor air particles (Brauner et al., 2008; Mills et al., 2005; Peretz et al., 2008b; Tornqvist et al., 2007).

**Toxicological Studies:** There were no studies that directly measured vasomotor function in the 2004 PM AQCD. Endothelin, an activator of vasoconstriction, was evaluated in one study that reported increased plasma ET-3 levels in rats following exposure to diesel PM. Six new studies evaluated vasoreactivity responses following PM exposure in rats or mice. Four measured vasorelaxation induced by endothelium-dependent and -independent agonists in the microvasculature and intrapulmonary arteries and report impaired vasodilation following ROFA or ambient $PM_{2.5}$ (SRM1648). $TiO_2$ was reported to have similar effects in 3 of the 4 studies (those that used the microvasculature). One study demonstrated decreased L/W ratio in the pulmonary artery of rats following CAPs exposure and another reported enhancement of ET-1-induced vasoconstriction in mesenteric veins of mice with exposure to DE. The former study findings were linked to the tracer element Si. Plasma ET-1 was increased with exposure to gasoline emissions and appeared to be particle-independent. In contrast, ET-2 was decreased in rats exposed to on-road highway aerosols. Increases in mRNA expression of ET-1 and ETA receptor in rat hearts were reported following CAPs. Elevated plasma ADMA was also observed after CAPs exposure in rats.

## Blood Pressure

**Epidemiologic Studies:** $PM_{2.5}$ was not associated with increased BP in a European multicity study of coronary artery disease patients (Ibald-Mulli et al., 2004). Findings from single city studies are inconsistent (Choi et al., 2007; Chuang et al., 2005b; Dales et al., 2007; Ebelt et al., 2005; Jansen et al., 2005; Mar et al., 2005b; Zanobetti et al., 2004). Right heart pressure increases among CHF patient with short-term $PM_{2.5}$ concentration has been reported in one pilot study (Rich et al., 2008).

**Human Clinical Studies:** No consistent effect of exposure to fine CAPs on BP was presented in two human clinical studies described in the 2004 PM AQCD. One new study observed no changes in BP following exposure to fine zinc oxide (Beckett et al., 2005). However, another study did observe a significant decrease in diastolic BP during exposure to fine CAPs relative to filtered air control (Urch et al., 2005). Findings from new studies evaluating changes in BP following exposure to DE have been inconsistent.

**Toxicological Studies:** One new CAPs study that evaluated mean BP reported a weak correlation with accumulated $PM_{2.5}$ mass and the other demonstrated elevated mean BP in SH rats during a dust storm event.

### Cardiac Contractility

**Toxicological Studies:** Only one CAPs study used an indirect measure of cardiac contractility (QA-interval) and found increased contractility with a dust storm event.

### Systemic Inflammation

**Epidemiologic Studies:** Most studies of inflammatory markers reviewed in the 2004 PM AQCD focused on $PM_{10}$; however, associations with BS were observed. New studies have focused on $PM_{2.5}$ and components (e.g. BC, EC, OC and sulfate) (Diez Roux et al., 2006; Dubowsky et al., 2006; O'Neill et al., 2007; Pope et al., 2004a; Riediker et al., 2004b; Ruckerl et al., 2007b; Sullivan et al., 2007; Zeka et al., 2006b). Although findings from from these studies were not consistent, effects of $PM_{2.5}$ on inflammatory markers were stronger with longer averaging times and among populations with preexisting diseases (Diez Roux et al., 2006).

**Human Clinical Studies:** Two studies cited in the 2004 PM AQCD found no effect of exposure to fine CAPs on markers of systemic inflammation including levels of serum amyloid A, number of lymphocytes, or levels of IL-6 and IL-8. The 2004 PM AQCD did include one study that reported increased peripheral blood neutrophils in subjects exposed to DE. New studies involving controlled exposures to DE have provided very little evidence of a PM-induced increase in markers of inflammation immediately following exposure, although one study did report significant increases in plasma levels of IL-6 and TNF-α 24-h after exposure (Tornqvist et al., 2007).

**Toxicological Studies:** There were mixed results reported in the 2004 PM AQCD in regard to systemic inflammation, with two studies that reported changes in WBC (i.e., increases in PMN and/or decreases in lymphocytes) following CAPs or ROFA in rats. One study reported no change in systemic inflammatory markers with CAPs. Colloidal carbon stimulated the release of PMN from bone marrow in rabbits. Two new CAPs studies demonstrate no change or decreased WBC. One study of coal fly ash reported elevated blood PMN and decreased lymphocytes. Fine carbon black did not induce any changes in blood leukocytes. All of the recent studies indicate relatively little change in systemic inflammation at 16-20 h post-exposure.

### Blood Coagulation

**Epidemiologic Studies:** Studies of markers of coagulation published since 2002 have focused on $PM_{2.5}$ and components (e.g. BC, EC OC, BC and sulfate) (Chuang et al., 2007a; Delfino et al., 2008; O'Neill et al., 2007; Pope et al., 2004a; Sullivan et al., 2007; Zeka et al., 2006b). The most consistent results have been observed for vWF and associations with fibrinogen are less constent. Studies of

1  components are too few to allow conclusions to be drawn (Delfino et al., 2008; O'Neill et al., 2007)

2  (Chuang et al., 2007a).

3  **Human Clinical Studies:** Two studies in the 2004 PM AQCD found increased fibrinogen following

4  controlled exposures to fine CAPs, while another observed a decrease in factor VII levels with no change

5  in fibrinogen. In addition, exposure to DE was reported by one study to increase peripheral blood

6  platelets. One new human clinical study did not observe any change in markers of blood coagulation

7  following exposure to fine zinc oxide. WS has recently been shown to increase plasma factor VIII and the

8  factor VIII/vWF ratio in plasma (Barregard et al., 2006). New studies of exposure to DE have provided

9  evidence of an attenuation of t-PA release 6 h post-exposure, although no consistent diesel-induced

10  changes in other blood coagulation markers have been observed (Mills et al., 2005; 2007).

11  **Toxicological Studies:** A few animal toxicological studies evaluated in the 2004 PM AQCD

12  examined blood coagulation markers with $PM_{2.5}$ exposure, with inconsistent results. One CAPs study

13  from Tuxedo, NY reported an increase in platelets, with another from New York City not finding any

14  change in blood coagulation markers. Increases in plasma fibrinogen were demonstrated for rats exposed

15  to ROFA or Ottawa PM (EHC-93). Of three new CAPs studies in SH rats, two reported increases in

16  plasma fibrinogen, while the other reported no change. Similarly, an on-road highway exposure induced

17  elevated plasma fibrinogen in rats. One study reported elevated von Willebrand factor in SH rats exposed

18  to fine CAPs. The recent studies with RBC measurements are limited to two CAPs studies and one coal

19  fly ash study that demonstrate mixed results.

### Cardiac or Systemic Oxidative Stress

20  **Epidemiologic Studies:** New studies have observed associations of $PM_{2.5}$ and components (EC,

21  OC, BC, vanadium and chromium) with several markers of systemic oxidative stress (Cu/Zn-SOD,

22  plasma proteins, 8-oxodG) (Chuang et al., 2007a; Delfino et al., 2008; Romieu et al., 2008; Sorensen et

23  al., 2003; 2005).

24  **Human Clinical Studies:** One study cited in the 2004 PM AQCD reported no diesel-induced

25  changes in plasma antioxidant concentrations or malondialdehyde. New studies have reported increases in

26  markers of systemic oxidative stress following controlled exposures to WS, urban traffic particles, and

27  DE.

28  **Toxicological Studies:** There are three new studies that report increased oxidative stress in cardiac

29  tissue of rats exposed to Boston CAPs; one of these also demonstrated increased levels of antioxidant

30  enzymes in the heart. One study found increased HO-1 mRNA expression in rat cardiac tissue following

31  CAPs exposure and another reported increased ROS and nitrotyrosine expression in the mouse left

1 ventricles after exposure to carbon black. One study demonstrated oxidative stress in rat systemic

2 microvasculature with ROFA instillation.

### Clinical Outcomes in Epidemiologic Studies

3 MCAPS investigators have observed clear increases in cardiovascular admissions related to $PM_{2.5}$.

4 CHF and IHD appear to have the strongest associations with $PM_{2.5}$. Metzger et al. (2004) found positive

5 statistically significant associations between $PM_{2.5}$ and all CVD visits, CHF visits, and peripheral vascular

6 visits (here defined as PVD and stroke). The French PSAS program found that $PM_{2.5}$ concentration

7 averaged over the current and previous days was associated with increased hospitalizations for the CVD

8 outcomes evaluated (e.g. IHD, total CVD, cardiac disease). Although estimates from studies of

9 cerebrovascular diseases are less precise and consistent, ischemic diseases appear to be more strongly

10 associated with $PM_{2.5}$ compared to hemorrhagic stroke. Too few studies have evaluated PVD to allow

11 conclusions to be drawn. Strong regional and seasonal heterogeneity has been observed with the strongest

12 estimates in the northeastern U.S. (Bell et al., 2008; Dominici et al., 2006). The null funding for $PM_{2.5}$ and

13 out of hospital cardiac arrest and onset of MI reported by Sullivan et al. (2003; 2007) may reflect this

14 regional heterogeneity.

15 Only the SOPHIA study examined $PM_{2.5}$ components and found EC and OC were associated with

16 cardiovascular ED visits. A handful of older publications have examined whether the associations

17 observed between ambient PM and CVD hospital admissions or ED visits may be attributable to particle

18 acidity (Burnett et al., 1997; Gwynn et al., 2000; Lippmann et al., 2000; Metzger et al., 2004).

19 Consistently in these studies, particle acidity has not been more strongly associated with CVD

20 hospitalizations or ED visits than other PM metrics.

21 A limited number of source apportionment studies have been conducted (Anderson and Bogdan,

22 2007; Sarnat et al., 2008; Schreuder et al., 2006). These studies indicate that the observed associations

23 between short-term increases in ambient levels of $PM_{2.5}$ are largely due to traffic-related pollution and

24 biomass burning. However, even exposure to crustal material associated with dust storms appears to have

25 adverse cardiovascular health effects.

## 6.2.11.4. Ultrafine PM

### Causal Determination

26 A limited number of epidemiologic studies have examined the association of ultrafine particles

27 with cardiovascular disease hospitalizations and ED visits. In the U.S., SOPHIA investigators in Atlanta

28 did not observe an association with ultrafine particles while $PM_{2.5}$ associations were present. A few

29 studies in Europe observing associations with UFP also observed associations with $PM_{10}$. Short-term

1   associations of UFP with subclinical markers of cardiovascular disease have been reported in a small
2   number of studies.

3        The effect of ultrafine particles on cardiovascular function has not been extensively evaluated in
4   human clinical studies. However, two studies have demonstrated significant decreases in HRV following
5   controlled human exposures to ultrafine CAPs. One of these studies also observed a significant increase in
6   D-dimer 18 h post-exposure in a group of healthy young adults. In addition, exposure to ultrafine EC was
7   recently shown to affect vasomotor function among healthy adult volunteers.

8        Four recent toxicological studies report cardiovascular effects with ultrafine PM exposure, although
9   one study used intratracheal instillation as the exposure route. The latter study reported increased infarct
10  size and an impaired vasodilatory response in PM-exposed mice following ischemia/reperfusion injury.
11  The only endpoints evaluated in multiple studies of ultrafine PM were systemic inflammation and the
12  results were inconsistent, perhaps due to differing blood collection times after exposure.

13       Based on the above findings, the **evidence is inadequate to determine that a causal relationship**
14  **exists between ultrafine PM exposure and cardiovascular morbidity**.

## Heart Rate Variability

15  **Epidemiologic Studies:** Findings from four recent studies investigating the effect of UFP on HRV
16  (Adar et al., 2007a; Chan et al., 2004; Park et al., 2005a; Timonen et al., 2006) were inconsistent.

17  **Human Clinical Studies:** Two new studies have demonstrated that exposure to ultrafine CAPs may
18  alter HRV in healthy adults and asthmatics with evidence of decreases in SDNN and LF power (Gong et
19  al., 2008; Samet et al., 2007). No such changes were observed following exposure to ultrafine zinc oxide
20  at relatively high concentrations (500 $\mu g/m^3$).

21  **Toxicological Studies:** In the only study of ultrafine CAPs, increased H and decreased SDNN
22  were reported only during the spring and not the summer exposure.

## Arrhythmia

23  **Epidemiologic Studies:** In a recent study, a non-significant increase in ICD recorded ventricular
24  arrhythmias with particle number was reported in Boston (Dockery et al., 2005a; 2005b). Berger et al.
25  (2006) reports associations of supraventricular tachycardia and number of runs of ventricular tachycardia
26  with 5-day mean UFP (0.01-0.1) counts. Adverse effects on repolarization parameters were also observed
27  in association with UFP count (Henneberger, 2005).

28  **Toxicological Studies:** One new study exposed older rats to ultrafine carbon black and did not
29  report any change in arrhythmia frequency.

### Ischemia

**Epidemiologic Studies:** One recent study examined UFP in relation to ST-segment depression and found associations that were comparable to those observed with other PM size fractions (e.g. $PM_{.1-1}$, $PM_{2.5}$, $PM_{10-2.5}$) (Pekkanen et al., 2002).

**Toxicological Studies:** In the first study of its kind, infarct size was nearly doubled in mice exposed to ultrafine PM followed by ischemia/reperfusion injury to the coronary artery.

### Vasomotor Function

**Epidemiologic Studies:** One study examining particle number count and vasomotor function reported a nonsignificant decrease in flow mediated and nitroglycerine mediated reactivity (O'Neill et al., 2005a).

**Human Clinical Studies:** Shah et al. (2008) recently demonstrated a decrease in peak forearm blood flow during reactive hyperemia, relative to filtered air control, following exposure to ultrafine EC.

**Toxicological Studies:** One new study reported an attenuation of ACh-induced relaxation in aortic rings of mice exposed to ultrafine PM that then underwent ischemia/reperfusion injury to the left anterior descending artery. There was no difference in constriction to phenylephrine.

### Blood Pressure

**Epidemiologic Studies:** Two recent studies examined BP in relation to PM concentration. Increases in BP were not observed in association with UFP in a European multicity study of CAD patients (Ibald-Mulli et al., 2004). By contrast, an increase in BP was reported in association with UFP 1-3 hours prior to the measurement among subjects with impaired lung function (Chuang et al., 2005b).

**Human Clinical Studies:** Several new studies have not observed any changes in BP following exposure to ultrafine laboratory generated surrogate particles (zinc oxide and EC).

**Toxicological Studies:** A new CAPs study in dogs demonstrated elevated BP that was partially attributable to α-adrenergic receptors. The other recent CAPs study reported elevated mean BP in SH rats during ultrafine PM exposure during spring and not summer.

### Cardiac Contractility

**Toxicological Studies:** There is one study that used an indirect measure of cardiac contractility (QA-interval) during ultrafine CAPs exposure and reported increased cardiac contractility during the spring, but not summer.

## Systemic Inflammation

**Epidemiologic Studies:** Previous studies included in the AQCD focused on $PM_{10}$. Asssociations with UFP and inflammatory markers (CRP, IL-6 and sP-selectin) have been observed in new studies, but not consistently across studies (Delfino et al., 2008; Ruckerl et al., 2007b).

**Human Clinical Studies:** The 2004 PM AQCD included one human clinical study that found no effect of exposure to ultrafine EC on leukocyte activation. Three new studies have reported no changes in markers of systemic inflammation following exposure to ultrafine particles (CAPs, zinc oxide, or EC). However, one study observed a decrease in total leukocyte count and monocyte expression of adhesion molecules CD54 and CD18 in peripheral venous blood following exposure to ultrafine EC (Frampton et al., 2006).

**Toxicological Studies:** There were mixed results reported in the 2004 PM AQCD in regard to systemic inflammation, but no studies were reviewed that used ultrafine PM. One new study employed ultrafine CAPs during a dust storm and demonstrated increased WBC even in a rodent model of pulmonary hypertension. Two studies of ultrafine carbon black found opposite responses (elevated WBC and lowered PMN), which may be attributable to differing post-exposure analysis times (48 and 6 h, respectively).

## Blood Coagulation

**Epidemiologic Studies:** Previous studies included in the AQCD focused on $PM_{10}$. Asssociations with UFP and markers of coagulation (fibrinogen, d-dimer) have been evaluated in new studies (Delfino et al., 2008; Ruckerl et al., 2007b), but studies examining these size fractions are too few in number to draw conclusions.

**Human Clinical Studies:** One human clinical study cited in the 2004 PM AQCD found no association between exposure to ultrafine EC and markers of blood coagulation. New human clinical studies have similarly found no pro-thrombotic effects of exposure to ultrafine EC or zinc oxide in healthy adults or adults with coronary artery disease. However, Samet et al. (2007) did observe an increase in concentrations of D-dimer among healthy adults following exposure to ultrafine CAPs.

**Toxicological Studies:** One new study of ultrafine carbon black reported increased TAT complexes in two older rat strains. Plasma fibrinogen results were inconsistent.

## Cardiac or Systemic Oxidative Stress

**Epidemiologic Studies:** Quasi ultrafine particles (PM $\leq$ 0.25 μm) were associated with Cu/Zn-SOD in one study (Delfino et al., 2008).

1     **Clinical Outcomes in Epidemiologic Studies:** Few time-series studies have compared results

2 using ultrafine PM. The SOPHIA study found no association between any outcome and 24-h mean levels

3 of UFP, but did find a number of positive associations with $PM_{2.5}$ (Metzger et al., 2004). Andersen et al.

4 (2007a) found statistically significant positive associations between CVD hospitalizations and $PM_{10}$ and

5 $PM_{2.5}$, but not with UFP. In the European HEAPSS study (Lanki et al., 2006a; von Klot et al., 2005),

6 results seemed qualitatively similar when comparing associations with $PM_{10}$ and UFP, but there were

7 insufficient data provided to standardize results to the IQR (or other distributional measure) specific to

8 each metric.

# 6.3. Respiratory Effects

## 6.3.1. Respiratory Symptoms and Medication Use

9     The 2004 PM AQCD presented evidence from epidemiologic studies of increases in respiratory

10 symptoms associated with PM, although this was not supported by the findings of a limited number of

11 human clinical studies. Recent epidemiologic studies have provided evidence of an increase in respiratory

12 symptoms and medication use associated with PM among asthmatic children, with less evidence of an

13 effect in asthmatic adults. The lack of an observed effect of PM exposure on respiratory symptoms in

14 human clinical studies does not necessarily contradict these findings, as no controlled human exposures to

15 PM have been conducted among groups of asthmatic or healthy children.

### 6.3.1.1. Epidemiologic Studies

16     The 2004 PM AQCD concluded that the effects of $PM_{10}$ on respiratory symptoms in asthmatics

17 tended to be positive, although they were somewhat less consistent than $PM_{10}$ effects on lung function.

18 Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although

19 these increases were generally not statistically significant for $PM_{10}$. The results from one study of

20 respiratory symptoms and thoracic coarse particles (Schwartz and Neas, 2000) found a statistically

21 significant association with cough with $PM_{10-2.5}$. The results of two studies examining respiratory

22 symptoms and $PM_{2.5}$ revealed slightly larger effects for $PM_{2.5}$ than for $PM_{10}$.
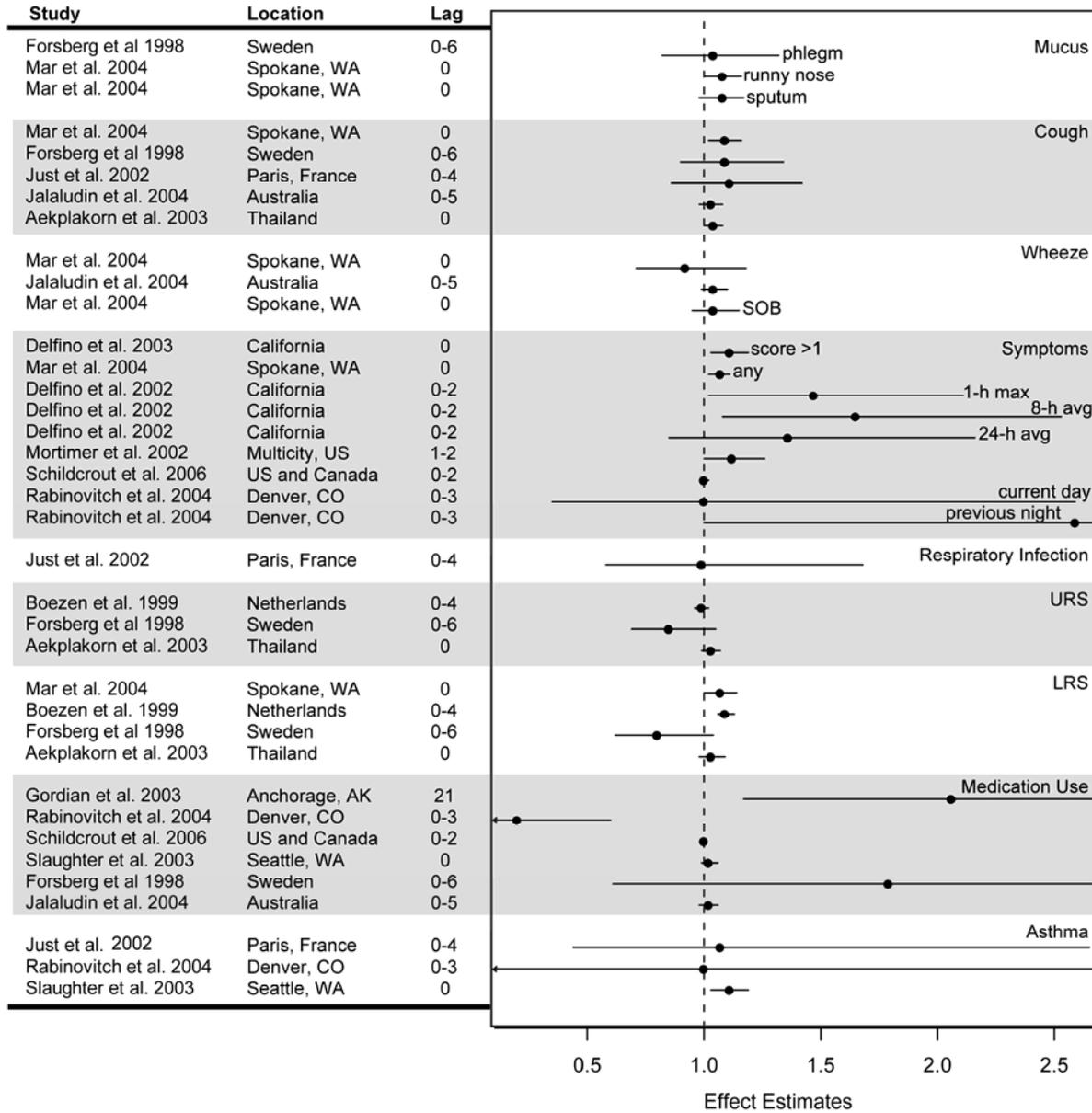
**Figure 6-5.** Respiratory symptoms and/or medication use among asthmatic children following acute exposure to $PM_{10}$. ORs and 95% CIs standardized to increments of 10 μg/m³.
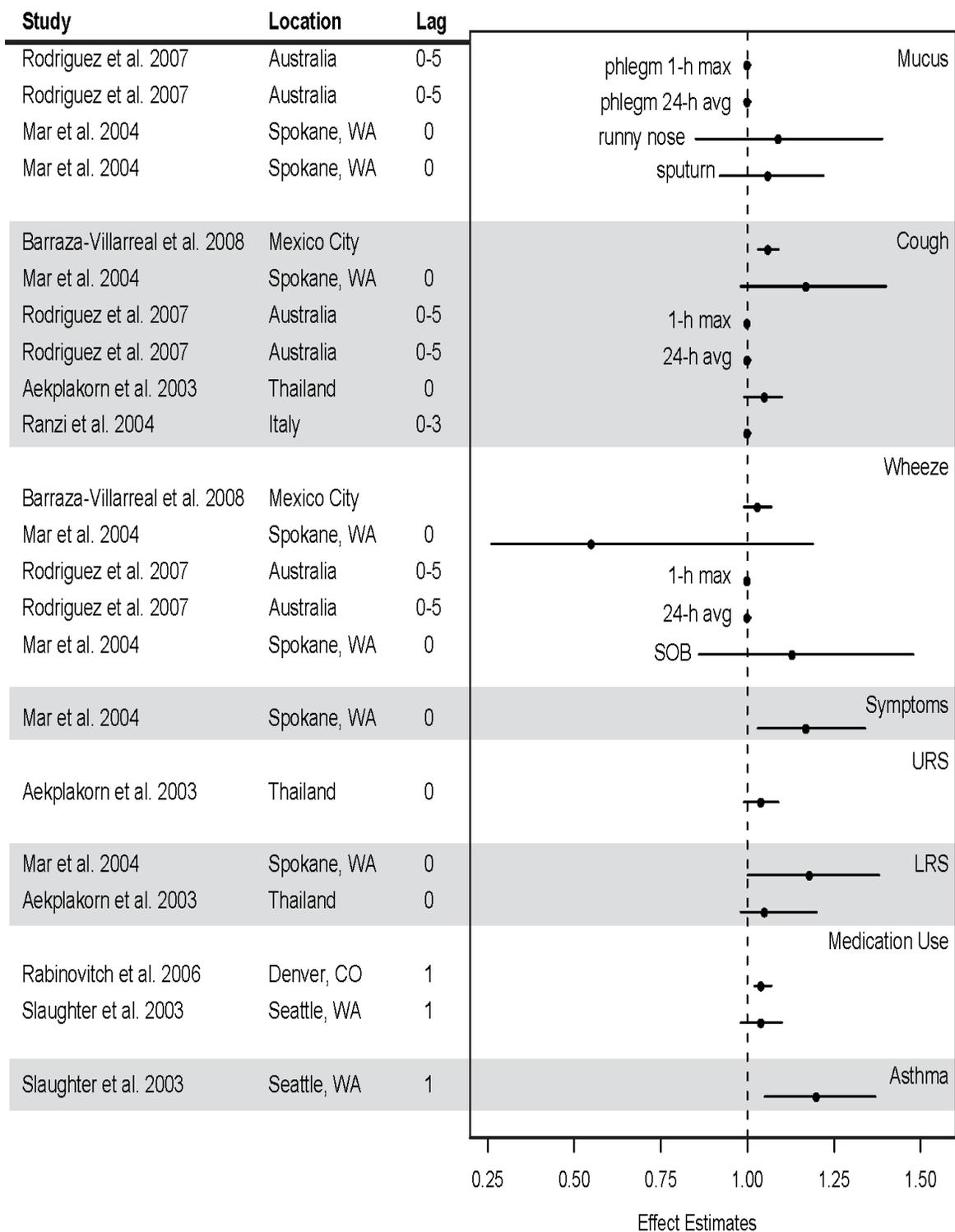
**Figure 6-6. Respiratory symptoms and/or medication use among asthmatic children following acute exposure to PM$_{2.5}$. ORs and 95% CIs standardized to increments of 10 μg/m$^3$.**

## Asthmatic Children

1   Since the 2004 PM AQCD, results have been published from several single- and multicity studies

2   investigating the effects of ambient PM levels on respiratory symptoms and medication use among

3   asthmatic children. The respiratory symptom and medication use results from these single and multicity

4   studies are summarized by particle size and displayed in Figures 6.5 and 6.6 and Table 6.6. A relatively

5   few number of studies examined these effects in healthy children, and did not identify a relationship

6   between ambient PM levels and respiratory symptoms or medication use. These studies are summarized

7   in Annex E, but will not be described in detail in this section.

8   Two large, longitudinal studies in urban areas of the U.S. investigated the effects of ambient PM on

9   respiratory symptoms and/or asthma medication use with similar analytic techniques (i.e. multistaged

10   modeling and generalized estimating equations [GEE]): the Childhood Asthma Management Program

11   (CAMP; Schildcrout et al., 2006), and the National Cooperative Inner-City Asthma Study (NCICAS;

12   Mortimer et al., 2002). A number of smaller panel studies conducted in the U.S. evaluated the effects of

13   ambient PM concentrations on respiratory symptoms and medication use among asthmatic children

14   (Delfino et al., 2002; 2003b; Gent et al., 2003; Rabinovitch et al., 2004; 2006; Slaughter et al., 2003).

15   In the CAMP study, the association between ambient air pollution and asthma exacerbations in

16   children (n = 990) from eight North American cities was investigated (Schildcrout et al., 2006). In

17   contrast to several past studies (Delfino et al., 1996; 1998), no associations were observed between $PM_{10}$

18   and asthma exacerbations or medication use. $PM_{10}$ concentrations were measured on less than 50% of

19   study days in all cities except Seattle and Albuquerque. While $PM_{10}$ effects were not observed for the

20   entire panel of children, they were observed in recent reports on the children participating at the Seattle

21   center (Slaughter et al., 2003; Yu et al., 2000).

22   The eight cities included in the NCICAS (Mortimer et al., 2002) were all in the East or Midwest:

23   New York City (Bronx, E. Harlem), Baltimore, Washington DC, Cleveland, Detroit, St. Louis, and

24   Chicago. In this study, 864 asthmatic children, aged 4–9 years, were followed daily for four, 2-week

25   periods over the course of nine months. Morning and evening asthma symptoms (analyzed as none vs.

26   any) and peak flow were recorded. For the three urban areas with data, each 10 $\mu g/m^3$ increase in the

27   mean of the previous 2 days (lag 1-2) $PM_{10}$, increased the risk for morning asthma symptoms (OR 1.12

28   [95% CI: 1.00-1.26]). This effect was robust to the inclusion of $O_3$ (OR 1.12 [95% CI: 0.98-1.27]), though

29   attenuated in models including $O_3$, $SO_2$, and $NO_2$ (OR 1.07[ 95% CI: 0.89-1.22]). In a related study,

30   O'Connor et al. (2008) examined the relationship between short-term fluctuations in outdoor air pollutant

31   concentrations and changes in pulmonary function and respiratory symptoms among children with asthma

32   in 7 U.S. inner-city communities. $PM_{2.5}$ concentration was not significantly associated with respiratory

33   symptoms in this study.

1    In a smaller panel study of asthmatic children (n = 133) enrolled in the CAMP study, daily particle

2    concentrations averaged over 3 central sites in Seattle was used as the exposure metric (Slaughter et al.,

3    2003). Children were followed for 2 months, on average. Daily health outcomes included both a

4    3-category measure of asthma severity based on symptom duration and frequency, and inhaled albuterol

5    use. In single-pollutant models, an increased risk of asthma severity was associated with a 10 $\mu g/m^3$

6    increase in lag 1 $PM_{2.5}$ (OR 1.20 [95% CI: 1.05-1.37]) and with a 10 $\mu g/m^3$ increase in lag 0 $PM_{10}$ (OR

7    1.12 [95% CI: 1.05-1.22]). In copollutant models with CO, the associations remained (OR for $PM_{2.5}$ 1.16

8    [95% CI: 1.03-1.30]; OR for $PM_{10}$ 1.11 [95% CI: 1.03-1.19]). Associations between inhaler use and PM

9    was significant in single-pollutant models (RR lag 1 $PM_{2.5}$ 1.08 [95% CI: 1.01-1.15]; RR lag 0 $PM_{10}$ 1.05

10   [95% CI: 1.00-1.09), but attenuated and no longer significant in copollutant models.

11   Mar et al. (2004) studied asthmatic children (n = 9) in Spokane, WA. Increases in either 0, 1 or 2

12   day lags of each of the PM size classes studied was associated with cough. When all lower respiratory

13   tract symptoms (wheeze, cough, shortness of breath, sputum production) were grouped together,

14   significant associations were seen for each 10 $\mu g/m^3$ increase in same-day $PM_{10}$ (OR 1.07 [95% CI:

15   1.00-1.14]), or lag 0 or lag 1 $PM_{2.5}$ (OR 1.18 [95% CI: 1.00-1.38]; OR 1.21 [95% CI: 1.00-1.46],

16   respectively), and 10 $\mu g/m^3$ increase in lag 0 and lag 1 $PM_{1.0}$ (OR 1.21 [95% CI: 1.01-1.44]; OR 1.25

17   [95% CI: 1.01-1.55], respectively). No significant effects were seen for $PM_{10-2.5}$ and grouped lower

18   respiratory tract symptoms (2004).

19   Gent et al. (2003) reported on daily symptom and medication use during one summer for 271

20   asthmatic children living in southern New England. In single-pollutant models for users of maintenance

21   medication (n = 130), $PM_{2.5} \geq 19$ $\mu g/m^3$ lagged by 1 day was associated with a 10 to 25% increase in risk

22   of symptoms compared to $PM_{2.5}$ <6.9 $\mu g/m^3$: OR for persistent cough 1.12 (95% CI: 1.02-1.24); OR for

23   chest tightness 1.21 (95% CI: 1.00-1.46); OR for shortness of breath 1.26 (95% CI: 1.02-1.54). Effects

24   were attenuated in models including $O_3$ (OR for persistent cough 1.00 95% CI: 0.88-1.15]; OR for chest

25   tightness 0.91 [95% CI: 0.71-1.17]; OR for shortness of breath 1.20 [95% CI: 0.94-1.52]). No statistical

26   associations between ambient particle exposure and respiratory health were found for asthmatic children

27   not on maintenance medication.

**Table 6-7. Characterization of ambient PM concentrations from studies of respiratory outcomes and short-term exposures in asthmatic adults.**

| Pollutant | Reference | Location | Mean Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|---|
| $PM_{10}$ | | | | |
| | Boezen et al. (2005) | The Netherlands | 26.6-44.1 | Max: 89.9-242.2 |
| | de Hartog et al. (2003) | Multicity, Europe | 19.6-36.5 | Max: 67.4-112.0 |
| | Delfino et al. (2002) | Alpine, CA | 20 | 90th: 32<br>Max: 42 |
| | Delfino et al. (2003a) | Los Angeles, CA | 59.9 | 90th: 86/0/Max: 126 |
| | Delfino et al. (2004) | Alpine, CA | 29.7 | 90th: 40.9<br>Max: 50.7 |
| | Delfino et al. (2006) | Southern CA | 35.7-70.8 | Max: 105.5-154.1 |
| | Desqueyroux et al. (2002) | Paris, France | 23-28 | Max: 63-84 |
| | Ebelt et al. (2005) | Vancouver, Canada | 17 | Max: 36 |
| | Jansen et al. (2005) | Seattle, WA | 18.0 | Max: 51 |
| | Mar et al. (2004) | Spokane, WA | 16.8-24.5 | |
| | Mortimer et al. (2002) | Multicity, UC | 53 | |
| | Rabinovitch et al. (2004) | Denver, CO | 28.1 | Max: 102.0 |
| | Segala et al. (2004) | Paris, France | 24.2 | Max: 97.4 |
| | Schildcrout et al. (2006) | Multicity, US | 17.7-32.4a | 75th: 26.2-42.7<br>90th: 32.5-53.9 |
| | Slaughter et al. (2003) | Seattle, WA | 21.0a | 75th: 29.3 |
| | Steinvil et al. (2008) | Tel Aviv, Israel | 64.5 | 75th: 60.7 |
| | von Klot et al. (2002) | Erfurt, Germany | 45.4 | 75th: 59.7<br>Max: 172.4 |
| $PM_{2.5}$ | | | | |
| | Adamkiewicz et al. (2004) | Steubenville, OH | 19.5 | 75th: 25.5<br>Max: 105.8 |
| | Adar et al. (2007) | St. Louis, MO | 14.8-16.5 | |
| | Allen et al. (2008) | Seattle, WA | 11.2 | |
| | de Hartog et al. (2003) | Multicity, Europe | 12.8-23.4 | Max: 39.8-118.1 |
| | Delfino et al. (2006) | Southern CA | 3.9-6.9 | Max: 8.8-11.6 |
| | DeMeo et al. (2004) | Boston, MA | 10.8 | |
| | Dubowsky et al. (2006) | St. Louis, MO | 16 | Max: 28 |
| | Ebelt et al. (2005) | Vancouver, Canada | 11.4 | Max: 28.7 |
| | Ferdinands et al. (2008) | Atlanta, GA | 27.2 | Max: 34.7 |
| | Gent et al. (2003) | CT & MA | 13.1 | 60th: 12.1<br>80th: 19.0 |
| | Giradot et al. (2006) | Smoky Mountains | 13.9 | Max: 38.4 |
| | Jansen et al. (2005) | Seattle, WA | 14.0 | Max: 44 |
| | Koenig et al. (2003) | Seattle, WA | 13.3 | Max: 40.4 |
| | Lewis et al. (2005) | Detroit, MI | 15.7-17.5 | Max: 56.1 |
| | Mar et al. (2004) | Spokane, WA | 8.1-11.0 | |
| | Mar et al. (2005) | Seattle, WA | 5-26 | |
| | Rabinovitch et al. (2004) | Denver, CO | 10.8 | Max: 53.5 |

| Pollutant | Reference | Location | Mean Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|---|
| | Rabinovitch et al. (2006) | Denver, CO | TEOM: 6.5-8.2 <br> FRM: 11.2-11.8 | 75th: 7.9-9.9 (TEOM) <br> 75th: 13.3-14.1 (FRM) |
| | Slaughter et al. (2003) | Seattle, WA | 7.3a | 75th: 11.3 |
| | Timonen et al. (2004) | Multicity, Europe | 12.7-23.1 | Max: 39.8-118.1 |
| | Trenga et al. (2006) | Seattle, WA | 8.6-9.6a | 75th: 13.1-14.8 <br> Max: 40.4-41.5 |
| $PM_{10-2.5}$ | | | | |
| | Ebelt et al. (2005) | Vancouver, Canada | 5.6 | Max: 11.9 |
| | Mar et al. (2004) | Spokane, WA | 8.7-13.5 | |
| | von Klot et al. (2002) | Erfurt, Germany | 10.3 | 75th: 14.6 <br> Max: 64.3 |

a Median PM concentration.

1    Two panel studies were conducted over the course of three winters at a school in Denver
2  (Rabinovitch et al., 2004; 2006). In the first report, approximately 86 different children contributed data
3  on asthma symptoms and medication use over three consecutive winters (Rabinovitch et al., 2004). The
4  exposure metric was a 3-day moving average of $PM_{2.5}$ measured at a site located next to the school for the
5  first 2 winters and from a central site located 4.8 km (3 miles) away for the third. A strong correlation was
6  observed during the first two winters between $PM_{2.5}$ values measured locally and at a downtown
7  monitoring station (Pearson product-moment correlation = 0.93) and between $PM_{10}$ values measured
8  locally and at a downtown monitoring station (correlation = 0.84). Therefore, in year 3, all ambient data
9  were collected from nearby community monitoring stations. No significant effects were found between
10  asthma symptoms or medication use and PM. Rabinovitch et al. (2006) enrolled a panel of 73 children
11  and evaluated associations with morning maximum $PM_{2.5}$ measured at the central site. PM measurements
12  were available hourly from 2 co-located monitors, an FRM and a TEOM monitor. Each 10 $\mu g/m^3$ increase
13  in morning maximum 1-h $PM_{2.5}$ concentration was associated with an increased likelihood of rescue
14  medication use (OR for FRM exposure data 1.02 [95% CI: 1.01-1.03]; OR for TEOM 1.03 [95% CI:
15  1.00-1.6]). Interestingly, the association between inhaler use and particle exposure was not evident when
16  the 24-h average $PM_{2.5}$ was used in the model.
17    Two smaller panel studies enrolling asthmatic children conducted by Delfino et al. (2002; 2003b)
18  in Southern California examined the health effects of different averaging times for $PM_{10}$ (1-h, 8-h, 24-h)
19  (Delfino et al., 2002), and 24-h average of two $PM_{10}$ components (EC and OC) (Delfino et al., 2003a). In
20  the first study, 22 children living in a "lower" pollution area were followed daily for two months in
21  spring. In contrast with Gent et al. (2003), significant associations with asthma symptoms (measured on a
22  6-point severity scale) were found only for the children not taking anti-inflammatory medication. For
23  these 12 children, in single-pollutant models each 10 $\mu g/m^3$ increase in lag 0 1-h max $PM_{10}$ nearly
24  doubled the risk of clinically meaningful symptoms (i.e., an asthma symptom score $\geq$ 3) (OR 1.14 [95%

1    CI: 1.04-1.24]) and each 10 µg/m$^3$ increase in 3-day average 24-h PM$_{10}$ increased the risk by 1.25 (95%

2    CI: 1.06-1.48). No significant associations were found between exposure to ambient particles and

3    symptoms in the 10 children who were taking anti-inflammatory medication. No multipollutant models

4    were reported. The second study enrolled 22 asthmatic children living in an area of higher pollution. For

5    children living in this community, each 10 µg/m$^3$ increase in lag 0, 24-h PM$_{10}$ was associated with an

6    increased risk of asthma symptom score >1: OR 1.10, (95% CI: 1.03-1.19) (Delfino et al., 2003a). The

7    correlation among PM$_{10}$, EC and OC was substantial: 0.80 between PM$_{10}$ and either EC or OC, and 0.94

8    between EC and OC. Associations between EC or OC and asthma symptoms were very similar to those

9    for PM$_{10}$: each 3 µg/m$^3$ increase in lag 0, 24-h EC or 5 µg/m$^3$ increase in lag 0, 24-h OC was associated

10   with an increased risk of asthma symptoms (OR 1.85 [95% CI: 1.11-3.08] or OR 1.88 [95% CI:

11   1.12-3.17], respectively) (Delfino et al., 2003a).

12       Studies from Australia (Rodriguez et al., 2007), Europe (Ranzi et al., 2004), and Asia (Aekplakorn

13   et al., 2003) provide additional evidence of an association between ambient PM and respiratory symptoms

14   and/or medication use among asthmatic children. Two studies (Jalaludin et al., 2004; Just et al., 2002)

15   found no association between ambient PM levels and these health endpoints (see Figures 6-5 and 6-6).

## *Asthmatic Adults*

16       Since the 2004 PM AQCD, one U.S. and several European studies have investigated the effects of

17   ambient PM levels on respiratory symptoms and medication use among asthmatic adults. The respiratory

18   symptom and medication use results from these studies are summarized by particle size and displayed in

19   Table 6.7 and Figure 6.7. Relatively few studies examined these effects in healthy adults, and they did not

20   identify a relationship between ambient PM levels and respiratory symptoms or medication use. These

21   studies are summarized in Annex E, but will not be described in detail in this section.

22       Mar et al. (2004) studied asthmatic adults (N = 16) in Spokane, WA over a 3-year time period. No

23   significant associations were found between PM and respiratory symptoms among the adults.

24       Several panel studies conducted in Europe have examined effects of daily exposures to air pollution

25   on adults with asthma, including studies in the Pollution Effects on Asthmatic Children in Europe

26   (PEACE) study (2005), Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air

27   (ULTRA) study (de Hartog et al., 2003), in Germany (von Klot et al., 2002), and in Paris (2002a; 2004).

28   Boezen et al. (2005) enrolled 327 elderly adults in the Netherlands to examine the role of AHR and IgE

29   levels in susceptibility to air pollution. For subjects with both AHR (defined as ≥ 20% FEV$_1$ decline at ≤

30   2 mg cumulative methacholine) and high total IgE (>20 kU/L), each 10 µg/m$^3$ increase in lag 2 PM$_{10}$

31   concentration was associated with an increased risk of upper respiratory symptoms (URS) among males

32   (OR 1.06 [95% CI: 1.02-1.10]), and at lag 0 with increased cough among females (OR 1.04 [95% CI:

1   1.00-1.08]). Each 10 µg/m$^3$ increase in BS at lag 0, lag 1, and the 5-day mean was associated with URS

2   and cough among males. The strongest association in both cases was for the 5-day mean (OR for URS

3   1.43 [95% CI: 1.20-1.69]; OR for cough 1.16 [95% CI: 1.05-1.29]). The authors suggest that the sex

4   differences observed may be expolained by differential daily exposure to traffic exhaust experienced by

5   men compared to women(Boezen et al., 2005)

6       As part of the multicenter ULTRA study, de Hartog et al. (2003) enrolled 131 older adults with

7   coronary artery disease in three cities (Amsterdam, Erfurt [Germany], and Helsinki). Pooling data from

8   all three cities, significant associations were observed between $PM_{2.5}$ and shortness of breath and phlegm:

9   each 10 µg/m$^3$ increase in the 5-day average $PM_{2.5}$ was associated with an increased risk of symptoms

10  (OR for shortness of breath 1.12 [95% CI: 1.02-1.24]; OR for phlegm 1.16 [95% CI: 1.03-1.32]). Unlike

11  fine particles, ultrafine particles were not consistently associated with symptoms.

12      In a study that took place in Erfurt, Germany, von Klot et al. (2002) examined daily, winter time

13  exposure to ambient $PM_{10-2.5}$, $PM_{2.5-0.01}$ and $PM_{0.1-0.01}$ particles and respiratory health effects in 53 adult

14  asthmatics. The authors examined associations between wheeze, use of inhaled short-acting $\beta_2$-agonists or

15  inhaled corticosteroids and exposure to particles in single and multipollutant models. Particle exposure

16  metrics examined included same-day, 5-day and 14-day averages. No significant effects were observed

17  for wheeze and exposure to $PM_{10-2.5}$ or $PM_{2.5-0.01}$ for any averaging time. The strongest association

18  between wheeze and exposure to ultrafine particles was for a 14-day average: each 7,700 increase in the

19  $NC_{0.01-0.1}$ increased the risk of wheeze by 27% (OR 1.27 [95% CI: 1.13-1.43]). The effect was attenuated

20  in copollutant models that also included $PM_{2.5-0.01}$ (OR 1.12 [95% CI: 1.01-1.24]), $NO_2$ (OR 1.12 [95% CI:

21  0.99-1.26]), CO (OR 1.05 [95% CI: 0.92-1.19]) or $SO_2$ (OR 1.14 [95% CI: 1.04-1.26]). The correlations

22  between ultrafine particles and two gaseous pollutants, $NO_2$ and CO, were high: 0.66 for each.

23      In the same study, no association was found between exposure to thoracic coarse, fine or ultrafine

24  particles and use of short-acting inhalers, though there was an association with maintenance medication.

25  Increased likelihood of maintenance medication was significantly associated with PM of all sizes and all

26  averaging times (same day, 5- and 14-day averages) and gaseous copollutants in single or multipollutant

27  models. The strongest effects were seen for 14-day averages of $PM_{10-2.5}$ (for each 10 µg/m$^3$ increase OR

28  1.43 [95% CI: 1.28-1.60]), $PM_{2.5-0.01}$ (for each 20 µg/m$^3$ increase OR 1.54 [95% CI: 1.43-1.66]), $NC_{0.01-0.1}$

29  (for each 7,700 increase OR 1.45 [95% CI: 1.29-1.63]). For $PM_{2.5-0.01}$, effects were unchanged in

30  copollutant models, including a model with ultrafine particles. The authors conclude that this is evidence

31  for independent effects of fine and ultrafine particles (von Klot et al., 2002).
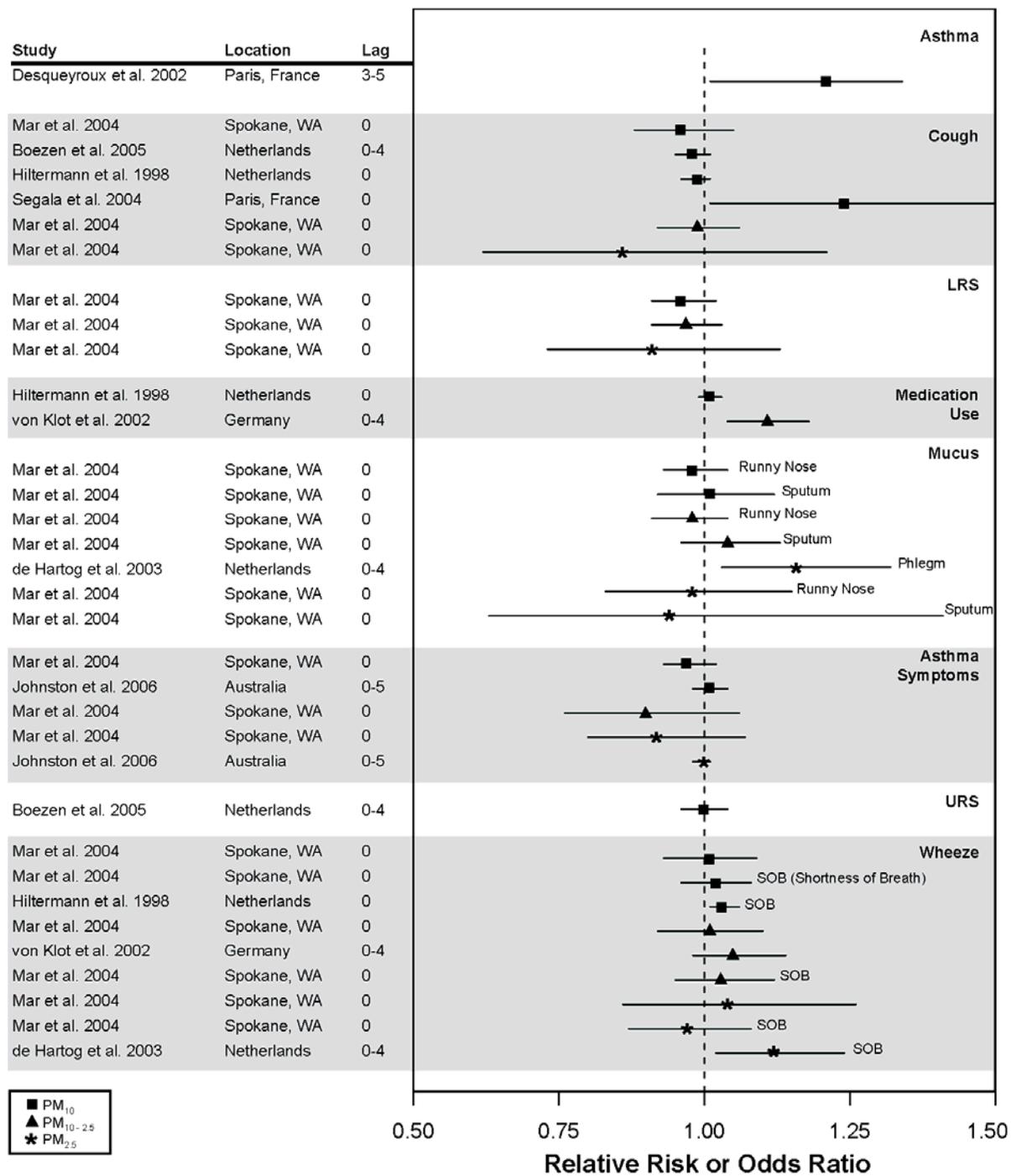
**Figure 6-7.** Respiratory symptoms and/or medication use among asthmatic adults following acute exposure to particles. Summary of studies using 24-h averages of $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$. ORs and 95% CIs were standardized to increments of 10 μg/m³.

1    In Paris, Segala et al. (2004) recruited 78 adults from an otolaryngology clinic and followed them

2    for three months. Both $PM_{10}$ and BS (which were very highly correlated [r =.88]) were associated with

1    cough: OR 1.24 (95% CI: 1.01-1.52) for a 10 μg/m$^3$ increase in mean 0-4 day $PM_{10}$ and OR 1.18 (95%

2    CI: 1.02-1.39) for a 10 μg/m$^3$ increase in BS.
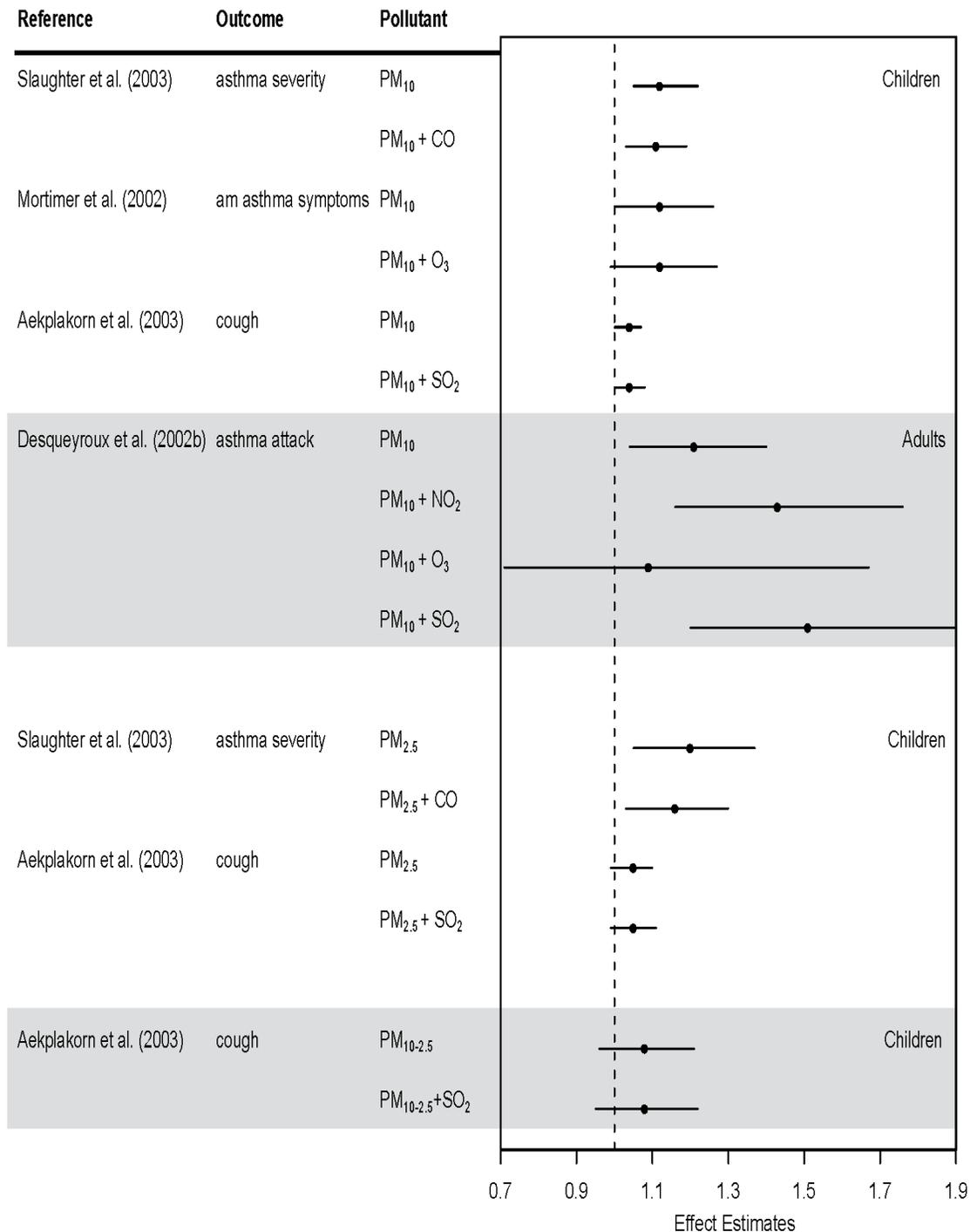


**Figure 6-8    Respiratory symptoms following acute exposure to particles and additional criteria pollutants.**

1   Also in Paris, 60 severe asthmatics were followed for 13 months and the relationship between daily

2   air quality (including 24-h $PM_{10}$ as measured at the site nearest to the subject's home) and asthma attack

3   (defined as the need to increase rescue medication use and one or more positive signs on clinical exam of

4   wheezing, expiratory brake, thoracic distention, hypertension with tachycardia, polypnea) were examined

5   with GEE models (Desqueyroux et al., 2002a). Each 10 $\mu g/m^3$ increase in $PM_{10}$ increased the risk of

6   asthma attack, but only after lags of 3 to 5 days. The strongest effect was seen for the mean lag of days 3

7   to 5 (OR 1.21 [95% CI: 1.04-1.40]). Effect sizes were larger among patients not on regular oral steroid

8   therapy: for $PM_{10}$ lag 3-5 (OR 1.41 [95% CI: 1.15-1.73]). This effect persisted in multipollutant models

9   for winter time levels of $PM_{10}$ and $SO_2$ (OR 1.51 [95% CI: 1.20-1.90]) or $NO_2$ (OR 1.43 [95% CI:

10  1.16-1.76]), but not in summer time models with ozone (OR 1.09 [95% CI: 0.71-1.67]).

### *Copollutant Models*

11  A limited number of respiratory symptoms studies reported results of copollutant models.

12  Generally, the associations between respiratory symptoms and PM were robust to the inclusion of

13  copollutants (Figure 6-8), though Desqueyroux et al. (2002a) indicate the effects of PM may be

14  potentiated by $NO_2$ and $SO_2$ during the winter months. Gent et al. (2003) also reported the results of

15  copollutant models, though the categorical exposure groups used in the analysis did not allow these

16  results to be included in Figure 6-8. As reported above, the investigators found that effects were

17  attenuated in models including $O_3$.

## 6.3.1.2. Human Clinical Studies

18  Neither new controlled human exposure studies, nor studies cited in the 2004 PM AQCD have

19  found significant effects of CAPs on respiratory symptoms among healthy or asthmatic adults, or among

20  older adults with COPD (Gong et al., 2000; 2003a; 2004a; 2004b; Petrovic et al., 2000). One new study

21  reported an increase in respiratory symptoms (upper and lower airways) among healthy volunteers (19–59

22  years old) during a 2-h exposure to road tunnel traffic (Larsson et al., 2007). However, information on

23  specific respiratory symptoms (e.g., throat irritation, wheeze or chest tightness) is not provided. In

24  addition, this study only evaluated respiratory symptoms pre- versus post-exposure, and did not compare

25  response with a filtered air control exposure. Pietropaoli et al. (2004) found no association between

26  exposure to ultrafine carbon particles and respiratory symptoms in healthy adults at concentrations

27  between 10 and 50 $\mu g/m^3$, or asthmatics at a concentration of 10 $\mu g/m^3$. Beckett et al. (2005) exposed

28  healthy subjects to ultrafine and fine zinc oxide (500 $\mu g/m^3$) and observed no difference in respiratory

29  symptoms compared to filtered air control 24-h following exposure. These new studies confirm previous

30  reports that have found no association between PM exposure and respiratory symptoms.

# 6.3.2. Pulmonary Function

1    Epidemiologic studies cited in the 2004 PM AQCD observed small decrements in pulmonary
2    function associated with both $PM_{10}$ and $PM_{2.5}$. The majority of human clinical studies reported no effect
3    of PM on pulmonary function, while the results from toxicological studies were mixed, with some
4    evidence of changes in tidal volume and respiratory rate following exposure to CAPs. Epidemiologic
5    studies published since the 2004 PM AQCD have reported an association between $PM_{2.5}$ concentration
6    and decrements in $FEV_1$, particularly among asthmatic children. These findings are coherent with results
7    from a number of recent toxicological studies which have observed increases in airways
8    hyperresponsiveness following CAPs exposure. Results from recent human clinical studies have been
9    inconsistent, with some studies demonstrating small decreases in arterial oxygen saturation or maximal
10   mid-expiratory flow following exposure to CAPs or elemental carbon. It is interesting to note that these
11   effects appear to be more pronounced among healthy adults than adults with asthma or COPD.

## 6.3.2.1. Epidemiologic Studies

12   The 2004 PM AQCD concluded that both $PM_{10}$ and $PM_{2.5}$ appeared to affect lung function in
13   asthmatics. Ultrafine particles did not appear to have any notably stronger effect than other
14   larger-diameter fine particles. Few analyses were able to clearly distinguish the effects of $PM_{10}$ and $PM_{2.5}$
15   from other pollutants. Results for $PM_{10}$ peak flow analyses in non-asthmatic studies were inconsistent,
16   with fewer studies reporting results statistically significant association.

### *Asthmatic Children*

17   Seven recent panel studies have been conducted in the U.S. examining the association of exposure
18   to ambient PM and lung function in asthmatic children (2003a in Southern California; 2004; Dusek et al.,
19   2006 and Allen et al., 2008 in Seattle; 2005 in Detroit; 2004 in Denver);O'Connor, 2008. Mean
20   concentration data from these studies are summarized in Figure 6-8.
21   In the Inner-City Asthma Study (ICAS), $FEB_1$ and PEFT were significantly related to the 5-day
22   average of $PM_{2.5}$, but not to the 1-day average concentration (O'Connor et al., 2008). The risk of
23   experiencing a percent-predicted $FEV_1$ more than 10% below personal best was significantly related to
24   the 5-day average concentration of $PM_{2.5}$ (1.14 [95% CI: 1.01-1.29]). The risk of experiencing a percent-
25   predicted PEFR more than 10% below personal best was significantly related to $PM_{2.5}$ (1.18 [95% CI:
26   1.03-1.35]). This effect remained statistically significant in multipollutant models with $O_3$ and $NO_2$ for the
27   FEV1 effect, but not the PEFR effect.

The Denver study (Rabinovitch et al., 2004), described in Section 6.3.1.1 also examined daily forced expiratory volume in 1 sec ($FEV_1$) and peak expiratory flow (PEF) in 86 asthmatic children over the course of 3 winters (some subjects participated in more than one winter). Lung function measurements were performed under supervision daily at the elementary school where all subjects attended, and without supervision every evening and on nonschool days. As described above, the authors chose to use a 3-day moving average of 24-h $PM_{2.5}$ or $PM_{10}$ as the exposure metric. No statistical associations were observed between morning or afternoon $FEV_1$ or PEF and particle exposure. The same group of researchers used regression calibration to estimate personal exposures to ambient $PM_{2.5}$ and found that a 10 µg/m$^3$ increase in $PM_{2.5}$ was associated with a 2.2% (95% CI: 0.0-4.3) decrease in $FEV_1$ at a 1-day lag as compared with the estimate of a 1.0% decrease in $FEV_1$ using ambient $PM_{2.5}$ concentrations from fixed monitors. These results underscore the effects of exposure error on epidemiologic study results; the effect estimate using an estimate of personal exposure to ambient $PM_{2.5}$ was twice that for central site $PM_{2.5}$.

From winter 2001 to the spring of 2002, the same number (n = 86) of primary school-age asthmatic children participated in six, 2-wk seasonal assessments of lung function in Detroit (Lewis et al., 2005). Using a protocol similar to that used in Rabinovitch et al. (2004), morning lung function measurements ($FEV_1$, PEF) were self-administered at school under supervision by research staff. Evening and weekend measurements were made without supervision by research staff at home. Community-level exposure was assessed using monitors placed on a school roof top of both of the 2 communities. Most of the subjects (82 of 86) lived within 5 km of their respective community monitors. In single-pollutant models using GEE and only among children reporting the use of maintenance medication (corticosteroids), each 10 µg/m$^3$ increase in lag 2 $PM_{10}$ was associated with a decrease in the lowest daily percent predicted $FEV_1$ (a reduction of 1.15%, [95% CI: -2.1 to -0.25]). Among children reporting presence of URI on the day of lung function measurement, increases in the average of lag 3-5 of either $PM_{2.5}$ or $PM_{10}$ resulted in a decrease in the lowest daily $FEV_1$ (for a 10 µg/m$^3$ increase in $PM_{2.5}$ the reduction was 2.24% [95% CI: -4.4 to -0.25]; and for a 10 µg/m$^3$ increase in $PM_{10}$ the reduction was 2.4% [95% CI: -4.5 to -0.3]). In copollutant models that included one particle pollutant and ozone, and among children using maintenance medication, lag 3-5 $PM_{2.5}$ continued to be associated with lowest daily $FEV_1$ as well as diurnal $FEV_1$ variability: each 10 µg/m$^3$ increase was associated with a 2.23% decrease in $FEV_1$ (95% CI: -3.92 to -0.57) and a 2.22% increase in $FEV_1$ variability (95% CI: 1.0 to 3.50). Increases in lag 1 or lag 2 of $PM_{10}$ were also significantly associated with $FEV_1$ and $FEV_1$ diurnal variability in copollutant models. The strongest association was with lag 2 for diurnal variability (for each 10 µg/m$^3$ increase variability increased by 7.0% [95% CI: 4.2 to 9.6). It is unclear what role the lack of supervision during the evening and weekend measures may have had on these diurnal results.

1    Two panel studies in Southern California examined the association of PM exposure on lung

2   function in asthmatic children (Delfino et al., 2003a; 2004). In Delfino et al. (2003a), described above, no

3   association between exposure to particles and PEF was found for 22 Hispanic, asthmatic children living in

4   an area of relatively high pollution. In Delfino et al. (2004) 19 asthmatic children aged 9-17 were

5   followed for 2 weeks and daily, self-administered $FEV_1$ measurements were taken. Particle exposures

6   studied included central-site $PM_{10}$ in addition to personal PM (in the range of 0.1-10 µm range, with the

7   highest response in the fine PM range), and home stationary measurements of both $PM_{10}$ and $PM_{2.5}$. The

8   authors found significant inverse associations between percent expected $FEV_1$ and PM indicators. The

9   strongest association for exposure to personal PM was for a 5-day moving average of 12-h daytime PM:

10   for each 10 µg/m$^3$ increase, $FEV_1$ decreased by 7.1% (95% CI: -9.9 to -2.9). Effects for all stationary sites

11   (inside and outside of residence, central site) for $PM_{2.5}$ were on the order of 1 to 2% reductions in $FEV_1$,

12   with the strongest associations for the 5-day moving average (given in figures only). Likewise for $PM_{10}$

13   measured at stationary sites, the strongest effects were for 5-day moving averages and ranged from

14   approximately 3.8% reduction associated with indoor monitors to about 1.5% for both the outdoor and

15   central site monitors (given in figures only). A helpful comparison among all 24-h measures is given for

16   10 µg/m$^3$ increases in personal PM and $PM_{2.5}$ associated with decreases in percent predicted $FEV_1$: an

17   increase of 10 µg/m$^3$ personal PM is associated with a decrease in $FEV_1$ of 3.0% (95% CI: -5.6 to -0.5);

18   10 µg/m$^3$ increase in indoor PM with 2.4% decrease (95% CI: -4.2 to -0.6); 10 µg/m$^3$ increase in outdoor

19   PM with 1.5% decrease (95% CI: -3.4, 0.1); 10 µg/m$^3$ increase in central site PM with 0.9% decrease

20   (95% CI: -2.6, 0.5).

21    Trenga et al. (2006) also reported associations among personal, residential, and central site $PM_{2.5}$

22   and lung function in 17 asthmatic children in Seattle. The only significant association with decline in

23   $FEV_1$ was with indoor measurements of $PM_{2.5}$: each 10 µg/m$^3$ increase in lag 1 indoor $PM_{2.5}$ was

24   associated with a decline in $FEV_1$ of 64.8 ml (95% CI: -111.3 to 18.3) (a 3.4% decline from the mean of

25   1.9 L). Indoor $PM_{2.5}$ (lag 1) was also associated with declines in PEF (by 9.2 L/min [95% CI: -17.5 to

26   -0.9], a 3.6% decline from the 254 L/min average) and in MMEF for the 6 subjects not taking

27   anti-inflammatory medication (by 12.6 L/min [95% CI: -20.7 to -4.6], a 13.7% decline from the 92 L/min

28   average). Personal $PM_{2.5}$ (lag 1) was only statistically associated with PEF for the 6 subjects not on

29   anti-inflammatory medication: each 10 µg/m$^3$ increase resulted in a 10.5 L/min ([95% CI: -18.7 to -2.3], a

30   4.5% decline from the 233 L/min average) reduction in PEF. Anti-inflammatory medication use

31   significantly attenuated associations with $PM_{2.5}$. No statistically significant association of the ambient

32   $PM_{2.5}$ mixture.

33    Also in Seattle, Allen et al. (2008) evaluated the effect of different $PM_{2.5}$ exposure metrics in

34   relation to lung function among children in woodsmoke-impacted areas. The authors found that the

1  ambient-generated component of $PM_{2.5}$ exposure was associated with decrements in lung function only

2  among children not using inhaled corticosteroids, whereas no association ewas reported with the

3  nonambient exposure component. All of the ambient concentrations were associated with decrements in

4  both PEF and MEF. There were no associations between any exposure metrics and FVC. The authors

5  suggest that lung function may be especially sensitive to the combustion-generated component of ambient

6  $PM_{2.5}$, whereas airway inflammation may be more closely related to some other consitutent

7      Moshammer and Neuberger (2003) used a novel technique for assessing exposure to PM in a study

8  they conducted in Austria. They employed a diffusion charging particle sensor (model LQ 1-DC, Matter

9  Engineering AG, Wohlen, Switzerland) and a photoelectric aerosol sensor (model PAS 2000 CE,

10  EcoChem Analytics, League City, TX) to relate the spirometry scores of Upper Austrian children

11  aged 7-10 to particle surface area and particle-bound PAH concentration, respectively. Details on these

12  methods for measuring surface area and PAH can be found in Shi et al. (2001) and Burtscher (2005),

13  respectively. By measuring the surface area distribution, it was possible to understand potential for

14  contact area with the respiratory tract cells. The authors found that acute decrements of pulmonary

15  function (FVC, $FEV_1$, $MEF_{50}$) were related to the active surface of particles after adjustment for $PM_{10}$.

16  For short-term lung impairments, this indicates that active particle surface is a better index of exposure

17  than PM mass.

18      A number of additional panel studies conducted outside of the U.S. also examined lung function

19  using more traditional exposure metrics. Several European and Asian studies reported associations with

20  decrements in pulmonary function ($FEV_1$, FVC, FEF, MEF, PEFR) (Hogervorst et al., 2006; Hong et al.,

21  2007; Moshammer et al., 2006; Peacock et al., 2003; Peled et al., 2005). Others found little evidence for a

22  relationship between PM and daily changes in PEF after correction for the confounding effects of

23  weather, trends in the data, and autocorrelation (Fischer et al., 2002; Holguin et al., 2007; Janssen et al.,

24  2003; Just et al., 2002; Preutthipan et al., 2004; Ranzi et al., 2004; Ward, 2003).

### Adults

25      Trenga et al. (2006) examined personal, residential, and central site monitoring of particles and the

26  relationship with lung function in Seattle. In models controlling for gaseous copollutants (CO, $NO_2$),

27  adults, regardless of COPD status, experienced a significant decline in $FEV_1$ associated only with

28  measurements of $PM_{2.5}$ at the central site: each 10 $\mu g/m^3$ increase in lag 0 $PM_{2.5}$ was associated with a

29  35.3 ml (95% CI: -70 to -1.0) decrease in $FEV_1$. This represents a 2.2% decline in mean $FEV_1$ (mean 1.6

30  L during the study). Results for personal, indoor and outdoor measures of $PM_{2.5}$ were inconsistent. No

31  significant associations were reported with outdoor $PM_{10-2.5}$.

1    Giradot et al. (2006) assessed the effects of $PM_{2.5}$ on the pulmonary function of adult day hikers in

2    the Great Smoky Mountains National Park. Hikers performed spirometry both before their hike and when

3    they returned from their hike. The authors reported no statistically significant responses in pulmonary

4    function with an average of 5 h of outdoor exercise at ambient $PM_{2.5}$ levels that were below the current

5    NAAQS. Specifically, posthike percentage changes in FVC, $FEV_1$, $FEV_1/FVC$, $FEF_{25-75}$, and PEF were

6    not associated with $PM_{2.5}$ exposure.

7    Ebelt et al. (2005) developed an approach to separately estimate exposures to PM of ambient and

8    nonambient origin based on a mass balance model. These exposures were linked with respiratory and

9    cardiovascular health endpoints for 16 patients with COPD in Vancouver, Canada (mean age 74 years).

10   Effect estimates for estimated ambient exposure were generally equal to or larger than those for the

11   respective ambient concentration levels for post-FEV and $\Delta FEV_1$, and were statistically significant for all

12   $\Delta FEV_1$ comparisons (estimated from figure).

13   Several studies outside of the U.S. and Canada examined the relationship between PM

14   concentrations and lung function and all reported a decrease in lung function in adults ($FEV_1$, FVC,

15   PEFR) associated with PM exposure (Boezen et al., 2005; Bourotte et al., 2007; Lagorio et al., 2006; Lee

16   et al., 2007; McCreanor et al., 2007; Penttinen et al., 2006).

## 6.3.2.2. Human Clinical Studies

17   As with respiratory symptoms, there is very little evidence from human clinical studies of

18   PM-induced changes in pulmonary function. One study cited in the 2004 PM AQCD noted a significant

19   decrement in thoracic gas volume in healthy adults following a 2 hour exposure to $PM_{2.5}$ CAPs

20   (92 $\mu g/m^3$); however, no significant changes were observed in spirometry, diffusing capacity (DLCO),

21   total lung capacity, or airway resistance (Petrovic et al., 2000). Other studies have found no significant

22   changes in pulmonary function in healthy adults following exposure to inhaled iron oxide particles (Lay

23   et al., 2001), or in healthy and asthmatic adults following exposure to CAPs (Ghio et al., 2000; Gong et

24   al., 2000; 2003a; 2004b). While Gong et al. (2004a) did not observe a significant association between

25   exposure to $PM_{2.5}$ CAPs and spirometry in older subjects (60-80 years old), the investigators did report a

26   decrease in oxygen saturation immediately following CAPs exposure. This effect was observed more

27   consistently in healthy older adults than in older adults with COPD. These findings were confirmed by a

28   subsequent study conducted by the same laboratory (Gong et al., 2005). The authors also observed a small

29   decrease in maximal mid-expiratory flow (MMEF) following a 2-h exposure to $PM_{2.5}$ CAPs (200 $\mu g/m^3$)

30   which was more pronounced in healthy subjects. Pietropaoli et al. (2004) observed a significant reduction

31   in MMEF and DLCO in healthy adults 21 hours after a 2-h exposure to ultrafine carbon particles

32   (50 $\mu g/m^3$). This reduction in DLCO may reflect a PM-induced vasoconstrictive effect on the pulmonary

1 vasculature. Among a group of healthy and asthmatic adults exposed to ultrafine particles (Los Angeles,

2 mean concentration 100 µg/m$^3$), Gong et al. (2008) observed small, yet statistically significant decrements

3 in arterial oxygen saturation immediately following exposure, 4 h post-exposure, and 22-h post-exposure

4 (0.5% mean decrease relative to filtered air across all time points, $p < 0.05$). A statistically significant

5 decrease in FEV$_1$ was also observed, but only at 22-h post-exposure (2% decrease relative to filtered air, p

6 $< 0.05$). The responses demonstrated in this study were not significantly affected by health status.

7 Conversely, Samet et al. (2007) did not observe any significant changes in pulmonary function in healthy

8 adults following exposures to ultrafine, fine, and thoracic coarse fraction CAPs generated from ambient

9 air in Chapel Hill, NC.

10 Taken together, the majority of human clinical studies do not provide evidence of PM-induced

11 changes in pulmonary function; however, some investigators have observed decrease in DLCO

12 (Pietropaoli et al., 2004), MMEF (Gong et al., 2005; Pietropaoli et al., 2004), and oxygen saturation

13 (Gong et al., 2004a; 2005; 2008) following exposure to PM.

## 6.3.2.3. Toxicological Studies

14 The 2004 PM AQCD included three animal toxicological studies which measured pulmonary

15 function following multi-day short-terminhalation exposure to CAPs. A decreased respiratory rate was

16 noted in one study involving dogs. Increased tidal volume was observed in one study involving rats while

17 no changes were observed in the other rat study. Airway hyperresponsiveness (AHR) was found in 4

18 studies of mice, healthy rats or spontaneously hypertensive (SH) rats exposed to ROFA by intratracheal

19 instillation or inhalation. Studies conducted since the last review are discussed below.

20 Spontaneously hypertensive Wistar Kyoto rats (SH rats) exposed to Tuxedo, NY CAPs via

21 nose-only inhalation for 4 h (mean concentration 73 µg/m$^3$; single-day concentrations 80 and 66 µg/m$^3$;

22 2/2001 and 5/2001 respectively) had a statistically significant decreased respiratory rate compared with

23 air-exposed controls (Nadziejko et al., 2002). This measure was obtained from BP fluctuations using

24 radiotelemetry. The decrease in respiratory rate of 25-30 breaths/min was an immediate response to

25 CAPs, beginning shortly after the exposure began and ceasing with the end of exposure. It was

26 accompanied by a decrease in HR (see Section 6.2.1.3). Rats were also exposed to fine (MMAD 160 nm;

27 49-299 µg/m$^3$) and ultrafine sulfuric acid (MMAD 50-75 nm; 140-750 µg/m$^3$) (Nadziejko et al., 2002);

28 because sulfuric acid aerosols have the potential to activate irritant receptors. Irritant receptors, found at

29 all levels of the respiratory tract, include rapidly-adapting receptors and sensory C-fiber receptors

30 (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001; 2006; 2003). Activation of these vagal

31 afferents causes central nervous system reflexes resulting in bronchoconstriction, mucus secretion,

32 mucosal vasodilation, cough, and apnea followed by rapid shallow breathing. Besides effects on the

1  respiratory system, effects on the cardiovascular system can also occur including bradycardia and

2  hypotension or hypertension. Fine sulfuric acid induced an overall decrease in respiratory rate, with

3  ultrafine sulfuric acid resulting in elevated respiratory rate compared to control (Nadziejko et al., 2002).

4  The authors suggested that both CAPs and fine sulfuric acid aerosols activated sensory irritant receptors

5  in the airways, resulting in a decreased respiratory rate. The response to ultrafine sulfuric acid aerosols

6  differed from the other responses and was thought to be due to deposition of ultrafine particles deeper into

7  the lung with the subsequent activation of pulmonary irritant receptors which trigger an increase in

8  respiratory rate. Since lung irritant receptors in both airways and pulmonary region act via

9  vagally-mediated parasympathetic pathways, this study indicates a role for neural reflexes in respiratory

10  responses to CAPs.

11    McQueen et al. (2007) also investigated the role of vagally-mediated pathways in respiratory

12  responses to PM. Respiratory min volume (RMV) was increased in anesthetized Wistar rats 6 h after

13  treatment with 500 µg DEP (SRM2975) by intratracheal instillation. This response was blocked by

14  sectioning the vagus nerves or pretreatment with atropine. The absence of respiratory response with

15  vagotomy or atropine indicated that the increase in RMV following DEP exposure involved a neural

16  reflex acting via vagal afferents. No statistically significant changes in mean BP, HR or HRV were

17  observed in response to DEP in this study. Vagally-mediated inflammatory responses to DEP were also

18  observed in this study and are discussed in Section 6.3.3.3.

19    Kodavanti et al. (2005) measured respiratory frequency 1 day after a 2-day exposure of SH and

20  WKY rats to CAPs from RTP, NC (mean mass concentration range 144-2,758 $\mu g/m^3$; less than 2.5 um in

21  size; 8/27–10/24/2001) for 4 h/day. Increases in inspiratory and expiratory times were seen in SH, but not

22  WKY rats exposed to CAPs compared with filtered air controls.

23    Effects of CAPs on pulmonary function were also investigated in a rat model of pulmonary

24  hypertension using Sprague Dawley rats pre-treated with monocrotaline (Lei et al., 2004b). In this study,

25  rats were exposed to CAPs from an urban high traffic area in Taiwan (mean mass concentration

26  371 $\mu g/m^3$) for 6 h/day on 3 consecutive days and pulmonary function was evaluated 5 hours

27  post-exposure using whole-body plethysmography. A statistically significant decrease in respiratory

28  frequency and increase in tidal volume were observed following CAPs exposure, along with an increase

29  in airway responsiveness (measured by Penh) following methacholine challenge.

30    Li et al. (2007) exposed BALB/c and C57BL/6 mice to clean air or to low dose DE (containing

31  100 $\mu g/m^3$ DEP) for 7 h/day and 5 days/week for 1, 4 and 8 weeks. Average gas concentrations were

32  reported to be 3.5 ppm CO, 2.2 ppm $NO_2$, and less than 0.01 ppm $SO_2$. Airways hyperresponsivenesss

33  was evaluated by whole body plethysmography at day 0 and after 1, 4 and 8 weeks of exposure. Exposure

34  to DE for 1 week resulted in an increased sensitivity of airways to methacholine measured as Penh, in

1    C57BL/6 but not BALB/c mice. Other responses of this study are discussed in Sections 6.3.3.3. and

2    6.3.4.2.

3        In a study by Last et al. (2004), BALB/c mice were exposed to 250 µg/m$^3$ laboratory-generated

4    iron-soot (size range 80-110 nm; about 200 µg/m$^3$ as soot) for 4 h/day and 3 days/week for 2 weeks. Lung

5    function was measured as Penh by whole-body plethysmography after challenge with methacholine. No

6    increase in airway responsiveness was observed following 2 week exposure to iron-soot. Other findings

7    of this study are reported in Sections 6.3.3.3, 6.3.5.2 and 7.3.2.2.

8        In summary, several recent studies demonstrated alterations in respiratory frequency and AHR

9    following short-term exposure to CAPs and DE. Two studies provide evidence for the involvement of

10   irritant receptors and vagally-mediated neural reflexes in mediating changes in respiratory functions.

# 6.3.3. Pulmonary Inflammation

11   The discussion of the effects of PM on pulmonary inflammation in the 2004 PM AQCD was

12   limited by a relative lack of information from human clinical and toxicological studies. Although no

13   epidemiologic studies of pulmonary inflammation were described in the 2004 PM AQCD, several recent

14   studies have observed a positive association between PM concentration and exhaled nitric oxide. New

15   human clinical and toxicological studies have also generally observed an increase in markers of

16   inflammation in the airways following exposure to PM.

## 6.3.3.1. Epidemiologic Studies

17   No epidemiologic studies of pulmonary inflammation were described in the 2004 PM AQCD.

### Exhaled Nitrogen Oxide – Asthmatic Children

18   Exhaled NO, a biomarker for airway inflammation, was the outcome studied in panels of asthmatic

19   children in Southern California (Delfino et al., 2006) and Seattle (2008; Koenig et al., 2003; Koenig et al.,

20   2005; Mar et al., 2005a). Mean concentration data from these studies are summarized in Table 6-7.

21   Delfino et al. (2006) followed 45 asthmatic children for 10 days with offline fractional eNO and

22   examined the associations with exposures to personal PM$_{2.5}$ and 24-h PM$_{2.5}$, EC and OC as well as

23   ambient PM$_{2.5}$, EC and OC. The strongest associations were between eNO and 2-day average pollutant

24   concentrations: for a 10 µg/m$^3$ increase in personal PM$_{2.5}$, eNO increased by 0.46 ppb (95% CI:

25   0.04-0.79); for 0.6 µg/m$^3$ personal EC, eNO increased by 0.7 ppb (95% CI: 0.3-1.1). An association with

26   exposure to ambient PM$_{2.5}$ was only statistically significant in 19 subjects taking inhaled corticosteroids:

27   for each 10 µg/m$^3$ increase in PM$_{2.5}$, eNO increased by 0.77 ppb (95% CI: 0.07-1.47).

1    In a panel of 19 asthmatic children in Seattle, effects were observed only among the 10 non-users

2    of inhaled corticosteroids. For each 10 μg/m$^3$ increase in personal, outdoor, indoor, or central site PM$_{2.5}$,

3    eNO increased from 3.82 ppb (associated with central site, 95% CI: 1.22-6.43) to 4.48 ppb (with personal

4    PM$_{2.5}$, 95% CI: 1.02-7.93) (Koenig et al., 2003). Further analysis examining the association between eNO

5    and outdoor and indoor-generated particles suggested that eNO was associated more strongly with

6    ambient particles, but only for non-users of medication: each 10 μg/m$^3$ increase in estimated ambient

7    PM$_{2.5}$ results in an increase in eNO of 4.98 ppb (95% CI: 0.28-9.69) (Koenig et al., 2005).

8    Also in Seattle, WA, Mar et al. (2005a) examined the association between eNO and ambient PM$_{2.5}$

9    concentration among children (aged 6-13 years) recruited from an asthma/allergy clinic. FeNo was

10   associated with hourly averages of PM$_{2.5}$ up to 10-12 hours after exposure. Each 10 μg/m$^3$ increase in

11   1-hour mean PM$_{2.5}$ concentration was associated with a 6.99 ppb increase in eNO (95% CI: 3.43-10.55)

12   among children not taking inhaled corticosteroids, but associated with only a 0.77 ppb decrease in eNO

13   (95% CI: -4.58to3.04) among those taking inhaled corticosteroids.

14   Allen et al. (2008) evaluated the effect of different PM$_{2.5}$ exposure metrics in relation to airway

15   inflammation among children in woodsmoke-impacted areas of Seattle. The authors found that the

16   ambient-generated component of PM$_{2.5}$ exposure was associated with respiratory responses, both airway

17   inflammation and decrements in lung function, whereas the nonambient PM$_{2.5}$ exposure component was

18   not. They did note, however, different relationships for airway inflammation and decrements in lung

19   function, with the former significantly associated with total personal PM$_{2.5}$, personal light-absorbing

20   carbon (LAC), and ambient generated personal PM$_{2.5}$ and the latter related to ambient PM$_{2.5}$ and its

21   combustion markers. The different results between forced exhaled nitric oxide (FENO) and lung function

22   were not unexpected; epidemiologic data show that airway inflammation indicated by FENO does not

23   correlate strongly with either respiratory symptoms or lung function (Smith and Taylor, 2005). The

24   authors conclude that lung function decrements may be associated with the combustion-generated

25   component of ambient PM$_{2.5}$, whereas airway inflammation may be related to some other constituent of

26   the ambient PM$_{2.5}$ mixture.

27   Several studies outside of the U.S. examined eNO in relation to PM exposure among children.

28   Fischer et al. (2002) and Murata et al. (2007) found a significant association between increases in PM and

29   increases in the percent of eNO. Holguin et al. (2007) found no association between exposure to PM and

30   eNO. However, they did see significant associations between increases in eNO for the 95 asthmatic

31   subjects and measures of road density of roads 50- and 75-m from the home.

## Exhaled Nitrogen Oxide – Adults

1    Three recent panel studies examined the effects of particle exposure on eNO measured in older

2    adults (Adamkiewicz et al., 2004) in Steubenville; (Jansen et al., 2005) in Seattle; Adar et al. 2007 in St.

3    Louis). Mean concentration data from these studies are characterized in Table 6-7. Breath samples were

4    collected weekly for 12 weeks from a group of 29 elderly adults in Steubenville (Adamkiewicz et al.,

5    2004). In single-pollutant models, each 10 $\mu g/m^3$ increase in 24-h ambient $PM_{2.5}$ increased eNO by 0.82

6    ppb (95% CI: 0.19-1.45), a change of 15% compared to mean eNO (9.9 ppb). Effects were essentially

7    unchanged in multipollutant models that included ambient and/or indoor NO. The effect estimates for the

8    7 COPD subjects were significantly higher than for normal subjects (2.20 vs. 0.45 ppb, p = 0.03)

9    (Adamkiewicz et al., 2004).

10    In the Seattle panel of older adults (aged 60-86 years), 7 subjects were asthmatic and 9 had a

11    diagnosis of COPD (5 with asthma and 4 without) (Jansen et al., 2005). Exhaled NO was measured daily

12    for 12 days, along with personal, indoor, outdoor and central site $PM_{10}$, $PM_{2.5}$ and BC. Significant

13    associations between 24-h average PM and eNO were found only for the asthmatic subjects: 10 $\mu g/m^3$

14    increases in outdoor levels (measured outside the subjects' homes) of $PM_{2.5}$ or $PM_{10}$ were associated with

15    increases in eNO of 4.23 ppb (95% CI: 1.33-7.13), an increase of 22% above the group mean of 19.2 ppb,

16    and 5.87 ppb (95% CI: 2.87-8.88), an increase of 31%, respectively. BC measured indoors, outdoors or

17    personally was also associated with significant increases in eNO (of 3.97, 2.32, and 1.20 ppb,

18    respectively) (Jansen et al., 2005).

19    Adar et al. (2007b) conducted a panel study of 44 non-smoking seniors residing in St. Louis, MO

20    (age = 60 years). As part of the study, subjects were taken on group trips to a theater performance, Omni

21    movie, outdoor band concert, and a Mississippi River boat cruise. Subjects were driven to and from each

22    event aboard a diesel bus. Before and after each bus trip, eNO was measured on each subject. Two carts

23    containing continuous air pollution monitors were used to measure group-level micro-environmental

24    exposures to $PM_{2.5}$, BC, and size-specific particle counts (0.3-2.5 µm and 2.5-10 µm) on the day of each

25    trip. Each 10 $\mu g/m^3$ increase in 24-h mean $PM_{2.5}$ concentration was associated with a 36% increase in

26    eNO pre-trip (95% CI: 5-71). Each 10 $\mu g/m^3$ increase in micro-environmental $PM_{2.5}$ concentration (i.e.

27    during the bus ride) was associated with a 27% increase in eNO post-trip (95% CI: 17-38).

28    These studies all demonstrated an association between increased levels of eNO and increases in

29    PM in the previous 4 to 24-h. Further, three studies demonstrated effects in elderly populations

30    (Adamkiewicz et al., 2004; Adar et al., 2007b; Jansen et al., 2005) while four others reported a similar

31    acute increase in eNO among children (Delfino et al., 2006; Koenig et al., 2003; Koenig et al., 2005;

32    2005a).

1    Outside of the U.S., one study examined eNO in a panel of 60 adult asthmatic subjects in London.

2    McCreanor et al. (2007) reported that 1 µg/m$^3$ increase in personal ezposure to EC was associated with

3    significant increases of approximately 1.75 to 2.25 % in eNO (results were presented graphically only) for

4    up to 22 h post-exposure.

### *Other Biomarkers of Pulmonary Inflammation*

5    Other biomarkers of respiratory distress that have been examined in recent panel studies include

6    urinary leukotriene E4 (LTE$_4$) in asthmatic children (Rabinovitch et al., 2006); and breath acidification in

7    adolescent athletes (Ferdinands et al., 2008). Mean concentration data from these studies are characterized

8    in Table 6-7.

9    In Rabinovitch et al. (2006), LTE$_4$, an asthma-related biological mediator, was used to study the

10   response to short-term particle exposure. In the second winter of their 2-year study of asthmatic children

11   (described above in Section 6.3.1.1., under respiratory symptom and medication use outcomes), urine

12   samples were collected at approximately the same time of day from 57 subjects for 8 consecutive days.

13   Controlling for days with URI symptoms, each 10 µg/m$^3$ increase in morning maximum PM$_{2.5}$ (measured

14   by TEOM), was associated with an increase in LTE$_4$ levels by 5.1% (95% CI: 1.6-8.7). No significant

15   effects were observed on the same day or up to 3 days later based on 24-h averaged concentrations from

16   the TEOM monitor or from the FRM central site monitor.

17   The effects of vigorous outdoor exercise during peak smog season in Atlanta, GA on breath pH, a

18   biomarker of airway inflammation, in adolescent athletes (n = 16, mean age = 14.9 years) were examined

19   by Ferdinands et al. (2008). Median pre-exercise breath pH was 7.58 (range 4.39-8.09) and median

20   post-exercise breath pH was 7.68 (range 3.78-8.17). The authors observed no significant association

21   between ambient PM and post-exercise breath pH. However both pre- and post-exercise breath pH were

22   strikingly low in these athletes when compared to 14 relatively sedentary healthy adults and to published

23   values of breath pH in healthy subjects. The authors speculate that repetitive vigorous exercise may

24   induce airway acidification.

## 6.3.3.2. Human Clinical Studies

25   Studies of intrapulmonary instillation of particles in human subjects have provided evidence of

26   lung inflammation induced by exposure to PM. Lay et al.  found that instillation of iron oxide (2.6 µm)

27   produced an increase in alveolar macrophages and neutrophils in BAL fluid collected 24-h

28   post-instillation. Ghio and Devlin (2001) evaluated the inflammatory response following instillation of

29   particles extracted from filters collected in the Utah Valley both prior to and after the closure of an area

30   steel mill. Subjects who underwent pulmonary instillation of particles (500 µg) collected while the steel

1 mill was operating (n = 16) had significantly higher levels of neutrophils 24-h post-instillation compared

2 with either saline instillation or with subjects (n = 8) who were instilled with the same mass of PM

3 collected during the mill's closure. This finding indicates that metals may be an important PM component

4 for this health outcome. A similar study by Schaumann et al. (2004) investigated the inflammatory

5 response of human subjects instilled with $PM_{2.5}$ (100 μg) collected from two different cities in Germany,

6 Hettstedt and Zerbst. Although instillation of PM from both cities were shown to induce airway

7 inflammation, instillation of PM from the more industrial area (Hettstedt) resulted in greater influxes of

8 BALF monocytes compared to PM collected from Zerbst. The authors postulated that the difference in

9 response between PM from the two cities may be due to the higher concentration of transition metals

10 observed in the samples collected from Hettstedt. In an inhalation study of exposure to fine CAPs

11 (23-311 $μg/m^3$) from Chapel Hill, NC, Ghio et al. (2000) observed an increase in airway and alveolar

12 neutrophils 18 hours after the 2-h exposure. Huang et al. (2003c) reported the increase in BAL neutrophils

13 demonstrated by Ghio et al. (2000) to be positively associated with the Fe, Se, and sulfate content of the

14 particles.

15    Samet et al. (2007) summarized the findings of Ghio et al. (2000) and presented preliminary data

16 from two studies that evaluated health effects of controlled 2-h exposures to ultrafine and thoracic coarse

17 PM. Ultrafine CAPs (47 $μg/m^3$) did not alter markers of pulmonary inflammation measured in BAL fluid

18 collected 18 hours after exposure. Pietropaoli et al. (2004) also observed a lack of airway inflammatory

19 response 21 hours after exposure to ultrafine carbon particles (10-50 $μg/m^3$). However, as described in

20 Samet et al. (2007), thoracic coarse CAPs (89 $μg/m^3$) were shown to significantly increase the percentage

21 of polymorphonuclear leukocytes (PMNs) in BAL fluid 20 hours after exposure. No thoracic coarse

22 PM-induced changes in macrophages, lymphocytes, monocytes, or eosinophils were observed. Alexis et

23 al. (2006) recently evaluated the effect of $PM_{10-2.5}$ on markers of airway inflammation, specifically

24 focusing on the impact of biological components of $PM_{10-2.5}$. Healthy men and women (n = 9) between the

25 ages of 18 and 35 inhaled nebulized saline (0.9%) as well as aerosolized $PM_{10-2.5}$ collected from ambient

26 air. Subjects were exposed to $PM_{10-2.5}$ on two separate occasions, once using $PM_{10-2.5}$ that had been heated

27 to inactivate biological material and once using non-heated $PM_{10-2.5}$. Approximately 0.65 mg $PM_{10-2.5}$ was

28 deposited in the respiratory tract of subjects during the exposures. Markers of inflammation and immune

29 function were analyzed in induced sputum collected 2-3 hours after inhalation of saline or $PM_{10-2.5}$. Both

30 heated and non-heated $PM_{10-2.5}$ were observed to increase the neutrophil response compared with saline.

31 Exposure to non-heated $PM_{10-2.5}$ was found to increase levels of monocytes, eotaxin, macrophage TNF-α

32 mRNA, and was also associated with an upregulation of macrophage cell surface markers. No such

33 effects were observed following exposure to biologically inactive $PM_{10-2.5}$. These results suggest that

34 while thoracic coarse fraction PM-induction of neutrophil response is not dependent on biological

1    components, heat sensitive components of coarse PM (e.g., endotoxin) may be responsible for

2    PM-induced alveolar macrophage activation.

3         Barregard et al. (2008) examined the effect of a short-term exposure (4 hours) to wood smoke

4    (240-280 $\mu g/m^3$) on markers of pulmonary inflammation in a group of healthy adults. Exposure to wood

5    smoke increased alveolar NO compared to filtered air (2.0 ppb versus 1.3 ppb) 3 hours after exposure.

6    Although these results provide some evidence of a PM-induced increase in pulmonary inflammation, the

7    physiological significance of the relatively small increase in alveolar NO is unclear. Larsson et al. (2007)

8    exposed 16 healthy adults to air pollution in a road tunnel for 2-h during the afternoon rush hour in

9    Stockholm, Sweden. The median $PM_{2.5}$ and $PM_{10}$ concentrations during the road tunnel exposures were

10   64 $\mu g/m^3$ and 176 $\mu g/m^3$, respectively. Bronchial biopsies were obtained and broncoscopy and

11   bronchoalveolar lavage were performed 14 hours after the exposure. The results were compared with a

12   control exposure which consisted of exposure to urban air during normal activity. The authors reported

13   significant BALF increases in lymphocytes, total cell number, and alveolar macrophages following

14   exposure to road tunnel exposure versus control. No changes in adhesion molecules or blood coagulation

15   factors were observed. These results provide evidence of a significant association between exposure to

16   road tunnel air pollution and airway inflammation. However, unlike other controlled exposure studies, the

17   control exposure was not a true clean air control, but only a lower dose exposure group. In addition, it is

18   not possible to separate out the contributions of each air pollutant, including PM, on the observed

19   inflammatory response.

20        In a recent study evaluating the effect of DE exposure on markers of airway inflammation, Behndig

21   et al. (2006) exposed healthy adults (n = 15) for 2-h with intermittent exercise to filtered air or DE with a

22   $PM_{10}$ concentration of 100 $\mu g/m^3$. Eighteen hours after exposure to DE, the authors found significant

23   increases in neutrophil and mast cell numbers in bronchial tissue, as well as significant increases in

24   neutrophil numbers and IL-8 in bronchial lavage fluid compared with filtered air control. Similarly,

25   Stenfors et al. (2004) observed an increase in pulmonary inflammation (e.g., airways neutrophilia and an

26   increase in IL-8 in bronchoalveolar lavage fluid) among healthy adults 6 h following exposure to DE

27   ($PM_{10}$ average concentration 108 $\mu g/m^3$). It is interesting to note, however, that no such inflammatory

28   effects were observed in a group of mild asthmatic subject in the same study. The diesel exhaust-induced

29   neutrophil response in the airways of healthy subjects observed in these two studies (Behndig et al., 2006;

30   Stenfors et al., 2004) is qualitatively consistent with the findings of Ghio et al. (2000) who exposed

31   healthy subjects to Chapel Hill fine CAPs. Another study reported no change in inflammatory markers in

32   nasal lavage fluid 4 and 96 h following intranasal instillation of DEP (300 $\mu g$/nostril) in asthmatics and

33   healthy adults (Kongerud et al.). Pre-exposure of DE particles to ozone was not shown to have any effect

34   on the response. Although not a cross-over design, these findings suggest that exposure to DE particles

1   without the gaseous component of DE may have little effect on inflammatory responses in human

2   subjects. In a group of healthy volunteers, Bosson et al. (2007) demonstrated that exposure to ozone (2 h

3   at 0.2 ppm) may enhance the airway inflammatory response of DE relative to clean air (1-h exposure to

4   300 μg/m$^3$). Exposure to DE was conducted h after exposure to ozone, and resulted in an increase in the

5   percentage of neutrophils in induced sputum collected 18 h after DE exposure. In a subsequent study

6   using a similar protocol at the same concentrations, DE was shown to increase the inflammatory effects of

7   ozone exposure, demonstrated as an increase in neutrophil and macrophage numbers in bronchial wash

8   (Bosson et al., 2008).

9       These new studies strengthen the evidence of PM-induced pulmonary inflammation, with the

10  majority of the evidence associated with fine and thoracic coarse fractions. Several studies suggest that

11  metal components of PM$_{2.5}$ may be responsible for inflammatory responses (Ghio and Devlin, 2001;

12  Huang et al., 2003c; Schaumann et al., 2004). Others have reported inflammatory responses to DEP.

13  Different inflammatory responses were found with heat-sensitive and non-heat-sensitive fractions of

14  PM$_{10-2.5}$ (Alexis et al., 2006).

## 6.3.3.3. Toxicological Studies

15      The 2004 PM AQCD discussed numerous studies investigating pulmonary inflammation in

16  response to CAPs, ROFA, DEPs, metals and acid aerosols. A wide variety of responses was reported

17  depending on the type of PM and route of administration. In general, exposure to fly ash and metal PM by

18  intratracheal instillation resulted in notable pulmonary inflammation. In contrast, inhalation of sulfates

19  and acid aerosols had minimal if any effect on pulmonary inflammation. More recent animal toxicological

20  studies using CAPs, DE and other relevant PM types are summarized below.

### CAPs Studies

21      The 2004 PM AQCD found that fine CAPs exposure of rats and dogs at concentrations of

22  100-1000 ug/m$^3$ for 1-6 h/day and 1-3 days generally resulted in minimal to mild inflammation in healthy

23  animals. Somewhat enhanced inflammation was observed in a model of chronic bronchitis. Since the last

24  review, numerous studies have investigated inflammatory responses to fine and ultrafine CAPs in both

25  healthy and compromised animal models.

26      In one study of healthy animals, Sprague Dawley rats were exposed to CAPs for 4 h/day on 3

27  consecutive days in Fresno, CA, in fall 200 and winter 2001, (PM$_{2.5}$; mean mass concentration

28  190-847 μg/m$^3$) (Smith et al., 2003). The particle concentrator used in these studies was capable of

29  enhancing the concentration of ultrafine as well as fine particles. Immediately after exposure on the third

30  day, BALF was collected and analyzed for total cells and neutrophils. Statistically significant increases

were observed in numbers of neutrophils during the first week of the fall exposure period and in numbers

of total cells, neutrophils and macrophages during the first week of the winter exposure period. CAPs

concentrations were >800 μg/m$^3$ during both or those weeks.

Two studies were conducted using the CAPs in Boston. In a study by Godleski et al. (2002),

healthy Sprague Dawley rats were exposed for 5 h/day for 3 consecutive days to CAPs ranging in

concentration from 73.5-733.0 μg/m$^3$. BALF and lung tissue were collected for analysis 1 day later.

Neutrophilic inflammation was indicated by a statistically significant increase in percent neutrophils in

BALF. Microarray analysis of RNA from lung tissue and BAL cells demonstrated increased gene

expression of proinflammatory mediators, markers of vascular activation and enzymes involved in

organic chemical detoxification. This study overlapped in part with previously described studies by

Saldiva et al. (2002, discussed in the 2004 PM AQCD) and Batalha et al. (2002); see Section 6.2.4.3.). In

another study, healthy Sprague Dawley rats were exposed for 5 h to CAPs (mean mass concentration

1228 μg/m$^3$; 6/20-8/16/2002; (Rhoden et al., 2004). A statistically significant increase in BALF

neutrophils was observed 24-h following CAPs exposure. Histological analysis confirmed the influx of

inflammatory cells (Section 6.3.5.2.). Inflammation was accompanied by injury which is discussed in

Section 6.3.5.2.

Kodavanti et al. (2005) reported two sets of studies involving fine CAPs exposure during fall

months in RTP, NC. In the first study, SH rats were exposed to filtered air or CAPs (mean mass

concentration range 1,138-1,765 μg/m$^3$; less than 2.5 μm in size) for 4 h and analyzed 1-3 h later. No

increase in BALF inflammatory cells or other measured parameter was observed. In the second study, SH

and WKY rats were exposed to filtered air or CAPs (mean mass concentration range 144-2,758 μg/m$^3$;

less than 2.5 μm in size) for 4 h/day on 2 consecutive days and analyzed 1 day afterward. Differences in

baseline parameters were noted for the two rat strains since SH rats had greater numbers of BALF

neutrophils than WKY rats. Following the 2-day CAPs exposure, increased BALF neutrophils were

observed in the WKY rats but not in the SH rats compared with filtered air controls. Inflammation was

accompanied by an increase in a BALF marker of injury (see Section 6.3.5.2.).

Two CAPs studies of SH rats were conducted in the Netherlands. In the first study, SH rats were

exposed by nose-only inhalation to CAPs (ranging in concentration from 270-3660 μg/m$^3$and in size from

0.15-2.5 μm) from 3 different sites in the Netherlands (suburban, industrial and near-freeway) for 6 h

(Cassee et al., 2005). Increased numbers of neutrophils were observed in BALF 2 d post-exposure

compared to air controls. When CAPs exposure was used as a binary term, the relationship between CAPs

concentration and number of PMN in BALF was statistically significant. In contrast, Kooter et al. (2006)

reported no changes in markers of pulmonary inflammation measured 18 h after a 2-day exposure

(6 h/day) of SH rats to fine or fine+ultrafine CAPs from sites in the Netherlands (mean mass

1  concentration range 399-3613 and 269–556 μg/m$^3$, respectively; fine CAPs site in Bilthoven and

2  ultrafine+fine site in freeway tunnel in Hendrik Ido Ambacht).

3      Pulmonary inflammation was investigated in 2 studies using a rat model of pulmonary

4  hypertension (i.e., Sprague Dawley rats pre-treated with monocrotaline). In the first study, rats were

5  exposed to fine CAPs from an urban high traffic area in Taiwan (mean mass concentration of 371 μg/m$^3$)

6  (Lei et al., 2004b) for 6 h/day on 3 consecutive days and BALF was collected 2 days later. A statistically

7  significant increase in total cells and neutrophils was observed in BALF. Levels of TNFα and IL-6 in the

8  BALF were not altered by CAPs exposure. In the second study, rats were exposed to fine CAPs (mean

9  mass concentration 315.6 and 684.5 μg/m$^3$ for 6 and 4.5 h, respectively; Chung-Li area, Taiwan) during a

10  dust storm event occurring 3/18–3/19/2002 (Lei et al., 2004b). Only one animal served as control during

11  the 6 h exposure (from 2100–300 on the first exposure day) and the data were combined with 3 control

12  animals from the 4.5 h exposure (from 300–730) on the second exposure day. A statistically significant

13  increase in total cells and neutrophils in BALF occurred in both CAPs-exposed groups. In addition,

14  increases in BALF IL-6 and markers of injury (see Section 6.3.5.2.) were observed as a function of CAPs

15  exposure.

16      In summary, pulmonary inflammation was noted in all 3 studies involving multi-day exposure of

17  healthy rats to CAPs from different locations. No pulmonary inflammation was seen in one study of SH

18  rats exposed to CAPs for 4 h and analyzed 1-3 h later. In studies involving multi-day exposure of SH rats,

19  two demonstrated pulmonary inflammation while one did not. In the rat monocrotaline model of

20  pulmonary hypertension, both single-day and multi-day exposures to CAPs resulted in mild pulmonary

21  inflammation.

## On-Road Exposures

22      In a study by Elder et al. (2004a), old Fisher 344 rats (21 mo) were exposed to on-road highway

23  aerosols (particle concentration range 0.95–3.13×10$^5$ particles/cm$^3$; mass concentration estimated to be

24  37-106 μg/m$^3$; Interstate 90 between Rochester and Buffalo, NY) for 6 h on 1 or 3 consecutive days. No

25  increase in BALF inflammatory cells was observed 18 h post-exposure in any of the treatment groups.

## Urban Air Studies

26      To evaluate inflammatory responses to ambient particles from vehicles, Wistar rats were exposed to

27  ambient urban air from a high traffic site (concentration range 22-225 μg/m$^3$ PM$_{10}$; Porto Alegre, Brazil)

28  or to the same air which was filtered to remove the PM (Pereira et al., 2007). Concentrations of gases

29  were not reported. Compared with filtered air controls, a significant increase in total number of BALF

cells was observed 24 h following the 20 h continuous exposure but not following the 6 hours of exposure to unfiltered urban air.

## Diesel Exhaust Studies

The 2004 PM AQCD summarized findings of the 2002 EPA Diesel Document regarding the health effects of DE. Short-term inhalation exposure to low levels of DE results in the accumulation of DPM in lung tissue, pulmonary inflammation and alveolar macrophage aggregation and accumulation near the terminal bronchioles. More recent studies are summarized below.

Pulmonary inflammatory responses were investigated in C57BL/6 mice exposed to diesel engine emissions 7 h/d for 6 consecutive days (Harrod et al., 2003). Compared with controls, inflammatory cell counts in BALF were increased in mice exposed to the higher concentration of DE (1000 $\mu g/m^3$ DEP) but not in mice exposed to the lower concentration of DE (30 $\mu g/m^3$ DEP). Concentrations of gases present in the higher dose DE were reported to be 43 ppm $NO_X$, 20 ppm CO and 364 ppb $SO_2$.

In a second study evaluating DE effects on BALF inflammatory cells, no increases in numbers of neutrophils, lymphocytes or eosinophils were observed in BALB/c mice exposed by inhalation to 500 or 2000 $\mu g/m^3$ DEP for 4 h/d on 5 consecutive days (Stevens et al., 2008). Concentrations of gases reported in this study at the higher concentration were 4.2 ppm CO, 9.2 ppm NO, 1.1 ppm $NO_2$, and 0.2 ppm $SO_2$ for the higher concentration of DE. Transcriptional microarray analysis demonstrated upregulation of chemokine and inflammatory cytokine genes, as well as genes involved in growth and differentiation pathways, in response to the higher concentration of DE. No gene expression results were reported for the lower concentration of DE. Sensitization and challenge with ovalbumin significantly altered these findings (see Section 6.3.6.2.). These results demonstrate that changes in gene expression can occur in the absence of measurable pulmonary inflammation or injury markers (see Section 6.3.5.2.).

Li et al. (2007) exposed BALB/c and C57BL/6 mice to clean air or to low dose DE (DEP 100 $\mu g/m^3$) for 7 h/day and 5 days/week for 1, 4 and 8 weeks. Concentrations of gases in the DE were reported to be 3.5 ppm CO, 2.2 ppm $NO_2$ and less than 0.01 ppm $SO_2$. Analysis of BALF and histology of lung tissues was carried out at day 0 and after 1, 4 and 8 weeks of exposure. Total numbers of cells and macrophages in BALF were significantly increased in C57BL/6 mice but not in BALB/c mice after 1 week exposure to DE compared with 0 day controls. Neutrophils and lymphocytes were increased after 1 week exposure to DE in both strains compared with 0 day controls. Differences in BALF cytokines were also noted between the 2 strains after 1 week exposure to DE. No changes were observed by histological analysis. Pulmonary function and oxidative responses were also evaluated (Sections 6.3.2.3. and 6.3.4.2.) Long-term exposure responses are discussed in Sections 7.3.2.2, 7.3.3.2 and 7.3.4.1.

1      Healthy Fisher 344 rats and A/J mice were exposed to 30, 100, 300 and 1000 $\mu g/m^3$ DE PM by

2      whole body inhalation for 6 h/day, 7 days/week for either 1 week or 6 months in a study by Reed et al.

3      (2004). Concentrations of gases were reported to be from 2.0-45.3 ppm NO, 0.1-4.0 ppm $NO_2$,

4      1.5-29.8 ppm CO and 8-365 ppb for $SO_2$ in these exposures. One week of exposure resulted in no

5      measurable effects on pulmonary inflammation. Long-term exposure responses are discussed in Section

6      7.3.3.2.

7      In a study by Wong et al. (2003) and Witten et al. (2005), Fisher 344/NH rats were exposed

8      nose-only to filtered room air or to DE at concentrations of 35.3 $\mu g/m^3$ and 669.3 $\mu g/m^3$ DEP (particle size

9      range 7.2-294.3 nm) for 4 h/day and 5 days/week for 3 weeks. Gases associated with the high dose

10     exposure were reported to be 3.59 ppm NO, 3.69 ppm $NO_X$, 0.1 ppm $NO_2$, 2.95 ppm CO, 518.96 ppm

11     carbon dioxide and 0.031 ppm total hydrocarbon. The focus of this study was on the possible role of

12     neurogenic inflammation in mediating responses to DE. Neurogenic inflammation is characterized by

13     both the influx of inflammatory cells and plasma extravasation into the lungs following the release of

14     neuropeptides from bronchopulmonary C-fibers. Pulmonary inflammation was evaluated by histological

15     analysis of lung tissue at the end of the 3 week exposure period. Following high, but not low,

16     dose-exposure to DE, a large number of alveolar macrophages was found in the lungs. Small black

17     particles, presumably DEP, were found in the cytoplasm of these alveolar macrophages. Perivascular

18     cuffing consisting of mononuclear cells was also observed in high dose-exposed animals. Influx of

19     neutrophils or eosinophils was not seen although mast cell number was increased in high-dose exposed

20     animals. Pulmonary plasma extravasation was measured by the $^{99m}$Technecium-albumin technique and

21     found to be dose-dependently increased in the bronchi and lung parenchyma. Alveolar edema was also

22     observed by histopathology in high dose-exposed animals. A significant decrease in Substance P content

23     in lung tissue was reported in DE-exposed rats. These responses initially suggested that DE resulted in

24     stimulation of C-fibers and activation of a local neuron reflex resulting in the repeated release of the

25     stored neuropeptide Substance P. Subsequent experiments were conducted using capsaicin pretreatment,

26     which inhibits neurogenic inflammation by activating C-fibers and causing the depletion of neuropeptide

27     stores. Pretreatment with capsaicin was found to reduce the influx of inflammatory cells but not plasma

28     extravasation in response to DE. Hence, DE is unlikely to act through bronchopulmonary C-fibers to

29     cause neurogenic inflammation in this model, although there may be a different role for

30     bronchopulmonary C-fibers in mediating the inflammatory cell influx.

31     Stimulation of bronchopulmonary C-fibers can result in activation of both local and CNS reflexes

32     through vagal parasympathetic pathways. McQueen et al. (2007) investigated the role of vagally-mediated

33     pathways in acute inflammatory responses to DEP. A statistically significant increase in BAL neutrophils

34     was observed 6 h after treatment of anesthetized Wistar rats with 500 $\mu g$ DEP (SRM2975) by

1    intratracheal instillation. This response was blocked by sectioning the vagus nerves or pretreatment with

2    atropine (McQueen et al., 2007). Similarly, atropine treatment blocked the increase in BAL neutrophils

3    seen 6 h after DEP exposure in conscious Wistar rats. These results provide evidence for the involvement

4    of a pulmonary vagal reflex in the inflammatory response to DEP.

5        In summary, several studies demonstrate that short-term inhalation exposure to DE

6    (100-1000 $\mu g/m^3$ DEP) causes pulmonary inflammation in rodents. No attempt was made in these studies

7    to determine whether the responses were due to PM components or to gaseous components. However, PM

8    from DE was found to be capable of inducing an inflammatory response, as demonstrated by the one

9    intratracheal instillation study described above. Evidence was presented suggesting that DEP may act

10   through bronchopulmonary C-fibers to stimulate pulmonary inflammation.

### Gasoline Emissions and Road Dust

11        Healthy male Swiss mice were exposed to gasoline exhaust (635 $\mu g/m^3$ PM and associated gases)

12   or filtered air for 15 min/day for 7, 14, and 21 days (Sureshkumar et al., 2005). BALF fluid was collected

13   for analysis 1-h after the last exposure. Histological analysis was also carried out at 7, 14, and 21 days.

14   The number of leukocytes in BALF fluid was increased after exposure to gasoline exhaust but this

15   increase did not achieve statistical significance. However, levels of the pro-inflammatory cytokines TNFα

16   and IL-6 were significantly increased in BALF following 14 and 21 days of exposure. Furthermore,

17   inflammatory cell infiltrate in the peribronchiolar and alveolar regions were observed by histology.

18   Evidence of lung injury was also found (see Section 6.3.5.2.). In this study, BALF analysis of

19   inflammatory cells was a less sensitive indicator of pulmonary inflammation than BALF analysis of

20   cytokines and histological analysis of lung tissue. Unfortunately results of this study cannot entirely be

21   attributed to the presence of PM in the gasoline exhaust since 0.11 $mg/m^3$ $SO_X$, 0.49 mg of $NO_X$ and 18.7

22   ppm of CO were also present during exposure.

23        Using ApoE$^{-/-}$ mice on a high-fat diet, Campen et al. (2006) studied the impact of inhaled gasoline

24   emissions and road dust (6 h/day × 3 day) on pulmonary inflammation. Moreover, the investigators used a

25   high efficiency particle filter to compare the whole exhaust with an atmosphere containing only the

26   gaseous components. For gasoline emissions, the PM-containing atmosphere (PM mean concentration

27   61 $\mu g/m^3$; $NO_X$ mean concentration 18.8 ppm; CO mean concentration 80 ppm) failed to increase

28   numbers of inflammatory cells in BALF collected 18 h after the last exposure. However, a statistically

29   significant increase in total cells and macrophages was observed in response to resuspended road dust

30   ($PM_{2.5}$) at 3500 $\mu g/m^3$, but not at 500 $\mu g/m^3$.

### *Fine and Ultrafine Carbon*

In a study by Elder et al. (2004b), pulmonary inflammation was investigated in two compromised, aged animal models (11–14 mo. SH and 23 mo. Fischer 344) exposed by inhalation to ultrafine carbon black (count median diameter = 36 nm) at a relevant concentration (150 μg/m$^3$). No changes in BALF cells were seen 24-h post-exposure in either model.

In a study by Gilmour et al. (2004c), adult Wistar rats were exposed for 7 h to fine and ultrafine carbon black particles (mean mass concentration 1400 and 1660 μg/m$^3$ for fine and ultrafine CB, respectively; mean number concentration $3.8×10^3$ and $5.2×10^4$ particles/cm$^3$, respectively; count median aerodynamic diameter 114 nm and 268 nm, respectively). Both treatments resulted in increased BAL neutrophils 16 h post-exposure, with the ultrafine particles having the greater response. Ultrafine particles also increased total BALF leukocytes and macrophage inflammatory protein-2 mRNA in BALF cells. Although these exposures may not be relevant to ambient exposures, this study demonstrated the greater propensity of ultrafine carbon black particles to cause a proinflammatory response compared with fine carbon black particles.

### *Iron-Soot*

In a study by Last et al. (2004), BALB/c mice were exposed to 250 μg/m$^3$ laboratory-generated iron-soot (size range 80-110 nm; about 200 μg/m$^3$ as soot) for 4 h/day and 3 days/week for 2 weeks. BALF was collected 1-h after the last exposure and analyzed for total cells. No increase in total cell number was observed following iron-soot exposure. Other findings of this study are described in Sections 6.3.2.3. and 6.3.5.2.

## 6.3.4. Oxidative Responses

The results of a small number of human clinical and toxicological studies presented in the 2004 PM AQCD provided some initial evidence of an association between exposure to PM and pulmonary oxidative stress. Recent human clinical studies have provided support to previous findings of an increase in markers of pulmonary oxidative stress following exposure to diesel exhaust, and one new study has observed a similar effect following controlled exposure to wood smoke. New findings from toxicological studies also provide further evidence that oxidative species are involved in PM-mediated effects. No epidemiological studies have evaluated the association between PM concentration and pulmonary oxidative response.

## 6.3.4.1. Human Clinical Studies

1    Two studies cited in the 2004 PM AQCD observed diesel-induced effects on airway oxidative

2    response following controlled human exposures (Blomberg et al., 1998; Nightingale et al., 2000). More

3    recently, Schaumann et al. (2004) demonstrated an increased oxidant radical generation of BAL cells

4    following instillation of urban particles compared with instillation of particles collected in a rural area.

5    The authors suggested that this difference was likely due to the greater concentration of transition metals

6    found in the urban particles. More recent studies have also evaluated the effect of exposure to WS and DE

7    on airway oxidative response in human subjects. Barregard et al. (2008) observed a significant increase in

8    malondialdehyde levels in breath condensate of healthy volunteers (n = 13) immediately following and 20

9    hours after a 4 hour exposure to WS (240-280 $\mu g/m^3$). Pourazar et al. (2005) exposed 15 adults (11 males

10   and 4 females) for 1-h to air or DE ($PM_{10}$ concentration 300 $\mu g/m^3$) in a controlled cross-over study.

11   Bronchoscopy with airway biopsy was performed 6 hours after exposure. The expression of NF-κB, AP-1

12   (c-jun and c-fos), p38, and JNK in bronchial epithelium was quantified using immunohistochemical

13   staining. DE was observed to significantly increase nuclear translocation of NF-κB, AP-1, phosphorylated

14   p38, and phosphorylated JNK; however, the findings of this study require confirmation with more

15   quantitative methods such as Western blot analysis. The observed activation of redox-sensitive

16   transcription factors by DE may result in the induction of proinflammatory cytokines. There is some

17   evidence to suggest that this bronchial response to DE is mediated through the epidermal growth factor

18   receptor signaling pathway (Pourazar et al., 2008). Behndig et al. (2006) evaluated the upregulation of

19   endogenous antioxidant defenses following exposure to DE (100 $\mu g/m^3$ $PM_{10}$) in a group of 15 healthy

20   adults. Increases in urate and reduced glutathione were observed in alveolar lavage 18 hours after

21   exposure; however, no changes in urate or glutathione levels were observed in bronchial lavage. Taken

22   together, these studies suggest that short-term exposure to PM at near ambient levels may produce mild

23   oxidative stress in the lung. Limited data suggest that proximal and distal lung regions may be subject to

24   different degrees of oxidative stress during exposures to different pollutant particles.

## 6.3.4.2. Toxicological Studies

25   The 2004 PM AQCD reported one study which provided evidence that ROS were involved in

26   PM-mediated responses. This particular study used pre-treatment with the antioxidant DMTU to block the

27   neutrophilic response to ROFA. More recently, several studies evaluated the effects of PM exposure on

28   pulmonary oxidative stress. Oxidative stress can be directly determined by measuring ROS or oxidation

29   products of lipids and proteins. An indirect assay involves measurement of the enzyme heme oxygenase-1

30   (HO-1) or of the antioxidant enzymes superoxide dismutase or catalase, all of which can be induced by

1   oxidative stress. Antioxidant interventions which inhibit or prevent responses are a further indirect

2   measure of oxidative stress playing a role in the pathway of interest.

3        Gurgueira et al. (2002) measured oxidative stress in Sprague Dawley rats immediately following a

4   5-h CAPs exposure ($PM_{2.5}$; mean mass concentration range 99.6–957.5 μg/m$^3$; Boston, MA) and reported

5   increased in situ chemiluminescence (CL) in lungs of CAPs-exposed animals. CL evaluated after CAPs

6   exposure durations of 3 h was also increased but did not achieve statistical significance compared to the

7   filtered air group. When animals were allowed to recover for 24-h following the 5 h CAPs exposure, CL

8   levels returned to control values. Interestingly, a decrease in lung CL was observed in rats breathing

9   filtered air for 3 days compared with rats breathing room air for the same duration. Exposure to CAPs for

10  3 and 5 h also increased lung wet/dry ratios, indicating the presence of mild edema. To compare potential

11  particle-induced differences in in situ CL, rats were exposed to ROFA (1.7 mg/m$^3$ for 30 min) or carbon

12  black (170 μg/m$^3$ for 5 h). Only the ROFA-treated animals exhibited increased CL in lung tissue.

13  Additionally, levels of antioxidant enzymes in the lung (MnSOD and catalase) were increased in

14  CAPs-exposed rats. A CAPs-associated increase in CL was also seen in the heart (see Section 6.2.9.3.) but

15  not the liver.

16       In a similar study, Rhoden et al. (2004) exposed Sprague Dawley rats for 5 h to CAPs from Boston

17  (mean mass concentration 1228 μg/m$^3$) or to filtered air. Significant increases in TBARS (a measure of

18  lipid peroxidation) and protein carbonyl content (a measure of protein oxidation) were observed 24-h

19  post-exposure to CAPs. Pretreatment with the thiol antioxidant N-acetylcysteine (NAC) (50 mg/kg ip) 1-h

20  prior to exposure prevented not only the lipid and protein oxidation observed in response to CAPs, but

21  also the increase in BALF neutrophils and and pulmonary edema in this model (see Sections 6.3.3.3. and

22  6.3.5.2.). Results of this study demonstrate the key role played by oxidative stress in these

23  CAPs-mediated effects.

24       Kooter et al. (2006) reported an increase in HO-1 in BALF and lung tissue measured 18 h after a

25  2-day exposure (6 h/day) of SH rats to fine or fine+ultrafine CAPs (mean mass concentration range

26  399-3613 and 269–556 μg/m$^3$, respectively; fine CAPs site in Bilthoven and ultrafine+fine site in freeway

27  tunnel in Hendrik Ido Ambacht). This occurred in the absence of any measurable pulmonary

28  inflammation (see Section 6.3.3.3.).

29       To evaluate oxidative stress responses to ambient particles from vehicles, Wistar rats were exposed

30  to ambient urban air from a high traffic site (concentration range 22-225 μg/m$^3$ $PM_{10}$; Porto Alegre,

31  Brazil) or to the same air which was filtered to remove the PM (Pereira et al., 2007). Several exposures

32  regimens were carried out: 6 and 20 h continuous exposures or to intermittent exposures of 5 h/day for 4

33  consecutive days. A significant increase in lipid peroxidation (measured as malondialdehyde) was seen in

1 lung tissue immediately following the 20 h continuous exposure but not following the 6 h exposure or the

2 intermittent exposures.

3       Li et al. (2007) exposed BALB/c and C56BL/6 mice to clean air or to low dose DE (DEP

4 100 μg/m$^3$) for 7 h/day and 5 days/week for 1, 4 and 8 weeks. Average gas concentrations were reported

5 to be 3.5 ppm CO, 2.2 ppm NO$_2$, and less than 0.01 ppm SO$_2$. HO-1 mRNA and protein were increased in

6 lung tissues of both mouse strains after 1 week of DE exposure. In addition, changes in airways

7 hyperresponsiveness and BAL cells and cytokines were observed (see Sections 6.3.2.3. and 6.3.3.3.).

8 Pretreatment with the thiol antioxidant NAC (320 mg/kg) IP on days 1-5 of DE exposure greatly

9 attenuated the increased airway hyperresponsiveness and increases in BAL inflammatory cells seen after

10 1 week of DE exposure. Long-term responses are discussed in Sections 7.3.2.2, 7.3.3.2 and 7.3.4.1.

11       A study by Whitekus et al. (2002) investigated the adjuvant effects of DEP in an allergic animal

12 model and is discussed in detail below (see Section 6.3.6.2.). Intervention with the thiol antioxidants

13 bucillamine and NAC inhibited the increase in allergen-specific IgE and IgG1 as well as the increase in

14 protein carbonyl and lipid hydroperoxides in the lung following DE exposure.

# 6.3.5. Pulmonary Injury

15       The 2004 PM AQCD presented evidence from several toxicological studies of small PM-induced

16 increases in markers of pulmonary injury including thickening of alveolar walls and increases in

17 bronchoalveolar lavage fluid protein. These findings are consistent with the results of recent toxicological

18 studies demonstrating mild pulmonary injury accompanying inflammatory responses to CAPs. One recent

19 epidemiologic study has also observed a positive association between PM and urinary concentrations of

20 lung Clara cell protein.

## 6.3.5.1. Epidemiologic Studies

21       One epidemiologic study examined biomarkers of pulmonary injury. The mean concentration data

22 from this study are characterized in Table 6-7. Timonen et al. (2004) enrolled subjects with coronary heart

23 disease in Amsterdam (n = 37), Erfurt, Germany (n = 47) and Helsinki (n = 47) to study daily variation in

24 PM and urinary concentrations of lung Clara cell protein (CC16). No associations were seen between the

25 particle number concentration of the smallest particles (NC$_{0.01-0.1}$) and CC16. Significant associations with

26 NC$_{0.1-1}$ and PM$_{2.5}$ (which were strongly correlated with each other [r = 0.8]) were seen only for Helsinki

27 subjects: same day, lag 3 and 5-day mean NC$_{0.1-1}$ increases of 1000/cm$^3$ were associated with increases in

28 ln (CC16/creatinine) of 15.5% (95% CI: 0.001-30.9), 17.4% (95% CI: 3.4-31.4), and 43.2% (95% CI:

29 17.4-69.0), respectively. Similar associations were seen for 10 μg/m$^3$ increases in PM$_{2.5}$: lag 0 and 5-day

1 mean $PM_{2.5}$ were associated with increases in ln (CC16/creatinine) of 23.3% (95% CI: 6.3-40.3) and

2 38.8% (95% CI: 15.8-61.8), respectively.

## 6.3.5.2. Toxicological Studies

3 The 2004 PM AQCD reported mild increases in BALF protein, a marker of pulmonary injury, in

4 several studies involving inhalation exposure to CAPs. In addition, histopathological analysis

5 demonstrated that the bronchoalveolar junction was the site of the greatest inflammation. Low level

6 exposure to DE was associated with Type 2 cell proliferation and thickening of alveolar walls near

7 alveolar macrophages according to the 2002 EPA Diesel Document. In addition, intratracheal instillation

8 of fly ash and metal-containing PM generally caused pulmonary injury as measured by increases in BALF

9 protein, LDH and albumin. Proliferation of bronchiolar epithelium was also noted. More recent studies of

10 BALF markers of pulmonary injury and histopathological analysis of lung tissue are summarized below.

### *BALF Markers of Pulmonary Injury and Increased Permeability*

11 Kodavanti et al. (2005) exposed SH and WKY rats to filtered air or CAPs from RTP, NC (mean

12 mass concentration range 144-2,758 $\mu g/m^3$; less than 2.5 $\mu m$ in size) for 4 h/day on 2 consecutive days

13 and analyzed 1 day afterward. Differences in baseline parameters were noted for the two rat strains since

14 SH rats had greater levels of protein and lower levels of levels of LDH, NAG, ascorbate and uric acid in

15 the BALF than WKY rats. CAPs exposure resulted in increased levels of GGT in BALF (a marker of

16 epithelial injury) of SH rats but not WKY rats compared with filtered air controls. Injury was

17 accompanied by inflammation (see Section 6.3.3.3.).

18 In a study by Cassee et al. (2005), SH rats were exposed by nose-only inhalation to CAPs (ranging

19 in concentration from 270-3660 $\mu g/m^3$ and in size from 0.15-2.5 um) from 3 different sites in the

20 Netherlands (suburban, industrial and near-freeway) for 6 h. The pulmonary injury marker Clara Cell 16

21 protein (CC16) was increased in BALF following CAPs exposure. Inflammation was also observed (see

22 Section 6.3.3.3.).

23 Gurgueira et al. (2002) exposed Sprague Dawley rats to CAPs ($PM_{2.5}$; mean mass concentration

24 range 99.6–957.5 $\mu g/m^3$; Boston, MA) and reported a small but statistically significant increase in lung

25 wet/dry ratios after 3 and 5 h of exposure, indicating the presence of mild edema. This response was

26 accompanied by increased oxidative stress as measured by in situ chemiluminescence (CL) (see Section

27 6.3.4.2). In a similar study, Rhoden et al. (2004) exposed Sprague Dawley rats for 5 h to CAPs from

28 Boston (mean mass concentration 1228 $\mu g/m^3$) or to filtered air. An increase in the wet/dry ratio (a

29 measure of edema) was observed 24-h following CAPs exposure which was diminished by pre-treatment

30 of the antioxidant N-acetylcysteine (see Section 6.3.4.2).

1    Pulmonary injury was investigated in 2 studies using a rat model of pulmonary hypertension

2    (Sprague Dawley rats pre-treated with monocrotaline; (Lei et al., 2004b). In the first study, rats were

3    exposed to CAPs from an urban high traffic area in Taiwan (mean mass concentration 371 $\mu g/m^3$) for 6

4    h/day on 3 consecutive days and BALF was collected 2 days later. A significant increase in BALF LDH

5    was observed in response to CAPs. In the second study, rats were exposed to ultrafine CAPs (mean mass

6    concentration 315.6 and 684.5 $\mu g/m^3$ for 6 and 4.5 h, respectively; Chung-Li area, Taiwan) during a dust

7    storm event occurring 3/18–3/19/2002 (Lei et al., 2004a). Only one animal served as control during the 6

8    h exposure (from 2100–300 on the first exposure day) and the data were combined with 3 control animals

9    from the 4.5 h exposure (from 300–730) on the second exposure day. Increases in BALF LDH and protein

10   were observed as a function of CAPs exposure. Pulmonary inflammation was observed in both of these

11   studies (see Section 6.3.3.3.).

12   In a study evaluating the effects of DE, no changes were observed in BALF protein and LDH in

13   BALB/c mice exposed by inhalation to concentrations of 50 and 2000 $\mu g/m^3$ DEP for 4 h/d on 5

14   consecutive days (Stevens et al., 2008). Concentrations of gases reported at the higher concentration of

15   DE were 4.2 ppm CO, 9.2 ppm NO, 1.1 ppm $NO_2$, and 0.2 ppm $SO_2$. Changes in gene expression were

16   measured in the higher exposure group. This study demonstrates that changes in gene expression can

17   occur in the absence of measurable markers of injury or pulmonary inflammation (see Section 6.3.3.3.)

18   In a study by Wong et al. (2003) and Witten et al. (2005), Fisher 344/NH rats were exposed

19   nose-only to filtered room air or to DE at concentrations of 35.3 $\mu g/m^3$ and 669.3 $\mu g/m^3$ DEP (particle size

20   range 7.2-294.3 nm) for 4 h/day and 5 days/week for 3 weeks. Gases associated with the high dose

21   exposure were reported to be 3.59 ppm NO, 3.69 ppm $NO_X$, 0.1 ppm $NO_2$, 2.95 ppm CO, 518.96 ppm

22   carbon dioxide and 0.031 ppm total hydrocarbon. The focus of this study was on the possible role of

23   neurogenic inflammation in mediating responses to DE. Neurogenic inflammation is characterized by

24   both the influx of inflammatory cells and plasma extravasation into the lungs following the release of

25   neuropeptides such as Substance P from bronchopulmonary C-fibers. Pulmonary plasma extravasation

26   was measured by the [99m]Technecium-albumin technique and found to be dose-dependently increased in

27   the bronchi and lung parenchyma. Alveolar edema was also observed by histological analysis of lung

28   tissue in high dose-exposed animals. A significant decrease in Substance P content in lung tissue was

29   reported in DE-exposed rats. These responses initially suggested that DE resulted in neurogenic

30   inflammation through the stimulation of bronchopulmonary C-fibers and activation of a local neuron

31   reflex resulting in the repeated release of the stored neuropeptide Substance P. Subsequent experiments

32   were conducted using capsaicin pretreatment, which inhibits neurogenic inflammation by activating

33   C-fibers and causing the depletion of neuropeptide stores. Pretreatment with capsaicin did not reduce

34   plasma extravasation following DE exposure. Hence, DE is unlikely to act through bronchopulmonary

1    C-fibers to cause neurogenic inflammation in this model. Inflammatory responses measured in this study

2    are discussed in Section 6.3.3.3.

3         Healthy male Swiss mice were exposed to gasoline exhaust (635 µg/m$^3$ PM and associated gases)

4    or filtered air for 15 min/day for 7, 14, and 21 days (Sureshkumar et al., 2005). BALF fluid was collected

5    for analysis 1-h after the last exposure. Statistically significant increases in BALF markers of lung injury,

6    alkaline phosphatase, gamma-glutamyl transferase and LDH, were observed at all time points studied.

7    Alveolar edema was noted following 14 and 21 d of exposure. Other findings of this study including

8    inflammation and histopathology are discussed in Section 6.3.3.3. Results of this study cannot entirely be

9    attributed to the presence of PM in the gasoline exhaust since 0.11 mg/m$^3$ SO$_X$, 0.49 mg of NO$_X$ and 18.7

10   ppm of CO were also present during exposure.

## Histopathology

11        Histopathological changes were demonstrated in Sprague Dawley rats exposed for 5 h to CAPs

12   from Boston (mean mass concentration 1228 µg/m$^3$; (Rhoden et al., 2004)) compared with air-exposed

13   controls. Slight bronchiolar inflammation and thickened vessels at the bronchiole were observed 24-h

14   post-exposure. These findings are consistent with the influx of polymorphonuclear leukocytes observed in

15   BALF 24-h post-exposure to CAPs (see Section 6.3.3.3.).

16        An interesting study demonstrating histopathological responses to PM in neonatal rats was reported

17   by Pinkerton et al. (Pinkerton et al., 2004). Rat pups (10 day old) were exposed to soot and iron particles

18   (mean mass concentration of 243 µg/m$^3$; iron concentration 96 µg/m$^3$; size range 10-50 nm) for 6 h/day

19   on 3 consecutive days. Cell proliferation in different lung regions was evaluated following

20   bromodeoxyuridine injection 2-h prior to necropsy. The rate of cell proliferation in the proximal alveolar

21   region (immediately beyond the terminal bronchioles) was significantly reduced in iron-soot exposed

22   animals compared to controls. This was a region-specific response since the rate of cell proliferation was

23   not altered in the terminal bronchioles or the general lung parenchyma. However, alveolar septation and

24   growth was not found to be altered by iron-soot exposure. The authors suggest the possibility of greater

25   susceptibility to air pollution during the critical postnatal lung development period which occurs in

26   animals and humans and that neonatal exposure to PM may contribute to impaired lung growth seen in

27   children.

28        In another study investigating the effects of iron-soot, healthy adult BALB/c mice were exposed to

29   250 µg/m$^3$ laboratory-generated iron-soot (size range 80-110 nm; about 200 µg/m$^3$ as soot) for 4 h/day

30   and 3 days/week for 2 weeks (Last et al., 2004). Analysis of airway collagen content was conducted by

31   histology and by biochemical analysis of microdissected airways. No increases in airway collagen content

32   were found by either method in mice exposed to iron-soot for 2 weeks. Furthermore, no goblet cells were

1 observed in airways of air or iron-soot exposed animals. Other findings of this study are described in

2 Sections 6.3.23.3. and 6.3.3.3.

3      Another study demonstrated histopathological responses to gasoline exhaust in healthy male Swiss

4 mice exposed to gasoline exhaust (635 $\mu g/m^3$ PM and associated gases) or filtered air for 15 min/day for

5 7, 14, and 21 days (Sureshkumar et al., 2005). Histological observations showed inflammatory cell

6 infiltrate in the peribronchiolar and alveolar region, alveolar edema and thickened alveolar septa at 14 and

7 21 days postexposure. Levels of pro-inflammatory cytokines and marker enzymes of lung damage were

8 also increased in BALF. The numbers of inflammatory cells in BALF was increased but not significantly,

9 demonstrating that BALF analysis of inflammatory cells was a less sensitive indicator of pulmonary

10 inflammation in this study than histophathological analysis. Results of this study cannot entirely be

11 attributed to the presence of PM in the gasoline exhaust since 0.11 mg/m$^3$ SO$_X$, 0.49 mg of NO$_X$ and 18.7

12 ppm of CO were also present during exposure.

13      In a study by Wong et al. (2003) and Witten et al. (Witten et al.), Fisher 344/NH rats were exposed

14 nose-only to filtered room air or to DE at concentrations of 35.3 $\mu g/m^3$and 669.3 $\mu g/m^3$ DEP (particle size

15 range 7.2-294.3 nm) for 4 h/day and 5 days/week for 3 weeks. Gases associated with the high dose

16 exposure were reported to be 3.59 ppm nitric oxide, 3.69 ppm NO$_X$, 0.1 ppm NO$_2$, 2.95 ppm CO, 518.96

17 ppm CO$_2$ and 0.031 ppm total hydrocarbon. Pulmonary inflammation was evaluated by histopathological

18 analysis of lung tissue. Following high, but not low, dose-exposure to DE, a large number of alveolar

19 macrophages was found in the lungs. Small black particles, presumably DEP, were found in the

20 cytoplasm of these alveolar macrophages. Perivascular cuffing consisting of mononuclear cells was also

21 observed in high dose-exposed animals. Influx of neutrophils or eosinophils was not seen although mast

22 cell number was increased.

## Relative Toxicity of PM Size Fractions

### Ambient PM Studies

23      A recently undertaken multinational project entitled "Chemical and biological characterization of

24 ambient thoracic coarse (PM$_{10-2.5}$), fine (PM$_{2.5-0.2}$), and ultrafine particles (PM$_{0.2}$) for human health risk

25 assessment in Europe" (PAMCHAR) takes a systematic approach to expanding the present knowledge

26 about the physiochemical and toxicological effects of these three PM size fractions. Six European cities

27 were selected that represented contrasting ambient PM profiles: Helsinki, Duisburg, Prague, Amsterdam,

28 Barcelona, and Athens. For PM collected at all sites, PM$_{10-2.5}$ induced the greatest pulmonary effects in

29 C57Bl/6J mice intratracheally instilled with 1, 3, or 10 mg/kg of particles (Happo et al., 2007; 2006).

30 Dose-response relationships in BALF parameters measured 24-h post-instillation, including BALF cell

31 number and protein, were observed for all sites following PM$_{10-2.5}$ instillation and neutrophils were the

1    predominant cell type (Happo et al., 2007). Prague $PM_{10-2.5}$ exposure resulted in decreased macrophages

2    in BALF at 12 h and Amsterdam, Barcelona, and Athens $PM_{10-2.5}$ induced lymphoplasmacytic cells in

3    BALF (Happo et al., 2007). No inflammatory responses were observed for ultrafine PM measured 12-h

4    after exposure. Protein was elevated for $PM_{10-2.5}$ at all locations with the 10 mg/kg dose; Athens ultrafine

5    PM induced protein release only at the two lowest doses 12 h post-exposure. For TNF-α and IL-6, the

6    greatest response was observed with $PM_{10-2.5}$ 4 h following exposure (Happo et al., 2007). Ultrafine

7    Duisburg PM exposure resulted in elevated TNF-α for the 1 and 3 mg/kg doses. Only the Helsinki sample

8    appeared to induce the same level of IL-6 release for $PM_{10-2.5}$ and $PM_{0.2}$ at 10 mg/kg, albeit the collection

9    times differed. In vitro TNF-α and IL-6 responses did not always reflect in vivo effects (Table 6-8), as the

10   Duisburg $PM_{10-2.5}$ sample was the most potent in vivo compared to the other sites and elicited much lower

11   cytokine release compared to other cities (except Helsinki) in vitro (Happo et al., 2007; Jalava et al.,

12   2006).

13   Helsinki PM was collected in the spring and generally had the lowest in vivo and in vitro activity

14   for $PM_{10-2.5}$ compared to the other cities (Happo et al., 2007; Jalava et al., 2007). Spring-time samples

15   were collected because episodes of resuspended road dust occur frequently during this season (Pennanen

16   et al., 2007). There was a high correlation between EC content in $PM_{2.5}$ and $PM_{10-2.5}$, indicating that traffic

17   impacted both size fractions (Sillanpaa et al., 2005). Duisburg PM collected in autumn had the greatest

18   amounts of Mn and Zn compared to PM samples from other locations (Pennanen et al., 2007). Metals

19   industries in Duisburg are likely contributors to the observed PM metals concentrations. For the Prague

20   winter PM samples, the As content was the higher than any other location (Pennanen et al., 2007). Prague

21   also had the highest PAH levels in all three size fractions, possibly attributable to stable atmosphere

22   conditions and incomplete combustion of coal and biomass in residential heating (Pennanen et al., 2007).

23   High levels of ammonium and nitrate in PM samples from Amsterdam suggest traffic as a large source of

24   air pollution (Pennanen et al., 2007). Approximately one-third of $PM_{10-2.5}$ mass from Amsterdam was

25   comprised of sea salt (Sillanpaa et al., 2006), double that of any other city. In Barcelona and Athens, high

26   calcium or $Ca^{2+}$ contents in spring and summer $PM_{2.5}$ and $PM_{10-2.5}$ are indicative of resuspended

27   soil-derived particles (Pennanen et al., 2007).

**Table 6-8.** PAMCHAR $PM_{10-2.5}$ inflammation results with ambient PM.

| City and Season | In vivo[a] (mg/kg) | | | | | | In vitro[b] (µg/ml) | | |
|---|---|---|---|---|---|---|---|---|---|
| | BALF protein | BALF TNF-α | BALF IL-6 | BALF KC | BALF PMN | BALF AM | TNF-α | IL-6 | MIP-2 |
| Helsinki spring | +10 | +10 | +10 | +3,10 | +10 | – | +150,300 | +150,300 | +150,300 |
| Duisburg autumn | +10 | +10 | +10 | +10 | +10 | – | +150,300 | +150,300 | +300 |
| Prague winter | +10 | +3,10 | +10 | +3,10 | +10 | +10 | +150,300 | +150,300 | +150,300 |
| Amsterdam winter | +10 | +10 | +10 | +10 | +10 | – | +150 | +150,300 | +150,300 |
| Barcelona spring | +10 | +10 | +3,10 | +10 | +10 | – | +150,300 | +150,300 | +150,300 |
| Athens summer | +10 | +3,10 | +3,10 | +3,10 | +10 | – | +150,300 | +150,300 | +150,300 |

[a]Source: Happo et al. (2007); 2 cells used for in vitro study were RAW264.7
[b]Source: Jalava et al. (2007); + indicates increased response and numbers that follow indicate at which dose the response was observed

1    Another study employed Duisburg PM. In contrast to the PAMCHAR study where animals were

2  administered PM suspended in pathogen-free water (Happo et al., 2007), animals received PM via

3  intratracheal instillation suspended in saline at a dose of 320 µg (Schins and Knaapen, 2007). In female

4  Wistar rats, neutrophils in BALF were significantly elevated for $PM_{10-2.5}$ from Duisburg and Borken

5  (Table 6-9), albeit the percent of neutrophils with the $PM_{10-2.5}$ from Borken was nearly double that of

6  Duisburg (Schins et al., 2004). The responses with $PM_{2.5}$ were much smaller. When these $PM_{10-2.5}$ particles

7  were introduced into whole blood to determine overall inflammogenic capacity, IL-8 and TNF-α were

8  released in greater quantities than in response to fine PM. Furthermore, $PM_{10-2.5}$ from Borken induced

9  higher cytokine responses than Duisburg $PM_{10-2.5}$.

10    An in vivo study conducted with SH rats that employed $PM_{10-2.5}$ and $PM_{2.5}$ from six different

11  European locations with varying traffic densities (3 or 10 mg/kg via intratracheal instillation; ultrafine PM

12  was not collected) reported that $PM_{10-2.5}$ generally induced greater responses than $PM_{2.5}$ (Gerlofs-Nijland

13  et al., 2007). $PM_{10-2.5}$ from a location with high traffic influence in Munich, Germany demonstrated the

14  greatest response in LDH activity, BALF protein, total cells, neutrophils, and lymphocytes 24-h

15  post-instillation (Gerlofs-Nijland et al., 2007). $PM_{10-2.5}$ collected from a low traffic site in Munich induced

16  the greatest cytokine response for TNF-α and MIP-2. Although some correlations were observed between

17  $PM_{10-2.5}$ components (Ba and Cu) and BALF parameters, they were largely driven by one location

18  (Gerlofs-Nijland et al., 2007).

19    In an in vivo study that employed ambient PM collected in fall 1996 from Research Triangle Park

20  (RTP), NC, neutrophilic influx was observed in BALF of female CD1 mice 18-h post-instillation (10, 50

21  or 100 µg) of coarse PM (3.5–20 µm), although a dose-response relationship was not evident (Dick et al.,

22  2003a). Only the two highest doses of PM for the smaller size fractions induced elevated neutrophils.

23  Significant responses in albumin and TNF-α were only observed for the fine PM (1.7-3.5 µm) exposure

24  group. Total protein, LDH, NAG, and responses were absent for all PM size fractions. Levels of IL-6 were

1 elevated in mice exposed to 100 μg for coarse, fine, and fine/ultrafine (< 1.7 μm) PM. When

2 dimethylthiourea (DMTU) was administered intravenously prior to exposure, the neutrophil response was

3 attenuated in all groups to levels below control.

4      Another study compared thoracic coarse, fine, and ultrafine PM collected in Seattle, WA, Salt Lake

5 City, UT, South Bronx, NY, and Sterling Forest, NY (Gilmour et al., 2007). In female BALB/c mice, the

6 100 μg dose of $PM_{10-2.5}$ (approximately 5 mg/kg) from Salt Lake City induced a significant increase in

7 protein in BALF and the level released was almost as high as that observed after LPS exposure (Gilmour

8 et al., 2007). $PM_{10-2.5}$ from the South Bronx resulted in dose-related increases in neutrophil number and

9 MIP-2 levels in BALF (Gilmour et al., 2007). The greatest amount of LPS was observed in the Salt Lake

10 City and Seattle $PM_{10-2.5}$ samples. There was a less discernable patter of response with fine and ultrafine

11 PM.

**Table 6-9.**    **Other ambient PM – in vivo $PM_{10-2.5}$ studies – BALF results, 18–24 h post-IT**

| Location | Endotoxin | Dose (mg/kg) | Cell Differentials | Cytokines | Injury Biomarkers | Reference |
|---|---|---|---|---|---|---|
| Germany, Borken; rural Feb–May 2000 | ~6.6 EU/mg | 0.58–0.91 | ↑* % PMN | ↑ TNF-α | | Schins et al. (2004) |
| Germany, Duisburg; heavy industry Feb–May 2000 | ~5.0 EU/mg | 0.58–0.91 | ↑ % PMN | ↑ MIP-2 | | Schins et al. (2004) |
| USA, Seattle, WA Feb–March 2004 | ~6.0 EU/mg | 1.25, 5.0 | | | | Gilmour, et al. (2007) |
| USA, Salt Lake City, UT Apr–May 2004 | ~6.3 EU/mg | 1.25, 5.0 | | | ↑ protein | Gilmour, et al. (2007) |
| USA, South Bronx, NY Dec 2003–Jan 2004 | ~2.8 EU/mg | 1.25, 5.0 | ↑ PMN | ↑ MIP-2 | | Gilmour, et al. (2007) |
| USA, Sterling Forest, NY Dec 2003–Jan 2004 | ~2.9 EU/mg | 1.25, 5.0 | | | | Gilmour, et al. (2007) |
| USA, RTP, NC Oct–Nov 1996 | ~0.96 EU/mg | 0.5, 2.5, 5.0 | ↑↑ PMN | ↑ IL-6 | | Dick, (2003a) |
| Germany, Munich Ost Bahnof; high traffic A Aug 2002 | ~2.9 EU/mg | 3, 10 | ↑↑* total cells ↑↑ AM ↑↑*PMN ↑↑* Lymph | ↑↑ MIP-2 ↑↑ TNF-α | ↑↑* LDH ↑* protein | Gerlofs-Nijland, et al. (2007) |
| Netherlands, Hendrik-Ido-Ambacht; high traffic Sept 2002 | ~6.5 EU/mg | 3, 10 | ↑↑ total cells ↑↑*AM ↑↑ PMN ↑↑ Lymph | ↑ MIP-2 ↑↑ TNF-α | ↑↑ LDH ↑ protein | Gerlofs-Nijland, et al. (2007) |
| Italy, Rome; high traffic Apr 2002 | ~1.5 EU/mg | 3, 10 | ↑ total cells ↑↑ AM ↑↑ PMN ↑↑ Lymph | ↑↑ MIP-2 ↑↑ TNF-α | ↑↑ LDH | Gerlofs-Nijland, et al. (2007) |

| Location | Endotoxin | Dose (mg/kg) | Cell Differentials | Cytokines | Injury Biomarkers | Reference |
|---|---|---|---|---|---|---|
| Netherlands, Dordrecht; moderate traffic<br>Apr 2002 | ~0.6 EU/mg | 3, 10 | ↑↑ total cells<br>↑ AM<br>↑↑ PMN<br>↑ Lymph | | ↑↑ LDH<br>↑ protein | Gerlofs-Nijland, et al. (2007) |
| Germany, Munich Grosshadern Hospital; low traffic<br>Jun–Jul 2002 | ~2.9 EU/mg | 3, 10 | ↑ total cells<br>↑↑ AM<br>↑↑ PMN<br>↑↑ Lymph | ↑↑* MIP-2<br>↑↑* TNF-α | ↑↑* LDH<br>↑ protein | Gerlofs-Nijland, et al. (2007) |
| Sweden, Lycksele; low traffic<br>Feb–March 2002 | ~0.9 EU/mg | 3, 10 | ↑↑ total cells<br>↑ AM<br>↑↑ PMN<br>↑ Lymph | | ↑↑ LDH<br>↑ protein | Gerlofs-Nijland, et al. (2007) |

For Gerlofs-Nijland study, composition data were averaged across seasons. ↑ significant only at highest dose. ↑↑ Significant at lowest and highest dose. * Greatest potency for that endpoint and study. Gilmour et al. exposure was via aspiration.

### Coal Fly Ash

1   Coal fly ash of differing size fractions and composition was injected into female CD1 mice

2   oropharynx (25 or 100 μg) and then aspirated to assess lung inflammation and injury 18 h following

3   exposure (Gilmour et al., 2004a). Montana (low-sulfur subbituminous; 0.83% sulfur, 11.72% ash content)

4   or Western Kentucky (high-sulfur bituminous; 3.11% sulfur, 8.07% ash content) coal was combusted

5   using a laboratory-scale down-fired furnace. Interestingly, no significant $PM_{10-2.5}$ effects for either coal fly

6   ash were observed for BAL neutrophils, TNF-α, MIP-2, albumin, total protein, LDH activity, or NAG

7   activity 18 h post-IT. However, the ultrafine fraction ($PM_{0.2}$) of combusted Montana coal induced greater

8   numbers of neutrophils than $PM_{10-2.5}$ or $PM_{2.5}$ at both doses. TNF-α was only elevated in animals exposed

9   to 100 μg of the Montana ultrafine PM; MIP-2 was also increased at both doses. The $PM_{2.5}$ Western

10   Kentucky coal fly ash caused increased BAL neutrophils, MIP-2, albumin, and protein (Gilmour et al.,

11   2004a).

12   In a similar study employing Montana subbituminous coal fly ash particles >2.5 μm, C57Bl/6J

13   mice were intratracheally instilled with PM alone or PM+LPS and BALF was obtained 18 h

14   post-exposure (Finnerty et al., 2007). TNF-α and IL-6 in lung homogenates were only elevated in the

15   animals exposed to PM+100 μg LPS, although it appeared that there was a greater-than additive effect.

16   Total cells and cell differentials were not measured (Finnerty et al., 2007).

### Summary

17   Biomarkers of injury and inflammation were measured in in vivo and in vitro studies comparing

18   the toxicity of different size fractions of ambient PM from various locations. Responses were measured in

19   BALF of rodents following intratracheal instillation or aspiration of PM. In general, the $PM_{10-2.5}$ size

1    fraction was more potent than fine or ultrafine PM and endotoxin levels did not appear responsible. In one

2    study, rural $PM_{10-2.5}$ from Germany induced a greater inflammatory and cytokine response than $PM_{10-2.5}$

3    from an industrial location. In contrast, $PM_{10-2.5}$ from Sterling Forest, NY did not lead to any change in

4    BALF inflammation or injury markers. A study that employed coal fly ash indicated that the ultrafine PM

5    fraction was the most inflammogenic. All of these studies were conducted using high doses of PM

6    (0.58-10 mg/kg) and it is unclear if similar effects would be observed at lower doses.

# 6.3.6. Allergic Responses

7    A large number of toxicological and human clinical studies cited in the 2004 PM AQCD reported

8    an exacerbation of existing allergic airway disease following exposure to laboratory-generated and

9    ambient particles. In addition, numerous studies have demonstrated that PM can alter the immune

10    response to challenge with specific antigens and suggest that PM may act as an adjuvant to promote

11    allergic sensitization. Recent toxicological studies have provided evidence of enhanced allergic response

12    and allergic sensitization following exposure to CAPs and diesel that is consistent with the findings

13    presented in the 2004 PM AQCD. Thus PM can enhance allergic responses by facilitating delivery of

14    allergenic material and promoting subsequent immune reactivity. The initiation or exacerbation of allergic

15    responses has important implications for allergic asthma, the most common form of asthma.

## 6.3.6.1. Human Clinical Studies

### *Exacerbation of Allergic Responses*

16    Exposure to DE particles was shown to increase the allergic response among atopic individuals in

17    several human clinical studies cited in the 2004 PM AQCD. Nordenhall et al. (2001) found that exposure

18    to DE significantly decreased the concentration of methacholine required to induce a 20% decrease in

19    $FEV_1$ in a group of atopic asthmatics 24-h post-exposure. In addition, Diaz-Sanchez et al. (1997)

20    demonstrated an increase in allergen-specific IgE following exposure via intranasal spray to ragweed plus

21    DE particles relative to ragweed allergen alone. Decreases in IFN-γ and IL-2, as well as increases in IL-4,

22    IL-5, IL-6, IL-10, and IL-13 were also observed when ragweed allergen was administered with exhaust

23    DE particles. One new study (Bastain et al., 2003) also observed an increase in IL-4 and allergen specific

24    IgE, as well as a decrease in IFN-γ following intranasal administration of ragweed allergen with DE

25    particles in atopic adults. The protocol was repeated in this study for all subjects, and the enhancement of

26    allergic response by co-exposure to DE particles was observed to be highly reproducible within

27    individuals.

### Allergic Sensitization

1    One controlled human exposure study has demonstrated that de novo sensitization to a neoantigen

2    can be induced by exposure to DE particles. In this study, Diaz-Sanchez et al. (1999) dosed 25 atopic

3    adults intranasally with 1 mg keyhole limpet hemocyanin (KLH), followed by 2 biweekly challenges with

4    100 μg KLH. In 15 of the 25 subjects, DE particles were administered intranasally 24-h prior to each

5    KLH exposure, while in the other 10 subjects, no diesel particles were administered. No KLH-specific

6    IgE was observed in the nasal lavage fluid of any of the subjects exposed to KLH without exposure to

7    diesel particles. However, KLH-specific IgE was present in the nasal lavage fluid of 9 out of 15 subjects

8    28 to 32 days after the initial KLH immunization when exposures were preceded by administration of DE

9    particles.

## 6.3.6.2. Toxicological Studies

### Exacerbation of Allergic Responses

10    Increased use of actual ambient air particle mixes in toxicological studies since the 2004 CD has

11    greatly expanded evidence relevant to assessing these and other immunotoxic effects. A number of studies

12    have also included ambient level doses, although many still include relatively high doses of questionable

13    relevance compared to the doses inhaled by humans. Recent dosimetric models reveal that a small

14    fraction of epithelial cells located at the carinal ridges of airway bifurcations can receive massive doses

15    that may be even a few hundred times higher than the average dose for the whole airway (see Chapter 4).

16    These areas, coincidentally, are locations of bronchus associated lymphoid tissues (BALT) which are sites

17    at which interaction of T and B lymphocytes with antigen presenting cells (APC) occurs. Hence the

18    deposited particles are in near-ideal proximity to immunologically active tissues. Doses used for assessing

19    PM immunotoxicity should be viewed with this perspective.

20    Existing allergic sensitization confers susceptibility to the effects of PM in rodent models. For

21    example, studies in allergic rats (Harkema et al., 2004; Morishita et al., 2004) suggest that allergic

22    sensitization enhances the retention of PM in the airways. OVA intranasally sensitized and challenged BN

23    rats were exposed to CAPs $PM_{2.5}$ for 4 or 5 consecutive 10-h days. Exposures were conducted in Detroit

24    during July or September (4 or 5 d, time weighted average mass concentration of $676 \pm 288$ or

25    $313 \pm 119 \, \mu g/m^3$, respectively). Recovery of anthropogenic trace elements (La, V, Mn, S) from lung tissue

26    24-h post-exposure was greater for CAPs exposed sensitized/challenged rats than for air exposed or

27    non-allergic CAPs exposed controls. Interestingly, temporal increases in these elements were associated

28    with eosinophil influx and BALF protein content, as well as significantly increased airway

29    mucosubstances, despite lower average mass concentration (September, $313 \pm 119$). During September,

1    the average number concentration of ultrafine particles was nearly double that in July (10,879 ± 5126 vs.

2    5753 ± 2566 particles/cm$^3$), and the authors speculated that this high concentration of ultrafine particles

3    facilitated particle penetration into the alveolar region of the lungs. Experiments were conducted using

4    intratracheal instillation of fractionated soluble and insoluble ambient $PM_{2.5}$ collected during the same

5    time period during September (Harkema et al., 2004). A mild pulmonary neutrophilic inflammation was

6    observed in healthy BN rats instilled with the insoluble fraction of $PM_{2.5}$, but instillation of total, soluble,

7    or insoluble $PM_{2.5}$ in allergic rats did not result in differential effects.

8         Research has also been conducted to determine the effect of proximity to the roadway on

9    exacerbation of existing allergic disease. OVA-allergic BALB/c mice were exposed to CAPs (fine, F, ≤

10    2.5 or ultrafine, UF, ≤ 0.15, avg. total concentration 400 μg/m$^3$) for five 4-h days a week over two weeks

11    at 50 or 150 m downwind of a heavily trafficked road (Kleinman et al., 2005). After two OVA inhalation

12    challenges, significantly higher concentrations of IL-5, OVA-specific IgE and IgG1, and eosinophils were

13    detected in serum and lavage samples from mice exposed to CAPs (UF or F) than in samples from

14    air-exposed mice. Mice exposed to CAPs closer to the roadway (50 m) had higher levels of IL-5, IgG1,

15    and eosinophils than mice exposed to CAPs 150 m downwind. The UF CAPs appeared to be more potent

16    in mediating these effects, and the authors suggest that the enhanced responses to exposure closer to the

17    roadway may reflect a greater proportion of UF particles in this vicinity, as the concentrations of

18    sub-25-nm particles decrease rapidly with distance from the roadway. Animal-to-animal variability among

19    the biomarkers tested made it necessary to combine values from two exposures spanning two years for

20    statistical power (determined prior to the start of the experiment). A subsequent publication (Kleinman et

21    al., 2007) included a third exposure regimen as well as compositional analysis. Fine CAPs mass

22    concentration was intentionally adjusted to an average concentration of approximately 400 μg/m$^3$, ranging

23    from 163 μg/m$^3$ to 500 μg/m$^3$. UF ranged from 146 to 430 μg/m$^3$. Analysis of results from the three

24    exposures indicated that OVA-sensitized mice exposed 50 m downwind of the roadway exhibited

25    increased levels of IL-5 and $IgG_1$ compared to mice exposed 150 m downwind or exposed to air. No

26    markers of allergy-related responses were observed in the 150 m exposure groups, and very little

27    difference was seen between fine and ultrafine CAPs responses, perhaps because fine material contained

28    20-32% ultrafine components. The strongest associations between component concentrations and

29    biological markers of allergy (IL-5 and IgG1) were to EC and OC. This study suggests that proximity to a

30    source may be an important factor in allergic responses.

31         Existing allergic sensitization also modulates airway responses following exposure to PM. AHR, as

32    measured by methacholine-induced airway resistance, was observed in ovalbumin (OVA) sensitized

33    C57BL/6J mice after aerosol challenge with OVA and a single 5 hour nose-only exposure to a

34    concentration of 870 μg/m$^3$ aerosolized filter-collected DEP ($PM_{2.5}$) (Farraj et al., 2006a). Intranasal

pretreatment with an antibody against the pan neurotrophin receptor p75 attenuated the DEP-induced increase in airflow obstruction, indicating a role for neurotrophins. Neurotrophins are expressed by various structural, nerve and immune cells within the respiratory tract and are linked to the etiology of asthma in both humans and animal models. DEP alone in unsensitized mice caused a significant increase in lung macrophages; this response was also inhibited by anti-p75, which may suggest mediation of macrophage influx by neurotrophin or alternatively may reflect anti-p75 dependent depletion of macrophages due to expression of the p75 receptor. Aside from increased macrophages, the single exposure to DEP had little effect on other markers of airway inflammation. In a similar subsequent study, these authors demonstrate neurotrophin-mediated DEP-induced airflow obstruction in OVA sensitized and challenged BALB/c mice (Farraj et al., 2006b), in this case using a higher 2000 $\mu g/m^3$ single 5 h exposure to aerosolized filter-collected $PM_{2.5}$. Differences between whole body plethysmography and tracheal ventilation measurements indicated that airflow obstruction may have originated in the nasal passages. Again, very few indices of inflammation were increased; however, similar neurotrophin-dependent increases in lung macrophages were observed after DEP exposure alone, and IL-4 protein levels were increased 5-fold in the BALF of sensitized, challenged, DEP-exposed mice. This neurotrophin-dependent IL-4 response was not evident in the first study, and may be related to the higher dose used in the second study or the characteristic allergic or Th2 bias of the BALB/c strain. Airflow obstruction in the absence of airway inflammation in OVA-sensitized animals seen in both studies by Farraj et al. (2006a, b) may reflect DEP-induced acute enhancement of neurogenic as opposed to immunologic inflammation. In these and other studies, particular effects such as airway obstruction are only evident when allergic sensitization precedes DEP exposure.

Exposure to relatively low doses of DE has been shown to exacerbate asthmatic responses in OVA sensitized and challenged BALB/c mice (Matsumoto et al., 2006). Mice were intraperitoneally sensitized and intranasally challenged one day prior to chamber exposure to DE (DEP 100 $\mu g/m^3$; CO, 3.5 ppm; $NO_2$, 2.2 ppm; $SO_2 < 0.01$ ppm) for 1 day or 1, 4, or 8 weeks (7h/day, 5 days/week, endpoints 12-h post-DE exposure). Results from the 8 week study are described in Section 7.3.7.1. It should be noted that control mice were left in a clean room as opposed to undergoing chamber exposure to filtered air. Significant AHR upon methacholine challenge was observed after 1 and 4 weeks of exposure, and airway sensitivity (provocative concentration of methacholine causing a 200% increase in Penh) was significantly increased after 1 week of exposure but not 4 weeks. DE had no effect on total cells in BALF, but transiently increased expression of IL-4, IL-5, and IL-13 after 1 day of exposure, MDC after 1 week, and RANTES after 2 and 3 weeks. Eotaxin, TARC, and MCP-1 were elevated, but did not achieve statistical significance, after short-term (1 day or week) exposure. Statistical power may have been lacking due to an n of 3. Protein levels of IL-4 and RANTES were significantly elevated after 1 day of

1   DE exposure, respectively. DE had no effect on OVA challenge-induced peribronchial inflammatory or

2   mucin positive cells. Therefore DE-induced airway hyperreactivity was observed in the absence of

3   cellular inflammation, similar to the responses described for aerosolized or nebulized DEP by Farraj et al.

4   (2006a, b) and Hao et al. (2003).

5        Exposures to an aerosol of soot and iron oxide generated from ethylene ($PM_{2.5}$, 0.235 mg/m$^3$) were

6   conducted to test whether the sequence of exposure to ovalbumin aerosol challenge and PM affected the

7   observed response of OVA sensitized BALB/c mice (Last et al., 2004). Though called $PM_{2.5}$, the authors

8   characterized the PM material as ultrafine, 80-110 nm, with the iron oxide crystals often spatially

9   segregated from the soot (200 µg/m$^3$ soot, remainder iron oxide, CO < 0.8 ppm, $NO_X$ < 0.4 ppm, PAH

10  below detection). Mice were exposed to PM via chamber inhalation for 2 weeks (4h/day, 3 days/wk)

11  before or after 4 weeks of OVA inhalation, or simultaneously to PM and OVA for 6 weeks. Among

12  endpoints (BAL cells, Penh, airway collagen, and goblet cells) only goblet cell counts were significantly

13  increased with PM exposure in any combination with ovalbumin. There was a trend toward increased

14  Penh responses with exposure to PM alone or with OVA, particularly when PM exposure immediately

15  preceded methacholine challenge (after or during OVA challenge). Results from this study are difficult to

16  interpret due to the varied elapsed times between cessation of PM or OVA treatment and endpoint

17  determination. The mild responses to PM may be related to the intraperitoneal sensitization protocol used,

18  reputed to generate a highly allergic mouse in which any additive effects of PM may be obscured by

19  maximal responses to antigen challenge (Deurloo et al., 2001; Hao et al., 2003).

20       Pregnancy or in utero exposure may confer susceptibility to PM-induced asthmatic responses.

21  Exposure of pregnant BALB/c mice to aerosolized ROFA leachate by inhalation or to DEP intranasally

22  increased asthma susceptibility in their offspring (2008; Hamada et al., 2007). The offspring from dams

23  exposed for 30 min to 50 mg/ml ROFA 1, 3, or 5 days prior to delivery responded to OVA immunization

24  and aerosol challenge with AHR and increased antigen-specific IgE and IgG1 antibodies. AHR was also

25  observed in the offspring of dams intranasally instilled with 50 µg of DEP or $TiO_2$, or 250 µg carbon

26  black, indicating that the same effect could be demonstrated using relatively "inert" particles. Pregnant

27  mice were particularly sensitive to exposure to DEP or $TiO_2$ particles, and genetic analysis indicated

28  differential expression of 80 genes in response to $TiO_2$ on the pregnant background. Thus pregnancy may

29  enhance responses to PM, and exposure to even relatively inert particles may result in offspring

30  predisposed to asthma.

## *Allergic Sensitization*

31       A large number of in vivo animal studies and in vitro studies have demonstrated that particles can

32  alter the immune response to challenge with specific antigens and suggest that PM may act as an adjuvant

to promote allergic sensitization. This phenomenon was introduced in the 2002 Diesel Document, and has been noted in multiple animal and human studies by the 2004 CD. Adjuvants enhance the immune response to antigens. Importantly, adjuvants may be major contributors to the development of inappropriate immune responses. These immune responses, mediated by T helper cells, fall along a continuum from T helper type 1 (Th1) to T helper type 2 (Th2). Th1 responses, characterized by IFN-γ, are inflammatory and in excess can lead to tissue damage. Alternatively, Th2 responses are characterized by IL-4, IL-5, IL-13, eosinophils, and IgE, and are associated with allergy and asthma. Autoimmune diseases may be driven by Th1, Th2, or mixed responses, but allergic diseases are Th2 mediated. Adjuvant activity can be exerted via chemoattraction, cytokines, or enhanced antigen presentation and costimulation, and may originate via effects on a number of cell types.

It has been suggested that the capacity of particles to enhance allergic sensitization is associated more strongly with particle number and surface area than particle mass, and several studies comparing size fractions of the same material show greater adjuvant activity for an equivalent mass dose of smaller particles (de Haar et al., 2006; Inoue et al., 2005; Nygaard et al., 2004). This is particularly true of inert or homogeneous materials, such as carbon, polystyrene, and $TiO_2$, which vary little in composition with size fraction. In studies of ambient PM, however, coarse particles have demonstrated equal and sometimes greater adjuvancy compared to fine particles (Nygaard et al., 2005; Steerenberg et al., 2004a; Steerenberg et al., 2005). It is difficult to ascertain the role of particle size in mediating adjuvancy due to a lack of inhalation studies performed to compare size fractions. The adjuvant effects of ambient PM appear to depend on composition, which differs among various size fractions and sources, and are associated with combustion related materials (Steerenberg et al., 2006) and metal content (Gavett et al., 2003).

DEP inhalation during allergen exposure has been shown to augment IgE production and alter methylation of T helper genes in BALB/c mice (Liu et al., 2008) Animals were exposed to 1280 µg/m³ DEP over a 3-week period, 5h per day, concurrent with periodic intranasal sensitization to the common fungus *Aspergillus fumigatus*. Gas concentrations were not reported. Total IgE and BALF eosinophils were elevated with *A. fumigatus* sensitization and further increased by concomitant DEP exposure. Greater methylation of the IFN-γ promoter was observed following DEP and *A. fumigatus* exposure (but not DEP alone) compared to *A. fumigatus* alone, indicating that combined DEP and allergen exposure might induce methylation and thus suppress expression of Th1 genes. Furthermore, hypomethylation of the IL-4 promoter was detected after exposure to *A. fumigatus* and DEP compared with exposure to *A. fumigatus* or DEP alone, suggesting pro-allergic Th2 gene activation upon combined exposure to allergen and DEP. The changes in methylation status of these genes were associated with alterations in IgE levels in individual animals, indicating that modifications at the genetic level could result in predicted

1  downstream effects. This study shows for the first time that DEP exposure can exert pro-allergic in vivo

2  effects on the mouse immune system at the epigenetic level.

3      Resuspended DE particles have been shown to enhance OVA-specific IgG1 and IgE in BALB/c

4  mice exposed via inhalation to doses as low as 200 and 600 $\mu g/m^3$, respectively (Whitekus et al., 2002).

5  Mice were exposed to DEP (200, 600 and 2000 $\mu g/m^3$) for 1-h daily for 10 days, followed by 20 min

6  exposure to aerosolized OVA. Compared with responses to OVA alone, antibody levels were increased by

7  all OVA+DEP exposures. Statistical significance was reached for IgG1 at all DEP exposure levels,

8  whereas OVA specific IgE was significantly increased at the 600 and 2000 $\mu g/m^3$ doses and total IgE was

9  significantly elevated at 2000 $\mu g/m^3$. Although strong adjuvant effects were observed, no general markers

10  of inflammation such as eosinophils, IL-5, GM-CSF, mucin, morphological changes, or eosinophilic

11  major basic protein (MBP) deposition in the airways were observed in exposed mice. In vitro experiments

12  using the RAW 264.7 macrophage-like cell line indicated a DEP-induced lipid peroxidation and protein

13  oxidation, which could be inhibited by a variety of antioxidants. Also observed was a decrease in the

14  GSH: GSSG ratio and an increase in HO-1 expression, both of which were inhibited only by the thiol

15  antioxidants NAC and BUC. These same thiol antioxidants were able to completely block DEP-related

16  increases in IgE and IgG1, as well as lipid peroxides and oxidized proteins recovered from lung lavage

17  fluids at the 2000 $\mu g/m^3$ dose. Thus solid correlations between in vivo and in vitro antioxidant activities

18  were found, and the reversal of adjuvant effects by antioxidants in vivo clearly indicates a link between

19  oxidative stress and DEP adjuvant activity. However, the intranasal adjuvant activity of Ottawa dust

20  (EHC-93) in the same strain of mice was not inhibited by NAC pretreatment (Steerenberg et al., 2004a),

21  suggesting that disparate pathways may be utilized by different materials to exert immune stimulation.

22      A toxicogenomic approach to investigate early response mechanisms of DEP adjuvancy was taken

23  by Stevens et al. (2008). BALB/c mice were chamber exposed to filtered air, 500 or 2000 $\mu g/m^3$ PM in

24  DE for 4 h/day over 5 consecutive days, and intranasally exposed to OVA on each of the first 3 days. In

25  the low vs. high PM exposures, CO, NO, $NO_2$, and $SO_2$ were < 0.1 vs. 4.3, < 2.5 vs. 9.2, < 0.25 vs. 1.1

26  and < 0.06 vs. 0.2 ppm, respectively. Lung tissues were assessed for alterations in global gene expression

27  (n = 4) 4 h after the last DE exposure on day 4. Mice were intranasally challenged with OVA or saline on

28  day 18 and then with OVA on day 28. Post-challenge results demonstrated mild adjuvancy with antigen

29  and DE exposure as evidenced by significant increases in eosinophils, neutrophils, lymphocytes, and IL-6

30  in the BALF. Antibody responses were not significantly affected by DE exposure, although a slight

31  increase in IgE after high dose exposure was observed. DE alone only increased neutrophils, indicating

32  the need for combined exposure to DE and antigen in the development of allergic outcomes. Comparison

33  of low DE (500 $\mu g/m^3$)/OVA versus air/OVA resulted in no significant changes in gene sets associated

34  with this treatment. Comparison of the high (2000 $\mu g/m^3$) DE/OVA versus air/OVA, however, showed

1 significant changes in 23 gene sets, including neutrophil homing chemokines, inflammatory cytokines,

2 numerous interleukins and TNF subtypes, growth and differentiation pathways, and an array of

3 chemokines.

4 Interestingly, although the adjuvant effects of DEP are reasonably well established, hardwood

5 smoke (HWS) exposure only minimally exacerbates indices of allergic airway inflammation in an

6 OVA-sensitized BALB/c mouse model and does not alter Th1/Th2 cytokine levels (Barrett et al., 2006).

7 Trend analysis indicated increasing BALF eosinophils with increasing dose of HWS, becoming

8 significantly elevated at 300 μg/m$^3$ (CO, $1.6 \pm 0.3$ ppm; total vapor hydrocarbon, $0.6 \pm 0.2$ ppm; NO$_X$,

9 below limit of quantitation), and increasing but not statistically significant OVA-specific IgE levels with

10 HWS up to 1000 μg/m$^3$.

### Summary

11 Studies conducted since the last review confirm and extend findings of the 2004 CD. Thus PM can

12 modulate immune reactivity in both humans and animals to promote allergic sensitization and exacerbate

13 allergic responses. Numerous forms of PM, including inert materials, have been shown to function as

14 adjuvants, and although studies of relatively homogeneous materials demonstrate greater adjuvancy for

15 smaller particles, analyses of ambient PM do not. Particle composition is likely more influential than size,

16 but few if any studies have compared size fractions of well-characterized ambient PM for adjuvant

17 activity in a direct, controlled fashion via inhalation exposure.

# 6.3.7. Host Defense

18 Several toxicological studies were cited in the 2004 PM AQCD that demonstrated increased

19 susceptibility to infectious agents following exposure to PM. A limited number of new studies have

20 evaluated the effect of PM on host defense in rodents. Two recent studies have observed an increase in

21 susceptibility to influenza infection and respiratory syncytial virus in mice. However, one new study

22 found that wood smoke had no effect on bacterial clearance in rodents.

## 6.3.7.1. Toxicological Studies

23 The normal, and very important, role of respiratory immune defense is the detection and/or

24 destruction of pathogens that enter the lung via inhalation and removal of damaged, transformed

25 (cancerous), or infected cells. Innate immune defenses of the respiratory tract include mucociliary

26 clearance, release of toxic antimicrobial proteins into airway surface liquid, and activation of alveolar

27 macrophages. The innate immune system is the earliest responder to irritation or infection, initiating the

1  normal inflammatory response including the majority of detrimental inflammatory processes discussed.

2  Activated macrophages and epithelial cells release cytokines and chemokines that can bring into play the

3  adaptive immune system, which in turn can produce long-lasting pathogen-specific immune responses

4  critical for resolving and preventing infections.

5       Several studies included in the 2004 CD demonstrated increased susceptibility to infectious agents

6  following exposure to various forms of PM, and studies of CAPs exposed aged rats demonstrated

7  increased *S. pneumoniae* burdens when a 24-h exposure (65 $\mu$g/m$^3$) followed infection (Zelikoff et al.,

8  2003). In another study, exposure to ROFA by intratracheal instillation was found to affect bacterial

9  clearance (Antonini et al., 2002). Examinations of mechanisms related to PM interference with host

10 defenses have demonstrated impaired mucociliary clearance and modified macrophage phagocytosis and

11 chemotaxis. Prolonged exposure to inhaled particles at sufficiently high concentrations can lead to

12 diminished clearance of PM from the alveolar region of the lung, resulting in the accumulation of retained

13 particles and an accompanying chronic alveolar inflammation. Diminished clearance of PM may also

14 increase susceptibility to pulmonary infection by impeding clearance of pathogens. Impaired phagocytosis

15 by alveolar macrophages may contribute to a decrease in the lung's capacity to deal with increased

16 particle loads (as occurs during high-pollution episodes) or infections and affect the local and systemic

17 responses through the release of biologically active compounds (cytokines, ROS, NO, isoprostanes).

18      Since the last review, several additional studies have reported impairment of pathogen clearance

19 following intratracheal instillation of PM. In a follow up study Antonini et al. (2004) compared sources of

20 ROFA in SD rats. Precipitator ROFA induced an inflammatory response and diminished pulmonary

21 clearance of *L. monocytogenes* while air heater ROFA had no effect on lung bacterial clearance at the

22 same dose of 1 mg/100g body weight. Precipitator ROFA generated a metal-dependent hydroxyl radical

23 suggesting that differences in metal composition were a determinant of the immunotoxicity of ROFA.

24      Viral respiratory infections in early life are associated with increased incidence of childhood

25 asthma and other pulmonary diseases. DE exposure can enhance the progression of influenza infection

26 when a virus is introduced following particle exposure. BALB/c mice that were chamber exposed to DE

27 and subsequently instilled with influenza A/Bangkok/1/79 virus had increased susceptibility to influenza

28 infection (Ciencewicki et al., 2007). Exposures to two doses of DEP were conducted: 500 $\mu$g/m$^3$ (0.9 ppm

29 CO, < 0.25 ppm NO$_2$, < 2.5 ppm NO, and 0.06 ppm SO$_2$) and 2000 $\mu$g/m$^3$ (5.4 ppm CO, 1.13 ppm NO$_2$,

30 10.8 ppm NO, and 0.32 ppm SO$_2$). Responses were greater for animals exposed to 500 $\mu$g/m$^3$ DEP than to

31 2000 $\mu$g/m$^3$, and were associated with a significant increase in IL-6 protein and mRNA expression and

32 IFN-$\beta$ expression. The authors present the possibility that damage to the epithelium at the higher dose

33 prevented viral infection and replication. After exposure to 500 $\mu$g/m$^3$ DEP alone or prior to infection,

1    decreased expression of surfactant proteins (SP) A and D was observed. These proteins are part of the

2    IFN-independent defense against influenza.

3        Similarly, Harrod et al. (2003) demonstrated decreased SP-A expression in the lungs following DE

4    exposure and linked it to increased susceptibility to respiratory syncytial virus (RSV), the most common

5    cause of respiratory infection in young children. C57BL/6 mice, a relatively RSV-resistant strain, were

6    exposed via inhalation to DE at a concentration of 30 or 1000 $\mu g/m^3$ DPM 6h/day for 7 consecutive days

7    prior to intratracheal viral inoculation. Gaseous copollutants ranged from 2.0–43.3 ppm for $NO_X$ (~ 90%

8    NO), 0.94–29.0 ppm CO, and 8.3–364.9 ppb $SO_2$. Exposure to 30 $\mu g/m^3$ DEP did not induce a

9    statistically significant increase in BALF cell numbers compared to air-treated, infected animals.

10   However, distinct consolidated inflammatory infiltrates were observed in the peribronchial regions of

11   RSV-infected animals exposed to this dose, along with alterations in Clara cell morphology, decreased

12   CCSP production by these cells, and occasional regional myofibril layer thickening. These changes were

13   more pronounced in RSV-infected animals exposed to 1000 $\mu g/m^3$, and the higher dose also resulted in

14   significant increases in inflammatory cells, predominantly macrophages, in both uninfected and infected

15   mice compared to air-exposed controls. Both doses elicited significant levels of TNF-α and IFN-γ in the

16   lungs of infected animals, but decreased levels of SP-A. Consistent with this study's finding of decreased

17   SP-A and increased viral gene and inflammatory cytokine expression after DE exposure, SP-A$^{-/-}$ mice

18   demonstrate decreased clearance of RSV concordant with increased lung inflammation (LeVine et al.,

19   1999). Thus, DEP may enhance susceptibility to respiratory viral infections by reducing the expression

20   and production of SP (Ciencewicki et al., 2007; Harrod et al., 2003), although the contribution of gaseous

21   copollutants, in some instances concentrated 1000x, should be considered for both studies. SP are also

22   essential for clearance of other pathogens, including group B Streptococcus (GBS), *Haemophilus*

23   *influenzae*, and *Pseudomonas aeruginosa* (LeVine and Whitsett, 2001).

24       In lung epithelial cells, DEP increased the mRNA expression of intercellular adhesion molecule-1

25   (ICAM-1), low-density lipoprotein (LDL) and platelet-activating factor (PAF) receptors, which can act as

26   receptors for viruses or bacteria (Ito et al., 2006b). DEP may therefore enhance the susceptibility to

27   infection by the upregulation of bacterial and viral invasion sites in the lungs. Expression of the

28   β-defensin-2 gene, which is one antimicrobial mechanism of host defense in the airway, was significantly

29   inhibited by V and not Ni or Fe in airway epithelial cells incubated with aqueous leachate of ROFA

30   (Klein-Patel et al., 2006).

31       HWS does not appear to have significant impact on pathogen clearance. Fisher 344 rats, SHR rats,

32   A/J mice and C57BL/6 mice were exposed to 30-1000 $\mu g/m^3$ HWS by whole body inhalation for one

33   week and 6 months (Reed et al., 2006). Long-term responses are discussed in Sections 7.3.3.2 and 7.3.8.

34   Concentrations of gases ranged from 229.0-14887.6 $mg/m^3$ for CO, 54.9-139.3 $\mu g/m^3$ for ammonia, and

1    177.6-3455.0 µg/m$^3$ nonmethane volatile organic carbon in these exposures. Bacterial clearance and

2    inflammation in response to instilled *Pseudomonas aeruginosa* were unaffected by HWS.

### *Immunosuppressive Effects of PM*

3    DEP may affect systemic immunity. Decreased thymus weight was observed in female F344 rats

4    exposed to 300 µg/m$^3$ DEP for one week by Reed et al. (2004). Concentrations of gases for this dose were

5    reported to be approximately 16.1 ppm for NO, 0.8 ppm for $NO_2$, 9.8 ppm for CO, 115 ppb for $SO_2$, and

6    1416 µg/m$^3$. Long-term responses are discussed in Section 7.3.8.

# 6.3.8. Respiratory ED Visits, Hospital Admissions and Physician Visits

7    The epidemiologic evidence presented in the 2004 PM AQCD of an association between PM and

8    respiratory hospitalizations and emergency department visits was consistently positive across studies.

9    Recent studies have provided further support to this relationship, with larger effect estimates observed

10    among children and older adults. However, effect estimates are clearly heterogeneous, with evidence of

11    both regional and seasonal differences at play.

12    Excess risk estimates for hospitalizations or ED visits for all respiratory diseases combined,

13    reported in studies reviewed in the 2004 PM AQCD fell within the range of approximately 1 to 4% per

14    10 µg/m$^3$ increase in $PM_{10}$. On average, excess risks for asthma were higher than excess risks for COPD

15    and pneumonia. The limited body of evidence reviewed in the 2004 PM AQCD also reported associations

16    with ambient fine particles ($PM_{2.5}$, $PM_1$) and coarse thoracic particles ($PM_{10-2.5}$). Excess risk estimates fell

17    within the range of approximately 2.0 to 6.0% per 10 µg/m$^3$ increases in $PM_{2.5}$ or $PM_{10-2.5}$ for both all

18    respiratory and COPD admissions, whereas larger estimates were reported for asthma admissions. Many

19    of the associations for respiratory admissions and ED visits and short-term $PM_{2.5}$ exposure were

20    statistically significant. The associations with $PM_{10-2.5}$ were less precise with fewer reaching statistical

21    significance (U.S. EPA, 2004). In addition, several studies had reported associations with outpatient

22    physician visits that suggested larger public health impacts.

23    Hospital admissions or ED visits for respiratory diseases and ambient concentrations of PM have

24    been the subject of approximately 80 peer-reviewed research publications since 2002 (see Annex D).

25    Included among these new publications are several large single-city and multicity studies. The new

26    studies complement those reviewed in the 2004 PM AQCD and based upon those reults to evaluate effect

27    modification by season and region as well as the effects of different PM size fractions and components on

28    admissions or visits for specific diseases of the respiratory system, including asthma, bronchitis and

29    emphysema, (collectively referred to as COPD), pneumonia, upper respiratory infections, lower

1  respiratory infections and other minor categories. ICD codes (both 9th and 10th revisions) from hospital

2  admission or discharge records are used to ascertain the outcomes in these studies (Table 6-10). Several

3  new studies have also evaluated associations between short-term PM exposure and outpatient physician

4  visits.

5      Specific design and methodological considerations of the studies reviewed were discussed

6  previously (Section 4.4.10.2). Like the CVD endpoints discussed, the respiratory endpoints examined in

7  these studies were also heterogeneous. MCAPS investigators included COPD (ICD-9: 490-492) and

8  respiratory tract infections (464-466, 480-487) among those 65 years and older in their analyses. SOPHIA

9  investigators included asthma (ICD-9: 493), wheezing (ICD-9: 786.09), COPD (ICD-9: 491, 492, 496),

10  lower respiratory infection (466.1, 480-486), and all respiratory diseases combined (ICD-9: 460-466, 477,

11  480-486, 491-493, 496, 786.09) among all ages. APHEA-2 investigators examined asthma among ages 0-

12  14 and 15-64, COPD and asthma (ICD-9: 490-496) among older adults and all respiratory diseases

13  combined among older adults (ICD-9: 460-519). French PSAS investigators examined all respiratory

14  diseases (ICD-10: J00-J99) and respiratory infection (ICD-10: J10-22) among children, adults and older

15  adults. Finally, investigators conducting the multicity studies in Australia and New Zealand examined all

16  respiratory diseases (ICD-10 J00-J99 excluding J95.4-J95.9, R09.1, R09.8); asthma (ICD-10 J45, J46,

17  J44.8) and pneumonia and acute bronchitis (ICD-10 J12-J17, J18.0, J18.1, J18.8, J18.9, J20, J21) among

18  children less than 14 years old (scheduled admissions, transfers from other hospitals and admissions

19  arranged through a general practitioner were excluded). Unless otherwise specified, effect estimates are

20  presented for an increment of 10 $\mu g/m^3$ increase in PM mass.

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**Table 6-10.  Description of ICD-9 and ICD-10 codes for diseases of the respiratory system.**

| Description | ICD 9 Codes | ICD 10 Codes |
|---|---|---|
| Diseases of the Respiratory System | 460-519 | J00-J99 |
| Asthma | 493 | J45 |
| COPD and allied conditions | 490-496 (asthma, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis) | |
| Chronic lower respiratory diseases | | J40-J47 (bronchitis, emphysema, other COPD, asthma, status asthmaticus, bronchiactasis) |
| Acute Respiratory Infections | 460-466 (common cold, sinusitis, pharyngitis, tonsillitis, laryngitis & tracheitis, bronchitis & bronchiolitis) | |
| Acute Upper Respiratory Infections | | J00-J06 (common cold, sinusitis, pharyngitis, tonsillitis, laryngitis & tracheitis, croup & epiglottitis) |
| Acute bronchitis and bronchiolitis | 466 | J20-J22 |
| Pneumonia | 480-486 | J13-J18 |
| Wheezing | 786.09 | |

### 6.3.8.1. All Respiratory Diseases

#### $PM_{10}$

1    Estimates of the effect of $PM_{10}$ on respiratory diseases combined are summarized in Figure 6-9.
2    Information on the PM concentrations during the relevant study periods is found in Table 6-11. Excess
3    risks reported for studies of respiratory hospitalization or ED visit and $PM_{10}$ reviewed in the 2004 PM
4    AQCD were in the range of approximately 1-4%.

**Table 6-11.    PM concentrations in studies of respiratory diseases published since 2002.**

| Pollutant | Author | Location | Mean Concentration ($\mu g/m^3$) | Upper Percentile: concentrations ($\mu g/m^3$) |
|---|---|---|---|---|
| *$PM_{10}$* | | | | |
| | Barnett et al. (2005) | 7 Cities, Australia, NZ | 16.5-20.6 | Max: 50.2 – 156.3 |
| | Ulirsch et al. (2007) | Idaho | 23.2 | Max: 183.0 |
| | Peel et al. (2005) | Atlanta, GA | 27.9 | Max: 44.7 |
| | Luginaah et al. (2005) | Ontario, Canada | 50.6 | Max: 349 |
| | Slaughter et al. (2005) | Spokane, WA | NR | Max: 41.9 (using 90% of concentrations) |
| | Fung et al. (2005b) | Ontario, Canada | 38 | Max: 248 |
| | Fung et al. (2006) | Vancouver, Canada | 13.3 | Max: 52.17 |
| | Chen et al. (2005b) | Vancouver, Canada | 13.3 | Max: 52.2 |
| | Jaffe et al. (2003) | Cincinnati<br>Cleveland<br>Columbus | 43<br>60.8<br>37.4 | Max: 90<br>Max: 183<br>Max: 87 |
| | Lin et al. (2002b) | Toronto, Canada | 30.16 | Max: 116.20 |
| | Chimonas and Gessner (2007) | Anchorage, Alaska | 27.6 | Max: 421 |
| | Medina-Ramon et al. (2006) | 36 US Cities | 15.9-44.0 | NR |
| | Yang et al. (2004b) | Vancouver, Canada | 13.3 | Max: 52.2 |
| | Andersen et al. (2007b) | Copenhagen, Denmark | 25/24 | 75th: 30 / 99th: 72 |
| | Sinclair and Tolsma (2004) | Atlanta, GA | 29.03 | NR |
| | Chardon et al. (2007) | Paris | 23 | Max: 97.3 |
| | Gordian and Choudhury (2003) | Anchorage, AK | 36.11 | Max: 210.0 |
| | Jalaludin et al. (2004) | Sydney, Australia | 22.8 | Max: 44.9 |
| *$PM_{2.5}$* | | | | |
| | Barnett et al. (2005) | 7 Cities Australia, NZ | 8.1-11 | Max: 29.3 – 122.8 |
| | Host et al. (2008) | 6 Cities France | 13.8-18.8 | 95th: 25.0-33.0 |
| | Peel et al. (2005) | Atlanta, GA | 19.2 | 90th: 32.3 |
| | Slaughter et al. (2005) | Spokane, WA | NR | Max: 20.2 (using 90% of concentrations) |
| | Bell et al. (2008a) | 202 US Counties | NR | NR |
| | Fung et al. (2006) | Vancouver, Canada | 7.72 | Max: 32 |
| | Chen et al. (2005b) | Vancouver, Canada | 7.7 | Max: 32 |
| | Babin et al. (2007) | Washington, DC | "low, never reached code red" | NR |

| Pollutant | Author | Location | Mean Concentration (µg/m³) | Upper Percentile: concentrations (µg/m³) |
|---|---|---|---|---|
| | Chimonas and Gessner (2007) | Anchorage, AK | 6.1 | Max: 69.8 |
| | Ito et al. (2007) | New York, NY | All year: 15.1<br>Warm months (Apr–Sep.): 17.5<br>Cold months (Oct–March): 15.0 | All year: 95th: 32<br>Warm months (Apr–Sep): 95th: 38<br>Cold months (Oct–March): 95th: 31 |
| | Dominici et al. (2006) | 204 US Counties | 13.4 | 75th: 15.2 |
| | Yang et al. (2004b) | Vancouver, Canada | 7.7 | Max: 32.0 |
| | Andersen et al. (2007b) | Copenhagen, Denmark | 10 | 99th: 28 |
| | Halonen et al. (2008) | Helsinki, Finland | NR; Median = 9.5 | Max: 69.5 |
| | Sinclair and Tolsma (2004) | Atlanta, GA | 17.62 | NR |
| | Chardon et al. (2007) | Paris, France | 14.7 | 75th: 18.2 |
| $PM_{10-2.5}$ | | | | |
| | Host et al. (2008) | 6 Cities France | 7.0 – 11.0 | 95th: 12.5–21.0 |
| | Peel et al. (2005) | Atlanta, GA | 9.7 | 90th: 16.2 |
| | Slaughter et al. (2005) | Spokane, WA | NR | NR |
| | Peng et al. (2008) | 108 U.S. Counties | NR; Median: 9.8 | 75th: 15.0 |
| | Fung et al. (2006) | Vancouver, Canada | 5.6 | Max: 27.07 |
| | Chen et al. (2005b) | Vancouver, Canada | 5.6 | Max: 24.6 |
| | Lin et al. (2002b) | Toronto, Canada | 12.17 | Max: 68.00 |
| | Yang et al. (2004b) | Vancouver, Canada | 7.7 | Max: 24.6 |
| | Halonen et al. (2008) | Helsinki, Finland | NR; Median: 9.9 | Max: 101.4 |
| | Sinclair and Tolsma (2004) | Atlanta, GA | 9.67 | NR |
| ULTRAFINE | | | | |
| | Andersen et al. (2007b) | Copenhagen, Denmark | Mean particles/cm³: 6847 | 99th: 19,895 |
| | Halonen et al. (2008) | | NR: Median particles/cm³: 8,203 | Max: 50,990 |

## Children

1    Barnett et al. (2005) used a case-crossover design to study respiratory hospital admissions (ICD-9

2    460-519) of children (age groups 0, 1 to 4, 5 to 14 years) in seven cities in Australia and New Zealand

3    during the study period (1998-2001). In this study, using a 0-1 day average lag, increases in respiratory

4    hospital admissions of 2.3% (95% CI: 1.9–7.3) among children 1-4 years old, 2.5% (95% CI: 0.1–5.1)

5    among children 5-14 years old and 2.0% (95% CI: -0.13 to 4.3) among infants less than 1 year old,

6    per 10 µg/m³ increase in 24-h average $PM_{10}$ were observed (2005). Luginaah et al. (2005) did not observe

7    significant increases in respiratory hospitalizations among male or female children in Ontario Canada,

8    while Ulirsch et al. (2007) reported increased admissions for respiratory hospitalizations, ED and urgent

9    care visits combined among children <17 years old.

### All Ages

1     In a study of 4 million emergency department visits from 31 hospitals in Atlanta, SOPHIA

2     investigators reported an excess risk of 1.3% (95% CI: 0.4-2.1) per 10 μg/m$^3$ increase in 24-h average

3     $PM_{10}$ for ED visits for respiratory causes combined (URI, asthma, pneumonia and COPD) among all ages

4     in Atlanta during the period August, 1998 to August, 2000 (Peel et al., 2005). Reanalyses with four

5     additional years of data to assess the robustness of estimates to adjustment for $PM_{10}$, $O_3$, CO and $NO_2$

6     found that associations for $PM_{10}$ and $O_3$ persisted in two-pollutant models (Tolbert et al., 2007). Luginaah

7     et al. (2005) studied hospitalizations in Ontario Canada. These authors stratified their results by age and

8     gender, compared time series to case crossover approaches and presented three single day lags. The

9     results for all ages combined, stratified by gender and all lags are presented in the figure; however, the

10    strongest, most significant estimate for $PM_{10}$ was for adult males (15-64 years old). Additional studies

11    conducted in Spokane, Washington and Ontario, Canada did not provide evidence of increased hospital

12    admissions for respiratory diseases among all ages (Fung et al., 2005a; Slaughter et al., 2005) while

13    Ulirsch et al. (2007) reported a significant positive association among all ages in two Southeast Idaho

14    cities for hospitalizations, ED and urgent care visits combined. This estimate was robust to adjustment for

15    gaseous pollutants.

### Older Adults

16    Results from one U.S. and three single city Canadian studies offer somewhat consistent evidence

17    for the effect of $PM_{10}$ on respiratory admissions among older age groups. Ulirsch et al. (2007) found

18    increases in hospitalizations, ED and urgent care visits combined among this age group in 2 cities of

19    Southeast Idaho. Two studies in Vancouver report increased admissions for respiratory causes with the

20    largest effects observed for a 3 day moving average (0-2 days) (Chen et al., 2005b; Fung et al., 2006).

21    Fung et al. (2005a) observed non-significant increases in admissions with $PM_{10}$ among older adults in

22    Ontario, Canada while the study by Luginaah et al. (2005), which was also conducted in Ontario, did not

23    provide compelling evidence for an effect that was robust to method selection, although some increases

24    among males were observed. Finally, a study of hospital admissions for cardiopulmonary conditions

25    combined among older adults (65+ years) in Allegheny County, PA found a positive association with

26    $PM_{10}$ at lag 0 (Arena et al., 2006).

27    In a study in Copenhagen Denmark, which was designed primarily to examine the effects of

28    ultrafine particles and PM sources, $PM_{10}$ was associated with hospitalization for respiratory disease

29    among older adults greater than 65 years (4.6% [95% CI: 1.5-6.9, per 10 μg/m$^3$, lag 0-4]) (Andersen et al.,

30    2007b). This association lost precision but was robust to adjustment for total number concentration (3.8%

1    95% [CI: 0.8-7.6]). After adjustment for CO the effect estimate was 2.5% (95% CI: 0.4-4.6) and after

2    adjustment for NO$_2$ the effect estimate was 2.3% (95% CI: 0.5-4.2) (Andersen et al., 2007a).
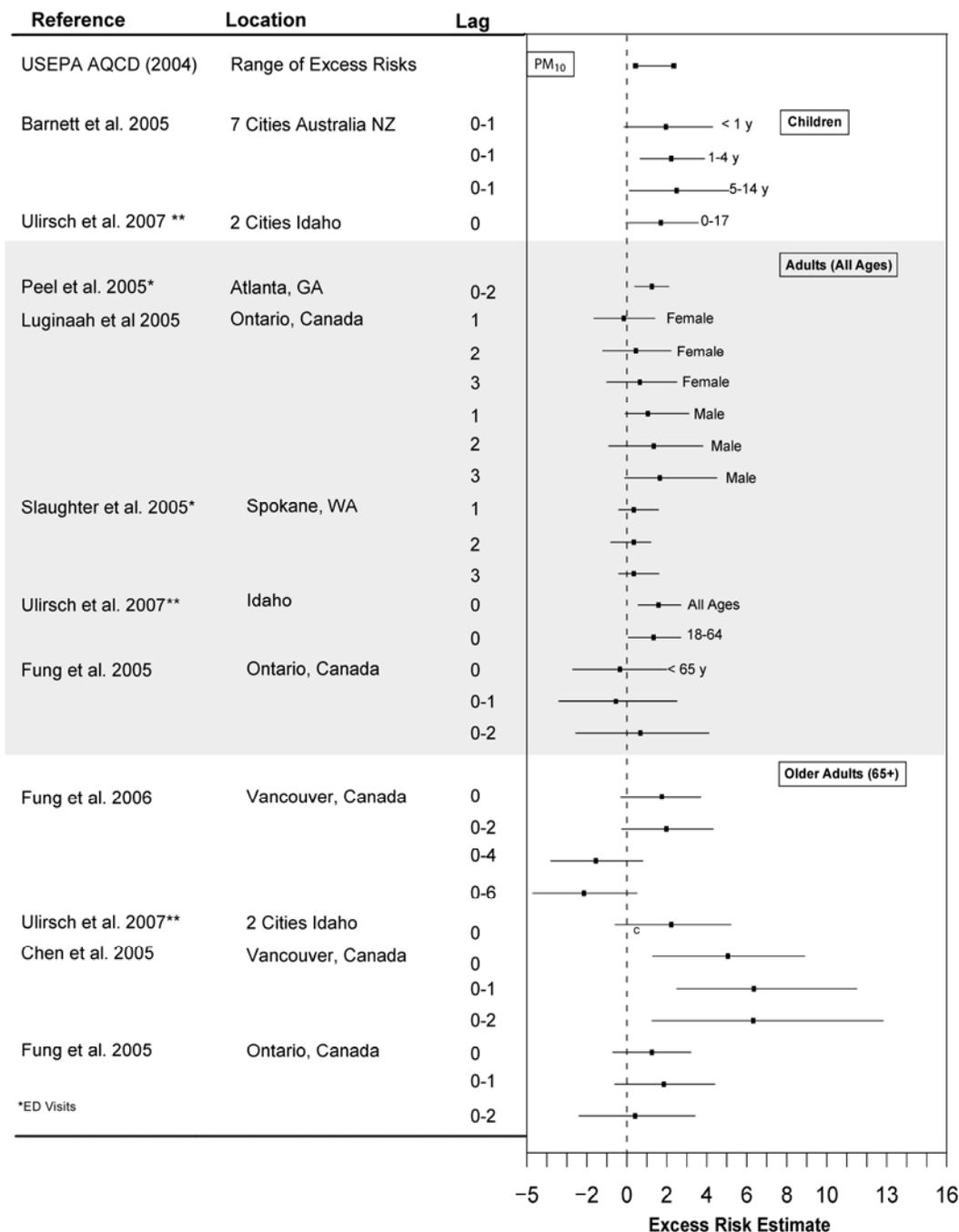


**Figure 6-9.    Excess risks estimates per 10 μg/m$^3$ 24-h average PM$_{10}$ concentration for studies of ED visits and hospitalizations for respiratory diseases. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. or Canada are also included.**

**Ulirsch et al. (2007) combines ED visits, hospitalizations and urgent care visits in their analyses.

### PM$_{2.5}$, PM$_{10-2.5}$ and Other Size Fractions

1      Studies of PM$_{2.5}$ and PM$_{10-2.5}$ and hospitalization or ED visits for respiratory diseases that were

2      conducted since 2002 are summarized in Figure 6-10.

#### Children

3      A study of seven cities in Australia and New Zealand reported significantly increased risk of

4      hospitalization associated with PM$_{2.5}$ among children (Barnett et al., 2005)}. Increases in respiratory

5      hospital admissions of 6.4% (95% CI: 2.7-10.3) among infants less than 1 year and 4.5% (95% CI: 1.9-

6      7.3) among children 1 to 4 years per 10 μg/m$^3$ increase in PM$_{2.5}$ (0-1 day average) were observed (2005).

7      In contrast to these results, French PSAS investigators report an increase of respiratory hospitalizations

8      associated with PM$_{10-2.5}$ of 6.2% (95% CI: 0.4, 12.3, 0-1 day avg.) per 10 μg/m$^3$ increase among children

9      0-14 years old Host et al. (2008). Non-significant increases of 0.8% or below were observed in

10     association with 10 μg/m$^3$ increases in PM$_{2.5}$ in all age categories (2008). A large effect for PM$_{10-2.5}$ (31%

11     95% CI: -4.7, 80) was also observed in a single city study of children less than 3 years old in Vancouver

12     (Yang et al., 2004b) but does not appear in the figure because its inclusion caused compression and

13     reduced the readability of other results presented. These authors also studied the effects of PM$_{10}$ and PM$_{2.5}$

14     but only reported effect estimates for PM$_{10-2.5}$ because PM$_{2.5}$ was not significantly associated with first

15     respiratory hospitalization.

#### Adults and All Ages Combined

16     During the most recent years of the SOPHIA study (August 1, 1998, through August 31, 2000)

17     PM$_{2.5}$, PM$_{10-2.5}$, ultrafine number count and PM$_{2.5}$ components (sulfate, acidity, EC, OC, and an index of

18     water-soluble transition metals) were included in the analyses. Study investigators reported similar

19     findings as MCAPS investigators for older adults (described below), with a larger increase in ED visits

20     for respiratory diseases associated with PM$_{2.5}$ compared to PM$_{10-2.5}$ (Peel et al., 2005). Using an a priori

21     lag of 0-2 days, excess risks of 1.6% (95% CI: -0.003 to 3.5) per 10 μg/m$^3$ increase in 24-h average PM$_{2.5}$

22     and 0.6% (95% CI: -3.6 to 5.1) per 10 μg/m$^3$ increase in PM$_{10-2.5}$ were observed. Weaker, less precise

23     associations with components were reported and no increase with ultrafine particle count was indicated.

24     In a recent analysis using data from 1998 through 2002 to compare source apportionment methods, Sarnat

25     et al. (2008) reported that PM$_{2.5}$ from mobile sources, PM$_{2.5}$ from biomass burning and sulfate-rich

26     secondary PM$_{2.5}$ were associated with respiratory ED visits and associations were robust to the choice of

1    the method (Sarnat et al., 2008). Excess risks were significant, ranging from approximately 2%-4%,

2    depending on the method.

3        French PSAS investigators did not report an association with hospital admissions and $PM_{2.5}$ or

4    $PM_{10-2.5}$ among adults 15-64 years old (Host et al., 2008) In a study of respiratory hospital admission and

5    ED visits (ICD-9 Codes 460-519) among all ages conducted in Spokane, Washington, no associations

6    were observed with any size fraction of PM considered (e.g. $PM_1$, $PM_{2.5}$, $PM_{10-2.5}$, $PM_{10}$) (Slaughter et al.,

7    2005). However, authors observe that there was a suggestion of greater effect estimates with $PM_{2.5}$

8    compared to $PM_{10-2.5}$ (Slaughter et al., 2005). Furthermore, several of the same investigators conducted a

9    source apportionment analysis using daily fine PM filter samples from the same residential monitor in

10   Spokane (Schreuder et al., 2006). In this investigation, $PM_{2.5}$ from vegetative burning in the previous day

11   (lag 1) was associated with respiratory hospital admissions (1.023 [95% CI: 1.009-1.038] per interquartile

12   range increase in the source marker).


### Older Adults

13       MCAPS investigators observed largely null findings for $PM_{2.5}$ and respiratory hospitalizations

14   (COPD, lower and upper respiratory infections) for the U.S. as a whole but reported heterogeneity in

15   effect estimates across the country that were explained by regional and seasonal factors (Bell et al.,

16   2008a). The nationwide excess risk of respiratory admissions with $PM_{2.5}$ was 0.22% (95% posterior

17   interval (PI): -0.12 to 0.56, lag 0) (Bell et al., 2008a). The largest increases were observed during the

18   winter in the Northeast (1.05% [95% PI: 0.29-1.82], lag 0) and the Southeast (1.76% [95% PI: 0.60-2.93],

19   lag 0). Significant increases in respiratory admissions were also observed at lag 2; an increase of 0.94%

20   (95% PI: 0.22-1.67, lag 2) was observed for the Southwest and an increase of 0.41 (95%PI: 0.09, 0.74)

21   was observed for the U.S. as a whole. In a multicity Australian study, Simpson et al. examined the

22   association between fine particles measured by nephelometry and respiratory hospital admissions (ICD-9

23   460-519) among older adults (65+ years) and reported significant associations (1.055 [95% CI: 1.008-

24   1.1045], lag 0-1 day average) from a meta-analysis combining effect estimates from all cities (Simpson et

25   al., 2005). Simpson et al. (2005) considered results from three statistical models, including standard

26   GAM, which produced similar results.

27       In an analysis of $PM_{10-2.5,}$ MCAPS investigators observed small imprecise increases in respiratory

28   admissions with 24-h $PM_{10-2.5}$ concentration (0.33% [95% PI: -0.21 to 0.86, per 10 $\mu g/m^3$, lag 0]) (Peng et

29   al., 2008), which decreased after adjustment for $PM_{2.5}$ (0.26% [95% PI: -0.32 to 0.84 per 10 $\mu g/m^3$ lag 0]).

30   Associations with $PM_{2.5}$ increased (0.7% [95% PI: 0-1.5, lag 0]) or persisted (0.6% [95% PI: -0.2, 1.25,

31   lag 2]), after adjustment for $PM_{10-2.5}$, however (excess risks estimated from graphs).
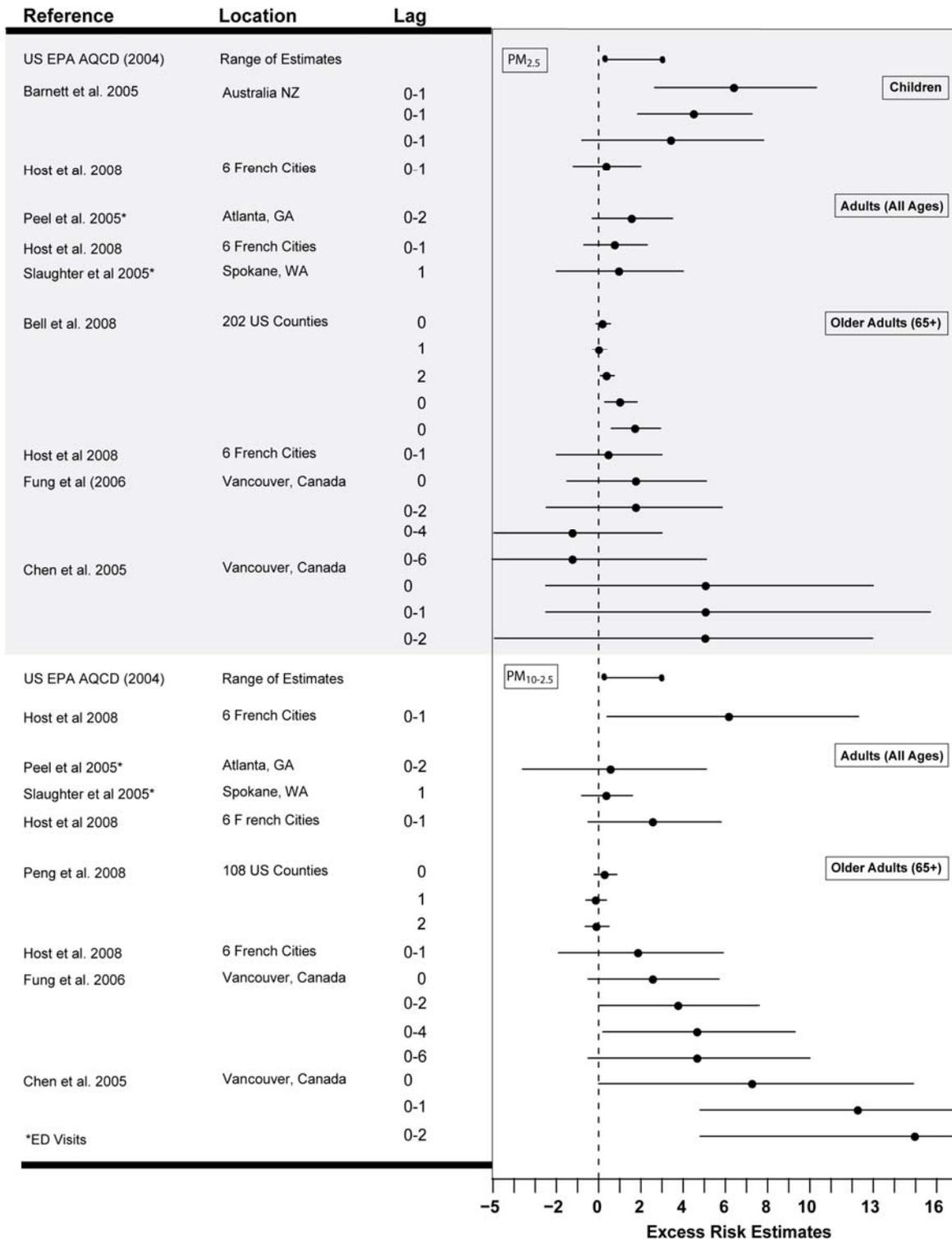
**Figure 6-10. Excess risks estimates per 10 μg/m³ increase in 24-h average PM₂.₅ and PM₁₀-₂.₅ for studies of ED visits and hospitalizations for respiratory diseases. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. or Canada are also included.**

1    French PSAS investigators reported a non-significant increase in hospitalizations for respiratory

2    diseases (ICD-10 J00-J99) with 24-h average $PM_{10-2.5}$ among older adults while $PM_{2.5}$ estimates were

3    closer to the null (Host et al., 2008). Unlike the previously described MCAPS study (Peng et al., 2008),

4    however, results from 2-pollutant models were not available in the study of Host et al. (2008). Positive

5    associations of first hospitalization, overall hospitalizations and readmission for respiratory diseases and

6    $PM_{10-2.5}$ were also reported among older adults in Vancouver (Chen et al., 2005b). $PM_{10-2.5}$ was associated

7    with an increase of 15% (95% CI: 4.8–22.8) in overall admissions per 10 $\mu g/m^3$. Increases associated with

8    $PM_{10-2.5}$ were larger for readmissions compared to overall admissions. The association for $PM_{2.5}$ with

9    overall admissions was 5.1% (95% CI: -4.9 to 13) and the association with readmissions was not larger. In

10   this study, effect estimates for $PM_{10}$ and $PM_{10-2.5}$ lost precision but were robust to adjustment for gaseous

11   pollutants while the estimate for $PM_{2.5}$ was null after adjustment for gaseous pollutants (Chen et al.,

12   2005b). In Vancouver, Fung et al. (2006) also report larger effect estimates for $PM_{10-2.5}$ than $PM_{2.5}$ among

13   adults 65 years and older (Fung et al., 2006). These authors report increased admissions of 1.8%

14   (95% CI: -2.5 to 5.8) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 3.8% (95% CI: 0–7.6) per 10 $\mu g/m^3$ increase in

15   $PM_{10-2.5}$ (lag 0-1 day average).

16       In two analyses of data collected in Copenhagen Denmark between 1999 and 2004, size

17   distribution and total number concentration of ultrafine, accumulation mode and $PM_{10}$ source

18   apportionment were investigated in relation to respiratory hospitalizations (J41-42, J43, J44-46) among

19   adults greater than 65 years of age (Andersen et al., 2007a; 2007b). Of the ultrafine particle metrics

20   examined, aged secondary long-range transported particles with a median diameter of 212 nm were

21   significantly associated with respiratory hospital admissions (1.04 [95% CI: 1.01-1.08], per 495

22   particles/$cm^3$) (2007b). The authors note that it was difficult to separate the effects of $PM_{10}$ and $NC_{a212}$,

23   which were highly correlated in these data. $PM_{2.5}$ was not associated with respiratory hospitalizations in

24   these data. However, $PM_{10}$ sources including biomass combustion, secondary inorganic compounds, oil

25   combustion and crustal were associated with respiratory hospitalizations (RR: 1.040, 95% CI: 1.009,

26   1.072: RR: 1.050, 95% CI: 1.021, 1.081, RR: 1.035 95% CI: 1.006, 1.065 and RR: 1.054, 95% CI: 1.028,

27   1.081 per interquartile range respectively) (Andersen et al., 2007b).

## *Summary*

28       As shown in Figure 6-9, excess risks reported for studies of respiratory hospitalization or ED visit

29   and $PM_{10}$ concentration are generally within the range observed in multi-city and large single-city studies

30   published prior to 2002 and included in the 2004 PM AQCD. The two largest new studies reported

31   positive findings for the association of $PM_{10}$ with respiratory diseases combined in children and among all

32   ages (Barnett et al., 2005; Peel et al., 2005). Not all single city studies report positive associations,

however. Design considerations may explain some of the heterogeneity in results. For example, Ulirsch et al. (2007) who reported positive findings examined hospitalizations, ED visits and urgent care visits combined. In general, studies comparing multiple statistical methods report consistency across methods (Fung et al., 2006; 2005; Simpson et al., 2005; Yang et al., 2004). The heterogeneity in effect estimates in single city studies may also be related to differences between locations in sources of PM, exposure patterns and climate conditions. In general, larger associations were reported for children and older adults.

Figure 6-10 shows that effect estimates for $PM_{2.5}$ and $PM_{10-2.5}$ from both single city U.S. and Canadian studies and multicity studies are more heterogeneous and less precise than those for $PM_{10}$, with effect estimates for multicity and large single-city studies generally falling in the range reported in the 2004 PM AQCD. The effects of these size fractions on admissions or visits for specific diseases will be discussed in the sections that follow. Time lags between exposure and hospital admission or ED visit for respiratory diseases have been shown to vary by both age, disease and other factors (Forastiere and Faustini, 2008) and will also be discussed in later sections in relation to specific disease outcomes.

Several additional studies conducted outside the U.S. and Canada reported positive associations of respiratory hospitalizations among a range of age groups using a variety of lags with $PM_{10}$ (Bedeschi et al., 2007; Chen et al., 2006a; Oftedal et al., 2003) and with $PM_{2.5}$ (Hinwood et al., 2006; Neuberger et al., 2004; Vigotti et al., 2007) and BS (Bartzokas et al., 2004). Other studies reported no associations with $PM_{10}$ or TSP (Llorca et al., 2005; Vegni and Ros, 2004).

### 6.3.8.2. Asthma

Results from multicity studies of hospital admissions and ED visits for asthma as well as single city studies conducted in the U.S. and Canada are summarized in Figure 6-11. Concentrations of PM for the relevant study period are found in Table 6-12.

#### *Children*

SOPHIA investigators (Peel et al., 2005) reported that, for several PM mass indicators, the largest effect estimate observed using the a priori lag (0-2 d average) was the association of $PM_{10}$ with pediatric (2-18 years) asthma ED visits (1.6% [95% CI: -0.2 to 3.4]). Asthma admissions in children were examined in the Australia / New Zealand multicity study (Barnett et al., 2005). Associations for asthma hospital admissions with $PM_{10}$ and $PM_{2.5}$ were reported but also did not reach statistical significance.

Lin et al. (2002b) used both time series and case crossover approaches to investigate the influence of PM on asthma hospitalization in children, 6-12 years old, in Toronto from 1981 to 1993. These authors report relatively small differences in results obtained through bi-directional case crossover and time series approaches but indicate that unidirectional case crossover methods may overestimate the relative risks. As

1 shown in Figure 3, single to 7-day average lags were investigated and authors note that estimates

2 increased and appeared to level off at the longer lags. Effect estimates for $PM_{2.5}$ are not easily

3 distinguished from the null but $PM_{10-2.5}$ is significantly associated with asthma admissions among boys

4 and among girls. These associations were imprecise but robust to adjustment for gaseous pollutants

5 among all children combined.

6  Babin et al. (2007) examined asthma-related ED visits among children 1-17 years old in

7 Washington DC from 2001 to 2004 in relation to $PM_{2.5}$, ozone and social economic status and reported an

8 increase in ED visits with ozone but not with $PM_{2.5}$ (Babin et al., 2007). $PM_{2.5}$ was not significantly

9 associated with pediatric hospitalizations for asthma in Oklahoma (Magas et al., 2007).

10  Two recent European studies evaluated the effect of $PM_{10}$, $PM_{2.5}$, ultrafine PM and $PM_{10}$ sources

11 (from source apportionment analysis) with asthma hospitalizations or ED visits (Andersen et al., 2007a;

12 2007b; Halonen et al., 2008). Anderson et al. (2007) found an association between $PM_{10}$ attributed to

13 vehicle emissions and asthma hospitalizations among children 5-18 years (5.4% 95% CI: 0.57, 22.9 per

14 10 μg/m$^3$, 0-5 d avg) in Copenhagen, Denmark (Andersen et al., 2007a). In their study examining PM size

15 fractions, accumulation mode particles number count was most strongly associated with asthma

16 admissions (e.g., $NC_{a212}$: 1.08 95% CI: 1.00, 1.17 per 495 particles per cm$^3$, lag 0-5) (Andersen et al.,

17 2007b).

18  Halonen et al. (2008) examined the association of various size fractions of PM with ED visits for

19 asthma among children < 15 years, and asthma and COPD combined in adults (15-64 years) and older

20 adults (65+ years) (Halonen et al., 2008). These authors evaluated lags 0 to 5 and noted a different lag

21 structure depending on age with children experiencing greater effects at lags 3 to 5 days compared to

22 adults at lag 0. Aitken, accumulation mode particles and traffic-related PM were significantly and most

23 strongly associated with asthma visits among children, while no association with $PM_{10-2.5}$ was observed.

24  Sinclair and Tolsma (2004) investigated respiratory ambulatory care visits using ARIES data in

25 Atlanta, GA (also used by SOPHIA investigators) and health insurance records (Sinclair and Tolsma,

26 2004). These authors evaluated three 3-day moving average lags (0-2, 2-5 and 6-8 days) and reported

27 relative risks, with no confidence intervals, for significant results only (not included in Figure 6-11). For

28 childhood asthma outpatient visits, OHC, $PM_{10-2.5}$, $PM_{10}$, EC and OC were significantly associated with

29 ambulatory care visits at lags 0-2 or 2-5 days.

30  Two recent studies in Anchorage used medical records to examine effects of particle exposure on

31 pediatric asthma outpatient visits, prescriptions for short-acting inhalers (Chimonas and Gessner, 2007),

32 and school-administered asthma medication (Gordian and Choudhury, 2003). Chimonas et al. (2007)

33 examined Medicaid claims for asthma-related and lower respiratory infection visits among children less

34 than 20 years of age for five years (approximately 25,000 children were enrolled in Medicaid each year

1    between 1999 and 2003). Citing work done in the mid-1980's, the authors describe their city's particles as

2    arising primarily from natural, geologic sources ($PM_{10}$), and to a lesser extent from local automotive

3    emissions ($PM_{2.5}$) (Pritchett and Cooper, 1985). Using GEE in a time-series analysis of daily and weekly

4    effects of particle exposure on health outcomes, the authors found that each 10 $\mu g/m^3$ increase in 24-h

5    average $PM_{10}$ was associated with a 0.6% increase (95% CI: 0.1–1.3)) in outpatient visits for asthma. The

6    same increase in weekly $PM_{10}$ concentration resulted in a 2.1% increase (95% CI: 0.4–3.8)) in asthma

7    visits, after adjustment for gaseous pollutants. No meaningful associations were observed for $PM_{2.5}$

8    (Chimonas and Gessner, 2007).

9    Gordian and Choudhury (2003) used school nurses' records from 1994-1997, in 12 Anchorage

10    neighborhood schools to examine the association between various moving averages of $PM_{10}$

11    concentration and asthma medication administration. Using a time-series regression model adjusted for

12    autocorrelation, they found that the best predictor of amount of medication administration was a 21-day

13    average of $PM_{10}$. The estimated coefficient, given for $PM_{10}$ x 100, was 7.25 (p = 0.01).

14    Jalaludin et al. (2004) described above under respiratory symptom outcomes found that for each

15    10 $\mu g/m^3$ increase in $PM_{10}$ (lag 0) there was an associated increased risk of doctor visits for asthma

16    (9.09% [95% CI: 3.32–15.6]). The strongest association was found for a two-day lag (12.09% 95% CI:

17    4.87, 19.20), and the effect of the lag 0 exposure was unchanged in multipollutant models with ozone or

18    $NO_2$. The mean $PM_{10}$ level during the study period of 22.8 $\mu g/m^3$. Another study of house calls in Greater

19    Paris reported an increased association for both $PM_{2.5}$ and $PM_{10}$ with asthma (4.4% [95% CI: -1.3 to 10.4]

20    and 2.5% [95% CI: -1.7 to 6.8], respectively, 0-3 day average) (Chardon et al., 2007). The mean levels

21    were 14.7 and 23 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10}$, respectively.

### All Ages and Adults

22    Results from the Atlanta SOPHIA study based on the a priori models examining a 3-day moving

23    average (lag 0-2 days) revealed no statistically significant associations with asthma (ICD-9 493, 786.09)

24    among all ages for any of the PM metrics studied ($PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, Particle Count, PM components)

25    (Peel et al., 2005). However, the 14-day unconstrained distributed lag model produced an excess risk of

26    9.9% (95% CI: 6.5, 13.5). The authors note that associations of $PM_{2.5}$ and OC with asthma tended to be

27    stronger during the warmer months. Sinclair and Tolsma (2004) report a significant association between

28    adult outpatient visits for asthma and ultravine particles, but not other PM size fractions.

29    In New York City, Ito et al. (2007) examined numbers of ED visits for asthma among all ages

30    (ICD-9 493) in relation to pollution levels from 1999 to 2002 (Ito et al., 2007); several weather models

31    were evaluated. Although the association with $NO_2$ was the strongest, $PM_{2.5}$ was significantly associated

1   with asthma ED visits in each weather model (strongest during the warm months) and remained

2   significant after adjustment for $O_3$, $NO_2$, CO and $SO_2$.

3       Jaffe et al. (2003) examined the effects of ambient pollutants ($PM_{10}$, ozone, $NO_2$ and $SO_2$) during

4   the summer months (June through August) on the daily number of ED visits for asthma among Medicaid

5   recipients aged 5 to 34 years from 1991 to 1996 in Cincinnati, Columbus and Cleveland. Lags 1 to 3 were

6   tested and only statistically significant lags were presented. For all cities combined, the overall effect

7   estimate for 24-h average $PM_{10}$ was 1.0% (95% CI: -1.44 to 3.54 per 10 μg/m$^3$ increase). The effect

8   estimate for Cleveland was the only significantly elevated estimate (2.3 95% CI: 0.0 to 4.9 per 10 μg/m$^3$

9   increase). The authors report results from analyses indicating a possible concentration response for ozone

10  but no consistent effects for $PM_{10}$.

11      Slaughter et al. (2005) reported no associations with ED visits or hospitalizations for asthma,

12  among all ages, in Spokane Washington for the PM size fractions studied ($PM_1$, $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$). An

13  association with CO, which the authors attribute to combustion related pollution in general, was observed,

14  however (Slaughter et al., 2005). The $PM_{2.5}$ air quality index (AQI) was not correlated with asthma ED

15  visits among military trainees in San Antonio, Texas (Letz and Quinn, 2005). Halonen et al. (2008)

16  reported that, for older adults, $PM_{2.5}$ and $PM_{10-2.5}$, long range transported and traffic-related particles were

17  associated with asthma and COPD visits combined. For adults 15-65 years, asthma hospitalizations were

18  associated with accumulation mode and thoracic coarse particles only. As noted above association with a

19  longer exposure lag was observed among children than adults. In the U.S., Michaud et al. (2004)reported

20  an association for asthma and COPD ED visits combined with $PM_1$ (lag 1) in Hilo, Hawaii in a study

21  designed to investigate the effect of volcanic fog (Michaud et al., 2004).

### Summary

22      As shown in Figure 6.11, excess risk estimates for asthma are generally larger than those reported

23  for diseases of the respiratory system combined. The larger effect estimates for asthma were also observed

24  in studies reviewed in the 2004 PM AQCD. A variety of factors including the underlying distribution of

25  individual sensitivity and severity, medication use and other personal behaviors can influence the lag time

26  observed in observational studies (Forastiere and Faustini, 2008). Still, excess risk estimates for asthma

27  increase with longer lag times in most studies that examine lag structure (2007a; Andersen et al., 2007b;

28  Chimonas and Gessner, 2007; Halonen et al., 2008; Lin et al., 2002; Peel et al., 2005). Positive

29  associations were observed with both $PM_{10-2.5}$ and $PM_{2.5}$ but not consistently across study locations.

30  Investigators from the only U.S. study (Ito et al., 2007) to observe a positive association for $PM_{2.5}$ with

31  childhood asthma hospitalization also reported an association with $PM_{10-2.5}$ that was stronger than the

32  association with $PM_{2.5}$ in the warm season (Ito et al., 2007).
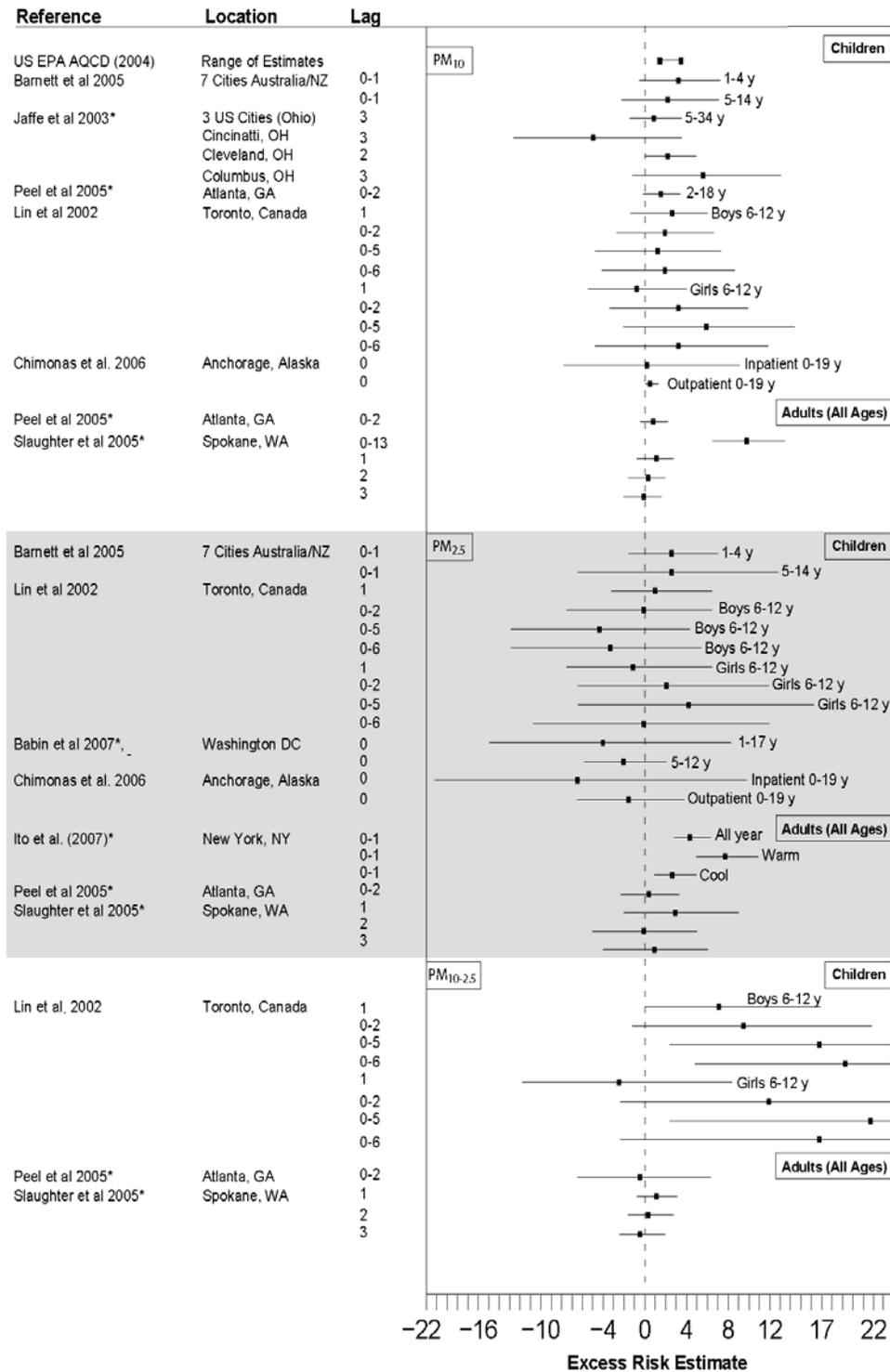
**Figure 6-11.** Excess risks estimates per 10 µg/m$^3$ increase in 24-h average PM$_{10}$, PM$_{2.5}$ and PM$_{10-2.5}$ for studies of asthma ED visits* and hospitalizations. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. or Canada are also included.

1    Most additional single city studies conducted in Europe, South America and Asia, have investigated

2    the associations of asthma hospitalizations or ED visits with TSP, $PM_{10}$ and $PM_{2.5}$ and most have reported

3    evidence of an association (Arbex et al., 2007; Bell et al., 2008b; Chen et al., 2006a; Erbas et al., 2005;

4    Galan et al., 2003; Kim et al., 2007b; Ko et al., 2007a; Kuo et al., 2002; Lee et al., 2002; Lee et al.,

5    2006b; Migliaretti and Cavallo, 2004; Migliaretti et al., 2005; Wong et al., 2002b) while a few have not

6    (Masjedi et al., 2003; Tsai et al., 2006c; Yang et al., 2007).

## 6.3.8.3. COPD

7    Results from multicity studies of hospital admissions and ED visits for COPD as well as single city

8    studies conducted in the U.S. and Canada are summarized in Figure 6-12. Concentrations of PM for the

9    relevant study period are found in Table 6-11. In one multicity study using MCAPS data for 204 counties

10   a significant association of about 1% increase in COPD (ICD-9 490-492) hospitalizations was observed

11   overall with $PM_{2.5}$, with the largest effects at lags 0 and 1. Heterogeneity in effect estimates was observed

12   across the U.S. with a significant increase of about 4% observed in the Southeast at lag 0. In another study

13   using Medicare data in 36 U.S. cities (1986 to 1999) short-term exposure to $PM_{10}$ was associated with an

14   increase in COPD hospital admissions (ICD-9 490-496, excluding 493) of 1.47% (95% CI: 0.93-2.01,

15   lag 1) during the warm season (Medina-Ramon et al., 2006).

16   In Atlanta, SOPHIA investigators reported a comparably sized effect estimate for COPD (ICD-9

17   491, 492, 496) and 24-h average $PM_{2.5}$ (1.5% [95% CI: -3.1-6.3, 0-2 d average]) (Peel et al., 2005). The

18   association of $PM_{10}$ with COPD reported by Peel et al. (2005) was 1.8% (95% CI: -0.6-4.3). No

19   associations were reported for $PM_{10-2.5}$, ultrafine or $PM_{2.5}$ components (Peel et al., 2005). Slaughter et al.

20   (2005) reported no associations between any size fraction of PM in Spokane, Washington ($PM_{10}$, $PM_{2.5}$,

21   $PM_{10-2.5}$) and COPD (ICD-9 491, 492, 494, 496) (Slaughter et al., 2005). However, in a study conducted

22   in Vancouver, Canada, Chen et al. (2004) reported significant increases in COPD admissions (ICD-9

23   490-492, 494, 496) for $PM_{10}$ (16.5% [95% CI: 6.88-27.02, 0-3 d average]) and $PM_{2.5}$ (17.1% [95% CI:

24   4.6-31.0) (Chen et al., 2004). These investigators reported a non-significant increase for $PM_{10-2.5}$ (10.0%

25   [95% CI: -1.2-22.8, 0-3 d average]). The effect estimates for PM metrics were diminished after

26   adjustment for $NO_2$, however.
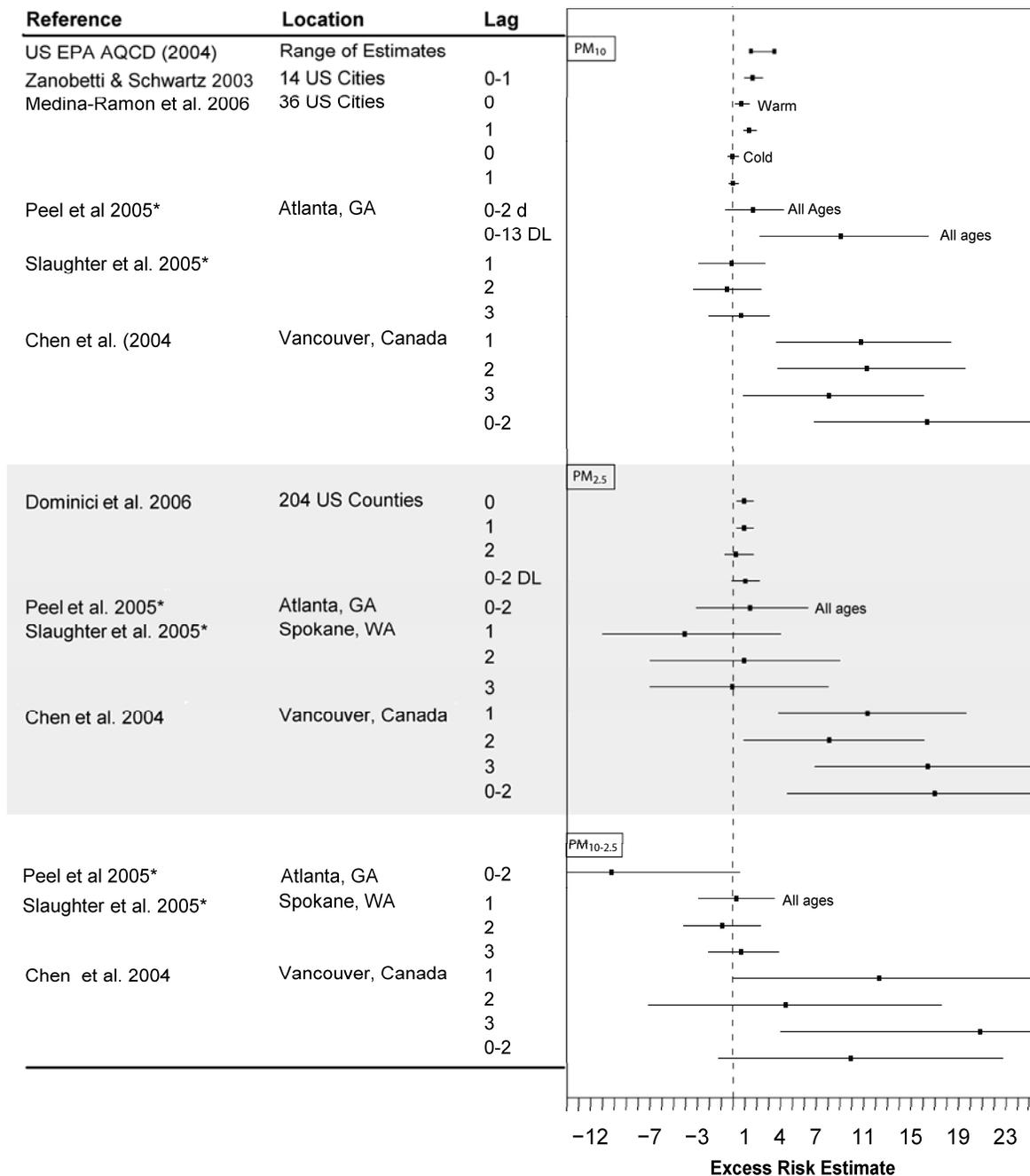
**Figure 6-12. Excess risks estimates per 10 µg/m³ increase in 24-h average PM$_{10}$, PM$_{2.5}$ and PM$_{10-2.5}$ for studies of COPD ED visits* and hospitalizations among older adults (65+ years, unless other age group is noted). Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. or Canada are also included.**

## *Summary*

1      With the exception of one study conducted in Spokane Washington (Slaughter et al., 2005),

2    associations have been consistently observed for $PM_{2.5}$ and $PM_{10}$ with COPD in multicity and single city

3    studies conducted in the U.S. and Canada. Associations with $PM_{10-2.5}$ are more variable. A study that

4    examined 7 single day lags in association with pooled COPD and asthma ED visits in Finland reports that

5    $PM_{2.5}$, $PM_{10-2.5}$, traffic sources as well as gaseous pollutants had a more immediate effect in older adults

6    (lags 0 and 1) compared to the children experiencing asthma (3-5 day lags) (Halonen et al., 2008). Several

7    single city studies conducted outside of the U.S. or Canada are inconsistent with regard to their findings

8    for PM and COPD (Agarwal et al., 2006; Hapcioglu et al., 2006; Ko et al., 2007b; Martins et al., 2002;

9    Masjedi et al., 2003; Tenias et al., 2002; Yang et al., 2007).

## 6.3.8.4. Pneumonia and Respiratory Infections

10      Results from multicity studies of hospital admissions and ED visits for respiratory infection as well

11    as single city studies conducted in the U.S. and Canada are summarized in Figure 6-13. Concentrations of

12    PM for the relevant study period are found in Table 6-11.

### *Children*

13      In the study of 7 cities in Australia and New Zealand, associations of $PM_{2.5}$ with pneumonia and

14    acute bronchitis were observed among infants less than one year old (4.54% [95% CI: 0.00–9.20]) and

15    children 1-4 years old (6.44% [95% CI: 0.26–12.85]) (Barnett et al., 2005).

16      In a study of inpatient and outpatient visits for lower respiratory tract infections among children in

17    Anchorage, Alaska, no significant associations were observed (Chimonas and Gessner, 2007). In contrast,

18    Lin et al. (2005) observed associations of respiratory infections (ICD-9 464, 466, 480-487) with $PM_{10-2.5}$

19    and $PM_{10}$ that persisted after adjustment for gaseous pollutants among children less than 15 years old (Lin

20    et al., 2005). Significant single pollutant excess risks ranged from 14%-35% per 10 $\mu g/m^3$, with the

21    largest effect estimates with $PM_{10-2.5}$ (results not included in the table because they were imprecise and

22    other results were compressed). $PM_{2.5}$ was not associated with respiratory infections in these data.

### *All Ages*

23      SOPHIA investigators examined ED visits for upper respiratory tract infections (URI) (ICD-9

24    460-466, 477) and pneumonia (ICD-9 480-486). An excess risk of 1.4% (95% CI: 0.4, 2.5 per 10 $\mu g/m^3$,

25    lag 0-2 d average) for $PM_{10}$ was associated with URI. With the exception of a small increase in risk for

26    OC of 2.8% (95% CI: 0.4, 5.3, per 2 $\mu g/m^3$, 0-2 d average) with pneumonia, Peel et al. (2005) reported no

27    association with other PM size fractions or components evaluated (Peel et al., 2005). However, Sinclair

1 and Tolsma, who also used ARIES data for their analysis found significant associations with outpatient

2 visits for LRI, generally at a 3-5 day moving average lag, with $PM_{10-2.5}$, $PM_{10}$, EC, OC, and $PM_{2.5}$ water

3 soluble metals (only significant results were reported) (Sinclair and Tolsma, 2004). No associations with

4 respiratory infections for any size fractions were observed among all ages in a study conducted in

5 Spokane, Washington (Slaughter et al., 2005).

### Older Adults

6 In a multicity study of older adults (65+ years) Medina-Ramon et al. (2006) examined hospital

7 admissions for pneumonia (ICD-9 480-487) in 36 U.S. cities in relation to 24-h average $PM_{10}$

8 concentration (Medina-Ramon et al., 2006). An increase in pneumonia admissions of 0.84% (95% CI:

9 0.50, 1.19, per 10 $\mu g/m^3$, lag 0) was reported by these investigators during the warm season. Cold season

10 associations were weaker (0.30% 95% CI: 0.07, 0.53, per 10 $\mu g/m^3$, lag 0) as were lag 1 associations.

11 Dominici et al. (2006) investigated hospital admissions for all respiratory infections including pneumonia

12 (ICD-9 464-466, 480-487) among older adults in 204 urban U.S. counties in relation to $PM_{2.5}$ and

13 reported a significant increased risk only at lag 2 (Dominici et al., 2006). Heterogeneity in effect

14 estimates were observed across the U.S. with an association close to the null value reported in the

15 Northeast (Dominici et al., 2006). In Boston, excess risks of pneumonia hospitalization in association

16 with $PM_{2.5}$, BC, and CO were observed among older adults (Zanobetti and Schwartz, 2006). A measure of

17 non-traffic PM, the residuals from the regression of $PM_{2.5}$ on BC, was not associated with pneumonia

18 hospitalization in these data. In a study of 4 cities in Australia, a statistically significant association of

19 pneumonia and acute bronchitis with $NO_2$ but not $PM_{2.5}$ was observed among older adults (Simpson et al.,

20 2005).

### Summary

21 Most of the large single-city and multicity studies of hospitalization for respiratory infection among

22 the adults, especially those over 65 years, consistently report excess risks associated $PM_{10}$ and $PM_{2.5}$.

23 Only the SOPHIA study of adults examined the association of respiratory infections with $PM_{10-2.5}$;

24 investigators reported an imprecise increase in ED visits that was not readily distinguishable from the null

25 value (Peel et al., 2005). In a study of COPD and respiratory infections combined, MCAPS investigators

26 did not observe an association with $PM_{10-2.5}$ after adjustment for $PM_{2.5}$ (Peng et al., 2008). The two studies

27 of children conducted in the U.S. or Canada were conflicting with regard to $PM_{10-2.5}$ (Chimonas and

28 Gessner, 2007; Lin et al., 2005).

| Reference | Location | Lag |
|-----------|----------|-----|

PM₁₀

Barnett et al 2005 — 7 Cities Australia NZ — 0-1 — < 1 y — Pneumonia, Acute Bronchitis

0-1 — 4 y

Medina-Ramon 2006 — 36 US Cities — 0 — 65+ — Pneumonia, Warm

1

0 — Pneumonia, Cold

1

Peel et al. 2005* — Atlanta, GA — 0-2 — All Ages — Upper Respiratory Infection

0-13 DL — Upper Respiratory Infection

0-2 — Pneumonia

0-13 DL — Pneumonia

PM₂.₅

Barnett et al 2005 — 7 Cities Australia NZ — 0-1 — < 1 — Pneumonia, Acute Bronchitis

1-4 y

Dominici et al. 2006 — 204 Urban Counties — 65+ — Respiratory Tract Infection

0 — Respiratory Tract Infection

1 — Respiratory Tract Infection

2 — Respiratory Tract Infection

Peel et al. 2005* — Atlanta, GA — 0-2 DL — All ages — Upper Respiratory Infection

0-2 — Pneumonia

PM₁₀₋₂.₅

Peel et al. 2005* — Atlanta, GA — 0-2 — Pneumonia (All ages)

0-2 — Upper Respiratory Infection

−5  −2  0  2  4  6  8  10  12  14

**Excess Risk Estimate**

**Figure 6-13. Excess risks estimates per 10 μg/m³ increase in 24-h average PM₁₀, PM₂.₅ and PM₁₀₋₂.₅ for studies of respiratory infection ED visits* and hospitalizations. Studies represented in the figure include all multicity studies. Single city studies conducted in the U.S. are also included.**

1     Several other single city studies conducted outside the U.S. and Canada reported associations

2    between PM and hospitalization or ED visits for respiratory infections (Cheng et al., 2007; Hinwood et

3    al., 2006; Hwang and Chan, 2002; Nascimento et al., 2006).

### 6.3.8.5. Copollutant Models

4     Some studies have investigated potential confounding by copollutants through the application of

5    2-pollutant models. In the MCAPS study the $PM_{10-2.5}$ effect of respiratory admissions was not robust to

6    adjustment for $PM_{2.5}$ (Peng et al., 2008). In studies of respiratory diseases combined, effect estimates for

7    $PM_{10}$ were robust to adjustment for gases in several studies (Tolbert et al., 2007; Ulirsch et al., 2007). The

8    $PM_{10-2.5}$ effect observed in Vancouver was robust to adjustment for gases while the $PM_{2.5}$ effect was not

9    (Chen et al., 2005b). In studies conducted in Copenhagen, $PM_{10}$ associations with respiratory disease did

10   not change in models also containing total number concentration, $NO_2$ and ozone (Anderson and Bogdan,

11   2007). The associations of $PM_{2.5}$ and $PM_{10}$ with asthma were not diminished in 2 pollutant models with

12   gases (Anderson and Bogdan, 2007; Chimonas and Gessner, 2007; Ito et al., 2007). However, the COPD

13   association reported by Chen et al. (2004b) in Vancouver was diminished when $NO_2$ was included in the

14   model. Lin et al. (2005) reported that associations between $PM_{10}$ and $PM_{10-2.5}$ and respiratory infection

15   remained after adjustment for gases. Studies attempting to distinguish the independent effect of sources

16   rather than individual highly correlated pollutants have observed effects for vegetative burning (Schreuder

17   et al., 2006) and traffic sources (Anderson and Bogdan, 2007; Sarnat et al., 2008).

**Table 6-12.   Characterization of ambient PM concentrations from studies of hospitalization or ED visits for respiratory diseases**

| Description | ICD 9 codes | ICD 10 Codes |
|---|---|---|
| Diseases of the Respiratory System | 460-519 | J00-J99 |
| Asthma | 493 | J45 |
| COPD and allied conditions | 490-496 (asthma, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis) | |
| Chronic lower respiratory diseases | | J40-J47 (bronchitis, emphysema, other COPD, asthma, status asthmaticus, bronchiactasis) |
| Acute Respiratory Infections | 460-466 (common cold, sinusitis, pharyngitis, tonsillitis, laryngitis & tracheitis, bronchitis & bronchiolitis) | |
| Acute Upper Respiratory Infections | | J00-J06 (common cold, sinusitis, pharyngitis, tonsillitis, l aryngitis & tracheitis, croup & epiglottitis) |
| Acute bronchitis and bronchiolitis | 466 | J20-J22 |
| Pneumonia | 480-486 | J13-J18 |
| Wheezing | 786.09 | |

# 6.3.9. Summary and Causal Determinations

## 6.3.9.1. $PM_{10}$

### Causal Determination

1   Overall, evidence from epidemiologic studies of respiratory symptoms and medication use provide
2   consistent evidence for an association with ambient concentrations of $PM_{10}$ among asthmatic children.
3   Similarly, new evidence of ED visits and hospital admissions builds upon the positive and statistically
4   significant evidence presented in the 2004 PM AQCD to support a consistent association with ambient
5   concentrations of $PM_{10}$, especially for older adults. Despite the lack of human clinical or toxicological
6   studies, the **consistent evidence from epidemiologic studies alone is sufficient to conclude that a**
7   **causal relationship is likely to exist between relevant $PM_{10}$ exposures and short-term respiratory**
8   **morbidity.**

### Respiratory Symptoms and Medication Use

9   **Epidemiologic Studies:** The 2004 PM AQCD concluded that the associations for $PM_{10}$ with
10  respiratory symptoms in asthmatics tended to be positive, although they were somewhat less consistent
11  than $PM_{10}$ effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing,
12  and bronchodilator use, although these increases were generally not statistically significant for $PM_{10}$. New
13  studies of respiratory symptoms and medication use provide further evidence of a consistent association
14  with $PM_{10}$ among asthmatic children (Figure 6-5) but less consistent evidence among asthmatic adults
15  (Figure 6-7). There was no evidence to suggest an association between respiratory symptoms or
16  medication use and $PM_{10}$ among healthy individuals.

### Pulmonary Function

17  **Epidemiologic Studies:** The peak flow analysis results for asthmatics reported in the 2004 PM
18  AQCD showed small decrements for $PM_{10}$. The effect estimates for morning PEF lagged one day showed
19  decreases, but the majority of the studies were not statistically significant. Several more recent studies
20  have reported inconsistent results for $FEV_1$ and PEF and $PM_{10}$.

### Pulmonary Inflammation

21  **Epidemiologic Studies:** There were no epidemiologic studies of pulmonary inflammation
22  described in the 2004 PM AQCD. Only one recent study looked at the association of $PM_{10}$ levels and
23  eNO (Jansen et al., 2005) and reported a positive effect.

## Hospital Admissions and ED Visits

1     **Epidemiologic Studies:** Most associations between $PM_{10}$ and hospital admissions for all

2     respiratory causes reviewed in the 2004 PM AQCD disease were positive and statistically significant.

3     Studies published since 2002 provide further evidence of a consistent association of $PM_{10}$ with respiratory

4     ED visits or hospitalizations within the epidemiologic literature (Barnett et al., 2005; Chen et al., 2005b;

5     Fung et al., 2006; Peel et al., 2005; Ulirsch et al., 2007). Effect estimates were generally larger among

6     children and older adults compared to adults or all ages combined. A large U.S. study (Peel et al., 2005)

7     and a multicity study (Barnett et al., 2005) published since 2002 provide additional evidence of an

8     association between $PM_{10}$ and asthma among children and adults. Also, increases in COPD and

9     respiratory infection admissions or ED visits with both $PM_{10}$ have been consistently observed in large,

10    recent studies (Barnett et al., 2005; Medina-Ramon et al., 2006; Peel et al., 2005). The few studies that

11    adjusted $PM_{10}$ estimates for the effect of gases in two pollutant models (Anderson and Bogdan, 2007; Lin

12    et al., 2005; Tolbert et al., 2007; Ulirsch et al., 2007) reported that the $PM_{10}$ appeared to be robust. Given

13    the limitations in distinguishing the independent effects of highly correlated pollutants, these findings

14    support the conclusion from the 2004 PM AQCD that $PM_{10}$, alone or in combination with covarying

15    pollutants is associated with hospital admissions or ED visits for respiratory causes.

## 6.3.9.2. $PM_{10-2.5}$

### Causal Determination

16    A recent analysis of MCAPS data provides new evidence that $PM_{10-2.5}$ may not be associated with

17    respiratory hospital admissions among older adults. However, several epidemiologic studies observed

18    increases in ED visits and hospital admissions for respiratory causes with acute exposure to $PM_{10-2.5}$ in

19    areas where the mean annual concentrations ranged from 5.6 to 12.2 $\mu g/m^3$. Although these associations

20    are most consistent in children, increased admissions with $PM_{10-2.5}$ concentration have also been observed

21    in older adults. Results of human clinical studies were mixed with one showing no effect of $PM_{10-2.5}$ on

22    respiratory symptoms or pulmonary function in healthy or asthmatic adults and two showing pulmonary

23    inflammation in healthy adults exposed to $PM_{10-2.5}$. This **evidence is suggestive of a causal**

24    **relationship between relevant $PM_{10-2.5}$ exposures and short-term respiratory outcomes.**

### Respiratory Symptoms and Medication Use

25    **Epidemiologic Studies:** The 2004 PM AQCD presented the results from one study of respiratory

26    symptoms and thoracic coarse particles (Schwartz and Neas, 2000), which found a statistically significant

association with cough. Two new studies examined this relationship and found no association with lower respiratory symptoms (Mar et al., 2004) or wheeze or medication use (von Klot et al., 2002).

**Human Clinical Studies:** There were no human clinical studies presented in the 2004 PM AQCD that evaluated the effect of coarse PM on respiratory symptoms. In the only human clinical study to examine respiratory symptoms following exposure to thoracic particles, Gong et al. (2004b) found no effect of exposure to coarse CAPs in healthy or asthmatic adults.

### Pulmonary Function

**Epidemiologic Studies:** The 2004 PM AQCD described two studies that used $PM_{10-2.5}$ as a coarse fraction particulate measure. Tiitanen et al. found that one day lag of $PM_{10-2.5}$ was related to morning PEF, but there was no effect on evening PEF. Neas et al. (1999) found no effects of $PM_{10-2.5}$ on PEF. There were no new studies examining the relationship between thoracic coarse particles and pulmonary function.

**Human Clinical Studies:** There were no human clinical studies presented in the 2004 PM AQCD that evaluated the effect of coarse PM on pulmonary function. One new human clinical study reported no change in lung function in healthy or asthmatic adults following a controlled exposure to coarse CAPs (2004b).

### Pulmonary Inflammation

**Human Clinical Studies:** The 2004 PM AQCD did not include any human clinical studies that assessed pulmonary inflammation following controlled exposure to coarse PM. In two new studies, evidence is presented of a coarse PM-induced increase in neutrophils in BAL fluid and induced sputum in healthy adults, with additional evidence of alveolar macrophage activation associated with biological components of coarse PM (Alexis et al., 2006; Samet et al., 2007).

### Pulmonary Injury

**Toxicological Studies:** The relationship between exposure to thoracic coarse PM and markers of pulmonary injury has not been evaluated in inhalation studies. However an important recent series of studies has evaluated the relative toxicity of PM size fractions by measuring markers of injury in BALF of mice following intratracheal instillation or aspiration of ambient PM from a variety of European and U.S. cities. Markers of inflammation in BALF were also evaluated. Thoracic coarse PM showed greater potency compared with the other size fractions. Using a similar approach, Gilmour et al. (2004a) evaluated the relative toxicity of Montana and Western Kentucky coal fly ash of differing size fractions.

1    In contrast to the results above, $PM_{10-2.5}$ fractions from Montana and Western Kentucky coal fly ash were

2    less potent than smaller size fractions (fine and ultrafine) in terms of markers of injury and inflammation.

### Hospital Admissions and ED Visits

3        **Epidemiologic Studies:** Among the key research questions when the 2004 PM AQCD was

4    published was the relationship between thoracic coarse particles and health outcomes. A number of recent

5    reports have shown significant associations between respiratory ED visits or hospitalization and acute

6    exposure to $PM_{10-2.5}$. The French PSAS program found excess risks for $PM_{10-2.5}$ and all respiratory

7    diseases in all age groups, with the strongest relationships observed among children (Host et al., 2008).

8    Other associations with hospitalizations include those in Vancouver for respiratory illness in children < 3

9    years of age (Yang et al., 2004b), COPD in the elderly, (Chen et al., 2004b) and respiratory illness in the

10   elderly (Chen et al., 2005b). Associations were also reported with hospitalization for asthma in children

11   (Lin et al., 2002b) and respiratory illness in children (Lin et al., 2005) in Toronto. These associations with

12   hospital admissions for respiratory disease in Canada were observed for $PM_{10-2.5}$ in both time-series and

13   case-crossover analyses, and the associations remained significant with adjustment for gaseous

14   copollutants in four of the five studies (except Chen et al., 2005b).

15       By contrast, MCAPS investigators found that respiratory diseases combined (COPD, upper and

16   lower respiratory tract infections) were not associated with $PM_{10-2.5}$ among older adults after adjustment

17   for $PM_{2.5}$ nor did they observe heterogeneity in effect estimates across the U.S. (Peng et al., 2008).

18   Several single city studies support these findings. Slaughter et al. (2005) observed no significant

19   associations between $PM_{10-2.5}$ and hospitals admissions or emergency room visits in Spokane, WA for all

20   ages taken together. Peel et al. (2005) reported no significant associations between $PM_{10-2.5}$ and

21   respiratory emergency department visits in Atlanta; however in another Atlanta study, significant

22   associations were reported between acute $PM_{10-2.5}$ exposure and outpatient medical visits for several

23   respiratory conditions (Sinclair and Tolsma, 2004).

24       Overall, these studies provide the most consistent evidence for associations between acute $PM_{10-2.5}$

25   exposure and respiratory morbidity among children, and less consistent evidence among adults, given the

26   recent MCAPS results. Locations with positive findings for $PM_{10-2.5}$ and respiratory morbidity reported

27   mean concentrations range from 5.6 to 12.2 $\mu g/m^3$, and maximum concentrations from 24.6 to 68 $\mu g/m^3$.


### 6.3.9.3. $PM_{2.5}$

### Causal Determination

28       Adverse associations between $PM_{2.5}$ and hospitalizations and ED visits for respiratory diseases

29   (e.g., COPD and respiratory infections) have been consistently observed among older adults while the

1      associations of asthma hospitalizations and ED visits with $PM_{2.5}$ are more heterogeneous. Epidemiologic

2      studies of asthmatic children have observed increases in respiratory symptoms and asthma medication use

3      associated with higher $PM_{2.5}$ concentrations. Additionally, a 10 μg/m$^3$ increase in $PM_{2.5}$ is associated with

4      a decrease in $FEV_1$ ranging from 1-3.4% and an increase in eNO ranging from 0.46 to 6.99 ppb in

5      asthmatic children. Human clinical studies provide coherence and biological plausibility for this

6      conclusion in that new studies in adults have demonstrated increased markers of pulmonary inflammation

7      following DE and other traffic-related exposures, oxidative responses to DE and woodsmoke, and

8      exacerbations of allergic responses and allergic sensitization following exposure to DE particles.

9      Numerous toxicological studies demonstrating a wide range of responses provide biological plausibility

10     for the associations between $PM_{2.5}$ and respiratory morbidity observed in epidemiologic studies. Altered

11     pulmonary function, mild pulmonary inflammation and injury, oxidative responses, AHR in allergic and

12     non-allergic animals, exacerbations of allergic responses and increased susceptibility to infections were

13     observed in a large number of studies involving exposure to CAPs, DE, other traffic-related PM and

14     woodsmoke. Therefore, **the evidence is sufficient to conclude that a causal relationship is likely to**

15     **exist between relevant $PM_{2.5}$ exposures and short-term respiratory morbidity.**

### *Respiratory Symptoms and Medication Use*

16     **Epidemiologic Studies:** The 2004 PM AQCD reported the results of two studies examining

17     respiratory symptoms and $PM_{2.5}$. A review of this limited evidence revealed slightly larger effects for

18     $PM_{2.5}$ than for $PM_{10}$. New studies of respiratory symptoms and medication use provide further evidence of

19     an association with $PM_{2.5}$ among asthmatic children (Figure 6-6) but less consistent evidence among

20     asthmatic adults (Figure 6-7). There was no evidence to suggest an association between respiratory

21     symptoms and medication use with $PM_{2.5}$ among healthy individuals. Delfino et al. (2003a) looked at the

22     EC and OC components of PM and found positive associations with asthma symptoms.

23     **Human Clinical Studies:** Studies cited in the 2004 PM AQCD found no effect of $PM_{2.5}$ CAPs on

24     respiratory symptoms in healthy adults, although several studies did observe an increase in upper

25     respiratory symptoms (e.g., nasal irritation) following exposure to DE. One new study found an increase

26     in respiratory symptoms following exposure to urban traffic $PM_{2.5}$ (Larsson et al., 2007); however, no

27     new human clinical studies have evaluated the effect of diesel exposure on respiratory symptoms. Two

28     new studies found that neither fine zinc oxide, nor fine CAPs caused respiratory symptoms in healthy

29     adults, or older adults with or without COPD (Beckett et al., 2005; Gong et al., 2004a).

## Pulmonary Function

**Epidemiologic studies:** The peak flow analysis results for asthmatics reported in the 2004 PM AQCD tended to show small decrements for $PM_{2.5}$. More recent studies of pulmonary function and $PM_{2.5}$ have yielded somewhat inconsistent results, though the majority of studies have found an association between $PM_{2.5}$ concentration and $FEV_1$, PEF, and/or MMEF. Among asthmatic children, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a decrease in $FEV_1$ ranging from 1-3.4%.

**Human Clinical Studies:** Very little human clinical evidence is presented in the 2004 PM AQCD of a relationship between fine particulate exposure and changes in pulmonary function. Although one study reported a significant decrement in thoracic gas volume in healthy adults following exposure to fine CAPs (Petrovic et al., 2000), several additional studies found no effect of $PM_{2.5}$ on spirometry or airway resistance. Two new studies have reported decreases in arterial oxygen saturation following exposure to $PM_{2.5}$ CAPs with more pronounced effects observed in healthy adults than in asthmatics or older adults with COPD (Gong et al., 2004; 2005). In one of these studies, healthy older adults were also reported to experience a decrease in maximal mid-expiratory flow following exposure to $PM_{2.5}$ CAPs.Some human clinical evidence of diesel-induced decrements in lung function was presented in the 2004 PM AQCD. However, this finding was not consistent across studies. One new study found that exposure to urban traffic PM did not affect pulmonary function. No human clinical studies have evaluated the effect of diesel exposure on pulmonary function since the publication of the 2004 PM AQCD.

**Toxicological Studies:** The 2004 PM AQCD reported changes in respiratory rate and tidal volume in two out of three studies involving short-term inhalation exposure to CAPs. Furthermore, AHR was observed in 4 studies of mice, healthy rats or SH rats, exposed to ROFA by inhalation or intratracheal instillation. Since the last review, SH rats and rats with monocrotaline-induced pulmonary hypertension demonstrated decreased respiratory rates (Lei et al., 2004b; Nadziejko et al., 2002), altered inspiratory and expiratory times (Kodavanti et al., 2005), increased tidal volumes (Lei et al., 2004b) and increased AHR (Lei et al., 2004b) following multi-day exposure to CAPs from a variety of locations. AHR was observed following 1 week exposure to DE in one mouse strain but not another (Li et al., 2007). Vagal-mediated pathways were found to be involved in the increased respiratory mean volume observed in rats exposed to DEP by intratracheal instillation (McQueen et al., 2007).

## Pulmonary Inflammation

**Epidemiologic Studies:** There were no epidemiologic studies of pulmonary inflammation described in the 2004 PM AQCD. Several recent studies examined $PM_{2.5}$ and eNO. All of the studies reported statistically significant, positive effect estimates, though there was inconsistency in the lag times and use of medication. Among asthmatic children, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an

1    increase in eNO ranging from 0.46 ppb to 6.99 ppb. One more recent study (Delfino et al., 2006) found a

2    positive association between EC concentrations and eNO.

3    **Human Clinical Studies:** The 2004 PM AQCD presented the results of one study that reported an

4    increase in airway neutrophils following exposure to $PM_{2.5}$ CAPs (Ghio et al., 2000). One new study

5    found that these effects could be largely attributed to the content of sulfate, iron, and selenium in the

6    soluble fraction of the PM (Huang et al., 2003c). In addition, the 2004 PM AQCD presents evidence from

7    human clinical studies of an increase in pulmonary inflammation following exposure to DE. This is

8    consistent with the observations of several new studies reporting traffic or diesel-induced increases in

9    markers of inflammation (e.g., neutrophils and IL-8) in airway lavage fluid from healthy adults. No

10   human clinical studies involving controlled exposures to woodsmoke were presented in the 2004 PM

11   AQCD. One new study observed an increase in eNO following exposure to woodsmoke in healthy adults.

12   **Toxicological Studies:** The 2004 PM AQCD reported that CAPs exposure in rats and dogs at

13   concentrations of 100-1000 $\mu g/m^3$ for 1-6 h/d and 1-3 d generally resulted in minimal to mild

14   inflammation in healthy animals. More recent studies demonstrate pulmonary inflammation in all three

15   studies involving multi-day exposure of healthy rats to CAPs from different locations (Godleski et al.,

16   2002; Rhoden et al., 2004; Smith et al., 2003). No pulmonary inflammation was seen in one study of

17   WKY and SH rats exposed to CAPs for 4 h and analyzed 1-3 h later (Kodavanti et al., 2005). However,

18   pulmonary inflammation was seen following a multiday exposure to CAPs in WKY but not SH rats

19   (Kodavanti et al., 2005). Other investigators using SH rats demonstrated pulmonary inflammation

20   following multiday CAPs exposure in one study (Cassee et al., 2005) but not another (Kooter et al.,

21   2006). In the rat monocrotaline model of pulmonary hypertension, multi-day exposures to CAPs resulted

22   in mild pulmonary inflammation (Lei et al., 2004b). Few studies involving exposure to traffic-related

23   $PM_{2.5}$ were discussed in the 2004 PM AQCD. Since then, inflammation was observed in healthy rats

24   exposed for 20 h, but not 6 h, to ambient air from a high traffic site (Pereira et al., 2007). In contrast, no

25   inflammation was observed in old rats exposed for 6 h/d for 1-3 day to on-road highway aerosols (Elder et

26   al., 2004a). The 2004 PM AQCD referred to the 2002 EPA Diesel Document which reported pulmonary

27   inflammation following short-term inhalation exposure to low levels of DE. Since then, pulmonary

28   inflammation was demonstrated in three out of five studies in healthy mice and rats exposed by short-term

29   inhalation to DE. In these three studies, positive effects were seen at concentrations of DEP 100 $\mu g/m^3$

30   and higher (Harrod et al., 2003; Li et al., 2007; Witten et al., 2005; Wong et al., 2003). No attempt was

31   made in these studies to determine whether responses were due to PM components or gaseous

32   components. However, intratracheal instillation of PM from DE resulted in an inflammatory response in

33   healthy rats (McQueen et al., 2007). This response involved vagally-mediated pathways. No

34   inflammatory response to gasoline exhaust was seen in one study (Campen et al., 2006) while in another

1 study, the inflammatory responses to gasoline exhaust were due to gaseous components (Sureshkumar et

2 al., 2005).

3      The 2004 PM AQCD reported pulmonary inflammation in healthy rats and mice exposed by

4 inhalation to fine particles of $TiO_2$ and carbon black at extremely high concentrations. Since then, one

5 study demonstrated an inflammatory response in healthy rats at a much lower concentration of carbon

6 black (1400 $\mu g/m^3$) (Gilmour et al., 2004c).

## *Oxidative Responses*

7      **Human Clinical Studies:** One study cited in the 2004 PM AQCD reported increases in alveolar CO

8 following controlled exposure to diesel (Nightingale et al., 2000), while another (Blomberg et al., 1998)

9 found a diesel-induced increase in ascorbic acid concentrations in nasal lavage immediately following

10 exposure. New studies have provided additional evidence in support of a pulmonary oxidative response to

11 DE including induction of redox-sensitive transcription factors, as well as increased urate and GSH

12 concentrations in nasal lavage. No human clinical studies involving controlled exposures to wood smoke

13 were presented in the 2004 PM AQCD. However, a recent human clinical study found an increase in the

14 levels of malondialdehyde in breath condensate of healthy adults following exposure to wood smoke

15 (Barregard et al., 2008).

16      **Toxicological Studies:** The 2004 PM AQCD reported one study which provided evidence that

17 ROS were involved in $PM_{2.5}$-mediated effects. New studies demonstrate that CAPs exposure in healthy

18 rats resulted in increased lung ROS measured by chemiluminescence; increased oxidation products of

19 lung lipids and proteins; and increased MnSOD and catalase (Gurgueira et al., 2002; Rhoden et al., 2004).

20 Lipid peroxidation was found in healthy rats exposed for 20 h to ambient PM from a high traffic site

21 (Pereira et al., 2007) and in allergic mice exposed to DE (Whitekus et al., 2002). Increased HO-1 was

22 observed in SH rats exposed to CAPs (Kooter et al., 2006) and in healthy mice exposed to DE (Li et al.,

23 2007). Further evidence for involvement of oxidative responses is provided by studies using pretreatment

24 with the thiol antioxidant NAC to inhibit the PM-mediated responses (Rhoden et al., 2004; Whitekus et

25 al., 2002) (Li et al., 2007).

## *Pulmonary Injury*

26      **Toxicological Studies:** The 2004 PM AQCD reported pulmonary injury in healthy and

27 compromised animals following inhalation or intratracheal instillation of ROFA or other metal-containing

28 PM. Intratracheal instillation of diesel PM also resulted in injury. Mild increases in markers of pulmonary

29 injury were noted in several studies involving inhalation exposure to CAPs. More recent studies

30 demonstrated mild injury accompanying the mild inflammatory responses to CAPs in SH rats (Cassee et

1    al., 2005; Kodavanti et al., 2005) and in rats with monocrotaline-induced pulmonary hypertension (Lei et

2    al., 2004b). In addition, CAPs exposure resulted in a mild lung edema in two studies involving healthy

3    rats (Gurgueira et al., 2002; Rhoden et al., 2004). Exposure to DE resulted in plasma extravasation in

4    healthy rats (Witten et al., 2005; Wong et al., 2003).

### Allergic Responses

5    **Human Clinical Studies:** Exposure to DE particles in controlled human exposures studies has been

6    shown to increase the allergic response among previously sensitized atopic subjects. In addition, one

7    human clinical study has demonstrated that exposure to DE particles is capable of inducing de novo

8    sensitization to an antigen in atopic individuals.

9    **Toxicological Studies:** The 2004 PM AQCD reported numerous studies which provided evidence

10   for an association of episodic exposure to PM and exacerbation of allergic asthma. The vast majority of

11   studies conducted since the last review focus on $PM_{2.5}$. Some of these new studies demonstrate that

12   existing allergic sensitization confers susceptibility to the effects of PM in rodent models. For example

13   increased PM retention and enhanced allergic responses were observed in ovalbumin-allergic rats exposed

14   by inhalation to CAPs (Morishita et al., 2004). Allergic responses were also enhanced in

15   ovalbumin-allergic mice exposed by inhalation to roadway CAPs (Kleinman et al., 2005; 2007). Greater

16   responses were observed with exposures closer to the highway. Furthermore, three studies observed AHR

17   in ovalbumin-allergic mice exposed to DE (Farraj et al., 2006a, b; Matsumoto et al., 2006). Neurotrophins

18   were found to mediate the response to DE (Farraj et al., 2006b). The 2004 PM AQCD also discussed the

19   role of PM in acting as an adjuvant to promote allergic sensitization. New studies in mice demonstrated

20   that inhalation of DE resulted in enhanced allergic sensitization to a common fungus (Liu et al., 2008) and

21   to ovalbumin (Stevens et al., 2008; Whitekus et al., 2002). In contrast, woodsmoke had minimal effects

22   on allergic sensitization to ovalbumin in mice (Barrett et al., 2006).

### Host Defense

23   **Toxicological studies:** The 2004 PM AQCD reported increased susceptibility to infection

24   following exposure to PM. Inhalation of CAPs prior to bacterial infection was found to increase the

25   bacterial burden in aged rats (Zelikoff et al., 2003). ROFA, administered by intratracheal instillation, was

26   also found to diminish bacterial clearance (Antonini et al., 2002). New studies evaluating the effects of

27   PM on host defense focused on $PM_{2.5}$. Inhalation exposure of mice to DE resulted in an increased

28   susceptibility to influenza infection (Ciencewicki et al., 2007) and respiratory syncytial virus (Harrod et

29   al., 2003). Decreased levels of surfactant proteins known to play an important role in viral clearance were

30   observed in both of these studies (Ciencewicki et al., 2007; Harrod et al., 2003). In contrast, woodsmoke

1   inhalation had no effect on bacterial clearance in four rodent species, including one which was

2   compromised (Reed et al., 2006).

### Hospital Admissions and ED Visits

3   **Epidemiologic Studies:** The majority of new evidence relating to the effect of $PM_{2.5}$ on HAs for

4   respiratory causes comes from several recent MCAPS analyses of older adults. MCAPS investigators

5   report consistent associations of $PM_{2.5}$ with COPD and respiratory infections with heterogeneity in these

6   estimates explained by regional and seasonal differences (Bell et al., 2008a; Dominici et al., 2006). In

7   another recent study, SOPHIA investigators observed non-significant increases in ED visits for respiratory

8   causes with $PM_{2.5}$ among all ages but $PM_{2.5}$ data were available for fewer years than $PM_{10}$ data (Peel et

9   al., 2005). However, a multicity study in France and several single-city studies that were conducted in

10  Canada that show weaker associations between hospitalization and acute exposure to $PM_{2.5}$ compared to

11  $PM_{10-2.5}$ (Chen et al., 2004b; Chen et al., 2005b; Fung et al., 2006; Host et al., 2007; Lin et al., 2002b; Lin

12  et al., 2005; Yang et al., 2004b). All were studies of hospitalization for respiratory diseases, though studies

13  differed in age group and respiratory endpoint.

14  Barnett et al. (2005) reported increased HAs with $PM_{2.5}$ concentration in 7 cities in Australia and

15  New Zealand among children. Heterogeneous effect estimates were observed across single city studies of

16  asthma admissions and ED visits (Babin et al., 2007; Barnett et al., 2005; Ito et al., 2007; Peel et al.,

17  2005; Slaughter et al., 2005).

18  A report from the SOPHIA study in Atlanta evaluated associations between short-term fine particle

19  component exposures, using ARIES data, and visits for respiratory diseases (Peel et al., 2005). No

20  significant associations were reported between any component and respiratory visits, except for an

21  association between OC and emergency department visits for pneumonia (Peel et al., 2005). Medical

22  visits for asthma in children and lower respiratory infections (all ages) were associated with the EC and

23  OC components of fine particles in Atlanta, but no associations were reported with sulfates or acidity

24  (Sinclair and Tolsma, 2004). Metals were positively associated with medical visits for lower respiratory

25  infection, but not for other outcomes. For adult asthma and upper respiratory infections, there were no

26  significant positive associations with any of the fine PM components; however, sulfates were negatively

27  associated with upper respiratory infection visits (Sinclair and Tolsma, 2004).

28  In the SOPHIA study in Atlanta, $PM_{2.5}$ from mobile sources, biomass burning and sulfate-rich

29  secondary $PM_{2.5}$ were associated with a 2-4% increase in respiratory hospital visits (Sarnat et al., 2008).

30  Biomass was associated with total respiratory hospitalizations and vehicle emissions with childhood

31  asthma hospitalizations (Andersen et al., 2007b). PM from traffic was linked to pneumonia HAs in

32  Boston (Zanobetti and Schwartz, 2006). Vegetative burning was associated with respiratory HAs in

1    Spokane despite the lack of association with PM size fractions studied (Schreuder et al., 2006; Slaughter

2    et al., 2005).

### 6.3.9.4. Ultrafine Particles

#### *Causal Determination*

3    Although a very limited number of epidemiologic studies have provided some evidence of an

4    association between short-term exposure to ultrafine particles and respiratory symptoms as well as asthma

5    hospitalizations, these findings have been inconsistent across studies. The effect of controlled exposures

6    to ultrafine particles has not been extensively examined in humans. Two human clinical studies have

7    observed small ultrafine particle-induced decreases in pulmonary function, however, no increases in

8    respiratory symptoms or pulmonary inflammation have been reported. The results from animal

9    toxicological studies examining the effect of ultrafine particles on respiratory morbidity are mixed, and

10    the interpretation of the findings limited by a relative lack of data. Thus, current collective **evidence is**

11    **inadequate to determine if a causal relationship exists between relevant UFP exposure and**

12    **short-term respiratory morbidity.**

#### *Respiratory Symptoms and Medication Use*

13    **Epidemiologic Studies:** One study found positive associations with UFP and wheeze and

14    medication use (von Klot et al., 2002), though another found no association with any respiratory

15    symptoms (de Hartog et al., 2003).

16    **Human Clinical Studies:** The 2004 PM AQCD did not include any human clinical studies that

17    assessed respiratory symptoms following controlled exposure to ultrafine PM. Three new studies have

18    found no increase in respiratory symptoms following exposure to ultrafine zinc oxide (Beckett et al.,

19    2005), CAPs (Gong et al., 2008) or EC (Pietropaoli et al., 2004).

#### *Pulmonary Function*

20    **Human Clinical Studies:** There were no human clinical studies presented in the 2004 PM AQCD

21    that evaluated the effect of ultrafine PM on pulmonary function. Two new studies (Gong et al., 2008;

22    Pietropaoli et al., 2004) have demonstrated ultrafine-induced decrements in pulmonary function,

23    measured as decreases in maximal mid-expiratory flow and CO diffusing capacity (EC) and decreases in

24    arterial oxygen saturation and $FEV_1$ (CAPs). One additional ultrafine CAPs study found no effect of

25    exposure on FVC, $FEV_1$, or CO diffusing capacity (Samet et al., 2007).

1    **Toxicological Studies:** Very few studies involving ultrafine PM were reviewed in the 2004 PM

2    AQCD. None of these evaluated pulmonary function effects. Since the last review, one study reported no

3    changes in AHR following a multiday exposure of mice to ultrafine iron-soot PM (Last et al., 2004).

### Pulmonary Inflammation

4    **Human Clinical Studies:** No human clinical studies evaluating the relationship between exposure

5    to ultrafine particles and pulmonary inflammation were presented in the 2004 PM AQCD. Three new

6    studies have not observed increases in any markers of pulmonary inflammation following exposure to

7    ultrafine CAPs, zinc oxide, or EC.

8    **Toxicological Studies:** The 2004 PM AQCD reported pulmonary inflammation in healthy rats and

9    mice exposed by inhalation to ultrafine and fine particles of $TiO_2$ at extremely high concentrations.

10   Ultrafine particles were more inflammogenic than fine particles. Since then, one study demonstrated an

11   inflammatory response in healthy rats at a much lower concentration of carbon black (1400 $\mu g/m^3$,

12   (Gilmour et al., 2004c), with ultrafine particles more inflammogenic than fine particles. Ultrafine carbon

13   black particles, at a concentration an order of magnitude lower, was found not to result in pulmonary

14   inflammation in 2 animal models of aged, compromised rats (Elder et al., 2004b). Furthermore, no

15   pulmonary inflammation was observed in healthy rats exposed to ultrafine iron-soot particles (Last et al.,

16   2004). However, a single day exposure to ultrafine CAPs resulted in pulmonary inflammation in the rat

17   monocrotaline model of pulmonary hypertension (Lei et al., 2004b).

### Pulmonary Injury

18   **Toxicological Studies:** No histophathological responses were seen in adult mice exposed to

19   ultrafine iron-soot particles. In contrast, exposure of neonatal rats to ultrafine iron-soot particles during

20   the neonatal period resulted in a significantly reduced rate of cell proliferation in the proximal alveolar

21   region (Pinkerton et al., 2004). Alveolar septation and growth were unaffected in this study. The authors

22   suggest the possibility of greater susceptibility to air pollution during the critical period of postnatal lung

23   development.

24   Other than the above study, the relationship between exposure to ultrafine PM and markers of

25   pulmonary injury has not been evaluated in inhalation studies. However an important series of studies has

26   evaluated the relative toxicity of PM size fractions by measuring markers of injury, as well as markers of

27   inflammation, in BALF of mice following intratracheal instillation or aspiration of ambient PM from a

28   variety of European and U.S. cities. Ultrafine PM was less injurious than the other size fractions. Gilmour

29   et al. (2004a) evaluated the relative toxicity of Montana coal fly ash of differing size fractions. In contrast

to the results above, the ultrafine fraction fractions from the Montana coal induced greater injury and inflammation than the $PM_{10-2.5}$ fraction.

### Allergic Responses

**Toxicological Studies:** Ultrafine CAPs were more potent than fine CAPS in exacerbating allergic responses in one study (Kleinman et al., 2005). Exposure to ultrafine iron-soot particles resulted in an increased number of goblet cells in allergic mice (Last et al., 2004).

### Hospital Admissions and ED Visits

**Epidemiologic Studies:** Studies conducted in Copenhagen, Denmark reported associations with ultrafine particles. Both accumulation mode and number concentration (< 100nm) were associated with childhood asthma admissions (Andersen et al., 2007b). Associations with ultrafine were not observed by SOPHIA investigators (Peel et al., 2005).

# 6.4. Central Nervous System Effects

While evidence of an effect of PM on the central nervous system was not presented in the 2004 PM AQCD, a limited number of recent human clinical and toxicological studies have provided some support to suggest that exposure to PM may be associated with changes in neurological function. Two epidemiologic studies evaluated the effect of ambient PM on the central nervous system (Calderon-Garciduenas et al., 2008; Suglia et al., 2008). These studies examined long-term exposure to non-specific PM indicators and are detailed in Annex E.

# 6.4.1. Human Clinical Studies

In a recent controlled human exposure study, Cruts et al. (2008) exposed 10 healthy males (18-39 years old) to filtered air and dilute DE (300 $\mu g/m^3$ particulate concentration) for 1-h using a randomized crossover study design. Changes in brain activity were measured during and following exposure using quantitative electroencephalography (QEEG). Exposure to DE was observed to significantly increase the median power frequency (MPF) in the frontal cortex during exposure, as well as in the hour following the completion of the exposure. While this study does provide some evidence of an acute cortical stress response to DE, it is important to note that the QEEG findings are very nonspecific, and could have been caused by factors other than diesel PM such DE gases (e.g., CO, NO and $NO_2$) or the odor of the DE.

## 6.4.2. Toxicological Studies

1   Evidence is mounting that the nervous system may be a critical target of PM and that adverse
2   health effects may result from PM exposure. Whether these health effects are a direct or indirect effect of
3   PM has not yet been established. One hypothesis suggests that ultrafine PM which deposits onto nasal
4   olfactory epithelium enters the central nervous system by axonal olfactory transport to the olfactory bulb
5   and leads to a cascade of effects involving inflammatory cytokines and ROS. An increased potential for
6   neurodegenerative processes may ensue. Evidence for translocation of ultrafine PM to the olfactory bulb
7   via olfactory neurons is discussed in Chapter 4, but its relevance to CNS health effects is unknown.
8   Another hypothesis suggests that brain inflammation occurs secondarily to PM-mediated systemic
9   inflammation. Finally, it has been suggested that PM-stimulation of autonomic nervous system receptors
10  in the respiratory tract results in inflammatory or other effects in the central nervous system. This is an
11  emerging field with many unknowns.

12  Calderon-Garciduenas et al. (2003) conducted a long-term exposure observational study in mongrel
13  dogs from Mexico City and Tlaxcala. DNA damage and inflammation in the brain and respiratory tract
14  were evaluated in dogs living in Mexico City (exposed group) and dogs living in Tlaxcala (control
15  group). These cities are similar in altitude but differ in air pollutant levels. Measurements of air pollutant
16  levels were presented only for Mexico City, the more polluted city. Statistically significant greater levels
17  of apurinic/apyrimidinic sites (an indicator of DNA damage) were observed in the olfactory bulbs and
18  hippocampus of Mexico City dogs compared with controls. These differences were not seen in other brain
19  regions examined or in nasal respiratory epithelium. In addition, Mexico City dogs demonstrated greater
20  histopathological changes in the respiratory and olfactory epithelium of the nasal cavity compared with
21  controls. Immunohistochemical staining of brain tissue from the Mexico City dogs demonstrated greater
22  immunoreactivity for NFκB, iNOS, cyclooxygenase-2, glial fibrillatory acidic protein (GFAP), ApoE,
23  amyloid precursor product and β-amyloid compared with controls. These results are indicative of
24  inflammation and stress protein responses. This study has several limitations given that the dogs were of
25  mixed breeds and of variable ages and that there was no standardization of exposures or diets. However
26  results indicate a further need for investigating the relationship between air pollution and brain
27  inflammation.

28  Several new inhalation studies have provided evidence of CNS effects due to ambient PM
29  exposures. In one study, Campbell et al. (2005) exposed ovalbumin-sensitized BALB/c mice to filtered air
30  or near-highway Los Angeles CAPs (a 20-fold concentration of fine+ultrafine or ultrafine only; mean
31  exposure concentration ultrafine 282.5 $\mu g/m^3$ and fine 441.7 $\mu g/m^3$ for 4 h/day, 5 days/week for 2 weeks.
32  The animals were subsequently challenged with ovalbumin to elicit an allergic response in the lungs;

1    brain tissue was obtained 1 day later. Exposure to CAPs, but not filtered air, resulted in activation of the

2    immune-related transcription factor NF-κB and the cytokines TNFα, and IL-1α in brain, demonstrating

3    proinflammatory responses that could contribute to neurodegenerative disease. While this study

4    demonstrates CAPs effects in an allergic animal model, futher studies are required to determine whether

5    these responses also occur in non-allergic animals.

6        In a second study, control or ovalbumin-sensitized and challenged Brown Norway rats were

7    exposed for 8-h to filtered air or fine CAPs (Grand Rapids, MI; 500 μg/m$^3$ fine PM) (Sirivelu et al.,

8    2006). Brain tissue was obtained 1 day later. CAPs exposure resulted in brain region-specific modulation

9    of neurotransmitters. In animals which were not pretreated with ovalbumin, statistically significant

10   increases in norepinephrine were observed in the paraventricular nucleus and olfactory bulb of

11   CAPs-exposed rats compared with filtered air controls. In animals which were pretreated with ovalbumin,

12   a statistically significant increase in dopamine was observed in the medial preoptic area in CAPs-exposed

13   rats compared with controls. Furthermore, exposure to CAPs resulted in a statistically significant increase

14   in serum corticosterone. These data suggest that the hypothalamo-pituitary-adrenal axis (i.e. stress axis)

15   may be activated by PM exposure, causing aggravation of allergic airway disease. The authors discuss the

16   possible role of the olfactory bulb in mediating neuroendocrine control of autonomic activities involved in

17   respiratory and cardiovascular functions; however further investigations are required to clarify these

18   relationships.

19       In a third study, normal (C57BL/6) mice and ApoE$^{-/-}$ mice were exposed to Tuxedo, NY, fine CAPs

20   for 4 mo (March, April or May through September 2003) (Veronesi et al., 2005). The average PM$_{2.5}$

21   exposure concentration was 110 μg/m$^3$. CAPs exposure resulted in a statistically significant decrease in

22   domaminergic neurons, measured by tyrosine hydroxylase immunoreactivity, in the substantia nigra of

23   ApoE$^{-/-}$ mice but not in control mice. This population of neurons is targeted in neurodegenerative diseases

24   such as Parkinson's. Furthermore, a statistically significant increase in GFAP immunoreactivity, a marker

25   for astrocytes, was observed in the nucleus compacta of CAPs-exposed ApoE$^{-/-}$ mice compared to

26   air-exposed ApoE$^{-/-}$ mice. These results suggest that the ApoE$^{-/-}$ mice, a genetic model for increased

27   oxidative stress, are susceptible to PM-induced neurodegeneration. Evidence for brain oxidative stress has

28   also been found in normal animals following intratracheal instillation of high concentrations of fine CAPs

29   from Taiyuan, China (Liu and Meng, 2005) and of gasoline exhaust (Che et al., 2007) and following

30   chronic exposure to ROFA by intranasal instillation (Zanchi et al., 2008).

31       In summary, PM may produce adverse effects in the CNS by direct or indirect mechanisms which

32   are at present incompletely understood. Two recent short-term fine CAPs inhalation studies demonstrate

33   proinflammatory responses in the brain and brain region-specific modulation of neurotransmitters and

34   suggest the involvement of neuroimmunological pathways. One recent chronic fine CAPs inhalation

1    study demonstrates loss of dopaminergic neurons in the substantia nigra and suggests that oxidative stress

2    contributes to neurodegeneration. Veronesi et al. (2005) have noted that the brain is very vulnerable to the

3    oxidative stress induced by PM due to the brain's high energy demands, low levels of endogenous free

4    radical scavengers, and high content of lipids and proteins. PM-mediated upregulation of inflammatory

5    cytokines and mediators may also contribute to neurodegeneration. Further investigations are required to

6    substantiate these mechanisms.

## 6.4.3. Summary and Causal Determination

7    A single human clinical study provides some evidence of an acute cortical stress response to diesel,

8    though these findings are nonspecific and could have been caused by DE gases rather than diesel PM.

9    Recent animal toxicological studies of CAPs have demonstrated proinflammatory responses in the brain,

10   brain region-specific modulation of neurotransmitters and loss of dopaminergic neurons in the substantia

11   nigra; however, the mechanisms underlying these effects need to be substantiated. Though the effect of

12   ambient air pollution on CNS outcomes has recently begun to draw more attention, the evidence for a

13   CNS effect associated with PM is limited. While most available studies have evaluated the effects of fine

14   particle exposures, there is insufficient evidence to draw conclusions regarding effects of specific PM size

15   fractions or components. Overall, the **evidence is inadequate to determine if a causal relationship**

16   **exists between relevant exposures to $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, ultrafine particles, or specific PM**

17   **components and CNS outcomes.**

# 6.5. Mortality Associated with Short-Term Exposure

18   The relationship between short-term exposure to PM and mortality is an important issue that has

19   been extensively addressed in previous PM assessments (U.S. EPA, 1982, 1996, 2004). A positive

20   association between PM concentration and mortality was consistently demonstrated across studies cited in

21   the 2004 PM AQCD. Although effect estimates have been shown to be dependent on regional and

22   seasonal differences, recent studies have provided additional support to previous findings. The current

23   body of evidence examines the association between short-term exposure to PM of various size fractions

24   (i.e., $PM_{10}$, $PM_{10-2.5}$, $PM_{2.5}$, and ultrafine particles [0.01-0.1 μm]) and mortality through the use of

25   time-series and/or case-crossover studies. Both study designs aim to disentangle the PM-mortality effect

26   through either complex modeling (i.e., time-series) or matching strategies (i.e., case crossover). The

27   scientific community has also continued to search for the specific PM components and sources that are

1    responsible for the health effects attributed to short-term exposure to PM, along with the

2    concentration-response relationship that most adequately explains the effect of PM on human health.


## 6.5.1. Summary of Findings from 2004 PM

3    The 2004 PM AQCD found strong evidence that ambient coarse ($PM_{10}$) and fine ($PM_{2.5}$), or one or

4    more $PM_{2.5}$ components, acting alone and/or in combination with gaseous copollutants, are associated

5    with total (non-accidental) mortality and various cause-specific mortality outcomes. For $PM_{10}$, several

6    multicity studies in the U.S., Canada, and Europe provided strong support for this conclusion, reporting

7    associations with total mortality highlighted by effect estimates ranging from ~0.2 to 0.7% (per 10 $\mu g/m^3$

8    increase in $PM_{10}$) (U.S. EPA, 2004). Numerous studies also reported $PM_{10}$ associations with

9    cause-specific mortality, specifically cardiovascular- and respiratory-related mortality. For $PM_{2.5}$, the

10   strength of the evidence varied across endpoints, with relatively stronger evidence for associations with

11   cardiovascular compared to respiratory endpoints. The resulting effect estimates reported from the U.S.

12   and Canadian based studies (both multi- and single-city) analyzed for these two endpoints ranged from

13   1.2 to 2.7% for cardiovascular-related mortality and 0.8 to 2.7% for respiratory-related mortality, per

14   10 $\mu g/m^3$ increase in $PM_{2.5}$ (U.S. EPA, 2004). In regards to thoracic coarse particles ($PM_{10-2.5}$), the PM

15   AQCD found a limited body of evidence that was suggestive of associations between short-term exposure

16   to ambient $PM_{10-2.5}$ and various mortality outcomes (e.g., 0.08 to 2.4% increase in total [non-accidental]

17   mortality per 10 $\mu g/m^3$ increase in $PM_{10-2.5}$). The positive effect estimates obtained from studies that

18   analyzed the association between $PM_{10-2.5}$ and mortality resulted in the conclusion that $PM_{10-2.5}$, or some

19   constituent component(s) (including those on the surface) of $PM_{10-2.5}$, may contribute, in certain

20   circumstances, to increased human health risks.

21   Some additional studies examined the association between specific $PM_{2.5}$ chemical components and

22   mortality. These studies observed associations for sulfate, nitrate, and CoH, but not crustal particles. The

23   strength of the association for each component varied from city to city (U.S. EPA, 2004). Source-oriented

24   analyses were also conducted to identify specific source-types associated with mortality. These studies

25   implicate fine particles from anthropogenic origin, such as motor vehicle emissions, coal combustion, oil

26   burning, and vegetative burning, as being important in contributing to increased mortality (U.S. EPA,

27   2004).

**Table 6-13. Overview of U.S. and Canadian multicity PM studies analyzed in the 2004 PM AQCD and the PM ISA[b]**

| Reference | Location | Mean Concentration (µg/m³)[c] | Upper Percentile: Concentrations (µg/m³) |
|---|---|---|---|
| *PM₁₀* | | | |
| Dominici et al. (2003a)[a] | 90 U.S. cities | 15.3 – 53.2 | NR |
| Burnett and Goldberg (2003)[a] | 8 Canadian cities | 25.9 | 95th: 54<br>Maximum: 121 |
| Peng et al. (2005) | 100 U.S. cities | 13 – 49 | 50th: 27.1<br>75th: 32.0 |
| Dominici et al. (2007b) | 100 U.S. cities | 13 – 49 | 50th: 27.1<br>75th: 32.0 |
| Welty and Zeger (2005) | 100 U.S. cities | 13 – 49 | 50th: 27.1<br>75th: 32.0 |
| Burnett et al. (2004) | 12 Canadian cities | NR | NR |
| Schwartz (2004b) | 14 U.S. cities | 23 – 36[d] | 75th: 31 – 57 |
| Schwartz (2004c) | 14 U.S. cities | 23 – 36[d] | 75th: 31 – 57 |
| Zeka et al. (2005) | 20 U.S. cities | 15.9 – 37.5 | NR |
| Zeka et al. (2006a) | 20 U.S. cities | 15.9 – 37.5 | NR |
| *PM₂.₅* | | | |
| Burnett and Goldberg (2003)[a] | 8 Canadian cities | 13.3 | 95th: 32<br>Maximum: 86 |
| Dominici et al. (2007b) | 100 U.S. cities | NR | NR |
| Franklin et al. (2007) | 27 U.S. cities | 9.3 – 28.5 | NR |
| Franklin et al. (2008) | 25 U.S. cities | Winter: 9.6 – 34.4<br>Spring: 6.7 – 27.6<br>Summer: 7.6 – 26.0<br>Fall: 9.5 – 32.1 | NR |
| Ostro et al. (2006) | 9 California counties | 14 – 29 | NR |
| Burnett et al. (2004) | 12 Canadian cities | 12.8 | NR |
| *PM₁₀₋₂.₅* | | | |
| Burnett and Goldberg (2003)[a] | 8 Canadian cities | 12.6 | 95th: 30<br>Maximum: 99 |
| Burnett et al. (2004) | 12 Canadian cities | 11.4 | NR |
| Villeneuve et al. (2003) | Vancouver, Canada | 6.1 | 90th: 13.0<br>Maximum: 72.0 |
| Klemm et al. (2004) | Atlanta, Georgia | 9.7 | 50th: 9.34<br>75th: 11.94<br>Maximum: 25.17 |
| Slaughter et al. (2005) | Spokane, Washington | NR | NR |
| Wilson et al. (2007b) | Phoenix, Arizona | NR | NR |

| Reference | Location | Mean Concentration (µg/m³)[c] | Upper Percentile: Concentrations (µg/m³) |
|---|---|---|---|
| Kettunen et al. (2007) | Helsinki, Finland | Cold season: 6.7[d]<br>Warm season: 8.4[d] | Cold season<br>50th: 6.7<br>75th: 12.5<br>Maximum: 101.4<br>Warm season<br>50th: 8.4<br>75th: 11.8<br>Maximum: 42.0 |
| Perez et al. (2008) | Barcelona, Spain | Saharan Dust Days: 16.4<br>Non-Saharan Dust Days: 14.9 | Saharan Dust Days<br>50th: 14.8<br>75th: 21.8<br>Maximum: 36.7<br>Non-Saharan Dust Days<br>50th: 12.6<br>75th: 18.9<br>Maximum: 93.1 |

[a] Multicity studies examined in the 2004 PM AQCD
[b] Because only one multicity study was identified that examined $PM_{10-2.5}$, single-city and International studies that examined $PM_{10-2.5}$ were analyzed in this ISA and are included in this table.
[c] The majority of multicity studies examined in the PM ISA provide the mean PM concentration of each individual city, not an overall PM concentration across all cities. As a result, the range of PM concentrations for a particular study are presented, which represents the lowest and highest mean PM concentrations reported across cities, if an overall mean is not provided within the study.
[d] Median PM concentration.

# 6.5.2. Associations of Mortality and Short-Term Exposure to PM

1    The recent literature examines the association between short-term exposure to various PM size

2    fractions (i.e., $PM_{10}$, $PM_{10-2.5}$, $PM_{2.5}$, ultrafine particles, or species [e.g., OC, EC, transition metals, etc.])

3    and mortality. This ISA, similar to previous AQCDs, focuses more heavily on multicity studies, and

4    specifically those conducted in the U.S. and Canada (see Table 6-13). By using this approach it is possible

5    to: (1) obtain a more representative sample of or insight to the PM-mortality relationship observed across

6    the U.S.; (2) analyze the association between short-term exposure to PM and mortality at ambient

7    conditions at or similar to those observed in the U.S.; (3) examine the potential heterogeneity in effect

8    estimates between cities and regions; and (4) analyze the confounders and/or effect modifiers that may

9    explain the PM-mortality relationship in the U.S. The one caveat to using this approach for the current

10    document is that fewer multicity studies have been conducted since the 2004 PM AQCD. This is because

11    most of the multicity PM studies that were reviewed in the 2004 PM AQCD utilized the multiple-cause of

12    death files from the National Center for Health Statistics (NCHS). However, due to a change in policy, the

13    NCHS no longer provides the day of death in national data sets of daily mortality records starting with

14    data for 2001. As a result, this led to fewer multicity studies analyzing mortality data beyond year 2000,

15    except for a few studies that requested data directly from state or city agencies. Although this section

16    focuses on mortality outcomes in response to short-term exposure to PM, it does not evaluate studies that

1  examine the association between PM and infant mortality. These studies are evaluated in Section 7.5,

2  Reproductive, Developmental, Prenatal and Neonatal Outcomes, although it is possible that short- and

3  long-term in utero exposures may contribute to infant mortality. In addition, the exposure windows of

4  interest for this unique health outcome can be difficult to characterize and may span both short- and long-

5  term periods.

### 6.5.2.1. $PM_{10}$

6  The majority of studies that examined the association between short-term exposure to PM and

7  mortality focused on effects attributed to $PM_{10}$. These studies analyzed the $PM_{10}$-mortality relationship

8  through either a time-series or case-crossover design.[1]

### *Time-Series Analyses*

9  Mortality associated with short-term exposure to $PM_{10}$ has been examined in several updated

10  time-series analyses of the National Morbidity and Mortality Air Pollution Study (NMMAPS). In the

11  previous NMMAPS analysis (Dominici et al., 2003a; Samet et al., 2000) of the 1987-1994 data, which

12  was reviewed in the 2004 PM AQCD, the strongest association was found for non-accidental mortality for

13  1-day lag, with a combined estimate across 90 cities of 0.21% (95% posterior interval [PI]: 0.09, 0.33) per

14  10 $\mu g/m^3$ increase in $PM_{10}$. The association was found to be robust to the inclusion of other gaseous

15  copollutants in the regression models, but the investigators found heterogeneity across regions, with the

16  strongest associations in northeastern cities. In the new updated analyses, the investigators examined

17  additional issues including: (1) seasonal effect modification; (2) change in risk estimates over time; and

18  (3) sensitivity of results to alternative weather models. In addition, a few international multicity studies

19  were conducted that provide information, which further clarifies the association between $PM_{10}$ and

20  mortality. There has also been an analysis which examines the $PM_{10}$ concentration-response relationship

21  in 20 of the NMMAPS cities (see Section 6.5.2.7).

### *Seasonal Analyses of $PM_{10}$-mortality associations in 100 U.S. Cities (NMMAPS)*

22  Peng et al. (2005) analyzed the updated NMMAPS data, which consisted of 100 U.S. cities for the

23  period 1987–2000. In their first stage regression model, for each city, the $PM_{10}$ effect was modeled to

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[1] Schwartz (2004b) used a case-crossover study design, but also conducted a time-series analysis to validate the results obtained using the case-crossover approach.

1   have a sinusoidal shape that completes a cycle in a year but was constrained to be periodic across years

2   using sine/cosine terms. The authors also considered a model that consisted of $PM_{10}$-season interactions

3   using season indicators. Both of these models also included covariates that were used in their earlier

4   NMMAPS analyses. In the second stage model, the seasonal patterns of $PM_{10}$ mortality coefficients were

5   estimated for seven geographic regions and on average for the entire U.S. Peng et al. (2005) found for

6   1-day lag, at the national level, season specific increases in non-accidental mortality per 10 µg/m$^3$

7   increase in $PM_{10}$ of: 0.15% (Posterior Interval (PI): -0.08, 0.39), 0.14% (PI: -0.14, 0.42), 0.36% (PI: 0.11,

8   0.61), and 0.14% (PI: -0.06, 0.34) for winter, spring, summer, and fall, respectively. The corresponding

9   all-season estimate was 0.19% (PI: 0.10, 0.28). After the inclusion of $SO_2$, $O_3$, or $NO_2$ in the model with

10  $PM_{10}$ in a subset of cities (i.e., 45 cities) for which data existed for all pollutants resulted in fairly robust

11  $PM_{10}$ risk estimates. An analysis by geographic region found a strong seasonal pattern in the Northeast.

12  Figure 6-14 presents the estimated seasonal pattern of $PM_{10}$ risk estimates by region from Peng et al.

13  (2005), which includes a sensitivity analysis aimed to determine the appropriate number of degrees of

14  freedom for temporal adjustment. It is clear from Figure 6-14 that the Northeast has the strongest

15  association, which peaks in the summer and is robust to the extent of temporal adjustment. The industrial

16  Midwest also shows the summer peak, but with smaller risk estimates. Other regions have either no

17  seasonal pattern (Southeast) or a suggestion of a spring peak that appears to be sensitive to the extent of

18  temporal adjustment. On a nationwide basis, the $PM_{10}$ risk estimates appear to peak between spring and

19  summer. Overall, this study identified an effect modifier that may be useful in identifying specific

20  chemical component(s) that are related to specific regions and times of the year.

## Change in $PM_{10}$-mortality associations in NMMAPS data, 1987 to 2000

21      Dominici et al. (2007b) conducted an analysis of the extended NMMAPS data set with the main

22  objective of examining any change in short-term $PM_{10}$-mortality risk estimates during the course of the

23  study period. They estimated the average $PM_{10}$ mortality risk coefficient for 1-day lag using essentially

24  the same model specification as in their 2003 analysis, separately for three time periods: 1987-1994,

25  1995-2000, and 1987-2000, for the ''eastern U.S.'' (62 counties), the ''western U.S.'' (38 counties), and

26  all 100 U.S. counties. To produce national and regional estimates, two-stage hierarchical models were

27  used as in the previous NMMAPS studies. As shown in Table 6-14, the authors found a continuation of

28  the $PM_{10}$-mortality association in the nationwide data for the entire study period. A comparison of the

29  relative risk estimates for 1987-1994 vs. 1995-2000 suggests weak evidence (not a significant difference)

30  that short-term effects declined. Most of the decline in the national estimate appears to be attributable to

31  the eastern U.S. counties. However, the decline in risk estimate in all-cause mortality in the eastern U.S.

32  appears to be disproportionately influenced by the reduction in risk estimate for the "other" mortality

1 category (i.e., all-cause minus cardio-respiratory category, which may be 40 to 50% of all-cause deaths in

2 U.S. cities) in the eastern U.S. Likewise, the apparent increase in the risk estimate for all-cause mortality

3 in the western U.S. appears to be affected by the increase in risk estimate for the "other" mortality

4 category. Because it is not clear what specific cause(s) in the "other" mortality category are affected by

5 PM, interpreting the reduction in risk estimates for all-cause mortality requires caution. In contrast, the

6 apparent reductions, ~23%, in $PM_{10}$ risk estimates for cardio-respiratory deaths were more comparable

7 between the two regions.
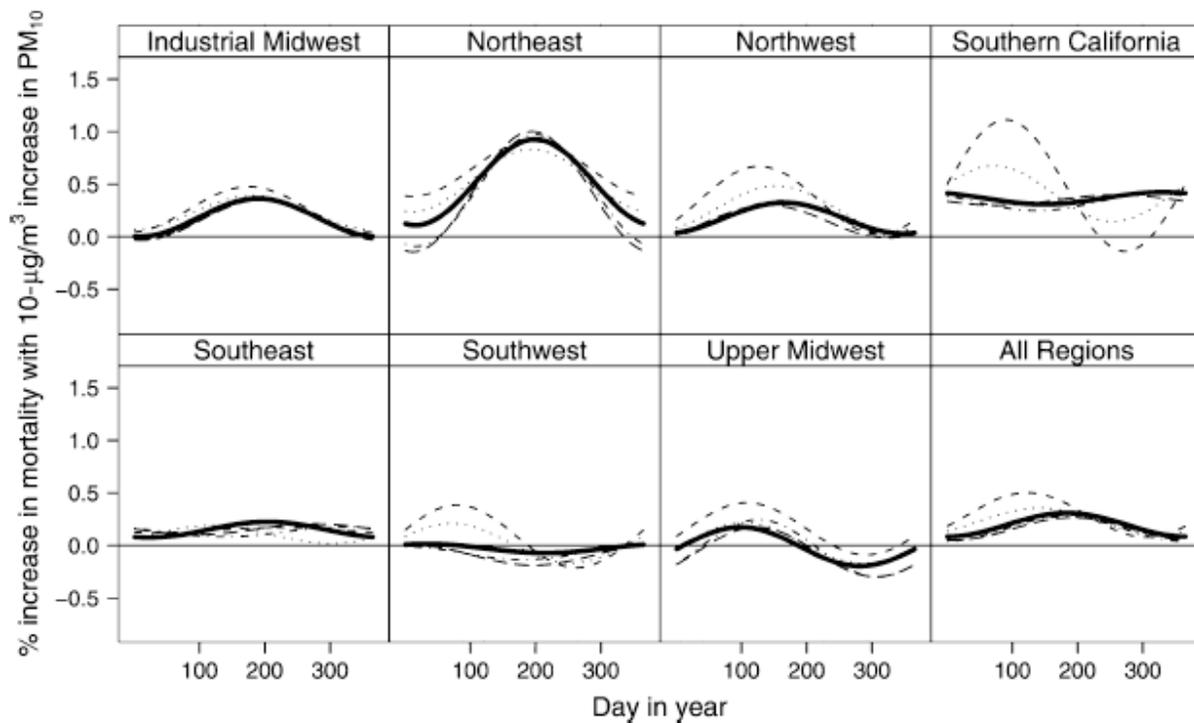


Source: Peng et al. (2005)

**Figure 6-14. National and regional estimates of smooth seasonal effects for $PM_{10}$ at a 1-day lag and their sensitivity to the degrees of freedom assigned to the smooth function of time in the updated NMMAPS data 1987-2000. Note: The degrees of freedom chosen were 3 df (short-dashed line), 5 df (dotted line), 7 df (solid line), 9 df (dotted-and-dashed line), and 11 df (long-dashed line) per year of data.**

8 In addition, the investigators estimated time-varying $PM_{10}$ mortality risk as a linear function of

9 calendar time for the period 1987–2000, producing the percentage rate change in $PM_{10}$ risk estimate with

10 a change in time of 1 year. The estimated rate of decline in slope for all-cause and the combination of

11 cardiovascular and respiratory mortality were -0.012 (PI: -0.037, 0.014) and -0.016 (PI: -0.058, 0.027),

1 respectively. The authors also estimated a $PM_{2.5}$ mortality risk for the period 1999-2000 (discussed in

2 Section 6.5.2.2.).

**Table 6-14.** **NMMAPS national and regional percentage increase in all-cause, cardio-respiratory, and other-cause mortality associated with a 10 μg/m³ increase in $PM_{10}$ at lag 1 day for the periods 1987–1994, 1995–2000, and 1987–2000.**

| | 1987-1994 | 95% PI | 1996-2000 | 95% PI | 1987-2000 | 95% PI |
|---|---|---|---|---|---|---|
| *ALL CAUSE* | | | | | | |
| East | 0.29 | 0.12, 0.46 | 0.13 | -0.19, 0.44 | 0.25 | 0.11, 0.39 |
| West | 0.12 | -0.07, 0.30 | 0.18 | -0.07, 0.44 | 0.12 | -0.02, 026 |
| National | 0.21 | 0.10, 0.32 | 0.18 | 0.00, 0.35 | 0.19 | 0.10, 0.28 |
| *CARDIORESPIRATORY* | | | | | | |
| East | 0.39 | 0.16, 0.63 | 0.30 | -0.13, 0.73 | 0.34 | 0.15, 0.54 |
| West | 0.17 | -0.07, 0.40 | 0.13 | -0.23, 0.50 | 0.14 | -0.05, 0.33 |
| National | 0.28 | 0.14, 0.43 | 0.21 | -0.03, 0.44 | 0.24 | 0.13, 0.36 |
| *OTHER* | | | | | | |
| East | 0.21 | -0.03, 0.44 | 0.00 | -0.49, 0.50 | 0.15 | -0.09, 0.39 |
| West | 0.09 | -0.21, 0.38 | 0.23 | -0.15, 0.62 | 0.11 | -0.10, 0.33 |
| National | 0.15 | -0.02, 0.32 | 0.17 | -0.07, 0.41 | 0.15 | 0.00, 0.29 |

Source: Dominici et al. (2007b)

3 The objective of the Dominici et al. (2007b) study described above was motivated by

4 accountability research, the idea of measuring the impact of policy interventions. However, unlike the

5 intervention studies conducted in Hong Kong (Hedley et al., 2002) and Dublin, Ireland (Clancy et al.,

6 2002) that were reviewed in the 2004 PM AQCD, this study was not designed to estimate a reduction in

7 mortality in response to a sudden change in air pollution. In fact, the figure of observed trend in $PM_{10}$

8 levels presented in the Dominici et al. (2007b) study indicates that the decline in $PM_{10}$ levels during the

9 study period was very gradual, with much of the decline appearing in the first few years (median values

10 of ~33 μg/m³ in 1987 to ~25 μg/m³ in 1992, then down to ~23 μg/m³ in 2000). A flaw in the use of the

11 time-series study design for this type of analysis is that it adjusts for long-term trends, and, therefore, does

12 not estimate the change in mortality in response to the gradual change in $PM_{10}$. The apparent change,

13 though weak, in the $PM_{10}$ risk estimates may also reflect a potential change in the chemical composition

14 of $PM_{10}$. The study listed a number of $PM_{10}$-related air pollution control programs that were implemented

15 between 1987 and 2000. Some of these programs, such as the Acid Rain Control Program, did result in

16 major reductions in emissions, and, therefore, could have contributed to the results observed, but the

17 analytic approached used in the study does not allow for a systematic analysis of the effect of air pollution

18 policies on the risk of mortality.

## Sensitivity of NMMAPS PM$_{10}$ risk estimates to alternative weather models

1    Welty and Zeger (2005) analyzed the updated NMMAPS 100 U.S. cities data to examine the
2    sensitivity of PM$_{10}$ mortality risk estimates to alternative weather models that consider longer lags. All of
3    the previous NMMAPS analyses only considered temperature and dew point up to 3-day lags. In this
4    analysis, the authors considered various forms of a constrained distributed lag model: (1) containing a
5    step function of temperature with steps at lag 0, 2, 7 and extended to 14 days; (2) similar to (1) but with
6    time-varying coefficients to change over season and study period; and, (3) containing a smooth function
7    to account for non-linearity in the temperature-mortality relationship. With a combination of degrees of
8    freedom for temporal trends and the number of distributed lags, more than 20 models were applied to
9    each of the three lag days (0, 1, and 2) of PM$_{10}$. These city-specific risk estimates were then combined
10   across the 100 cities in the second stage Bayesian model. The combined PM$_{10}$ risk estimates were
11   generally consistent within the lag. In particular, the risk estimates for non-accidental mortality for lag
12   1-day ranged between 0.15% and 0.25% per 10 µg/m$^3$ increase in PM$_{10}$, and were always statistically
13   significant regardless of the model used. In addition, the range of these point estimates across the models
14   was found to be much narrower than the regression posterior intervals. Thus, the PM$_{10}$ risk estimates at
15   lag 1 day were robust to alternative temperature models that considered temperature effects lasting up to a
16   two-week period.

17   In summary, the above three analyses of the updated NMMAPS data provided useful information
18   on PM$_{10}$ mortality risks, resulting in the following conclusions: (1) estimated PM$_{10}$ risk is particularly
19   high in the northeast and in the summer; (2) there remains an overall PM$_{10}$-mortality association in the
20   1987-2000 time period as well as the 1995-2000 time period; (3) there is a weak indication that PM$_{10}$
21   mortality risk estimates are declining; and (4) PM$_{10}$ risk estimates were not sensitive to alternative
22   temperature models.

## PM$_{10}$ Mortality Studies Conducted in Canada and Europe

23   Burnett et al. (2004) examined the association between mortality and various air pollutants in 12
24   Canadian cities, and reported that the most consistent association was found for NO$_2$. For this analysis,
25   PM was measured every 6th day for the majority of the study period, and the PM$_{10}$ concentrations used in
26   the study represent the sum of the PM$_{2.5}$ and PM$_{10-2.5}$ measurements obtained. The authors found that the
27   simultaneous inclusion of NO$_2$ and PM$_{10}$ in a model, on those days with PM data, greatly reduced the
28   PM$_{10}$ association with non-accidental mortality, from 0.47% (95% CI: 0.04–0.89) to 0.07% (95% CI:
29   -0.44 to 0.58) per 10 µg/m$^3$ increase. The previous Canadian multicity analysis (Burnett and Goldberg,
30   2003), a re-analysis of Burnett et al. (2000) reviewed in the 2004 PM AQCD, did not consider gaseous

1   pollutants. Thus, $PM_{10}$ risk estimates in the Canadian data appear to be more sensitive to $NO_2$ than those

2   estimates reported in U.S. studies.

3        The association between $PM_{10}$ and mortality in Europe was also reviewed in the 2004 PM AQCD

4   through Katsouyanni et al. (2003), which presented results from the Air Pollution and Health: a European

5   Approach (APHEA2) study, a multicity study that examined $PM_{10}$ effects on total mortality in 29

6   European cities. Analitis et al. (2006) published a brief report on effect estimates for cardiovascular and

7   respiratory deaths also based on the 29 European cities, within the APHEA2 study. They reported for the

8   average of 0- and 1-day lags, $PM_{10}$ risk estimates per 10 $\mu g/m^3$ of 0.76% (95% CI: 0.47–1.05) for

9   cardiovascular deaths and 0.71% (95% CI: 0.22–1.20) for respiratory deaths in random effects models.

### Case-Crossover Analyses

10       Since the 2004 PM AQCD investigators have used the case-crossover study design more frequently

11  as an alternative to time-series analyses to examine the association between short-term exposure to PM

12  and mortality. This study design allows for the control of seasonal variation, time trends, and slow time

13  varying confounders without the use of complex models. However, similar to any study design, biases can

14  be introduced into the study depending on the control (i.e., referent) period selected (Janes et al., 2005).

15  The multicity case-crossover analyses discussed below match cases (i.e., days in which a death occurred)

16  to controls (i.e., days in which a death did not occur), to control for (1) seasonal patterns and gaseous

17  pollutants, or (2) temperature. In addition the studies attempt to examine the heterogeneity of effect

18  estimates through the analysis of individual-level and city-specific effect modification.

### $PM_{10}$ and Mortality in 14 U.S. Cities: Controlling for Temperature

19       Schwartz (2004b) investigated the $PM_{10}$-mortality association in 14 U.S. cities for the years

20  1986-1993 (some cities started in later years because of $PM_{10}$ data availability) using a case-crossover

21  study design. Note that in this analysis, four more cities (Boulder, CO; Cincinnati, OH; Columbus, OH;

22  and Provo-Orem, UT) were added to the cities Schwartz (2003) previously analyzed using a time-series

23  study design. These cities were chosen for this analysis because they collected daily $PM_{10}$ data, unlike

24  most U.S. cities, which only monitor $PM_{10}$ every six days. Lag 1-day $PM_{10}$ risk estimates were computed

25  using several methods. Models (1) (i.e., the main model) and (2) were constructed from a case-crossover

26  analysis with bidirectional control days (7-15 days before and after the case). Model (1) obtained

27  city-specific estimates in the first stage analysis, followed by a second stage random-effects model to

28  obtain a combined estimate. Model (2) is the same as model (1), but consisted of a single stage model,

29  which included data from all 14 cities. Models (3) and (4) were also constructed from a case-crossover

30  analysis, but used time-stratified control days (i.e., matched on season and temperature within the same

1  degree in Celsius). Model (3) obtained single-city estimates in the first stage analysis, followed by a

2  second stage random-effects model to obtain combined estimates. Model (4) used the same approach as

3  model (3), but consisted of a single stage model including data from all 14 cities. The final model, (5),

4  consisted of a two-stage Poisson time-series model, which produced city-specific estimates in the first

5  stage, and combined estimates across cities in the second stage. In the main model, (1) above, the

6  estimated excess risk for non-accidental mortality was 0.36% (CI: 0.22, 0.50) per 10 $\mu g/m^3$ increase in

7  $PM_{10}$. The other models yielded a similar magnitude of effect estimates, ranging from 0.32% (model 2) to

8  0.53% (model 4). Thus, the methods used to select control days and adjust for weather in the

9  case-crossover design did not result in major differences in effect estimates, and in addition, were

10  comparable to the estimates obtained from the time-series analysis, 0.40% (model 5).

## $PM_{10}$ and Mortality in 14 U.S. Cities: Controlling for Gaseous Pollutants

11  In a subsequent analysis, Schwartz (2004a) analyzed the same 14 cities data described above, using

12  a case-crossover design, to investigate the potential confounding effects of gaseous pollutants. For each

13  case day, control days were selected from all other days of the same month of the same year. In addition,

14  case days were matched to control days that had gaseous pollutant levels that were within a defined

15  concentration: 1 ppb, 1 ppb, 2 ppb, and 0.03 ppm for $SO_2$, $NO_2$, 1-h max $O_3$, and CO, respectively. Unlike

16  the study described above (Schwartz, 2004b), in this analysis, the excess risk was estimated for the

17  average of 0- and 1-day lag $PM_{10}$ (rather than 1-day lag). In addition, apparent temperature (a composite

18  index of temperature and humidity) was used rather than temperature and humidity individually. The

19  case-crossover analysis was conducted in each city, and a combined estimate was computed in a

20  second-stage random effects model. The number of cities analyzed varied across pollutants depending on

21  the availability of monitors. The study reported $PM_{10}$ risk estimates for non-accidental mortality of 0.81%

22  (CI: 0.47, 1.15), 0.78% (CI: 0.42, 1.15), 0.45% (CI: 0.12, 0.78), and 0.53% (CI: 0.04, 1.02) per 10 $\mu g/m^3$

23  increase, for the analysis matched by $SO_2$ (10 cities), $NO_2$ (8 cities), $O_3$ (13 cities), and CO (13 cities),

24  respectively.

25  Schwartz (2004c) only presented $PM_{10}$ risk estimates matched by gaseous pollutants, therefore, it is

26  unclear in this analysis how matching by gaseous pollutants affected (i.e., reduced or increased)

27  unmatched $PM_{10}$ risk estimates. The estimates reported were computed using the average of 0- and 1-day

28  lagged $PM_{10}$ and, therefore, cannot be directly compared to the 1-day lag $PM_{10}$ risk estimates obtained in

29  the Schwartz (2004b) 14-city study described above. The estimates reported in Schwartz (2004c) are

30  generally larger than those obtained in the Schwartz (2004b) analysis, which was expected since the

31  Schwartz (2004c) analysis used two-day average $PM_{10}$. However, the estimates reported in Schwartz

32  (2004c) are comparable to the average of 0- and 1-day lagged $PM_{10}$ risk estimate for non-accidental

1    mortality (0.55% [CI: 0.39, 0.70]) per 10 µg/m$^3$ increase from the 10-city study (Schwartz, 2003), which

2    was reviewed in the 2004 PM AQCD. Overall, Schwartz (2004c) provided an alternative method to assess

3    the influence of gaseous copollutants. The results suggest that $PM_{10}$ is significantly associated with

4    all-cause mortality after controlling for each of the gaseous copollutants.

### *$PM_{10}$ and Mortality in 20 U.S. Cities: City-level Effect Modification*

5    Zeka et al. (2006a) expanded the 14 cities analysis conducted by Schwartz (2004b, c) to 20 cities,

6    added more years of data (1989-2000), and investigated $PM_{10}$ effects on total and cause-specific mortality

7    using a case-crossover design. Individual 0-, 1-, and 2-day lags as well as an unconstrained distributed lag

8    model with 0, 1, and 2 lag days were examined. For each case day, control days were defined as every

9    third day in the same month of the same year, to eliminate serial correlation. The authors also investigated

10   potential effect modifiers in the second stage regression using city-specific variables including percent

11   using air conditioning, population density, standardized mortality rates, the proportion of elderly in each

12   city, daily minimum apparent temperature in summer, daily maximum apparent temperature in winter, and

13   the estimated percentage of primary $PM_{10}$ from traffic sources.

14   The investigators found that, for all-cause (non-accidental) mortality, lag 1-day showed the largest

15   risk estimate (0.35% [CI: 0.21, 0.49] per 10 µg/m$^3$) among the individual lags. Respiratory mortality

16   exhibited associations at lag 0, 1, and 2 days (0.34, 0.52, and 0.51%, respectively), whereas

17   cardiovascular mortality was most strongly associated with $PM_{10}$ at lag day 2 (0.37%). The sum of the

18   distributed lag risk estimates (e.g., 0.45% [CI: 0.25, 0.65] for all-cause mortality) was generally larger

19   than those for single-day lag estimates. The excess risk estimates for single-day lags for specific

20   respiratory and cardiovascular causes had generally wider confidence intervals due to their smaller daily

21   mortality counts, but some of the categories showed markedly larger estimates when included in the

22   combined distributed lag model (e.g., pneumonia 1.24% [CI: 0.46, 2.02]). As shown in Figure 6-15, Zeka

23   et al. (2005) also found evidence indicative of several $PM_{10}$ effect modifiers including higher population

24   density and the estimated percentage of primary $PM_{10}$ from traffic. When 25th vs. 75th percentiles of

25   these city-specific variables were evaluated, the estimated percent increase in mortality attributed to $PM_{10}$

26   appears to contrast substantially (e.g., 0.09 vs. 0.52% for variance of summer time apparent temperature).
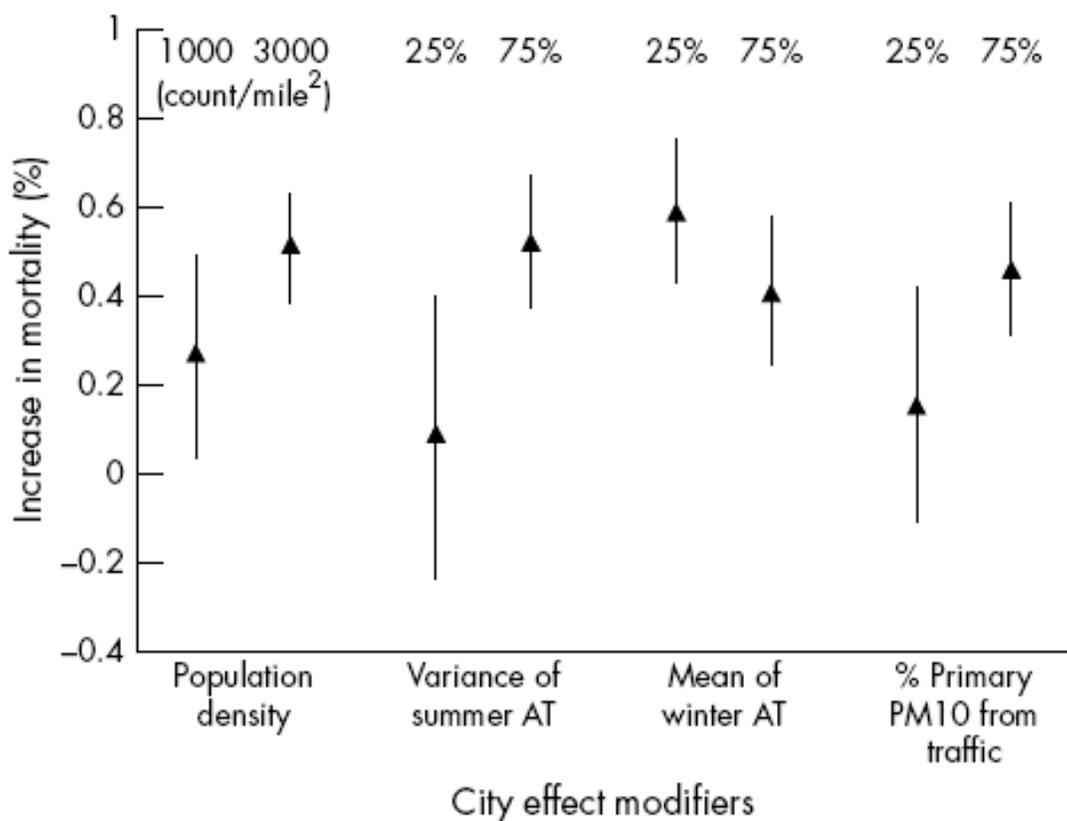
Source: Zeka et al. (2005)

**Figure 6-15.** **Effect modification by city characteristics in 20 U.S. cities. Note: The two estimates and their CI for each of the modifying factors represent the percentage increase in mortality for a 10 µg/m³ increase in $PM_{10}$, for the 25th percentile, and 75th percentile of the modifier distribution across the 20 cities.**

1    The effect modifiers investigated by Zeka et al. (2005) consisted of city-specific variables. Some of

2  these variables are ecological in nature, and therefore, interpreting the meaning of "effect modification"

3  requires some caution. As the investigators pointed out, the population density and the estimated

4  percentage of primary $PM_{10}$ from traffic were correlated in this data set (r = 0.65)[1]. These variables may

5  also be a surrogate for another or composite aspects of "urban" characteristics. Thus, the apparent effect

6  modification by traffic associated $PM_{10}$ needs further investigation. Interestingly, the percent of homes

7  with central air conditioning was not a significant effect modifier of $PM_{10}$ risk estimates, which questions

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[1] The correlation coefficient was calculated based on the numbers provided in Table 1 of Zeka et al. (2005).

1 the impact of reduced ventilation rates on PM exposure. Overall, this study presented $PM_{10}$ risk estimates

2 that are consistent with those found in other analyses, but also provided new information on the risk

3 estimated for broad and specific respiratory and cardiovascular mortality, along with possible effect

4 modifying city characteristics.

## $PM_{10}$ and Mortality in 20 U.S. Cities: Individual-level Effect Modification

5 Zeka et al. (2006a) examined individual-level, instead of city-specific, effect modification of

6 $PM_{10}$-mortality associations in the 20 U.S. cities described above using the same case-crossover design.

7 City-specific estimates were obtained in the first stage model, followed by a second stage model which

8 estimated the overall effects across all cities. Figure 6-16 shows $PM_{10}$ excess risks by four of the

9 individual characteristics examined in the study (i.e., gender, race, age group, and education). It should be

10 noted that the lag and averaging of days of associations reported varied across the outcomes: all-cause and

11 heart disease deaths used the average of lag 1 and 2 days; respiratory deaths used the average of lag 0

12 through 2 days; myocardial infarction deaths used lag 0 day; and stroke deaths used lag 1 day. $PM_{10}$ risk

13 estimates do not appear to differ by gender or by race. However, significant differences were found for the

14 youngest vs. oldest age groups for all-cause and heart disease mortality. For all-cause mortality, the level

15 of education appeared to be inversely related to the $PM_{10}$ risk estimates, but this observation was not

16 statistically significant. The study also examined effect modification by location of death

17 ("out-of-hospital" vs. "in-hospital") and season (see Figure 6-17). The "out-of-hospital" deaths showed

18 larger $PM_{10}$ risk estimates than were found for "in-hospital deaths" with a significant contrast per

19 10 $\mu g/m^3$ for all-cause (0.71% vs. 0.22%) and heart disease (0.93% vs. 0.15%) deaths. Stroke deaths also

20 showed a significant contrast (0.87% vs. 0.06%, not shown in Figure 6-17).
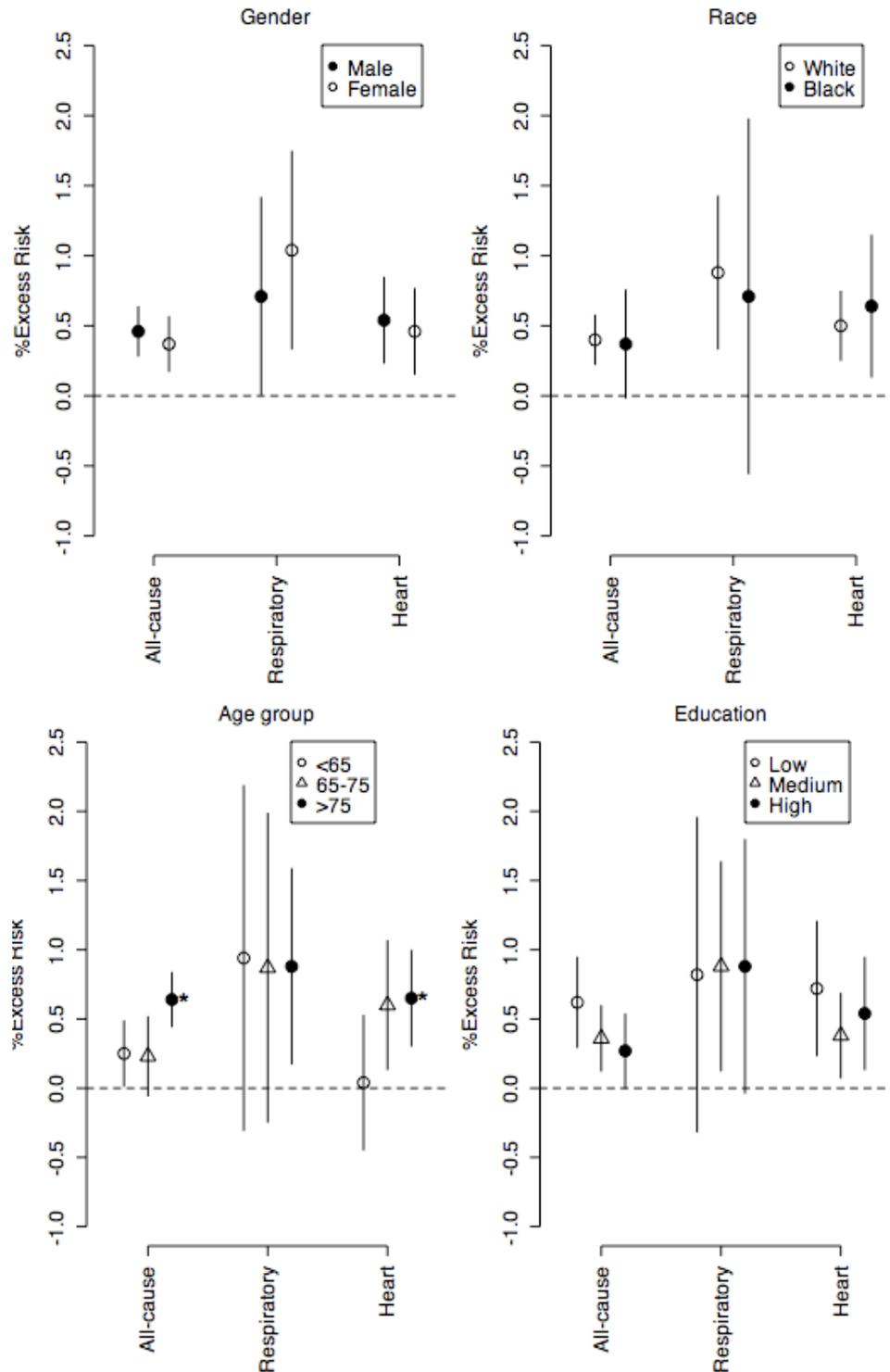
**Figure 6-16.** PM$_{10}$ risk estimates (per 10 µg/m$^3$) by individual-level characteristics. The risk estimates and 95% confidence intervals were plotted using numerical results from tables in Zeka et al. (2006a). The estimates with '*' next to them are significantly higher than the lowest estimate in the group.
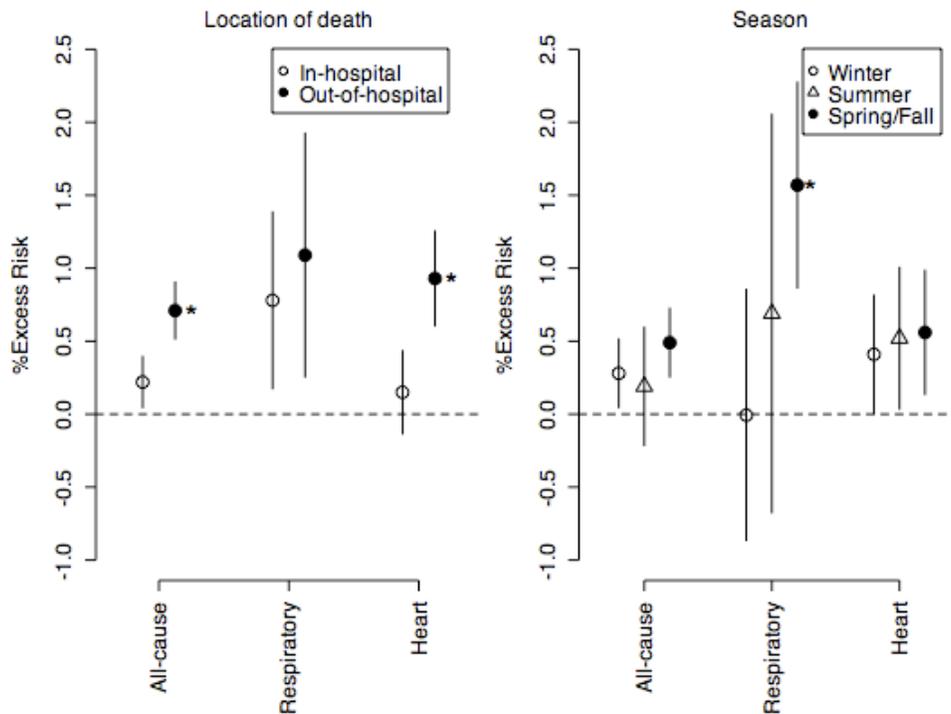
**Figure 6-17.** PM$_{10}$ risk estimates (per 10 µg/m$^3$) by location of death and by season. The risk estimates and 95% confidence intervals were plotted using numerical results from tables in Zeka et al. (2006a). The estimates with '*' next to them are significantly higher than the lowest estimate in the group.

1    Overall, Zeka et al. (2006a) showed a consistent pattern of effect modification by contributing

2    causes of death (i.e., pneumonia, stroke, heart failure, and diabetes) on PM$_{10}$ risk estimates for primary

3    causes of death (Figure 6-18; not all results for contributing cause are shown). However, because the

4    contributing causes of death counts were relatively small, as reflected in the wide confidence bands in

5    Figure 6-18, most of the contrasts observed did not achieve statistical significance.
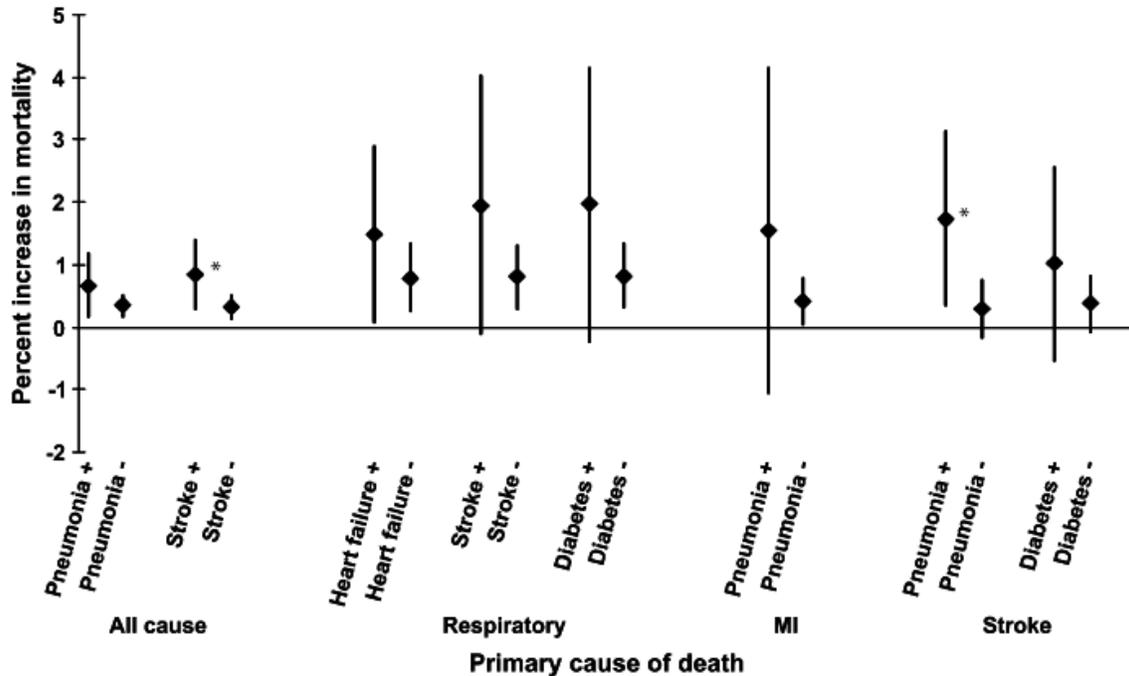
**Figure 6-18.** PM$_{10}$ risk estimates (per 10 µg/m$^3$) by contributing causes of deaths. The estimates with '*' (added to the original figure) indicates a significant difference.

1      In addition, when examining the other effect modifiers, the results that show no gender or race

2      differences in PM$_{10}$ risk estimates for all-cause and cardiovascular deaths are important, given the

3      relatively narrow confidence bands of these estimates. The effect modification by the location of death

4      has been reported previously in smaller studies, but the large contrast found for all-cause and

5      cardiovascular mortality in this large multicity analysis is noteworthy. The elevated PM$_{10}$ risks reported

6      by Zeka et al. (2006a) for all-cause, heart disease (and stroke) "out-of-hospital" deaths are also consistent

7      with the hypothesis of acute PM$_{10}$ effects on "sudden deaths" brought on by systemic inflammation or

8      dysregulation of the autonomic nervous system. The finding regarding the seasonal effect modification,

9      though significant only for respiratory deaths, is somewhat in contrast with the Peng et al. (2005) analysis

10     of the extended NMMAPS data, which observed the greatest effects during the summer season. The

11     apparent inconsistency may be due to the difference in geographic coverage (i.e., 20 vs. 100 cities) or

12     methodology (i.e., case-crossover with referent days in the same month of the same year vs. time-series

13     analysis with adjustment for temporal trend in the regression model).

### *Summary of PM$_{10}$ Risk Estimates*

14      Of those studies discussed in the text, depending on the lag/averaging time and the number of cities

15     included, the estimates for all-cause (non-accidental) mortality for all ages ranged from 0.12% (Dominici

1    et al., 2007b) to 0.53% (Schwartz, 2004b) per 10 µg/m$^3$ increase in $PM_{10}$, regardless of the study design

2    used (i.e., time-series vs. case crossover) (see Figure 6-19). The majority of studies examined present

3    estimates for either a lag of 1 day or a 2-day average (lag 0-1), both of which have been found to be

4    strongly associated with the risk of death (Schwartz, 2004b, c). However, the use of a distributed lag

5    model was found to result in slightly larger (by ~30%) estimates compared to those for single-day lags

6    (Zeka et al., 2005). Overall, an examination of the $PM_{10}$ risk estimates stratified by cause-specific

7    mortality and age, for all U.S.- and Canadian-based studies, further supports the findings of the multicity

8    studies discussed in the 2004 PM AQCD and this ISA, but there is a larger degree of variability and

9    uncertainty in risk estimates derived from single-city studies (see Figure 6-20).

10       The variability in $PM_{10}$ mortality risk estimates reported within and between multicity studies may

11   be due to the difference in the cities analyzed and the potential regional differences in PM composition.

12   The NMMAPS studies have found that geographic regions and seasons are the two most important factors

13   that determine the variability in risk estimates, with estimates being larger in the Eastern U.S. and during

14   the summer, respectively. These findings were fairly consistent across studies, but Zeka et al. (2006a) did

15   observe the strongest association during the transition period (spring and fall); however, this may be due

16   to the difference in geographic coverage or the difference in the model specification used compared to

17   Peng et al. (2005).

18       Finally, examination of potential confounders showed that the size of $PM_{10}$ risk estimates are fairly

19   robust to the inclusion of gaseous copollutants in models (Peng et al., 2005) or by matching days with

20   similar gaseous pollutant concentrations (Schwartz, 2004b). These findings further confirmed that $PM_{10}$

21   risk estimates are not, at least in a straightforward manner, confounded by gaseous copollutants.
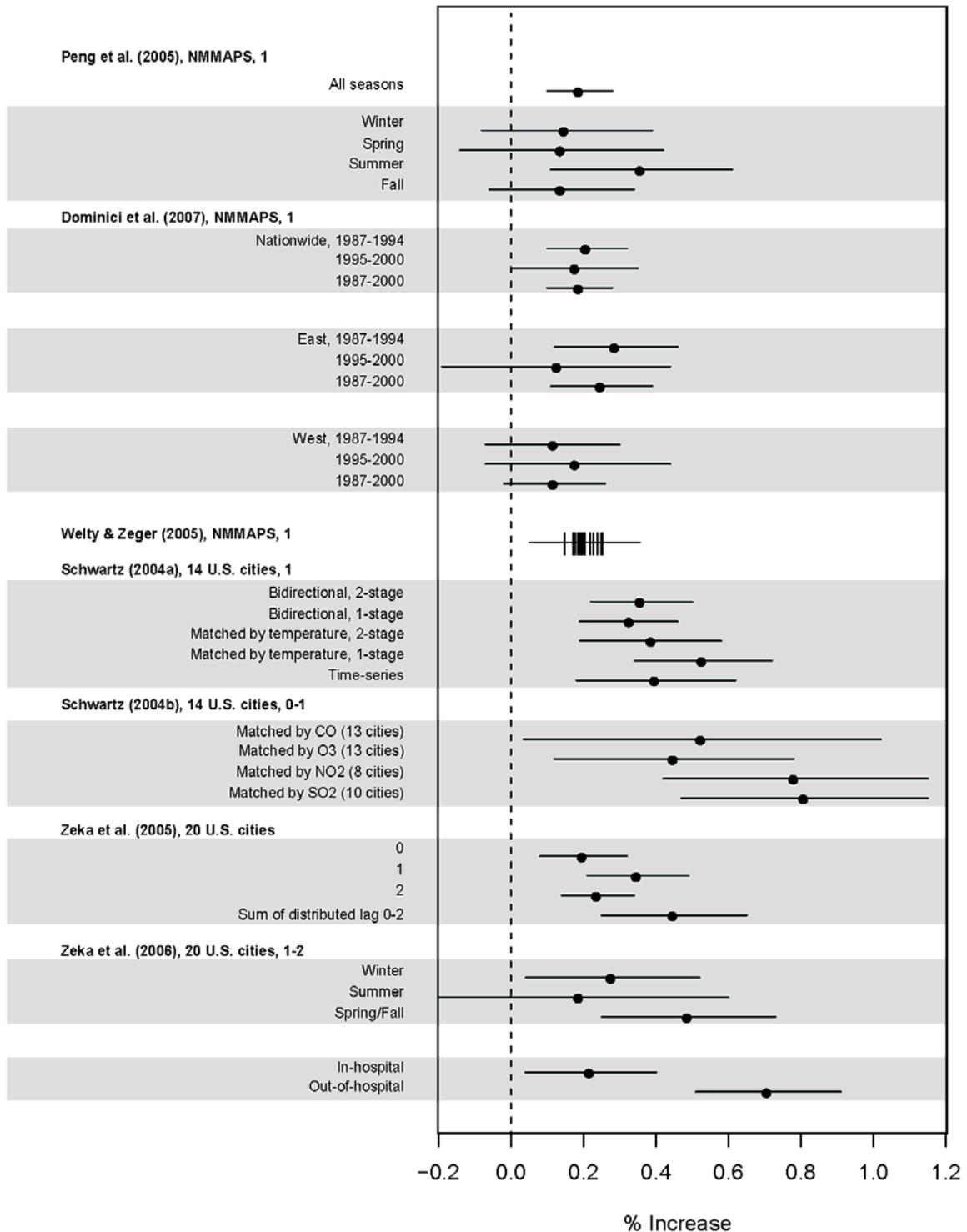
**Figure 6-19. Summary of PM$_{10}$ risk estimates (per 10 μg/m$^3$) for all-cause mortality from recent multicity studies. The number after the study location indicates lag/average used for PM$_{10}$ (e.g., "01" indicates the average of lag 0 and 1 days). For Welty and Zeger (2005), the vertical lines represent point estimates for 23 different weather models, and the horizontal band spans the 95% posterior intervals of these point estimates.**
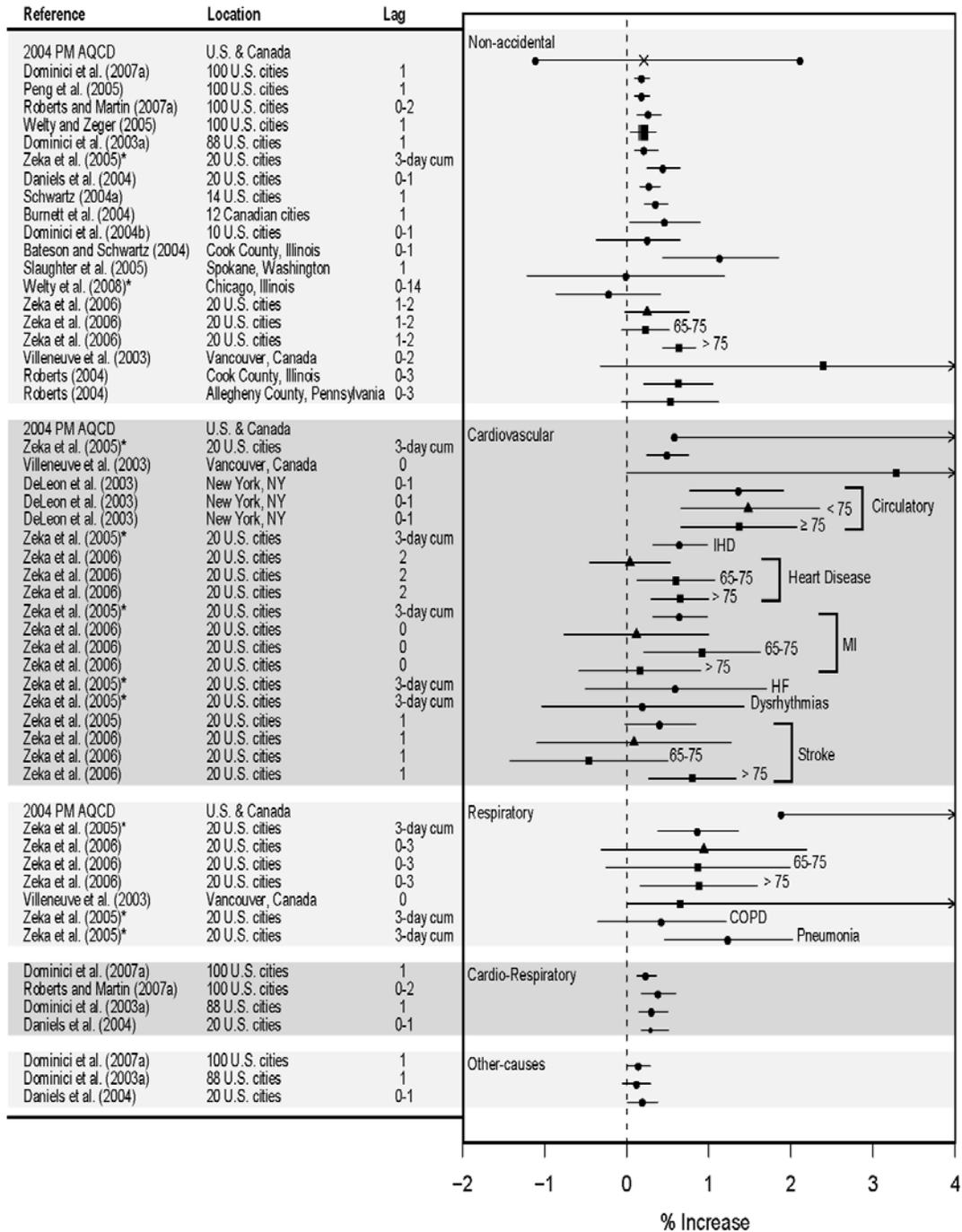
**Figure 6-20.** Summary of PM$_{10}$ risk estimates (per 10 μg/m$^3$) for cause-specific mortality for all U.S.-and Canadian-based studies. The estimates provided for "2004 PM AQCD" represent the lowest and highest central estimates for the U.S.- and Canadian-based studies evaluated in the previous AQCD. The "x" presesented in the non-accidental mortality range represents the lone multicity study evaluated (Dominici et al., 2003a). For Welty and Zeger (2005) the vertical lines represent point estimates for 23 different weather models, and the horizontal band spans the 95% posterior intervals of these point estimates. Circle: all ages; triangle: < 65; square ≥ 65; *:- distributed lag model.

### 6.5.2.2. PM$_{2.5}$

1    Nationwide collection of PM$_{2.5}$ data began in 1999. This in conjunction with the unavailability of

2    nationwide mortality data from the NCHS starting with year 2001 data, as discussed previously, resulted

3    in only a few multicity studies (i.e., studies in which mortality data was obtained from state or city

4    agencies), which could examine the mortality effects of PM$_{2.5}$ for an extended period of time.

### PM$_{2.5}$ - Mortality Associations in 100 U.S. cities, 1999 to 2000

5    The Dominici et al. (2007b) NMMAPS study (described in Section 6.5.2.1.), also examined

6    PM$_{2.5}$-mortality associations using the same methodology and data for 1999-2000. The PM$_{2.5}$ risk

7    estimates at lag 1-day were 0.29% (PI: 0.01, 0.57) and 0.38% (PI: -0.07, 0.82) per 10 µg/m$^3$ increase for

8    all-cause and cardio-respiratory mortality, respectively. The authors also conducted a sensitivity analysis

9    of the risk estimates based on the extent of adjustment for temporal trends in the model, changing the

10   degrees of freedom (df) of temporal adjustment from 1 to 20/yr (the main result used 7 df/yr). In

11   comparison to the PM$_{10}$ results, the PM$_{2.5}$ risk estimates appeared more sensitive to the extent of temporal

12   adjustment between 5 and 10 df/yr, but this may be in part due to the much smaller sample size used for

13   the PM$_{2.5}$ analysis compared to the PM$_{10}$ analysis.

### PM$_{2.5}$ - Mortality Associations in 27 U.S. Cities, Variable between 1997 and 2002

14   Franklin et al. (2007) analyzed 27 cities that had PM$_{2.5}$ monitoring and daily mortality data for at

15   least 2 years of a 6-year period 1997 to 2002. The mortality data up to year 2000 were obtained from the

16   NCHS, while the 2001-2002 data were obtained from six states (CA, MI, MN, PA, TX, and WA),

17   resulting in 12 out of the 27 cities having data up to 2002. The start year for each city included in the

18   study was set at 1999, except for Milwaukee, WI (1997) and Boston, MA (1998), which is due to PM$_{2.5}$

19   data availability in these two cities. In the case-crossover analysis in each city, control days for each death

20   were chosen to be every third day within the same month and year that death occurred in order to reduce

21   auto-correlation. The first stage regression examined the interaction of effects with age and gender, while

22   the second stage random effects model combined city-specific PM$_{2.5}$ risk estimates and examined possible

23   effect modifiers using city-specific characteristics (e.g., prevalence of central air conditioning and

24   geographic region). For all of the mortality categories, the estimates for lag 1-day showed the largest

25   estimates. The combined estimates at lag 1 day were: 1.2% (CI: 0.29, 2.1), 0.94% (CI: -0.14, 2.0), 1.8%

26   (CI: 0.20, 3.4), and 1.0% (CI: 0.02, 2.0) for all-cause, cardiovascular, respiratory, and stroke deaths,

27   respectively, per 10 µg/m$^3$. When examining the city-specific risk estimates most of the cities with

28   negative estimates are also those with a high prevalence of central air conditioning (Dallas, 89%;

1 Houston, 84%; Las Vegas, 93%; Birmingham, 77%). It is unclear why these cities exhibit negative (and

2 significant) risk estimates rather than null effects.

3 In the analysis of effect modifiers, Franklin et al. (2007) found that individuals $\geq 75$ showed

4 significantly higher $PM_{2.5}$ risk estimates. The estimated effects were also found to vary by geographic

5 location with larger estimates in the East than in the West, which are consistent with the regional pattern

6 found in the NMMAPS $PM_{10}$ risk estimates. In addition, a higher prevalence of central air conditioning

7 was associated with decreased $PM_{2.5}$ risk estimates when comparing the lower (25th percentile) vs. the

8 higher (75th percentile) air conditioning use rates, especially in the cities where $PM_{2.5}$ concentrations peak

9 in the summer. Finally, the risk estimates were not found to be different between communities with $PM_{2.5}$

10 levels less than or equal to vs. higher than 15 $\mu g/m^3$. The risk estimates for each effect modifier are

11 presented in Figure 6-21. Note the wide confidence intervals associated with each of the risk estimates,

12 specifically for Franklin et al. (2007) and Ostro et al. (2006), which suggests low statistical power for

13 testing the differences between effect modifiers.

## $PM_{2.5}$ - Mortality Associations in 25 U.S. Cities between 2000 and 2005

14 Franklin et al. (2007) analyzed 25 cities that had $PM_{2.5}$ monitoring and daily mortality data between

15 the years 2000 to 2005 (with the study period varying from city to city). The choice of the 25

16 communities was based on the availability of $PM_{2.5}$ mass concentrations and daily mortality records for at

17 least 4 years, along with $PM_{2.5}$ speciation data for at least two years between 2000 and 2005. Similar to

18 Franklin et al. (2007), all-cause, cardiovascular, respiratory, and stroke deaths were examined; however,

19 of the 25 cities included in the study, only 15 overlap with the 27 cities analyzed in Franklin et al. (2007).

20 The authors obtained mortality data from the NCHS and various state health departments (California,

21 Massachusetts, Michigan, Minnesota, Missouri, Ohio, Pennsylvania, Texas, and Washinton). Although the

22 main objective of the study was to examine the role of $PM_{2.5}$ chemical species in the second stage

23 analysis, the first stage analysis conducted a time-series regression of mortality on $PM_{2.5}$. In addition, the

24 first stage regression performed a seasonal analysis in order to take advantage of seasonal variation in

25 $PM_{2.5}$ chemical species across cities and to possibly explain the city-to-city variation in $PM_{2.5}$ mortality

26 risk estimates. From this analysis a strong seasonal pattern was observed with the greatest effects

27 occurring in the spring and summer seasons (see Figure 6-21).

28 Overall, the risk estimates for all-cause, cardiovascular, and respiratory deaths reported by Franklin

29 et al. (2008) are comparable to those presented in the 27 cities study (Franklin et al., 2007) and the

30 California 9 counties study (Ostro et al., 2006), as shown in Figure 6-21. When comparing the 2007 and

31 2008 studies conducted by Franklin et al., although only 15 cities overlap between the two studies and

32 each study was designed differently (i.e., time-series vs. case-crossover), the magnitude of the $PM_{2.5}$ risk

1    estimates reported were similar for the same averaging time, and both studies reported a regional pattern

2    (East > West) similar to that found in NMMAPS for $PM_{10}$ risk estimates.

### PM$_{2.5}$ - Mortality Associations in Nine California counties, 1999-2002

3    Ostro et al. (2006) examined associations between $PM_{2.5}$ and daily mortality in nine heavily

4    populated California counties (Contra Costa, Fresno, Kern, Los Angeles, Orange, Riverside, Sacramento,

5    San Diego, and Santa Clara) using data from 1999 through 2002. The authors used a two-stage model to

6    examine all-cause, respiratory, cardiovascular, ischemic heart disease, and diabetes mortality individually

7    and by potential effect modifier (i.e., age, gender, race, ethnicity, and education level). The a priori

8    exposure periods examined included the average of 0- and 1-day lags (lag 0-1) and the 2-day lag (lag 2).

9    The authors selected these non-overlapping lags (i.e., rather than selecting lag 1 as the single-day lag)

10   because previous studies have reported stronger associations at lags of 1 or 2 days or with cumulative

11   exposure over three days. It is unclear why the investigators chose these non-overlapping lags

12   (i.e., single-day lag of 2 instead of 1) even though they state they based the selection of their lag days on

13   results presented in previous studies, which found the strongest association for PM lagged 1 or 2 days.

14   Using the average of 0- and 1-day lags Ostro et al. (2006) reported combined estimates of: 0.6% (CI: 0.2,

15   1.0), 0.6% (CI: 0.0, 1.1), 0.3% (CI: -0.5, 1.0), 2.2% (CI: 0.6, 3.9), and 2.4% (CI: 0.6, 4.2) for all-cause,

16   cardiovascular, ischemic heart disease, respiratory, and diabetes deaths, respectively, per 10 $\mu g/m^3$. The

17   risk estimates for the major underlying causes and for potential effect modifiers are presented in Figures

18   6-21 and 6-22. The authors also conducted a sensitivity analysis of risk estimates based on the extent of

19   temporal adjustment, which showed monotonic reductions for all of the death categories examined when

20   4, 8, and 12 degrees of freedom per year were used.

21   Five of the nine counties examined in the Ostro et al. (2006) analysis are among the 27 cities

22   examined in the Franklin et al. (2007) analysis for the same period, 1999-2002. While the lags used were

23   different between these two studies, both presented $PM_{2.5}$ risk estimates in individual cities (graphically in

24   the Franklin et al. study; in a table in the Ostro et al. study), which allowed for a cursory evaluation of

25   consistency between the two analyses. In Franklin et al. (2007) $PM_{2.5}$ risk estimates at lag 1 day for Los

26   Angeles and Riverside were slightly negative, whereas Fresno, Sacramento, and San Diego showed

27   positive values above 1% per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The 2-day lag result presented in Ostro et al.

28   (2006) is qualitatively consistent, with Los Angeles and Riverside, both of which show slightly negative

29   estimates, while the other 3 locations all show positive, but somewhat smaller estimates, than those

30   reported by Franklin et al (2007). The estimates for the average of 0- and 1-day lags for these five cities in

31   Ostro et al. (2006) were all positive. Thus, these two $PM_{2.5}$ studies showed some consistencies in risk

32   estimates even though they used different lag periods. Although the risk estimates for Franklin et al.

1    (2007) and Ostro et al. (2006), stratified by various effect modifiers (gender, race, etc.), are summarized

2    in Figure 6-21 there is one noteworthy contrast. Ostro et al. (2006) observed comparable risk estimates for

3    "in-hospital" vs. "out-of-hospital" deaths, which is in contrast to the large difference between the two

4    found for $PM_{10}$ risk estimates in the 20 cities study discussed earlier (Zeka et al., 2006a).
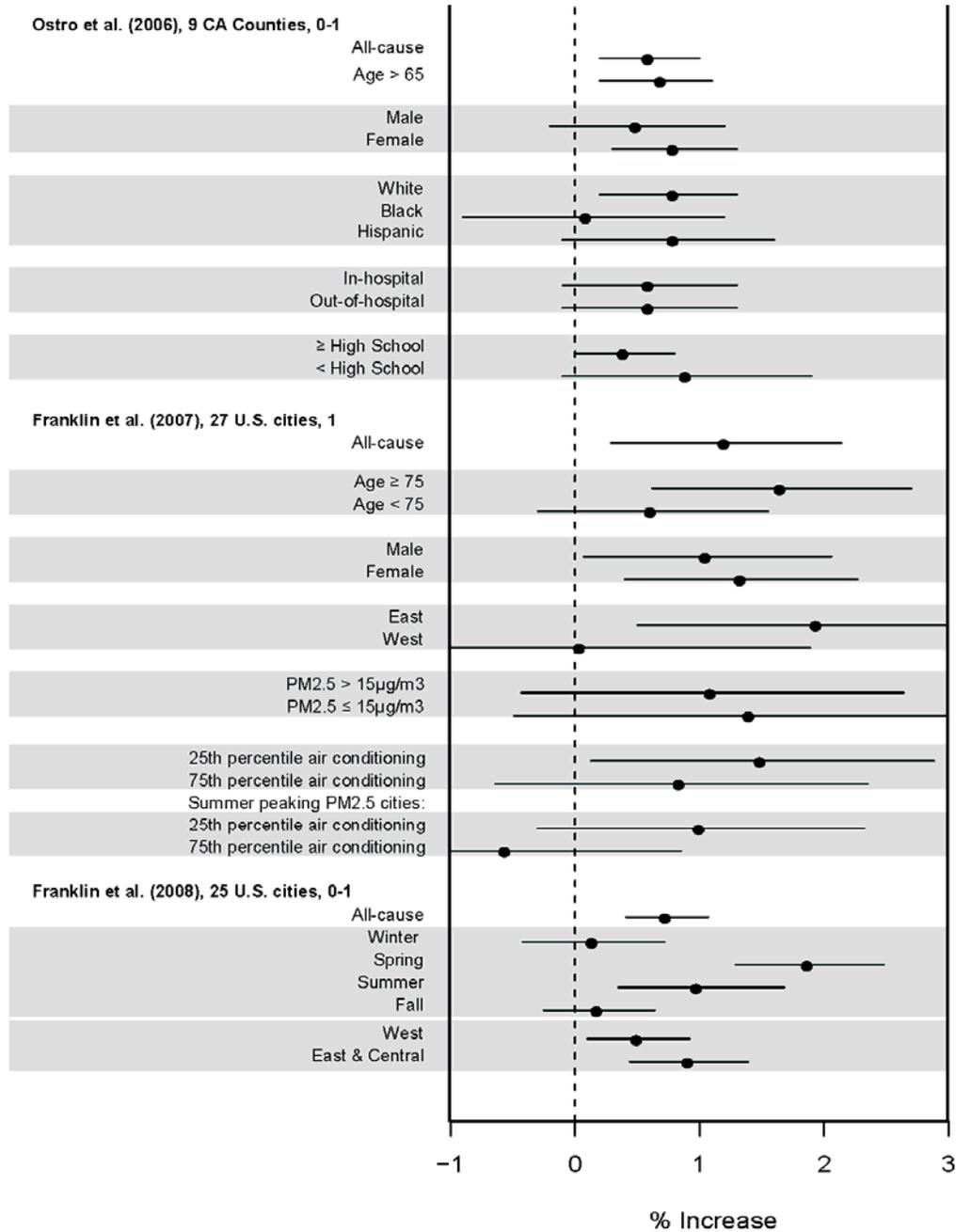


**Figure 6-21.   Summary of all-cause mortality PM$_{2.5}$ risk estimates per 10 µg/m³ by various effect modifiers.**

## *Multi-city Studies on PM$_{2.5}$ Mortality Effects in Other Countries*

1  Burnett et al.'s study of multiple pollutants in 12 Canadian cities found the most consistent

2  associations for NO$_2$ (2004). In this analysis, PM$_{2.5}$ was only measured every sixth day in much of the

3  study period, and a simultaneous inclusion of NO$_2$ and PM$_{2.5}$ in a model on the days when PM$_{2.5}$ data

4  were available eliminated the PM$_{2.5}$ association (from 0.60% to -0.10% per 10 µg/m$^3$ increase in PM$_{2.5}$).

5  However, the investigators noted that during the later study period of 1998-2000 when daily TEOM PM$_{2.5}$

6  data were available for 11 of the 12 cities, a simultaneous inclusion of NO$_2$ and PM$_{2.5}$ resulted in

7  considerable reduction of the NO$_2$ risk estimate, while the PM$_{2.5}$ risk estimate was only slightly reduced

8  from 1.1% to 0.98% (CI: -0.16, 2.14). Thus, the relative importance of NO$_2$ and PM$_{2.5}$ on mortality effect

9  estimates has not been resolved when using the Canadian data sets.

## *Summary of PM$_{2.5}$ Risk Estimates*

10  The risk estimates for all-cause mortality for all ages ranged from 0.29% (Dominici et al., 2007) to

11  1.21% (Franklin et al., 2007) per 10 µg/m$^3$ increase in PM$_{2.5}$ (see Figure 6-22). An examination of

12  cause-specific risk estimates found that PM$_{10}$ risk estimates for cardiovascular deaths are similar to those

13  for all-cause deaths (0.30-1.03%), while the effect estimates for respiratory deaths were consistently

14  larger (1.01-2.2%), albeit with larger confidence intervals as well, than those for all-cause or

15  cardiovascular deaths using the same lag/averaging indices. Figure 6-23 summarizes the PM$_{2.5}$ risk

16  estimates for all U.S.- and Canadian-based studies by cause-specific mortality and age.

17  An examination of lag structure observed results similar to those reported for PM$_{10}$ with most

18  studies reporting either single day lags or two-day average lags with the strongest effects observed on lag

19  1 or lag 0-1. In addition, seasonal and regional patterns of PM$_{2.5}$ risk estimates were found to consistently

20  support those reported for PM$_{10}$, with the warmer season and Eastern U.S. showing the strongest

21  association. However, unlike the examination of PM$_{10}$ risk estimates, no U.S.-based multicity studies

22  analyzed potential confounding of PM$_{2.5}$ risk estimates by gaseous pollutants. Burnett et al. (2004) in a

23  Canadian multicity study did analyze gaseous pollutants and found mixed results, with possible

24  confounding by NO$_2$. Therefore, it is unclear if gaseous pollutants confound the PM$_{2.5}$ mortality

25  association.
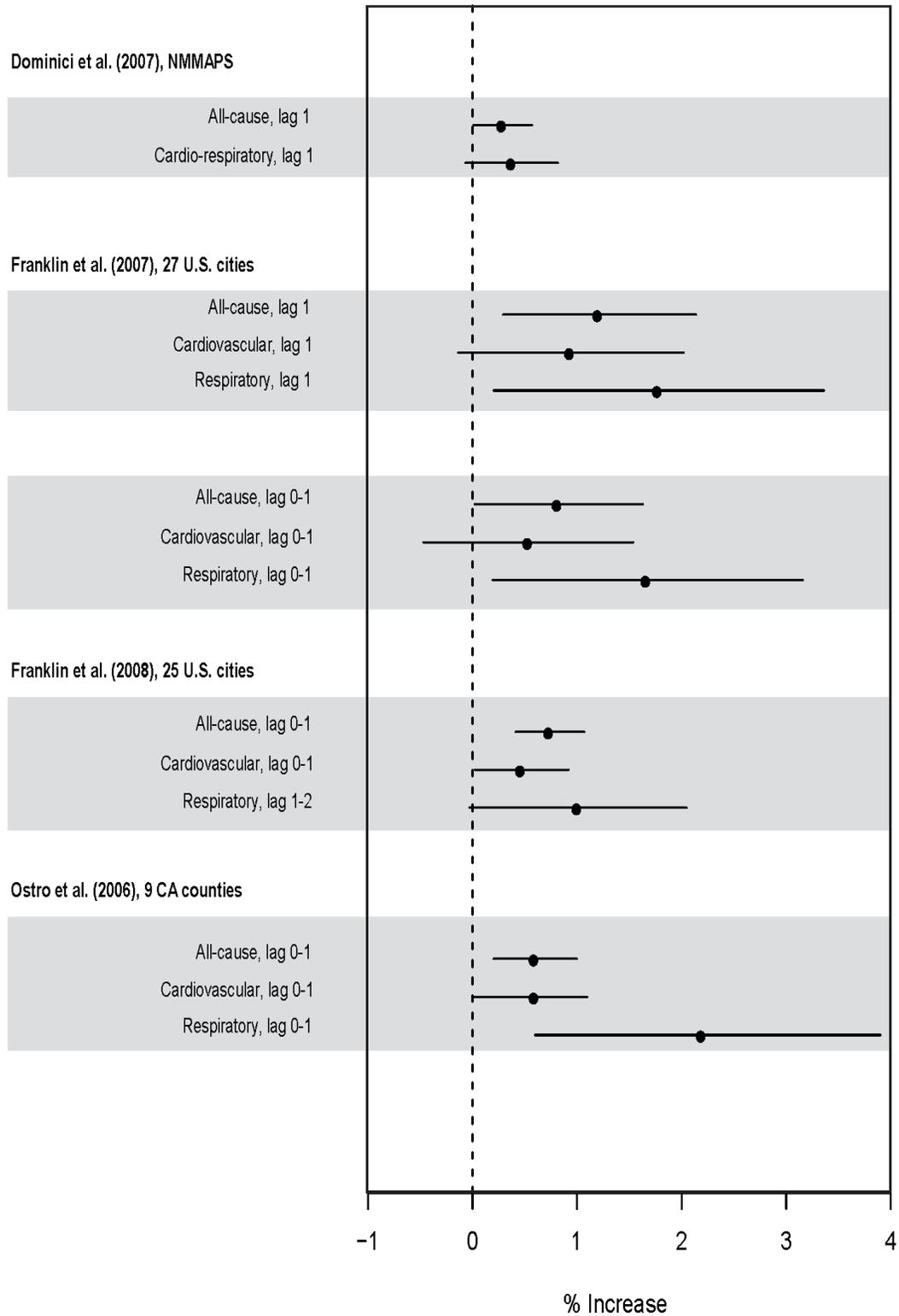
**Figure 6-22.** Summary of PM$_{2.5}$ risk estimates per 10 µg/m$^3$ for major underlying causes of death.
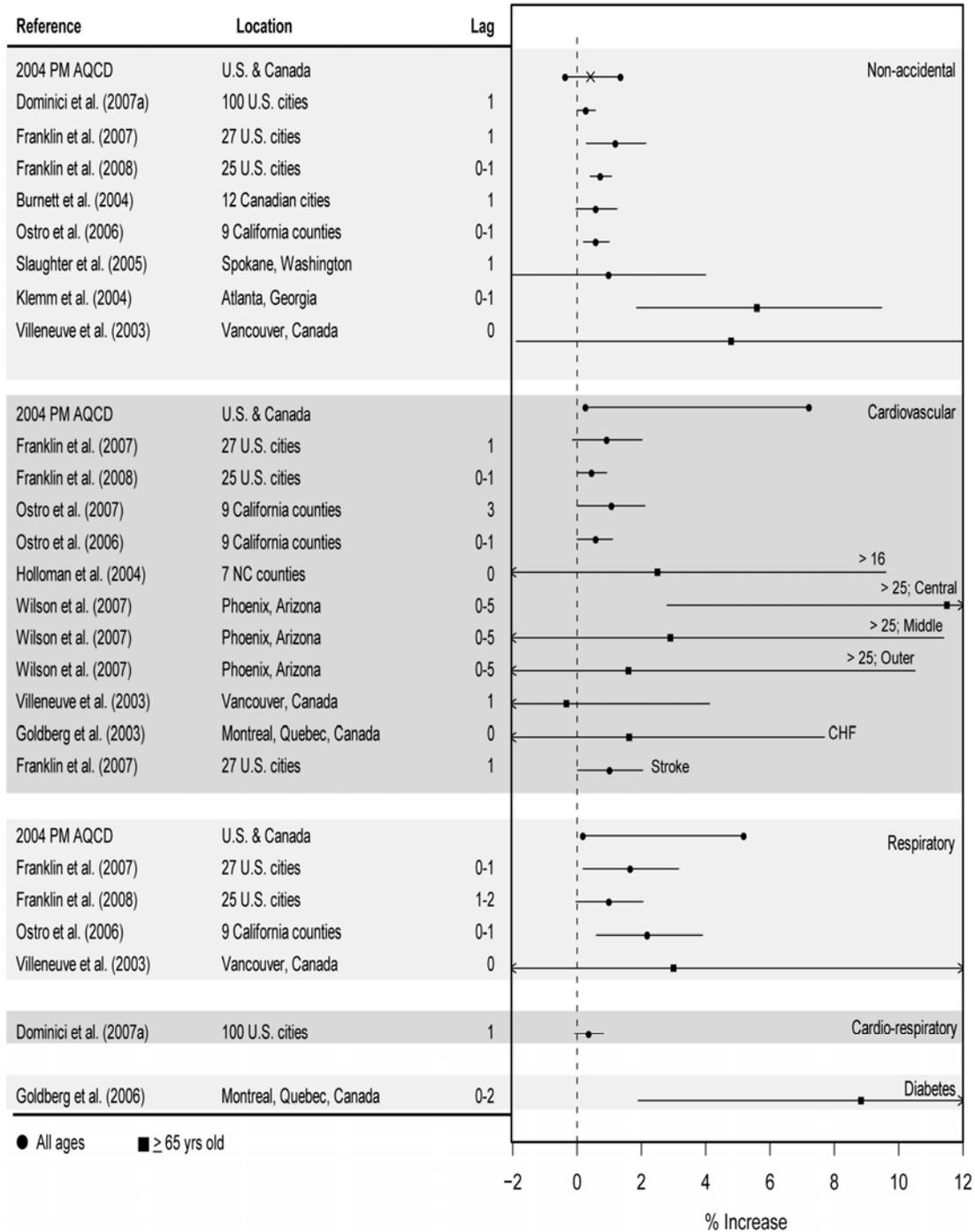
**Figure 6-23.** Summary of PM$_{2.5}$ risk estimates (per 10 µg/m$^3$) for cause-specific mortality for all U.S.- and Canadian-based studies. The estimates provided for "2004 PM AQCD" represent the lowest and highest central estimates for the U.S.- and Canadian-based studies evaluated in the previous AQCD. The "x" presented in the non-accidental mortality range represents the lone multi-city study evaluated (Burnett and Goldberg, 2003).

### 6.5.2.3. Other Size-fractionated PM Indices

1    Currently, the U.S. does not have a monitoring network in place to measure size-fractionated PM
2    indices other than $PM_{10}$ and $PM_{2.5}$; as a result, no U.S.-based multicity studies have recently been
3    conducted that examine other PM size fractions. In the 2004 PM AQCD, there were several U.S.-based
4    studies that examined both fine ($PM_{2.5}$) and thoracic coarse ($PM_{10-2.5}$) PM for their associations with
5    mortality. However, since then, very few U.S.- and Canadian-based studies have examined $PM_{10-2.5}$. Due
6    to the limited body of literature that has examined the association between short-term exposure to $PM_{10-2.5}$
7    and mortality, unlike previous sections which focused specifically on U.S.- and Canadian-based studies,
8    this section will review single-city studies and those studies conducted in other countries that have $PM_{10-}$
9    $_{2.5}$ concentrations similar to those found in the U.S. and Canada. Due to the varying model specifications
10   and lags examined in these studies, quantitative synthesis of the risk estimates requires caution.

### *Thoracic Coarse Particles (PM$_{10-2.5}$)*

11   While a large percent of the composition of coarse particles may consist of crustal materials by
12   mass, depending on available sources, the surface chemical characteristics of $PM_{10-2.5}$ may also vary from
13   city to city. Thus, without information on the chemical speciation of $PM_{10-2.5}$, the apparent variability in
14   observed associations between $PM_{10-2.5}$ and mortality across cities is difficult to characterize.
15   Nevertheless, the relative importance of the associations observed between $PM_{10-2.5}$ and mortality in the
16   following studies is of interest.
17   In Burnett et al. (2004), which analyzed the association of multiple pollutants with mortality in
18   12 Canadian cities, described previously, the authors also examined $PM_{10-2.5}$. In this study the authors
19   collected $PM_{10-2.5}$ using dichotomous samplers with an every-6th-day schedule. When both $NO_2$ and
20   $PM_{10-2.5}$ were included in the regression model, the $PM_{10-2.5}$ effect estimate was reduced from 0.65% (CI:
21   -0.10, 1.4) to 0.31% (95% CI: -0.49 to 1.1) per 10 $\mu g/m^3$ increase in 1-day lag $PM_{10-2.5}$. These risk
22   estimates are similar to those reported for $PM_{2.5}$, which were also reduced upon the inclusion of $NO_2$ in
23   the two-pollutant model, but to a greater extent from 0.60% (95% [CI: -0.03 to 1.2]) to -0.1% (95% [CI:
24   -0.86 to 0.67]).
25   Villeneuve et al. (2003) analyzed the association between $PM_{2.5}$, $PM_{10-2.5}$, TSP, $PM_{10}$, sulfate, and
26   gaseous copollutants in Vancouver, Canada, using a cohort of approximately 550,000 whose vital status
27   was ascertained between 1986 and 1999. The authors examined each air pollutant's association with
28   all-cause, cardiovascular, and respiratory mortality, but only observed significant results for
29   cardiovascular mortality at lag 0 for both $PM_{10-2.5}$ and $PM_{2.5}$. They found that $PM_{10-2.5}$, (5.4% [95% CI:
30   1.1, 9.8] per 10 $\mu g/m^{3)}$, was more strongly associated with cardiovascular mortality than $PM_{2.5}$, (4.8%
31   [95% CI: -1.9 to 12.0] per 10 $\mu g/m^{3)}$.

1    Klemm et al. (2004) analyzed various components of PM and gaseous pollutants for their

2  associations with mortality in Fulton and DeKalb Counties, Georgia for the two-year period, 1998-2000.

3  In this analysis the authors adjusted for temporal trend using quarterly, monthly, and biweekly knots, and

4  reported estimates for all-cause, circulatory, respiratory, cancer, and other causes mortality for each

5  scenario. Overall, $PM_{2.5}$ was, generally, more strongly associated with mortality than $PM_{10-2.5}$. For

6  example, using the average of 0- and 1-day lags, the risk estimates for $PM_{2.5}$ and $PM_{10-2.5}$ in the monthly

7  knots model for all-cause mortality, ages $\geq$ 65 were 5.6% (95% [CI: 1.9, 9.5]) and 6.4% (95% [CI: -0.5,

8  14.1]) per 10 $\mu g/m^3$ increase, respectively.[1]

9    Slaughter et al. (2005) examined the association of various PM size fractions ($PM_1$, $PM_{2.5}$, $PM_{10}$,

10  $PM_{10-2.5}$) and CO with ED visits, HAs, and mortality in Spokane, WA for the period 1995-2001. Although

11  the authors did not report mortality risk estimates for $PM_{10-2.5}$, they did not find an association with any

12  PM size fraction (or CO) with mortality or cardiac HAs at the 0- to 3-day lag.

13    Wilson et al. (2007b) examined the association between size-fractionated PM ($PM_{2.5}$ and $PM_{10-2.5}$)

14  and cardiovascular mortality in Phoenix for the study period 1995-1997, using mortality data aggregated

15  for three geographic regions: "Central Phoenix," "Middle Ring," and "Outer Phoenix," which were

16  constructed as a composite of ZIP codes of residence in order to compare population size among the three

17  areas. The authors reported apparently different patterns of associations between $PM_{2.5}$ and $PM_{10-2.5}$ in

18  terms of the size of the risk estimate across the three areas and temporal patterns of associations. In the

19  "Middle Ring" where $PM_{10-2.5}$ showed the strongest association, the estimated risk per 10 $\mu g/m^3$ increase

20  for a 1 day lag was 3.4% (95% CI: 1.0-5.8). The estimated risk for $PM_{2.5}$ found for "Central Phoenix" was

21  6.6% (95% CI: 1.1-12.5) for lag 1. The authors speculated that the apparent difference in estimated risks

22  across the areas might be due to the lower SES in "Central Phoenix" or the lower exposure error, but the

23  relatively wide confidence bands of these estimates make it difficult to establish such relationships.

24    Kettunen et al. (2007) analyzed ultra-fine particles, $PM_{2.5}$, $PM_{10}$, $PM_{10-2.5}$, and gaseous pollutants

25  for their associations with stroke mortality in Helsinki during the study period of 1998-2004. The authors

26  did not observe an association between air pollution and mortality for the whole year or cold season, but

27  they did find associations for $PM_{2.5}$ (13.3% [95% CI: 2.3-25.5] per 10 $\mu g/m^3$), $PM_{10}$, and CO during the

28  warm season, most strongly at lag 1 day. An association was also observed for $PM_{10-2.5}$ during the warm

29  season (7.8% [95% CI: -7.4-25.5] per 10 $\mu g/m^3$ at lag 1 day); however, it was weaker than $PM_{2.5}$.

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[1] The monthly knot model was selected for comparison because, overall, $PM_{2.5}$ showed the strongest association with all-cause mortality among
the 15 air pollution indices examined when using this model.

1    The Perez et al. (2008) analysis tested the hypothesis that outbreaks of Saharan dust exacerbate the

2    effects of $PM_{2.5}$ and $PM_{10-2.5}$ on daily mortality. Changes of effects between Saharan and non-Saharan dust

3    days were assessed using a time-stratified case-crossover design involving 24,850 deaths between March

4    2003 and December 2004 in Barcelona, Spain. Saharan dust days were identified from back-trajectory

5    and satellite images. Chemical speciation, but not an analysis for microbes or fungi, was conducted

6    approximately once a week during the study period. On Saharan dust days, mean concentrations were 1.2

7    times higher for $PM_{2.5}$ (29.9 $\mu g/m^3$) and 1.1 times higher for $PM_{10-2.5}$ (16.4 $\mu g/m^3$) than on non-Saharan

8    dust days. During Saharan dust days (90 days out of 602), the $PM_{10-2.5}$ risk estimate was 8.4% (95% [CI:

9    1.5–15.8]) per 10 $\mu g/m^3$ increase at lag 1 day, compared with 1.4% (95% CI: -0.8% to 3.4%]) during

10   non-Saharan dust days. In contrast, there was not an additional increased risk of daily mortality for $PM_{2.5}$

11   during Saharan dust days (5.0% [95% CI: 0.5-9.7]) compared with non-Saharan dust days (3.5%

12   [95% CI: 1.6-5.5]). However, differences in chemical composition (i.e., $PM_{2.5}$ primarily composed of

13   nonmineral carbon and secondary aerosols; whereas, $PM_{10-2.5}$ dominated by crustal elements) did not

14   explain these observations. Note also when examining all days combined, both size fractions were

15   associated with mortality, but the $PM_{2.5}$ association was found to be stronger.

## Summary of $PM_{10-2.5}$ Risk Estimates

16   The results from newly available studies that examined the association between short-term

17   exposure to $PM_{10-2.5}$ and mortality are mixed, as was the case in the 2004 PM AQCD. Due to the

18   relatively wide confidence bands for the mortality risk estimates from the single-city studies evaluated

19   along with the city-to-city variation in the chemical components of $PM_{10-2.5}$, a quantitative summary of

20   $PM_{10-2.5}$ effects may not be informative at this point. In addition, the mortality risk estimates associated

21   with $PM_{10-2.5}$ may also be influenced by effect modifying conditions (e.g., season, relative exposure error,

22   and dust storms), and to date have not been extensively examined. Clearly, more data are needed to

23   characterize the chemical and biological components that may modify the potential toxicity of coarse

24   particles. Figure 6-24 summarizes the $PM_{10-2.5}$ risk estimates for all U.S.-, Canadian-, and international-

25   based studies by cause-specific mortality and age.
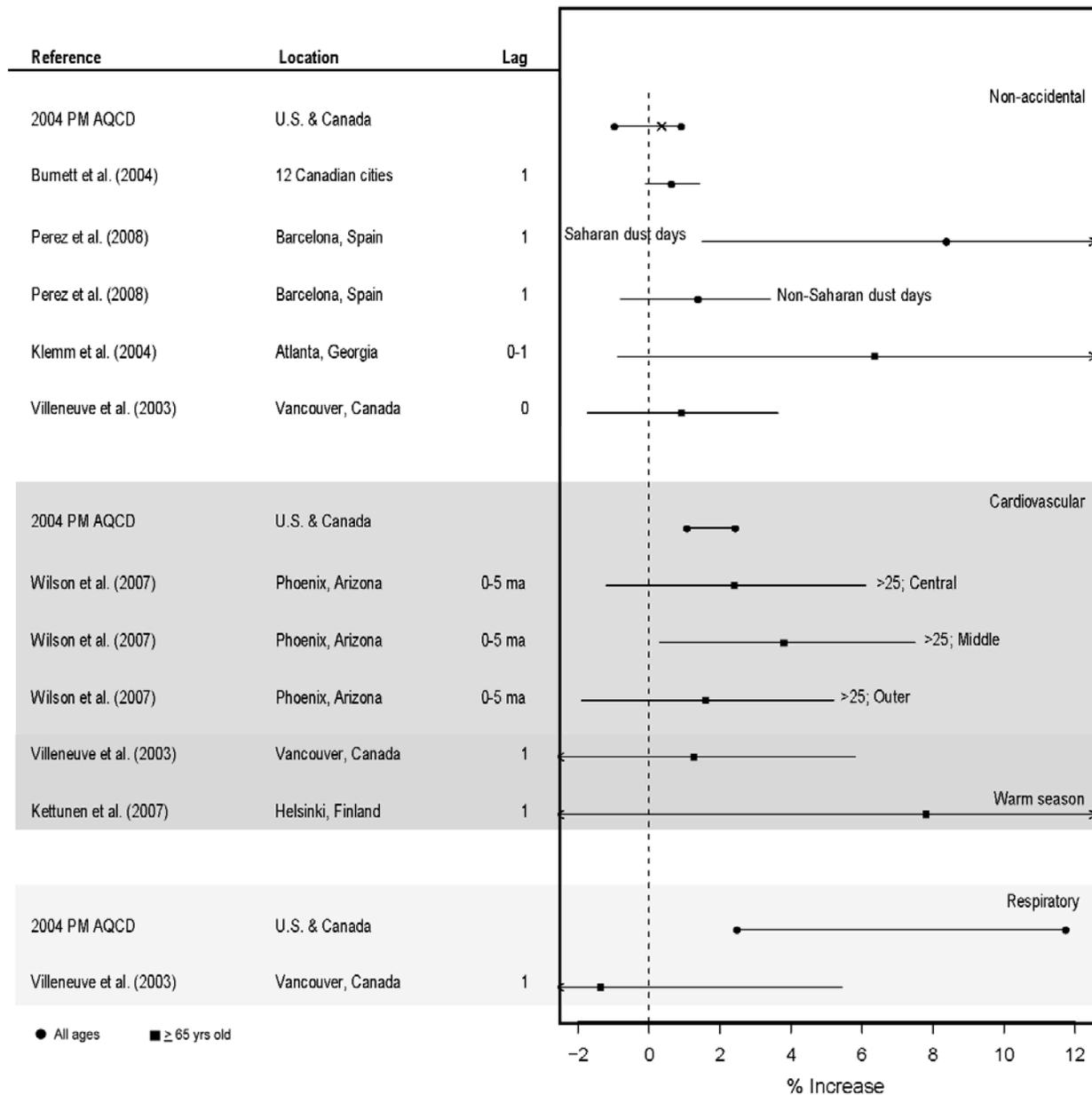
**Figure 6-24.** **Summary of PM$_{10-2.5}$ risk estimates (per 10 μg/m$^3$) for cause-specific mortality for all U.S.-, Canadian-, and international-based studies. The estimates provided for "2004 PM AQCD" represent the lowest and highest central estimates for the U.S.- and Canadian-based studies evaluated in the previous AQCD. The "x" presented in the non-accidental mortality range represents the lone multi-city study evaluated (Burnett and Goldberg, 2003).**

## 6.5.2.4. Ultrafine Particles

1      The 2004 PM AQCD reviewed Wichmann et al.'s (re analyzed by Stölzel et al., 2003; 2000) study

2      of fine and ultrafine particles (UFP) (diameter: 0.01–0.1 μm) in Erfurt, Germany for the study period

1  1995-1998. Stölzel et al. (2007) extended the study period to include the years 1995-2001 and updated the

2  analysis. Number concentrations (NC) for four size ranges of UFP (0.01–0.1, 0.01–0.03, 0.03–0.05, and

3  0.05–0.1 μm) as well as mass concentration (MC) for three size ranges (0.01–2.5, 0.1–0.5, and 10 μm)

4  were analyzed. They found associations with UFP NC and all-cause as well as cardio-respiratory

5  mortality, each for a 4 day lag. The risk estimates associated with a 9,748/cm$^3$ increase in UFP NC was

6  2.9% (95% CI: 0.3–5.5) for all-cause mortality and 3.1% (95% CI: 0.3–6.0) for cardio-respiratory

7  mortality. The UFP-mortality association, and the lag structure of association, is consistent with the

8  results from their earlier analysis, but the $PM_{2.5}$ association found in the previous study was not observed

9  in the updated analysis. Both UFP and $PM_{2.5}$ concentrations were higher during the cold season in this

10 locale.

11     Kettunen et al.'s (2007) study in Helsinki also examined the relationship between UFP and stroke

12 mortality. As described earlier, $PM_{2.5}$, $PM_{10}$, and CO was associated with stroke mortality only during the

13 warm season. The association with UFP was borderline non-significant (8.5% [95% CI: -1.2 to 19.1] per

14 4,979/cm$^3$ increase in UFP at lag 1 day), but its lag structure of association and the magnitude of the

15 effect estimate per interquartile-range are similar to those for $PM_{2.5}$. Note that the UFP NC levels in

16 Helsinki (median equals 8,986/cm$^3$ during the cold season and 7,587/cm$^3$ during the warm season) are

17 lower than those in Erfurt (mean = 13,549/cm$^3$), but clearly higher in the cold season.

### *Summary of Ultra-Fine Particle Risk Estimates*

18     Only two new studies reported associations between UFP and mortality. In Erfurt, UFP showed the

19 strongest associations with mortality among all of the PM indices, but its lag structure of association is

20 unique (strongest association at lag 4 days) and not consistent with the lag structures of mortality found

21 for other PM indices in past studies. In Helsinki, the association between UFP and stroke mortality was

22 weaker than that for $PM_{2.5}$, but its lag structure of association was similar to that for $PM_{2.5}$ (strongest at

23 lag 1 day). However, Kettunen et al. (2007) only examined lags 0 through 3 days. Clearly, more research

24 is needed to further investigate the role of UFP on PM-mortality associations.

## 6.5.2.5. Chemical Components of PM

25     To date, there have only been a few studies that examined the association between mortality and

26 components of $PM_{2.5}$. This endeavor has been undertaken by some investigators through the use of the

27 newly available $PM_{2.5}$ chemical speciation network data. The $PM_{2.5}$ chemical speciation network consists

28 of more than 250 monitors that have been collecting over 40 chemical species since 2000; however, most

29 sites started collecting data in 2001. One caveat to the new network is that because the sampling

30 frequencies of the monitors are either every third day or every sixth day, there have not been, generally, a

1 sufficient number of days to examine associations with mortality in single cities. To circumvent this issue,

2 some investigators (Dominici et al., 2007a; Franklin et al., 2008; Lippmann et al., 2006) have used the

3 $PM_{2.5}$ chemical species data in a second stage regression to explain heterogeneity of $PM_{10}$ or $PM_{2.5}$

4 mortality risk estimates across cities. However, there have been some studies that directly analyzed $PM_{2.5}$

5 data (e.g., Klemm et al., 2004 and Ostro et al., 2007).
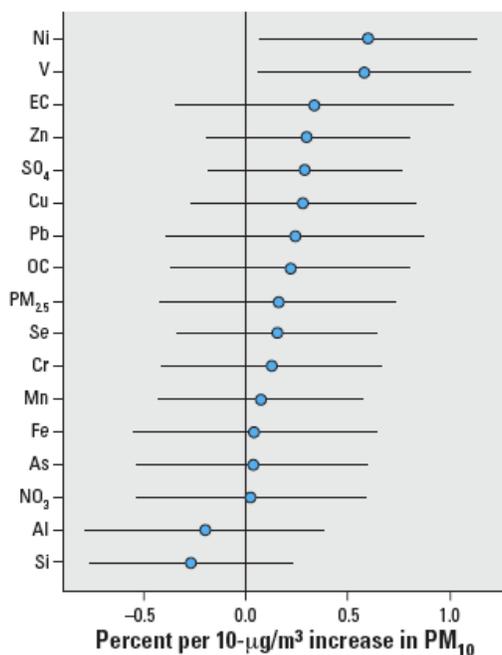
**Figure 6-25. Percent increase in $PM_{10}$ risk estimates (point estimates and 95% confidence intervals) associated with a 5th-to-95th percentile: increase in $PM_{2.5}$ and $PM_{2.5}$ chemical components. The $PM_{2.5}$ chemical components were log-transformed in the regression. The $PM_{10}$ risk estimates were for 60 NMMAP cities for 1987-1994.**

### *Explaining Heterogeneity of $PM_{10}$ Risk Estimates Using $PM_{2.5}$ Chemical Speciation Data in the Second Stage Regression*

6 Lippmann et al. (2006), in addition to their primary analysis[1], investigated the consistency of the

7 associations between specific elements and health outcomes by examining the heterogeneity of published

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[1] The main focus of the study was to examine the role of $PM_{2.5}$ chemical components in a mouse model of atherosclerosis (ApoE$^{-/-}$) exposed to concentrated fine PM (CAPs) in Tuxedo, NY.

1    1-day lagged NMMAPS $PM_{10}$ mortality risk estimates for 1987-1994 across cities as a function of the

2    average $PM_{2.5}$ chemical components across cities. They matched $PM_{2.5}$ chemical species in 60 out of 90

3    cities. Lippmann et al. (2006) noted that the concentrations of the 16 chemical species examined averaged

4    over the years 2000-2003 were highly skewed across cities. They, therefore, regressed $PM_{10}$ risk estimates

5    on each of the $PM_{2.5}$ components, raw and log-transformed, with weights based on the standard error of

6    the $PM_{10}$ risk estimates. The log-transformed values yielded better predictive power, and, the authors

7    subsequently, presented the results with log-transformed values. As shown in Figure 6-25, the 16 $PM_{2.5}$

8    species showed varying extent of predictive power in explaining the $PM_{10}$ risk estimates across 60 cities,

9    with nickel (Ni) and vanadium (V) being the best predictors.
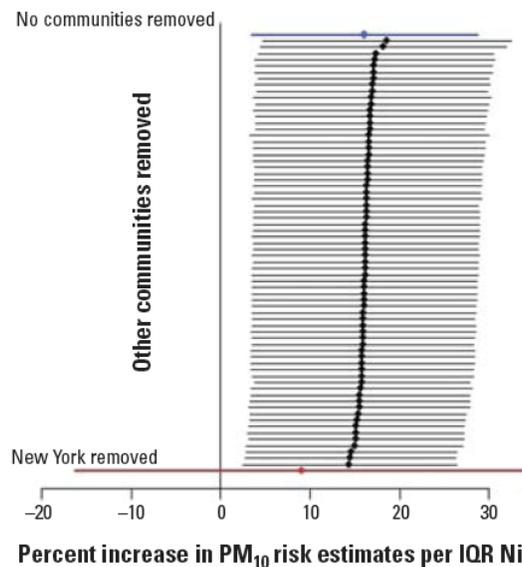


<div align="right">Source: Dominici et al. (2007a)</div>

**Figure 6-26.  Sensitivity of the percent increase in $PM_{10}$ risk estimates (point estimates and 95% confidence intervals) associated with an interquartile increase in Ni. The Ni concentration was not log-transformed in this regression model. The $PM_{10}$ risk estimates were for 72 NMMAP cities for 1987-2000. The top estimate is achieved by including data for all the 69 communities. The other estimates are calculated by excluding one of the 69 communities at a time.**

10    Dominici et al. (2007a) examined the influence of Ni and V on the updated NMMAPS $PM_{10}$

11    mortality risk estimates for 1987-2000, using 72 counties in which Ni and V data were collected. A

12    Bayesian hierarchical model was used to estimate the role of Ni and V on the heterogeneity of $PM_{10}$ risk

13    estimates. While they found both Ni and V to be significant predictors of variation in $PM_{10}$ mortality risk

14    estimates across cities, they also noted that this result was sensitive to inclusion of the New York City

1    data. Lippmann et al. (2006) and Dominici et al. (2007a) both reported that the Ni levels in New York

2    City are particularly high (~10 times the national average). Figure 6-26 shows the result of the sensitivity

3    analysis for Ni. Note that the Ni in this result was not log-transformed, as clearly reflected in the change

4    in the width of confidence bands when the New York data were removed (i.e., a skewed distribution

5    produces narrow bands). Dominici et al. (2007a) further noted that they reached "the same conclusion"

6    when log-transformed data were used in the analysis, but the results were not presented.

### *Explaining Heterogeneity of PM$_{2.5}$ Risk Estimates Using PM$_{2.5}$ Chemical Speciation Data in a Second Stage Regression*

7    The first stage of the Franklin et al. (2008) 25 cities study, described previously, focused on a

8    time-series regression of mortality on PM$_{2.5}$ by season. In the second stage random effects meta

9    regression, the PM$_{2.5}$ mortality risk estimates (25 cities x 4 seasons = 100 estimates) were regressed on the

10   ratio of mean seasonal PM$_{2.5}$ species to the total PM$_{2.5}$ mass. The authors included those species that had

11   at least 25% of the reported concentrations above the minimum detection limit, which resulted in 18

12   species being included in the analysis. Their rationale for using species proportions as effect modifiers,

13   according to the investigators, was that "in the first stage of the analysis the mortality risk was estimated

14   per unit of the total PM$_{2.5}$ mass, which encompassed all measured species, and therefore it would not be

15   meaningful to use the species concentrations directly as the effect modifier" (Franklin et al., 2008). In the

16   second stage regression model, Franklin et al. also included a quadratic function of seasonally averaged

17   temperature to capture the inverted U-shape relationship between PM$_{2.5}$ penetration and temperature.

18   They found that the fitted relationship between PM$_{2.5}$ risk estimates across cities and seasonally averaged

19   temperature substantiates the use of temperature as a surrogate for ventilation (Franklin et al., 2008).

20   Table 6-15 shows the resulting effect modification by PM$_{2.5}$ species. Al, As, Ni, Si, and sulfate were found

21   to be significant effect modifiers of PM$_{2.5}$ risk estimates, and simultaneously including Al, Ni, and sulfate

22   together, or Al, Ni, and As together further increased explanatory power. Of all the species examined, Al

23   and Ni explained the most residual heterogeneity. Franklin et al. also examined the effect of demographic

24   variables on PM$_{2.5}$ risk estimates and found that only median household income was significantly

25   associated with mortality.

**Table 6-15.** Effect modification of composition on the estimated percent increase in mortality with a 10 µg/m$^3$ increase in PM$_{2.5}$.

| Cause | Species | p-value for effect modification by species to PM$_{2.5}$ mass proportion | % increase in non-accidental mortality per 10 µg/m$^3$ increase in PM$_{2.5}$ for an interquartile increase in species to PM$_{2.5}$ mass proportion* | Heterogeneity explained (%)† |
|---|---|---|---|---|
| Non-accidental Univariate | Al | < 0.001 | 0.58 | 45 |
| | As | 0.02 | 0.55 | 35 |
| | Br | 0.11 | 0.38 | 5 |
| | Cr | 0.12 | 0.33 | 16 |
| | EC | 0.79 | 0.06 | 0 |
| | Fe | 0.43 | 0.12 | 3 |
| | K | 0.10 | 0.41 | 28 |
| | Mn | 0.42 | 0.14 | 10 |
| | Na+ | 0.22 | 0.20 | 14 |
| | Ni | 0.01 | 0.37 | 41 |
| | NO$_3$ | 0.07 | -0.49 | 28 |
| | NH4 | 0.84 | 0.04 | 3 |
| | OC | 0.59 | -0.02 | 4 |
| | Pb | 0.31 | 0.17 | 11 |
| | Si | 0.03 | 0.41 | 25 |
| | SO$_4{}^{2-}$ | 0.01 | 0.51 | 33 |
| | V | 0.28 | 0.30 | 3 |
| | Zn | 0.19 | 0.23 | 15 |
| Non-accidental Multivariate (1) | Al | < 0.001 | 0.79 | |
| | Ni | 0.01 | 0.34 | 100 |
| | SO$_4{}^{2-}$ | < 0.001 | 0.75 | |
| Non-accidental Multivariate (2) | Al | < 0.001 | 0.61 | |
| | Ni | 0.01 | 0.35 | 100 |
| | As | < 0.001 | 0.58 | |

Adjusted for temperature
†Includes heterogeneity explained by temperature
Source: Franklin et al. (2008)

1    Although Lippmann et al. (2006) used NMMAPS PM$_{10}$ risk estimates and Franklin et al. (2008)

2    used PM$_{2.5}$ risk estimates to examine effect modification due to various PM species, 14 out of the 18

3    species analyzed in these two studies overlap (see Figure 6-25 and Table 6-15). Both studies found that Ni

4    explained the heterogeneity in PM risk estimates. Note that New York City was not included in the 25

5    cities examined in Franklin et al. and, thus, could not influence the result. Sulfate positively, but not

6    significantly, explained the PM$_{10}$ risk estimates in the Lippmann et al. (2006) analysis. However, sulfate

7    was a significant predictor of PM$_{2.5}$ risk estimates in the Franklin et al. (2008)analysis. Al and Si were

8    negative (i.e., less than the average PM$_{10}$ risk estimates across cities), though not significant, predictors in

9    the Lippmann et al. (2006) analysis. Unlike the Franklin et al. analysis, arsenic (As) showed no

10    association in the Lippmann et al. (2006) analysis. The source of these differences may be due to the

11    difference in geographic coverage, PM size (PM$_{2.5}$ may represent more secondary aerosols than PM$_{10}$), or

1    the difference in the analytical methods used in each study. Specifically, the analytical approach used by
2    Franklin et al. (2008) does have an advantage of delineating seasonal variations in PM components and
3    the associated potential seasonal mortality effects.
4        In light of the results presented in speciation studies it must be noted that second stage analyses that
5    use PM chemical species as effect modifiers have some limitations. Unlike analyses that directly examine
6    the associations between chemical species and mortality, if an effect modification is observed it may be
7    confounded if the variations of the mean levels of the chemical species examined are correlated with other
8    demographic factors that vary across cities. Thus, more concrete conclusions could be formulated if direct
9    associations are found between mortality and PM chemical components in time-series analyses.

### Association between $PM_{2.5}$ Chemical Components and Mortality in Six California Counties

10   Ostro et al. (2007) examined associations between $PM_{2.5}$ chemical components and mortality in six
11   California counties (Fresno, Kern, Riverside, Sacramento, San Diego, and Santa Clara), which had at least
12   180 days of speciation data for the years 2000 to 2003. The study examined all-cause, cardiovascular, and
13   respiratory mortality for individual lags of 19 specific $PM_{2.5}$ chemical components. The second stage
14   random-effects model combined risk estimates at each lag across cities. The number of available days for
15   chemical species data ranged from 243 (San Diego County) to 395 (Sacramento County). The authors
16   found an association between mortality, especially cardiovascular mortality, and several chemical
17   components. For example, cardiovascular mortality was associated with EC, OC, nitrate, Fe, K, and Ti at
18   various lags.
19   Even though this was a multicity study, the relatively small number of available days and the
20   every-third-day (or every-sixth-day) sampling frequency for $PM_{2.5}$ chemical species made it difficult to
21   interpret the results of the lag structure of associations observed for the chemical species. To evaluate the
22   impact of non-daily sampling frequency, Ostro et al. (2007) examined both the $PM_{2.5}$ series that coincides
23   with the speciation sampling days (for the initial six counties [i.e., $PM_{2.5c}$]) and $PM_{2.5}$ data that was
24   available on all days for an extended set of counties (the initial six counties plus Contra Costa, Los
25   Angeles, and Orange Counties [i.e., $PM_{2.5ext}$]). Figure 6-27 shows the association between all-cause
26   mortality and selected $PM_{2.5}$ chemical species as well as for $PM_{2.5c}$ and $PM_{2.5ext}$. Note the wide confidence
27   bands for the risk estimates for each $PM_{2.5}$ chemical species and $PM_{2.5c}$, apparently reflecting the low
28   statistical power of the data. The lag structure of associations is more clearly defined for $PM_{2.5ext}$, and
29   appears to be different from that for $PM_{2.5}$.
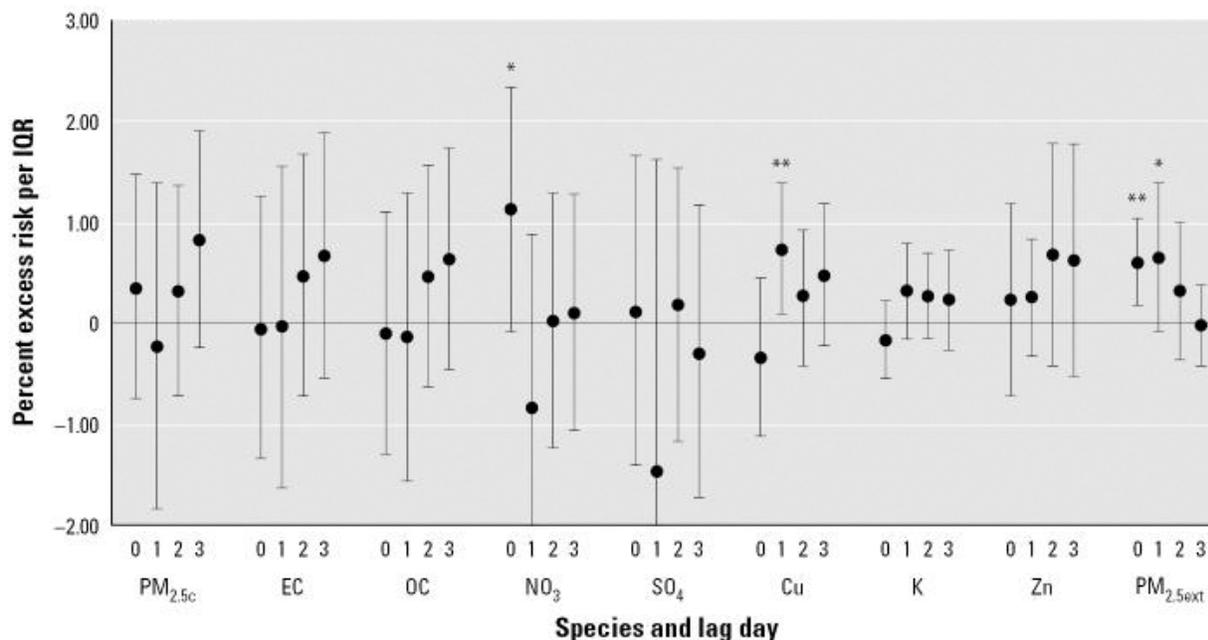
**Figure 6-27. Excess risk (CI) of total mortality per IQR of concentrations. Note: $PM_{2.5}$ has the same sampling days as chemical species. $PM_{2.5}$ has all available $PM_{2.5ext}$ data for nine counties. * p < 0.10; ** p < 0.05**

1    Ostro et al. (2008) used the speciation data from the six counties analyzed in their 2007 analysis,

2    described above, in an additional analysis to examine effect modification of cardiovascular mortality

3    effects, which showed the strongest association in the 2007 analysis, attributed to $PM_{2.5}$ and 13 chemical

4    components by socio-economic and demographic factors. The results of the analysis were combined using

5    random effects meta-analysis. The investigators tested statistical differences in risk estimates between

6    strata using a t-test, and reported that, for many of the $PM_{2.5}$ chemical species; there were significantly

7    higher effect estimates among those with lower educational attainment and Hispanics. While these

8    patterns were apparent in their results table, interpretation of the results is not straightforward because the

9    table only presented the most significant (and positive) lags, and they were often different between the

10   strata (e.g., the most frequent significant lag for the Hispanic group was 1-day, while it was 2- or 3-day

11   for the White group). As the investigators pointed out, the every-third-day sampling frequency of the

12   speciation data also complicates the interpretation of the results for different lags.

13   Overall, the two studies by Ostro et al. (2007) were the first attempt to directly analyze associations

14   between the newly available chemical speciation data and mortality. While suggestive associations

15   between several chemical species and mortality were reported, a longer length of observations is needed

16   to more clearly determine the associations.

## 6.5.2.6. Use of Source-Apportioned PM

1      Chemically speciated PM data allow for the source apportionment of PM. The idea of using

2  source-apportioned PM for health effects analyses is appealing because, if such source-apportionment

3  could be reliably conducted, it will allow for an evaluation of $PM_{2.5}$ mass concentrations by source types.

4  However, the uncertainties associated with source-apportionment methods have not been well

5  characterized.

6      To address this issue, in 2003, several groups of EPA-funded researchers organized a workshop and

7  independently conducted source apportionment on two sets of data: Phoenix, AZ, and Washington, DC,

8  compared the results (Hopke et al., 2006), and then conducted time-series mortality regression analyses

9  using each group's source-apportioned data (Ito et al., 2006a; Mar et al., 2006; Thurston et al., 2005). The

10  various research groups generally identified the same major source types, each with similar elemental

11  compositions. Inter-group correlation analyses indicated that soil-, sulfate-, residual oil-, and

12  salt-associated mass concentrations were most unambiguously identified by various methods, whereas

13  vegetative burning and traffic were less consistent. Aggregate source-specific mortality relative risk (RR)

14  estimate confidence intervals overlapped each other, but the sulfate-related $PM_{2.5}$ component was most

15  consistently significant across analyses in these cities.

16      The results from the source-apportionment workshop quantitatively characterized the uncertainties

17  associated with the factor analysis-based methods, but they also raised new issues. The mortality analyses

18  conducted in Phoenix, AZ, and Washington, DC, both found that different source-types showed varying

19  lag structure of associations with mortality. For example, Figure 6-28 shows cardiovascular mortality risk

20  estimates for three of the $PM_{2.5}$ sources from the Phoenix, AZ, analysis (Mar et al., 2006). The strongest

21  associations for "traffic" $PM_{2.5}$ was found for lag 1-day, while for "secondary sulfate" $PM_{2.5}$, it was lag 0,

22  with a monotonic decline towards longer lags. It is conceivable that PM from different source types

23  produces different lagged effects, but it is also likely that different PM species have varying lagged

24  correlations with the covariates in the health effects regression models (e.g., temperature, day-of-week)

25  resulting in apparent differences in lagged associations with mortality. Thus, interpretation of these

26  source-apportioned PM health effect estimates remains challenging.
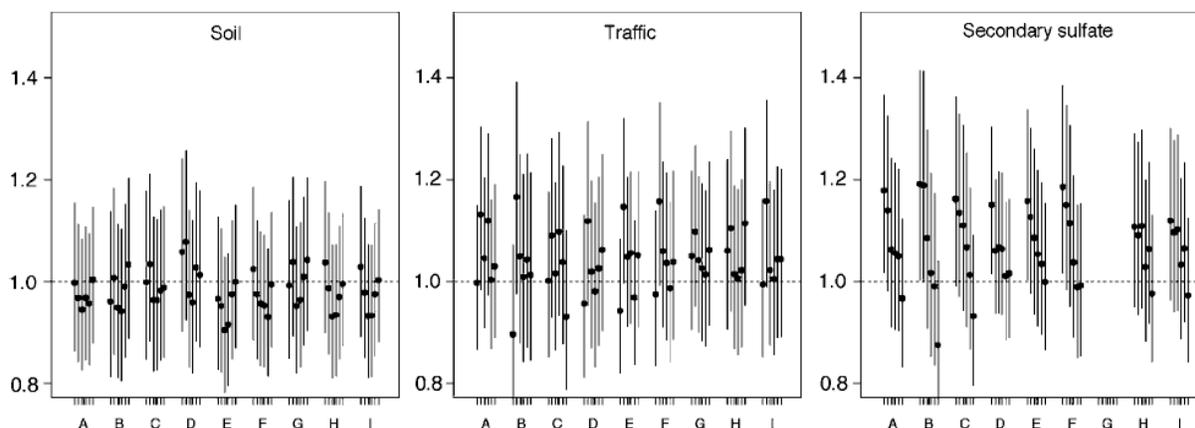
Source: Mar et al. (2006)

**Figure 6-28.** **Relative risk and CI of cardiovascular mortality associated with estimated PM$_{2.5}$ source contributions. Y-axis: relative risk per 5th-to-95th percentile increment of estimated PM$_{2.5}$ source contribution. X-axis: the alphabet denotes investigator/ method; lagged PM$_{2.5}$ source contribution for lag 0 through 5 days, left to right, are shown for each investigator/method.**

## 6.5.2.7. Investigation of Concentration-Response Relationship

1   The results from large multicity studies reviewed in the 2004 PM AQCD suggested that strong

2   evidence did not exist for a clear threshold for PM mortality effects. However, as discussed in the 2004

3   PM AQCD, there are several challenges in determining and interpreting the shape of PM-mortality

4   concentration-response functions and the presence of a threshold, including: (1) limited range of available

5   concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of susceptibility in

6   at-risk populations; and (3) the influence of measurement error. Regardless of these limitations, studies

7   have continued to investigate the PM-mortality concentration-response relationship.

8   Daniels et al. (2004) evaluated three concentration-response models: (1) log-linear models (i.e., the

9   most commonly used approach, from which the majority of risk estimates are derived); (2) spline models

10   that allow data to fit possibly non-linear relationship; and (3) threshold models, using PM$_{10}$ data in 20

11   cities from the 1987-1994 NMMAPS data. They reported that the spline model, combined across the

12   cities, showed a linear relation without indicating a threshold for the relative risks of death for all-causes

13   and for cardiovascular-respiratory causes in relation to PM$_{10}$, but "the other cause" deaths (i.e., all cause

14   minus cardiovascular-respiratory) showed an apparent threshold at around 50 μg/m$^3$ PM$_{10}$, as shown in

15   Figure 6-29. For all-cause and cardio-respiratory deaths, based on the Akaike's Information Criterion

16   (AIC), a log-linear model without threshold was preferred to the threshold model and to the spline model.

17   The HEI review committee commented that interpretation of these results required caution, because

18   (1) the measurement error could obscure any threshold; (2) the city-specific concentration-response

1    curves exhibited a variety of shapes; and (3) the use of AIC to choose among the models might not be

2    appropriate due to the fact it was not designed to assess scientific theories of etiology. Note, however, that

3    there has been no etiologically credible reason suggested thus far to choose one model over others for

4    aggregate outcomes. Thus, at least statistically, the result of Daniels et al. (2004) suggests that the

5    log-linear model is appropriate in describing the relationship between $PM_{10}$ and mortality.
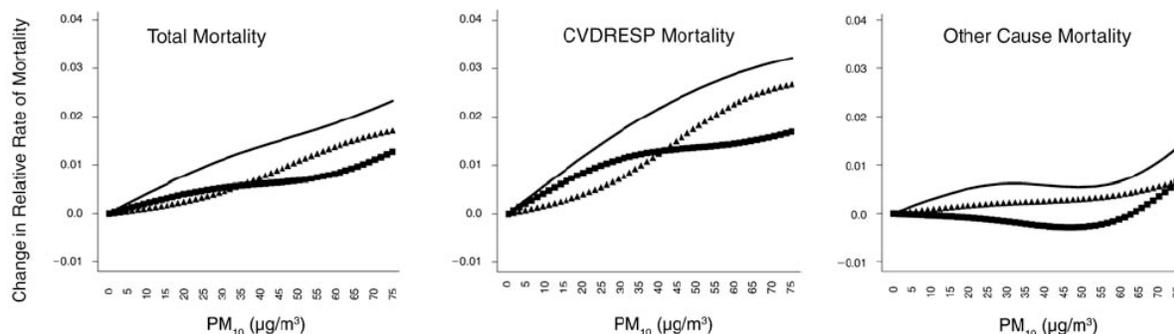
**Figure 6-29.  Concentration–response curves (spline model) for all-cause, cardiovascular-respiratory and other cause mortality from the 20 NMMAPS cities.  Estimates are posterior means under Bayesian random effects model. Solid line is mean lag, triangles are lag 0 (current day), and squares are lag 1 (previous day).**

6          The Schwartz (2004b) analysis of $PM_{10}$ and mortality in 14 U.S. cities, described in

7    Section 6.5.2.1., also examined the shape of the concentration-response relationship by including

8    indicator variables for days when concentrations were between 15 and 25 $\mu g/m^3$, between 25 and

9    34 $\mu g/m^3$, between 35 and 44 $\mu g/m^3$, and 45 $\mu g/m^3$ and above. In the model, days with concentrations

10   below 15 $\mu g/m^3$ served as the reference level. This model was fit using the single stage method,

11   combining strata across all cities in the case-crossover design. Figure 6-30 shows the resulting

12   relationship, which does not provide sufficient evidence to suggest that a threshold exists. The authors did

13   not examine city-to-city variation in the concentration-response relationship in this study.
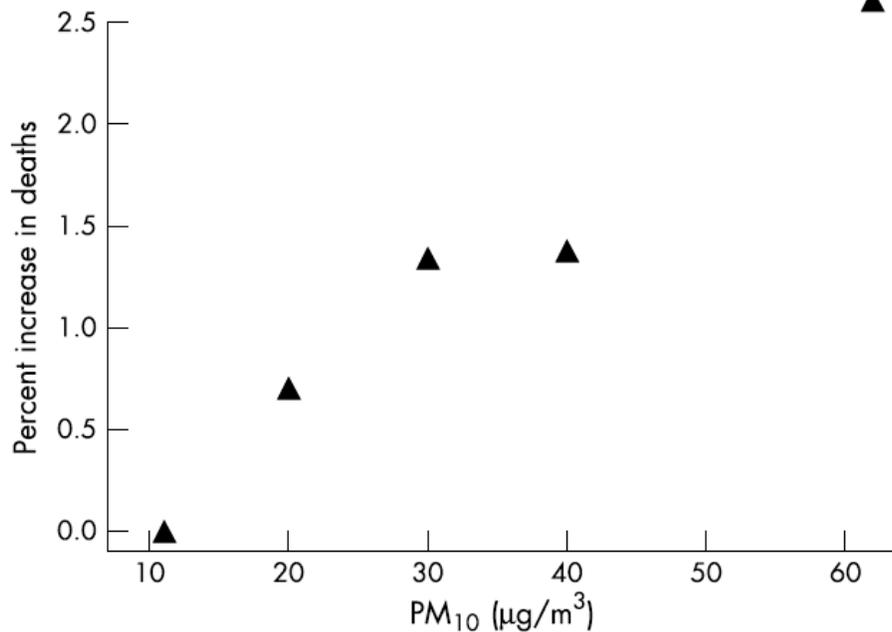
**Figure 6-30.   Percent increase in the risk death on days with PM$_{10}$ concentrations in the ranges of 15–24, 25–34, 35–44, and 45 µg/m$^3$ and greater, compared to a reference of days when concentrations were below 15 µg/m$^3$.  Risk is plotted against the mean PM$_{10}$ concentration within each category.**

1    Samoli et al. (2005) investigated the concentration-response relationship between PM$_{10}$ and

2    mortality in 22 European cities (and BS in 15 of the cities) participating in the APHEA project. In nine of

3    the 22 cities, PM$_{10}$ levels were estimated using a regression model relating co-located PM$_{10}$ to BS or TSP.

4    They used regression spline models with two knots (30 and 50 µg/m$^3$) and then combined the individual

5    city estimates of the splines across cities. The investigators concluded that the association between PM

6    and mortality in these cities could be adequately estimated using the log-linear model. However, in an

7    ancillary analysis of the concentration-response curves for the largest cities in each of the three distinct

8    geographic areas (western, southern, and eastern European cities): London, England; Athens, Greece; and

9    Cracow, Poland, Samoli et al. (Samoli et al., 2005) observed a difference in the shape of the

10   concentration-response curve across cities. Thus, while the combined curves (Figure 6-31) appear to

11   support no-threshold relationships between PM$_{10}$ and mortality, the heterogeneity of the shapes across

12   cities makes it difficult to interpret the biological relevance of the shape of the combined curves.
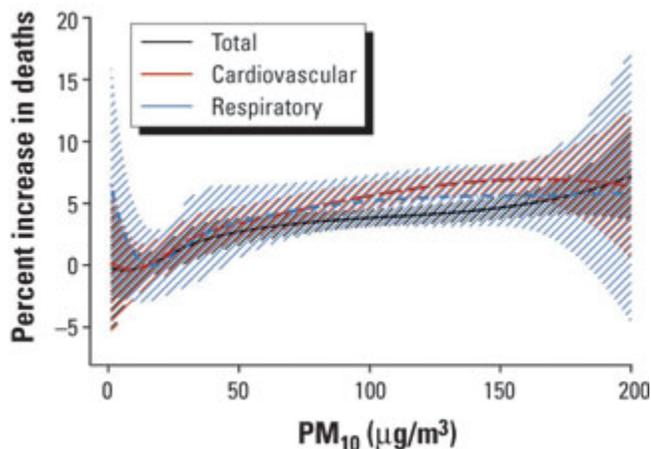
Source: Samoli et al. (Samoli et al.)

**Figure 6-31. Combined concentration–response curves (spline model) for all-cause, cardiovascular, and respiratory mortality from the 22 APHEA cities.**

1    The results from the three multicity studies discussed above support no-threshold log-linear
2    models, but issues such as possible influence of exposure error and heterogeneity of shapes across cities
3    remains to be resolved. Also, given the pattern of seasonal and regional differences in PM risk estimates
4    depicted in recent multicity study results (e.g., Peng et al., 2005), the very concept of the
5    concentration-response relationships estimated across cities and for all-year data may not be very
6    informative.

# 6.5.3. Summary of Causal Determinations by PM Metric

## 6.5.3.1. PM$_{10}$

7    The epidemiologic evidence for **the effect of short-term exposure to PM$_{10}$ on mortality is**
8    **sufficient to conclude that a causal relationship is likely to exist at ambient concentrations**. The
9    epidemiologic studies report consistent positive associations between short-term exposure to PM$_{10}$ and
10    all-cause mortality. The multi-city studies evaluated reported effect estimates for all-cause mortality
11    ranging from 0.12% (Dominici et al., 2007b) to 0.81% (Schwartz, 2004b) per 10 μg/m$^3$ increase in PM$_{10}$.
12    Although respiratory- and cardiovascular-related mortality also show consistant positive effects, only a
13    few multi-city studies conducted cause -specific mortality analyses. The heterogeneity in the range of
14    these effects is most likely dependent on the lag, averaging time, number of cities and/or copollutants
15    included in regression models. Although respiratory and cardiovascular-related mortality also show
16    consistent, positive effects, only a few multicity studies conducted causes-specifici mortality analyses.

1   Risk estimates from single-city studies for all-cause and respiratory- and cardiovascular-related mortality

2   were similar to those from the multicity studies but consisted of smaller samples sizes which resulted in

3   wider confidence intervals and lower statistical power (Figure 6-20). An analysis of the lag structures

4   used in these studies found that the greatest effects were observed at lag 1 or lag 0-1, and the use of a

5   distributed lag model resulted in slightly larger (by ~30%) estimates compared to single-day lags (Zeka et

6   al., 2005). The NMMAPS studies (Dominici et al., 2007b; Peng et al., 2005) confirmed the regional

7   heterogeneity in $PM_{10}$ risk estimates observed in previous analyses, with the greatest effects being

8   observed in the Eastern U.S. Seasonal patterns in risk estimates also were observed, but the results

9   differed between studies, with NMMAPS (Peng et al., 2005) showing the greatest effects during the

10  summer, while the 20 cities study (Zeka et al., 2005) observed the greatest effects during the transition

11  seasons, spring and fall. An analysis of potential confounders (i.e., temperature and copollutants) using

12  both time-series and case-crossover analyses found that neither is likely to account for differences in risk

13  estimates between $PM_{10}$-mortality studies. However, one study (Burnett et al., 2004), observed a

14  reduction in the effect estimate upon the inclusion of $NO_2$ in the model.

## 6.5.3.2. $PM_{2.5}$

15      The epidemiologic evidence on **the effect of short-term exposure to $PM_{2.5}$ on mortality is**

16  **sufficient to conclude that a causal relationship is likely to exist at ambient concentrations**. $PM_{2.5}$

17  risk estimates were found to be consistently positive, and slightly larger than those reported for $PM_{10}$ for

18  all-cause, and respiratory- and cardiovascular-related mortality. The risk estimates for all-cause

19  (non-accidental) mortality ranged from 0.29% (Dominici et al., 2007b) to 1.21% (Franklin et al., 2007)

20  per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Cardiovascular-related mortality risk estimates were found to be similar

21  to those for all-cause mortality; whereas, the risk estimates for respiratory-related mortality were

22  consistently larger: 1.01% (Franklin et al., 2007) to 2.2% (Ostro et al., 2006) using the same lag and

23  averaging indices. Regional and seasonal patterns in $PM_{2.5}$ risk estimates were observed with results

24  similar to those presented for $PM_{10}$, with the greatest effects occurring in the Eastern U.S. (Franklin et al.,

25  2007; Franklin et al., 2008) and during the spring (Franklin et al., 2007). Few studies conducted detailed

26  analyses of the potential confounding of risk estimates by gaseous pollutants, though Burnett et al. (2004)

27  analyzed gaseous pollutants and found mixed results, with possible confounding by $NO_2$. An examination

28  of effect modifiers (e.g., demographic and socioeconomic factors), specifically air conditioning use,

29  which is sometimes used as a surrogate for ventilation rate, has suggested that $PM_{2.5}$ risk estimates

30  increase as the percent of the population with access to air conditioning decreases.

### 6.5.3.3. PM$_{10-2.5}$

1    The epidemiologic evidence on **the effect of short-term exposure to PM$_{10-2.5}$ on mortality is**

2    **suggestive of a causal relationship at ambient concentrations**. Currently, a limited body of evidence

3    exists which has examined the potential association between short-term exposure to PM$_{10-2.5}$ and

4    mortality. The majority of studies that examined PM$_{10-2.5}$ reported mixed results in terms of the relative

5    impact of PM$_{10-2.5}$ on mortality primarily due to the majority of studies being conducted in individual

6    cities and the city-to-city variation in the chemical composition of PM$_{10-2.5}$. However, one well conducted

7    multi-city Canadian study was identified that does provide evidence for an association between short-

8    exposure to PM$_{10-2.5}$ and mortality, but these estimates along with those obtained from the other studies

9    may be confounded by gaseous copollutants or influenced by effect modifying conditions (e.g., season,

10   relative exposure error, dust storms). Overall, although more data is needed to adequately characterize the

11   chemical and biological components that may modify the potential toxicity of thoracic coarse particles,

12   the consistent association between short-term exposure to PM$_{10}$ (which includes PM$_{10-2.5}$) and mortality

13   provides some evidence for the presence of an association between PM$_{10-2.5}$ and mortality.

### 6.5.3.4. Ultra-fine particles (UFP: diameter: 0.01–0.1 μm)

14   The epidemiologic evidence on **the effect of short-term exposure to UFP on mortality is**

15   **inadequate to infer a causal association at ambient concentrations**. Only two new studies were

16   identified, which examined the association between short-term exposure to UFP and mortality.

17   Inconsistencies were observed in the lag structure of association reported by each study in terms of both

18   the lag day with the greatest association and the number of lag days considered in the study. The limited

19   number of studies and the discrepancy in results between studies further confirms the need for additional

20   data to examine the UFP-mortality relationship.

# 6.6. Attribution of Health Effects to Specific Constituents or Sources

21   The chemical composition of PM may be a better predictor of health effects than particle size, but

22   despite the clear mechanistic plausibility of this hypothesis, only recently have researchers begun to

23   evaluate relationships between specific health effects and specific constituents or sources of ambient PM.

24   Prior to the 2004 PM AQCD, only a handful of epidemiologic studies attempted quantify these

1  relationships. Approximately 30 new epidemiologic, human clinical, and toxicological studies have been

2  conducted to address this research question.

## 6.6.1. Evaluation Approach

3      The demands of conducting analyses that relate all PM constituents at once with an assortment of

4  health outcomes are very high for three reasons that are related to both the nature of PM data and

5  methodology. First, the number of PM constituents is large, and the correlations among them are

6  inherently high. Reducing this number has been accomplished in most of the recent studies through

7  various forms of factor analysis, which limits correlations by grouping the most highly correlated PM

8  constituents into less correlated groups. A subset of these studies identifies the resulting groups or factors

9  with named sources of PM. The methods for estimating source contributions to ambient PM are reviewed

10  in Section 3.5.4. Second, the number of potential health effects examined is also very high and includes

11  definitive outcomes (e.g., HAs) as well as physiologic alterations (e.g., increased inflammatory response).

12  Furthermore, examining the relationship between those two large sets of variables – PM constitutents or

13  sources on one hand, health variables on the other – involves analyzing the larger set of combinations

14  between them. Third, there are also multiple statistical methods and analytic approaches that can be used

15  to analyze the potential association.

16      A total of 34 studies are discussed below that attempted to link PM constituents or sources with

17  health outcomes, including four reviewed in the 2004 PM AQCD. All these studies included all measured

18  PM constituents in the analyses and most grouped PM constituents into specific PM sources. Studies that

19  used an a priori decision to consider only one or two constituents, or grouped PM constituents into only

20  two classes (e.g., soluble and insoluble), are not included. With the exception of the four studies reviewed

21  in the 2004 PM AQCD, and the toxicological in vitro studies, all remaining studies have been discussed

22  individually in Chapters 6 or 7 under the relevant health outcome. The studies evaluated include 14

23  epidemiologic studies, 15 toxicological studies, and five human clinical studies, and all used quantitative

24  methods to analyze possible associations between health effects and multiple PM constituents or sources.

25  Studies that presented PM composition and health data side by side without explicitly investigating

26  relationships or in which relationships were only discussed qualitatively, are excluded.

27      There are some differences in the type of PM constituent data used in epidemiologic, human

28  clinical and toxicological studies. In epidemiologic studies, PM speciation data is obtained from

29  atmospheric monitors; for human clinical and toxicological studies, the type of PM data varies with

30  experimental exposure technique. Thus, all 14 epidemiologic studies relied on monitor data, all of the

31  clinical studies and 11 of the toxicological studies used CAPs. The remaining four toxicology studies used

1   PM samples collected on filters at various U.S. sites. Within the 15 toxicological studies evaluated, 11

2   conducted inhalation exposures, while suspensions were used in the other 5 – 4 consisted of in vitro

3   studies and 1 used in vivo intratracheal instillation.

4       Regardless of how PM was measured, all 34 studies provided data for between 7 and 20 PM

5   elements, with EC and OC, along with $SO_4$, and $NO_3$ also commonly measured. Most studies reduced the

6   number of PM variables by various factorization or source apportionment procedures, before using a

7   separate analysis to examine the association between the reduced PM dataset and health effects. In the

8   studies that reduced the number of PM variables, all human clinical studies and 8 of the toxicological

9   studies relied on PCA, while 2 more toxicological studies used CMB. Two toxicology studies used a

10  Partial Least Squares (PLS) procedure to simultaneously (1) reduce the PM data, and (2) examine the

11  association between PM and health effects, rather than decoupling the two parts of the analysis. One of

12  these two studies used both CMB and PLS. One toxicology study used a Structural Equation Model

13  (SEM) to simultaneously reduce the PM data and examine the association between PM and health effects.

14  Finally, three toxicological and two human clinical studies did not apply any kind of grouping to the

15  speciation data. All but three epidemiologic studies reduced the number of PM variables, using either

16  PCA, or other established source apportionment methods such as CMB, PMF, or UNMIX (Table 6-16).

17  Factorization and apportionment methods were reviewed in Section 3.5.4.

18      Of particular interest are five epidemiologic studies that compared source apportionment methods

19  and the associated results. (Ito et al., 2006a; Mar et al., 2006; Thurston et al., 2005), compared PCA,

20  PMF, and UNMIX (Hopke et al., 2006) independently applied by separate research groups. Schreuder et

21  al. (2006) compared UPM and two versions of UNMIX and Sarnat et al. (2008) compared CMB, PMF,

22  and literature-based a priori groupings. In all five, results based on the different methods were generally

23  in close agreement. When applied to monitoring data, the explicit aim of many of these grouping or

24  factorization methods is to apportion PM species to their most likely sources. All but three epidemiology

25  studies labeled the groupings according to their presumed common source. However, only four toxicology

26  studies and two clinical studies explicitly named PM sources corresponding to factors. Eight out of the 11

27  toxicological studies that employed CAPs and grouped PM species, but did not name sources, were

28  conducted in Boston by the same research group.

29      One important difficulty in interpreting these 34 studies as a group is that few, if any of the results

30  of the various grouping procedures are easily comparable, due to both differences in PM constituents that

31  comprise the factors identified in separate studies, and the subjectivity involved in labeling those factors.

32  There are no well-established objective methods for operating the various forms of factor analysis and

33  source apportionment used in these studies, leaving much of the model operation and factor assignment

34  open to judgment by the individual investigator. For example, it is not possible to easily compare the

1    Al/Si factor isolated in one study, with the Al/Ca/Fe/Si factor from another study, and the "Resuspended

2    Soil" factor from a third study.

3        After factorization or apportionment of the PM data, various methods were used for analyzing the

4    potential association between PM constituents or sources and health effects. Except for the three studies

5    that used PLS or SEM, and thus did not decouple the two phases of analysis, human clinical and

6    toxicological studies all used univariate mixed model regression for every PM factor or source. One of

7    these toxicological studies was of subchronic duration, and repeated samples were collected over an

8    extended period, thus supporting the addition of regressional effect of time. Six toxicological studies

9    followed the univariate step with multivariate regression for all factors. Epidemiologic studies generally

10   related sources with health outcomes through various forms of Poisson regression, and four used GAMs.

11   One epidemiologic study used linear regression, and one long-term exposure study used time-to-event

12   data analysis (survival analysis) methodology.

# 6.6.2. Findings

## 6.6.2.1. Results from the 2004 PM AQCD

13        Four epidemiologic studies were evaluated in the 2004 PM AQCD that examined the association

14   between PM constituents or sources and specific health effects. Of these studies, one study associated

15   daily mortality with mobile sources in Knoxville, TN and St. Louis, MO and coal in Boston, MA; while

16   the crustal factor was not found to be significant for any of the six cities studied (Laden et al., 2000).

17   Another study demonstrated an association between regional sulfate and total mortality at lag 0 in

18   Phoenix and regional sulfate, motor vehicles, and vegetative burning with cardiovascular mortality at lags

19   of 0, 1, and 3, respectively (Mar et al., 2000; Mar et al., 2003). Negative associations were observed

20   between total mortality and regional sulfate at lag 3, along with local $SO_2$ and soil factors (Mar et al.,

21   2000; Mar et al., 2003). Finally, Tsai et al. (2000) identified significant associations between

22   $PM_{15}$-derived industrial sources and total daily deaths in Newark and Camden, NJ; sulfate was also linked

23   to cardiopulmonary deaths in both locations. Total mortality and cardiopulmonary deaths were also

24   significantly associated with oil burning sources in Camden (2000).

## 6.6.2.2. Epidemiologic Studies

25        For the comparative study described in Hopke et al. (2006), the results of which are reported in

26   Thurston et al. (2005), Ito et al. (2006a), and Mar et al. (2006), total (nonaccidental) mortality was

27   associated with secondary sulfate in both Phoenix and Washington D.C., although lag times differed (0

1  and 3, respectively) (Ito et al., 2006a; Mar et al., 2006). Primary coal was also associated with total

2  mortality in Washington D.C. (Ito et al., 2006a) and copper smelter, traffic, sea salt, and biomass/wood

3  burning were associated with cardiovascular mortality in Phoenix at various lag times (Mar et al., 2006).

4  In an additional source apportionment analysis, Sarnat et al. (2008) found in Atlanta that

5  cardiovascular disease-related ED visits were associated with same-day mobile sources (gasoline and

6  diesel) and biomass combustion (primarily prescribed forest burning and residential wood combustion),

7  whereas secondary sulfate was associated with respiratory disease ED visits (Sarnat et al., 2008). Sarnat et

8  al. (2008) also found that the power plant source identified by the CMB approach was negatively

9  associated with respiratory ED visits while no association was found for soil and secondary

10  nitrates/ammonium nitrate.

11  Other epidemiological studies (i.e., panel studies) have examined the association between PM

12  sources and physiologic alterations in cardiovascular function. Lanki et al. (2006a) reported associations

13  between local traffic and ST-segment depression in elderly adults in a study conducted in 3 European

14  cities (i.e., Helsinki, Amsterdam, and Erfurt) (Lanki et al., 2006a). Yue et al. (2007) found that adult males

15  with coronary artery disease demonstrated changes in repolarization parameters associated with

16  traffic-related PM, with increased vWF linked to traffic and combustion-generated particles (Yue et al.,

17  2007). In addition, elevated CRP levels were associated with all sources (soil, local traffic, secondary

18  aerosols from local fuel combustion, diesel, and secondary aerosols from multiple sources). Reidiker et al.

19  (2004b), in a study of young highway patrol officers, found that the most significant effects (HRV,

20  supraventricular ectopic beats, hematological markers, vWF) were associated with a "speed-change"

21  factor (Riediker et al., 2004b). In addition, Riediker et al. (2004b) observed an association between crustal

22  factor and cardiovascular effects, but no association with steel wear and gasoline.

23  The only epidemiologic study that evaluated respiratory ED visits was conducted in Spokane, WA

24  and used tracers as indicators of PM sources (Schreuder et al., 2006). In this study, only vegetative

25  burning (total carbon) was associated with increased respiratory ED visits while motor vehicles (Zn) and

26  soil (Si) were not associated with any health outcomes.

27  There were four epidemiologic studies that did not group PM constituents and differed in study

28  design. In a study of long-term exposure to $PM_{2.5}$, total mortality was associated with EC in a cohort of

29  U.S. military veterans (Lipfert et al., 2006b). Long-term exposure to Ni and V on daily risk of total

30  mortality was found in residents of New York (Lippmann et al., 2006). Short-term exposure to $PM_{2.5}$

31  constituents was associated with total mortality for EC, OC, $SO_4$, Ca, Fe, K, Mn, Pb, S, Si, Ti, and Zn in

32  winter in a cohort of six California counties (Ostro et al., 2007). Similarly, cardiovascular mortality was

33  associated with EC, $NO_3$, $SO_4$, Fe, K, S, Ti, and Zn in susceptible individuals living in six California

1    counties (Ostro et al., 2008), plus OC, Mn, and V for Ostro et al. (Ostro et al., 2007). For the latter two

2    studies, lag times were 2 or 3 days.

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### Table 6-16.    Epidemiologic studies of PM sources, factors, or individual components.

| **Reference:** Lippmann et al. (2000) **Location:** rural location upwind from NYC | **Subjects:** mice (ApoE) **Exposure:** CAPs (avg. mass concentration 85.6 µg/m³) | **n:** 12 ApoE mice (6/group) | **Number of constituents considered for grouping:** NR | **Grouping method:** no grouping was performed **# of groups:** NR | **Groups/ Factors/ Sources:** NR | **PM variables used:** Mass contribution of every constituent in CAPs portion of study, contribution of 16 constituents in epi portion |
|---|---|---|---|---|---|---|
| | **Results:** Lag for HR elevations on 14 days with wind from NW was same day. Lag for SDNN reduction on 14 days with wind from NW was 0, 1 and 2. | | | | | |
| | **GAM analysis:** Beta coefficient significant for Ni and HR (but not V, Cr, or Fe). Beta coefficient significant for Ni and log SDNN (but not V, Cr, or Fe). | | | | | |
| | **Epi results:** The strongest associations were between PM₁₀ mortality risk and Ni and V. | | | | | |
| **Reference:** Laden et al. (2000) **Location:** Monitors in 6 Eastern US cities (Harvard Six Cities Study) | **Subjects:** NR **Exposure:** NR | **n:** NR | **Number of constituents considered for grouping:** 15 elements | **Grouping method:** PCA **# of groups:** 8 | **Groups/ Factors/ Sources:** Soil/Crustal (PM fine), Mobile vehicle exhaust (PM fine), Coal (PM fine), Fuel oil; Metals, Salt' Manganese, Residual | **PM variables used:** Tracers: Si, V, Cl, Pb, Se |
| | **Results:** Lag 0-1 average for all results. Over all 6 cities, mobile source factor (Pb) had greatest association with daily mortality (3.4%) with 10 ug/m³ increase. The greatest effects for mortality due to mobile sources were observed in Madison (Portage), Knoxville (Kingston-Harriman), and St. Louis, although the Madison results were not statistically significant. The coal source factor was only significant in Boston (Watertown) - 2.8% increase in mortality and the overall percent increase was also significant (1.1%). Deaths from pneumonia attributable to coal combustion sources was 7.9% (CI, 3.1-12.7%) and statistically significant. The crustal factor was not associated with mortality in any city, although this factor was not a significant predictor in the regression model for Boston (Watertown) due to its low contribution to PM₂.₅ mass. For specific elements included simultaneously, sulfur, Pb, and Ni were significantly associated with overall mortality (3.0, 1.6, 1.5%, respectively). Boston had the greatest percent increase in mortality for sulfur (7.9%), Knoxville for Pb (15.0%), and Steubenville for Ni (8.2%), although the CIs are all quite large. | | | | | |
| | **Reanalysis results** (Schwartz et al., 2003): Effects changed slightly. New percent increases in mortality for combined cities are 3.5 and 0.79 for traffic and coal, respectively. The coal factor in Boston decreased to 2.1% increased mortality. A residual oil factor in Boston and Steubenville resulted in at 22.9% increase in daily deaths (but was not significant in the original analysis). | | | | | |
| **Reference:** Mar et al. (2000) **Location:** one monitor in Phoenix, AZ | **Subjects:** elderly only **Exposure:** NR | **n:** NR | **Number of constituents considered for grouping:** 10 elements, OC, EC, CO, NO₂; SO₂ | **Grouping method:** unspecified type of factor analysis **# of groups:** 3 or 5 | **Groups/ Factors/ Sources:** motor exhaust/road dust, soil, vegetative burning, local SO₂, regional SO₄ | **PM variables used:** first used individual constituents: S, Zn, Pb, K, OC, EC, TC (AL+Si+Ca+Fe+Ti), then factor scores |
| | **Results:** Cardiovascular mortality associated with PM₂.₅ mass on lag 1 and 4 (6 and 4%, respectively). EC and TC associated with CV mortality for lag 1 (RR = 1.05); OC was weakly associated with CV mortality for lags 1 and 3. For total mortality, regional suflate was positively assocated at lag 0, but negatively associated at lag 3. The local SO₂ and the soil factors were nagatively associated with total mortality. For CV mortality, secondary sulfate was positively associated at lag 0, motor vehicle at lag 1, and vegetative buring at lag 3. | | | | | |
| | **Reanalysis results** (Mar et al., 2003): Similar associations were observed. | | | | | |
| **Reference:** Tsai et al. (2000) **Location:** 3 NJ sites for 2 summers (ATEOS study) | **Subjects:** NR **Exposure:** NR | **N:** NR | **Number of constituents considered for grouping:** 8 metals, IPM, FPM, SO₄, CX, DCM, ACE, CO | **Grouping method:** unspecified type of factor analysis **# of groups:** 5 | **Groups/ Factors/ Sources:** oil burning, motor emissions, resuspended dust, secondary aerosol, industrial sources | **PM variables used:** Used individual constituents, then factor scores, then tracers |
| | **Results:** RR associated with 10 ug/m³ increases: Newark - 1.03 for industrial and total daily deaths; 1.02 for sulfate and total daily deaths; 1.04 for sulfate and cardiopulmonary deaths. Camden - 1.11 for oil burning sources and total daily deaths; 1.10 industrial and total daily deaths; 1.12 for oil buring sources and cardiopulmonary daily deaths; 1.02 for sulfate and cardiopulmonary daily deaths | | | | | |

| Reference: Riediker et al. (2004)<br><br>Location: Inside 9 state police patrol cars | Subjects: healthy male young police officers<br><br>Exposure: 9, on 4 consecutive days | n: NR | Number of constituents considered for grouping: 10 elements; 3 gaseous pollutants; 2 physical variables | Grouping method: PCA<br><br># of groups: 4 when 13+2 constituents included; 3 when only 9 "PM-associated" constituents included | Groups/ Factors/ Sources: soil; automotive steel wear; gasoline combustion; speed-changing traffic | PM variables used: Mass contribution or score (?) of sources |
|---|---|---|---|---|---|---|
| Results: Using two different factor analysis models found most significant effects (MCL, SDNN, PNN50, supraventricular ectopic beats, % neutrophils, % lymphocytes, MCV, von Willebrand Factor, and protein C) were for "speed-change factor" (i.e., copper, sulfur, aldehydes). Some associations observed for "crustal" and none for "steel wear" and "gasoline." | | | | | | |
| Reference: Ito et al. (2006a)<br><br>Location: Washington, DC | Subjects: NR<br><br>Exposure: NR | n: NR | Number of constituents considered for grouping: NR | Grouping method: comparison of: PMF; (absolute) PCA; UNMIX<br><br># of groups: 6-10<br><br>Groups/ Factors/ Sources: Different research groups gave different names to sources (see Hopke et al, table 2) | Sources for which association with health was analyzed: Soil, traffic, Secondary $SO_4$, $NO_3$ (Wash DC only), residual oil (Wash DC only), Wood smoke/ biomass combustion, Sea salt, incinerator (Wash DC only), primary coal (Wash DC only), Cu smelter (Phoenix only) | PM variables used: mass contribution of sources |
| Results: Overall, $PM_{2.5}$ effects observed at lag 3. Lag structure of association varied across source types, but consistent across investigators for total (non-accidental mortality): soil factor - mostly positive at various lags (not significant); secondary sulfate - strongest association at lag 3; nitrate - mostly negative except at lag 3; residual oil - strongest association at lag 2 (not significant); wood-burning - increasing association as lag increases (not significant); incinerator - significant negative associations at lag 0; primary coal - significant assocation at lag 3. | | | | | | |
| Reference: Lanki et al. (2006a)<br><br>Location: Monitors in Helsinki, Finland, Amsterdam,The Netherlands and Erfurt, Germany | Subjects: NR<br><br>Exposure: NR | n: NR | Number of constituents considered for grouping: 13 elements | Grouping method: Absolute PCAx<br><br># of groups: 5 | Groups/ Factors/ Sources: crustal; long range transported; oil combustion; soil; traffic | PM variables used: Tracers: Si (crustal); S (long-range transport); Ni (oil combustion); Cl (salt); ABS (local traffic). |
| Results: Highest observed effects were for crustal sources and salt at lag 3 (when analyzing sources), but not consistent or significant. In multipollutant models only ABS associated with ST-segment depression, but wide CIs. When examining indicator elements of a source, local traffic found to be the most toxic, but when examined per IQR long-range transport and traffic had similar effects. | | | | | | |
| Reference: Mar et al. (2006)<br><br>Location: Phoenix, AZ | Subjects: NR<br><br>Exposure: NR | n: NR<br><br>Number of constituents considered for grouping: Unknown | Grouping method: comparison of: PMF (absolute); PCA; UNMIX<br><br># of groups: 6-10 | Groups/ Factors/ Sources: Different labs gave different names to sources (see Hopke et al, table 2) | Sources for which association with health was analyzed: Soil, Traffic, secondary $SO_4$, $NO_3$, (Wash DC only), residual oil (Wash DC only), woodsmoke/ biomass combustion, sea salt, incinerator (Wash DC only); primary coal (Wash DC only); Cu smelter (Phoenix only) | PM variables used: mass contribution of sources |
| Results: Using daily $PM_{2.5}$ data found the following associations with cardiovascular mortality: Secondary sulfate - greatest effect observed for all sources and at lag 0; traffic - associated at lag 1; copper smelter associated at lag 0; sea salt - had the greatest statistical significance and observed at lag 5; biomass/wood burning - less consistent lag structure but greatest association at lag 3; soil - did not show an association or consistent lag structure. For total (non-accidental) mortality associations were weaker and consistently observed for only: copper smelter - lag 0; sea salt - lag 5. | | | | | | |
| Reference: Schreuder et al. (2006)<br><br>Location: One monitor in Spokane, WA for 7 years | Subjects: NR<br><br>Exposure: NR | n: NR | Number of constituents considered for grouping: 11 elements, TC, $NO_3$ | Grouping method: Comparison of: PMF, UNMIX, Multilinear Engine<br><br># of groups: 8 | Groups/ Factors/ Sources: Vegetative burning; As-rich Vehicle; $SO_4$; $NO_3$; Soil; Cu-rich; Marine | PM variables used: Tracers: TC (vegetative burning); As (As-rich); Zn (vehicle); Si (soil) |
| Results: Si, As, and Zn were not associated with any health outcomes; while an IQR increase in TC (vegetative burning) was associated with a 2% increase in respiratory ED visits. | | | | | | |

| Reference: Yue et al. (2007)<br>Location: one monitor in German city, 30.000 samples | Subjects: adult males<br>Exposure: CAD | n: 56, data collected 12 times over 6 month for every subject, but extended period missing PM data | Number of constituents considered for grouping: Apportionment based on particle size distribution. | Grouping method: PMF<br># of groups: 5 | Groups/ Factors/ Sources: airborne soil, local traffic, loacal fuel combustion, remote traffic (diesel), secondary aerosols | PM variables used: Mass contribution or score (?) of sources |
|---|---|---|---|---|---|---|
| **Results:** Overall, repolarization parameters influenced by traffic-related particles; vWF increased in response to traffic-related particles and combustion-generated aerosols. All source factors contributed to increasing CRP levels. | | | | | | |
| Reference: Sarnat et al. (2008)<br>Location: one monitor in Atlanta. GA for 2 yrs | Subjects: NR<br>Exposure: NR | n: NR | Number of constituents considered for grouping: NR | Grouping method: Comparison of: PMF, CMB-LGO, SOP ("a priori")<br># of groups: 9,11 (6 of them common between methods) | Groups/ Factors/ Sources: gasoline, diesel, wood smoke/biomass burning, soil, secondary $SO_4$/ ammonium sulfate, secondary nitrate/ ammonium nitrate, metal processing, railroad, bus and highway, cement kiln, power plants, other OC, ammonium bisulfate | PM variables used: Mass contribution or score (?) of sources and tracers |
| **Results:** Sulfate secondary associated with 1.2 - 2.0% increase in RD visits, significant negative association RD visits and primary emissions from coal-fired power plants. CVD significantly associated with other OC (1.014), biomass (1.033), diesel and gas for CMB-LGO. For PMF and CVD visits: diesel (1.025), gas, wood smoke, metal processing (1.013). Year-long associations: PMF diesel, EC, CMB-LGO gas, Zn and biomass combustion sources (CMB-LGO biomass burning, PMF wood smoke, and K). Diesel and gas sources association with RD in the warm season (1.2-2.1% per IQR). | | | | | | |
| Reference: Lipfert et al. (2006a)<br>Location: Many US locations (STN), large cohort of US Veterans | Subjects: n/a<br>Exposure: n/a | n: n/a | Number of constituents considered for grouping: 15 elements, EC, OC, $SO_4$, $NO_3$ | Grouping method: no grouping was performed<br># of groups: | Groups/ Factors/ Sources: mass contribution of every constituent, and other pollution-related variables | PM variables used: Time to event analysis (semi parametric proportional hazards model = Cox regression), single and multi pollutants models, some including several constituents of PM, non-PM pollutants, and other pollution-related variables. |
| **Results:** All showed significant associations with mortality with traffic density and EC showing the greatest effects. | | | | | | |
| Reference: Ostro et al. (2007)<br>Location: monitors in 6 CA counties, some with 2 monitors, for 4 years | Subjects: n/a<br>Exposure: n/a | n: n/a | Number of constituents considered for grouping: 15 elements, EC, OC; $NO_3$; $SO_4$, $PM_{2.5}$ mass | Grouping method: no grouping was performed<br># of groups: n/a | Groups/ Factors/ Sources: | PM variables used: mass contribution of every constituent |
| **Results:** Effects were greater during the winter months. In the all year analysis, at 3-day lag associations observed for EC, OC, $NO_3$ and Zn. During winter months (Oct -March) effects observed for most species for both all-cause and cardiovascular mortality at lag 3 (EC, OC, $SO_4$, Ca, Fe, K, Mn, Pb, S, Si, Ti, Zn) and (OC, $NO_3$, $SO_4$, Fe, Mn, S, V, Zn), respectively. | | | | | | |
| Reference: Ostro et al. (2008)<br>Location: monitors in 6 CA counties, some with 2 monitors/4 years | Subjects: n/a<br>Exposure: n/a | n: n/a | Number of constituents considered for grouping: 9 elements,EC, OC, $PM_{2.5}$ mass, $SO_4$, $NO_3$ | Grouping method: no grouping was performed<br># of groups: | Groups/ Factors/ Sources: | PM variables used: mass contribution of every constituent |
| **Results:** The following associations were observed with cardiovascular mortality: $PM_{2.5}$ (lag 3); EC (lag 2); $NO_3$ (lag 3); $SO_4$ (lag 3); Fe (lag 2); K (lag 2); S (lag 3); Ti (lag 2); Zn (lag 3). | | | | | | |

## 6.6.2.3. Human Clinical Studies

1    Three human clinical studies employed PCA, although only one linked groupings of PM
2   constituents to the measured physiologic parameters (Table 6-17). Huang et al. (2003c) demonstrated
3   associations between increased fibrinogen and Cu/Zn/V and increased BALF neutrophils and Fe/Se/SO$_4$
4   in young, healthy adults exposed to RTP, NC CAPs; however, only water-soluble constituents were
5   analyzed. In the other study that examined physiologic cardiovascular effects, Fe and EC were associated
6   with changes in ST-segment, while sulfate was associated with decreased systolic BP in asthmatic and
7   healthy human volunteers exposed to Los Angeles CAPs (2003a). In Gong et al. (2003a) the majority of
8   the PM was in the thoracic coarse fraction. In the other study that used Los Angeles CAPs, the only
9   observed association was between sulfate content and decreased lung function (FEV$_1$ and FVC) in elderly
10  volunteers with and without COPD (2005). Two additional human clinical studies that did not perform
11  grouping and employed Toronto CAPs plus ozone demonstrated increased diastolic BP and increased
12  brachial artery vasoconstriction associated with carbon content (Urch et al., 2004; Urch et al., 2005).

**Table 6-17.    Human clinical studies of PM sources, factors, or individual components.**

| Study:<br>Gong et al. (2003a)<br>**Location:** Los Angeles, CA | **Subjects:** Adult 18-45, healthy vs. asthmatic<br>**Exposure:** CAPs healthy and asthmatic exposed at different times | **N:** 12 healthy, 12 asthmatic<br>**Constituents considered for grouping:** 7 elements, EC, NO$_3$, SO$_4$ | **Grouping method:** PCA<br>**# of groups:** 4 (note: OC data was unavailable) | **Factors/Source:** crustal (Al Si CA K Fe)<br>S (2 metrics of SO$_4$ + elemental S)<br>Total Mass+NO$_3$, EC | **PM variables used:** Total mass<br>Tracers: SO$_4$, EC, Fe |
|---|---|---|---|---|---|
| | **Results:** Fe and EC associated with a decrease in ST-segment voltage 2 days post-exposure. EC associated with an increase in ST-segment voltage immediately following exposure. Sulfate content associated with a decrease in systolic BP 4 h post-exposure. | | | | |
| Study:<br>Gong et al. (2005)<br>**Location:** Los Angeles, CA | **Subjects:** elderly, COPD vs. healthy/ CAPs<br>**Exposure:** NO$_2$ (full factorial) | **N:** 6 healthy, 18 COPD<br>**Constituents considered for grouping:** 7 elements + EC | **Grouping method:** PCA<br>**# of groups:** 3 (note: OC was unavailable) | **Factors/Source:** crustal (Al Si CA K Fe)<br>S (= SO$_4$)<br>Na | **PM variables used:** Total mass, Tracers:, SO$_4$, Si, Fe, EC |
| | **Results:** Mass concentration of CAPs not observed to significantly affect lung function. However, sulfate content was associated with a decrease lung function (FEV$_1$ and FVC), which was enhanced by co-exposure to NO$_2$. | | | | |
| Reference:<br>Huang et al. (2003c)<br>**Location:** Chapel Hill, NC | **Subjects:** healthy adults<br>**Exposure:** CAPs | **N:** 35 male; 2 female<br>**Constituents considered for grouping:** 8 elements and SO$_4$ | **Grouping method:** PCA<br>**# of groups: 2** | **Factors/Source:**<br>Fe/SO$_4$/Se/V/Zn/Cu | **PM variables used:** factor scores, then mass contribution of all 9 constituents |
| | **Results:** Associations observed between sulfate, zinc, and selenium content and increases in BAL neutrophils. Increases in fibrinogen associated with copper, zinc, and vanadium content. | | | | |
| Reference:<br>Urch et al. (2004)<br>**Location:** Toronto, Canada | **Subjects:** healthy adults 19-50 yrs/CAPs<br>**Exposure:** O$_3$ | **N:** 23<br>**Constituents considered for grouping:** unknown | **Grouping method:** no grouping was performed<br>**# of groups:** NR | **Factors/Source:**<br>NR | **PM variables used:** every constituent in uni-variate analysis, then OC and SO$_4$ in multivariate analysis |
| | **Results:** CAPs-induced increase in diastolic BP significantly associated with carbon content of the particles. | | | | |
| Reference:<br>Urch et al. (2004)<br>**Location:** Toronto, Canada | **Subjects:** healthy adults/CAPs<br>**Exposure:** O$_3$ | **N:** 24<br>**Constituents considered for grouping:** 14 elements, EC, OC | **Grouping method:** no grouping was performed<br>**# of groups:** NR | **Factors/Source:**<br>NR | **PM variables used:** every constituent in univariate analysis, then OC and SO$_4$ in multivariate analysis |
| | **Results:** Both organic and EC content of CAPs associated with an increase in brachial artery vasoconstriction. | | | | |

## 6.6.2.4. Toxicological Studies

1       The single toxicological in vivo study that characterized PM sources corresponding to identified
2    sources was conducted in Tuxedo, NY, over a 5-month period (Table 6-18). This study reported that all
3    sources (regional sulfate, resuspended soil, residual oil, traffic and other unknown sources) were linked to
4    HR or HRV changes in mice at one time or another during or after daily exposure (Lippmann et al.,
5    2005a). In a similar in vitro study using CAPs from the same location for an in vitro exposure, NF-κB in
6    BEAS-2B cells were correlated with the oil combustion factor (Maciejczyk and Chen, 2005). The other in
7    vitro toxicological study (Duvall et al.) that named sources employed samples from five U.S. cities and
8    found a high correlation between increased IL-8 release in primary human airway epithelium cells and
9    coal combustion ($R^2$=0.79), secondary nitrate ($R^2$=0.63), and mobile sources ($R^2$=0.39). In addition, soil
10   ($R^2$=0.48), residual oil combustion ($R^2$=0.38), and wood combustion ($R^2$=0.33) were associated with
11   COX-2 effects; whereas, secondary sulfate ($R^2$=0.51) was correlated with HO-1. Wood combustion and
12   soil were negatively correlatted with HO-1.

13       There were six toxicological studies that employed Boston CAPs and identified at least four
14   groupings of PM constituents (V/Ni, S, Al/Si, and Br/Pb), but only partially and tentatively named
15   sources (Batalha et al., 2002; Clarke et al., 2000; Godleski et al., 2002; Nikolov et al., 2008; Saldiva et al.,
16   2002; Wellenius et al., 2003). When examining cardiovascular effects these studies found that Si was
17   associated with changes in the ST-segment of dogs (Wellenius et al., 2003) and decreased lumen/wall
18   ratio in rat pulmonary arteries (Batalha et al., 2002) in multivariate analyses. In addition, blood
19   hematological results were associated with V/Ni, Al/Si, Na/Cl, and S in dogs (Clarke et al., 2000). An
20   examination of respiratory effects found that V/Ni and Br/Pb were associated with increased
21   inflammation in BALF for only the 3rd day of exposure (Clarke et al., 2000). Decreased respiratory rate
22   and increased airway irritation (Penh) in dogs were associated with road dust (Al) and motor vehicles
23   (OC), respectively (Nikolov et al., 2008). Individual $PM_{2.5}$ constituents associated with elevated
24   neutrophils in BALF were Br, EC, OC, Pb, and sulfate (Godleski et al., 2002), which is consistent with
25   the findings (Br, EC, OC, Pb, V, and Cl) of Saldiva et al. (Saldiva et al., 2002). Univariate regression of
26   two Boston CAPs studies that did not group PM constituents demonstrated that lung oxidative stress was
27   correlated with Mn, Zn, Fe, Cu, and Ca (Gurgueira et al., 2002) and Al, Si, Fe, K, Pb, and Cu (Rhoden et
28   al.) in rats.

29       The two toxicological studies that used PLS methodologies identified $PM_{2.5}$ constituents linked to
30   respiratory parameters. Seagrave et al. (2006) demonstrated associations between cytotoxic responses and
31   gasoline plus nitrates (OC, Pb, hopanes/steranes, nitrate, and As) along with inflammatory responses and
32   gasoline plus diesel (including major metal oxides) in rats exposed via intratracheal instillation. In the
33   other study, Veranth et al. (2006) collected loose surface soil from 28 sites in the Western U.S. and

1    exposed BEAS-2B cells to $PM_{2.5}$. In the multivariate redundancy analysis, OC1, OC3, OC2, EC2, Br,

2    EC1, and Ni correlated with IL-8 release, decreased IL-6 release, and decreased viability at low and high

3    doses (10 and 80 $\mu g/cm^2$, respectively).

4        One in vitro toxicological study that employed Chapel Hill PM used PCA but did not name specific

5    PM sources (Becker et al., 2005b). In this study, the release of IL-6 from human alveolar macrophages

6    and IL-8 from normal human bronchial epithelial cells was associated with a $PM_{10}$ factor comprised of

7    Cr, Al, Si, Ti, Fe, and Cu. No statistically significant effects were observed for a second PM factor (Zn,

8    As, V, Ni, Pb, and Se).

9        Those toxicological studies that did not apply groupings to the PM speciation data demonstrated a

10    variety of results. As reported above, two Boston CAPs studies demonstrated lung oxidative stress

11    correlated with Mn, Zn, Fe, Cu, and Ca (Gurgueira et al., 2002) and Al, Si, Fe, K, Pb, and Cu (Rhoden et

12    al., 2004) in rats. The remaining toxicological study that did not use PM species groupings reported a

13    correlation between Zn and plasma fibrinogen in SH rats when constituents were normalized per unit

14    mass of CAPs (Kodavanti et al., 2005).

## Table 6-18. Toxicological studies of PM sources, factors, or individual constituents

| Reference: Becker et al. (2005a) Location: Chapel Hill, NC; repeated sampling for 1 year | Subjects: normal human bronchial epithelial and human AM Exposure: (2-3x105 cells/ml; 11 or 50 ug/ml) | n: not provided Constituents considered for grouping: 12 elements | Grouping method: PCA # of groups: 2 | Groups/ Factors/ Sources: Cr/Al/Si/Ti/Fe/Cu ("crustal"), Zn/As/V/Ni/Pb/ Se | PM variables used: not provided |
|---|---|---|---|---|---|
| | Results: Cr/Al/Si/Ti/Fe/Cu associated with IL-8 release in normal human bronchial epithelial cells and IL-6 release in AM. Zn/As/V/Ni/Pb/Se not associated with any endpoints. Stepwise linear regression with individual constituents Fe and Si assoicated with IL-6 release in AM. Cr associated with IL-8 release in NHBE cells. | | | | |
| Reference: Batalha et al. (2002) Location: Boston, MA | Subjects: rats Exposure: CAPs (3-day mean CAPs concentration range: 126.1-481.0 ug/m3) CAPs (3-day mean CAPs concentration range: 126.1-481.0 ug/m3) | n: 7-10 rats × 2 levels CAPs × 2 levels $SO_2$ × 6 runs in different seasons Constituents considered for grouping: 20 elements; OC; EC | Grouping method: Previous study in same city (Clarke et al.), and PCA of this experiment's data # of groups: 6 independent variables in univariate regression (4 elements,EC,OC)4 in the multivariate step (all of them tracers) The 4 tracer elements corresponded to the 4 groupings identified by PCA) | Groups/ Factors/ Sources: V/Ni, S, Al/Si, Br/Pb | PM variables used: Tracers: Si, $SO_4$, V, Pb. Other: EC, OC |
| | Results: Univariate analyses for first day not significant for L/W ratio. Univariate analyses for second and third day and second+third day mean were similar. Presented second+third day mean regression data. CAPs mass, Si, Pb, $SO_4$, EC, OC significant for decreased L/W ratio in normal+CB rats exposed to CAPs. Si, $SO_4$ significant for decreased L/W ratio in normal rats. Si, OC significant for decreased L/W ratio in CB rats. Multivariate analysis using normal+CB rats for Si, $SO_4$, V, Pb - only Si remained significant with decreased L/W ratio. | | | | |
| Reference: Clarke et al. (2000) Location: Boston, MA | Subjects: dogs Exposure: CAPs (average for all studies, paired: 203.4, crossover: 360.8 ug/m3) repeated exposure with several weeks in between | n: 10 dogs, 20 paired exposures, 24 crossover Constituents considered for grouping: 19 elements, black C | Grouping method: PCA # of groups: 4 for exposure in paired runs 6 for exposure in crossover runs | Groups/ Factors/ Sources: V/Ni, S, Al/Si, Br/Pb, S, Na/Cl Cr | PM variables used: all elements, then factor scores |

**Results:** No significant differences between baseline, sham, or CAPs group for BAL cell differential percentages. Total BAL protein increased with CAPs compared to sham. No significant hematological effects with CAPs exposure. Mixed linear regression analyses (statistics not provided): Al and Ti (3-day ave. concentrations) associated with dose-dependent decreases in BAL AM and increases in BAL PMN percentages. Sulfate associated with increased WBC. BC, Al, Mn, Si, Zn, Ti, V, Fe, Ni associated with increased blood PMN. Na associated with increased blood lymphocytes. Al, Mn, Si associated with decreased blood lymphocytes. CAPs mass and BC associated with decreased blood eosinophils. CAPs mass associated with decreased platelet count. Regression using results of factor analysis: None for 3-day ave. concentration for BAL parameters. V/Ni for increased AM percentage and Br/Pb for increased PMN percentage for 3rd-day only concentration. V/Ni and Al/Si for increased blood PMN percentage and decreased blood lymphocyte percentage. Al/Si also for increased WBC counts. Na/Cl for increased blood lympyocyte percentage. S for decreased RBC and hemoglobin.

| Reference: Godleski et al. (2002) **Location:** Boston, MA | **Subjects:** rats **Exposure:** CAPs (3-day mean CAPs concentration range: 126.1-481.0 ug/m³) | **n:** 7-10 rats × 2 levels CAPs × 2 levels SO₂ × 6 runs in different seasons **Constituents considered for grouping:** 20 elements, OC, EC | **Grouping method:** Previous study in same city (Clarke et al.), and PCA of this experiment's data **# of groups:** 6 independent variables in univariate regression (4 elements,EC,aOC) | **Groups/ Factors/ Sources:** V/Ni, S, Al/Si/Ca, Br/Pb | **PM variables used:** Tracers: , I, SO₄,V, Pb Other: , EC, OC |
|---|---|---|---|---|---|

**Results:** Increased percent of PMNs in BALF in CAPs-exposed rats at 24 h. CAPs affected lung tissue mRNA involved in pro-inflammation, immune, and vascular endothelial responses. **Linear regression:** Increased PMN associated with CAPs mass, Br, Pb, SO₄, EC, and OC.

| Reference: Nikolov et al. (2008) **Location:** Boston, MA | **Subjects:** dogs **Exposure:** | **n:** 8 dogs, 24 exposure-days in 1997-98; 4 dogs, 21 exposure-days in 2001-02 **Constituents considered for grouping:** 13 elements, BC, EC, OC | **Grouping method:** Compared 3 factor-analytic models within a SEM model **# of groups:** 4 | **Groups/ Factors/ Sources:** Oil Combustion V/Ni ; Power Plants S Road dust Al/Si Motror vehicles BC/OC/EC | **PM variables used:** mass contribution of every constituent |
|---|---|---|---|---|---|

**Results:** Univariate respones for respiratory outcomes; Road dust and oil combustion assoicated with decreased respiratory frequency; motor vehicles assoicated with increased respiratory frequency. Motor vehicles assoicated with increased PEF. Road dust assoicated with decreased penh and motor vehicles assoicated with increased penh. Multivariate responses for respiratory outcomes; Road dust assoicated with decreased respiratory rate. Motor vehicles assoicated with increased airway irritation.

| Reference: Saldiva et al. (2002) **Location:** Boston, MA | **Subjects:** rats (Sprague Dawley) **Exposure:** CAPs (3-day ave. mass concentration range 126.1-481 ug/m³) | **n:** 7-10 rats/group (air/sham, SO₂/sham, air/CAP, SO₂/CAP) × 6 runs in different seasons **Constituents considered for grouping:** 15 elements (used Clarke 2000 to pick out tracers) | **Grouping method:** Previous study in same city (Clarke et al.) **# of groups:** 9 independent variables in univariate regression (mass and 8 elements) | **Groups/ Factors/ Sources:** V/Ni S Al/Si Br/Pb ———— Na/Cl Cr | **PM variables used:** Tracers: Si SO₄ V Pb Br Cl Other: EC, OC |
|---|---|---|---|---|---|

**Results:** Increased percent and number of PMN in majority of air and SO₂ rats exposed to CAPs, but significance levels not provided. Other responses (protein, LDH, NAG) were variable and depended upon the CAPs exposure. No CAPs effect on histopathology. **Linear regression:** V, Br, Pb, SO₄, EC, OC, Si, CAP mass associated with increased PMN and lymphocytes for normal+CB rats. Only V not associated with PMN in normal rats. Lymphocyte response due to CB rats, but not observed for SO₄ , Si, or mass in this group. Br, Pb, SO₄, EC, OC, Si assocaited with increased total protein in CB rats. Cl and V associated with decreased LDH in CB rats. No BAL effects in normal rats exposed to CAPs. V, Br, Pb, EC, OC, and Cl associated with increased neutrophil density in lungs of normal rats.

| Reference: Wellenius et al. (2003) **Location:** Boston, MA | **Subjects:** dogs **Exposure:** CAPs (ave. mass concentration range 161.3-957.3 ug/m³) repeated exposure with several weeks in between | **n:** 6 dogs, 20 exposures **Constituents considered for grouping:** 15 elements (+EC OC?) (taken from Clarke et al. 2000) | **Grouping method:** 8 independent variables in univariate regression (mass, number, and 6 elements) 4 in the multivariate step **# of groups:** x | **Groups/ Factors/ Sources:** V/Ni S Al/Si Br/Pb ———— Na/Cl Cr | **PM variables used:** Univariate: Mass Number Ni, S, Si, BC Multivariate: Ni, S, Si , BC |
|---|---|---|---|---|---|

**Results:** ST-segment elevation increased with CAPs.

**Univariate regression:** Si and Pb associated with peak ST-segment elevation and integrated ST-segment change.

CAPs mass or number concentration were not associated with any change.

**Multivariate regression:** Si associated with peak ST-segment elevation and integreated ST-segment change.

| Reference: Lippmann et al. (2005b) **Location:** rural location upwind from NYC | **Subjects:** mice (C57 and ApoE) **Exposure:** CAPs (ave. mass concentration 113 ug/m³) | **n:** C57: 3-6 mice/group ApoE: 9-10 mice/group **Constituents considered for grouping:** 19 elements + OC, EC, NO₃ | **Grouping method:** (Absolute) PCA **# of groups:** 4 | **Groups/ Factors/ Sources:** Regional SO₄ (S/Si/OC). Resuspended soil (CA/Fe/Al/Si) RO power plants (V/Ni/Se) Traffic and unknown | **PM variables used:** mass contribution of sources |
|---|---|---|---|---|---|

**Results: ApoE null mice:** Reuspended soil associated with decreased HR during exposure, but increased HR after exposure. Secondary sulfate associated with decreased HR after exposure. Resdiual oil associated with increased RMSSD and SDNN in afternoon following exposure. Secondary sulfate associated with decreased RMSSD and SDNN in night following exposure. Resuspended soil associated with increased RMSSD at night following exposure. PM mass associated with decreased HR during exposure and decreased RMSSD at night following exposure. **C57 mice:** Motor vehicle/other source category associated with decrease in RMSSD in afternoon following exposure

| Reference: Maciejczyk and Chen (2005) | **Subjects:** NR<br>**Exposure:** CAPs (90000/well; 300 ug/ml) | **n:** 110 samples<br>**Constituents considered for grouping:** 19 elements + OC, EC, NO$_3$ | **Grouping method:** (Absolute) PCA<br>**# of groups:** 4 | **Groups/ Factors/ Sources:** Regional SO$_4$ Soil; Unknown Oil combustion | **PM variables used:** mass contribution of sources |
|---|---|---|---|---|---|
| **Location:** rural;upwind from NYC | | | | | |

**Results: Correlation**: V and Ni positively correlated with NF-kappaB. Oil combustion corrrelated the greatest with NF-kappaB (0.316). Significance not provided. Only 2% of mass contribution originates from this source.

| Reference: Seagrave et al. (2006)<br>**Location:** 4 SE US sites for 2 seasons | **Subjects** rats (Fisher 344)<br>**Exposure:** 0.75, 1.5 and 3 mg/rat via intratracheal instillation | **n:** 5 rats/dose<br>**Constituents considered for grouping:** NR | **Grouping method:** CMB: secondary NO$_3$; secondary NH$_4$; secondary SO$_4$; coke production; vegetative detritus; natural gas combust; road dust; wood combust; meat cooking gasoline; diesel other OM; other mass<br>**# of groups:** 13 | **Groups/ Factors/ Sources:** NR | **PM variables used:** mass contribution of every constituent, then mass contribution of sources |

**Results:** Potency depended upon season and site of sample collection. In general, effects were greater in the winter. **PLS analysis:** 2 major constituents identified (OC, Pb, hopanes/steranes, nitrate, As for first and major metal oxides for the second), gasoline most important predictor for both constituents, with diesel influencing second constituent and nitrate influencing first constituent. First constituent affected cytotoxic responses, second constituent affected inflammatory responses.

| Reference: Veranth et al. (2006)<br>**Location:** 8 sites in the Western US | **Subjects** BEAS-2B cells (35000 cells/cm$^2$; 10, 20, 40, 80 ug/cm$^2$)<br>**Exposure:** Loose surface soil sweepings through mechanical tumbler and cascade impactor | **n:** 6; 16 runs over 6 months.<br>**Constituents considered for grouping:** 13 elements, TC, 5 OC variables, 4 EC variables, 2 ions, EU, one ratio (Ca: Al), OP, CO3 | **Grouping method:** PLS<br>**# of groups:** NR | **Groups/ Factors/ Sources:** NR | **PM variables used:** mass contribution (?) of every |

**Results:** Dose-related increase in IL-6 and decreases in cell viability for all soil types. IL-8 responses more variable and dependent upon soil type. Univariate correlations. Low correlations for all constituents tested with IL-6. Highest correlations for EC1 (R2 = 0.50) and pyrolyzed OC (R2 = 0.46), then Ca/Al (R2 = 0.21). Carbonate carbon, EC3, and Sr correlated with IL-8 (R2 = 0.27, 0.13, and 0.25, respectively). EC and Ni correlated with IL-8 trend over the range of 10-80 ug/cm$^2$ (R2 = 0.39 and 0.27, respectively). Multivariate redundancy analysis OC1, OC3, OC2, EC2, Br, EC1, Ni correlated with IL-8 release, decreased viability, and decreased IL-6 at low and high doses. Ni, EC1, and EC2 correlated with IL-6 release at the high dose, decreased IL-6 at the low dose, decreased IL-8 release, and decreased viability. Br was negatively associated.

| Reference: Duvall et al. (2008)<br>**Location:** 5 US cities | **Subjects** primary human airway epithelial cells (100,000 cells/ml; dose not provided)<br>**Exposure:** NR | **n:** NR<br>**Constituents considered for grouping:** NR | **Grouping method:** CMB, but not on coarse and ultrafine<br>**# of groups:** 6 or 7 | **Groups/ Factors/ Sources:** Mobile, residual, oil, wood, soil, secondary SO$_4$, secondary NO$_3$ | **PM variables used:** mass contribution of sources |

**Results: Linear regression with individual constituents**: Sulfate associated with increased IL-8 mRNA expression. Sr associated with increased COX-2 and decreased HO-1 mRNA expressions. K associated with decreased HO-1 mRNA expression. **Linear regression with source categories:** Only R$^2$ values provided; significance levels not provided.

| Reference: Gurgueira et al. (2002)<br>**Location:** Boston, MA | **Subjects** rats (Sprague Dawley)<br>**Exposure:** CAPs (ave. mass concentration 600 ug/m$^3$); also carbon black and ROFA | **n:** 13 experiments (1 rat/group at each time point)<br>**Constituents considered for grouping:** 20 elements | **Grouping method:** not performed<br>**# of groups: NA**x | **Groups/ Factors/ Sources:** mass contribution of every constituent | **PM variables used:** NR |

**Results:** Increased oxidative stress in heart and lungs following CAPs exposure (and ROFA exposure). **Univariate regression**: Mn, Zn, Fe, Cu, and Ca most significant responses for lung (r2>0.40). Al, Si, Ti, Fe, and total mass most significant response for heart (r2>0.49).

| Reference: Rhoden et al. (2004)<br>**Location:** Boston, MA | **Subjects** rats (Sprague Dawley)<br>**Exposure:** CAPs (avg. mass concentration range 150-2520 ug/m$^3$) acetylcysteine full factorial | **n:** 4-8 rats (1-2 per group - sham, CAPs, sham/NAC, CAP/NAC) 10 exposures<br>**Constituents considered for grouping:** Boston, MA | **Grouping method:** 20 elements<br>**# of groups:** grouping not performed | **Groups/ Factors/ Sources:** NR | **PM variables used:** mass contribution of every constituent |

**Results:** Increased oxidative stress and inflammation in lungs of CAPs animals that was attenuated with NAC. **Univariate regression**: Al, Si, Fe, K, Pb, and Cu most significantly correlated with lung TBARS. No significant correlations for lung carbonyls or lung PMN.

| Reference: Kodavanti et al. (2005)<br>**Location:** RTP, NC | **Subjects** rats (SH and WKY)<br>**Exposure:** CAPs (144-2758 μg/m$^3$) | **n:** 6 1-day , 1-strain runs, 7 2-day, 2-strain runs, 4-9 rats per run.<br>**Constituents considered for grouping:** NR | **Grouping method:** Not performed<br>**# of groups:** NR | **Groups/ Factors/ Sources:** mass contribution of every constituent | **PM variables used:** NR |

**Results:** No significant correlations between biologic responses and exposure variables (i.e., CAP mass, OC, inorganic C, sulfate, and other major elemental constituents). Al, Cu, Zn correlated with biologic responses when constitents normalized per unit mass of CAP (ug/mg). Zn correlated with plasma fibrinogen in SH rats (P = 0.0023).

# 6.6.3. Summary

1      Recent epidemiologic, human clinical and toxicological studies have begun to evaluate the health

2    effects associated with ambient PM constituents and sources, as opposed to PM mass. This evaluation is

3    conducted using a variety of quantitative methods applied to the full set of PM constituents, rather than

4    selecting constituents a priori. As shown in Table 2-1, over 19 individual PM constituents have been

5    linked to cardiovascular and/or pulmonary responses. Similarly, a number of different PM, primarily fine

6    PM, source categories have been associated with health effects, including crustal and soil, traffic, second-

7    dary sulfate, power plants, and oil combustion. These varying results underscore the difficulty of the task.

8    Overall, there is no consistent trend or pattern that links particular constituents or sources with specific

9    health outcomes, but a number of $PM_{2.5}$ constituent groupings that are commonly associated with sources

10    such as crustal/soil, secondary sulfate/long-range transport, traffic, oil combustion and

11    woodsmoke/vegetative burning were linked with health effects.

12      Comparisons among these studies are difficult because of differences in handling the data, in

13    approaches used to model source contributions, and in the level of experience in applying source appor-

14    tionment techniques among research groups. In an intercomparison study, several research groups used

15    the same data sets (which contained the composition of ambient $PM_{2.5}$ and daily mortality counts) and

16    their choice of source apportionment models to identify PM sources (see Section 6.5.2.6). In these stu-

17    dies, when examining the association between various PM sources and mortality risk estimates, it was

18    found that the between source category variation in risk estimates for daily mortality was significantly

19    larger than the between group variation in reported risks. The results of this exercise indicated that the

20    choice of source apportionment models has a much smaller effect on variations in risk estimates com-

21    pared with the variations in risk caused by the different source components. Further, the most strongly

22    associated source types were consistent across all groups. This study indicates that source apportionment

23    methods can add useful insights into those source components that contribute to $PM_{2.5}$ health effects.

24      In terms of establishing linkages between PM constituents or sources and health effects, additional

25    studies that increase the number of different geographic locations while examining similar health

26    endpoints or outcomes may help uncover a trend or pattern. In addition, the integration of results from

27    these types of studies would be less difficult if the methods employed for grouping PM constituents

28    across studies and disciplines were more consistent.

# Chapter 7. Integrated Health Effects of Long-Term PM Exposure

## 7.1. Introduction

1      This chapter summarizes, reviews and integrates the evidence on relationships between health
2   effects with long-term exposures to various size fractions and sources of PM. Cardiopulmonary health
3   effects of long-term exposure to PM have been examined in an extensive body of epidemiologic, human
4   clinical, and toxicological studies. Both epidemiologic and toxicological studies provide a basis for
5   examining reproductive and developmental and cancer health outcomes with regard to long-term
6   exposure to PM. In addition, there is a large body of epidemiologic literature evaluating the relationship
7   between mortality and long-term exposure to PM.
8      Conclusions from the 2004 PM AQCD are summarized briefly at the beginning of each section,
9   and the evaluation of evidence from recent studies builds upon what was available during the previous
10  review. For each health outcome (e.g., respiratory infections, lung function), results are summarized for
11  studies from the specific scientific discipline, i.e., epidemiologic, human clinical, and toxicological
12  studies. The sections conclude with summaries of the evidence on the various health outcomes and
13  integration of the findings that leads to conclusions regarding causality based upon the framework
14  described in Chapter 1. Determination of causality is made for the overall health effect category, such as
15  cardiovascular effects, with coherence and plausibility being based upon the evidence from across
16  disciplines and also across the suite of related health outcomes. In these summary sections, the evidence is
17  summarized and independent conclusions drawn for relationships with $PM_{10}$, $PM_{10-2.5}$, $PM_{2.5}$, and ultrafine
18  particles.

## 7.2. Cardiovascular and Systemic Effects

19     Studies examining associations between long-term exposure to ambient PM (over months to years)
20  and CVD morbidity were not included in the 1996 or 2004 PM Air Quality Criteria Documents
21  (U.S. EPA, 1996, 2004), and only one study of this type (Kunzli et al., 2005) was included in the July
22  2006 Provisional Assessment for PM (U.S. EPA, 2004). There were no toxicological studies presented in
23  the 2004 PM AQCD that evaluated chronic atherosclerotic effects of PM exposure in animal models.
24  However, a subchronic study that evaluated atherosclerosis progression in hyperlipidemic rabbits was

1    discussed and this study provided the foundation for the subsequent work that has been conducted in this

2    area (Suwa et al., 2002). No previous toxicological studies evaluated effects of subchronic or chronic PM

3    exposure on HR or HRV changes nor were there animal toxicological studies included in the 2004 PM

4    AQCD that evaluated systemic inflammatory or blood coagulation markers following subchronic or

5    chronic PM exposure.

6          Several new epidemiologic studies have examined the long-term PM-CVD association among U.S.

7    and European populations. The studies investigate the association of both $PM_{2.5}$ and $PM_{10}$ exposures with

8    a variety of clinical and subclinical CVD outcomes. Epidemiologic and toxicological studies have

9    provided evidence of the adverse effects of long-term exposure to $PM_{2.5}$ on cardiovascular effects,

10   including atherosclerosis and clinical and subclinical markers of cardiovascular morbidity. The evidence

11   of these effects from long-term exposure to $PM_{10}$ and $PM_{10-2.5}$ is weaker.


# 7.2.1. Atherosclerosis

12         Atherosclerosis is a chronic inflammatory disease that contributes to several adverse outcomes,

13   including myocardial infarction and aortic aneurysm. It is a multifaceted disease, beginning with an early

14   injury or inflammation that promotes the extravasation of inflammatory cells. Under conditions of

15   oxidative or nitrosative stress and high lipid or cholesterol concentrations, the vessel wall undergoes a

16   chronic remodeling that is characterized by the presence of foam cells, migrated and differentiated

17   smooth muscle cells, and ultimately a fibrous cap. The advanced lesion that develops from this process

18   can occlude perfusion to distal tissue, causing ischemia, and erode, degrade, or even rupture, revealing

19   coagulant initiators (tissue factor) that cause major clotting disorders and infarction or stroke. Several

20   detailed reviews of atherosclerosis pathology have been published elsewhere (Ross, 1999; Stocker and

21   Keaney, 2004).


## 7.2.1.1. Epidemiologic Studies

### *Measures of Atherosclerosis*

22         There are four preclinical markers that have been used in the epidemiologic studies of

23   atherosclerosis. These measures are described briefly below.

24         CAC is a measure of atherosclerosis assessed by non-contrast, cardiac-gated electron beam

25   computed tomography (EBCT) or multidetector computed tomography (MDCT) of the coronary arteries

26   in the heart (Greenland and Kizilbash, 2005; Hoffmann et al., 2005; Mollet et al., 2005). The prevalence

27   of CAC is strongly related to age. Few people have detectable CAC in their second decade of life;

1    however, the prevalence of CAC rises to approximately 100% by age 80 (Ardehali et al., 2007). Previous

2    studies suggest that while the absence of CAC does not rule out atherosclerosis, it does imply a very low

3    likelihood of significant arterial obstruction (Achenbach and Daniel, 2001; Arad et al., 1996; Shaw et al.,

4    2003; Shemesh et al., 1996). Conversely, the presence of CAC confirms the existence of atherosclerotic

5    plaque and the amount of calcification varies directly with the likelihood of obstructive disease (Ardehali

6    et al., 2007). CAC is often quantified using the Agatston method (1990). Agatston scores are frequently

7    used to classify individuals into one of five groups (zero; mild; moderate; severe; extensive) or according

8    to age- and sex-specific percentiles of the CAC distribution (Erbel et al., 2007).

9        CIMT is a measure of atherosclerosis assessed by high-resolution, B-mode ultrasonography of the

10   carotid arteries in the neck, the walls of which have inner (intimal), middle (medial) and outer

11   (adventitial) layers (Craven et al., 1990; O'Leary et al., 1999; Wendelhag et al., 1993). CIMT estimates

12   the distance in mm or μm between the innermost (blood-intima) and outermost (media-adventitia)

13   interfaces, often by averaging over three arterial segments in the common carotid, carotid bulb, and

14   internal carotid artery (Amato et al., 2007). CIMT has been associated with atherosclerosis risk factors

15   (Heiss et al., 1991; O'Leary et al., 1992; Salonen and Salonen, 1991), prevalent coronary heart disease

16   (Chambless et al., 1997; Geroulakos et al., 1994), and incident coronary and cerebral events (O'Leary et

17   al., 1999; van der Meer et al., 2004). Several studies have indicated that CIMT measurements are accurate

18   (Girerd et al., 1994; Pignoli et al., 1986; Wendelhag et al., 1991) and reproducible (Montauban van

19   Swijndregt et al., 1999; Smilde et al., 1997; Willekes et al., 1999), perhaps most so for the common

20   carotid artery (Montauban van Swijndregt et al., 1999).

21       ABI—also known as the ankle-arm or resting (blood) pressure index—is a measure of lower

22   extremity arterial occlusive disease commonly caused by advanced atherosclerosis (Weitz et al., 1996). It

23   is assessed by continuous wave Doppler and manual or automated oscillometric sphygmomanometry, the

24   latter having been shown to have higher repeatability and validity (Weitz et al., 1996). ABI is defined as

25   the unitless ratio of ankle to brachial systolic blood pressures measured in mm Hg. As ankle pressure is

26   normally equal to or slightly higher than arm pressure (resulting in an ABI ≥ 1.0), epidemiologic studies

27   typically define the normal ABI range as 0.90 to 1.50 (Resnick et al., 2004). Low ABI has been associated

28   with all-cause and CVD mortality (Newman et al., 1993; Vogt et al., 1993), as well as myocardial

29   infarction and stroke (Karthikeyan and Lip, 2007).

30       AAC is a measure of atherosclerosis assessed by non-contrast, EBCT or MDCT of the abdominal

31   aorta. It is scored much like CAC (Agatston et al., 1990), but the age-specific prevalence and extent of

32   AAC is greater, particularly among women and at ages >50 years. Although AAC has not been studied as

33   extensively as CAC, it is associated with carotid and coronary atherosclerosis as well as cardiovascular

1   morbidity and mortality (Allison et al., 2004; 2006; Hollander et al., 2003; Khoury et al., 1997; Oei et al.,

2   2002; Walsh et al., 2002; Wilson et al., 2001; Witteman et al., 1986).

### Study Findings

3       Two studies examined the long-term PM-CAC association (Diez Roux et al., 2008; Hoffmann et

4   al., 2007). Diez Roux et al. (2008) studied 5,172 residents of Baltimore, MD; Chicago, IL; Forsyth Co,

5   NC; Los Angeles, CA; New York, NY; and St. Paul, MN (age range 45–84 yr; 53% female) at the

6   baseline exam of the MESA (2000–2002). In this cross-sectional ancillary study, the authors used spatio-

7   temporal modeling of pollutant concentrations, National Climatic Data Center climate, and U.S. Census

8   demographic data to impute 20-year average exposures to $PM_{2.5}$ and $PM_{10}$. They found that 10 μg/m$^3$

9   increases in $PM_{10}$ and $PM_{2.5}$ were associated with 1% (95% CI: -2 to 4) and 0.5% (95% CI: -2 to 3)

10   increases in the relative prevalence of CAC, respectively. Among the subset of 2,586 participants with

11   EBCT-identified calcification, corresponding increases in CAC were 0.5% (95% CI: -7 to 9) and 0.5%

12   (95% CI: -5 to 7) or approximately 1 (95% CI: -10 to 13) and 1 (95% CI: -13 to 16) Agatston units,

13   respectively. There was little evidence of effect modification by demographic, socioeconomic or clinical

14   characteristics.

15       Hoffman et al. (2007) studied 4,494 residents of Essen, Mülheim and Bochum, Germany (age

16   range: 45–74 yr; 51% female) at the baseline exam of the Heinz Nixdorf Recall Study (2000-2003). In

17   this cross-sectional study the authors used dispersion modeling of emissions, climate and topography data

18   to estimate one-year average exposure to $PM_{2.5}$. They found that a 10 μg/m$^3$ increase in $PM_{2.5}$ was

19   associated with a 43% (95% CI: 15-115) or 102 (95% CI: 77-273) Agatston increase in CAC. Differences

20   in strength of association between subgroups defined by demographic and clinical characteristics were

21   small.

22       Two studies examined the chronic PM-CIMT association (Diez Roux et al., 2008; Kunzli et al.,

23   2005). Diez Roux et al. (2008) used cross-sectional data from the MESA cohort (described previously)

24   and Kunzli et al. (2005) used cross-sectional data from the the Vitamin E Atherosclerosis Progression

25   Study (VEAPS) and B-Vitamin Atherosclerosis Intervention Trial (BVAIT).

26       Diez Roux et al. (2008) found that 10 μg/m$^3$ increases in 20-year average $PM_{10}$ and $PM_{2.5}$

27   concentrations were associated with 1% (95% CI: 0-1.4) and 0.5% (95% CI: 0-1) or approximately

28   8 (95% CI: 0-12) and 7 (95% CI: 0-14) μm increases in CIMT, respectively. Evidence of age-, gender-,

29   lipid-and smoking-related susceptibility was lacking in this context.

30       Kunzli et al. (2005) studied 798 residents of the greater Los Angeles, CA area (age >40 yr; 44%

31   female) at the baseline exams of two randomized, placebo-controlled clinical trials (VEAPS and BVAIT,

32   1998-2003). In this cross-sectional ancillary study of these extant cohorts, the authors used universal

1    kriging of $PM_{2.5}$ data from 23 state and local monitors operating in 2000 to estimate 1-year average

2    exposure to $PM_{2.5}$ at each participant's geocoded U.S. Postal Service ZIP code. They found that a

3    10 $\mu g/m^3$ increase in exposure was associated with a 4.2% (95% CI: -0.2 to 8.9) or approximately 32

4    (95% CI: -2 to 68) $\mu m$ increase in CIMT. In contrast to findings from the relatively large, ethnically

5    diverse, yet geographically overlapping MESA ancillary study described above, PM-related increases in

6    CIMT were two- to three-fold larger among older and female participants taking anti-hyperlipidemics in

7    this study. They were also higher in never than in current or former smokers.

8        In addition to examining the PM-CIMT association, Diez Roux et al. (2008) examined the chronic

9    PM-ABI association (Diez Roux et al., 2008). The authors found that 10 $\mu g/m^3$ increases in 20-year

10   average $PM_{10}$ and $PM_{2.5}$ concentratins were associated with 0 (95% CI: -0.003 to 0.004) and -0.001 (95%

11   CI: -0.005 to 0.005) mean differences in ABI, respectively. These largely null findings exhibited little

12   heterogeneity among participant subgroups and were similarly null when ABI was modeled as a

13   dichotomous outcome using a cutpoint of 0.9 units.

14      One study examined the chronic $PM_{2.5}$-AAC association in a residentially stable subset of 1,147

15   participants (mean age = 66 yr; 50% female) randomly selected from all MESA centers (except

16   Baltimore, MD) for enrollment in its Aortic Calcium Ancillary Study (Allen et al., in press). The authors

17   used kriging and inverse residence-to-monitor distance-weighted averaging of EPA AQS data to estimate

18   two-year mean exposures to $PM_{2.5}$. In cross-sectional analyses, the authors found that 10 $\mu g/m^3$ increases

19   in $PM_{2.5}$ exposures were associated with 6% (95% CI: -4 to 16) excess risk of AAC and 8% (95%

20   CI: -30 to 46) increases in AAC, i.e. approximately 50 (95% CI: -251 to 385) Agatston units. These

21   associations were stronger among users than non-users of anti-hyperlipidemics.

22      The ambient PM concentrations from these studies are characterized in Table 7-1.


## 7.2.1.2. Toxicological Studies

23      In the only study of this kind described in the 2004 PM AQCD, Suwa et al. (2002) conducted an

24   experiment to evaluate atherosclerosis progression in rabbits exposed to $PM_{10}$. The rabbits exposed to

25   $PM_{10}$ (5 mg/kg, 2 times/wk × 4 wk) demonstrated more advanced atherosclerotic lesions based on

26   phenotype and volume fraction in the left main and right coronary arteries. More extensive atherosclerosis

27   was also observed in the aorta of $PM_{10}$-exposed animals, with increased extracellular lipid pools and total

28   amount of lipids in the lesions. Although this study was conducted at a relatively high dose, it provided

29   the first experimental evidence that PM exposure may result in progression of atherosclerosis.

## CAPs

1    Sun et al. (2005) conducted a 6-month exposure of ApoE$^{-/-}$ mice to Tuxedo, NY CAPs from July
2    2004 to January 2005 and demonstrated an enhancement of atherosclerosis. Mice were exposed to PM$_{2.5}$
3    concentrated to roughly 85 μg/m$^3$ for 6 h/d×5 d/wk; the average exposure concentration when normalized
4    over the entire 6 month period (24 h/d×7d/wk) was 15.2 μg/m$^3$. PM$_{2.5}$ exposure had no effect on the net
5    concentrations of cholesterol or triglycerides. Plaque area in the aortic arch and abdominal aorta was
6    significantly increased in ApoE$^{-/-}$ mice exposed to CAPs on a high-fat diet compared to filtered air mice
7    fed high-fat chow (41.5% and 26.2%, respectively), and lipid content in the thoracic aorta reflected the
8    plaque area response with the PM-exposed high fat-chow group having greater lipid staining vs. the
9    control group on a high fat diet (30.0 and 20.0, respectively). Macrophage infiltration in the abdominal
10    aorta (primarily in the intimal and medial areas) was also observed in the groups exposed to CAPs.
11    Significant enhancement of 3-nitrotyrosine and inducible NOS were observed in the abdominal aorta in
12    the PM$_{2.5}$-exposed mice for the normal and high-fat chow groups. Furthermore, aortas from the PM$_{2.5}$-
13    exposed animals exhibited increased vasoconstrictor responsiveness to serotonin and reduced dilatation to
14    acetylcholine.

15    A recent study (Sun et al., 2008) that was part of the research described above (Sun et al., 2005)
16    investigated tissue factor (TF) expression in aortas, which is a major regulator of hemostasis and
17    thrombosis following vascular injury or plaque erosion. In PM$_{2.5}$-exposed ApoE$^{-/-}$ mice on a high-fat diet,
18    TF was significantly elevated in the plaques of aortic sections compared to air-exposed mice on the high-
19    fat diet. There was no difference in TF immunohistochemistry staining in the CAPs-exposed or control
20    groups fed normal chow. TF expression was generally detected in (1) the extracellular matrix surrounding
21    macrophages and foam cell-rich areas and (2) around smooth muscle cells. Vascular macrophage
22    infiltration was increased with PM$_{2.5}$ exposure independent of diet and was found predominantly in the
23    intimal surface and within the plaque.

24    Several other projects have examined the subchronic effects of PM and other air pollutants on
25    ApoE$^{-/-}$ mice. Chen and Nadziejko (2005) investigated histopathological changes in the aortas of both
26    ApoE$^{-/-}$ mice and the double-knockout ApoE$^{-/-}$/LDLR$^{-/-}$ mice following a 4-5 month (March, April or May
27    through September 2003) exposure to Tuxedo, NY CAPs. The average PM$_{2.5}$ exposure concentration
28    ranged from 110 to 131 μg/m$^3$. This study reported increased mortality in the double-knockout mice
29    exposed to air (n = 9) and CAPs (n = 11) and it appeared that the CAPs-exposed animals died earlier than
30    the air controls. At the end of exposure, the number of double-knockout mice with coronary artery disease
31    was greater in the CAPs-exposed group, with 7 of 10 having some degree of lipid deposition (compared
32    to 3 of 13 for the air group). The enhancement of aortic lesion area was consistent with the findings of
33    Sun et al. (2005) and both lesion area and lesion cellularity were enhanced by CAPs exposure in the male

1 double-knockout mice, although there was no change in lipid content and there were no differences in
2 grossly discernible plaque with mice on the high-fat diet. The percentage of aortic intimal surface covered
3 by atherosclerotic lesions in ApoE$^{-/-}$ mice was increased by 57% in the CAPs-exposed group compared to
4 the air-exposed group.

5      One new study of fine or ultrafine PM derived from traffic was conducted. Araujo et al. (2008)
6 compared the relative impact of ultrafine (0.01-0.18 μm) and fine (0.01-2.5 μm) PM inhalation on aortic
7 lesion development in ApoE$^{-/-}$ mice following a 40-day exposure (5 h/d×3 d/wk for 75 total h). Animals
8 were on a normal chow diet and exposed to CAPs from November through December 2005 in a mobile
9 inhalation laboratory that was parked 300 m from the 110 Freeway in downtown Los Angeles. Particles
10 were concentrated to ~440 μg/m$^3$ for the fine exposures and to ~110 μg/m$^3$ for the ultrafine exposures,
11 representing a roughly 15-fold concentration from ambient levels; the number concentration of PM in the
12 fine and ultrafine chambers were roughly equivalent (4.56×10$^5$ and 5.59×10$^5$ particles/cm$^3$, respectively).
13 The authors noted significant increases in plaque size (estimated by lesions at the aortic root) in the
14 ultrafine PM-exposed mice compared to both control and fine PM-exposed, with no difference observed
15 between control and fine PM-exposed mice. The lesions were largely comprised of macrophage
16 infiltration with intracellular lipid accumulation. Increased total cholesterol measured at the end of the
17 exposure protocol was observed only in the fine PM group. High density lipoprotein isolated from the
18 ultrafine PM-exposed mice demonstrated decreased HDL anti-inflammatory protective capacity against
19 LDL-induced monocyte chemotactic activity in an in vitro assay. The livers from the ultrafine
20 PM-exposed mice demonstrated significant increases in lipid peroxidation and several stress-related gene
21 products (catalase, glutathione S-transferase Y$_a$, NADPH-quinone oxidoreductase1, superoxide
22 dismutase 2). Thus, ultrafine PM in these exposures had a substantially greater impact on the systemic
23 response than did fine PM, despite 85% of the total particle number concentration for PM$_{2.5}$ being
24 comprised of ultrafine PM. The authors suggested that the proportional difference in organic carbon
25 composition of the two atmospheres or increased particle surface area may be responsible for the
26 observed differences in biological outcome.

### PM$_{10}$

27      A study employing young BALB/c mice examined the effects of a 4 month exposure (24 h/d ×
28 7 d/wk) to ambient air on arterial histopathology (Lemos et al., 2006). Outdoor exposure chambers were
29 located in downtown Sao Paulo, Brazil next to streets of high traffic density and the gases were not
30 filtered. In the control chamber, PM$_{10}$ and NO$_2$ were filtered with 50% and 75% efficiency, respectively.
31 The average pollutant concentrations were 2.06 ppm for CO (8-h mean), 104.75 μg/m$^3$ for NO$_2$ (24-h
32 mean), 11.07 μg/m$^3$ for SO$_2$ (24-h mean), and 35.52 μg/m$^3$ for PM$_{10}$ (24-h mean) at a monitoring site

within 100 m of the inhalation chambers. The pulmonary and coronary arteries demonstrated significant decreases in lumen/wall (L/W) ratio for animals exposed to the entire ambient mixture compared to controls, indicating thicker walls in these vessels. There was no difference reported for the L/W ratio in renal arteries. Morphologic examination suggested that the increases in L/W ratio were due to muscular hypertrophy rather than fibrosis. The results of this study indicate vascular remodeling of the pulmonary and coronary arteries, as opposed to changes in tone.

To examine the role of systemic inflammation and recruitment of monocytes into plaque tissue as a possible pathway for accelerated atherosclerosis, Yatera et al. (2008) exposed female Watanabe heritable hyperlipidemic rabbits (42 wks old) to Ottawa $PM_{10}$ (EHC-93) via intratracheal instillation (5 mg/rabbit; approximately 1.56 mg/kg) twice a week for 4 weeks. Transfusion of whole blood harvested to from exposed and non-exposed animals to donor rabbits supplied labeled monocytes for assessment of monocyte recruitment from the blood to the aortic wall. The fraction of aortic surface and volume of aortic wall taken up by atherosclerotic plaque was increased and the number of labeled monocytes in the atherosclerotic plaques was elevated in rabbits exposed to $PM_{10}$. In addition, labeled monocytes were attached onto the endothelium overlying atherosclerotic plaques and the number that migrated into the smooth muscle underneath plaques in aortic vessel walls was greater with $PM_{10}$ exposure compared to control. These responses were not observed in normal vessel walls. ICAM-1 and VCAM-1 expression was elevated in atherosclerotic lesions, likely indicating enhanced monocyte adhesion to endothelium and migration into plaques. Monocytes in plaque tissue stained with immunogold demonstrated foam cell characteristics, which were more numerous in the rabbits exposed to $PM_{10}$.

## Gasoline Exhaust

Lund and colleagues (2007) used whole emissions from gasoline exhaust to investigate changes in the transcriptional regulation of several gene products with known roles in both the chronic promotion and acute degradation/destabilization of atheromatous plaques. These 50-day exposures (6 h/d×7 d/wk) employed ApoE$^{-/-}$ mice on high-fat chow and the concentrations of the high exposure group were 61 $\mu g/m^3$ for PM, 19 ppm for $NO_X$, 80 ppm for CO, and 12.0 ppm for total hydrocarbons. The average particle number median diameter was approximately 15 nm (McDonald et al., 2007). Dilutions of gasoline engine emissions induced a concentration-dependent increase in transcription of matrix metalloproteinase (MMP) isoform 9, ET-1, and HO-1 in aortas; MMP-3 and -9 mRNA levels were only increased in animals in the highest exposure group. Strong increases in oxidative stress markers (nitrotyrosine and TBARS) in the aortas were also observed. However, using a high-efficiency particle trap, they established that most of the effects were caused by the gaseous portion of the emissions and not the particles. This study did not directly address lesion area and is not directly comparable to the studies

1 by Sun et al. (2005), Chen and Nadziejko (2005), and Araujo et al. (2008), although it suggests that the

2 gases are important contributors to overall toxicity.


# 7.2.2. Thromboembolism

3      The relationship between PM exposure and health outcomes indicative of thrombosis or embolism

4 formation was evaluated in one epidemiologic study. Prothrombin and partial thomboplastin times (PT;

5 PTT) are laboratory measures of hemostasis. PT and PTT measure the extrinsic and intrinsic blood

6 coagulation pathways, the former activated in response to blood vessel injury, the latter, key to subsequent

7 amplification of the coagulation cascade and propagation of thrombus (Mackman et al., 2007).


## 7.2.2.1. Epidemiologic Studies

8      Baccarelli et al. (2007b) studied 2,081 residents of the Lombardy region of Italy (age range 18-84

9 yr; 56% female). In this case-control study of 871 patients with ultrasonographically or venographically

10 diagnosed lower extremity deep vein thrombosis (DVT) and 1,210 of their healthy friends or relatives

11 (1995-2005), the authors used arithmetic averaging of $PM_{10}$ data available at 53 monitors in nine

12 geographic areas to estimate one-year average residence-specific exposures. They found that a 10 μg/m$^3$

13 increase in $PM_{10}$ was associated with -0.09 (95% CI: -0.16 to 0) and -0.18 (95% CI: -0.35 to 0) decreases

14 in standardized correlation coefficients for PT as well as 0.02 (95% CI: -0.05 to 0.06) and -0.11 (95%

15 CI: -0.29 to 0.12) decreases in standardized correlation coefficients for activated partial thromboplastin

16 time (aPTT) among cases and controls, respectively. Shortened PT and aPTT reflect hypercoagulability.

17 However, patients with DVT who were taking heparin or coumarin anticoagulants were not asked to stop

18 taking them before measurement of PT and aPTT. Moreover, PT was neither adjusted for differences in

19 reagents used to determine it nor conventionally reported as the International Normalized Ratio (INR).

20 The ambient PM concentrations from this study are characterized in Table 7-1.


# 7.2.3. Systemic Inflammation and Blood Coagulation

## 7.2.3.1. Toxicological Studies

21      In addition to the $PM_{2.5}$ study above that showed increased TF expression (an important initiator of

22 thrombosis) in aortas of ApoE$^{-/-}$ following subscronic CAPs exposure (Sun et al., 2008), three recent

23 studies conducted by the same group examined hematology and clotting parameters in rats and mice

24 exposed to DE, gasoline exhaust, or HWS for 1 week or 6 months (Reed et al., 2004; 2006; 2008). In all

1    studies, male and female F344 rats were exposed to the mixtures by whole-body inhalation for 6 h/day,

2    7 day/wk. The target PM concentrations in the diesel and HWS studies were 30, 100, 300, and

3    1000 μg/m$^3$ (Reed et al., 2004; 2006); the dilutions for the gasoline exhaust were 1:10, 1:15 or 1:90 and

4    filtered PM at the 1:10 dilution (Reed et al., 2008). PM mass in the latter study ranged from 6.6 to

5    59.1 μg/m$^3$, with the corresponding number concentration between $2.6 \times 10^4$ and $5.0 \times 10^5$ particles/cm$^3$.

6    Respiratory effects for these studies are presented in Section 7.3.4.

7         Male and female rats exposed to DE at the highest concentration (NO concentration 45.3 ppm; NO$_2$

8    concentration 4.0 ppm; CO concentration 29.8 ppm; SO$_2$ concentration 365 ppb) for 6 months

9    demonstrated decreased serum Factor VII, but no change in plasma fibrinogen or TAT (Reed et al., 2004).

10   Together, these findings likely do not support an exposure-related stimulation of blood coagulation. White

11   blood cells were decreased only in female rats in the highest exposure group.

12        In male rats exposed to HWS, the mid-low group (PM concentration 113 μg/m$^3$; NO concentration

13   0 ppm; NO$_2$ concentration 0 ppm; CO concentration 1832.3 ppm; SO$_2$ concentration 0 ppb) had the

14   greatest responses in hematology parameters, including increased hematocrit, hemoglobin, lymphocytes,

15   and decreased segmented neutrophils (Reed et al., 2006). Platelets were elevated in male and female rats

16   after 1 week of exposure, but this response returned to control values following the 6 month exposure. No

17   changes were observed for any coagulation markers at 6 months.

18        Similar to the responses observed with HWS, male and female rats in the mid and high gasoline

19   exhaust exposure groups (NO concentrations 11.9 and 18.4 ppm; NO$_2$ concentrations 0.5 and 0.9 ppm;

20   CO concentration 73.2 and 107.3 ppm; SO$_2$ concentration 0.38 and 0.62 ppm, respectively) demonstrated

21   elevated hematocrit and hemoglobin; red blood cell count was also elevated in these groups (Reed et al.,

22   2008). The only response that appeared somewhat dependent on the presence of particles was increased

23   RBC in female rats at 6 months, although the authors attributed the observed increases to the high

24   concentration of CO.

25        Collectively, these studies do not indicate robust systemic inflammation or coagulation responses in

26   F344 rats following 6-month exposures to diesel, HWS, or gasoline exhaust. The limited effects that were

27   observed could possibly be due to the varying gas concentrations in the exposure mixtures.

## 7.2.4. Renal and Vascular Function

28        Two recent epidemiologic studies have tested associations between PM exposure and indicators of

29   renal (urinary albumin to creatinine ratio [UACR]) or vascular (blood pressure) function. UACR is a

30   measure of urinary albumin excretion (National Kidney Foundation, 2008). When calculated as the ratio

31   of albumin to creatinine concentrations in untimed ("spot") urine samples, UACR approximates 24-h

urinary albumin excretion and can be used to identify albuminuria, a marker of generalized vascular

endothelial damage (Xu et al., 2008). Values $\geq$ 30 mg/g (3.5 mg/mmol) and $\geq$ 300 mg/g (34 mg/mmol)

usually define micro- and macroalbuminuria, both of which are associated with increases in CVD

incidence and mortality (Bigazzi et al., 1998; Deckert et al., 1996; Dinneen and Gerstein, 1997; Gerstein

et al., 2001; Mogensen, 1984). Several researchers have called the dichotomization of albuminuria into

question, observing that there is no threshold below which risk of cardiovascular and end-stage kidney

disease disappears (Forman and Brenner, 2006; Knight and Curhan, 2003; Ruggenenti and Remuzzi,

2006).

Systolic, diastolic, pulse, and mean arterial blood pressures (SBP; DBP; PP; MAP) in mm Hg have

also been used as measures of cardiovascular disease. Franklin et al. (1997) suggested that SBP and PP

were the only two measures predictive of carotid stenosis in a multivariable analysis considering all four

measures (Franklin et al., 1997), whereas Khattar et al. (2001) suggested that their prognostic significance

in hypertensive populations may differ by age, with SBP and PP being most predictive among those $\geq$ 60

and DBP among those <60 years old (Khattar et al., 2001).

### 7.2.4.1. Epidemiologic Studies

One epidemiologic study examined the long-term PM-UACR association (O'Neill et al., 2007).

Although this study also was based on MESA ancillary study data described previously (Diez Roux et al.,

2008), its cross-sectional and longitudinal analyses focused on a subset of 3,901 MESA participants

(mean age = 63 yr; 52% female) with complete covariate, outcome and exposure data at their first through

third exams (2000-2004). In cross-sectional analyses, the authors found that after adjustment for

demographic and clinical characteristics, 10 μg/m$^3$ increases in 20-year imputed exposures to $PM_{2.5}$ and

$PM_{10}$ were associated with (1) 0.002 (95% CI: -0.048 to 0.052) and -0.002 (95% CI: -0.038 to 0.035)

mean differences in baseline log AUCR; and (2) -2% (95% CI: -16 to 14) and -2% (95% CI: -13 to 10)

decreases in the baseline prevalence of microalbuminuria (defined in this setting as $\geq$ 25 mg/g). These

largely null cross-sectional findings mirrored those based on the study's shorter-term (30- and 60-day)

$PM_{2.5}$ and $PM_{10}$ exposures. Moreover, longitudinal analyses revealed only a weak association between

three-year change in log UACR and 20-year $PM_{10}$ exposure. Evidence of effect modification by

demographic and geographic characteristics was negligible in cross-sectional and longitudinal analyses

alike.

In another study, Auchincloss et al. (2008) focused on automated, oscillometric,

sphygmomanometric measures of blood pressures in mm Hg (SBP; DBP; PP; MAP). Like O'Neill et al.

(2007), Diez Roux et al. (2008) and Allen et al (in press). Auchincloss et al. (2008) based their

examination on the previously described MESA population. The authors studied 5,112 participants (age

1    range = 45-84 yr; 52% female) who were free of clinically manifested CVD at their baseline exam in one

2    of six, primarily urban U.S. locations (2000-2002). In this cross-sectional study, they used arithmetic

3    averaging of EPA AQS $PM_{2.5}$ data available at the monitor nearest to each participant's geocoded U.S.

4    Postal Service ZIP code centroid to estimate 30- and 60-day average exposures to $PM_{2.5}$. They found that

5    a 10 μg/m$^3$ increase in 60-day average $PM_{2.5}$ exposure was associated with 1.20 (95% CI: -1.0 to 3.4) to -

6    0.1 (95% CI: -1.2 to 1.0), 1.3 (95% CI: -0.4 to 2.9), and 0.4 (95% CI: -1.01 to 1.7) mm Hg increases in

7    SBP, DBP, PP and MAP. Associations were slightly stronger for 30-day average $PM_{2.5}$ exposure,

8    particularly for SBP and PP among participants with hypertension or taking anti-hypertensives, during

9    warmer weather, in the presence of high $NO_2$, residing ≤ 300 m from a highway, or surrounded by higher

10    road density.

11       Finally, Calderon-Garciduenas et al. (2007) studied ET-1 and pulmonary artery pressure in two

12    cohorts of healthy children aged 6-13 years old in Mexico. The exposed cohort consisted of children from

13    two areas in Mexico City with different pollution profiles. The control group was drawn from a less

14    polluted area in Mexico (Polotitlan). Children enrolled in the study were lifelong residents in their

15    community, and, lived and attended school within 5 miles of one of the air monitoring stations used to

16    estimate ambient exposures. Cardiovascular function was assessed using Doppler echocardiography and

17    fasting blood was collected and analyzed for complete blood count and ET-1. The authors reported that

18    long-term exposure to air pollution (e.g. residence and school attendance in Mexico City compared to the

19    control city) was associated with elevated mean pulmonary arterial pressure (17.3 ± 0.5 vs. 14.6 ±

20    -0.4 mmHg, p<0.01) and increased ET-1 (2.24 ± -0.12 vs. 1.23 ± -0.06, $p<0.001$). ET-1 levels were

21    significantly higher in children from the Northeast section of Mexico City compared to children from the

22    Southwest section of the city. In order to distinguish the effect of $PM_{2.5}$ from $PM_{10}$ and ozone

23    investigators examined the differences in pollution profiles of these two areas of Mexico City. $PM_{2.5}$ level

24    in the Northeast was significantly higher than in the Southwest. This was not true for $PM_{10}$ and ozone

25    level, which was higher in the Southwest. Further, cumulative $PM_{2.5}$ level 7 days prior to the blood draw

26    was correlated with increased levels of circulating ET-1 (r = 0.28, p = 0.03). PM concentrations from

27    these epidemiologic studies are characterized in Table 7-1.

**Table 7-1.** Characterization of ambient PM concentrations from studies of subclinical measures of cardiovascular diseases.

| Reference | Location | Mean Concentration (µg/m³) | Upper Percentile Concentrations (µg/m³) |
|---|---|---|---|
| *PM₁₀* | | | |
| Diez-Roux (2008) | MESA: 6 Cities U.S. | 20 year imputed mean: 34 | NR |
| O'Neill et al. (2007) | MESA: 6 Cities U.S. | Long-Term Exposure: 1982-2002: 34.7 1982-1987: 40.5 1988-1992: 38 1993-1997: 30.6 1998-2002: 29.7 Previous Month: 27.5 | NR |
| Baccarelli et al. (2008) | Lombardy Italy | Annual avg: 41 | NR |
| Rosenlund et al. (2006) | Stockholm, Sweden | 30-y avg PM₁₀ (traffic) Cases: 2.6 Controls: 2.4 | 5th-95th %: 0.5-6 0.6-5.9 |
| *PM₂.₅* | | | |
| Hoffman et al. (2007) | HNRS, 3 Cities Germany | Annual avg: 22.8 | NR |
| Allen et al. (in press) | MESA: 5 Cities | Annual avg: 15.8 | Min-Max: 10.6-24.7 |
| Kunzli et al. (2005) | VEAPS BVAIT | Annual avg: 20.3 | Min-Max: 5.2-26.9 |
| Auchincloss et al. (2008)` | MESA: 6 Cities | Prior 30 d: 16.8 Prior 60 d: 16.7 | NR |
| O'Neill et al. (2007) | MESA: 6 Cities U.S. | Previous Month: 16.5 | NR |
| Diez-Roux et al. (2008) | MESA: 6 Cities U.S. | 20-y imputed mean: 21.7 | NR |

MESA: Multi-Ethnic Study of Atherosclerosis
HNRS: Heinz Nixdorf Recall Study
VEAPS: Vitamin E Atherosclerosis Progression Study
BVAIT: B-Vitamin Atherosclerosis Intervention Trial
WHI: Womens Health Initiative

## 7.2.4.2. Toxicological Studies

In a CAPs study of shorter duration (10 weeks; 6 h/d×5 d/wk) in Tuxedo, NY (mean chamber concentration of PM₂.₅ of 79.1 µg/m³), there was no difference in mean arterial pressure (MAP) in Sprague Dawley rats between groups (Sun et al., 2008). When angiotensin II (Ang II) was infused during the last week of exposure to induce systemic hyptertension, the MAP slope was consistently greater in the CAPs-exposed rats compared to the filtered air group. Furthermore, thoracic aortic rings were more responsive to phenylephrine-induced constriction and less responsive to ACh-induced relaxation in the PM+Ang II vessels. In contrast to the latter findings, the relaxation response was exaggerated in the PM+Ang II aortic segments with a Rho-kinase (ROCK) inhibitor. Superoxide production in aortic rings increased in the PM+Ang II group compared to the filtered air group and the addition of NAD(P)H oxidase inhibitor (apocymin) or a NOS inhibitor (L-NAME) attenuated the superoxide generation. The levels of tetrahydrobiopterin (BH₄) were decreased in mesenteric vasculature and the heart by 46% and

1 41% in the PM+Ang II group compared to controls, respectively; furthermore, levels of $BH_4$ in the liver

2 were similarly reduced, which is consistent with a systemic effect of CAPs. Together, these findings

3 indicate that CAPs potentiate Ang II-induced hypertension and alter vascular reactivity, perhaps through

4 activated NADPH oxidase and eNOS uncoupling that result in oxidative stress generation and triggering

5 of the Rho/ROCK signaling pathway.


## 7.2.5. Autonomic Function

### Toxicological Studies

6 Hwang et al. (2005) and Chen and Hwang (2005) used radiotelemetry to examine the chronic

7 changes in HR, HRV, physical activity (PA), and temperature ($T_{co}$) resulting from the same CAPs

8 exposures described above (Chen and Hwang, 2005). The overall average CAPs exposure concentration

9 was 133 μg/m$^3$ and results indicate differing responses to CAPs between ApoE$^{-/-}$ mice and their genetic

10 background strain, C57BL/6J mice (Hwang et al., 2005). Using the time period of 1:30 to 4:30 a.m.,

11 C57BL/6J mice showed a 0.4°C $T_{co}$ increase over the entire exposure period, with HR only demonstrating

12 elevations over the last month of exposure. In contrast, ApoE$^{-/-}$ mice had chronic decreases of 1.0°C for

13 $T_{co}$ and a 33.8 beat/min for HR. Changes in HRV (SDNN and rMSSD) were somewhat more complicated,

14 with biphasic responses in ApoE$^{-/-}$ mice over the 5 month period (initial increase over first 6 wk, decrease

15 over next 12 wk, and slight upward turn for remainder of the study) (Chen and Hwang, 2005). Increasing

16 linear trends were observed in C57BL/6J mice for SDNN and rMSSD. The average CAPs concentration

17 for the HRV study was 110 μg/m$^3$. However, only 3 C57BL/6J mice in the exposure group were included

18 in the analysis compared to 10 ApoE$^{-/-}$ animals, thus making it difficult to interpret the C57BL/6J mice

19 responses (Chen and Hwang, 2005; Hwang et al., 2005).


## 7.2.6. Clinical Outcomes in Epidemiologic Studies

20 Several epidemiologic studies of U.S. and European populations have examined associations

21 between long-term PM exposures and clinical CVD events (Baccarelli et al., 2008; Hoffmann et al., 2006;

22 Maheswaran et al., 2005a, b; Miller et al., 2007b; Rosenlund et al., 2006; Solomon et al., 2003; Zanobetti

23 and Schwartz, 2007). Results from these studies are summarized in Figure 7-1. The ambient PM

24 concentrations from these studies are characterized in Table 7-1.

## Coronary Heart Disease (CHD)

1    Several studies examined the chronic PM (or BS)-CHD association (Hoffmann et al., 2006;

2    Maheswaran et al., 2005a; Miller et al., 2007b; Rosenlund et al., 2006; Solomon et al., 2003; Zanobetti

3    and Schwartz, 2007). In these studies, CHD was variably defined and included incident (versus prevalent)

4    disease and validated (versus hospital-coded or self-reported) history of angina pectoris, myocardial

5    infarction (MI), coronary artery revascularization (bypass graft; angioplasty; stent; atherectomy), and

6    congestive heart failure (CHF). Results pertaining to death from CHD are described in Section 7.6.

7    Puett et al. (2008) studied incident, validated CHD, CHD death, and non-fatal MI among 66,250

8    female residents (mean age = 62 yr) of metropolitan statistical areas in thirteen northeastern U.S. states

9    who were enrolled in the Nurses' Health Study (NHS, 1992-2002). In this prospective cohort study of

10   women without a history of non-fatal MI at baseline (maximum duration of follow-up = 4 yr), the authors

11   used two-stage, spatially smoothed, land use regression to estimate residence-specific, one-year moving

12   average $PM_{10}$ exposures from U.S. EPA AQS and emissions, IMPROVE, and Harvard University monitor

13   data. They found a 10 $\mu/m^3$ increase in $PM_{10}$ exposure was associated with a 30% (95% CI: 0 -71)

14   increase in CHD death. Associations with CHD death were higher in the obese and in the never smokers.

15   The association of $PM_{10}$ with incident CHD was non-significantly elevated and the association of $PM_{10}$

16   with MI was close to the null value.

17   Miller et al. (2007b) studied incident, validated MI, revascularization, and CHD death, both

18   separately and collectively, among 58,610 post-menopausal female residents of 36 U.S. metropolitan

19   areas (age range = 50-79 yr) enrolled in the Women's Health Initiative Observational Study (WHI OS,

20   1994-1998). In this prospective cohort study of participants free of CVD at baseline (median duration of

21   follow-up = 6 yr), the authors used arithmetic averaging of year 2000 EPA AQS $PM_{2.5}$ data available at

22   the monitor nearest to each participant's geocoded U.S. Postal Service five-digit ZIP code centroid to

23   estimate one-year average exposures. They found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was

24   associated with 6% (95% CI: -15 to 34), 20% (95% CI: 0 to 43) and 21% (95% CI: 4 to 42) increases in

25   the overall hazard of MI, revascularization, and their combination with CHD death, respectively. Hazards

26   were higher within than between cities and in the obese.
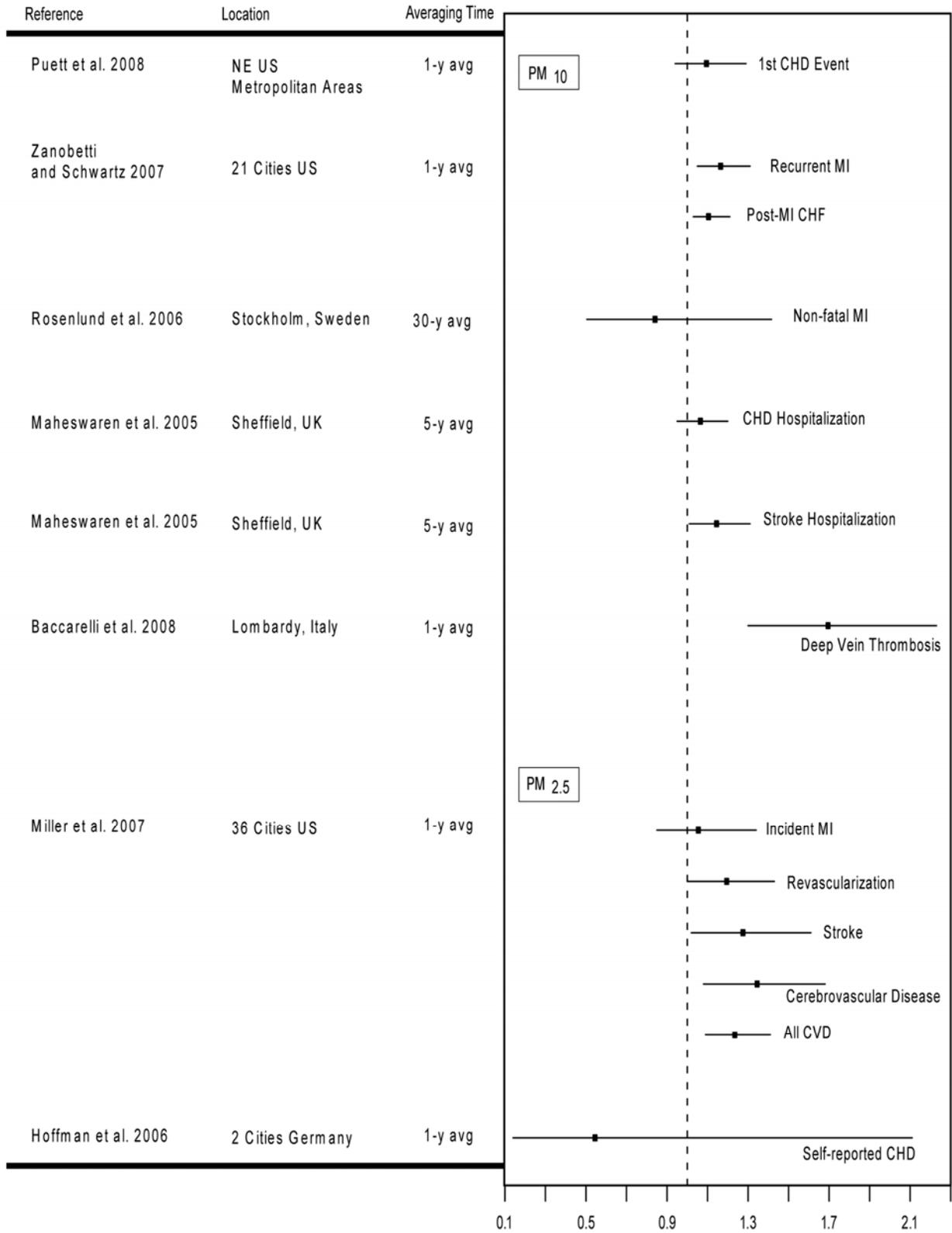
**Figure 7-1.** Risk estimates for the associations of clinical outcomes with long-term exposure to ambient $PM_{2.5}$ and $PM_{10}$

1     Zanobetti and Schwartz (2007) studied ICD-coded recurrent MI (ICD-9 410) and post-infarction

2 CHF (ICD-9 428) among 196,131 Medicare recipients (age ≥ 65 yr; 50% female) discharged alive

3 following MI hospitalization in 21 cities from 12 U.S. states (1985-1999). In this ecologic, open cohort

4 study of re-hospitalization among MI survivors (mean duration of follow-up = 3.6 and 3.7 yr for MI and

5 CHF, respectively), the authors used arithmetic averaging of EPA AQS $PM_{10}$ data available in the county

6 of hospitalization to estimate one-year average exposures. They found that a 10 μg/m$^3$ increase in $PM_{10}$

7 exposure was associated with 17% (5%, 31%) and 11% (3%, 21%) increases in the hazard of recurrent MI

8 and post-infarction CHF, respectively. Hazards were somewhat higher among persons aged >75 years.

9     Hoffman et al. (2006) studied self-reported CHD (MI or revascularization) among 3,399 residents

10 of Essen and Mülheim, Germany (age range = 45-75 yr; 51% female) at the baseline exam of the Heinz

11 Nixdorf Recall Study (2000-2003) introduced previously. In this cross-sectional ancillary study, the

12 authors used dispersion modeling of emissions, climate and topography data to estimate one-year average

13 exposure to $PM_{2.5}$ (mean = 23.3 μg/m$^3$). They found that after adjustment for geographic, demographic

14 and clinical characteristics, a 10 μg/m$^3$ increase in exposure was associated with a -45% (-86%, 211%)

15 decrease in the odds of prevalent CHD.

16     Rosenlund et al. (2006) studied 2,938 residents of Stockholm County, Sweden (age range = 45-70

17 yr; 34% female). In this case-control study of 1,085 patients with their first, validated non-fatal MI and an

18 age-, gender- and catchment-stratified random sample of 1,853 controls without MI (1992-1994), the

19 authors used street canyon-adjusted dispersion modeling of emissions data to estimate 30-year average

20 exposure to $PM_{10}$ (median = 2.4 μg/m$^3$). They found that the OR for prevalent MI associated with a 10

21 μg/m$^3$ increase in $PM_{10}$ was 0.85 (95% CI: 0.50-1.42). The OR for fatal MI was somewhat larger.

22     In the study of 1030 census enumeration districts in Sheffield, UK described previously,

23 Maheswaran et al. (2005a) studied 11,407 ICD-10-coded emergency HAs for CHD (I20-25) among

24 199,682 residents (age ≥ 45 yr; 45% female). In this ecologic study, the authors used dispersion modeling

25 of emissions and climate data to estimate five-year average exposure to $PM_{10}$. They found that after

26 adjusting for smoking prevalence, controlling for socioeconomic factors, and smoothing, the age- and

27 gender-standardized rate ratios for CHD admission were 1.01 (0.92, 1.11), 1.04 (0.93, 1.15), 0.97 (0.87,

28 1.08), and 1.07 (0.95, 1.20) across $PM_{10}$ quintiles. The linear trend was somewhat stronger for CHD

29 mortality (see Section 7.3).

## *Stroke*

30     Two studies examined the long-term PM-stroke association (Maheswaran et al., 2005b; Miller et

31 al., 2007b). The former examined emergency room HAs in Sheffield, UK using an ecologic design and

1    the latter is based on the prospective cohort study of the WHI OS population (both introduced

2    previously).

3        Miller et al. (2007b) found a 10 μg/m$^3$ increase in one-year average PM$_{2.5}$ exposure was associated

4    with 28% (95% CI: 2-61), 35% (95% CI: 8-68) and 24% (95% CI: 9-41) increases in the overall hazard of

5    validated stroke, cerebrovascular disease, and a combined outcome, CVD (MI; revascularization; stroke;

6    CHD death; cerebrovascular disease), respectively. Hazards were higher within than between cities. For

7    the combined CVD outcome, they also were also higher among participants at higher than lower quintiles

8    of body mass index, waist-to-hip ratio, and waist circumference. Counter to the authors' hypothesis, the

9    PM$_{2.5}$-CVD association was nonetheless stronger among non-diabetic than diabetic participants.

10        In the study of 1030 Census of enumeration districts in Sheffield, UK described previously,

11    Maheswaran et al. (2005b) studied 5,122 ICD-10-coded emergency hospital admissions for stroke (I60-

12    69) among 199,682 residents (age ≥ 45 yr; 45% female) of 1,030 census enumeration districts in

13    Sheffield, UK (1994-1999). In this ecologic study, the authors used dispersion modeling of emissions and

14    climate data to estimate five-year average exposure to PM$_{10}$. They found that the age- and gender-

15    standardized rate ratios for stroke admission were 1.05 (95% CI: 0.94-1.17), 1.07 (95% CI: 0.95-1.20),

16    1.06 (95% CI: 0.94-1.20), and 1.15 (95% CI: 1.01-1.31) across PM$_{10}$ quintiles. Linear trend was

17    somewhat stronger for stroke mortality (see Section 7.6).

### *Deep Vein Thrombosis*

18        The Italian case-control study (introduced in Section 7.2.1.2) also examined the chronic PM$_{10}$-DVT

19    association (Baccarelli et al., 2008). The authors found that a 10 μg/m$^3$ increase in one-year average PM$_{10}$

20    exposure was associated with an OR of 1.7 (95% CI: 1.30–2.23) for 70% (30%, 223%) for DVT increase

21    in the odds of DVT, a finding consistent with the decreases in PT and aPTT also observed among controls

22    in this context. Strength of the PM$_{10}$-DVT association was weaker among women and among users of oral

23    contraceptives, hormone therapy, or either class of endocrinologic therapy.

## 7.2.7. Overall Summary and Causal Determination

### 7.2.7.1. PM$_{10}$

24        PM$_{2.5}$ has been the focus of the majority of new research on the long-term effects of exposure to

25    ambient PM and studies of PM$_{10}$ are relatively few. Within this small body of literature, the epidemiologic

26    evidence is not consistent. Two recent epidemiologic studies of the effect of long-term exposure to

27    ambient PM$_{10}$ report large increases in CVD morbidity from recurrent MI, post-infarction CHF and DVT.

1   Two additional studies failed to find meaningful associations with clinical cardiovascular outcomes and

2   epidemiologic studies of pre-clinical markers of cardiovascular diseases reported largely null findings.

3   However, two toxicological studies, including one exposing mice to ambient air (including gasses) have

4   indicated a possible role for $PM_{10}$ in the development of atherosclerosis. Methods used in the

5   toxicological (e.g. inhalation versus intratracheal installation) and epidemiologic (e.g. variable exposure

6   assessment strategies) were not entirely comparable limiting our ability to fully assess consistency within

7   and coherence across disciplines. However, in light of two epidemiologic studies showing large

8   associations, **the evidence is determined to be suggestive but not sufficient to infer a causal**

9   **relationship.**

### Atherosclerosis

10  Several measures of atherosclerosis were examined in the epidemiologic study of the MESA

11  cohort, including CAC, CIMT, and ABI (Diez Roux et al., 2008). Overall, associations were largely null,

12  with the exception of a rather weak associations of $PM_{10}$ with CIMT. There were no toxicological studies

13  included in the 2004 PM AQCD that evaluated atherosclerosis development or progression following

14  subchronic or chronic $PM_{10}$ exposure. One new study exposed mice to ambient air (including gases) and

15  reported decreases in lumen/wall ratio of arteries. A second study demonstrated increased plaque surface

16  and volume in aortas of rabbits exposed to $PM_{10}$ (EHC-93) via intratracheal instillation, as well as

17  increased monocyte recruitment into these plaques.

### Renal and Vascular Function

18  One epidemiologic study of UACR was conducted (O'Neill et al., 2007). Findings from this study

19  were largely null with the exception of a weak association of three-year change in log UACR and 20 year

20  $PM_{10}$ (O'Neill et al., 2007).

### Thromboembolism

21  Decreases in PT and aPTT were reported in one epidemiologic study of DVT cases and controls in

22  Lombardy Italy (Baccarelli et al., 2008).

### Clinical Outcomes in Epidemiologic Studies

23  Since 2002, several studies of populations in the U.S. and Europe have examined associations

24  between CVD morbidity and chronic $PM_{10}$ exposure. Only Puett et al. (2008), Rosenlund et al. (2006) and

25  Baccarelli et al. (2008a) examined hospitalization for validated events. Other investigators relied on ICD

26  codes (Maheswaran et al., 2005a, b; Zanobetti and Schwartz, 2007).

1     With the exception of Puett et al. (2008), a prospective cohort study restricted to women, the

2     populations under study were ≥ 45 years of age and almost equally balanced in their ratio of men to

3     women. The studies employed a range of designs including ecologic (Maheswaran et al., 2005a, b), case-

4     control (Baccarelli et al., 2008; Rosenlund et al., 2006) and open cohort (Zanobetti and Schwartz, 2007).

5     Definitions of chronic $PM_{10}$ exposure were based on either U.S. EPA AQS monitor data (Diez Roux et al.,

6     2008; O'Neill et al., 2007; Zanobetti and Schwartz, 2007), a combination of monitoring and emissions

7     data (Puett et al., 2008) or European emissions (Maheswaran et al., 2005a, b; Rosenlund et al., 2006), or

8     monitor data (Baccarelli et al., 2008). Duration of chronic $PM_{10}$ exposure varied across studies.

9     The studies collectively present somewhat inconsistent an evidence of association between CVD

10    morbidity and chronic $PM_{10}$ exposure. Zanobetti and Schwartz (2007) and Baccarelli et al. (2008a) found

11    large increases in the adjusted risk of recurrent MI, post-infarction CHF, and DVT with standardized

12    increments in $PM_{10}$. Puett et al. (2008) reported large increases in the risk of CHD death but not incident

13    CHD or non-fatal MI. Maheswaran et al. (2005b) and Rosenlund et al. (2006) did not find association

14    between $PM_{10}$ and risk of hospitalization for stroke, CHD, or MI. The striking evidence for effect

15    modification of the $PM_{10}$-DVT association by gender and endocrinologic therapy presented by Baccarelli

16    et al. (2008a) has not been observed again within this body of literature.

### 7.2.7.2. $PM_{10-2.5}$

17    No epidemiologic or toxicological studies of long-term exposure to ambient $PM_{10-2.5}$ have been

18    conducted to date. **Evidence is inadequate to infer the presence or absence of a causal relationship.**

### 7.2.7.3. $PM_{2.5}$

19    Epidemiologic evidence of the adverse effect of $PM_{2.5}$ on subclinical markers of atherosclerosis is

20    available from the majority of recent studies on this topic. In addition, a large U.S. study reports

21    associations of 1-year average $PM_{2.5}$ concentration with cardiovascular diseases among post-menopausal

22    women. Further, modification of the $PM_{2.5}$-CVD association by smoking status and use of anti-

23    hyperlipidemics has been reported in more than one epidemiologic study. The toxicological studies

24    provide evidence for accelerated development of atherosclerosis in $ApoE^{-/-}$ mice exposed to CAPs for

25    4-6 months in Tuxedo, NY. Another CAPs study conduced in southern California demonstrated increased

26    lesion area similar to that observed, with Tuxedo, NY CAPs and the effect was attributable to ultrafine

27    traffic PM that contained particles in the fine size range (0.18 μm). Two additional toxicological studies of

28    CAPs from Tuxedo, NY showed effects on coagulation, experimentally-induced hypertension, and

29    vascular reactivity. The two available studies of clinical cardiovascular disease outcomes did not report

1    consistent results. Still, evidence of short-term $PM_{2.5}$ effects (e.g. increased mortality, incidence and

2    progression of cardiovascular disease) reported in a large number of studies spanning multiple disciplines,

3    supports a role for long-term exposure to $PM_{2.5}$ in cardiovascular disease. Based on the above findings,

4    **the epidemiologic and toxicological evidence is sufficient to infer a relationship that is likely to be**

5    **causal between long-term $PM_{2.5}$ exposures and cardiovascular morbidity.**

### Atherosclerosis

6    Several epidemiologic analyses have reported associations between $PM_{2.5}$ exposure and subclinical

7    measures of atherosclerosis including CAC (Diez Roux et al., 2008; Hoffmann et al., 2007), CIMT (Diez

8    Roux et al., 2008; Kunzli et al., 2005), AAC (Allen et al., in press) and ABI (Diez Roux et al., 2008).

9    Findings from these studies are consistent with regard to the observed effects modification. There is

10   consistency in the findings of these studies. Two studies report larger increases in the long-term

11   $PM_{2.5}$-CIMT and $PM_{2.5}$-AAC associations among users than non-users of anti-hyperlipidemics (Allen et

12   al., in press; Kunzli et al., 2005). Similarly, the long-term $PM_{2.5}$-CIMT and $PM_{10}$-CHD death associations

13   are stronger in never compared to former or current smokers (Kunzli et al., 2005; Puett et al., 2008).

14   Nonetheless, the remaining associations in MESA, including those of baseline CAC and ABI with 20-

15   year mean $PM_{2.5}$, were largely null (Diez Roux et al., 2008).

16   A group of new toxicological studies demonstrate increased plaque and lesion areas, lipid

17   deposition and content, and TF in aortas of $ApoE^{-/-}$ mice exposed to CAPs for 4-6 months. An additional

18   study of traffic-derived CAPs demonstrated increased atherosclerotic lesion area in the aorta that was

19   greater for the ultrafine PM, although the upper size fraction included PM in the fine size (0.18 μm).

### Systemic Inflammation and Blood Coagulation Markers

20   One CAPs study demonstrated elevated TF expression in aortas of $ApoE^{-/-}$ mice. Three new

21   toxicological studies utilized diesel or gasoline exhaust, or HWS over a 6-month exposure period and the

22   findings were largely inconsistent. The limited effects reported in the latter studies may be attributable to

23   the gases.

### Renal and Vascular Function

24   Cross-sectional and longitudinal epidemiologic analyses of $PM_{2.5}$ and UACR in the MESA cohort

25   revealed no evidence of an effect (O'Neill et al., 2007). Auchincloss et al. (2008) reported increased blood

26   pressure with 60-day average $PM_{2.5}$ concentration. A toxicological study of 10 weeks exposure duration

27   did not show changes in MAP with CAPs, but indicated a CAPs-related potentiation of experimentally-

28   induced hypertension and altered vasoreactivity.

### Autonomic Function

1  A recent toxicological study reported chronic decreases in HR over 4–5 month CAPs exposure in

2  ApoE$^{-/-}$ mice, with biphasic responses in HRV (SDNN and rMSSD) observed.

### Clinical Outcomes in Epidemiologic Studies

3  Two epidemiologic studies of the PM$_{2.5}$-CVD morbidity relationship focused on clinical CVD

4  events: in one case, on incident, validated MI, coronary revascularization, and stroke in 36 U.S.

5  metropolitan areas (Miller et al., 2007b), and in the other, on prevalent, self-reported CHD in Essen and

6  Mülheim, Germany (Hoffmann et al., 2006). Miller et al. (2007b) was a prospective, cohort study with the

7  population restricted to women (Miller et al., 2007b). Authors used arithmetic averaging of year 2000

8  AQS PM$_{2.5}$ data at the monitor most proximate to each participant's geocoded U.S. Postal Service ZIP

9  code. The one year average PM$_{2.5}$ exposure used in the German study was based on dispersion-modeled

10  emissions data (Hoffmann et al., 2006). The inconsistent findings between theswe two studies may be

11  driven by differences in study design and location. Miller et al. (2007b) found large increases in the

12  adjusted risk of MI, revascularization, and stroke with standardized increments in PM$_{2.5}$, but for the same

13  increment, Hoffman et al. (2006) found no such increase in the odds of prevalent CHD. Furthermore,

14  striking evidence for effect modification by anthropometric measures (e.g., BMI and waist-to-hip ratio)

15  presented by Miller et al. (2007b) has been tested, e.g. by Diez Roux et al. (2008), but not observed again

16  within this body of literature.

## 7.2.7.4. Ultrafine PM

17  Only one toxicological study of long-term exposure to ulftrafine PM has been conducted to date.

18  Evidence from one study alone is **inadequate to infer the presence or absence of a causal**

19  **relationship.** Increased plaque size was found in ApoE$^{-/-}$ mice exposed for 40 days to ultrafine PM

20  derived from traffic that included particles in the fine size range (0.18 μm); effects were also observed in

21  high density lipoprotein and lipid peroxidation was elevated in the liver. Another study evaluated the

22  effects of 50-day exposures of whole and filtered gasoline exhaust in ApoE$^{-/-}$ mice and reported increases

23  in gene products involved in atheromatous plaque formation and/or degradation, but it appeared that these

24  effects were due to the gaseous emissions.

**Table 7-2.** Characterization of ambient PM concentrations from studies of clinical cardiovascular diseases.

| Reference | Location | Mean Annual Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|
| *PM_{10}* | | | |
| Zanobetti and Schwartz (2007) | 21 U.S. Cities | 28.8 | Overall range NR |
| Rosenlund et al. (2006) | Stockholm, Sweden | 30 y avg $PM_{10}$ (traffic)<br>Cases: 2.6<br>Controls: 2.4 | 5th-95th Percentile<br>0.5-6.0<br>0.6-5.9 |
| Maheswaran (2005a) | Sheffield, UK | Range of means in each quintile: 16-23.3 | NR |
| Baccarelli et al. (2007b) | Lombardy, Italy | Sep-Nov: 51.2<br>Dec-Feb: 68.5<br>Mar-May:64.1<br>Jun-Aug: 44.3 | 148.9<br>238.3<br>158.5<br>94.7 |
| *PM_{2.5}* | | | |
| Miller et al. (2007b) | WHI: 36 Metropolitan areas | Citywide average (year 2000): 13.5 | Min-max: 4-19.3 |
| Hoffman et al. (2006) | HNRS: 2 Cities Germany | 23.3 | NR |

WHI: Womens Health Initiative
HNRS: Hans Nixdorf Recall Study

# 7.3. Respiratory Effects

1    Several cohort studies reviewed in the 2004 PM AQCD provided evidence for relationships

2    between long-term PM exposure and effects on the respiratory system. In 12 southern California

3    communities in the Children's Health Study (CHS), Gauderman et al. (2000; 2002) found that the largest

4    decreases in lung function growth among school children were associated with long-term exposure to PM.

5    Declines in pulmonary function were reported with all three major PM size classes – $PM_{10}$, $PM_{10-2.5}$ and

6    $PM_{2.5}$- though the three PM measures were highly correlated. In an earlier cross-sectional analysis, Peters

7    et al. (1999) found no significant relationships between respiratory symptoms and long-term exposure to

8    $PM_{10}$. McConnell et al. (1999), in another analysis of data from the CHS cohort, reported an increased

9    risk of bronchitis symptoms in children living in communities with higher PM concentrations. These

10    results were found to be consistent with results of cross-sectional analyses of the 24-cities study by

11    Dockery et al. (1996) and Raizenne et al. (1996), that had been assessed in the 1996 PM AQCD. These

12    studies reported associations between decreased peak flow and increased bronchitis rates with fine

13    particle sulfate and acidity. However, the high correlation of $PM_{10}$ and acid precluded clear attribution of

14    the bronchitis effects reported by McConnell et al. (1999) to PM specifically. Finally, among a subset of

1   children in the CHS (n = 110) who moved to other locations during the study period, Avol et al. (2001)

2   reported that those subjects who moved to areas of lower $PM_{10}$ showed increased growth in lung function

3   compared with subjects who moved to communities with higher $PM_{10}$ concentrations.

4       The 2004 PM AQCD (U.S. EPA, 2004) concluded that the evidence for an association between

5   long-term exposure to PM and respiratory effects was inconsistent and potentially confounded by high

6   correlations between studied pollutants. Quantitatively, Gauderman et al. (2002) reported declines for

7   $FEV_1$ for $PM_{10}$ and $PM_{2.5}$ of -0.04 mL (95% CI: -0.2 to 0.12) and -0.17 mL (95% CI: -0.47 to 0.13), per

8   10 $\mu g/m^3$ increase, respectively; and McConnell et al. (1999) reported increased ORs for bronchitic

9   symptoms in asthmatics for $PM_{10}$ and $PM_{2.5}$ of 1.19 (95% CI: 1.05-1.36) and 1.25 (95% CI: 0.93-1.74)

10  per 10 $\mu g/m^3$ increase, respectively. Very few subchronic and chronic toxicological studies investigating

11  respiratory effects were available in the 2004 PM AQCD. However, the 2002 EPA Health Assessment

12  Document for DE reported that long-term exposure to DE was associated with histopathology including

13  alveolar histiocytosis, aggregation of alveolar macrophages, tissue inflammation, increased

14  polymorphonuclear leukocytes, hyperplasia of bronchiolar and Type 2 epithelial cells, thickened alveolar

15  septa, edema, fibrosis, emphysema and lesions of the trachea and bronchi. Since then a number of

16  inhalation studies have been conducted using CAPs, urban air, DE and woodsmoke.

17      Recent epidemiologic literature focuses on prospective cohort studies, which found consistent,

18  positive associations between long-term exposure to PM and $PM_{2.5}$ and respiratory morbidity. Subchronic

19  and chronic toxicological studies provide some evidence of altered pulmonary function, amid

20  inflammatory oxidative responses and histopathological changes following $PM_{2.5}$ exposures. These results

21  are summarized below; further details of these studies are summarized in Annexes D and E.

# 7.3.1. Respiratory Symptoms and Disease Incidence

## 7.3.1.1. Epidemiologic Studies

22      New longitudinal cohort studies provide the best evidence to evaluate the relationship between

23  long-term exposure to ambient PM and increased incidence of respiratory symptoms or disease. A

24  summary of the mean PM concentrations reported for the studies characterized in this section is presented

25  in Table 7-3.

26      Bayer-Oglesby et al. (2005) examined the decline of ambient pollution levels and improved

27  respiratory health demonstrated by a reduction in respiratory symptoms and diseases in school children

28  (n = 9591) in Switzerland. They state that if reduced air pollution exposure resulted in improved

29  respiratory health of children, this would argue in favor of a causal relation. Further, the average reduction

1    of symptom prevalence would be more pronounced in areas with stronger reduction of air pollution

2    levels. The average decline of $PM_{10}$ between 1993 and 2000 across the nine study regions was 9.8 $\mu g/m^3$

3    (29%). Röösli et al. (2000; 2001) have demonstrated that $PM_{10}$ levels are homogeneously distributed

4    within regions of Switzerland and are not significantly affected by local traffic, justifying the single-

5    monitor approach for assignment of $PM_{10}$ exposures. Declining levels of $PM_{10}$ were associated with

6    declining prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis

7    symptoms, but no significant associations were reported for wheezing, sneezing, asthma, and hay fever, as

8    shown in Figure 7-2. In Figure 7-2, Panel (B) illustrates that on an aggregate level across region, the mean

9    change in adjusted prevalence of chronic cough is associated with the mean change in $PM_{10}$ levels

10   ($r = 0.78$; $p = 0.02$). Similar associations were seen for nocturnal dry cough and conjunctivitis symptoms

11   and $PM_{10}$ levels. Gehrig and Buchmann (2003) conducted co-located parallel measurements of $PM_{2.5}$ and

12   $PM_{10}$ at seven sites in Switzerland since January, 1998. The long-term averages of the $PM_{2.5}/PM_{10}$ ratios

13   of the daily values vary from 0.75 to 0.76. The correlations between daily values of $PM_{2.5}$ and $PM_{10}$ at all

14   sites are generally high (0.8 to 0.58 for the seven cities).

**Table 7-3.** Characterization of ambient PM concentrations from studies of respiratory symptoms/disease and long-term exposures.

| Reference | Location | Mean Annual Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|
| *PM₁₀* | | | |
| Bayer-Oglesby et al. (2005) | Nine study regions in Switzerland | | Max: 46 |
| Dockery et al. (1996) | 24 U.S./Canadian communities | 23.8 | |
| Kim et al. (2004) | San Francisco, CA | 30 | |
| McConnell et al. (1999) | 12 CHS/CA communities | 34.8 | Max: 70.7 |
| McConnell et al. (2003) | 12 CHS/CA communities | 30.8 | Max: 63.5 |
| Pierse et al. (2006) | Leicestershire, UK | 1.33 | 75th: 1.84 |
| *PM₂.₅* | | | |
| Brauer et al. (2007) | The Netherlands | 16.9 | 75th: 18.1<br>90th: 19.0<br>Max: 25.2 |
| Dockery et al. (1996) | 24 U.S./Canadian communities | 14.5 | |
| Islam et al. (2007) | 12 CHS/CA communities | | Max: 29.5 |
| Kim et al. (2004) | San Francisco, CA | 12 | |
| McConnell et al. (1999) | 12 CHS/CA communities | 15.3 | Max: 31.5 |
| McConnell et al. (2003) | 12 CHS/CA communities | 13.8 | Max: 28.5 |
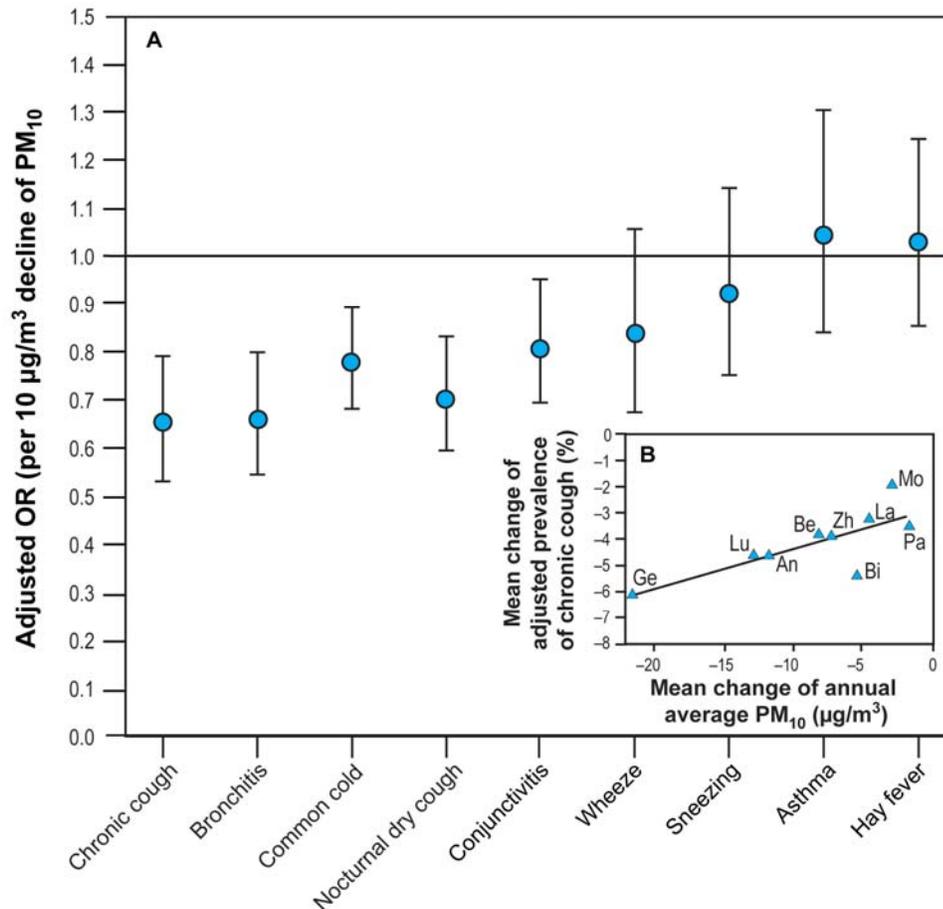
Source: Bayer-Oglesby et al. (2005)

**Figure 7-2.   Adjusted ORs and 95% CIs of symptoms and respiratory diseases in Swiss Surveillance Program of Childhood Allergy and Respiratory Symptoms with respect to air pollution and climate associated with a decline of 10 μg/m$^3$ PM$_{10}$ levels (A)[1]. Mean change in adjusted prevalence[2] (1998-2001 to 1992-1993) versus mean change in regional annual averages of PM$_{10}$ (1997-2000 to 1993) for chronic cough, across nine SCARPOL regions. (B)**

[1] Adjusted for age, sex, nationality, parental education, number of siblings; farming status, low birth weight, breastfeeding, child who smokes, family history of asthma, bronchitis, and/or atopy, mother who smokes, indoor humidity, mode of heating and cooking, carpeting, pets allowed in bedroom, removal of carpet and/or pets for health reasons, person who completed questionnaire, month when questionnaire was completed, number of days with the maximum temperature <0°C, and belief of mother that there is an association between environmental exposures and children's respiratory health.

[2] An: Anières. Be: Bern. Bi: Biel. Ge: Geneva. La:, Langnau. Lu: Lugano. Mo: Montana. Pa: Payerne. Zh: Zürich.

1    A matched case-control study of infant bronchiolitis (ICD 9 code 466.1) hospitalization and two

2    measures of long-term exposure – the month prior to hospitalization (subchronic) and the lifetime average

3    (chronic) – to PM$_{2.5}$ and gaseous air pollutants in the South Coast Air Basin of southern California was

4    conducted by Karr et al. (2007) in 18,595 infants born between 1995-2000. For each case, 10 controls

5    matched on date were randomly selected from birth records. Exposure was based on PM$_{2.5}$ measurements

6    collected every third day; the mean distance between the subjects' residential ZIP code and the assigned

1      monitor was in the range of 4-6 miles with a maximum distance of 30 miles. For 10-$\mu g/m^3$ increases in

2      both sub-chronic and chronic $PM_{2.5}$ exposure an adjusted odds ratio of 1.09 (95% CI: 1.04-1.14) was

3      observed. In multipollutant model analysis the association with $PM_{2.5}$ was robust to the inclusion of

4      gaseous pollutants. Also, Morgenstern et al. (2008) provides a preliminary examination of modeled PM

5      data at birth addresses and 1-year and 2-year incidence of respiratory symptoms that show initial positive

6      findings.

7         McConnell et al. (2003) conducted a prospective study examining the association between air

8      pollution and bronchitic symptoms in 475 children with asthma in 12 Southern California communities as

9      part of the CHS from 1996 to 1999. They investigated both of the differences between communities with

10      4-year average and yearly variation in pollutants (including $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, EC, and OC) within-

11      communities. Based on a 10 $\mu g/m^3$ change in $PM_{2.5}$, within-communities effects were larger (OR 1.90

12      [95% CI: 1.10-2.70]) than those for between-communities assessment (OR 1.30 [95% CI: 1.10-1.50]).

13      The OR for the 10 $\mu g/m^3$ range in 4-yr avg $PM_{2.5}$ concentrations across the 12 communities was 1.29

14      (95% CI: 1.06–1.58). Similar results were reported for $PM_{10}$ and $PM_{10-2.5}$ but the effect estimates were

15      smaller in magnitude and generally not statistically significant. Within-community associations were not

16      confounded by any time-fixed personal covariates in this study. In two pollutant models, the within-

17      community effect estimates for $PM_{2.5}$ and OC were significant in the presence of several other pollutants.

18      The single-pollutant effect of $PM_{2.5}$ ($\beta = 0.085/\mu g/m^3$) was only modestly attenuated by other pollutants

19      and remained significant after adjusting for other pollutants. The effects of $PM_{2.5}$ were markedly reduced

20      after adjusting for $NO_2$ or OC. The between-community effect estimates were generally not significant in

21      the presence of other pollutants in two-pollutant models.

22         Pierse et al. (2006) studied the association between primary $PM_{10}$ (particles directly emitted from

23      local sources/traffic) and the prevalence and incidence of respiratory symptoms in a randomly sampled

24      cohort of 4400 children (aged 1-5 years) in Leicestershire, England surveyed in 1998 and again in 2001.

25      Annual exposure to primary $PM_{10}$ was calculated for the home address using the Airviro statistical

26      dispersion model. After adjusting for confounders, mean annual exposure to locally generated $PM_{10}$ was

27      associated with an increased prevalence of cough without a cold in both the 1998 and 2001 surveys: 1998

28      OR 1.21 (95% CI: 1.07-1.38), n = 2164; 2001 OR 1.56 (95% CI: 1.32-1.84), n = 1756.

29         Kim et al. (2004) conducted a school-based cross-sectional study in the San Francisco metropolitan

30      area in 2001 comprised of 10 neighborhoods to examine the relationship between traffic-related pollutants

31      and current bronchitic symptoms and asthma obtained by parental questionnaire (n = 1109). They found

32      associations (per 10 $\mu g/m^3$ increase in PM) between traffic-related pollutants and bronchitic ($PM_{10}$ 1.02

33      [95% CI: 0.99–1.05]; $PM_{2.5}$ 1.33 [95% CI: 1.00–2.01) and asthma ($PM_{10}$ OR = 1.01 [95% CI: 0.97–1.06;

34      $PM_{2.5}$ OR = 1.00 95% CI 0.65 to 1.75) symptoms in the past 12 months.

1      In the CHS discussed earlier, Islam et al. (2007) examined the hypothesis that ambient air pollution
2    attenuates the reduced risk for childhood asthma that is associated with higher lung function (n = 2057).
3    At each age a distribution of pulmonary functions exists. Haland et al. (2006) found evidence that
4    children with high lung function have a reduced risk for asthma. Islam et al. (2007) hypothesize that
5    evolutionary selection has resulted in lung function characteristics that promote better respiratory health.
6    Therefore, better lung function may be a marker for lower susceptibility to airway pathophysiology. Islam
7    et al. (2007) used the CHS data to study how the association of asthma incidence with lung function is
8    modified by long-term PM exposure. They used linear regression to adjust the log of sex-specific lung
9    function for various known covariates. From that regression, they obtained the percent predicted lung
10   function (PPFL) variable. This was 100 times the antilog of the residuals. Next, for each of 12
11   communities, the Cox proportional hazards model was used to relate baseline PPFL (year-1994) and other
12   individual level covariates such as race/ethnicity to the incidence of asthma during the subsequent years
13   up to 2003. In that regression, the PPFL was scaled by dividing by its range from the 10th to the 90th
14   percentile. The estimated 12 lung function coefficients were then used as the dependent variable in a
15   meta-regression on the 12 long-term average community-specific pollution levels. The hazard ratio was
16   also calculated for 3 categories of PPFL to better explain the relationship.

17      The incidence rate (IR) of newly diagnosed asthma increased from 9.5/1000 person-years for
18   children with percent-predicted $FEF_{25\text{-}75}$ values $\geq$ 120% to 20.4/1000 person-years for children with
19   $FEF_{25\text{-}75}$ value $\leq$ 100%. Over the 10th-90th percentile range for $FEF_{25\text{-}75}$ (57.1), the hazard ratio of new
20   onset asthma was 0.50 (95% CI: 0.35-0.71). The IR of asthma for $FEF_{25\text{-}75} \geq$ 120% in the "high" $PM_{2.5}$
21   (13.7–29.5 $\mu g/m^3$) communities was 15.9/1000 person-years compared to 6.4/1000 person-years in "low"
22   $PM_{2.5}$ (5.7–8.5 $\mu g/m^3$) communities. Loss of protection by high lung function against new onset asthma in
23   the "high" $PM_{2.5}$ communities was observed for all the lung function measures. Figure 7.3 shows the
24   effect of $PM_{2.5}$ on the association of lung function with asthma. Of all the pollutants examined ($NO_2$,
25   $PM_{10}$, $PM_{2.5}$, acid vapor, ozone, EC, and OC), $PM_{2.5}$ appeared to have the strongest modifying effect on
26   the association between lung function with asthma as it had the highest $R^2$ value (0.42). Over the 10th–
27   90th percentile range of $FEF_{25\text{-}75}$ (57.1%) the hazard ratio of new onset asthma was 0.34 (95% CI: 0.21–
28   0.56) in a community with low $PM_{2.5}$ (less than 13.7 $\mu g/m^3$) and 0.76 (95% CI: 0.45–1.26) in a
29   community with high $PM_{2.5}$ (equal to or greater than 13.7 $\mu g/m^3$). The data do not indicate that PM
30   exposure increased rates of incident asthma among children with poor lung function at study entry
31   because rates among those with poor lung function were similar in both low and high pollution
32   communities.
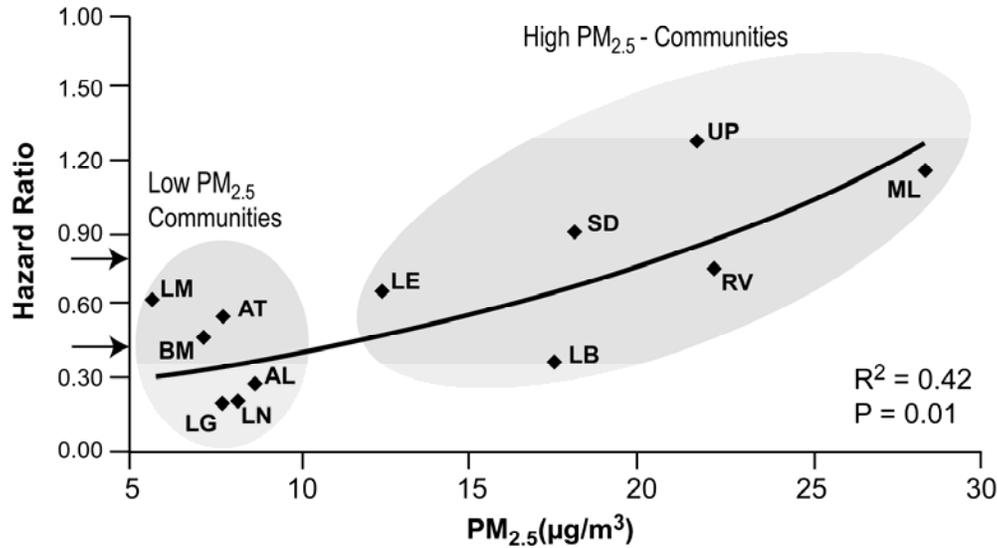
**Figure 7-3.** **Effect of PM$_{2.5}$ on the association of lung function with asthma. Community-specific hazard ratio of newly diagnosed asthma over 10-90th percentile range (57.1%) of FEF$_{25-75\%}$ by level of ambient PM$_{2.5}$ (µg/m$^3$). The 12 CHS communities are shown.**

1    During the first four years of life in a birth cohort study (n = 4,000) in The Netherlands, Brauer

2    et al. (2007) assessed the development of asthma, allergic symptoms, and respiratory infection in relation

3    to long-term pollution concentration at the home address with a validated model using GIS. PM$_{2.5}$ was

4    associated with doctor-diagnosed asthma (OR = 1.32 [95% CI: 1.04–1.69]) for a cumulative lifetime

5    indicator. Annesi-Maesano et al. (2007) relate individual data on asthma and allergy from 5338 school

6    children (10.4 ± 0.7 years) attending 108 randomly chosen schools in 6 French cities to the concentration

7    of PM$_{2.5}$ (monitored in school yards) that was dichotomized as high (20.7 µg/m$^3$) vs. low (8.7 µg/m$^3$).

8    Atopic asthma was related to PM$_{2.5}$ (OR 1.43 [95% CI: 1.07–1.91]). The report is consistent with the

9    results in an earlier paper (Penard-Morand et al., 2005) in the same sample of children that related the

10   findings to PM$_{10}$.

11   Schikowski et al. (2005) examined the relationship between both long-term air pollution exposure

12   and living close to busy roads and COPD in the Rhine-Ruhr Basin of Germany from 1985 to 1994 using

13   consecutive cross-sectional studies. Seven monitoring stations that were not more than 8 km to a woman's

14   home address provided TSP data from which PM$_{10}$ was estimated as a conversion factor calculated from

15   parallel measurement of TSP and PM$_{10}$ conducted at the 7 sites in the Ruhr area. Distance to a major road

16   was determined using GIS. The results of the study suggest that long-term exposure to air pollution from

17   PM$_{10}$ and living near a major road might increase the risk of developing COPD and can have a

1   detrimental effect on lung function. All ORs for 5-year exposures were stronger than those for 1-year

2   exposures.

3       Goss et al. (2004) conducted a national study examining the relationship between air pollutants and

4   health effects in a cohort of 11,484 cystic fibrosis (CF) patients over the age of 6 years (mean [SD] 18.4

5   [10]) enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Exposure

6   was assessed by linking air pollution values from the closest population monitor from the Aerometric

7   Information Retrieval System (AIRS) with the centroid of the patient's home ZIP code that was within 30

8   miles. $PM_{2.5}$ and $PM_{10}$ 24-h averages were collected every 1 to 12 days. CF diagnosis involves genetic

9   screening panels. A common severe mutation used is the loss of phenylalanine at the 508th position.

10  Genotyping was available in 74% of the population and of those genotyped, 66% carried one or more

11  delta F508 deletions. The mean distance from the patient's zip code to monitors for $PM_{10}$ and $PM_{2.5}$ was

12  11.5 miles (SD 7.9) and 10.8 miles (SD 7.8) respectfully. After adjusting for confounders a 10 $\mu g/m^3$ rise

13  in $PM_{10}$ and $PM_{2.5}$ was associated with a 8% (95% CI: 2–15) and 21% (95% CI: 7–33), respectively,

14  increase in the odds of two or more exacerbations defined as a CF-related pulmonary condition requiring

15  admission to the hospital or use of home intravenous antibiotics. The estimate for the associations

16  between pulmonary exacerbations and $PM_{10}$ and $PM_{2.5}$ were attenuated when the models were adjusted

17  for lung function. Brown et al. (2001) found that particulate deposition was increased in CF and that the

18  distribution of particle deposition was enhanced in the tracheobronchial regions of poorly ventilated lung

19  regions in CF patients. Such focal deposition may partially explain the association of particulate air

20  pollutants and pulmonary exacerbation rate.

# 7.3.2. Pulmonary Function

## 7.3.2.1. Epidemiologic Studies

21      New longitudinal cohort studies have evaluated the relationship between long-term exposure to PM

22  and changes in measures of pulmonary function (FVC and $FEV_1$, and measures of expiratory flow).

23  Cross-sectional studies also offer supportive information (see Annex E) and may provide insights derived

24  from within community analysis. From the major longitudinal cohort studies, associations between

25  changes in $FEV_1$, FVC, and expiratory flow with a 10 $\mu g/m^3$ change in $PM_{10}$ standardized per year of

26  follow up are shown in Figure 7-4. Lung function increases continually through early adulthood with

27  growth and development, then declines with aging (Stanojevic et al., 2008; Thurlbeck, 1982; Zeman and

28  Bennett, 2006) thus, the order of results presented in this section is from studies of postnatal exposures

1    through adulthood. A summary of the mean PM concentrations reported for the studies characterized in
2    this section is presented in Table 7-4.
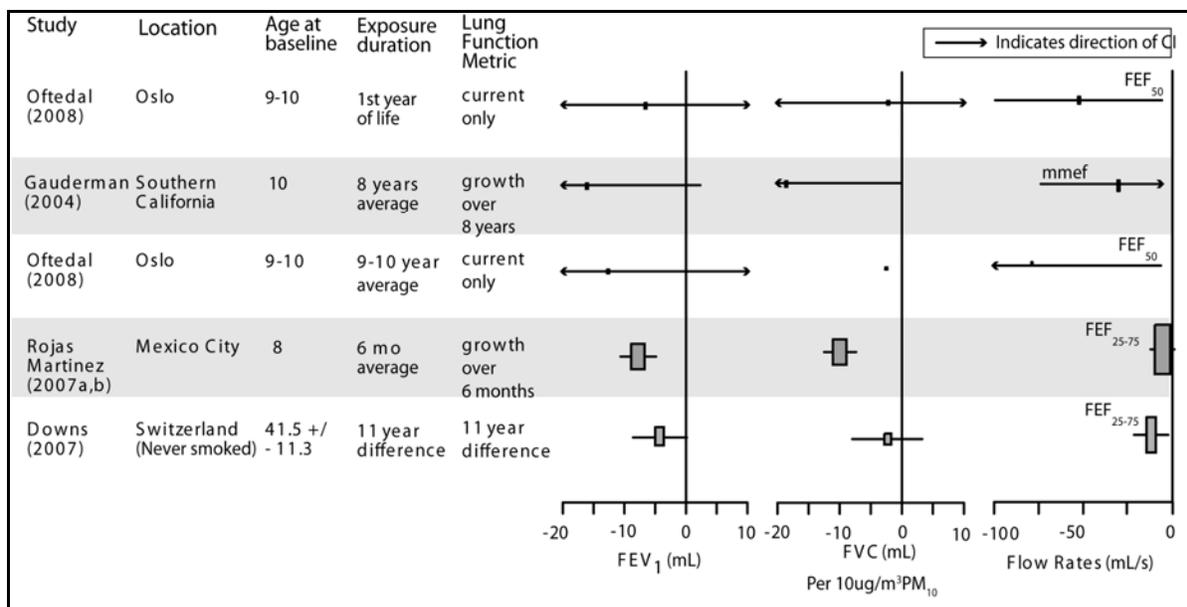


**Figure 7-4.    Decrements in FEV$_1$, FVC, FEF$_{50\%}$, FEF$_{25-75}$, and MMEF and a 10 µg/m$^3$ change in PM$_{10}$.**

**Table 7-4.    Characterization of ambient PM concentrations from studies of FEV$_1$ and long-term exposures.**

| Reference | Location | Mean Annual Concentration (µg/m$^3$) | Upper Percentile Concentrations (µg/m$^3$) |
|---|---|---|---|
| *PM$_{10}$* | | | |
| Downs et al. (2007) | 8 cities in Switzerland | 9-46 | |
| Gauderman et al. (2002) | 12 CHS/CA communities | 13-78 | |
| Gauderman et al. (2004) | 12 CHS/CA communities | 18-68 | |
| Oftedal et al. (2008) | Oslo, Norway | 14.5 | |
| Raizenne et al. (1996) | 22 U.S./Canadian communities | 23.8 | Max: 32.7 |
| Rojas-Martinez et al. (2007) | Mexico City, Mexico | 75.6 | 75th: 92.2 90th: 112.7 |
| *PM$_{2.5}$* | | | |
| Dales et al. (2008) | Windsor, Ontario | 15.62 | 95th: 17.17 |
| Gauderman et al. (2002) | 12 CHS/CA communities | 5-30 | |
| Gauderman et al. (2004) | 12 CHS/CA communities | 6-27 | |
| Goss et al. (2004) | U.S. | 13.7 | 75th: 15.9 |
| Gotschi et al. (2008) | 21 European cities | 3.7-44.7 | |
| Oftedal et al. (2008) | Oslo, Norway | 12.3 | |
| Raizenne et al. (1996) | 22 U.S./Canadian communities | 14.5 | Max: 20.7 |

1    In a birth cohort (n = 2170) in Oslo, Norway, Oftedal et al. (2008) examined effects of long- and
2    short-term exposure to $PM_{10}$ and $PM_{2.5}$ on lung function (FVC, $FEV_1$, $FEF_{50\%}$) in early life (first year of
3    life) and later (9 to 10-year-old children). The EPISODE statistical dispersion model, a GIS approach
4    (Slørdal, 2003), was used for the exposure estimate in which an evaluation concluded that the modeled
5    PM levels represent the long-term exposure concentrations reasonably well. Only single pollutant models
6    were evaluated because air pollutants were highly correlated (r = 0.83-0.95). The effects of $PM_{10}$ in the
7    first year of life and the results of total lifetime exposure on expiratory flow variables ($FEF_{50\%}$) and forced
8    volumes ($FEV_1$ and FVC) are shown in Figure 7.4. No associations were found with shorter exposures
9    (<30 days) to $PM_{10}$ and $PM_{2.5}$, which suggested permanent impairment. A 10 μg/m$^3$ increase in $PM_{10}$ and
10   $PM_{2.5}$ was associated with change in adjusted peak respiratory flow of -113.8 mL/s (95% CI: -189.7 to -
11   39.7) and -161.1 mL/s (95% CI: -261.1 to -58.3), respectively. Adjusting for contextual socioeconomic
12   factors diminished associations. Results for $PM_{2.5}$ were similar to those for $PM_{10}$. Independent effects of
13   each pollutant could not be discerned because of their strong correlation related to their traffic-related
14   primary source emissions. The authors present the notion that the forced volumes results provide
15   information on central airways, and expiratory flow variables represent peripheral airways.
16   In an exploratory study, Mortimer et al. (2008) examined the association of prenatal and lifetime
17   exposure to air pollutants that are most predictive of current pulmonary function in a San Joaquin Valley,
18   California cohort of 232 children (aged 6-11) with asthma. The data suggested that first and second
19   trimester $PM_{10}$ exposures had a negative effect on pulmonary function at age 6-11 years and may relate to
20   prenatal exposures affecting the lungs as they begin to develop at 6 weeks gestation continuing through
21   distinct phases of development.
22   Nordling et al. (2008) examined the relationship between estimated PM exposure levels and
23   respiratory health effects in a Swedish birth cohort (n = 4089) of preschool children. Persistent wheezing
24   (cumulative incidence up to age 4) was associated with exposure to traffic-generated $PM_{10}$ (OR 2.28
25   [95% CI: 0.84–6.24] per 10 μg/m$^3$ increase). Lower peak expiratory flow (not shown in the summary
26   figure) at age 4 was associated with exposure to traffic-$PM_{10}$ (-8.93 L/min [95% CI: -17.78 to -0.088]).
27   The spatial distributions of PM from traffic in the study area were estimated with emission databases and
28   statistical dispersion modeling. Children were examined at 2 months and 1, 2, and 4 years of age. Using
29   GIS methods, the average contribution above regional background to the children's residential outdoor air
30   pollution levels was determined. To evaluate the exposure assessment, the authors compared the estimated
31   levels of traffic-generated $PM_{10}$ with $PM_{2.5}$ measurements from 42 locations (Hoek et al., 2002).
32   In a prospective dynamic cohort study consisting of students (n = 3170) who were 8 years of age at
33   the beginning of the study, who had not been diagnosed with asthma and were located in Mexico City,

1    Rojas-Martinez et al. (2007) evaluated the association between long-term exposure to $PM_{10}$, $O_3$ and $NO_2$

2    and lung function growth every 6 months from April 1996 through May 1999. Exposure data were

3    provided by 10 air quality monitor stations located within 2 km of each student's school. The

4    multipollutant model effects of $PM_{10}$ over the age of 8 to 10 years of life in this cohort on FVC, $FEV_1$,

5    and $FEF_{25-75}$ are shown in Figure 7-4. Single pollutant models showed an association between ambient

6    pollutants ($O_3$, $PM_{10}$ and $NO_2$) and deficits in lung growth. No significant effect of $PM_{10}$ was observed on

7    $FEF_{25-75}$. While the estimates from two-pollutant models were not substantially different than single

8    pollutant models, independent effects for pollutants could not be estimated accurately because the traffic-

9    related pollutants were correlated.

10       The CHS prospectively examined the relationship between air pollutants and lung function (FVC,

11   $FEV_1$, MMEF) in a cohort (n = 1759) between the ages of 10 and 18 years, a period of rapid lung

12   development (Gauderman et al., 2004). Air pollution monitoring stations provided data in each of the 12

13   study communities from 1994-2000. The results for $O_3$, $PM_{10}$, $NO_2$, $PM_{2.5}$, acid vapor, and EC and are

14   depicted in Figure 7-5. In general, two-pollutant models for any pair of pollutants did not provide a

15   significantly better fit to the data than the corresponding single-pollutant models due to the strong

16   correlation between most pollutants. The pollution-related deficits in the average growth in lung function

17   over the eight-year period resulted in clinically important deficits in attained lung function at the age of

18   18 years. Since lung development is basically completed by the age of 18 years, it is unlikely that these

19   clinically significant deficits in lung function will be reversed. Since associations are seen between the

20   three measures of lung function this suggests that more than one biological process is involved. FVC is

21   largely a function of the number and size or growth of alveoli. A possible effect of air pollution on lung

22   development may be airway inflammation, as occurs in bronchiolitis.
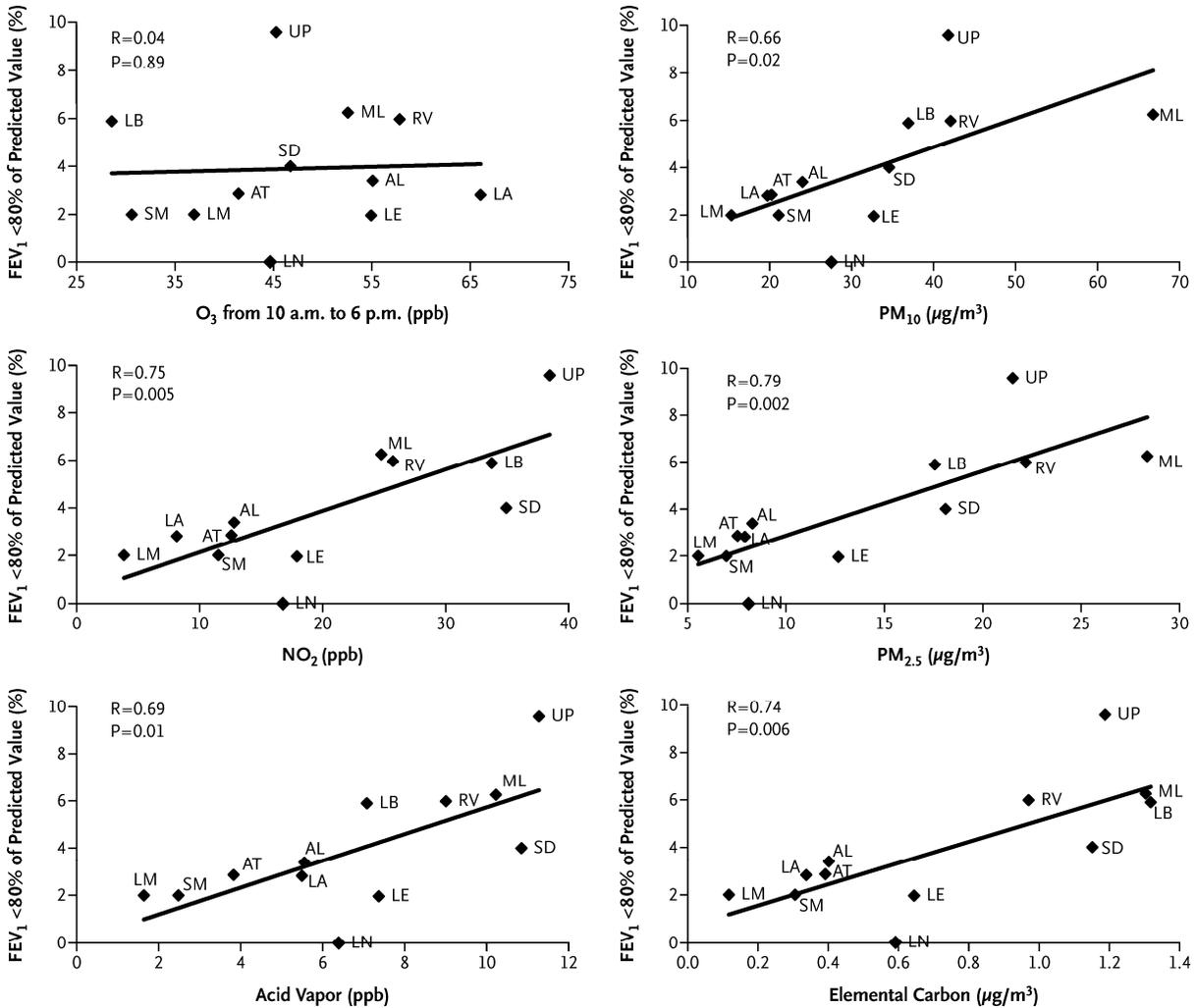
Source: Adapted from Gauderman et al. (2004).

**Figure 7-5. Proportion of 18-year olds with a FEV₁ below 80% of the predicted value plotted against the average levels of pollutants from 1994 through 2000 in the 12 southern California communities of the Children's Health Study. [1]**

1    In Leicester, England, investigators examined the carbon content of airway macrophages in

2    induced sputum in 64 of 114 healthy children 8 to 15 years of age (Grigg et al., 2008; Kulkarni et al.,

3    2006). The carbon content of airway macrophages (Finch et al., 2002; Strom et al., 1990) was used as a

4    marker of individual exposure to $PM_{10}$. Near each child's home, modeled exposure to $PM_{10}$ was

[1] AL = Alpine; AT = Atascadero; LA = Lake Arrowhead; LB = Long Beach; LE = Lake Elsinore; LM = Lompoc; LN = Lancaster; ML = Mira Loma; RV = Riverside; SD = San Dimas; SM = Santa Maria; UP = Upland

1    determined using the Airviro statistical dispersion model (Pierse et al., 2006). The authors reported a

2    dose-dependent inverse association between the carbon content of airway macrophages and lung function

3    in children and note that they found no evidence that reduced lung function itself causes an increase in

4    carbon content. Consistent results were obtained for both FVC and $FEF_{25-75}$. The authors conclude that

5    since they directly assessed the carbon content of airway macrophages, their data strengthen the evidence

6    for a causal association between the inhalation of carbonaceous particles and impaired lung function in

7    children. HEI Reports (Grigg et al., 2008) suggest caution when interpreting these results: the accuracy of

8    the estimates on individual $PM_{10}$ exposures obtained by using the Airvivo dispersion model was not

9    validated; potential for confounding by ethnic origin; and concern that the magnitude of the changes in

10   pulmonary function associated with increased particle area appear large thus casting doubt on the results.

11   Dales et al. (2008) examined the relationship of pulmonary function and PM measures, other

12   pollutants, and indicators of motor vehicle emissions in Windsor, Ontario, in a cohort of 2402 school

13   children, with $PM_{2.5}$ and $PM_{10}$ concentrations estimated for each child's residence at the postal code level.

14   Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7.0% decrease in FVC expressed in a percentage

15   of predicted (p = 0.39).

16   Some new studies are using individual estimates of exposure to ambient PM to reduce the impact

17   of exposure error (Downs et al., 2007; Jerrett et al., 2005a). Downs et al. (2007) prospectively examined

18   9,651 randomly selected adults (18 to 60 years of age) in 8 cities in Switzerland (see also Ackermann-

19   Liebrich et al., 1997) to ascertain the relationship between reduced exposure to $PM_{10}$ and age-related

20   decline in lung function (FVC, $FEV_1$, and $FEF_{25-50}$). An evaluated statistical dispersion model (Liu et al.,

21   2007c) provided spatially resolved concentrations of $PM_{10}$ that enabled assignment to residential

22   addresses for the participant examinations in 1991 and 2002 that yielded a median decline of 5.3 $\mu g/m^3$

23   (IQR 4.1 - 7.5). The decreasing exposure to $PM_{10}$ attenuated the decline in lung function (see Figure 7.4.)

24   Effects were greater in tests reflecting small airway function. No other pollutant relationships were

25   evaluated, though a related study indicated that levels of $NO_2$ also declined over the same period

26   (Ackermann-Liebrich et al., 2005). Generalized cross-validation essentially chose a linear fit for the dose-

27   response curve.

28   These data show that improvement in air quality may slow the annual rate of decline in lung

29   function in adulthood indicating positive consequences for public health. Further evidence on

30   improvement in respiratory health with reduction in air pollution levels was provided in studies conducted

31   in East Germany related to dramatic emissions reductions after the reunification in 1990 (Fryer and

32   Collins, 2003; Heinrich et al., 2002; Sugiri et al., 2006). This type of "natural experiment" provides

33   additional support for epidemiologic findings that relatively low levels of airborne particles have

34   respiratory effects.

1    Figure 7-4 presents risk estimates for three lung function measurements ($FEV_1$, FVC, and flow

2    rates) from this group of studies. It is important to recognize that these measurements have been made at

3    different ages in the cohorts of children, and different lung function indicators have been measured, so the

4    results are not directly comparable. It can be seen, however, that all estimates are negative

5    (i.e., decreasing lung function) and the pattern of effects are similar between the studies for FVC and

6    $FEV_1$. Thus, the data are consistent and coherent across several designs, locations, researchers, and other

7    factors. With cautions noted, the results relating carbon content of airway macrophages to decreased

8    measures of pulmonary function add plausibility to the epidemiologic findings.

9        Gotschi et al. (2008) examined the relationship between air pollution and lung function in adults in

10   the European Community Respiratory Health Survey (ECRHS). $FEV_1$ and FVC were assessed at baseline

11   and after 9 years of follow-up from 21 European centers (followed-up sample n = 5610). $PM_{2.5}$ was

12   measured in 2000-2001 using central monitors. No significant associations were found between city-

13   specific annual mean $PM_{2.5}$ and average lung function levels which is in contrast to the results seen by

14   Ackermann-Liebrich et al. (1997) (SAPALDIA) and Schikowski et al. (2005) (SALIA) which compared

15   across far more populations than is the case for ECRHS. The authors presented concerns for potential

16   misclassification and confounding.

17       As was found in the 2004 PM AQCD, the studies report associations with $PM_{10}$ and $PM_{2.5}$, and

18   most did not evaluate $PM_{10-2.5}$. Associations have been reported with fine particle components, particularly

19   EC and OC. Source apportionment methods generally have not been used in these long-term exposure

20   studies, however, numerous studies have evaluated exposures to PM related to traffic or motor vehicle

21   emissions. For example, Meng et al. (2007b) investigated the associations between traffic and outdoor

22   pollution levels and poorly controlled asthma among adults who were respondents to the California

23   Health Interview Survey and found associations for traffic density and $PM_{10}$ but not $PM_{2.5}$.

### 7.3.2.2. Toxicological Studies

*Urban Air*

24       An important new study evaluated the effects of chronic exposure to ambient levels of urban

25   particles on lung development in the mouse (Mauad et al., 2008). Both functional and anatomical indices

26   of lung development were measured. Male and female BALB/c mice were continuously exposed to

27   ambient or filtered Sao Paolo air for 8 months. Concentrations in the "polluted chamber" vs. "clean

28   chamber" were 16.8 vs. 2.9 $\mu g/m^3$ $PM_{2.5}$. Thus PM levels were reduced by filtration but not entirely

29   eliminated. Ambient concentrations of CO, $NO_2$ and $SO_2$ were 1.7 ppm, 89.4 $\mu g/m^3$ and 8.1 $\mu g/m^3$,

30   respectively. Concentrations of gaseous pollutants were assumed to be similar to ambient levels in both

1   chambers. After 4 months, the animals were mated and the offspring were divided into 4 groups to

2   provide for a prenatal exposure group, a postnatal exposure group, a pre and postnatal exposure group and

3   a control group. Animals were sacrificed at 15 and 90 days of age for histological analysis of lungs.

4   Pulmonary pressure-volume measurements were also conducted in the 90 day old offspring. Statistically

5   significant reductions in inspiratory and expiratory volumes were found in the pre and postnatal exposure

6   group, but not in the prenatal or postnatal exposure group, compared with controls. These changes in

7   pulmonary function correlated with anatomical changes which are discussed in Section 7.3.5.1.

### Diesel Exhaust

8   Li et al. (2007) exposed BALB/c and C56BL/6 mice to clean air or to low dose DE (at a PM

9   concentration of 100 $\mu g/m^3$) for 7 hours/day and 5 days/week for 1, 4 and 8 weeks. Average gas

10   concentrations were reported to be 3.5 ppm CO, 2.2 ppm $NO_2$, and less than 0.01 ppm $SO_2$. AHR was

11   evaluated by whole body plethysmography at Day 0 and after 1, 4 and 8 weeks of exposure. Short-term

12   responses are discussed in Section 6.3.11.3. The increased sensitivity of airways to methacholine

13   (measured as $P_{enh}$) seen in C57BL/6 but not BALB/c mice at 1 week was also seen at 4 weeks but not at 8

14   weeks. This study suggests that adaptation occurs during prolonged DE exposure. Influx of inflammatory

15   cells, histopathology, markers of oxidative stress and effects of antioxidant intervention were also

16   evaluated (see Sections 7.3.3.2 and 7.3.4.1). Although no attempt was made in this study to determine the

17   effects of gaseous components of DE on the measured responses, concentrations of gases were very low

18   suggesting that PM may have been responsible for the observed effects.

### Woodsmoke

19   One study evaluated the effects of subchronic woodsmoke exposure on pulmonary function in

20   Brown Norway rats, which are considered an animal model of allergy. Rats were exposed 3 h/day and 5

21   days/week for 4 and 12 weeks to air or to 1000-10,000 $\mu g/m^3$ concentrated wood smoke from the pinon

22   pine which is native to the U.S. Southwest (Tesfaigzi et al., 2002). PM concentrations in the woodsmoke

23   were 1,000 and 10,000 $\mu g/m^3$ PM. The particles in this woodsmoke had a bimodal size distribution with

24   the smaller size fraction (74%) characterized by a MMAD of 0.405 $\mu m$ and the larger size fraction (26%)

25   characterized by a MMAD of 6.7-11.7 $\mu m$. Many of these larger particles would not be inhalable by the

26   rat since 8 $\mu m$ MMAD particles are about 50% inhalable (Ménache et al., 1995). Concentrations of gases

27   were reported to be 15-106.4 ppm CO, 2.2-18.9 ppm NO, 2.4-19.7 ppm $NO_X$ and 3.5-13.8 ppm total

28   hydrocarbon in these exposures. Respiratory function measured by whole-body plethysmography

29   demonstrated a statistically significant increase in total pulmonary resistance in rats exposed to

1    1000 µg/m$^3$ woodsmoke. Additional effects were found at 10,000 µg/m$^3$. Inflammatory and

2    histopathological responses were also evaluated (see Sections 7.3.3.2 and 7.3.5.1).


# 7.3.3. Pulmonary Inflammation

## 7.3.3.1. Epidemiologic Studies

3    One epidemiologic study examined the relationship of airway inflammation (eNO) and PM

4    measures, other pollutants, and indicators of motor vehicle emissions in Windsor, Ontario (Dales et al.,

5    2008). This cohort of 2402 school children estimated PM$_{2.5}$ and PM$_{10}$ for each child's residence at the

6    postal code level with an evaluated statistical model (Wheeler et al., 2006b). Each 10 µg/m$^3$ increase in

7    1 year PM$_{2.5}$ was associated with a 39% increase in eNO (p = 0.058). Associations between eNO and

8    PM$_{10-2.5}$ were positive but not statistically significant.


## 7.3.3.2. Toxicological Studies

### CAPs Studies

9    An important set of subchronic studies involved exposure of normal (C57BL1/6) mice, ApoE$^{-/-}$ and

10   the double-knockout ApoE$^{-/-}$/LDLR$^{-/-}$ mice to Tuxedo, NY CAPs for 5-6 month (March, April or May

11   through September 2003; (Lippmann et al., 2005a). The average PM$_{2.5}$ exposure concentration was

12   110 µg/m$^3$. Animals were fed a normal chow diet during the CAPs exposure period. No pulmonary

13   inflammation was observed in response to CAPs exposure as measured by BALF cell counts and

14   histology. The lack of a persistent pulmonary response may have been due to adaptation of the lung

15   following repeated exposures. In fact, a parallel but preliminary study examined CAPs-related gene

16   expression in the double-knockout animals and found upregulation of numerous genes in lung tissue

17   (Gunnison and Chen, 2005). A second parallel study found daily variations in CAPs-mediated NFκB

18   activation in cultured human bronchial epithelial cells, suggesting that transcription factor-mediated gene

19   upregulation could occur in response to CAPs (Maciejczyk et al., 2005; Maciejczyk and Chen, 2005). It

20   should be noted that significant cardiovascular effects were observed in these subchronic studies which

21   are discussed in Section 7.2.1.2.

22   Araujo et al. (2008) compared the relative impact of ultrafine (0.01–0.18 µm) versus fine

23   (0.01-2.5 µm) PM inhalation in ApoE$^{-/-}$ mice following a 40 day exposure (5 hours/day × 3 days/week for

24   75 total hours). Animals were on a normal chow diet and exposed to PM from November 3–December 12,

25   2005 in a mobile inhalation laboratory that was parked 300 m from the 110 Freeway in downtown Los

26   Angeles. Particles were concentrated to ~440 µg/m$^3$ for the fine exposures and ~110 µg/m$^3$ for the

1    ultrafine exposures, representing a roughly 15-fold increase in concentration from ambient levels; the

2    number concentration of PM in the fine and ultrafine chambers were roughly equivalent ($4.56\times10^5$ and

3    $5.59\times10^5$ particles/cm$^3$, respectively). Over 50% of the ultrafine PM was comprised of organic carbon

4    compared to only 25% for PM$_{2.5}$. No major increase in BALF inflammatory cells was found in response

5    to PM. However ultrafine PM exposure resulted in significant cardiovascular and systemic effects (see

6    Section 7.2.1).

### Diesel Exhaust

7    Ishihara and Kagawa (2003) exposed Wistar rats to filtered air and DE containing

8    PMconcentrations of 200, 1,000 and 3,000 μg/m$^3$ for 16 /day and 6 days/week for 6, 12, 18 or 24 months.

9    The mass median particle diameter was reported to be between 0.3 and 0.5 μm. Concentrations of gases

10    ranged from 2.93-35.67 ppm NO$_X$, 0.23-4.57 ppm SO$_2$, 1.8-21.9 ppm CO in the DE exposures.

11    Statistically significant increases in total numbers of inflammatory cells and neutrophils in BALF were

12    observed beginning at 6-12 months of exposure to DE containing 1,000 and 3,000 μg/m$^3$ PM. When rats

13    were exposed to DE containing 1,000 μg/m$^3$ PM, which was filtered to remove PM, the inflammatory cell

14    response was significantly diminished. These results indicate that the PM fraction of DE was mainly

15    responsible for the observed influx of inflammatory cells into the lung under those exposure conditions.

16    The PM fraction was also found to mediate the increase in protein levels (see Section 7.3.4.1), decrease in

17    PGE$_2$ levels and alterations in mucus and surfactant components observed in BALF.

18    Li et al. (2007) exposed BALB/c and C56BL/6 mice to clean air or to low dose DE (low dose DE

19    at a PM concentration of 100 μg/m$^3$) for 7 h/day and 5 days/week for 1, 4 and 8 weeks. Average gas

20    concentrations were reported to be 3.5 ppm CO, 2.2 ppm NO$_2$, and less than 0.01 ppm SO$_2$. Increases in

21    numbers of BALF macrophages and total inflammatory cells were observed in BALB/c mice at eight

22    weeks but not four weeks of DE exposure. Persistent increases in numbers of BALF neutrophils and

23    Lymphocytes were observed in both strains at four and eight weeks of DE exposure. Persistent increases

24    in BALF cytokines also were observed at four and eight weeks of DE exposure, although the responses

25    differed between the two strains. These results should be interpreted with caution since comparisons were

26    made with Day 0 controls rather than age-matched controls. No histopathological changes in the lungs

27    were seen at any time point after DE exposure. This study demonstrates differences in pulmonary

28    responses to low dose DE between 2 mouse strains. Airway hyperresponsiveness, pulmonary

29    inflammation, markers of oxidative stress and effects of antioxidant intervention were also evaluated (see

30    Sections 7.3.2.2 and 7.3.4.1). Although no attempt was made in this study to determine the effects of

31    gaseous components of DE on the measured responses, concentrations of gases were very low suggesting

32    that PM may have been responsible for the observed effects.

1    In a study by Hiramatsu et al. (2003), BALB/c and C57BL/6 mice were exposed to DE (PM

2    concentrations 100 and 3000 $\mu g/m^3$) for 1 or 3 months. Concentrations of gases were reported to be 3.5-

3    9.5 ppm CO, 2.2-14.8 ppm $NO_X$, and less than 0.01 ppm $SO_2$. Modest increases in BALF neutrophils and

4    lymphocytes were observed in response to DE in both mouse strains at 1 and 3 months. Histological

5    analysis demonstrated DEP-laden alveolar macrophages in alveoli and peribronchial tissues at both time

6    points. Bronchus-associated lymphoid tissue developed after 3 months exposure to the higher

7    concentration of DE in both mouse strains. Mac-1 positive cells (a marker of phagocytic activation of

8    alveolar macrophages) were also increased in BALF of BALB/c mice exposed to the higher concentration

9    of DE for 1 and 3 months. Increased expression of several cytokines and decreased expression of iNOS

10   mRNA was observed in DE-exposed mice at 1 and 3 months. NFκB activation was also noted following 1

11   month exposure to the lower concentration of DE. No attempt was made in this study to determine the

12   responses to gaseous components of the DE.

13   In a study by Reed et al. (2004), healthy Fisher 344 rats and A/J mice were exposed to DE (PM

14   concentration = 30, 100, 300 and 1000 $\mu g/m^{3)}$ by whole body inhalation for 6 h/day, 7 days/week for

15   either 1 week or 6 months. Concentrations of gases were reported to be 2.0-45.3 ppm NO, 0.1-4.0 ppm

16   $NO_2$, 1.5-29.8 ppm CO and 8-365 ppb $SO_2$. Short-term responses are discussed in Section 6.3.3.3 and

17   6.3.7.1, and sub-chronic systemic effects are presented in Section 7.2.3.1. Six months of exposure resulted

18   in no measurable effects on pulmonary inflammation. However numerous black particles were observed

19   within alveolar macrophages after 6 months of exposure.

20   Seagrave et al. (2005b) evaluated pulmonary responses in male and female CDF (F-344)/CrlBR

21   rats exposed 6 h/day for 6 months to filtered air or DE at concentrations ranging from 30-1000 $\mu g/m^3$ PM.

22   Concentrations of gases were reported for the highest exposure as 45.3 ppm NO, 4.0 ppm $NO_2$, 29.8 ppm

23   CO and 2.2 ppm total vapor hydrocarbon. No changes in BALF cells were noted. A small decrease in

24   TNFα was seen in BALF of female rats exposed to the highest concentration of DE for 6 months.

25   Pulmonary injury also was evaluated (Section 7.3.5.1). Thus changes in BALF markers are modest and

26   gender specific.

## *Woodsmoke*

27   Seagrave et al. (2005b) also evaluated pulmonary responses in male and female CDF (F344)/CrlBR

28   rats exposed 6 h/day for 6 months to filtered air or HWS concentrations ranging from 30-1000 $\mu g/m^3$ PM.

29   Concentrations of gases were reported for the highest exposure as 3.0 ppm CO and 3.1 ppm total vapor

30   hydrocarbon. A small increase in BALF neutrophils was observed in male rats exposed to the lowest

31   concentration of HWS. Pulmonary injury was evaluated in Section 7.3.5.1. Female rats exhibited a

32   decrease in BALF MIP-2 at the highest concentration of HWS. Pulmonary injury also was evaluated

1    (Section 7.3.5.1). In general, responses to HWS were more remarkable than responses to DE seen in the

2    same study. However these gender-specific responses are modest and difficult to interpret.

3    In a study by Reed et al. (2006), Fisher 344 rats, SHR rats, A/J mice and C57BL/6 mice were

4    exposed to clean air or HWS (PM concentrations 30, 100, 300 and 1000 $\mu g/m^{3)}$ by whole body inhalation

5    for 6 h/day, 7 days/week for either 1 week or 6 months. Concentrations of gases ranged from 229.0-

6    14887.6 $mg/m^3$ for CO, 54.9-139.3 $\mu g/m^3$ for ammonia, and 177.6- 3455.0 $\mu g/m^3$ nonmethane VOC in

7    these exposures. Short-term responses are discussed in Section 6.3.7.1 and sub-chronic effects are

8    presented in Section 7.2.3.1. Histological analysis of lung tissue showed minimal increases in alveolar

9    macrophages. The effects of HWS on bacterial clearance are discussed below (Section 7.3.7.1).

10   Another study evaluated the effects of subchronic woodsmoke exposure in Brown Norway rats,

11   which are considered an animal model of allergy. Rats were exposed 3 h/day and 5 days/week for 4 and

12   12 weeks to air or to concentrated woodsmoke from the pinon pine which is native to the U.S. Southwest

13   (Tesfaigzi et al., 2002). PM concentrations in the woodsmoke exposures were 1,000 and 10,000 $\mu g/m^{3.}$

14   The particles in this woodsmoke had a bimodal size distribution with the smaller size fraction (74%)

15   characterized by a MMAD of 0.405 $\mu m$ and the larger size fraction (26%) characterized by a MMAD of

16   6.7-11.7 $\mu m$. Many of these larger particles would not be inhalable by the rat since 8 $\mu m$ MMAD particles

17   are about 50% inhalable (Ménache et al., 1995). Concentrations of gases were reported to be 15-106.4

18   ppm CO, 2.2-18.9 ppm NO, 2.4-19.7 ppm $NO_X$ and 3.5-13.8 ppm total hydrocarbon in these exposures.

19   Numbers of alveolar macrophages in BALF were significantly increased in rats exposed to 1000 $\mu g/m^3$

20   woodsmoke for 12 weeks, but no changes were seen in numbers of other inflammatory cells. A large

21   percent of BALF macrophages contained carbonaceous material. Histological analysis of lung tissue

22   showed minimal to mild inflammation in the epiglottis of the larynx in rats exposed to both

23   concentrations of woodsmoke.

# 7.3.4. Pulmonary Oxidative Response

## 7.3.4.1. Toxicological Studies

### *Diesel Exhaust*

24   Li et al. (2007) exposed BALB/c and C56BL/6 mice to clean air or to low dose DE (PM

25   concentration 100 $\mu g/m^3$) for 7 h/day and 5 days/week for 1, 4 and 8 weeks. Average gas concentrations

26   were reported to be 3.5 ppm CO, 2.2 ppm $NO_2$, and less than 0.01 ppm $SO_2$. Markers of oxidative stress

27   and effects of antioxidant intervention were evaluated in this model. While HO-1 mRNA and protein were

28   increased in lung tissues of both mouse strains after 1 week of DE exposure (see Section 6.3.4.2), at

1   8 weeks of DE exposure, HO-1 protein levels remained high in C57BL/6 mice but returned to control

2   values in BALB/c mice. This study demonstrates differences in pulmonary responses to low dose DE

3   between two mouse strains. Furthermore, this study suggests that adaptation occurs in BALB/C mice

4   during prolonged DE exposure since the increase in HO-1 protein seen in both strains at 1 week of

5   exposure was only seen in C57BL/6 mice at 8 weeks. Airway hyperresponsiveness (Section 7.3.2.2) and

6   pulmonary inflammation (Section 7.3.3.2) were also evaluated. Although no attempt was made in this

7   study to determine the effects of gaseous components of DE on the measured responses, concentrations of

8   gases were very low. This suggests that PM may have been responsible for the observed effects.

## 7.3.5. Pulmonary Injury

### 7.3.5.1. Toxicological Studies

#### *Urban Air*

9    Prolonged exposure to low levels of ambient air pollution beginning in early life has been linked to

10   secretory changes in the nasal cavity of mice, specifically increased production of acidic mucosubstances

11   (Pires-Neto et al., 2006). Six day-old Swiss mice were continuously chamber exposed to ambient or

12   filtered Säo Paulo air for 5 months. Concentrations in the "polluted chamber" vs. "clean chamber" were

13   (in $\mu g/m^3$) 59.52 vs. 37.08 for $NO_2$, 12.52 vs. 0 for BC, and 46.49 vs. 18.62 for $PM_{2.5}$. Thus, pollutant

14   levels were reduced by filtration but not entirely eliminated. Compared to filtered air, exposure to ambient

15   air resulted in increased total mucus and acidic mucus in the epithelium lining the nasal septum, but no

16   statistically significant differences in other parameters (amount of neutral mucus, volume proportions of

17   neutral mucus, total mucus, or nonsecretory epithelium, epithelial thickness, or ratio between neutral and

18   acidic mucus). The physicochemical properties of mucus glycoproteins are critical to the protective

19   function of the airway mucus layer. Acidified mucus is more viscous, and is associated with a decrease in

20   mucociliary transport. Thus acidic mucosubstances may represent impaired defense mechanisms in the

21   respiratory tract.

22   An important new study evaluated the effects of chronic exposure to ambient levels of urban

23   particles on lung development in the mouse (Mauad et al., 2008). Both functional and anatomical indices

24   of lung development were measured. Male and female BALB/c mice were continuously exposed to

25   ambient or filtered Säo Paulo air for 8 months. Concentrations in the "polluted chamber" vs. "clean

26   chamber" were 16.8 vs. 2.9 $\mu g/m^3$ $PM_{2.5}$. Thus PM levels were reduced by filtration but not entirely

27   eliminated. Ambient concentrations of CO, $NO_2$ and $SO_2$ were 1.7 ppm, 89.4 $\mu g/m^3$ and 8.1 $\mu g/m^3$,

28   respectively. Concentrations of gaseous pollutants were assumed to be similar to ambient levels in both

1    chambers. After 4 months, the animals were mated and the offspring were divided into 4 groups to

2    provide for a prenatal exposure group, a postnatal exposure group, a pre- and postnatal exposure group

3    and a control group. Animals were sacrificed at 15 and 90 days of age for histological analysis of lungs.

4    Histological analysis demonstrated the presence of mild foci of macrophages containing black dots of

5    carbon pigment in the prenatal and postnatal exposure group at 90 days. In addition, the alveolar spaces of

6    15-day old mice in the prenatal and postnatal exposure group were enlarged compared with controls.

7    Morphometric analysis demonstrated statistically significant decreases in surface to volume ratio at 15

8    and 90 days in the pre and postnatal group compared with controls. Since alveolarization is normally

9    complete by 15 days of age, these results suggest incomplete alveolarization in the 15-day old group and

10   an enlargement of air spaces in the 90-day old group. These anatomical changes correlated with

11   decrements in pulmonary function which are discussed in Section 7.3.2.2.

12       Kato et al. (2003) exposed Wistar rats to roadside air contaminated mainly with automobile

13   emissions (55.7 to 65.2 ppb $NO_2$ and 63 to 65 $\mu g/m^3$ suspended PM [SPM]) and examined the effects on

14   respiratory tissue after 24, 48, or 60 weeks of exposure. The surface of the lungs was light gray in color

15   after all durations of exposure, and BC particle deposits accumulated with prolonged exposure. These

16   characteristics were not evident in filtered air-exposed control animals, although filtered air contained low

17   levels of air pollutants ($\leq 6.2$ ppb $NO_2$ and 15 $\mu g/m^3$ SPM). The most common change observed using

18   transmission electron microscopy was the presence of particle laden (anthracotic) alveolar macrophages,

19   or anthracosis, in a wide range of pulmonary tissues, including the submucosa, tracheal- and bronchiole-

20   associated lymph nodes, alveolar wall and space, pleura, and perivascular connective tissue. These

21   changes were evident after 24 weeks and increased with duration of exposure. Other changes included

22   increases in the number of mucus granules in goblet cells, mast cell infiltration (but no degranulation)

23   after 24 weeks, and increased lysosomes in ciliated cells, some altered morphology of Clara cells, and

24   hypertrophy of the alveolar walls after 48 weeks. No goblet cell proliferation was observed, but slight,

25   variable acidification of mucus granules appeared after 24 and 48 weeks and disappeared after 60 weeks.

26   Anthracotic macrophages were seen in contact with plasma cells and lymphocytes in the lymphoid tissue,

27   suggesting immune cell interaction in the immediate vicinity of particles. Even after 60 weeks, no lymph

28   node anthracosis was observed in the filtered air group.

29       In a post-mortem study of lung tissues from 20 female lifelong residents of Mexico City, a high PM

30   locale, histology demonstrated significantly greater amounts of fibrous tissue and muscle in the airway

31   walls compared to subjects from Vancouver (Churg et al., 2003), a city with relatively low PM levels.

32   Electron microscopy showed carbonaceous aggregates of ultrafine particles, which the authors conclude

33   penetrate into and are retained in the walls of small airways. The study shows an association between

34   retained particles and airway remodeling in the form of excess muscle and fibrotic walls. The subjects

1   were deemed suitable for examination based on never-smoker status, no use of biomass fuels for cooking,

2   no known occupational particle/dust exposure, death by cause other than respiratory disease, and

3   extended residence in each locale (lifelong for Mexico City and >20 years for Vancouver). However,

4   subjects from the two locales were not matched with respect to ethnicity, sex (20 females from Mexico

5   City vs. 13 females and 7 males from Vancouver), or mean age at death ($66 \pm 9$ vs. $76 \pm 11$), and other

6   possibly influential factors such as exercise or diet were not considered.

### Diesel Exhaust

7   Ishihara and Kagawa (2003) exposed Wistar rats to filtered air and DE (PM concentrations of 200,

8   1000 and 3000 $\mu g/m^{3)}$ for 16/day and 6 days/week for 6, 12, 18 or 24 months. Concentrations of gases

9   ranged from 2.93-35.67 ppm $NO_X$, 0.23-4.57 ppm $SO_2$, 1.8-21.9 ppm CO in the DE exposures. A

10  statistically significant increase in BALF protein was observed at 12 months of exposure to DE

11  containing 1000 $\mu g/m^3$ PM. This response was attenuated when the DE was filtered to remove PM.

12  Pulmonary inflammation was noted also (Section 7.3.4).

13  Seagrave et al. (2005b) evaluated pulmonary responses in male and female CDF (F-344)/CrlBR

14  rats exposed 6 h/day for 6 months to filtered air or DE at PM concentrations ranging from 30-1000 $\mu g/m^3$.

15  Concentrations of gases were reported for the highest exposure as 45.3 ppm NO, 4.0 ppm $NO_2$, 29.8 ppm

16  CO and 2.2 ppm total vapor hydrocarbon. A small increase in LDH was seen in BALF of female rats

17  exposed to the highest concentration of DE for 6 months. Pulmonary inflammation was evaluated also

18  (Section 7.3.3.2). The changes in BALF markers in this study were modest and gender specific.

### Woodsmoke

19  Seagrave et al. (2005b) also evaluated pulmonary responses in male and female CDF

20  (F-344)/CrlBR rats exposed 6 h/day for 6 months to filtered air or HWS with PM concentrations ranging

21  from 30-1000 $\mu g/m^3$. Concentrations of gases were reported for the highest exposure as 3.0 ppm CO and

22  3.1 ppm total vapor hydrocarbon. Increases in BALF LDH and protein were seen in male but not female

23  rats exposed to 100 and 300 $\mu g/m^3$ HWS. Female rats exhibited a decrease in BALF glutathione at the

24  highest concentration of HWS. Decreases in BALF alkaline phosphatase were found in both males and

25  females exposed to 1000 $\mu g/m^3$ HWS. Male rats exposed to 100 and 300 $\mu g/m^3$ HWS exhibited a

26  decrease in BALF β-glucuronidase activity. Pulmonary inflammation was evaluated also (Section

27  7.3.3.2). These changes in BALF markers in this study were modest and gender specific.

28  Another study evaluated the effects of subchronic woodsmoke exposure in Brown Norway rats.

29  Animals were exposed 3 h/day and 5 days/week for 4 and 12 weeks to air or concentrated wood smoke

30  from the pinon pine which is native to the U.S. Southwest (Tesfaigzi et al., 2002). PM concentrations in

1    the woodsmoke exposure were 1,000 and 10,000 µg/m$^{3.}$ The particles in this woodsmoke had a bimodal

2    size distribution with the smaller size fraction (74%) characterized by a MMAD of 0.405 µm and the

3    larger size fraction (26%) characterized by a MMAD of 6.7-11.7 µm. Many of these larger particles

4    would not be inhalable by the rat since 8 µM MMAD particles are about 50% inhalable (Ménache et al.,

5    1995). Concentrations of gases were reported to be 15-106.4 ppm CO, 2.2-18.9 ppm NO, 2.4-19.7 ppm

6    NO$_X$ and 3.5-13.8 ppm total hydrocarbon in these exposures. Exposure to 1,000 µg/m$^3$ woodsmoke for

7    12 weeks resulted in a statistically significant increase in Alcian Blue- (AB) and Periodic Acid Schiff-

8    (PAS) positive airway epithelial cells compared to controls, indicating an increase in mucous secretory

9    cells containing neutral and acid mucus, respectively. More significant histopathological responses were

10   found following exposure to 10,000 µg/m$^3$ of DE. Pulmonary function and inflammation were evaluated

11   also but are not discussed here due to the extremely high exposure level (Sections 7.3.2.2 and 7.3.3.2).

# 7.3.6. Allergic Responses

## 7.3.6.1. Toxicological Studies

### Diesel Exhaust

12   Exposure to relatively low doses of DE has been shown to exacerbate asthmatic responses in OVA

13   sensitized and challenged BALB/c mice (Matsumoto et al., 2006). Mice were intraperitoneally sensitized

14   and intranasally challenged 1day prior to inhalation exposure to DE (PM concentration 100 µg/m$^3$; CO,

15   3.5 ppm; NO$_2$, 2.2 ppm; SO$_2$ <0.01 ppm) for 1 day or 1, 4, or 8 weeks (7/h/day, 5 days/week, endpoints

16   12-h post DE exposure). Results from the 1- and 4-week exposures are described in Section 6.3.6.2. It

17   should be noted that control mice were left in a clean room as opposed to undergoing chamber exposure

18   to filtered air. The significant increases in AHR and airway sensitivity observed following shorter

19   exposure periods did not persist at 8 weeks. BALF cytokines were altered by DE exposure with only

20   RANTES significantly elevated after 8 weeks. DE had no effect on OVA challenge-induced peribronchial

21   inflammatory or mucin positive cells. These results suggest that adaptive processes may have occurred

22   during prolonged exposure to DE.

### Woodsmoke

23   In a study by Tesfaigzi et al. (2005), Brown Norway rats were sensitized and challenged with

24   ovalbumin. Rats were exposed for 70 days to filtered air or to 1000 µg/m$^3$ HWS. Particles were

25   characterized by a MMAD of 0.36 µm. Concentrations of gases were reported to be 13.0 ppm CO and 3.1

26   ppm total vapor hydrocarbon with negligible NO$_X$. Respiratory function was measured in anesthetized

1   animals by whole-body plethysmography and demonstrated a significant increase in functional residual

2   capacity as well as a significant increase in dynamic lung compliance in HWS-exposed animals compared

3   to controls. No change in total pulmonary resistance or airway responsiveness to methacholine was

4   observed. BALF inflammatory cells were not increased, although histological analysis demonstrated focal

5   inflammation including granulomatous lesion and eosinophilic infiltrations in HWS-exposed rats.

6   Alterations of several cytokines in BALF and plasma were noted. Changes in airway epithelial mucus

7   cells and intraepithelial stored mucosubstances were modest and did not achieve statistical significance.

8   Results of this study demonstrate that subchronic exposure to HWS had minimal effects on pulmonary

9   responses in a rat model of allergen sensitization and challenge.

# 7.3.7. Host Defense

## 7.3.7.1. Toxicological Studies

### *Diesel Exhaust*

10  DE may affect systemic immunity. The proliferative response of A/J mouse spleen cells following

11  stimulation with T cell mitogens was suppressed by 6 months of daily exposure to DE at concentrations at

12  or above 300 µg/m$^3$ PM (Burchiel et al., 2004). B cell proliferation was increased at 300 µg/m$^3$ but

13  unaffected at higher concentrations (up to 1000 µg/m$^3$). Concentrations of gases were not reported. The

14  immunosuppressive effects of DE were not due to PAHs or benzo(a)pyrene (BaP)-quinones (BPQs) since

15  there were little, if any, of these compounds present in the chamber atmosphere. It should be noted that

16  sentinel animals were negative for mouse parvovirus at the start of the study, but seroconverted by the end

17  of the study, indicating possible infection. Parvovirus can interfere with the modulation of lymphocyte

18  mitogenic responses (Baker, 1998).

### *Woodsmoke*

19  One study demonstrated immunosuppressive effects of HWS (Burchiel et al., 2005). Exposure to

20  HWS increased proliferation of T cells from A/J mice exposed daily to 100 µg/m$^3$ PM for 6 months, but

21  produced a concentration-dependent suppression of proliferation at PM concentrations >300 µg/m$^3$. No

22  effects on B cell proliferation were observed. Concentrations of NO and NO$_2$ were not detectable or <40

23  ppb for all exposure levels. CO was reported to be 2, 4, and 13 ppm for the 100, 300 and 1000 µg/m$^3$ PM

24  concentrations, respectively. Exposure atmospheres contained significant levels of naphthalene and

25  methylated napthalenes, fluorene, phenanthrene, and anthracene, as well as low concentrations of several

26  metals (K, Ca, and Fe) (Burchiel et al., 2005). It should be noted that serologic analysis of study sentinel

1   animals indicated infection with parvovirus, which can interfere with the modulation of lymphocyte

2   mitogenic responses (Baker, 1998).

# 7.3.8. Summary and Causal Determination

## 7.3.8.1. PM$_{10}$

3       Recent long-term, prospective cohort studies support the positive association between respiratory

4   symptoms and ambient PM$_{10}$ concentrations reported in the 2004 PM AQCD. This includes evidence for a

5   reduction of symptoms corresponding to decreasing PM$_{10}$ levels in a "natural experiment" in a cohort of

6   Swiss school children. Epidemiologic studies provide evidence of a consistent and coherent relationship

7   between PM$_{10}$ levels and decrements in lung function and lung function growth (Figure 7.4), confirming

8   the relationship reported in the 2004 PM AQCD. **Overall, the evidence is sufficient to conclude that**

9   **the relationship between long-term PM$_{10}$ exposure and respiratory morbidity is likely to be causal.**

10      The epidemiologic studies reviewed in the 2004 PM AQCD suggested positive relationships

11  between long-term PM$_{10}$ exposure and increased incidence of respiratory symptoms and disease. The

12  expanded body of evidence available now includes prospective cohort studies conducted by different

13  researchers in different locations. In the U.S., studies include those from the CHS cohort (e.g., Islam et

14  al., 2007; McConnell et al., 2003), the national cystic fibrosis study (Goss et al., 2004) and a study in San

15  Francisco by Kim et al. (2004). These, along with studies conducted in Europe, build upon the evidence

16  available in the 2004 PM AQCD. Bayer-Oglesby et al. (2005) provide evidence, in a cohort consisting of

17  school children, for respiratory symptoms reduction where PM levels are decreasing. A major challenge to

18  interpreting the results of these studies is that the PM measures and concentrations of other air pollutants

19  are often correlated; however, the consistency of findings across different locations supports an

20  independent effect of PM$_{10}$. Overall there is a growing database relating respiratory symptoms and disease

21  incidence to long-term PM$_{10}$ exposure in U.S. communities that is supported by similar results from other

22  studies outside the U.S.

23      The 2004 PM AQCD also suggested positive relationships for pulmonary function declines with

24  long-term exposure to PM$_{10}$. Recent studies have been conducted in the U.S. with the national cystic

25  fibrosis cohort by Goss et al. (2004) and the CHS by Gauderman et al. (2004). These build on the

26  database for the U.S. of the previously reviewed studies in other U.S. locations (Raizenne et al., 1996)

27  and on earlier CHS results (e.g., Avol et al., 2001; Gauderman et al., 2000; 2002), showing a pattern of

28  reductions in lung function with increased long-term PM$_{10}$ exposures. These are supported by other

29  longitudinal cohort studies conducted in other countries (Nordling et al., 2008; Oftedal et al., 2008; Rojas-

1 Martinez et al., 2007). In addition, Downs et al. (2007) report an association between a decrease in PM

2 and pulmonary function declines in a cohort of adults. The studies provide a consistent and coherent

3 relationship between PM exposure and change in lung function. However, the strong correlation between

4 PM and other pollutants again complicates the identification of PM as an independent causal factor.

### 7.3.8.2. PM$_{2.5}$

5 The 2004 PM AQCD suggested a positive relationship between PM$_{2.5}$ and lung function

6 decrements reported in the CHS and increased bronchitis. Recent epidemiologic studies support these

7 findings and provide additional evidence of associations between PM$_{2.5}$ and lung function decrements and

8 increased respiratory symptoms/asthma medication use. In the 2004 PM AQCD, no long-term exposure

9 toxicological studies were available. Recent subchronic and chronic toxicological studies provide some

10 evidence of altered pulmonary function, mild inflammation, oxidative responses, histopathological

11 changes including mucus cell hyperplasia and immune suppression in response to CAPs, DE, roadway air

12 and woodsmoke. Allergic animals demonstrated AHR in response to DE. In some cases, adaptation to

13 prolonged exposures was observed. In addition, pre- and postnatal exposure to ambient levels of urban

14 particles was found to affect mouse lung development. Impaired lung development is one mechanism by

15 which PM exposure may decrease lung function growth in children. **Collectively, the evidence is**

16 **sufficient to conclude that the relationship between long-term PM$_{2.5}$ exposure and respiratory**

17 **morbidity is likely to be causal.**

### *Respiratory symptoms/disease*

18 The epidemiologic studies reviewed in the 2004 PM AQCD suggested relationships between PM$_{2.5}$

19 (PM$_{2.1}$) and bronchitis in the 24-city cohort of Dockery et al. (1996). In the U.S., new PM$_{2.5}$ studies show

20 associations with respiratory symptoms and with asthma (Goss et al., 2004; Islam et al., 2007; Kim et al.,

21 2004; McConnell et al., 2003). These are supported by studies outside the U.S. (Annesi-Maesano et al.,

22 2007; Brauer et al., 2007). Brauer et al. (2007) confirm the results of Islam et al. (2007) for the

23 relationship between asthma and PM. Because they represent a different research group, in a different

24 cohort and a different design and analysis, their results add to the strength of the observations. The within-

25 community results of McConnell et al. (2003) for bronchitic symptoms were larger than the between-

26 community results. There are less likely confounding effects because of the within community aspect.

27 This provides direct evidence that reduction in air pollutants could result in improved respiratory health in

28 children.

## Pulmonary Function

1   The epidemiologic studies reviewed in the 2004 PM AQCD suggested relationships between long-
2   term exposure to $PM_{2.5}$ and pulmonary function decrements in the CHS (Gauderman et al., 2000; 2002)
3   which added to the database of the earlier 22-city study of $PM_{2.1}$ (Raizenne et al., 1996). In the U.S., new
4   $PM_{2.5}$ studies show associations with reduced pulmonary function (Gauderman et al., 2004; Goss et al.,
5   2004; Islam et al., 2007). These are supported by studies outside the U.S. (Dales et al., 2008; Oftedal et
6   al., 2008). A subset of the $PM_{2.5}$ measurements in the CHS also show associations for EC, OC, and acid
7   vapor as presented by Gauderman et al. (2004) and Islam et al. (2007).

8   Recent toxicological studies demonstrate alterations in pulmonary function; AHR was increased
9   following 4, but not 8, weeks of exposure to low dose DE in one of two non-allergic mouse strains (Li et
10  al., 2007). Adaptation may have occurred during the prolonged exposure. Total pulmonary resistance was
11  increased in rats exposed for 4 and 12 weeks to woodsmoke (Tesfaigzi et al., 2002). In addition, an
12  important new study demonstrated that pre- and postnatal exposure to ambient levels of urban particles
13  affected mouse lung development, as measured by anatomical and functional indices (Mauad et al., 2008).
14  These results provide biological plausibility for the epidemiologic findings of reduced lung function
15  growth in children.

## Pulmonary Inflammation

16  One epidemiologic study found an increase in eNO among schoolchildren (Dales et al., 2008).
17  Recent toxicological studies demonstrate variable inflammatory responses with PM exposure.
18  Toxicological studies involving subchronic exposure to CAPs found little or no pulmonary inflammation
19  (Araujo et al., 2008; Lippmann et al., 2005a). Pulmonary inflammation was observed in 3 out of 5 studies
20  involving subchronic exposure to DE (Hiramatsu et al., 2003; Ishihara and Kagawa, 2003; Li et al., 2007).
21  One of the three studies with positive results found that gaseous components of DE had minimal effects
22  (Ishihara and Kagawa, 2003). Subchronic woodsmoke exposure resulted in pulmonary inflammation in 2
23  (Seagrave et al., 2005b; Tesfaigzi et al., 2002) out of 3 studies.

## Oxidative Responses

24  One new toxicological study demonstrated increases in lung HO-1 protein and mRNA levels
25  following 4 weeks of DE exposure in two mouse strains (Li et al., 2007). This effect persisted over 8
26  weeks of DE exposure in one strain but not the other.

## Pulmonary Injury

1    Recent toxicological studies demonstrate mild injury as assessed by BALF markers and
2    histopathological responses. Injury was observed in rats exposed for 12 months to DE (Ishihara and
3    Kagawa, 2003). This effect was attenuated when the exhaust was filtered to remove PM.
4    Histopathological changes were observed in some long-term studies. Nasal and airway mucous cell
5    hyperplasia was seen in mice following long-term exposure to urban air from a heavily-trafficked area.
6    These changes were accompanied by an increase in total and acidic mucus production which can lead to a
7    loss of mucus-mediated protective functions (Pires-Neto et al., 2006). Long-term exposure of rats to
8    roadside air resulted in mast cell infiltration and hypertrophy of alveolar walls (Kato and Kagawa, 2003).
9    Airway mucous cell hyperplasia was observed in rats following long-term woodsmoke exposure
10    (Tesfaigzi et al., 2002). Both neutral and acidic mucus producing cells were increased in number. In
11    addition, an important new study demonstrated that pre- and postnatal exposure to ambient levels of urban
12    particles affected mouse lung development, as measured by changes in pulmonary surface to volume
13    ratios and by changes in lung function (Mauad et al., 2008). A study reviewed in Section 6.3.4.2 also
14    suggested that the developing lung may be susceptible to PM since acute exposure to ultrafine-soot PM
15    decreased cell proliferation in the proximal alveolar region of neonatal rats (Pinkerton et al., 2004).
16    Impaired lung development is a viable mechanism by which PM may reduce lung function growth in
17    children.

## Allergic Responses

18    Recent toxicological studies suggest that adaptive processes may have occurred during prolonged
19    exposures. Allergic mice exposed for 8 weeks to DE did not exhibit the AHR response observed at 1 and
20    4 weeks of exposure (Matsumoto et al., 2006). A long-term exposure study of woodsmoke exposure in
21    allergic rats demonstrated no increased AHR although focal inflammation and eosinophilic infiltration
22    was observed (Tesfaigzi et al., 2005).

## Host Defense

23    Recent toxicological studies demonstrate immune suppression, indicated by decreased proliferative
24    responses of T-cells in spleen, in mice exposed chronically to DE and woodsmoke (Burchiel et al., 2004;
25    Burchiel et al., 2005). In another study, exposure to woodsmoke did not alter bacterial clearance in
26    response to bacterial infection (Reed et al., 2006).

### 7.3.8.3. Ultrafine PM

1    The evidence is **inadequate to determine if a causal relationship exists between relevant UFP**

2    **exposures and long-term respiratory morbidity**. The 2004 PM AQCD did not report long-term

3    exposure studies for ulrafine PM. More recent studies involving subchronic exposure to ultrafine CAPs

4    found no major pulmonary inflammation (Araujo et al., 2008).

# 7.4. Reproductive, Developmental, Prenatal and Neonatal Outcomes

## 7.4.1. Epidemiologic Studies

5    This section evaluates and summarizes the scientific evidence on PM and developmental and

6    pregnancy outcomes and infant mortality. Infants and fetal development processes may be particularly

7    vulnerable to PM exposure, and although the physical mechanisms are not fully understood, several

8    hypotheses have been proposed involving direct effects on fetal health, altered placenta function, or

9    indirect effects on the mother's health (Bracken et al., 2003; Clifton et al., 2001; Glinianaia et al., 2004;

10   Maisonet et al., 2004; Schatz et al., 1990; Šrám et al., 2005). Study of these outcomes can be difficult

11   given the need for detailed data and potential residential movement of mothers during pregnancy. Two

12   recent articles have reviewed methodological issues relating to the study of outdoor air pollution and

13   adverse birth outcomes (Ritz and Wilhelm, 2008; Slama et al., 2008). Some of the key challenges to

14   interpretation of these study results include the difficulty in assessing exposure as most studies use

15   existing monitoring networks to estimate individual exposure to ambient PM; the inability to control for

16   potential confounders such as other risk factors that affect birth outcomes (e.g., smoking); evaluating the

17   exposure window (e.g., trimester) of importance; and the need to study the physiological mechanism of

18   these effects (Ritz and Wilhelm, 2008; Slama et al., 2008). Another uncertainty is whether PM effects

19   differ by the child's sex. A review of pre-term birth and low birth weight studies found limited indication

20   that effects may differ by gender, however sample size was limited (Ghosh et al., 2007).

21   Previous summaries of the association between PM concentrations and pregnancy outcomes and

22   infant mortality were presented in periodic PM AQCDs. The 1996 PM AQCD concluded that while few

23   studies had been conducted on the link between PM and infant mortality, the research "suggested an

24   association," particularly for post-neonates (U.S. EPA, 1996). At the writing of the 2004 PM AQCD,

25   several studies conducted since the 1996 version provided additional evidence of PM's effect on fetal and

early postnatal development and mortality (U.S. EPA, 2004). At that time, it was concluded that while some studies indicated a relationship between PM and pregnancy outcomes, others did not. Studies identifying associations found that exposure to $PM_{10}$ early during pregnancy (first month of pregnancy) or late in the pregnancy (six weeks prior to birth) were linked with higher risk of preterm birth, including models adjusted for other pollutants, and that $PM_{2.5}$ during the first month of pregnancy was associated with interuterine growth restriction. However, other work did not identify relationships between $PM_{10}$ exposure and low birth weight. The state of the science at that time, as indicated in the 2004 PM AQCD, was that the research provided mixed results based on studies from multiple countries, and that additional research was required to better understand the impact of PM on pregnancy outcomes and infant mortality. The relationship between PM and these health responses, with particular emphasis on findings since the previous PM document, are summarized here. Over all, epidemiologic studies consistently report associations between $PM_{10}$ and $PM_{2.5}$ exposure and low birth weight and infant mortality, especially during the post-neonatal period. Animal evidence supports these associations with $PM_{2.5}$, but provides little mechanistic information or biologic plausibility. Information on the ambient concentrations of $PM_{10}$ and $PM_{2.5}$ in these study sites can be found in Table 7-5.

### Low Birth Weight

A large number of studies have investigated exposure to ambient PM and low birth weight at term. After briefly reviewing three older studies that measured total suspended particulates (TSP), this review will concentrate on studies that measured PM distinguished by size fraction.

In 1997, Wang et al. reported increased risks for low birth weight related to TSP exposure in Beijing, China (Wang et al., 1997). Women in four residential districts in Beijing were studied. Exposure was analyzed in quintiles and women in the fourth (437-497 $\mu g/m^3$) and fifth (498-618 $\mu g/m^3$) quintiles were at increased risk for low birth weight (OR = 1.15 [95% CI: 1.00–1.32], OR = 1.24 [95% CI: 1.08–1.42) compared to the lowest quintile. These are very high exposures and substantially in excess of current EPA standards, however, the comparison group was exposed to 211-280 $\mu g/m^3$. Actual risks of exposure may have been much higher, if compared to an unexposed group.

Lower levels of TSP were reported by Bobak in the Czech Republic (25th percentile = 54.8 $\mu g/m^3$, 50th percentile = 71.5 $\mu g/m^3$, 75th percentile = 86.9) (Bobak and Leon, 1999b). A 50 $\mu g/m^3$ increase in TSP was not associated with increased risk for low birth weight when the model was adjusted for gestational age. In Seoul, Korea slightly higher levels of TSP (25th percentile = 76.7 $\mu g/m^3$, 50th percentile = 82.3 $\mu g/m^3$, 75th percentile = 91.0 $\mu g/m^3$) were associated with increased risks of low birth weight for exposure in the first trimester (OR = 1.04 [95% CI: 1.00–1.08]), but not in the third trimester (OR = 0.95 [95% CI: 0.90–0.99]) (Ha et al., 2001).

1  More recent studies of the effect of PM on birth weight in the U.S. may be more relevant to EPA

2 regulation. Since 2000 one national study, as well as two studies in the northeast U.S., and four in

3 California have been conducted. Parker and Woodruff (2008) linked U.S. birth records for singletons

4 delivered at 40 weeks gestation in 2001-2003 during the months of March, June, September and

5 December to quarterly estimates of PM exposure by county of residence and month of birth. They found

6 an association between $PM_{10-2.5}$ and birthweight (-13 g [95% CI: -18.3 to -7.6]) per 10 $\mu g/m^3$ increase),

7 but no such association for $PM_{2.5}$.

8  Maisonet et al. (2001) analyzed 89,557 births (1994-96) in six northeastern cities (Boston and

9 Springfield MA, Hartford CT, Philadelphia and Pittsburgh PA, Washington DC). Each city had three $PM_{10}$

10 monitors measuring every sixth day. Results from multiple monitors were averaged in each city. Exposure

11 was determined for each trimester of pregnancy and categorized by quartiles, (<25, 25-30, 31-35, 36-

12 43 $\mu g/m^3$) and 95th percentile (>43$\mu g/m^3$). There was no increased risk for low birth weight at term

13 associated with $PM_{10}$ exposure during any trimester of pregnancy. When birth weight was considered as a

14 continuous outcome, exposure to $PM_{10}$ was not associated with a reduction in mean birth weight.

**Table 7-5. Characterization of ambient PM concentrations from studies of reproductive, developmental, prenatal and neonatal outcomes and long-term exposure.**

| Reference | Location | Mean Annual Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|
| *PM10* | | | |
| Bell et al. (2007b) | CT & MA | 22.3 | |
| Brauer et al. (2008) | Vancouver, Canada | 12.7 | Max: 35.4 |
| Chen et al. (2002) | Washoe County, NV | 31.53 | 75th: 39.35; Max: 157.32 |
| Gilboa et al. (2005) | TX | 23.8[a] | 75th: 29 |
| Ha et al. (2003) | Seoul, South Korea | 69.2 | 75th: 87.7; Max: 245.4 |
| Hansen et al. (2006) | Brisbane, Australia | 19.6 | Max: 171.7 |
| Hansen et al. (2007a) | Brisbane, Australia | 19.6 | 75th: 22.7; Max: 171.7 |
| Jalaludin et al. (2007) | Sydney, Australia | 16.3 | |
| Kim et al. (2007b) | Seoul, Korea | 88.7-89.7 | |
| Lee et al. (2003a) | Seoul, Korea | 71.1 | 75th: 89.3; Max: 236.9 |
| Leem et al. (2006) | Incheon, Korea | 53.8[a] | 75th: 64.6; Max: 106.39 |
| Lipfert et al. (2000) | U.S. | 33.1 | Max: 59 |
| Maisonet et al. (2001) | NE U.S. | 31.0[a] | 75th: 36.1; Max: 46.5 |
| Mannes et al. (2005) | Sydney, Australia | 16.8 | 75th: 19.9; Max: 104.0 |
| Pereira et al. (1998) | Sao Paulo, Brazil | 65.04 | Max: 192.8 |
| Ritz et al. (2000) | CA | 49.3 | Max: 178.8 |
| Ritz et al. (2006) | CA | 46.3 | Max: 83.5 |
| Rogers and Dunlop (2006) | GA | 3.2-7.8[a] | 75th: 15.07 |
| Romieu et al. (2004) | Ciudad Juarez, Mexico | 33.0-45.9 | |

| | | | |
|---|---|---|---|
| Salam et al. (2005) | CA | 45.4-46.6 | |
| Tsai et al. (2006b) | Kaohsiung, Taiwan | 81.5 | 75th: 111.5; Max: 232.0 |
| Wilhelm and Ritz (2005) | Los Angeles, CA | 39.1-42.2 | Max: 74.6-103.7 |
| Woodruff et al. (2008) | U.S. | 28.6-29.8[a] | 75th: 33.8-36.5 |
| Yang et al. (2006) | Taipei, Taiwan | 53.2 | 75th: 64.9; Max: 234.9 |
| *PM$_{2.5}$* | | | |
| Basu et al. (2004) | CA | 14.5-18.2 | Max: 26.3-34.1 |
| Bell et al. (2007b) | CT & MA | 22.3 | |
| Brauer et al. (2008) | Vancouver, Canada | 5.3 | Max: 37.0 |
| Huynh et al. (2006) | CA | 17.5-18.8 | |
| Jalaludin et al. (2007) | Sydney, Australia | 9.0 | |
| Liu et al. (2007b) | Multicity, Canada | 12.2 | 75th: 15 |
| Loomis et al. (1999) | Mexico City | 27.4 | Max: 85 |
| Mannes et al. (2005) | Sydney, Australia | 9.4 | 75th: 11.2; Max: 82.1 |
| Parker et al. (2005) | CA | 15.4 | |
| Ritz et al. (2007) | Los Angeles, CA | 18.6-21.4 | |
| Sagiv et al. (2005) | PA | 25.3-27.1 | Max: 68.9-156.3 |
| Wilhelm and Ritz (2005) | Los Angeles, CA | 21.0 | Max: 38.9-48.5 |
| Woodruff et al. (2006) | CA | 19.2[a] | 75th: 22.7 |
| Woodruff et al. (2008) | U.S. | 14.5-14.9 | 75th: 18.5-18.7 |

[a]Median concentration

1    In contrast, Bell et al. (2007b) reported positive associations for both PM$_{10}$ and PM$_{2.5}$ with birth

2    weight in a study of births (n = 358,504) in Connecticut and Massachusetts (1999-2002). Birth data

3    indicated county, not street address or ZIP code, so women were assigned exposure based on county

4    residence at delivery. The difference in birth weight per 10 μg/m$^3$ associated with PM$_{2.5}$ was -66.8 (95%

5    CI: 77.7 to -55.9) gm. For PM$_{10}$ it was -11.1 (95% CI: -15.0 to -7.2) gm. The increased risk for low birth

6    weight was OR = 1.054 (95% CI: 1.022–1.087) for PM$_{2.5}$ and OR = 1.027 (95% CI: 0.991–1.064) for

7    PM$_{10}$, based on average exposure during pregnancy. Reductions in birth weight were also associated with

8    third trimester exposure to PM$_{10}$ and second and third trimester exposure to PM$_{2.5}$. Comparing this study

9    to Maisonet et al. (2001), a larger sample size was able to detect a small increase in risk. In addition, birth

10    weight was reduced more by exposure to PM$_{2.5}$ than by exposure to PM$_{10}$. Measured PM$_{2.5}$ concentrations

11    were not available in the earlier study.

12    The Children's Health Study is a population based cohort of children living in 12 southern

13    California communities, selected on the basis of differing levels of air pollution (Salam et al., 2005). The

14    children in grades 4, 7 and 10 were recruited through schools. A subset of this cohort (n = 6,259) were

15    born in California from 1975-1987. Of these, birth certificates were located for 4,842, including 3,901

16    infants born at term and 72 cases of low birth weight at term. Using the mother's ZIP code at the time of

17    birth, exposure was determined by inverse distance weighting of up to 3 PM$_{10}$ monitors within 50 km of

18    the ZIP code centroid. If there was a PM$_{10}$ monitor within 5 km of the ZIP code centroid (40% of data),

1    exposure from that monitor was used. Exposure was calculated for the entire pregnancy, and for each

2    trimester of pregnancy. A 10 $\mu g/m^3$ increase in $PM_{10}$ during the third trimester reduced mean birth weight

3    -10.9 g (95% CI: -21.1 to -0.6) in single pollutant models, but became non-significant in multipollutant

4    models controlling for the effects of $O_3$. Increased risks of low birth weight (<2500 gm) were not

5    statistically significant (OR = 1.3 [95% CI: 0.9–1.9]). A strength of this study was the cohort data

6    available included information on SES and smoking during pregnancy. A limitation is the assignment of

7    exposure based on monitoring stations up to 50 km distant; this may have introduced significant

8    misclassification obscuring some associations.

9         Parker et al. examined births in California within 5 miles of a monitoring station (n = 18,247)

10   (Parker et al., 2005). Only infants born at 40 weeks gestation were included. Thus all infants were the

11   same gestational age, and had been exposed in the same year. Exposure to $PM_{2.5}$ in quartiles (<11.9,

12   11.9-13.9, 14.0–18.4, >18.4) was associated with decrements in birth weight. Infants exposed to

13   >13.9 $\mu g/m^3$ experienced reductions in birth weight (third quartile -13.7 g (95% CI: -34.2 to 6.9), fourth

14   quartile -36.1 g (95% CI: -55.8 to -16.5). These are larger reductions than have been seen in some other

15   studies. However, this study reduced misclassification by including only women living within 5 miles of a

16   monitoring station, and only included births at 40 weeks gestation. Reducing misclassification should lead

17   to a stronger association, if the association is causal.

18        The effects of spatial variation in exposure were also investigated by Wilhelm and Ritz (2005).

19   Their study included all women living in ZIP codes where 60% of the ZIP code was within two miles of a

20   monitoring station in the Southern California Basin, and women with known addresses in Los Angeles

21   County within 4 miles of a monitoring station. Exposure to average $PM_{10}$ in the third trimester was

22   analyzed for increased risk of low birth weight at term ($\geq$ 37 weeks gestation). Analysis at the ZIP code

23   level did not detect increased risk (per 10 $\mu g/m^3$ $PM_{10,}$ OR = 1.03 [95% CI: 0.97-1.09]). However the

24   analysis based on geocoded addresses indicated that increasing exposure to $PM_{10}$ was associated with

25   increased risk of low birth weight for women living within 1 mile of the station where $PM_{10}$ was

26   measured. For these women (n = 247 cases, 10,981 non-cases), each 10 $\mu g/m^3$ increase in $PM_{10}$ was

27   associated with a 22% increase in risk of term low birth weight (OR = 1.22 [95% CI: 1.05-1.41]). In the

28   categorical analysis, exposure to $PM_{10}$ >44.4 $\mu g/m^3$ was associated with a 48% increase in risk

29   (OR = 1.48 [95% CI: 1.00-2.19]). Increased risk of low birth weight also was associated with exposure to

30   CO in single pollutant models. However, when multipollutant models were considered, the effects of CO

31   were attenuated but the effects of $PM_{10}$ increased. Controlling for CO, $NO_2$, and $O_3$, each 10 $\mu g/m^3$

32   increase in exposure to $PM_{10}$ increased risk of low birth weight 36% (OR = 1.36 [95% CI: 1.12-1.65]).

33        Spatial variation in $PM_{2.5}$ exposure was investigated by Basu et al. (2004). They included only

34   mothers who lived within 5 miles of a $PM_{2.5}$ monitor and within a California county with at least one

1     monitor. To minimize potential confounding, they included only white (n = 8597) or Hispanic (n = 8114)

2     women, who were married, between 20-30 years of age, completed at least high school and were having

3     their first child. Consistently, $PM_{2.5}$ exposure measured by the county monitor was more strongly

4     associated with reductions in birth weight than exposure measured by the neighborhood monitor. The

5     results were replicated in both the white and the Hispanic samples. Reductions in birth weight ranged

6     from 15.2 g to 43.5 g per 10 $\mu g/m^3$ increase in $PM_{2.5}$.

7     In the remaining U.S. study, Chen et al. (2002) analyzed 33,859 birth certificates of residents of

8     Washoe County in northern Nevada (1991-1999). There were four sites monitoring $PM_{10}$ during the study

9     period, it appears (not stated) that exposure was averaged over the county. A 10 $\mu g/m^3$ increase in

10    exposure to $PM_{10}$ during the third trimester of pregnancy was associated with an 11 gm reduction in birth

11    weight (95% CI: -2.3 to -19.8). Effects on risk of low birth weight were not significant. For exposure in

12    the third trimester of 19.77 to 44.74 $\mu g/m^3$ compared to <19.74 $\mu g/m^3$ the odds ratio for low birth weight

13    was 1.05 (95% CI: 0.81-1.36). Comparing exposure >44.74 to the same reference category, the odds ratio

14    was 1.10 (95% CI: 0.71-1.71). Misclassification of exposure may have occurred when exposure was

15    averaged over a large geographic area (16,968 $km^2$).

16    Recent international studies investigating effects of particles on low birth weight include one in

17    Munich (Slama et al., 2007), two in Canada (Brauer et al., 2008; Dugandzic et al., 2006), two in Australia

18    (Hansen et al., 2007a; Mannes et al., 2005), two in Taiwan (Lin et al., 2004b; Yang et al., 2003a), one in

19    Korea (Ha et al., 2003) and two in Sao Paulo, Brazil (Gouveia et al., 2004; Medeiros and Gouveia, 2005).

20    The majority of these studies found that PM concentrations were associated with low birth weight, though

21    two studies (Hansen et al., 2007a; Lin et al., 2004b) found no associations. The effect estimates were

22    similar in magnitude to those reported in the U.S. studies.

## *Issues in Interpreting Results of Low Birth Weight Studies*

23    Studies included subjects at distances from monitoring stations varying from as close as 1 mile or 2

24    km, to as far as 50 km or the size of the county. However, studies that only included subjects living within

25    a short distance (1 mile, 2 km) of the monitoring station (thus likely reducing exposure measurement

26    error) were more likely to find that exposure was associated with increased risk of low birth weight.

27    However, Basu et al. (2004) reported a stronger association between $PM_{2.5}$ exposure and birth weight

28    when exposure was estimated based on the county monitor, rather than the monitor within 5 miles of the

29    residence. They suggest that county level exposure may be more representative of where women spend

30    their time, including not only home, but also other time spent away from home. Other pollutants also

31    appeared to influence the risk associated with particle exposure. In one study, exposure to $PM_{10}$ in a single

32    pollutant model reduced birth weight by 11 grams, but became non-significant in multipollutant models

1    with $O_3$ (Salam et al., 2005). In another study the risk associated with $PM_{10}$ exposure increased from 22%

2    to 36% when other pollutants were included in the model (Wilhelm and Ritz, 2005). All but one study in

3    the U.S. found some association between particle exposure and reduced birth weight (Maisonet et al.,

4    2001). The results of international studies were mixed. This might be related to the chemical composition

5    of particles in the U.S., or to differences in the pollutant mixture. Studies with negative results must be

6    interpreted with caution when the comparison groups have significant exposure. This was certainly the

7    situation in studies in Taiwan and Korea (Lee et al., 2003a; Lin et al., 2004b; Yang et al., 2003a).

8    Differences in geographical locations, study samples and linkage decisions may contribute to the diverse

9    findings in the literature on the association between PM and birthweight, even within the U.S. (Parker and

10   Woodruff, 2008).

### Preterm Birth

11   A potential association of exposure to airborne particles and preterm birth has been investigated in

12   numerous epidemiologic studies, including some conducted in the U.S. and others in foreign countries.

13   Three U.S. studies have been carried out by the same group of investigators in California.

14   A natural experiment occurred when an open-hearth steel mill in Utah Valley was closed from

15   August 1986 through September 1987. Parker et al. (2008) compared birth outcomes for Utah mothers

16   within and outside of the Utah Valley, before, during, and after the mill closure. They report that mothers

17   who were pregnant around the time of the closure of the mill were less likely to deliver prematurely than

18   mothers who were pregnant before or after. The strongest effect estimates were observed for exposure

19   during the second trimester (14% decrease in risk of preterm birth during mill closure). Preterm birth

20   outside of the Utah Valley did not change during the time of the mill closure.

21   In 2000, Ritz et al. (2000) published the first study investigating the association of preterm birth

22   with PM in the U.S. The study population was women living in the southern California Basin. There were

23   8 monitoring stations measuring $PM_{10}$ every sixth day during the study period. Birth certificates (1989-

24   1993) were analyzed for women living in zip codes within 2 miles of a monitoring station. Women with

25   multiple gestations, chronic disease prior to pregnancy and women who delivered by cesarean section

26   were excluded resulting in a study population of 48,904 women. The risk of preterm birth increased by

27   4% (RR = 1.04 [95% CI: 1.02-1.6]) per 10 $\mu g/m^3$ increase in $PM_{10}$ averaged in the six weeks before birth.

28   Exposure to $PM_{10}$ in the first month of pregnancy, resulted in a 3% increase in risk (RR = 1.03 [95% CI:

29   1.01-1.05]). These results were robust in multipollutant models.

30   Wilhelm and Ritz (2005) reinvestigated this association among women in the same area in 2005,

31   when air pollution had declined. Birth certificate data from 1994-2000 was analyzed for women living in

32   ZIP codes within 2 miles of a monitoring station, or with addresses within 5 miles of the monitoring

1    station. No significant effects of exposure to $PM_{10}$ were reported. Exposure to $PM_{2.5}$ six weeks before

2    birth resulted in an increase in preterm birth (RR = 1.19 [95% CI: 1.02-1.40]) for the highest quartile of

3    exposure ($PM_{2.5}$ >24.3 μg/m$^3$). Using a continuous measure of $PM_{2.5}$, there was a 10% increase in risk for

4    each 10 μg/m$^3$ increase in $PM_{2.5}$ (RR = 1.10 [95% CI: 1.00-1.21]).

5         There have been two major criticisms of air pollution studies using birth certificate data. First, that

6    birth certificates only indicate the address at birth and the exposure of women who moved during

7    pregnancy may be misclassified; second, that information about some important confounders may not be

8    available (e.g. smoking). To obtain more precise information about these variables, Ritz et al. (2007)

9    conducted a case control study nested within a cohort of birth certificates (Jan 2003–Dec 2003) in Los

10   Angeles county. Births to women residing in ZIP codes (n = 24) close to monitoring stations or major

11   population centers or roadways (n = 87) were eligible (n = 58,316 births). All cases of low birth weight or

12   preterm birth and an equal number of randomly sampled controls in the 24 zip codes close to monitors

13   were selected. In the other 87 ZIP codes, 30% of cases and an equal number of controls were randomly

14   sampled. Of 6,374 women selected for the case control study, 2,543 (40%) were interviewed. The

15   association of preterm birth with exposure to $PM_{2.5}$ differed between women responding to the survey and

16   women who did not respond. Among responders, exposure to each 10 μg/m$^3$ increase in $PM_{2.5}$

17   concentration in the first trimester increased risk to preterm birth by 23% (RR = 1.23 [95% CI:

18   1.02-1.48]). There was no increase in risk among non-responders (RR = 0.95 [95% CI: 0.82-1.10]), or in

19   the entire birth cohort (RR = 1.00 [95% CI: 0.94-1.07]).

20        An additional case control study of preterm birth and $PM_{2.5}$ exposure (Huynh et al., 2006) used

21   California birth certificate data. Singleton preterm infants (24-36 weeks gestation) born in California

22   (1999-2000) whose mothers lived within 5 miles of a $PM_{2.5}$ monitor were eligible. Each of these 10,673

23   preterm infants were matched to three term (39-44 weeks gestation) controls (having a last menstrual

24   period within 2 weeks of the case infant), resulting in a study population of 42,692. Controlling for

25   maternal race/ethnicity, education, marital status, parity and CO exposure, exposure to $PM_{2.5}$ >17.7 μg/m$^3$

26   increased the risk of preterm birth by 14% (OR = 1.14 [95% CI: 1.07-1.23]). Averaging $PM_{2.5}$ exposure

27   over the first month of pregnancy, the last 2 weeks before birth, or the entire pregnancy did not

28   substantially change the risk estimate.

29        Two additional studies of preterm birth and exposure to particulate air pollution have been

30   conducted in the U.S. Each has used a unique methodology. Sagiv et al. (2005) used time series to analyze

31   births in four Pennsylvania counties between January 1997 and December 2001. In this analysis, exposure

32   is compared to the rate of preterm births each day. Both acute exposure (on the day of birth) and longer

33   term exposure (average exposure for the preceding six weeks) were considered in the analysis. An

34   advantage of this analysis is that days, rather than individuals are compared, so confounding by individual

1    risk factors is minimized. For exposure averaged over the six weeks prior to birth, there was a non-

2    significant increase in risk (RR = 1.07 [95% CI: 0.98-1.18]); for acute exposure with a 2 day lag

3    (RR = 1.10 [95% CI: 1.00-1.21]) and 5 day lag (RR = 1.07 95% CI: 0.98-1.18]) results were marginal.

4         Rogers and Dunlop (2006) examined exposure to particles and risk of delivery of an infant

5    weighing less than 1500 grams (all of which were preterm) from 24 counties in Georgia. The study

6    included 69 preterm small for gestational age (SGA) infants, 59 preterm appropriate for gestational age

7    (AGA) infants and 197 term AGA controls. Exposure was estimated using an environmental transport

8    model that considered $PM_{10}$ emissions from 32 geographically located industrial point sources,

9    meteorological factors, and geographic location of the birth home. Exposure was categorized by quartiles.

10   Comparing women who delivered a preterm AGA infant to those who delivered a term AGA infant,

11   exposure to $PM_{10}$>15.07 μg/m$^3$ tripled the risk (OR = 3.68 [95% CI: 1.44-9.44]).

12        Brauer et al. (2008) evaluated the impacts of $PM_{2.5}$ on preterm birth using spatiotemporal exposure

13   metrics in Vancouver, Canada. The authors found similar results when they used a land-use regression

14   model or inverse distance weighting as the exposure metric. For preterm births <37 weeks, they reported

15   an OR of 1.06 (95% CI: 1.01-1.11), and for preterm births <35 weeks the OR increased to 1.12 (95% CI:

16   1.02-1.24). There were no consistent trends for early or late gestational period to be more strongly

17   associated with preterm births.

18        In Incheon, Korea, Leem et al. (2006) estimated $PM_{10}$ exposure spatially as well as temporally.

19   Exposure was based on 26 monitors and kriging was used to determine exposure for 120 dongs

20   (administrative districts, mean area 7.82 km$^2$, median area 1.42 km$^3$). The sample included 52,113 births,

21   from 2001-2002. $PM_{10}$ was very weakly correlated with other pollutants. Exposure was compared in

22   quartiles for the first and third trimester of pregnancy. In the first trimester, relative risks for the second,

23   third and fourth quartiles were RR = 1.14 (95% CI: 0.97-1.34), RR = 1.07 (95% CI: 0.94-1.37), and

24   RR = 1.24 (95% CI: 1.09-1.41), respectively. Exposure to $PM_{10}$ in quartile one (reference group) was 26.9

25   - 45.9 μg/m$^3$; fourth quartile exposure equaled 64.6–106.4 μg/m$^3$. The p-value for trend was 0.02.

26   Exposure in the third trimester was not related to preterm birth, however no information was provided to

27   determine how exposure in the third trimester was adjusted for women who delivered preterm.

28        Two studies investigating risks of preterm birth related to particle exposure have been reported

29   from Australia. In Brisbane, Hansen et al. (2006) studied 28,200 births (2000-2003) in an area of low

30   $PM_{10}$ concentrations. Exposure to an interquartile range increase in $PM_{10}$ exposure in the first trimester

31   resulted in a 15% increased risk of preterm birth (OR = 1.15 [95% CI: 1.06-1.25]). This result was

32   strongly influenced by the effect of $PM_{10}$ exposure in the first month of pregnancy (OR = 1.19 [95% CI:

33   1.13-1.26]). $PM_{10}$ was correlated with ozone r = (0.77) in this study and ozone also increased risk in the

34   first trimester. No effects were associated with exposure to $PM_{10}$ in the third trimester.

In Sydney, associations between exposure to particles and preterm birth varied by season. Jalaludin et al. (2007) obtained information on all births in metropolitan Sydney (1998-2000). Exposure to $PM_{2.5}$ in the three months preceding birth was associated with an increased risk of preterm birth (OR = 1.11 [95% CI: 1.04-1.19]). Additional effects were dependent on season of conception. Both $PM_{10}$ (OR = 1.3 95% CI: 1.2-1.5]) and $PM_{2.5}$ (OR = 1.4 [95% CI: 1.3-1.6]) were associated with increased risk for conceptions in the winter. Conceptions in summer were associated with reductions in risk ($PM_{10}$ OR = 0.91 [95% CI: 0.88-0.93]), ($PM_{2.5}$ OR = 0.87 [95% CI: 0.84-0.92]). Due to both positive and negative findings, the authors recommend caution in interpreting their results.

## *Issues in Analyzing Environmental Exposures and Preterm Birth*

A major issue in studying environmental exposures and preterm birth is selecting the relevant exposure period, since the biological mechanisms leading to preterm birth and the critical periods of vulnerability are poorly understood (Bobak, 2000). Exposures proximate to the birth may be most relevant if exposure causes an acute effect. However, exposure occurring in early gestation might affect placentation, with results observable later in pregnancy, or cumulative exposure during pregnancy may be the most important determinate. The studies reviewed have dealt with this issue in different ways. Many have considered several exposure metrics based on different periods of exposure.

Often the time periods used are the first month (or first trimester) of pregnancy and the last month (or six weeks) prior to delivery. Using a time interval prior to delivery introduces an additional problem since cases and controls are not in the same stage of development when they are compared. For example, a preterm infant delivered at 36 weeks, is a 32 week fetus four weeks prior to birth, while an infant born at term (40 weeks) is a 36 week fetus four weeks prior to birth. Only one study (Huynh et al., 2006) adjusted for this in the design.

Many of these studies compare exposure in quartiles, using the lowest quartile as the reference (or control) group. No studies use a truly unexposed control group. If exposure in the lowest quartile confers risk, than it may be difficult to demonstrate additional risk associated with a higher quartile. Thus negative studies must be interpreted with caution.

Preterm birth occurs both naturally (idiopathic preterm), and as a result of medical intervention (iatrogenic preterm). Ritz et al. (2000; 2007) excluded all births by Cesarean section, to limit their studies to idiopathic preterm. No other studies attempted to distinguish the type of preterm birth, although exposure maybe associated with only one type. This is another source of potential misclassification.

## *Growth Restriction*

1      Low birth weight has often been used as an outcome measure because it is easily available and

2      accurately recorded on birth certificates. However, low birth weight may result from either short

3      gestation, or inadequate growth in utero. Most of the studies investigating air pollution exposure and low

4      birth weight, limited their analysis to term infants to focus on inadequate growth. Five studies were

5      identified that specifically addressed growth restriction in utero by identifying infants who failed to meet

6      specific growth standards. Usually these infants had birth weights less than the 10th percentile for

7      gestational age, using an external standard. All five of these studies have been previously discussed, since

8      they also examined other reproductive outcomes (low birth weight or preterm delivery).

9      Two studies in the U.S. examined intrauterine growth and both were conducted in California.

10    Parker et al. (2005) reported a positive association between exposure to $PM_{2.5}$. Since this study only

11    included singleton live births at 40 weeks gestation, birth weights less than 2872 grams for girls and 2986

12    grams for boys were designated SGA, based on births in California. Infants exposed to the highest

13    quartile $PM_{2.5}$ (>18.4 $\mu g/m^3$) compared to the lowest quartile $PM_{2.5}$ (<11.9 $\mu g/m^3$) were 23% more likely

14    to be small for gestational age (OR = 1.23 [95% CI: 1.03-1.50]). Very similar results were found for

15    exposure in each of the three trimesters respectively (OR = 1.26 [95% CI: 1.04-1.51], OR = 1.24 [95%

16    CI: 1.04-1.49], OR = 1.21 [95% CI: 1.02-1.43]). These results controlled for exposure to CO, which did

17    not increase risk for SGA.

18    In contrast, Salam (2005) found no association between exposure to $PM_{10}$ and intrauterine growth

19    retardation (IUGR) in the California Children's Health Study. IUGR was defined as less than the 15th

20    percentile of predicted birth weight based on gestational age and sex in term infants. Apparently no

21    external standard was used since 15% of infants in the study were designated as IUGR. An IQR increase

22    in $PM_{10}$ exposure was not significantly associated with IUGR for the whole pregnancy (OR = 1.1 [95%

23    CI: 0.9-1.3]) or for any specific trimester. Differences between this study and the study by Parker et al.

24    (2005) include measurement of $PM_{10}$ vs. $PM_{2.5}$, a less stringent definition of IUGR, and exposures

25    determined by monitors located much farther away from the subjects' residences (up to 50 km vs. within

26    5 miles). All of these factors could lead to misclassification.

27    Two studies investigating particle exposure and SGA were conducted in Australia, with differing

28    results (Hansen et al., 2007a; Mannes et al., 2005). Mannes et al. (2005) defined SGA as birth weight less

29    than two standard deviations below the national mean birth weight for gestational age. In this study there

30    was a statistically significant effect of exposure to both $PM_{10}$ (OR = 1.10 [95% CI: 1.00-1.48], per

31    10 $\mu g/m^3$ increase) and $PM_{2.5}$ (OR = 1.34 [95% CI: 1.10-1.63], per 10 $\mu g/m^3$ increase) for exposure during

32    the second trimester. When analysis was restricted to births within 5 km of the monitoring station, the

1 association for $PM_{10}$ became slightly stronger (OR = 1.22 [95% CI: 1.10-1.34]). Exposure during other

2 trimesters of pregnancy was not associated with IUGR.

3  In Brisbane, Hansen et al. (2007a) examined head circumference (HC), crown heel length (CHL)

4 and risk of SGA, defined as less than the tenth percentile of weight for gestational age and gender based

5 on an Australian national standard. There was no consistent relationship between $PM_{10}$ exposure and

6 SGA, HC or HCL in any trimester of pregnancy. $PM_{10}$ exposure was determined by averaging values

7 from the five monitoring stations. Due to the sample size and limited number of monitoring stations, it

8 was not possible to analyze the data for women living within 5 km of a monitoring station, as was done in

9 Sydney.

10  In Canada, Liu (2007d) investigated the effect of $PM_{2.5}$ exposure on fetal growth in three cities,

11 Calgary, Edmonton and Montreal. Intrauterine growth retardation (IUGR) was defined as birth weight

12 below the tenth percentile, by sex and gestational week (37-42) for all singleton live births in Canada

13 between 1986 and 2000. Models were adjusted for maternal age, parity, infant sex, season of birth, city of

14 residence, and year of birth. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increased risk for IUGR

15 (OR = 1.07 [95% CI: 1.03-1.10]) in the first trimester, and similar risks were associated with exposure in

16 the second or third trimesters. The effect of $PM_{2.5}$ was reduced in multipollutant models including CO and

17 $NO_2$.

18  Brauer et al. (2008) observed consistent increased risks of SGA for $PM_{2.5}$, $PM_{10}$, $NO_2$, NO and CO

19 in Vancouver, Canada (20% increase in risk in $PM_{2.5}$ and $PM_{10}$ per 10 $\mu g/m^3$ increase). The effects were

20 similar for exposure estimates based on nearest monitor, inverse distance weighting, and land-use

21 regression modeling. ORs for early or late pregnancy exposure windows were remarkably similar to those

22 for the full duration of pregnancy.

23  One additional study investigating fetal growth was conducted in the Czech Republic (Bobak,

24 2000). There was no association between total suspended particulate (TSP) exposure and IUGR (defined

25 as less than the tenth percentile of weight for gestational age and gender). For example the odds ratio for a

26 50 $\mu g/m^3$ increase in TSP was OR = 0.89 [95% CI: 0.75-1.06].

### Birth Defects

27  Three recent articles examined PM and birth defects. The Seoul, Korea study mentioned above also

28 considered congenital anomalies, defined as a defect in the child's body structure (Kim et al., 2007a).

29 $PM_{10}$ levels were associated with higher risk of birth defects for the second trimester, with a 16% (95%

30 CI: 0-34) increase in risk per 10 $\mu g/m^3$ in $PM_{10}$.

31  Two U.S. studies specifically examined air pollution and risk of birth defects. Data were collected

32 from the California Birth Defects Monitoring Program for four counties in Southern California (Los

1  Angeles, Riverside, San Bernardino, and Orange) for the period 1987 to 1993, although each county

2  included a subset of this period (Ritz et al., 2002). Cases (i.e., infants with birth defects) were identified as

3  live birth infants and fetal deaths from 20 weeks gestation to 1 year post birth, with isolated, multiple,

4  syndrome, or chromosomal cardiac or orofacial cleft defects. Cases were restricted to those with registry

5  data for gestational age and residence zip code, and those with residences <10 miles from an air pollution

6  monitor. Six types of categories were included: aortic defects; atrium and atrium septum defects;

7  endocrinal and mitral value defects; pulmonary artery and valve defects; conotruncal defects; and

8  ventricular septal defects not part of the conotruncal category. $PM_{10}$ measurements were available every

9  six days. While results indicated increased risk of birth defects for higher levels of CO or $O_3$, the authors

10 determined that results for $PM_{10}$ were inconclusive, finding no consistent trend of effect after adjustment

11 for CO and $O_3$.

12 The other U.S. study examined birth defects through a case-control design in seven Texas counties

13 for the period 1997 to 2000 (Gilboa et al., 2005). Births were excluded for parents <18 years and several

14 non-air pollution risk factors known to be associated with birth defects (e.g., maternal diabetes,

15 holoprosencephaly in addition to oral clef). Comparison of the highest ($\geq 29.0$ $\mu g/m^3$) and lowest

16 (<19.521 $\mu g/m^3$) quartiles of $PM_{10}$ for exposure defined as the third to eighth weeks of pregnancy

17 generated an OR of 2.27 (95% CI: 1.43–3.60) for risk of isolated artrial septal defects and 1.26 (95% CI:

18 1.03–1.55) for individual artrial septal defects. Including other pollutants (CO, $NO_2$, $O_3$, $SO_2$) in the

19 model did not greatly alter results; numerical results for copollutant analysis were not provided. Strong

20 evidence was not observed for a relationship between $PM_{10}$ and the other birth defect categories. Review

21 articles have concluded that the scientific literature is not sufficient to conclude a relationship between air

22 pollution and birth defects (Šrám et al., 2005).

### Infant Mortality

23 Many studies have identified strong associations between exposure to particles and increased risk

24 of mortality in adults or the general population, including for short- and long-term exposure (Pope and

25 Dockery, 2006; U.S. EPA, 2004). Less evidence is available for the potential impact on infant mortality,

26 although studies have been conducted in several countries. The results of these infant mortality studies are

27 presented here with the other reproductive and developmental outcomes because it is likely that in vitro

28 exposures contribute to this outcome. Both long-term and short-term exposure studies of infant mortality

29 are included in this section. Results on PM and infant mortality includes a range of findings, with some

30 studies finding associations and many non-statistically significant or null effects. Yet, more consistency is

31 observed when results are divided into the type of health outcome based on the age of infant and cause of

32 death.

1       An important question regarding the association between PM and infant mortality is the critical

2 window of exposure during development for which infants are susceptible. Several age structures have

3 been explored: infants (<1 year); neonatal (<1 month); and postneonatal (1 month to 1 year). Within these

4 various age categories, multiple causes of deaths have been investigated, particularly total deaths and

5 respiratory-related deaths. The studies reflect a variety of study designs, particle size ranges, exposure

6 periods, regions, and adjustment for confounders.

### Stillbirth

7       Only one study of stillbirths and PM published from 2002 to present was identified. A prospective

8 cohort of pregnant women in Seoul, Korea from 2001 to 2004 was examined with respect to exposure to

9 $PM_{10}$ (Kim et al., 2007a). Gestational age was estimated by the last menstrual period or by ultrasound.

10 Whereas many of the previously discussed studies of PM and pregnancy outcomes were based on national

11 registries, this study examined medical records and gathered individual information through interviews on

12 socio-economic condition, medical history, pregnancy complications, smoking, second-hand smoke

13 exposure, and alcohol use. Mother's exposure to $PM_{10}$ was based on residence for each month of

14 pregnancy, each trimester defined as a three month period, and the six weeks prior to death. Exposure was

15 assigned by the nearest monitor. A 10 $\mu g/m^3$ increase in $PM_{10}$ in the third trimester was associated with an

16 8% (95% CI: 2-14) increase in risk of stillbirth.

17       Earlier research investigating PM and stillbirths includes an ecological study of the Czech Republic

18 for the period 1986 to 1988 based on the frequency of stillbirths and TSP levels (Bobak and Leon, 1999a).

19 Risk of stillbirths, defined as a deceased infant >1000 g or ≥ 28 weeks gestation, was not associated with

20 TSP in this research. In São Paulo, Brazil, Poisson regression of stillbirth counts for the period 1991 and

21 1992 found that a 10 $\mu g/m^3$ increase in $PM_{10}$ was associated with a 0.8% increase in stillbirth rates

22 (Pereira et al., 1998). When other pollutants ($NO_2$, $SO_2$, CO, $O_3$) were included simultaneously in the

23 model, the association did not remain. Stillbirths were defined as fetal loss at >28 weeks of pregnancy

24 age, weight >1000 g, or length of fetus >35 cm.

25       In summary, while there exists some evidence for a link between PM and stillbirths, the scientific

26 literature is not sufficient to draw this definitive conclusion. A review article concluded that there is

27 insufficient evidence to determine an effect of PM exposure and risk of stillbirth (Heinrich and Slama,

28 2007).

### Infant Mortality and Infant Respiratory Mortality, <1 year

29       A literature search did not reveal new studies on PM and infant mortality (<1 year) since the

30 previous PM AQCD. Previously conducted studies include a case-control study that reported associations

1   between infant mortality and TSP levels over the period between birth and death for infants in the Czech

2   Republic (Bobak and Leon, 1999a); a 50 $\mu g/m^3$ increase in TSP was associated with a 77% (95% CI:

3   5-301) increase in respiratory-related infant mortality. An ecological study evaluated U.S. $PM_{10}$ data for

4   the year 1990 using long-term pollution levels in 180 U.S. counties (Lipfert et al., 2000). The authors

5   found a 9.64% (95% CI: 4.60-14.9) increase in risk of infant mortality for non-low birth weight infants

6   per 10 $\mu g/m^3$ increase in $PM_{10}$, a 13.4% (95% CI: -10.3 to 43.5%) increase in non-low birth weight

7   respiratory-disease related deaths (ICD-9 460-519) and a 19.5% (95% CI: 0.07-42.8) increase in all non-

8   low birth weight respiratory-related infant deaths (ICD 9 460-519, 769, 770).


### Neonatal Mortality and Neonatal Respiratory Mortality, <1 month

9   Studies on PM and neonatal mortality (<1 month) included a time-series analysis of $PM_{10}$ for four

10  years of data (1998-2000) for São Paulo, Brazil (Lin et al., 2004a). The analysis used daily counts of

11  deaths from government registries and adjusted for temporal trend, day of the week, weather, and

12  holidays. Findings indicated that a 10 $\mu g/m^3$ increase in $PM_{10}$ was associated with a 1.71% (95% CI:

13  0.31-3.32) increase in risk of neonatal death.

14  A case-crossover study of 11 years (1989-2000) in Southern California did not find an association

15  between $PM_{10}$ and neonatal deaths (Ritz et al., 2006). Numerical results were not provided. The authors

16  considered adjustment for season, county, parity, gender, prenatal care, and maternal age, education, and

17  race/ethnicity. The overall levels of $PM_{10}$ in these studies were similar.

18  These results add to previous work on PM and neonatal death, including studies identifying higher

19  risk of neonatal mortality with higher TSP in the Czech Republic in an ecological analysis (Bobak and

20  Leon, 1992) and case-crossover study (Bobak and Leon, 1999a), and a Poisson model study in

21  Kagoshima City, Japan (Shinkura et al., 1999). An ecological study evaluated U.S. $PM_{10}$ data for the year

22  1990 using long-term pollution levels in 180 U.S. counties (Lipfert et al., 2000). Analysis considered birth

23  weight, sex, month of birth, location by state and county, prenatal care, and mother's race, age,

24  educational level, marital status, and smoking status. County-level variables were included for socio-

25  economic status, altitude, and climate. Results indicate a 13.1% increase in neonatal mortality (95% CI:

26  4.4-22.6) per 10 $\mu g/m^3$ $PM_{10}$ for non-low birth weight infants. Statistically significant associations were

27  also observed considering all infants or low birth weight infants. However, higher levels of $SO_2$ were

28  associated with lower risk of infant mortality. When sulfate and an estimate of non-sulfate particles were

29  included in the regression simultaneously, associations were observed with non-sulfate particles and an

30  inverse relationship with sulfate particles. Respiratory neonatal mortality was not associated with higher

31  TSP in the Czech Republic case-control study (Bobak and Leon, 1999a).

## Postneonatal Mortality and Post-neonatal Respiratory Mortality, 1 month-1 year

Several studies have been conducted on PM and postneonatal mortality since the previous PM AQCD, including three from the U.S., one from Mexico, and three from Asia. Two case-control studies examined the risk of PM to postneonatal death in California. Research focused on Southern California for the period 1989 to 2000 linked birth and death certificates and considered $PM_{10}$ two months prior to death with adjustment for prenatal care, gender, parity, county, season, and mother's age, race/ethnicity, and education (Ritz et al., 2006). As previously noted, this study did not find an association between $PM_{10}$ and neonatal mortality (<1 month), however an association was observed for postneonatal mortality, with a 10 $\mu g/m^3$ increase in $PM_{10}$ associated with a 4% (95% CI: 1-6) increase in risk. The exposure period of two weeks before death was also considered, producing effect estimates of 5% (95% CI: 1-10) for the same $PM_{10}$ increment. Even stronger estimates were observed for those who died at ages 4 to 12 months. When CO, $NO_2$, and $O_3$ were simultaneously included with $PM_{10}$ in the model, the central estimate reduced to 2% for the 2-week exposure period and 4% for the 2-month exposure period, and both estimates lost statistical significance. The other case-control study of California considered $PM_{2.5}$ from 1999 to 2000 for infants born to mothers within five miles of a $PM_{2.5}$ monitoring station (Woodruff et al., 2006). Infants who died during the postneonatal period were matched to infants with date of birth within two weeks and birth weight category. Exposure was estimated from the time of birth to death. Models considered parity and maternal race, education, age, and martial status. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7% (95% CI: -7 to 24) increase in postneonatal death

County-level $PM_{10}$ and $PM_{2.5}$ for the first two months of life for births in urban U.S. counties ($\geq$ 250,000 residents) from 1999 to 2002 were evaluated in relation to postneonatal mortality with GEE models (Woodruff et al., 2008). Analyses were adjusted for primiparity (first born), community-level poverty, region, month, year, and mother's race, marital status, education, and age. Births were restricted to singleton births with gestational age $\leq$ 44 weeks, same county of residence at birth and death, and non-missing data on birth order, birth weight, and maternal race, education, and martial status. Higher levels of either PM metric were associated with higher risk of postneonatal mortality, with 4% (95% CI: -1 to 10) increase in mortality risk per 10 $\mu g/m^3$ in $PM_{10}$ and 4% (95% CI: -2 to 11) increase in mortality risk for the same increment of $PM_{2.5}$. This work builds on a previous study of 86 U.S. urban areas from 1989 to 1991, finding a 4% (95% CI: 2 to 7) increase in postneonatal mortality per 10 $\mu g/m^3$ county-level $PM_{10}$ over the first two months of life (Woodruff et al., 1997).

In Ciudad Juarez, Mexico, a case-crossover approach was applied to data from 1997 to 2001 based on death certificates and the cumulative $PM_{10}$ for the day of death and previous two days (Romieu et al., 2004). A case-crossover study of Kaohsiung, Taiwan from 1994 to 2000 compared the average of $PM_{10}$ on the day of death and two previous days to $PM_{10}$ in control periods a week before and week after death

1    (Tsai et al., 2006b). A similar approach was also applied to 1994 to 2000 data from Taipei, Taiwan, also

2    using case-crossover methods for the lag 0-2 $PM_{10}$ with referent periods the week before and after death

3    (Yang et al., 2006). In these case-crossover studies, season was addressed through matching in the study

4    design. A 10 $\mu g/m^3$ increase in $PM_{10}$ was associated with a 2.0% (95% CI: -2.8 to 7.0) increase in the

5    Mexico study, a 0.59 (95% CI: -15.0 to 18.8) increase in postneonatal death in the Kaohsiung study, and a

6    1.02% (95% CI: -13.2 to 17.6) increase in the Taipei study. A study in Seoul, South Korea from 1995 to

7    1999 used time-series approaches adjusted for temporal trend and weather, based on national death

8    registries excluding accidental deaths (Ha et al., 2003). A 10 $\mu g/m^3$ increase in $PM_{10}$ was associated with

9    a 3.14% (95% CI: 2.16 to 4.14) increase in risk of death for postneonates.

10       These studies add to evidence from two earlier studies in the Czech Republic, described above,

11   which found higher risk of postneonatal mortality with higher PM levels. The association was uncertain in

12   a case-control study based in the Czech Republic (Bobak and Leon, 1999a). In an ecological study of 45

13   Czech Republic districts, a statistically significant trend was observed with higher risk of postneonatal

14   mortality at higher quintiles of TSP-10 (TSP up to 10 $\mu m$) (Bobak and Leon, 1992).

15       A subset of the studies examining postneonatal mortality also considered the subset of postneonatal

16   deaths from respiratory causes. These include the time-series study in South Korea, finding a 17.8% (95%

17   CI: 14.4 to 21.2) increase in respiratory-mortality per 10 $\mu g/m^3$ increase in $PM_{10}$ (Ha et al., 2003) and the

18   case-crossover study in Mexico, for which the same increment in $PM_{10}$ was associated with a 1.5% (95%

19   CI: -14.1 to 13.0) decrease in risk (Romieu et al., 2004). Both case-control California studies identified

20   associations, with a 5% (1, 10%) increase in risk in Southern California (Ritz et al., 2006) and 57.4%

21   (95% CI: 7.0 to 132) increase in California per 10 $\mu g/m^3$ $PM_{10}$ (Woodruff et al., 2006). The U.S. study

22   found this increment in $PM_{10}$ to be linked with a 16% (95% CI: 6.0 to 28.0) increase in respiratory

23   postneonatal mortality, although effect estimates for $PM_{2.5}$ were not statistically significant (Woodruff et

24   al., 2008). Studies conducted prior to 2002 on respiratory-related postneonatal mortality include both

25   Czech Republic studies and the study of 86 U.S. urban areas, all finding statistically significant effects

26   (Bobak and Leon, 1992, 1999a; Woodruff et al., 1997).

### Sudden Infant Death Syndrome

27       Three studies examining the relationship between PM and sudden infant death syndrome have been

28   published from 2002 onward. These studies examined infant mortality and were thereby discussed in this

29   section previously. A case-control study over a 12-year period (1989 to 2000) matched 10 controls to

30   deaths (cases) in Southern California (Ritz et al., 2006). A 10 $\mu g/m^3$ increase in $PM_{10}$ the two months

31   prior to death was associated with a 3% (95% CI: -1 to 8) increased in SIDS. Adjusted for other pollutants

32   ($CO$, $NO_2$, and $O_3$), the effect estimate reduced to 1% (95% CI: -5 to 7).

1       A case-control study, also based in California, found an OR of 1.008 (95% CI: 1.006-1.012) per

2    10 $\mu$g/m$^3$ increase in $PM_{2.5}$, considering a SIDS definition of ICD 10 R95(Woodruff et al., 2006). Due to

3    changes in SIDS diagnosis, another SIDS definition was explored for ICD 10 R99 in addition to ICD 10

4    R95. Under this SIDS definition, the effect estimate changed to 1.03 (95% CI: 0.79-1.35). The authors

5    also examined whether the relationship between $PM_{2.5}$ and SIDS differed by season, finding no significant

6    difference. $PM_{10}$ and $PM_{10-2.5}$ were not associated with risk of SIDS; numerical results were not provided

7    for these PM metrics. The third recent study of PM and SIDS examined U.S. urban counties from 1999 to

8    2002 (Woodruff et al., 2008). Non-statistically significant relationships were observed between SIDS and

9    $PM_{10}$ or $PM_{2.5}$ in the first two months of life.

10      These studies add to earlier work, such as a U.S. study that found higher risk of SIDS with higher

11   annual $PM_{2.5}$ levels, including in a separate analysis of normal birth weight infants (Lipfert et al., 2000),

12   and a U.S. study identifying a 12% (95% CI: 7-17) increase in SIDS risk per 10 $\mu$g/m$^3$ in $PM_{10}$ for the

13   first two months of life for normal weight births (Woodruff et al., 1997). A study based on Taiwan found

14   higher SIDS risk with lower visibility (Knöbel et al., 1995), whereas a 12 city Canadian time-series study

15   identified no significant associations (Dales et al., 2004).

16      Deaths by SIDS were identified by different methods in the studies, partly due to transition from

17   ICD 9 to ICD 10, but also due to different choices within the research design. Two studies examined

18   multiple approaches (ICD 10 R95, ICD 10 R95 and R99) (Woodruff et al., 2006; 2008), and other studies

19   investigated ICD 9 798.0 and ICD 10 R95 (Ritz and Wilhelm, 2008), ICD 9 798.0 (Woodruff et al., 1997),

20   ICD 9 798.0 and 799.0 (Knöbel et al., 1995), as well as a sudden unexplained death of infant <1 year for

21   which an autopsy did not identify a specific cause of death (Dales et al., 2004). These variations in the

22   definition of health outcomes add to differences in populations and study designs.

23      While some findings indicate a potential effect of PM on risk of SIDS, with the strongest evidence

24   perhaps from the case-control study in California (Woodruff et al., 2006), others do not find an effect or

25   observe an uncertain association. For the relationship between PM and SIDS, a 2004 review article

26   concluded consistent evidence exists compared to evidence for other infant mortality effects (Glinianaia

27   et al., 2004), whereas other reviews found weaker or insufficient evidence (Heinrich and Slama, 2007).

28   Another review concluded that the scientific literature on air pollution and SIDS suggests an effect, but

29   that further research is needed to draw a conclusion (Tong and Colditz, 2004).

### Comparisons Across Studies and Key Issues

30      Comparison of results across studies can be challenging due to several issues, including differences

31   in methodologies, populations and study areas, pollution levels, and the exposure timeframes used. Given

32   the large variation in study designs, the methods to address potential confounders vary. For example,

1    weather and season were addressed in the case-control studies by matching, in the time-series study

2    through non-linear functions of temperature and temporal trend, and in the ecological study through

3    county-level variables. All studies included consideration of seasonality and weather, with the exception

4    of an older study based on the Czech Republic (Bobak and Leon, 1992). Researchers used different

5    definitions of respiratory-related deaths, including ICD 9 460-519 (Bobak and Leon, 1999a; Lipfert et al.,

6    2000); ICD 9 460-519, 769-770 (Lipfert et al., 2000); ICD 9 codes 460-519, 769, 770.4, 770.7, 770.8,

7    770.9, and ICD 10 J00-J98, P22.0, P22.9, P27.1, P27.9, P28.0, P28.4, P28.5, and P28.9 (Ritz et al., 2006);

8    and ICD 9 460-519 and ICD 10 J00-J99 for any cause on death certificate (Romieu et al., 2004); ICD 10

9    J00-99 and P27.1 excluding J69.0 (Woodruff et al., 2006; 2008); and ICD 9 460-519 (Woodruff et al.,

10   1997).

11        Socio-economic conditions were included at the individual level, typically through maternal

12   education, in many studies (e.g., Bobak and Leon, 1999a; Ritz et al., 2006; Woodruff et al., 1997;

13   Woodruff et al., 2006; 2008) and at the community-level in others (e.g., Bobak and Leon, 1992; Penna

14   and Duchiade, 1991), or for both individual and community-level data (e.g., Lipfert et al., 2000). The

15   time-series approach is unlikely to be confounded by socio-economic and other variables that do not

16   exhibit day-to-day variation. Similarly, case-crossover methods use each case as his/her own control,

17   thereby negating the need for individual-level confounders such as socio-economic status (e.g., Romieu et

18   al., 2004; Tsai et al., 2006b; Yang et al., 2006). All studies published after 2001 incorporated individual-

19   level socio-economic data or were of case-crossover or time-series design. One study specifically

20   examined whether socio-economic status modified the PM and mortality relationship, dividing subjects

21   into three socio-economic strata based on the zip code of residence at death (Romieu et al., 2004). This

22   work, based in Mexico, found that at lower socio-economic levels the association between $PM_{10}$ and

23   postneonatal mortality increased. While the overall association showed higher risk of death with higher

24   $PM_{10}$ with statistical uncertainty, for the lowest socio-economic group, a 10 $\mu g/m^3$ increment in

25   cumulative $PM_{10}$ over the two days before death was associated with a 60% (95% CI: 3-149) increase in

26   post-neonatal death. A trend of higher effect for lower socio-economic condition is observed in all three

27   lag structures.

28        Studies differ in terms of the timeframe of pregnancy that was used to estimate exposure. Exposure

29   to PM for infant mortality (<1 year) was estimated as the levels between birth and death (Bobak and

30   Leon, 1999a), annual community levels (Lipfert et al., 2000; Penna and Duchiade, 1991), and the 3 to 5

31   days prior to death (Loomis et al., 1999). For neonatal deaths, exposure timeframes considered were the

32   time between birth and death (Bobak and Leon, 1992, 1999a), annual levels (Bobak and Leon, 1999a;

33   Lipfert et al., 2000), monthly levels (Shinkura et al., 1999), the same day concentrations (Lin et al.,

34   2004a), and the two months or two weeks prior to death (Ritz et al., 2006). Postneonatal mortality was

1  examined with PM concentrations based on annual levels (Bobak and Leon, 1992; Lipfert et al., 2000),

2  between birth and death (Bobak and Leon, 1999a; Woodruff et al., 2006), two months before death (Ritz

3  et al., 2006), the first two months of life (Woodruff et al., 1997; 2006), the day of death (Ha et al., 2003),

4  and the average of the same day as death and previous two days (Romieu et al., 2004; Tsai et al., 2006b;

5  Yang et al., 2006). Thus, no consistent window of exposure was identified across the studies.

6      Pollution levels were highest in the Czech Republic (68.5 $\mu g/m^3$) (Bobak and Leon, 1992), South

7  Korea (69.2 $\mu g/m^3$) (Ha et al., 2003), and Taiwan (81.45 $\mu g/m^3$) (Tsai et al., 2006b), and lowest in the

8  U.S. (29.1 $\mu g/m^3$) (Woodruff et al., 2008) and Japan (21.6 $\mu g/m^3$) (Shinkura et al., 1999). All studies used

9  community-level exposure information based on ambient monitors, as opposed to exposure measured at

10  the individual level (e.g., subject's home) or personal monitoring.

11      Given similar sources for multiple pollutants (e.g., traffic), disentangling the health responses of

12  copollutants is a challenge in the study of ambient air pollution. Several studies examined multiple

13  pollutants, most by estimating the effect of different pollutants through several univariate models. Some

14  studies noted the difficulty of separating particle impacts from those of other pollutants, but noted

15  stronger evidence for particles than other pollutants (Bobak and Leon, 1999a). A few studies applied

16  copollutant models by including multiple pollutants simultaneously in the same model. Effect estimates

17  for the relationship between $PM_{10}$ and neonatal deaths in São Paulo were reduced to a null effect when

18  $SO_2$ was incorporated (Lin et al., 2004a). Associations between $PM_{10}$ and postneonatal mortality or

19  respiratory postneonatal mortality remained but lost statistical significance in a multiple pollutant model

20  with CO, $NO_2$, and $O_3$ (Ritz et al., 2006).

21      Several review articles in recent years have examined whether exposure to PM affects risk of infant

22  mortality, generally concluding that more consistent evidence has been observed for postneonatal

23  mortality, particularly from respiratory causes (Glinianaia et al., 2004; Heinrich and Slama, 2007;

24  Lacasaña et al., 2005; Šrám et al., 2005). In one review authors identified 14 studies on infant mortality

25  and air pollution and determined that studies on PM and infant mortality do not provide consistent results,

26  although more evidence was present for an association for some subsets of infant mortality such as

27  postneonatal respiratory-related mortality (Glinianaia et al., 2004). The relationship between PM and

28  postneonatal respiratory mortality was concluded to be causal in one review (Šrám et al., 2005), and

29  strong and consistent in another (Heinrich and Slama, 2007). Meta-analysis using inverse-variance

30  weighting of $PM_{10}$ studies found that a 10 $\mu g/m^3$ increase in acute $PM_{10}$ exposure was associated with

31  3.3% (95% CI: 2.4-4.3) increase in risk of postneonatal mortality, whereas the same increment of chronic

32  $PM_{10}$ exposure was linked with a 4.8% (95% CI: 2.2-7.2) increase in postneonatal mortality and a 21.6%

33  (95% CI: 10.2-34.2) increase for respiratory postneonatal mortality (Lacasaña et al., 2005). This review

34  noted that "The studies on infant mortality and exposure to particles show an outstanding consistency in

1    the magnitude of the effects, regardless of the different designs used" (Lacasaña et al., 2005). Another

2    meta-analysis of five studies found a 10 μg/m$^3$ increase in PM$_{10}$ to be associated with a 5.6% (95% CI:

3    2.6-8.8) increase in infant mortality (Röösli et al., 2005). Other reviews note that there exists

4    "considerable evidence" that maternal exposure to PM is linked with adverse pregnancy health responses

5    (Schwartz, 2004a).
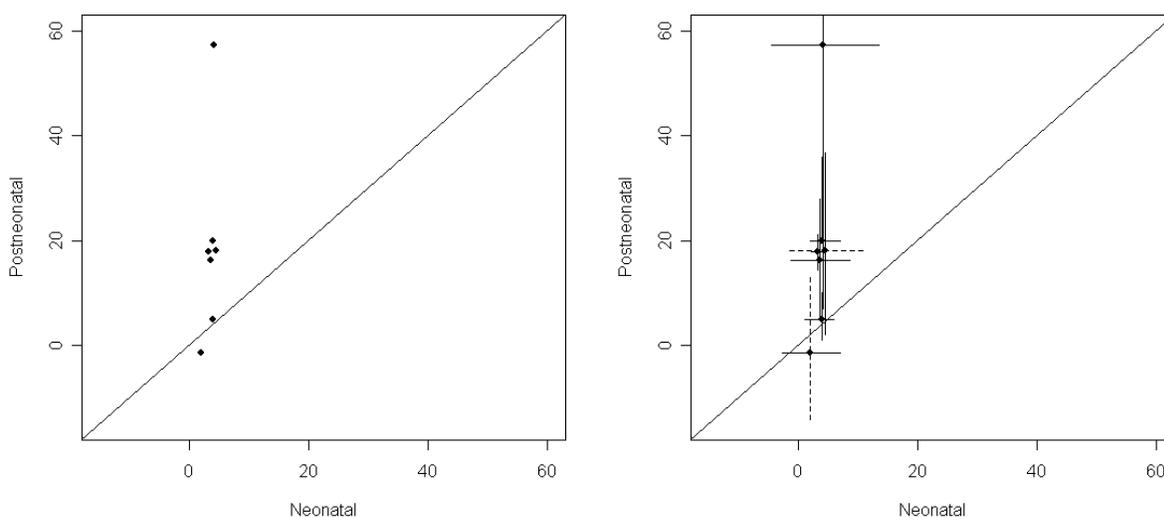


**Figure 7-6.    Percent increase in postneonatal mortality per 10 μg/m$^3$ in PM$_{10}$, comparing risk for total and respiratory mortality. Panel a (left) provides central estimates; panel b (right) also adds the 95% intervals. The points reflect central estimates and the lines the 95% intervals. Solid lines represent statistically significant effect estimates; dashed lines represent non-statistically significant estimates.[1]**

6    Studies that examined multiple outcomes and ages of death allow a direct comparison based on the

7    same study population and methodologies, thereby negating the concern that inconsistent results are due

8    to underlying variation in population, approaches, etc. In this review, one study finds higher effect

9    estimates for postneonatal mortality, for both total and respiratory-related mortality, and the other study

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[1] Studies included are Bobak and Leon, 1999; Ha et al., 2003; Ritz, 2006; Romieu et al., 2004, 2008; Woodruff et al., 1997, 2006). Findings from Bobak and Leon (1999a) were based on TSP and were converted to PM$_{10}$ estimates assuming PM$_{10}$/TSP = 0.8 as per summary data in the original article (Bobak and Leon, 1999a). Findings from Woodruff et al. (1997) for respiratory-related mortality were based on non-low birth weight infants. Results for Woodruff et al. (2006) were based on PM$_{2.5}$ and were converted to PM$_{10}$ assuming PM$_{2.5}$/PM$_{10}$ = 0.6.

1  found higher effects for risk in the neonatal period. Another study, based in Southern California identified

2  no association for neonatal effects (numerical results not provided) but statistically significant results for

3  postneonatal mortaliy (Ritz et al., 2006). Figure 7.6 compares risk for the postneonatal period for

4  respiratory and total mortality. In six of the seven studies, higher effect estimates were observed for

5  respiratory-related mortality. Results from the neonatal period found higher effects for total mortality

6  compared to respiratory mortality (Bobak and Leon, 1999a) and the reverse for a study examining infant

7  mortality (Lipfert et al., 2000). Thus, there exists evidence for a stronger effect at the postneonatal period

8  and for respiratory-related mortality, although this trend is not consistent across all studies.

### *Decrements in Sperm Quality*

9  Limited research conducted in the Czech Republic on the effect of ambient air pollution on sperm

10  production has found associations between elevated air pollution and decrements in proportionately fewer

11  motile sperm, proportionately fewer sperm with normal morphology or normal head shape,

12  proportionately more sperm with abnormal chromatin (Selevan et al., 2000), and an increase in the

13  percentage of sperm with DNA fragmentation (Rubes et al., 2005). These results were not specific to PM,

14  but for exposure to a high-, medium- or low-polluted air mixture. Research in Los Angeles, California

15  examined 5134 semen samples from 48 donors in relation to ambient air pollution measured 0-9, 10-14,

16  70-90 days before semen collection over a two year period (1996-1998). Ambient ozone during all

17  exposure periods had a significant negative correlation with average sperm concentration, and no other

18  pollutant measures were significantly associated with sperm quality parameters, or presented

19  quantitatively (Sokol et al., 2006).

## 7.4.2. Toxicological Studies

20  This section summarizes recent evidence on reproductive health effects reported with exposure to

21  ambient PM; no evidence was available in this area in the 2004 PM AQCD. Studies from different

22  toxicological rodent models allow investigation of specific mechanisms and modes of action for

23  reproductive changes. Emphasis is placed here on results from different windows of development, i.e., if

24  exposure in utero, neonatally or as an adult can lead to similar reproductive outcomes as an adult. In

25  addition, studies evaluating whether fertility is affected in female and/or male animals equally by a

26  similar exposure, and how exposures are transmitted to the fertility of the F1 offspring, are summarized.

27  Hormonal changes which can lead to decreased sperm count or changes in the estrous cycle are also of

28  interest. Pregnancy losses and placental sufficiency are also followedT. Most recently, the role of

1    environmental chemicals in shifting sex ratios (also seen in epidemiologic studies) and in affecting

2    heritable DNA changes have become endpoints of interest.

## *Female Reproductive Effects*

3        Significant work has been done in male rodent models to determine the effect of PM exposure on

4    reproductive success; fewer studies have been done on female rodents. Tsukue et al. (2004) exposed

5    pregnant C57-BL mice to DE 0.1 mg DEP/$m^3$ diluted in charcoal and HEPA-filtered clean air or to for 8

6    h/day GD 2-13 and at GD 14 collected the female fetuses for analysis of mRNA for Ad4BP-1/SF-1 and

7    MIS, and found no significant changes. The concentration of the gaseous materials including NO, $NO_X$,

8    $NO_2$, CO and $SO_2$ are 2.2 + 0.34 ppm, 2.5 + 0.34 ppm, 0.0 ppm, 9.8 +/- 0.69 ppm, and <0.1ppm (not

9    detectable), respectively. Work by Yoshida et al. (2006b) showed changes in these two transcripts in male

10   ICR fetuses exposed to similar doses of DEP, albeit with different daily durations of exposure. Further

11   work by Yoshida et al. showed that of three mouse strains tested, ICR male fetuses were the most

12   sensitive to DE-dependent changes in these two genes. Nonetheless, strain sensitivity to DEP may also

13   differ by sex. Tsukue et al. (2004) also looked at mRNA transcript levels of other steriodogenic and

14   oocyte-affecting genes [aromatase, Cytochrome P450 1A1 (CYP 1A1), MIS, x-chromosome gene-1

15   (DAX-1), estrogen receptor (ER), Wingless-4 (Wnt), Wnt-7a, Growth differentiation factor-9 (GDF-9),

16   bone morphogenetic protein-6 (BMP-6) and BMP-15]. Among these genes, they found significant mRNA

17   reduction of BMP-15, a gene related to oocyte development. Thus, it appears that female mice exposed in

18   utero to DE show a lack of response at the mRNA level of MIS or Ad4bP-1/SF-1, important genes in

19   male sexual differentiation that showed DE-dependent changes in male pups from dams exposed in utero.

20   Female fetuses do however show a decrease in BMP-15, which is related to oocyte development. Possible

21   ingestion exposure from grooming cannot be ruled out in this study.

22        Windows of exposure are important in determining reproductive success as an adult. Exposure as a

23   neonate may have a drastically more profound impact than does a similar adult exposure in females. To

24   test this, female BALB/C mice were exposed to ambient air in Sao Paulo as neonates or as adults and then

25   were bred to non-exposed males (Mohallem et al., 2005). Concentrations of pollutants in this ambient air

26   including CO, $NO_2$, $PM_{10}$, and $SO_2$ as measured locally were 2.2 ± 1.0, 107.8 ± 42.3, 35.5 ± 12.8, and

27   11.2 ± 5.3, respectively. They reported decreased fertility in newborn but not adult female BALB/c mice

28   after exposure to ambient air. There were a significantly higher number of liveborn pups from dams

29   housed in filtered chambers (PM removed as well as chemical substances) versus animals exposed to

30   ambient air as newborns. There was also a higher incidence of implantation failures in dams reared as

31   newborns in polluted chambers. Sex ratio (unlike in epidemiologic studies), number of pregnancies per

32   group, resorptions, fetal deaths, and fetal placental weights did not differ significantly by treatment group.

1    Thus, in these studies, exposure to ambient air pollution and its associated PM affected future

2    reproductive success of females if they were exposed as neonates and not if they are exposed as adults.

3        Environmental chemicals have been shown to act as endocrine disruptors by acting on the

4    androgen pathway, including the phthalates, which have manifested their anti-androgenic activity in

5    numerous pathways including decreased anogenital distance in male rodents (Foster et al., 1980; Foster et

6    al., 2001). To access the role of DE exposure on reproductive success and anti-androgenic effects on

7    offspring, Tsuke et al. (2002) exposed 6 week old female C57-BL mice to 4 months of DE (0.3, 1.0, or 3.0

8    mg/m$^3$) or filtered air (controls). Some animals were euthanized at the end of this exposure; DE-exposed

9    estrous females from this group were found to have significantly decreased uterine weight (1.0 mg/m$^3$).

10   Some of these DE-exposed females were bred to unexposed males. It was determined that DE-exposure

11   led to increased but not significant rates of pregnancy loss in mated females (up to 25%). The rate of good

12   nest construction of the pregnant exposed dams at the highest dose group was significantly lower than

13   control (3.0 mg DEP/m$^3$). Offspring were weighed after birth with significant decreases in body weight

14   seen at 6 and 8 weeks (males and females 1.0 and 3.0 mg DEP/m$^3$) and in female offspring (9 weeks of

15   age, 1.0 and 3.0 mg/m$^3$). Anogenital distance, a sensitive marker of anti-androgen activity in males, was

16   significantly decreased in 30-day old DEP exposed male offspring (0.3 mg DEP/m$^3$) v. controls. Thymus

17   weight was significantly decreased in 30-day old female offspring (3.0 mg DEP/m$^3$) and remained

18   decreased at 70 days (0.3 and 1.0 mg DEP/m$^3$). Ovary weight of female offspring was significantly

19   decreased (3.0 mg DEP/m$^3$) at 30 days, but no longer significantly different at 70 days. In males at 70

20   days of age, body weights were significantly decreased and AGD was significantly shorter (3.0 mg

21   DEP/m$^3$). In females at 70 days of age, the 1.0mg DEP/m$^3$ group showed significantly lower organ

22   weights (adrenals, liver, and thymus) and the 3.0 mg DEP/m$^3$ group had decreased body weight. Thymus

23   weight of the 0.3 mg/m$^3$ females was significantly lower at 70 days. Also, crown to rump length in

24   females from dams exposed to DEP (1.0 and 3.0 mg DEP/m$^3$) was also significantly lower. In conclusion,

25   adult exposure to DEP led to maternal dependent reproductive changes that affected outcomes in

26   offspring manifesting as decreased pup body weight, anti-androgenic effects like decreased AGD and

27   decreased organ weight (which may be confounded by changes in body weight).

### *Male Reproductive Effects*

28   Rodent strains differ in their sensitivity and response to various environmental chemicals. Studies

29   were performed to determine PM-dependent strain sensitivity using male steroidogenic enzymes as the

30   model pathway. In utero exposure of 3 strains of pregnant mice (ICR, C57Bl/6J or ddY mice) via

31   inhalation exposure of DE at 0.1 mg DE particles (DEP)/m$^3$ in HEPA-filtered clean air occurred or clean

32   air as controls continuously over gestational days 2-13 (Yoshida et al., 2006b). At gestational day 14,

1    dams were euthanized and fetuses were collected from the uteri. Male fetuses were collected from each

2    dam for mRNA analysis of genes related to male gonad development including mullerian inhibiting

3    substance (MIS), steroid transgenic factor (Ad4BP/SF-1), an enzyme in the testosterone synthesis

4    pathway, cytochrome P450 cholesterol side chain cleavage enzyme (P450scc), and other steroidogenic

5    enzymes [17β-hydroxysteroid dehydrogenase (HSD), cytochrome P450 17-α-hydroxylase (P450c17), and

6    3-βhydroxysteroid dehydrogenase (3βHSD)]. There were significant decreases in MIS (ICR, and

7    C57BL/6 mice) and Ad4BP/SF-1 (ICR mice) versus control at gestational day (GD) 14. SF-1

8    transcriptionally regulates T secretion. MIS is crucial in for sexual differentiation including mullerian duct

9    regression in males. The ddY strain showed no significant changes in Ad4BP/SF-1 or MIS which the

10   authors hypothesized may be due to changes in 3β-hD, which had marked changes in expression in the

11   ddY strain when compared to non-DE exposed controls. From these studies, it appears that mouse strains

12   with in utero exposure to DE show differential sensitivity in gonadal differentiation genes (mRNA) of

13   male offspring; ICR are the most sensitive, followed by C57BL/6 with ddY mice the least sensitive.

14        Yoshida et al. (2006a) also monitored changes in the male reproductive tract after in utero exposure

15   to DE. Timed-pregnant ICR dams were exposed during gestation (2dpc to 16dpc) to continuous DE

16   generated to concentrations of 0.3, 1.0 or 3.0 mg DEP/m$^3$ in HEPA-filtered air or clean air as controls. PM

17   deposition on the fur and ingestion of the dams by grooming is another possible exposure route in this

18   study. The reproductive tracts of male offspring were monitored at 4 weeks postnatally. These pups

19   received possible exposure through lactation as dams exposed to DE during gestation nursed pups. There

20   was a threshold effect; 0.3 mg/m$^3$ had no effect on male reproductive organ weight or serum testosterone

21   (T). Exposure to the higher doses (1.0 and 3.0 mg/m$^3$) of DEP led to significant increases in reproductive

22   gland weight [testis, prostate, seminal vesicle (3.0 mg DEP/m$^3$ only) and coagulating gland]. The

23   intermediate dose of 1.0 mg DEP/m$^3$ induced significant increases in serum T. The organ weights are

24   presented as absolute numbers and not adjusted for body weight, which is sometimes problematic for

25   complete representation of hormonal changes as body weight may confound absolute organ weight

26   changes. Nonetheless, there were also significant decreases in mRNA for the steroidogenesis related

27   enzymes 3βHSD (3.0 mg DEP/m$^3$) and aromatase (3.0 mg DEP/m$^3$). Transcripts relating to male sexual

28   differentiation [Mullerian inhibitory substance (mis) and steroid transgenic factor (AD4BP/SF-1), 1.0 and

29   3.0 mg DEP/m$^3$] were also significantly decreased. Sexual differentiation is a tightly regulated process.

30   For example, SF-1 missense mutations result in XY individuals with external female genitalia. Thus the

31   effect of environmental DE-exposure should not be underscored.

32        This study demonstrated effects of DE exposure on male spermatogenesis. Exposure of pregnant

33   ICR mice to DE (2 dpc-16 dpc continuous inhalation exposure to 1.0 mg DEP/m$^3$ in filtered air or to

34   filtered clean air) led to impaired spermatogenesis in offspring (Ono et al., 2007). Male offspring were

1    followed at PND 8, 16, 21 (3 weeks), 35 (5 weeks) and 84 (12 weeks). After 16dpc but before termination

2    of the study, all of the animals were transferred to a regular animal care facility. No cross fostering was

3    performed in this experiment, so pups that were born to DE-exposed dams were also nursed on these

4    dams and may have received lactational exposure to DE from milk. The gaseous components of the

5    diluted DE included nitric oxide (NO), $NO_2$, sulfur dioxide ($SO_2$), and carbon dioxide ($CO_2$) at

6    concentrations of 11.75+/-1.18, 4.62+/-0.36, 0.21 +/- 0.01, and 4922 +/-244 ppm, respectively. The

7    average proportion of sulfur in the fuel during this study was 0.043%. Body weight was significantly

8    depressed at PNDs 8 and 35. Accessory gland relative weight was significantly increased at PND 8 and 16

9    only. Serum testosterone was significantly decreased at 3 weeks and at 12 weeks was significantly

10   increased. At 5 and 12 weeks, daily sperm production (DSP) was significantly decreased. FSH receptor

11   and star mRNA levels were significantly increased at 5 and 12 weeks, respectively. Relative testis weight

12   and relative epididymal weight were unchanged at all time points. All endpoints were measured at each

13   time point and if not mentioned above, those data reported no significant changes. Histological changes

14   showed sertoli cells with partial vacuolization and a significant increase in testicular multinucleated giant

15   cells in the seminiferous tubules of DE exposed animals compared to control. This study indicates that in

16   utero exposure to DE had effects on spermatogenesis in offspring.

17       In utero exposure to DE and its effect on adult body weight, sex ratio, and male reproductive gland

18   weight was measured by Yoshida et al. (2006a). Pregnant ICR mice were exposed by inhalation to DE

19   (0.3, 1.0 or 3.0 mg DEP/$m^3$ or to clean air) from 2dpc to 16dpc. Pups were allowed to nurse in clean air

20   on exposed dams until weaning and at PND 28, male pups were sacrificed. At this time, serum

21   testosterone and pup reproductive gland weight was determined. Significant increases in relative

22   reproductive organ weights were reported at 1.0 and 3.0 mg DEP/$m^3$ for the seminal vesicle, testis,

23   epididymis, coagulating gland, prostate and liver. Male pup serum testosterone was significantly

24   increased at 1.0 mg DEP/$m^3$. Mean testosterone positively correlated with testis weight, daily sperm

25   production, aromatase and steroidogenic enzyme message level (P450cc, c17 lyase, and P450 aromatase).

26   Sex ratio did not differ in DE-exposed animals versus control. Male pup body weight of DE-exposed

27   animals was significantly increased at PND 28 (1.0 and 3.0 mg DEP/$m^3$). These studies show that in utero

28   DE-exposure led to increased serum testosterone and increased reproductive gland weight in male

29   offspring early in life.

30       The effects of DE on murine adult male reproductive function were studied by exposing ICR male

31   mice (6 weeks of age) to DE (clean air control, 0.3, 1.0 or 3.0 mg DECP/$m^3$) for 12 h/day for six months

32   with another group receiving a one month recovery of clean air exposure post-exposure (Yoshida and

33   Takedab, 2004). After six months exposure, there was a dose-dependent significant increase in

34   degeneration of seminiferous tubules of mice exposed to DEP. After six months, there was a significant

1  decrease in daily sperm production (DSP)/g of testis tissue in DEP exposed animals. After six months

2  exposure to DEP plus one month recovery with clean air exposure, significant decreases remained in DSP

3  at the higher doses; the effect was lost at 0.3 mg/m$^3$. This adult exposure and other work with in utero

4  exposure to DE showed similar outcomes. The effect of ingestion of deposited PM from the fur during

5  inhalation exposure cannot be ruled out as a possible mechanism of exposure in this experiment.

6      Earlier studies showed an inverse correlation between environmental levels of PM and sperm count

7  in adult men (Mehta and Anad Kumar, 1997). To expand on PM-dependent changes in spermatogenesis,

8  an eloquent DE-exposure model was designed to determine if PM or the gaseous phase of DE was

9  responsible for changes in sperm production in rodents (Watanabe, 2005). Pregnant dams (F344/DuCrj

10  rats) exposed to DE (6 hours/day exposure to 0.17 or 1.71 mg DEP/m$^3$) or filtered air (removing PM only,

11  high dose filtered air and low dose filtered air) from GD7 to parturition produced adult offspring with a

12  decreased number of sertoli cells and decreased daily sperm production (PND 96) when compared to

13  control mice exposed to clean air (Watanabe, 2005). The concentrations of NO$_2$ for the high filtered and

14  low filtered exposure groups were 0.8 and 0.1 ppm, respectively. Because both filtered and DE-exposure

15  groups showed the same outcomes, the effects are likely due to gaseous components of DE.

16      Another source of PM emissions that is common around the world is motorcycle exhaust. Adult

17  male (8 week old) Wistar rats were exposed to motorcycle exhaust (ME) for 1-h in the morning and 1-h in

18  the afternoon Monday through Friday at 1:50 dilution in filtered clean air for 4 weeks (group A) or 1:10

19  for 2 (group B) or 4 weeks (group C) or to clean air (Huang et al., 2008) via a head and nose inhalation

20  chamber. After 4 weeks of exposure, both exposed groups had significantly decreased body weight v.

21  control. All three groups showed a decreased number of spermatids in the testis after ME exposure. Both

22  1:10 exposure groups also showed a decrease in caudal epididymal sperm counts. Group C showed

23  significant decreases in testicular weight. Group C had decreased mRNA for the cytochrome P450

24  substrate 7-ehtoxycoumarin O-de-ethylase, and increased IL-6, IL-1B, and cox-2 mRNA control.

25  Decreased protein levels of antioxidant superoxide dismutase and increased IL-6 protein were reported

26  for group C when compared to control. Serum testosterone was significantly decreased in group C and co-

27  treatment of group C with the antioxidant vitamin E resulted in partial rescue of serum T levels and

28  caudal epididymal sperm counts (albeit still significantly decreased versus control), and returned IL-6,

29  IL-1β, and COX-2 ME-exposure-dependent message levels to baseline. The glutathione antioxidant

30  system and lipid peroxidation were unchanged after these ME exposures at the time points measured.

31  Male animals exposed to ME in this experiment showed significant decrements in body weight, spermatid

32  number, and serum testosterone with an increase in inflammatory cytokines. Vitamin E co-treatment with

33  ME-exposure led to an attenuation of inflammation and a partial rescue of testosterone levels and sperm

1   numbers. No filtration was done in this experiment to determine if the toxic phase of the exposure was

2   gas or particulate-dependent.

## Developmental Effects

### Sex Ratio

3       A direct correlation between air pollution ($PM_{10}$) exposure and a decrease in standardized sex ratios

4   (SSRs) has been reported in humans exposed to air pollution (Lichtenfels et al., 2007), with fewer

5   numbers of male births reported. To understand this shift, two groups (control and exposed) of male Swiss

6   mice were housed concurrently in Sao Paulo and received either ambient air exposure or filtered air

7   (chemical and particulate filtering) from PND10 for four months. Filtration efficiency for $PM_{2.5}$, carbon

8   black, and $NO_2$ inside the chamber was found to be 55%, 100%, and 35%, respectively. After this

9   exposure, non-exposed females were placed in either chamber to mate. After mating, the males were

10  sacrificed and testes collected; males exposed to ambient air showed decreased testicular and epididymal

11  sperm counts, decreased total number of germ cells, and decreased elongated spermatids, but no

12  significant change in litter size. Females were housed in the chambers and sacrificed on GD19 when the

13  number of pups born alive and the sex ratio were obtained. There was a significant decrease in the SSR

14  for pups born after living in the ambient air-exposed chamber compared to the filtered chamber. In this

15  study, a shift in SSR has been shown for both humans and rodents exposed to air pollution, but other

16  studies with DE exposure (Yoshida et al., 2006a) or ambient air in Sao Paulo (Mohallem et al., 2005)

17  showed no changes in rodent sex ratio. Possible exposure to PM and other components of ambient air via

18  ingestion during grooming cannot be ruled out in this rodent model.

### Immunological Effect-Placenta

19      Placental insufficiency can lead to the loss of a pregnancy or to adverse fetal outcomes. DE-

20  exposure has been shown to induce inflammation in various models. Fujimoto et al. (2005) accessed

21  cytokine/immunological changes of DE-dependent inhalation exposure on the placenta during pregnancy.

22  Pregnant Slc: CR mice were exposed to DE (0.3, 1.0, or 3.0 mg $DEP/m^3$ in HEPA and charcoal-filtered

23  clean air from 2dpc to 13 dpc) or clean air in inhalation chambers; dams, placenta, and pups were

24  collected at 14dpc. There was a significant increase in the number of absorbed placentas in DE exposed

25  animals (0.3 and 3.0 mg $DEP/m^3$) with a significant decrease in the number of absorbed placentas in DE

26  exposed animals at the middle dose (1.0 mg $DEP/m^3$). Absorbed placentas from DE exposed mice had

27  undetectable levels of CYP1A1 and two fold increases in TNF-α; CYP1A1 placental mRNA from healthy

28  placentas of DE-exposed mice was unchanged versus control. Interleukin (IL)-2, IL-5, IL-12α, IL-12-β

29  and granulocyte macrophage colony-stimulating factor (GM-CSF) mRNA significantly increased in

placentas of DE-exposed animals (0.3 and 3 mg DEP/m$^3$). Placental IL-6 mRNA was increased ten-fold in DE-exposed mice (3.0 mg DEP/m$^3$). Fujimoto et al. reported DE-induced significant increases in multiple inflammatory markers in the placenta with significant increases in the number of absorbed placentas.

### Immunological Effects: Asthma

In utero exposure may confer susceptibility to PM-induced asthmatic responses in offspring. Exposure of pregnant BALB/c mice to aerosolized ROFA leachate by inhalation or to DEP intranasally increases asthma susceptibility to their offspring (Fedulov et al., 2008; Hamada et al., 2007). The offspring from dams exposed for 30 min to 50 mg/ml ROFA 1, 3, or 5 days prior to delivery responded to OVA immunization and aerosol challenge with airway hyperreactivity and increased antigen-specific IgE and IgG1 antibodies. Airway hyperreactivity was also observed in the offspring of dams intra-nasally instilled with 50 µg of DEP or TiO$_2$, or 250 µg CB, indicating that the same effect could be demonstrated using relatively "inert" particles. Pregnant mice were particularly sensitive to exposure to DEP or TiO$_2$ particles, and genetic analysis indicated differential expression of 80 genes in response to TiO$_2$ in pregnant dams. Thus pregnancy and in utero exposure may enhance responses to PM, and exposure to even relatively inert particles may result in offspring predisposed to asthma.

### Placental Weights and Birth Outcomes

Pregnant female Swiss mice were exposed to ambient air (Sao Paulo) or filtered air over various portions of gestation to determine if there was an association between fetal or placental weight or birth outcomes with exposure to air pollution. The concentration of various components of the ambient air as measured by a State Environmental Sanitation Agency 100 meters away from the rodent exposure chambers reported PM$_{10}$ (42 ± 17 µm/m$^3$), NO$_2$ (97 ± 39 µg/m$^3$), and SO$_2$ (9 ± 4 µg/m$^3$) concentrations. By using six windows of exposure that covered one to three weeks of gestation, which is all of gestation in a mouse, these authors (Silva et al., 2008) determined that a significant decrease in near-term fetal weight (GD19) could be induced by ambient air-exposure at least during the first week of gestation. Decreased placental weight could be induced by ambient air exposure during any of the three weeks of gestation. These studies point to possible windows of exposure that may be important in evaluating epidemiologic study results.

### Neurodevelopmental Effects

The diagnosis of autism is on the rise in the Western world with its etiology mostly unknown. Autism is associated cell loss in specific brain regions that is hypothesized to be developmental in origin.

1    Sugamata et al. (2006) exposed pregnant ICR mice to DE (0.3 mg DEP/m$^3$) continuously from 2 days

2    post-coitus (dPC) to 16 dPC. Pups with in utero exposure to DE were nursed in clean air chambers but

3    may have received gastro-intestinal exposure via lactational transfer of various components of DE. At 11

4    weeks of age, cerebullar brain tissue was collected. Twenty animals were in each group (10 females, 10

5    males) with one group receiving clean air exposure and one receiving DE; no filtration was used to

6    compare PM v. gaseous DE exposure. Earlier work has shown that DEP (<0.1 μm) have been detected in

7    the brains (cerebral cortex and hippocampus) of newborn pups who were born to dams who were exposed

8    to DE during pregnancy (Sugamata et al., 2006). Histological analysis of DE-exposed pup cerebella

9    revealed significant increases in caspase-3 (c-3) positive cells compared to control and significant

10   decreases in cerebella Purkinje cell numbers in DE-exposed animals versus control. The ratio of cells

11   positive for apoptosis (c-3 positive) showed a nearly significant sex difference with males displaying

12   increased apoptosis versus females (p = 0.09). In humans with autism, the cerebellum has a decreased

13   number of Purkinje cells, which is thought to be fetal and developmental in origin; further, these authors

14   speculate that humans may be more sensitive to DE-dependent neuronal brain changes as the human

15   placenta is 2 layers thick whereas the mouse placenta is 4 layers thick.

### Behavioral Effects

16   Body weight decrements at birth have recently been associated through the Barker hypothesis with

17   adverse adult outcomes. Thus, many publications have begun to focus on decreased birth weight for

18   gestational age and associated adult changes. Hougaard et al. (2008) exposed 40 timed-pregnant C57BL/6

19   dams to DEP reference materials (aged DE particulate extract) via inhalation chamber over GD7-19 of

20   pregnancy. They found significantly decreased pup weight at weaning, albeit not at birth. PM-dependent

21   liver changes were monitored by following various inflammatory and gentoxicity-related mRNA

22   transcripts; there were no significant differences in pups at PND2. The comet assay from PND2 pup livers

23   showed no significant differences between DEP-exposed and control animals. Thyroxine was unchanged

24   in control and DEP-exposed dams and offspring at weaning. At two months, female DEP-exposed pups

25   required less time than controls to locate the platform in its new location during the first trial of the spatial

26   reversal learning task in the Morris water maze (p<0.05). DEP extract exposure during in utero

27   development led to decreased body weight at weaning and no changes in inflammatory markers, or

28   thyroid hormone levels.

### Lactation

29   Lactational exposure to various environmental compounds is an area of research that is often

30   overlooked. Breast milk is a complex matrix, which is essential for the survival of many species.

1    Compounds that are especially lipophilic are commonly found in breast milk of exposed dams and this

2    maternal load can be transferred to the developing neonate. PM in DE adsorbs many chemicals, including

3    polycyclic aromatic hydrocarbons (PAHs), which have been shown to have to be mutagenic and to be

4    estrogenic/antiestrogenic and antiandrogenic (Hirose et al., 2001; Kizu et al., 2003). Thus, Tozuka et al.

5    (2004) monitored the transfer of aromatic hydrocarbons to fetuses and breast milk of Fisher 344 rats

6    exposed to DE for two weeks from GD7 to GD 20 (minus four days of the weekend with no exposures)

7    for 6h/day with $PM_{10}$ concentration of 1.73 mg/m$^3$. Concentrations of individual PAHs were monitored in

8    the inhalation chambers including Ace, Fle, Phe, Ant, Flu, Pyr, BaA, Chr, BbF, BkF, BaP, DBA, BghiP,

9    and IDP at $150 \pm 34$, $3160 \pm 401$, $2280 \pm 291$, $70.3 \pm 10.9$, $148 \pm 19$, $133 \pm 5$, $17.2 \pm 2.7$, $39.9 \pm 6.8$,

10   $9.9 \pm 2.1$, $4.9 \pm 1.1$, $3.7 \pm 0.5$, $<1.4$, $<6.0$, and $4.2 \pm 0.1$ ng/m$^3$, respectively. At PND 14, milk was

11   collected from exposed and control rats. Fifteen PAHs were monitored in DE-generated air. Seven of

12   these were quantified in dam blood with levels of phenanthrene (Phe), anthracene (Ant) and

13   benz[a]anthracene (BaA) in the DE group being significantly higher than control group. In breast milk,

14   acenaphthene (Ace), fluorene (Fle), Phe, Ant, fluoranthene (Flu), pyrene (Pyr), BaA and chrysene (Chr)

15   were quantified. Ant, Flu, Pyr and Chr showed significant increases in the DE group compared to control

16   milk. BaA tended to be about four fold higher than the control group in breast milk, but the increase was

17   not significant. PAHs in dam livers of DE versus control were not significantly different. PAHs are

18   transferred across the placenta from the DE-exposed dam to the fetus. Lactational transfer through the

19   breast milk is also likely as PAHs are detected in dam breast milk, but this should be confirmed in future

20   studies that cross foster control and exposed dams and pups. The lipophilicity of the PAH based on its

21   structure affected its uptake to the dam from the air as PAHs with 3 or 4 rings were found in maternal

22   blood and PAHs with 5 or 6 rings were not detected in dam blood.


## 7.4.3. Summary and Causal Determination

### 7.4.3.1. $PM_{10}$

23       In summary, epidemiologic studies do not consistently report associations between $PM_{10}$ exposure

24   and preterm birth, growth restriction, birth defects or decreased sperm quality; however evidence is

25   accumulating for effects on low birth weight and infant mortality, especially due to respiratory causes

26   during the post-neonatal period. The most striking results were that three U.S. studies reported 11 gram

27   decrements in birth weight associated with $PM_{10}$ exposure. The consistency of these results strengthens

28   the interpretation that particle exposure may be causally related to reductions in birth weight. Similarly,

29   animal evidence supported an association between $PM_{10}$ exposure and adverse reproductive and

1    developmental outcomes, but provided little mechanistic information or biologic plausibility for an

2    association between long-term PM exposure and adverse birth outcomes, including low birth weight, or

3    infant mortality. New evidence from animal toxicological studies on heritable mutations is promising, and

4    warrants further investigation. **Overall, the epidemiologic and toxicological evidence is suggestive of**

5    **a causal relationship between long-term exposures to PM$_{10}$ and reproductive and developmental**

6    **outcomes.**

7         The epidemiologic studies generally show consistency and coherence across the different health

8    outcomes assessed; though interpretation of the results remains challenging given methodological issues

9    discussed previously. Three epidemiologic studies in the U.S. (Bell et al., 2004; Chen et al., 2002; Salam

10   et al., 2005) reported 11 gram decrements in **birth weight** associated with PM$_{10}$ exposure. The

11   consistency of these results, in different studies by different investigators in different regions of the U.S.,

12   strengthens the interpretation that particle exposure may be causally related to reductions in birth weight.

13   In epidemiologic studies, all but one of the studies (Wilhelm and Ritz, 2005) that examined the

14   relationship between PM$_{10}$ and **preterm birth** found at least some positive associations for the exposure

15   periods analyzed. The effects tended to be the strongest for exposures during the first trimester. Three

16   epidemiologic studies evaluated the association between PM$_{10}$ and **growth restriction**; two found no

17   association (Hansen et al., 2007a; Salam et al., 2005) and one study found a positive association with

18   exposures during the second trimester (Mannes et al., 2005). The results of three epidemiologic studies

19   examining PM$_{10}$ and **birth defects** have produced inconsistent results; two found a positive association

20   (Gilboa et al., 2005; Kim et al., 2007a) and one found inconclusive results (Ritz et al., 2002). Finally,

21   epidemiologic studies of **infant mortality** (<1 year) found positive associations, although not all were

22   statistically significant. For total neonatal deaths (<1 month), again all studies found positive associations,

23   not including a study that did not provide numerical results for this analysis, although some associations

24   were uncertain (Ritz et al., 2006). Evidence is strongest for the link between PM$_{10}$ and postneonatal (>1

25   month to <1 year) respiratory-related mortality.

26         Toxicological studies of female reproductive outcomes provide some evidence of PM-related

27   effects. Windows of exposure are important in effects seen in reproductive fecundity of female mice.

28   Neonates or adult female BALB/C mice were exposed to PM (ambient urban air in Sao Paulo), and then

29   were bred to monitor pregnancy and birth outcomes. Adult exposed animals experienced no adverse

30   outcomes but, nenonatally exposed females had decreased fertility, decreased number of live born

31   animals, and an increased number of implantation failures pointing to neonatal exposure to PM being a

32   more critical window for effects in pregnancy and birth outcomes than adult exposure.

1    In a toxicological study to assess placental weights and birth outcomes, pregnant Swiss mice were

2    exposed to ambient air in Sao Paulo over multiple portions of gestation, which is 3 weeks in mice, and

3    fetuses were collected near term. Dams exposed to ambient air during the first week of gestation had pups

4    with significantly decreased fetal weight. Exposure to ambient air over any portion of gestation induced

5    significant decreases in placental weight. Birth weight is affected by exposure early in pregnancy whereas

6    exposure during any portion of pregnancy affects placental weight, pointing to windows of exposure to

7    consider for birth outcomes.

### 7.4.3.2. $PM_{2.5}$

8    In summary, epidemiologic studies do not consistently report associations between PM exposure

9    and preterm birth, growth restriction, birth defects or decreased sperm quality; however evidence is

10   accumulating for effects on low birth weight and infant mortality, especially due to respiratory causes

11   during the post-neonatal period. Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth

12   weight than exposure to $PM_{10}$. Similarly, animal evidence supported an association between $PM_{2.5}$

13   exposure and adverse reproductive and developmental outcomes, but provided little mechanistic

14   information or biologic plausibility for an association between long-term PM exposure and adverse birth

15   outcomes, including low birth weight, or infant mortality. **Overall, the epidemiologic and toxicological**

16   **evidence is suggestive of a causal relationship between long-term exposures to $PM_{2.5}$ and**

17   **reproductive and developmental outcomes.**

18   Three epidemiologic studies in the U.S. and one in Europe were able to examine the effects of

19   $PM_{2.5}$, and all found an increased risk of **low birth weight** specifically related to $PM_{2.5}$ exposure (Bell et

20   al., 2007b; Parker et al., 2005). Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth

21   weight than exposure to $PM_{10}$. All of the studies that examined the relationship between $PM_{2.5}$ and

22   **preterm birth** report positive associations, though the results from Sagiv et al. (2005) were not

23   statistically significant. Additionally, Ritz et al. (2007) only found significant positive associations among

24   a subset of the cohort they were examining, and not for the full cohort. Three studies evaluated the

25   association between $PM_{2.5}$ and **growth restriction** and all three found positive associations, with the

26   strongest evidence coming when exposure was assessed during the first or second trimester (Liu et al.,

27   2007d; Mannes et al., 2005; Parker et al., 2005). For infant mortality (<1 year), one study examined $PM_{2.5}$

28   and found a positive and statistically significant association (Loomis et al., 1999). Two more recent

29   studies also found positive, though not statistically significant results (Woodruff et al., 2006; 2008).

30   In toxicological studies of female reproductive outcomes, adult female Slc: ICR mice exposed to

31   DEP developed significantly decreased uterine weight versus control. A subset of these adult-exposed

1     animals was bred to unexposed males and the exposed females showed maternal behavioral changes

2     (decreased rate of good nest construction). The offspring had decrements in body weight, with decreases

3     in organ weights (females), decreased anogenital distance in males (anti-androgen indicator), and

4     decreased crown to rump length (females). Adult exposure prior to mating affects offspring development

5     and maternal behavior. In utero DEP exposure in Slc: ICR mice led to decreased mRNA expression of

6     BMP-15, a gene related to oocyte development, in female offspring with no changes in the message level

7     of MIS and SF-1, two sexual differentiation genes that are affected in male offspring with in utero DEP

8     exposure.

9     Several studies also provided some limited evidence of male reproductive effects. In utero DEP-

10     exposure induced changes in male fetal mRNA for MIS and SF-1, two genes important in male sexual

11     differentiation. These changes were differentially regulated based on the mouse strain used (most

12     sensitive, ICR > C57BL/6 > ddY, least sensitive).

13     DE-exposure in utero led to conflicting reports of reproductive outcomes in male offspring (ICR

14     mice). Some have reported decreased body weight and decrements in spermatogenesis (PND 8-84 at

15     various time points) including decreased serum testosterone, decreased male accessory reproductive gland

16     weight, histological vacuolization of sertoli cells in the seminiferous tubules, and decreased daily sperm

17     counts. Others showed DE-exposure in utero induced increased serum testosterone and increased

18     reproductive gland weight and increased body weight in male offspring (ICR mice) at one time period

19     early in life (PND28) or dose-dependent increased reproductive gland weight, increased serum

20     testosterone, and decreased expression of mRNA transcripts related to sexual differentiation at 4 weeks of

21     age. In utero exposure of mice to DE, filtered air (PM removed), or clean air demonstrated that the

22     gaseous phase of DE was responsible for the decrements in sperm production seen in mice exposed to DE

23     during gestation.

24     DE exposure to adult male mice (ICR strain) daily for 6 months led to dose-dependent significant

25     increases in degradation of seminiferous tubules, and significant decreases in daily sperm production at 6

26     months of age.

27     Adult Wistar rats exposed to motorcycle exhaust (MEP) daily for four weeks developed significant

28     decreases in body weight, spermatids (testis and caudal epididymal), testicular weight, superoxide

29     dismutase, and serum testosterone with increased expression of inflammatory cytokines. Vitamin E co-

30     treatment with MEP induced a partial rescue of serum T and sperm counts with a return of inflammatory

31     cytokines to baseline levels. MEP exposure affected sperm production but this decrement was partially

32     restored by treatment with the antioxidant Vitamin E.

33     Toxicological studies also reported effects for several development outcomes:

- Immunological effects – placenta: Placental insufficiency after in utero DE-exposure was followed with an emphasis on immunological parameters. Exposed dams developed increased levels of inflammatory placental cytokines, with dose discrepancies in the number of placental absorptions. Greater n should be used in future studies to address the effect of DE exposure on placental absorptions.

- Immunological effects related to asthma: Gestational exposure to PM (ROFA leachate by inhalation or DEP by intratracheal instillation) made offspring (Slc: CR mice) more susceptible to asthma. There were significant increases in airway hyper-reactivity seen after aerosol challenge in ROFA or DEP exposed animals. Pregnant mice were also sensitive to DEP. Pregnancy and in utero exposure to PM enhances future responses to PM in both dams and offspring.

- Neurodevelopmental effecs: Exposure to DE continuously during gestation manifests as changes in the rodent (ICR mice) cerebellum that resemble changes seen in humans with autism, i.e., significant decreases in Purkinje cell numbers.

- Behavioral effects: Female offspring of dams exposed during gestation to DEP required less time that control animals to locate platforms in the Morris water maze in spatial reversal learning task. After in utero DE exposure, thyroid hormone levels were unchanged as were inflammatory markers in the liver.

### 7.4.3.3. PM$_{10-2.5}$

**Evidence is inadequate to determine if a causal relationship exists between long-term exposure to PM$_{10-2.5}$ or other PM components and developmental and reproductive outcomes** because studies have not been conducted in sufficient quantity or quality to draw any conclusion.

# 7.5. Cancer Incidence, Mutagenicity, and Genotoxicity

## 7.5.1. Epidemiologic Studies

A limited number of epidemiologic studies have evaluated associations between long-term exposure to PM and incidence of cancer; studies of mortality from cancer are discussed in the following section. A summary of the mean PM concentrations reported for the studies characterized in this section is presented in Table 7.6.

**Table 7-6.  Characterization of ambient PM concentrations from select studies of cancer and long-term exposures.**

| Reference | Location | Pollutant | Mean Annual Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|---|
| Beelen et al. (2008b) | The Netherlands | $PM_{2.5}$ | 28.3 | Max: 36.8 |
| Bonner et al. (2005) | Western NY State | TSP | 44 | |
| Palli et al. (2008) | Florence, Italy | $PM_{10}$ | NR | |
| Pedersen et al. (2006) | Czech Republic | $PM_{2.5}$ | | Max: 46-120 |
| | | $PM_{10}$ | | Max: 120-238.6 |
| Sorensen et al. (2005) | Copenhagen, Germany | $PM_{2.5}$ | 12.6-20.7 | 75th: 24.3-27.7 |
| Vinzents et al. (2005) | Copenhagen, Germany | $PM_{10}$ | 16.9-23.5 | |

1      Beelen et al. (2008b) looked at the association of BS, $PM_{2.5}$, and traffic intensity variables

2      (intensity on nearest road, intensity in a 100 meter buffer zone, and an indicator variable for living close

3      to a major road) with lung cancer incidence in the Netherlands Cohort Study of Diet and Cancer

4      (n = 114,378). This portion of the study was conducted between September 1986 and December 1997.

5      Adjusted analyses included 1,940 cases in the full cohort, and 1,295 cases in a case-cohort analysis of the

6      same data source. The results of this study are presented in Table 7-7.

**Table 7-7.  Association of average air pollution concentrations and traffic variables with lung cancer incidence in full cohort and case-cohort analyses.**

| Pollutant | Increment | Full Cohort | Case-Cohort | Never Smokers | Ex Smokers | Current Smokers |
|---|---|---|---|---|---|---|
| BS | 10 $\mu g/m^3$ | 0.96 (0.83-1.11) | 1.03 (0.78-1.34) | 1.47 (1.01-2.16) | 0.91 (0.68-1.23) | 0.85 (0.70-1.03) |
| $PM_{2.5}$ | 10 $\mu m/m^3$ | 0.81 (0.63-1.04) | 0.65 (0.41-1.04) | | | |
| Traffic intensity on nearest road | 10,000 mvh/24 h | 1.05 (0.92-1.19) | 1.07 (0.84-1.36) | 1.11 (0.88-1.41) | 0.98 (0.77-1.25) | 1.04 (0.91-1.19) |
| Traffic intensity in a 100-m buffer | 335,000 mvh/24 h | 1.05 (0.92-1.19) | 1.07 (0.84-1.36) | 1.36 (0.99-1.87) | 1.06 (0.82-1.38) | 0.96 (0.81-1.14) |
| Living near a major Road | | 1.11 (0.91-1.34) | 1.10 (0.74-1.62) | 1.55 (0.98-2.43) | 1.24 (0.85-1.81) | 0.95 (0.73-1.23) |

Source: Beelen et al. (2008b)

7      Bonner et al. (2005) conducted a population-based, case-control study of the association between

8      ambient exposure to polycyclic aromatic hydrocarbons (PAHs) in early life and breast cancer incidence

9      among women living in Erie and Niagara counties in the state of New York. Cases (n = 1166) were

10     women with primary breast cancer, and controls (n = 2105) were frequency matched to the cases by age,

11     race, and county of residence. TSP was used as a proxy for PAH exposure. Annual average TSP

concentrations (1959–1997) were obtained from the New York State Department of Environmental
Conservation for Erie and Niagara Counties. Among postmenopausal women, exposure to high
concentrations of TSP (>140 $\mu g/m^3$) at birth was associated with an OR of 2.42 (95% CI: 0.97-6.09)
relative to low concentrations of TSP (<84 $\mu g/m^3$). ORs also were elevated for pollution exposures at age
of menarche (OR: 1.45 [95% CI: 0.74-2.87]) and age at first birth (OR: 1.33 [95% CI: 0.87-2.06]) among
postmenopausal women. Among premenopausal women, exposure to high concentrations of TSP at birth
was associated with an OR of 1.79 (95% CI: 0.62-5.10) relative to low exposure levels, exposure at age of
menarche was associated with an OR of 0.66 (95% CI: 0.38-1.16), and exposure at age of first birth was
associated with an OR of 0.52 (95% CI: 0.22-1.20).

## *Markers of Exposure or Susceptibility*

Several researchers conducted studies that looked at markers of exposure or susceptibility as the
outcome associated with short-term exposure. These studies are included here because they may be
relevant to the mechanism that leads to cancer associated with long-term exposures. Investigators
conducted a family pilot study in the Czech Republic to test the hypothesis that exposure to air pollution
with PM in children results in detectable effects indicated by a number of biomarkers of exposure and
early effects (Pedersen et al., 2006). In this pilot study 24 families, from Prachatice and Teplice, were
identified and the mothers and any children age 5-11 were asked to participate. Exposures were assessed
using air sampling at the front door of participants' homes, monitoring data from two stationary air
monitoring stations, biomarkers of exposure, and questionnaires. Repeated short-term air sampling was
performed during five days at participants' residences. Time series of the levels of common air pollutants
were available for each area. Cotinine, a biomarker of nicotine, was measured in samples of urine to
assess exposures to environmental tobacco smoke. Participants also provided 5 ml of blood sample and
the frequency of micronuclei in peripheral blood lymphocytes was analyzed the cytogenetic effects in
study subjects. Significantly higher frequencies of micronuclei were found in younger children living in
Teplice compared to those living in Prachatice. This finding is noteworthy considering micronuclei
formation in peripheral blood lymphocytes is assumed to be biologically relevant for carcinogenesis.

Palli et al. (2008) investigated the correlation between ambient $PM_{10}$ concentrations and individual
levels of DNA bulky adducts. Study participants were 214 healthy adults aged 35–64 years at enrollment
who resided in the city of Florence, Italy. This study was conducted between 1993 and 1998. $PM_{10}$
exposure levels were based on daily environmental measures provided by two types of urban monitoring
stations (high-traffic and low-traffic). The researchers assessed correlation between DNA bulky adducts
measured in blood samples and $PM_{10}$ concentrations prior to blood sample collection. Time windows of
$PM_{10}$ exposure evaluated in this study were 0–5 days, 0–10 days, 0–15 days, 0–30 days, 0–60 days, and

1   0–90 days prior to blood sample collection. Overall, average $PM_{10}$ concentrations decreased during the

2   study period, with some fluctuations. Exact values were not reported, but $PM_{10}$ appeared to range between

3   approximately 30 and 100 $\mu g/m^3$ for high-traffic stations, and between approximately 20 and 50 $\mu g/m^3$ for

4   low-traffic stations. This study found that levels of DNA bulky adducts among non-smoking workers with

5   occupational traffic exposure were significantly correlated with cumulative $PM_{10}$ levels from high-traffic

6   stations during approximately 2 weeks preceding blood sample collection (0–5 days: $r = 0.55$, $p = 0.03$;

7   0–10 days: $r = 0.58$, $p = 0.02$; 0–15 days: $r = 0.56$, $p = 0.02$). DNA bulky adducts were not associated

8   with $PM_{10}$ levels among Florence residents with no occupational exposure to vehicle emissions or among

9   smokers. DNA bulky adducts were not associated with $PM_{10}$ levels assessed by low-traffic urban

10  monitoring stations.

11      Sorensen et al. (2005) investigated the association between personal exposure to water-soluble

12  transition metals in $PM_{2.5}$ and oxidative stress-induced DNA damage. This study was conducted among

13  49 students from Central Copenhagen, Denmark. Researchers assessed $PM_{2.5}$ exposure by personal

14  sampling over two week-day periods twice in one year (November, 1999 and August, 2000), and

15  determined the concentration of water-soluble transition metals (vanadium, chromium, iron, nickel,

16  copper, and platinum) in these samples. In addition, students donated lymphocyte and 24-h urine samples

17  which were analyzed for DNA damage in terms of 7-hydro-8-oxo-2'-deoxyguanosine (8-oxodG). Mean

18  concentrations and corresponding IQR of these metals differed between months of sample collection. This

19  study found that 8-oxodG concentration in lymphocytes was significantly associated with vanadium and

20  chromium concentrations, with a 1.9% increase in 8-oxodG per 1 $\mu g/L$ increase in vanadium

21  concentration and a 2.2% increase in 8-oxodG per 1 $\mu g/L$ increase in chromium concentration. Vanadium

22  and chromium were associated with the 8-oxodG concentration in lymphocytes independent of the $PM_{2.5}$

23  mass concentration. Platinum, nickel, copper, and iron were not significantly associated with the 8-oxodG

24  concentration in lymphocytes, and none of the six measured transition metals was associated with the 8-

25  oxodG concentration in urine.

26      Vinzents et al. (2005) investigated the association between UFP and $PM_{10}$ concentrations with levels

27  of purine oxidation and strand breaks in DNA using a crossover design. Study participants were 15

28  healthy nonsmoking individuals with a mean age of 25. UFP exposure was evaluated in terms of number

29  concentrations in the breathing zone by using portable instruments in six 18-h weekday periods from

30  March to June 2003. Ambient concentrations for $PM_{10}$ and UFP were also measured on all exposure days

31  at curbside street stations and at one urban background station. Oxidative DNA damage was assessed by

32  evaluating strand breaks and oxidized purines in mononuclear cells isolated from venous blood the

33  morning after exposure measurement. Mean concentration of UFPs (street station) was 30.4 x $10^3$

34  UFPs/mL (standard deviation [SD]: 1.38), mean concentration of $PM_{10}$ at a background monitoring station

1  was 16.9 µg/m$^3$ (SD: 1.53), and mean concentration of PM$_{10}$ at a street station was 23.5 µg/m$^3$ (SD: 1.48).

2  Mean personal exposure to UFPs was 32.4 x 10$^3$ UFPs/mL (SD: 1.49) while bicycling (5 occasions), 19.6

3  x 10$^3$ UFPs/mL (SD: 1.78) during other outdoor activities (6 occasions), and 13.4 x 10$^3$ UFPs/mL (SD:

4  1.96) while indoors (6 occasions). The regression coefficients of the mixed-effects models looking at level

5  of purine oxidation were estimated as $1.50 \times 10^{-3}$ (95% CI: $0.59 \times 10^{-3}$ to $2.42 \times 10^{-3}$; $p = 0.002$) for

6  cumulated outdoor exposure and $1.07 \times 10^{-3}$ (95% CI: $0.37 \times 10^{-3}$ to $1.77 \times 10^{-3}$; $p = 0.003$) for

7  cumulated indoor exposure. Cumulated outdoor and cumulated indoor exposures to UFPs were not

8  associated with strand breaks. Neither ambient air concentrations of PM$_{10}$ nor number concentrations of

9  UFPs at monitoring stations were significant predictors of DNA damage.

### Summary

10  Though several studies have reported an association between lung cancer mortality and long-term

11  PM exposure, the single study (2008a) that looked at lung cancer incidence found no association with

12  PM$_{2.5}$. There are known constituents of PM that have varying levels of toxicity, including some that have

13  been classified as possible or probable carcinogens. An epidemiologic study looked at PM constituents

14  (using TSP as a surrogate for PAHs) and found a positive association. Overall, there is limited evidence

15  available to evaluate the relationship between relevant PM exposures and cancer incidence, though future

16  studies of the effects of PM on DNA damage and other precursors to carcinogenesis are warranted.

## 7.5.1.1. Toxicological Studies

17  Over the past 30 years numerous mutagenicity and genotoxicity studies of ambient PM and their

18  contributing sources have been done to assess the relative mutagenic/genotoxic potential and health risks

19  associated with human exposure to PM. The results from many of these studies were previously described

20  in the 2004 PM AQCD (U.S. EPA, 2004). Most of the data published since then have focused on acute

21  cardiovascular or respiratory effects associated with short-term exposure to ambient PM, mobile

22  combustion sources, or selected constituents. Building on results of earlier studies in the 2004 PM AQCD,

23  data from newly published studies that evaluated the mutagenic and/or genotoxic effects of PM, PM-

24  constituents, and combustion emission source particles are reviewed. A summary table of the pertinent

25  studies is provided in Annex D.

26  Studies previously reviewed in the 2004 PM AQCD (U.S. EPA, 2004) provide compelling evidence

27  that ambient PM as well as PM from specific combustion sources (e.g., fossil fuels) is mutagenic in vivo

28  and in vitro. Studies of neat PM, extracts, and specific components identified in different types of PM

29  have reported positive results in *Salmonella typhimurium* mutation tests (Ames), and mutations,

30  micronuclei (MN), sister chromatid exchange (SCE), chromosomal aberrations, and/or DNA damage in

1    various types of human or laboratory animal cells. One caveat to interpretation of these data is that there

2    is not a simple linear relationship between mutagenic potential and carcinogenic potential in animals or

3    humans. Usually studies focus on organic fractions of PM extracts for mutagenicity testing using bacteria

4    and mammalian cell lines.

5    PM and/or PM extracts from ambient air samples (e.g., southern California), wood smoke, and

6    coal, diesel, or gasoline combustion have all been reported to induce mutation in *S. typhimurium* and in

7    cultured human cells. The effect of seasonal and spatial factors on the activity of ambient PM appears to

8    be related to the overall stationary vs. mobile contributory sources. A limited number of studies evaluated

9    the impact of the season on the genotoxic effects of ambient PM. A few studies however have indicated

10   that greater genotoxic effects were associated with samples collected during the winter months compared

11   to those collected in the summer (Abou Chakra et al., 2007; Gábelová et al., 2007a; Gábelová et al.,

12   2007b). Comparatively, Hannigan et al. (1997) indicated that no seasonal variation was observed. Studies

13   have also shown that greater genotoxic effects were associated with smaller particle size extracts (e.g.,

14   $PM_{2.5}$>$PM_{10}$) and from samples collected in urban areas or closer to higher trafficked areas (Abou Chakra

15   et al., 2007; Avogbe et al., 2005; Hornberg et al., 1998).

16   Studies also have found that unsubstituted polyaromatic compounds were responsible for much of

17   the mutagenic activity of PM. These compounds included benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene,

18   benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, and cyclopenta[cd]pyrene. Studies of PM

19   samples from several European locations also reported PM was mutagenic in numerous test systems.

20   PM and related constituents induced mutations at the HPRT locus in Chinese hamster ovary (CHO)

21   cells and alveolar type II cells, APRT and Ouar loci in CHO cells, thymidine kinase (TK) locus in the

22   TK6 human lymphoblast cells and specific-locus mutations in mice (source). DNA damage, unscheduled

23   DNA synthesis, and SCE were induced in mammalian (e.g., Chinese hamster) cells in vitro (source).

24   Mutagenicity studies of PM and PM extracts from gasoline- powered engines also reported positive

25   results for most of these same endpoints, however the activity was generally lower (source).

26   Test results from studies of point source PM (e.g., wood or coal smoke) often show that organic

27   extracts of the PM samples have greater mutagenic potency than untreated PM. Similarly, the PM sample

28   source generally affects mutagenic potency. For example, PM from wood smoke was weakly mutagenic

29   compared to coal, which was slightly less mutagenic than DEP. Direct-acting frameshift mutations were

30   induced in *S. typhimurium* in studies of fluidized-bed combustion fly ash but coal combustion fly ash was

31   not mutagenic. PM samples and extracts collected from homes in Yunnan Province, China that burn

32   smoky-coal for heating and cooking were highly mutagenic in bacteria in the presence of S-9 (Mumford

33   et al., 1987).

## Carcinogenesis

1    HWS-dependent lung cancer induction was studied in a mouse model that spontaneously develops
2    lung tumors, strain A/J mice (Reed et al., 2006). These mice were exposed to HWS for 6 months followed
3    by 6 months of recovery with no HWS exposure. At 14 months, these mice were collected and tumor
4    multiplicity and tumor incidence were measured. Gaseous components of the HWS included $NO_X$, $NO_2$,
5    CO, $SO_2$, $NH_3$, and non-methane volatile organic carbon with concentration from control levels to high
6    dose HWS exposure ranging from 0 to 0 ppm, 0 to 0 ppm, $229 \pm 31$ to $14887.6$ +/- $832.3$ ppm, 0 to 0 ppb,
7    $139.3$ +/- $2.3$ to $54.9$ +/- $1.2$ $\mu g/m^3$, and $177.6$+/-$10.4$ to $3455.0$ +/- $557.2$ $\mu g/m^3$, respectively. Total PM
8    mass ranged from $6.4$+/-$6.9$ in control groups to $40.5$+/-$9.2$ in the low group to $1041.1$+/-$123.5$ $\mu g/m^3$ in
9    the high group. Cancer indicators showed no significant differences versus control animals. However,
10   HWS from this study was mutagenic in the Ames reverse mutation assay. HWS did not enhance lung
11   cancer development in this rodent model. Similar studies with exposure to environmental levels of DE
12   revealed similar outcomes, namely no increase in lung adenomas in A/J mice after 6 months of exposure
13   to DE followed by six months of recovery (Reed et al., 2004). The concentration of gases in this DE
14   experiment including $NO_X$, $NO_2$, CO, $SO_2$, $NH_3$, methane, non-methane volatile organic carbon, and FID
15   total hydrocarbon ranged from control to high dose group values of 0 to $50.4$ +/- $0.6$ ppm, $0.2$ +/- $0.2$ to
16   $6.9$ +/- $3.3$ ppm, $0.3$ +/- $0.1$ to $30.9$ +/- $4.5$ ppm, not detectable to $955.2$ +/- $58.4$ ppb, $176.5$ +/- $8.8$ to
17   $9.1$ +/- $0.2$ $\mu g/m^3$, $1406.5$ +/-$253.2$ to $2642.1$ +/- $455.9$ $\mu g/m^3$, $134.0$ +/- $52.1$ to $1578.6$ +/- $256.2$ $\mu g/m^3$,
18   $0.1$ +/- $0.1$ to $2.2$ +/- $0.2$ ppm, respectively. Total PM mass was $8.7$+/-$8.5$ $\mu g/m^3$ in controls, $43.6$+/-
19   $8.4$ $\mu g/m^3$ in low dose, and $1005.0$+/-$74.6$ $\mu g/m^3$ in high dose exposures. Micronucleated reticulocytes
20   (MN), a genotoxicity marker, did not differ between DE-exposed and control groups. Exposure to
21   environmentally relevant concentrations of DE or HWS did not cause an increased rate of lung tumors in
22   a rodent model of lung cancer.

## DNA Damage

23   Sato et al. (2003a) examined DNA adduct formation in lungs, nasal mucosa and livers of adult
24   male Wistar rats exposed to ambient urban roadside air for 4, 12, 24, 48, or 60 weeks in Kawasaki, Japan
25   (1995-1996). They also monitored message levels of cytochrome P450 (CYP) enzymes that catalyze the
26   transformation of PAHs to reactive metabolites. PM was measured as suspended PM (SPM).
27   Concentrations of gases were reported to be 12-182 ppb NO and 0-9 ppb $NO_2$ in the filtered air chamber
28   and 33-280 ppb NO and 42-81 ppb $NO_2$ in the experimental group chamber. SPM concentrations were
29   reported to be 11-19 $\mu g/m^3$ in the filtered air chamber and 42-100 $\mu g/m^3$ (average 63 $\mu g/m^3$) in the
30   experimental group chamber. Body weight significantly decreased in exposed animals at 24, 48 and 60
31   weeks. With the most acute exposure of 4 weeks, there were significant increases in multiple DNA

1    adducts (lung, nasal, and liver DNA adducts). With longer exposures, there were significant increases in

2    lung (48 weeks), nasal (60 weeks), and liver DNA adducts (60 weeks). Changes were seen in CYP1A2

3    mRNA at 4 weeks with 2.3 fold increased message level in exposed animals compared to the control

4    group with no change seen at 60 weeks; at 4 and 60 weeks, CYP1A1 was unchanged. These results

5    indicate that exposure to ambient air in this roadside area can induce DNA adduct formation, which may

6    be important for carcinogenicity as earlier studies (Ichinose et al., 1997) have shown that 8-oxo-dG is

7    elevated along with tumor formation in a dose-dependent manner in mice administered diesel particles.

8    The finding of adducts in the liver indicate that deposition of PM and its associated PAHs in the lung can

9    have effects at downstream organ (liver). However, PM deposition on the fur and ingestion during

10   grooming cannot be ruled out as a possible exposure route.

### Mutagenesis and Genotoxicity

11       The specific effects produced by PM and particle constituents include induction of MN formation,

12   DNA adduct formation, SCE, DNA strand breaks, frameshifts and inhibition of gap-junctional

13   intercellular communication (Alink et al., 1998; Arlt et al., 2007; Avogbe et al., 2005; Gábelová et al.,

14   2007a; Gábelová et al., 2007b; Healey et al., 2006; Hornberg and Seemayer, 1996; Hornberg et al., 1998;

15   Sevastyanova et al., 2007).

16       Assessment of the constituents adsorbed onto individual particles played a significant role in the

17   genotoxic potential of PM. Studies by Poma et al. (2006) showed that the genotoxic potential of fine

18   carbon black particles was consistently less genotoxic than similar concentrations of $PM_{2.5}$ extracts,

19   suggesting that the adsorbed components play a role in the genotoxic potential of PM. Studies indicated

20   that total PAH and carcinogenic PAH content is correlated with the genotoxic effects of PM (de Kok et

21   al., 2005; Sevastyanova et al., 2007). Comparison of different extracts (water vs. organic) by Gutierrez-

22   Castillo et al. (2006) indicated that water soluble extracts were more genotoxic than the corresponding

23   organic extracts. Sharma et al. (2007) reported that mutagenic activity of samples collected in and around

24   a waste incineration plant was found mostly in the moderately polar and polar fractions of filter extracts.

25   No mutagenic activity was observed from any of the nonpolar samples evaluated. The polar and crude

26   fractions were mutagenic without metabolic activation, suggesting a direct mutagenic effect. Arlt and

27   colleagues (2007) have shown that the known PM constituents 2-nitrobenzanthrone and 3-

28   nitrobenzanthrone were genotoxic in a variety of bacterial and mammalian cell systems.

29       Conflicting data have been reported for the role of metabolic enzymes on the genotoxicity of PM

30   and their adsorbed constituents. Arlt et al. (2007) reported that the PM constituent 2-nitrobenzanthrone (2-

31   NB) was genotoxic in bacterial and mammalian cells. However, metabolic activation with the human N-

32   acetyltransferase 2 or SULT1A1 enzyme was needed for the effect to be observed in human cells.

1    Erdinger et al. (2005) demonstrated that mutagenic activity was not affected when metabolism was

2    induced. de Kok et al. (2005) evaluated the relationship between the physical, chemical, and genotoxic

3    effects of ambient PM. TSP, $PM_{10}$, and $PM_{2.5}$ were sampled at different locations and the organic extracts

4    were assessed for mutagenicity and induction of DNA adducts in cells. Overall, induction of rat liver S9

5    metabolism generally reduced the mutagenic potential via the Ames assay of the particle fractions and

6    DNA reactivity (induction of DNA adducts) was generally higher after metabolic activation. Binková et

7    al. (2003) found that the addition of S9 increased $PM_{10}$-dependent DNA adduct formation.

## Bacterial Test Systems

### Wood smoke

8    The mutagenicity of wood smoke (WS) and cigarette smoke (CS) extracts was assayed in

9    *Salmonella typhimurium* strains TA98 and TA100 (Ames assay) using the pre-incubation assay with

10   exogenous metabolic activation (rat liver S-9). Extracts of both samples (62.5 or 125 µg TPM

11   equivalent/ml) were equally mutagenic to strain TA98 but the WS extract was less mutagenic than the CS

12   extracts in strain TA100 (Iba et al., 2006).

### Traffic-related Ambient Air

13   de Kok et al. (de Kok et al., 2005) found the direct mutagenicity (Ames assay) and the direct

14   DNA reactivity (DNA adduct formation) of the $PM_{2.5}$ size fraction was significantly higher than that of the

15   larger size fractions (TSP, $PM_{10}$) at most locations.

### Diesel and Gasoline

16   Automobile DEP (A-DEP) was tested in *S. typhimurium* strains TA98, TA100, and its derivatives

17   (e.g., TA98NR and YG1021) and found to be more mutagenic than forklift DEP (i.e., SRM2975)

18   particles, based on PM mass. A-DEP had 227 times more PAH-type mutagenic activity and 8–45 times

19   more nitroarene-type mutagenic activity due to the different conditions for generating and collecting the

20   two DEP samples (DeMarini et al., 2004). Using a diesel engine without an oxidation catalytic converter

21   (OCC), the diesel engine exhaust particle (DEP) extract produced the highest number of revertant

22   colonies in strains TA98 and TA100 with and without S9 at several tested loads when compared to

23   extracts from low-sulfur diesel fuel (LSDF), rapeseed oil methyl ester (RME), and soybean oil methyl

24   ester (SME). When an OCC was installed in the exhaust pipe of the engine, all extracts reduced the

25   number of revertant colonies in both strains with and without S9 at partial loads but increased the number

26   of revertant colonies without S9 at rated power. At idling, DEP extracts increased the number of revertant

1  colonies with and without S9 (Bunger et al., 2006). In a separate study, engine emissions (particle extracts

2  and condensates) from rapeseed (canola) oil were found to produce greater mutagenic effects in *S.*

3  *typhimurium* strains TA98 and TA100 than DEP (Bunger et al., 2007a). Additionally, DE extract (DEE)

4  from diesel fuel containing various percentages of ethanol was also observed to induce mutational

5  response in two *Salmonella* strains. Base diesel fuel DEE and DEE from fuel with 20% ethanol caused

6  more significant DNA damage in rat fibrocytes L-929 cells than extracts containing 5, 10, or 15% ethanol

7  (Song et al., 2007).

8      DE and gasoline engine exhaust particles, as well as their SVOC extracts, induced mutations in the

9  two *S. typhimurium* strains YG1024 and YG1029 in the absence and presence of S9; the PM extracts were

10  more mutagenic than the SVOC extracts. Additionally, all extracts except the DE SVOC extract induced

11  DNA damage and MN in Chinese hamster lung V79 cells (Liu et al., 2005b).

12      In an early study, Löfroth (1981) compared the mutagenic activity of PM from diesel and gasoline

13  engine exhaust and found both to be mutagenic in the Ames assay, in the absence of mammalian

14  metabolic activation; the DE mutagenic response was far greater than the mutagenic response of gasoline.

15  Another older study demonstrated low mutagenicity in cars burning liquified petroleum and cars with

16  catalysts and high mutagenicity (in TA100 ± S9) in light-duty diesel vehicles (Rannug et al., 1983). Also,

17  more mutagenesis was observed in exhaust from cold starts (0 °C) than in starts at 23 °C. Another study

18  demonstrated that gasoline engine exhaust significantly increased colony formation in TA98 with and

19  without S9 (Zhang et al., 2007b).

20      Strandell et al. (1994) fractionated the extracts of gasoline and DE from Volvos to find the most

21  potent mutagens among the subfractions. Mutagenicity testing was done with the Ames assay with strain

22  TA98, both with and without S9 metabolic activation, and with strain TA98NR (a nitro reductase-

23  deficient strain used to determine the presence of nitro aromatic mutagens). The most polar subfraction

24  was also the most mutagenic and comprised 51% of the total mutagenicity for gasoline exhaust and 39%

25  of the total for DE. This fraction contained low-boiling point components and some phenol derivatives.

26  Both fuels had a similar TA98NR ± S9 response that was less than TA98, but differed significantly in

27  their TA98 ± S9 response, which suggests difference in some nitro-reductase-dependent mutagens. A

28  reduction in mutagenicity was observed with the addition of S9 activation, which the authors attributed to

29  possible enzymatic deactivation of direct-acting mutagens or activation of uncharacterized compounds.

## In Vitro *Test Systems*

### Ambient PM

30      DNA damage was assessed by the Comet assay in A549 cells exposed to PM collected from a high

31  traffic area in Copenhagen, Denmark (TSP approximately 30 µg/m$^3$) and compared to the results from

1    exposure of A549 cells to standard reference materials (SRM1650 or SRM2975) at the same

2    concentrations (2.5–250 µg/ml) (Danielsen et al., 2008a). All three particles induced strand breaks and

3    oxidized purines in a dose-dependent manner and there were no obvious differences in potency. In

4    contrast, only the ambient PM formed 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) when incubated

5    with calf thymus DNA and the authors suggested that this may be due to the levels of transition metals.

### Woodsmoke

6        One recent study measured the effect of freshly generated red oak WS on CYP1A1 activity based

7    on ethoxyresorufin O-deethylase in pulmonary microsomes recovered from male Sprague-Dawley rats

8    exposed to WS by nose-only inhalation exposure (Iba et al., 2006). CYP1A1 activity in rat lung explants

9    treated with extracts of the total PM (TPM) from WS samples and from freshly generated cigarette smoke

10   (CS) was also evaluated. Unlike CS, WS did not induce pulmonary CYP1A1 activity or mRNA (assessed

11   by northern blot analysis) nor did extracts of WS TPM induce CYP1A1 protein (assessed by western blot

12   analysis) in cultured rat lung explants. The results suggest that unique constituents that are activated by

13   CYP1A1 may be present in CS but not WS that are mutagenic for both WS and CS in *S. typhimurium*

14   strain TA100.

### Diesel and Gasoline

15       Jacobsen et al. (2008) used the FE1-Muta$^{TM}$ Mouse lung epithelial cell line to investigate putative

16   mechanisms of DEP-induced mutagenicity. Mutation ion frequencies and ROS were determined after

17   cells were incubated with 37.5 or 75 µg/ml DEP (SRM1650) for 72-h (n = 8). The mutation frequency at

18   the 75 µg/ml dose was significantly increased (1.55-fold; $p<0.001$) in contrast to cells treated with

19   37.5 µg/ml DEP. DEP induced ROS generation 1.6–1.9-fold in the epithelial cell cultures after 3 h of

20   exposure compared with the 3–10-fold increase in ROS production previously reported for carbon black.

21   The authors concluded that the mutagenic activity of DEP is likely attributable to activity from the

22   organic fraction that both contains reactive species and can generate ROS.

23       In human A549 and CHO-K1 cells, the organic fraction of DEP significantly increased the amount

24   of Comet and MN formation, respectively, in the presence and absence of SKF-525A (a CYP450

25   inhibitor) and S9, respectively (Oh and Chung, 2006). The organic base and neutral fractions of DEP also

26   significantly induced DNA damage but only without SKF-525A, and all fractions but the moderately

27   polar fraction (phthalates and PAH oxyderivatives) induced MN formation with and without S9 (Bao et

28   al., 2007). Gasoline engine exhaust significantly induced DNA damage as measured in the Comet assay

29   and increased the frequency of MN in human A549 cells (Zhang et al., 2007b). In human-hamster hybrid

1  ($A_L$) cells, DEP (SRM 2975) dose-dependently increased the mutation yield at the *CD59* locus; this was

2  significantly reduced by simultaneous treatment with phagocytosis inhibitors (Bao et al., 2007).

## In Vivo Test Systems

### Ambient PM

3  After earlier work showed increased germline mutation rates in herring gulls nesting near steel

4  mills on Lake Ontario (Yauk and Quinn, 1996) further work was conducted to address air-dependent

5  contribution to germline mutations by housing male and female Swiss Webster mice in the same location

6  and comparing mutation rates in those animals with mutation rates of animals housed in a rural setting

7  with less air pollution (Somers et al., 2002). Six to eight week old mice received 10 week exposures to

8  ambient air with a six week break after exposure before breeding to allow for sperm maturation (i.e. so

9  sperm used in fertilization would be generated during ambient air exposures); DNA from pups, dams and

10  males used in breeding was collected at PND5. These studies showed heritable mutation frequency was

11  significantly increased (1.5- to 2-fold) when compared to the rural site. Further, these studies confirmed

12  that this increased mutation frequency was primarily due to increases in mutation frequency mediated

13  through the paternal germline.

14  One study by Somers et al. (2004) showed that offspring of mice exposed to ambient air in urban

15  regions inherited paternal origin expanded simple tandem repeat (ESTR) mutations 1.9- to 2.1-times more

16  frequently than offspring of mice exposed to HEPA filtered air or those in exposed to rural ambient air.

17  Mouse expanded simple tandem repeat (ESTR) DNA is composed of short base pair repeats which are

18  unstable in the germline and tend to mutate by insertion or deletion of repeat units. In vivo and in situ

19  studies have shown that murine ESTR loci are susceptible to ionizing radiation, and other environmental

20  mutatgen-dependent germline mutations, and are thus good markers of exposure to environmental

21  contaminants.

22  To determine if PM or the gaseous phase of the urban air was responsible for these heritable

23  mutations, Yauk et al. (2008) exposed mature male C57BlxCBA F1 hybrid mice to either HEPA-filtered

24  air or to ambient air in Hamilton, Ontario, Canada for three, ten, or ten weeks plus 6 weeks of clean air

25  exposure. Sperm DNA was monitored for expanded simple tandem repeat (ESTR) mutations, testicular

26  sample bulky DNA adducts, and DNA single or double strand breaks. This area in Hamilton is near 2 steel

27  mills and a major highway. Air composition provided by the Ontario Ministry of the Environment showed

28  TSP concentration of $9.38 \pm 17$ µg/m$^3$, PAH concentration of $8.3 \pm 1.7$ ng/m$^3$, and metal at

29  $3.6 \pm 0.7$ mg/m$^3$. Mutation frequency at ESTR Ms6-hm locus in sperm DNA from mice exposed 3 or 10

30  weeks did not show elevated ESTR mutation frequencies, but there was a significant increase in ESTR

31  mutation frequency at 16 weeks in ambient air exposed males versus HEPA-filter exposed animals,

1   pointing to a PM-dependent mechanism of action. No detectable adducts were observed in testes samples
2   at any of the time points monitored. To verify inhalation exposure to particles, DNA adducts were
3   monitored in the lungs of exposed mice and at 3 weeks, ambient-air exposed mice showed significant
4   increases in lung DNA adducts versus control (filtered-air exposed animals); no other time points showed
5   detectable DNA adduct formation. Thus, these studies indicate that the ambient PM phase and not the
6   gaseous phase is responsible for the increased frequency of heritable DNA mutations.

### Diesel

7        An in vivo study employed *gtp* delta transgenic mice carrying the lambda EG10 on each
8   Chromosome 17 from a C57BL/6J background to investigate the effects of DEP on mutation frequency
9   (Hashimoto et al., 2007). Mice were exposed via inhalation to DEP or via IT instillation to DEP or DEP
10  extract and lambda EG10 phages were rescued; *E. coli YG6020* was infected with the phage and screened
11  for 6-thioguanine resistance. The mutagenic potency (mutation frequency per mg) caused by DEP extract
12  was twice that of DEP, suggesting that the mutagenicity of DEP is attributed primarily to compounds in
13  the extract, since ≈50% of the weight of DEP was provided by the extract. Interestingly, there was no
14  difference in mutation frequency between the 1 and 3 mg/m$^3$ DEP groups after 12 weeks of exposure.

## *Summary*

15       A number of recent in vivo and in vitro studies indicate that ambient urban PM is mutagenic.
16  Research evaluating the mutagenicity of ambient PM from the Los Angeles area has pointed to ubiquitous
17  emission sources as being responsible for mutagenic activity observed in vitro (Hannigan et al., 1997;
18  1998). Fractionation of these ambient samples and subsequent mutagenicity assessment has indicated that
19  six unsubstituted polyaromatic compounds and two semi-polar compounds are the likely mutagens.
20  Mutagenicity of urban air from Germany has also shown (Hornberg and Seemayer, 1996; Hornberg et al.,
21  1998; Seemayer and Hornberg, 1998), evidence that the fine fraction of PM exerted greater toxicity.
22  Additionally, ambient PM from high traffic areas in the Netherlands also induced genotoxic activity.
23       Emissions from wood/biomass burning have been shown to be mutagenic. Characterization of
24  wood smoke fractions to assign mutagenicity has shown that the organic fraction is mutagenic and that
25  the condensate is not. Wood smoke emissions can induce both frameshift and base pair mutations but
26  have not yet been shown to produce DNA adducts.
27       Emissions from coal combustion have been shown to be mutagenic, especially the polar and
28  aromatic fractions. Recent work characterizing the mechanism of genotoxicity has examined the mutation
29  spectra of coal smoke emissions from Chinese homes burning smoky coal (Granville et al., 2003).
30  Sequencing the revertants has shown that the mutations in *Salmonella* exposed to coal smoke extract are

1    similar to mutations seen in lung tumors of women exposed environmentally to the coal smoke, which

2    differs in notable ways from coal combustion emissions in the U.S.

3       Extensive studies have demonstrated mutagenic activity in both the particle and gaseous fractions

4    of DE. By sequential fractionation of DE, apportionment of the mutagenicity is possible, which has

5    implicated nitrated polynuclear aromatic compounds as being responsible for a substantial portion of the

6    mutagenicity. Other mutagenically active compounds include ethylene, benzene, 1,3-butadiene, acrolein,

7    and several PAHs in the gas phase. In addition to Ames assay studies, the induction of gene mutations has

8    been reported in several in vitro mammalian cell lines after exposure to extracts of DPM. Structural

9    chromosome aberrations and SCE in mammalian cells have been induced by DE particles and extracts.

10       Early studies comparing the mutagenicity of gasoline and DE showed that the PM component of

11    the exhaust is more mutagenic than the condensate fraction, and that overall, DE is more mutagenic than

12    gasoline exhaust. More mutagenicity is also observed in exhaust from cold starts than from exhausts at

13    room temperature. Examining the fractional mutagenicity of gasoline and DEs, it was shown that, as with

14    coal smoke, the polar component has the most mutagenicity, and further, that nitro-PAH is present in the

15    fraction. A comprehensive study comparing gasoline and DE genotoxicity, using both the PM and SVOC

16    fractions, demonstrated that both exhausts are mutagenic, but, in general, DE is more mutagenic. Further,

17    the study implicates PAH and nitroarenes in the genotoxicity. Another current study corroborates these

18    finding, and includes data suggesting that DNA adduct formation is a component of the mutagenicity.

19       Exact comparisons of the mutagenicity of combustion emissions of these fuels are not possible

20    because data provided in the studies vary so greatly in units in which mutagenicity is expressed. Thus,

21    there is qualitative evidence for the mutagenic/genotoxic potential of both ambient PM and some fuel

22    combustion products. Many of the published in vitro studies failed to provide details regarding the dose of

23    PM extract delivered to the cells in vitro. In general, equal volumes of air or amounts of time were

24    sampled and reported, but only limited, if any, characterization of the amount of PM mass or size was

25    done or reported in many studies. Thus, any quantitative extrapolation of the reported findings would be

26    quite difficult. Nevertheless, they collectively do appear to provide some evidence tending to substantiate

27    the biologic plausibility of potential epidemiologic associations between long-term human exposure to

28    ambient PM and lung cancer at a cellular level.

29       The potential for the non-organic constituents of particles to induce oxidative DNA damage has

30    been less well studied but could also provide support for modes of action for mutagenicity or genotoxicity

31    of long-term PM exposures. A few studies have demonstrated that redox cycling of persistent quinoid

32    radicals and Fenton reactions by transition metals in PM can generate ROS that induce DNA damage and

33    are likely to be key events that contribute to the cytotoxic and carcinogenic potential of PM (Valavanidis

34    et al., 2005).

## 7.5.2. Summary and Causal Determinations

1       In summary, only one epidemiologic study examined the effect of a specific size fraction of PM

2 ($PM_{2.5}$) and cancer incidence (Beelen et al., 2008a), and found no evidence of an association with lung

3 cancer. An additional study used TSP as a surrogate for PAHs and found an elevated, though not

4 statistically significant, risk for breast cancer. Similarly, animal toxicological studies did not focus on

5 specific size fractions of PM, but rather conducted studies of ambient PM, woodsmoke, and DEP. A

6 number of recent studies indicate that ambient urban PM, emissions from wood/biomass burning,

7 emissions from coal combustion, and gasoline and DE are mutagenic and that PAHs and nitroarenes are

8 genotoxic. Due to the nonspecific measure of PM size fractions in epidemiologic and animal toxicological

9 studies and the limited and inconsistent epidemiologic studies, **the evidence is inadequate to determine**

10 **if a causal relationship exists between relevant $PM_{10}$, $PM_{2.5}$, $PM_{10-2.5}$, or ultrafine exposures and**

11 **incident cases of cancer.**

# 7.6. Mortality Associated with Long-term Exposure

## 7.6.1. Review of 1996 and 2004 PM AQCDs

12       In the 1996 PM AQCD, results were presented for three prospective cohort studies of adult

13 populations: the Six Cities Study (Dockery et al., 1993); the ACS Study (Pope et al., 1995); and, the

14 California Seventh Day Adventist (AHSMOG) Study (Abbey et al., 1995). The 1996 AQCD concluded

15 that the chronic exposure studies, taken together, suggested associations between increases in mortality

16 and long-term exposure to fine PM (U.S. EPA, 1996).

17       Discussions of mortality and long-term exposure to PM in the 2004 PM AQCD emphasized the

18 results of four U.S. prospective cohort studies, but the greatest weight was placed on the findings of the

19 American Cancer Society (ACS) and the Harvard Six Cities studies, which had undergone extensive

20 independent reanalysis, and which were based on cohorts that were broadly representative of the U.S.

21 population. The 2004 PM AQCD concluded that the results from the Seventh-Day Adventist (AHSMOG)

22 cohort provided some suggestive (but less conclusive) evidence for associations, while results from the

23 Veterans Cohort provided inconsistent evidence for associations between long-term exposures to $PM_{2.5}$

24 and mortality. Collectively, the 2004 PM AQCD found that these studies provided strong evidence that

25 long-term exposure to $PM_{2.5}$ was associated with increased risk of human mortality. Effect estimates for

26 all-cause mortality ranged from 6 to 13% increased risk per 10 $\mu g/m^3$ $PM_{2.5}$, while effect estimates for

1 cardiopulmonary mortality range from 6 to 19% per 10 $\mu g/m^3$ $PM_{2.5}$. For lung cancer mortality, the effect

2 estimate was a 13% increase per 10 $\mu g/m^3$ $PM_{2.5}$, based upon the results of the extended analysis from the

3 ACS cohort (Pope et al., 2002). With regard to thoracic coarse particles, the 2004 PM AQCD reported

4 that no association was observed between mortality and long-term exposure to $PM_{10-2.5}$ in the ACS study

5 (Pope et al., 2002), while a positive but statistically non-significant association was reported in males in

6 the AHSMOG cohort (McDonnell et al., 2000). Thus, the 2004 PM AQCD concluded that there was

7 insufficient evidence for associations between long-term exposure to thoracic coarse particles and

8 mortality. Overall, the 2004 PM AQCD concluded that there was strong epidemiologic evidence for

9 associations between long-term exposures to $PM_{2.5}$ and/or sulfates and excess all-cause and

10 cardiopulmonary mortality.

11     At the time of the 2004 PM AQCD, only a limited number of the chronic-exposure cohort studies

12 had considered direct measurements of constituents of PM. With regard to source-oriented evaluations of

13 mortality associations with long-term exposure, the 2004 PM AQCD noted only the study by Hoek et al.

14 (2002), in which the authors concluded that long-term exposure to traffic-related air pollution may

15 shorten life expectancy. However, Hoek et al. (2002) also noted that living near a major road might

16 include other factors that contribute to mortality associations. There was not sufficient evidence at the

17 time of the 2004 PM AQCD to draw conclusions on effects associated with specific components or

18 sources of PM.

19     The following sections will summarize the science since the previous PM AQCD (U.S. EPA,

20 2004), and build upon the conclusions of that document to reflect more recent key studies for the PM size

21 components, constituents, and emission sources, as available. New epidemiologic evidence reports a

22 consistant association between long-term exposure to $PM_{2.5}$ and increased risk of mortality. There is little

23 evidence for the long-term effects of $PM_{10}$ and $PM_{10-2.5}$ on mortality. Although this section focuses on

24 mortality outcomes in response to long-term exposure to PM, it does not evaluate studies that examine the

25 association between PM and infant mortality. These studies are evaluated in Section 7.5: "Reproductive,

26 developmental, prenatal and neonatal outcomes associated with long-term exposure to PM" because it is

27 possible that in utero exposures contribute to infant mortality. A summary of the mean PM concentrations

28 reported for the studies characterized in this section is presented in Table 7-8.

**Table 7-8. Characterization of ambient PM concentrations from studies of mortality and long-term exposures.**

| Reference | Location | Mean Annual Concentration ($\mu g/m^3$) | Upper Percentile Concentrations ($\mu g/m^3$) |
|---|---|---|---|
| *PM$_{10}$* | | | |
| Chen et al. (2005a) | Multicity, CA | 52.6 | |
| Gehring et al. (2006) | North Rhine, Germany | 43.7-48.0 | Max: 52.5-56.1 |
| Goss et al. (2004) | U.S. | 24.8 | 75th: 28.9 |
| Puett et al. (2008) | NE U.S. | 21.6 | |
| *PM$_{2.5}$* | | | |
| Chen et al. (2005a) | Multicity, CA | 29.0 | |
| Eftim et al. (2008) | U.S. | 13.6-14.1 | Max: 19.1-25.1 |
| Enstrom 2005 (2005) | CA | 23.4 | Max: 36.1 |
| Goss et al. (2004) | U.S. | 13.7 | 75th: 15.9 |
| Janes et al. (2007) | U.S. | | |
| Jerrett et al. (2005b) | Los Angeles, CA | | |
| Laden et al. (2006) | Multicity, U.S. | 10.2-29.0 | |
| Miller et al. (2007b) | U.S. | 13.4 | 75th: 18.3 <br> Max: 28.3 |
| Pope et al. (2004b) | U.S. | 17.1 | |
| Schwartz et al. (2008) | Multicity, U.S. | 17.5 | Max: 40 |
| Zeger et al. (2007) | U.S. | | |
| *PM$_{10-2.5}$* | | | |
| Chen et al. (2005a) | Multicity, CA | 25.4 | |
| Lipfert et al. (2006a) | U.S. | 15.0 | Max: 25.0 |

# 7.6.2. PM$_{2.5}$

1    Studies since the last PM AQCD include results of new analyses and insights for the ACS and

2   Harvard Six Cities studies, further analyses from the AHSMOG and Veterans study cohorts, as well as

3   analyses of a Cystic Fibrosis cohort and a subset of the ACS from California. The historical and more

4   recent results of both the ACS and the Harvard Six Cities studies are compiled in Figure 7-7. Moreover,

5   since the last PM AQCD, there is a major new cohort analyzed in the literature: the Women's Health

6   Initiative (WHI) study (2007b). Most recently, an ecological cohort study of the nation's Medicare

7   population has also been completed (Eftim et al., 2008). These new findings further strengthen the

8   evidence linking long-term exposure to PM$_{2.5}$ and mortality, while providing indications that the

9   magnitude of the PM$_{2.5}$ -mortality association is larger than previously estimated (Figure 7-8).
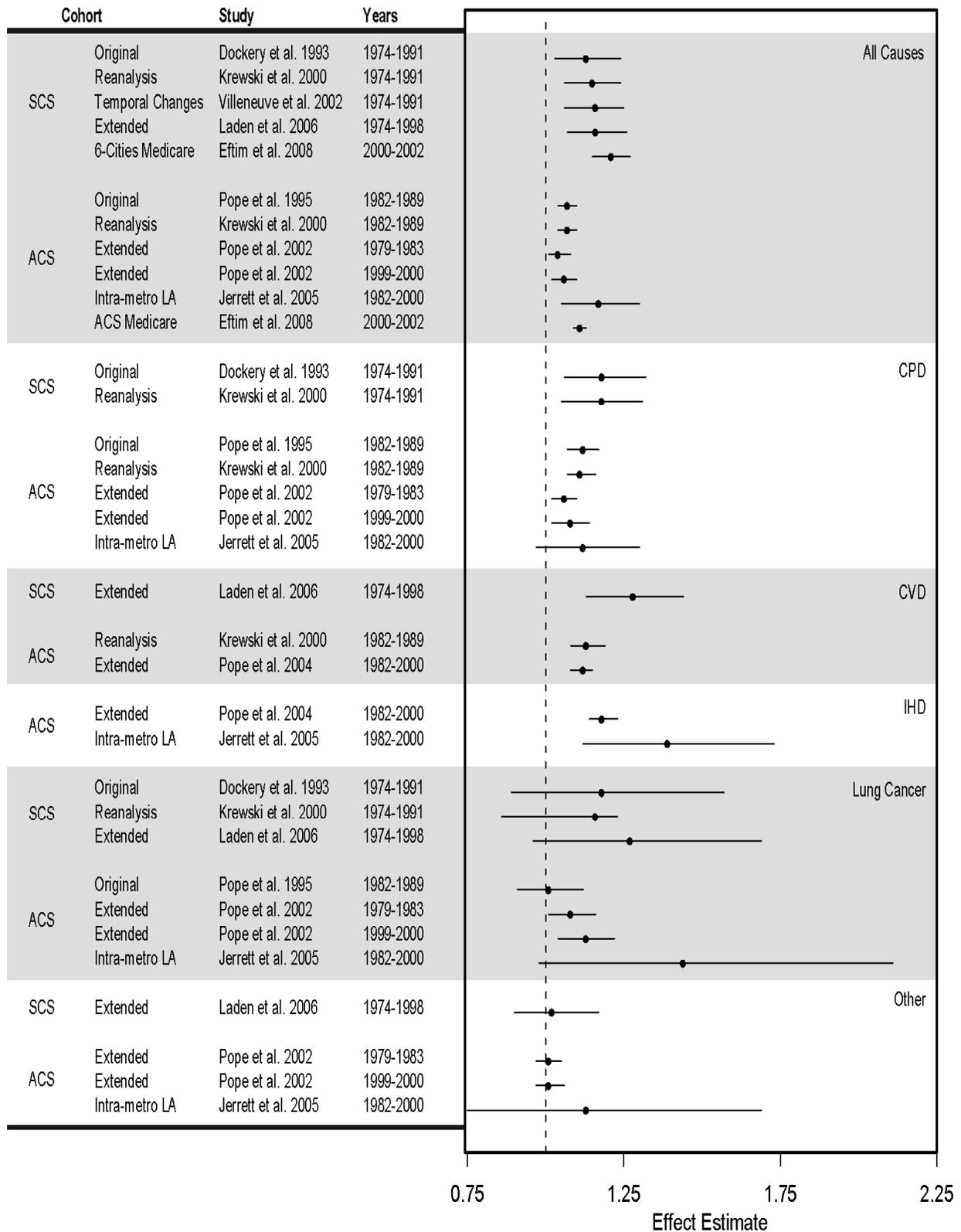
**Figure 7-7.** Mortality risk estimates associated with long-term exposure to $PM_{2.5}$ from the Harvard Six Cities Study (SCS) and the American Cancer Society Study (ACS).
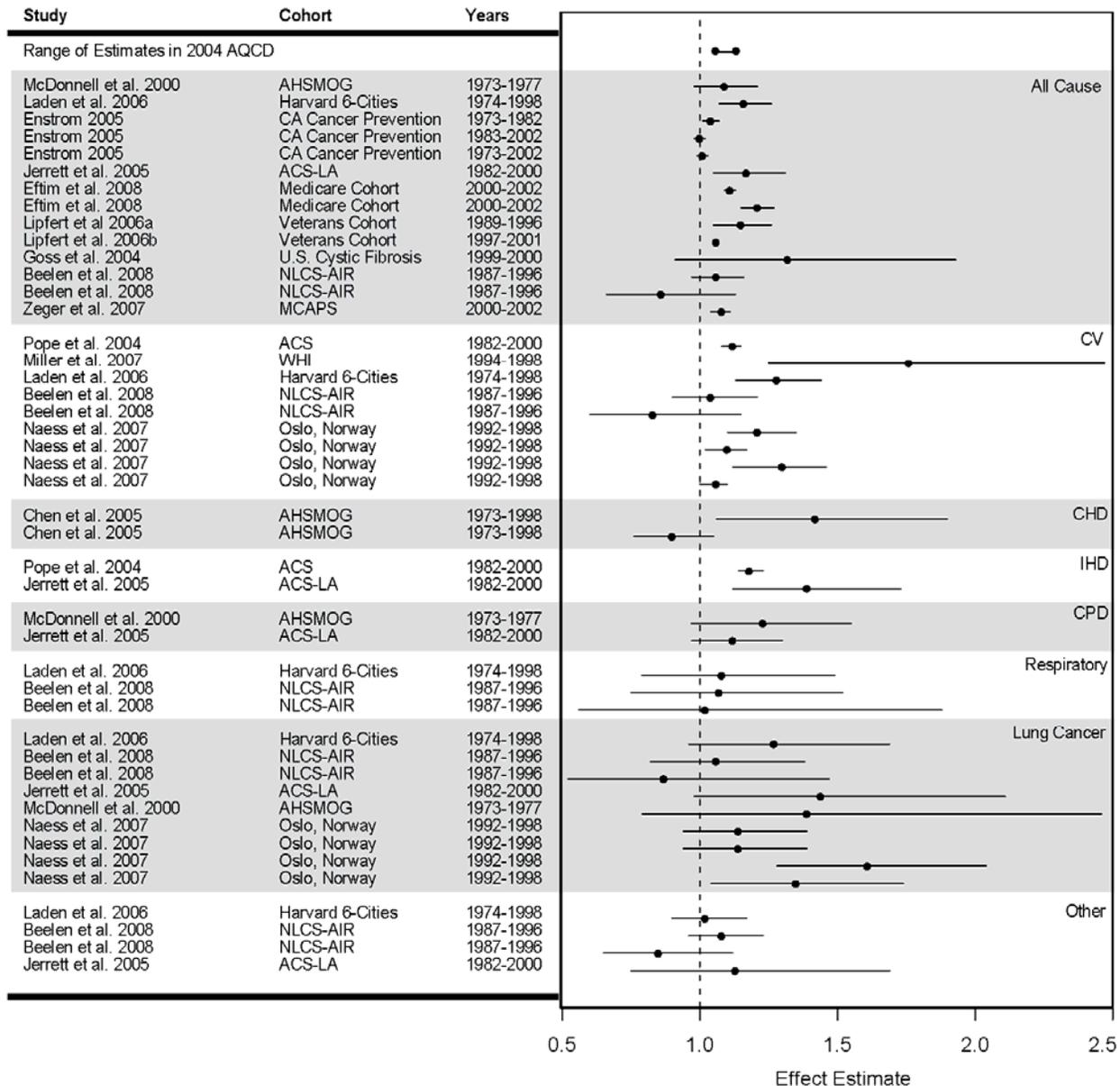
**Figure 7-8.** Mortality risk estimates associated with long-term exposure to $PM_{2.5}$ in cohort studies.

1       **Harvard Six Cities:** A follow-up study has used updated air pollution and mortality data; an

2  additional 1,368 deaths occurred during the follow-up period (1990-1998) vs. 1,364 deaths in the original

3  study period (1974-1989) (Laden et al., 2006). Statistically significant associations are reported between

4  long-term exposure to $PM_{2.5}$ and mortality for data for the two periods (RR = 1.16 [95% CI: 1.07-1.26]

5  per 10 $\mu g/m^3$ $PM_{2.5}$). Of note, however, is a statistically significant **reduction** in mortality risk reported

6  with **reduced** long-term fine particle concentrations (RR = 0.73 [95% CI: 0.57-0.95] per 10 $\mu g/m^3$ $PM_{2.5}$).

7  This is equivalent to an RR of 1.27 for reduced mortality risks. This reduced mortality risk was observed

1    for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths. The $PM_{2.5}$

2    concentrations for recent years were estimated from visibility data, which introduces some uncertainty in

3    the interpretation of the results from this study. Coupled with the results of the original analysis (Dockery

4    et al., 1993), this study strongly suggests that a reduction in fine PM pollution yields positive health

5    benefits.

6    **ACS Extended Analyses:** One new analysis further evaluated the associations of long-term $PM_{2.5}$

7    and sulfate exposures with risk of mortality in 50 U.S. cities reported by Pope and colleagues (2002),

8    adding new details about deaths from specific cardiovascular and respiratory causes (Pope et al., 2004b).

9    Significant associations were reported with deaths from specific cardiovascular diseases, particularly

10   ischemic heart disease, and a group of cardiac conditions including dysrhythmia, heart failure and cardiac

11   arrest (RR for cardiovascular mortality = 1.12, 95% CI 1.08-1.15 per 10 $\mu g/m^3$ $PM_{2.5}$), but no PM

12   associations were found with respiratory mortality.

13   **California Cancer Prevention Study:** In a cohort of elderly people in 11 California counties (mean

14   age 73 years in 1983), an association was reported for long-term $PM_{2.5}$ exposure with all-cause deaths

15   from 1973-1982 (RR = 1.04 [95% CI: 1.01-1.07] per 10 $\mu g/m^3$ $PM_{2.5}$) (Enstrom, 2005). However, no

16   significant associations were reported with deaths in later time periods when $PM_{2.5}$ levels had decreased

17   in the most polluted counties (1983-2002) (RR = 1.00 [95% CI: 0.98-1.02] per 10 $\mu g/m^3$ $PM_{2.5}$). The

18   $PM_{2.5}$ data were obtained from the EPA's Inhalation Particle Network (collected circa 1980), and the

19   locations represented a subset of data used in the 50-city ACS study (Pope et al., 1995). However, the use

20   of average values for California counties as exposure surrogates likely leads to significant exposure error,

21   as many California counties are large and quite topographically variable.

22   **AHSMOG:** In this analysis for the Seventh-Day Adventist cohort in California, a positive,

23   statistically significant, association with coronary heart disease mortality was reported for 92 deaths

24   among females (RR = 1.42 [95% CI: 1.06-1.90] per 10 $\mu g/m^3$ $PM_{2.5}$), but not for 53 deaths among males

25   (RR = 0.90 [95% CI: 0.76-1.05] per 10 $\mu g/m^3$ $PM_{2.5}$) (Chen et al., 2005a). Associations were strongest in

26   the subset of postmenopausal women (80 deaths; RR = 1.49 [95% CI: 1.17-1.89] per 10 $\mu g/m^3$ $PM_{2.5}$).

27   The authors speculated that females may be more sensitive to air pollution-related effects, based on

28   differences between males and females in dosimetry and exposure.

29   **U.S. Cystic Fibrosis cohort:** A positive, but not statistically significant, association was reported

30   in this cohort (RR = 1.32 [95% CI: 0.91-1.93] per 10 $\mu g/m^3$ $PM_{2.5}$) in a study that primarily focused on

31   evidence of exacerbation of respiratory symptoms (Goss et al., 2004). However, only 200 deaths had

32   occurred in the cohort of over 11,000 people (average age in cohort was 18.4 years), so the power of this

33   study to detect associations was low.

1     **Women's Health Initiative (WHI) Study:** This nationwide cohort study considered 65,893

2     postmenopausal women with no history of cardiovascular disease who lived in 36 U.S. metropolitan areas

3     from 1994 to 1998 (Miller et al., 2007b). The study had a median subject follow-up time of six years.

4     Miller and colleagues assessed each woman's exposure to air pollutants using the monitor located nearest

5     to their residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race

6     or ethnic group, smoking status, educational level, household income, body-mass index, and presence or

7     absence of diabetes, hypertension, or hypercholesterolemia. Overall, this study concludes that "long-term

8     exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and

9     death among postmenopausal women." In terms of effect size, the study found that each increase of 10

10    $\mu g/m^3$ of $PM_{2.5}$ was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio,

11    1.24 [95% CI: 1.09-1.41]) and a 76% increase in the risk of death from cardiovascular disease (hazard

12    ratio, 1.76 [95% CI: 1.25-2.47]). While this study found results confirmatory to the ACS and Six Cities

13    Study, it derives much larger relative risk estimates per $\mu g/m^3$ $PM_{2.5}$. This may be due to the fact that,

14    since the study included only women without pre-existing cardiovascular disease, it could potentially be a

15    healthier cohort population than that considered by the ACS and Six Cities Study. Indeed, the WHI Study

16    reported only 216 cardiovascular deaths in 349,643 women-years of followup, or a rate of 0.075% deaths

17    per year (Miller et al., 2007b), while the ACS Study reported that 10% of subjects died of cardiovascular

18    disease over a 16 year followup period, yielding a rate of 0.625% per year, or approximately 8 times the

19    cardiovascular mortality rate of the WHI population (Pope et al., 2004b). Thus, $PM_{2.5}$ impacts may yield

20    higher relative risk estimates in the WHI population because the $PM_{2.5}$ risk is being compared to a much

21    lower prevailing risk of cardiovascular death in this select study population.

22          The WHI study not only confirms the Six City Study and ACS Study associations with mortality in

23    yet another well characterized cohort with detailed individual-level information, it also has been able to

24    consider the individual medical records of the thousands of WHI subjects over the period of the study.

25    This has allowed the researchers to examine not only mortality, but also related morbidity in the form of

26    heart problems (cardiovascular events) experienced by the subjects during the study. As reported in this

27    paper, this examination confirmed that there is an increased risk of cardiovascular morbidity, as well (see

28    section 7.2.1). These morbidity co-associations with $PM_{2.5}$ in the same population lend even greater

29    support to the biological plausibility of the air pollution-mortality associations found in this study.

30          **Medicare Cohort Study:** Using Medicare data, Eftim and co-authors (2008) have assessed the

31    association of $PM_{2.5}$ with mortality for the same locations included in the Six City Study and the ACS

32    studies. For these locations, they estimated the chronic effects of $PM_{2.5}$ on mortality for the period

33    2000-2002 using mortality data for cohorts of Medicare participants and average $PM_{2.5}$ levels from

34    monitors in the same counties included in the two studies. Using aggregate counts of mortality by county

for three age groups, they estimated mortality risk associated with air pollution adjusting for age and sex and area-level covariates (education, income level, poverty, and employment), and controlled for potential confounding by cigarette smoking by including standardized mortality ratios for lung cancer and COPD. This study is, therefore, an ecological analysis, similar to past published cross-sectional analyses, in that area-level covariates (education, income level, poverty, and employment) are employed as controlling variables, since individual level information is not available from the Medicare database (other than age and sex), which includes virtually all Americans aged 65 or greater. Exposures are also ecological in nature, as central site data are used as indices of exposure. These results indicated that a 10 $\mu g/m^3$ increase in the yearly average $PM_{2.5}$ concentration is associated with 10.9% (95% CI: 9.0-12.8) and with 20.8% (95% CI: 14.8-27.1) increases in all-cause mortality for the American Cancer Society and Harvard Six Cities study counties, respectively. The estimates are somewhat higher than those reported by the original investigators, and several possible explanations for this apparent increase are posited by the authors, especially that this is an older population than the ACS cohort. Perhaps the most likely is that the lack of personal confounder information (e.g., past personal smoking information) led to an insufficient control for the effects of these other variables' effects on mortality, inflating the pollution effect estimates somewhat, similar to what has been found in the ACS analyses when only ecological-level control variables were included. The ability of the Eftim et al. (2008) study results to qualitatively replicate the original individual-level cohort study (e.g., ACS and Six Cities Study) results suggests that past ecological cross-sectional mortality study results may also provide useful insights into the nature of the association, especially when used for consideration of time trends, or for comparisons of the relative (rather than absolute) sizes of risks between different pollutants or PM components in health effects associations.

Janes et al. (2007) use the same nationwide Medicare mortality data to examine the association between monthly averages of fine particles ($PM_{2.5}$) over the preceding 12 months and monthly mortality rates in 113 U.S. counties from 2000 to 2002. They decompose the association between $PM_{2.5}$ and mortality into 2 components: (1) the association between "national trends" in $PM_{2.5}$ and mortality; and (2) the association between "local trends," defined as county-specific deviations from national trends. This second component is posited to provide evidence as to whether counties having steeper declines in $PM_{2.5}$ also have steeper declines in mortality relative to their national trends. They report that the exposure effect estimates are different at these 2 spatiotemporal scales, raising concerns about confounding bias in these analyses. The authors assert that the association between trends in $PM_{2.5}$ and mortality at the national scale is more likely to be confounded than is the association between trends in $PM_{2.5}$ and mortality at the local scale and, if the association at the national scale is set aside, that there is little evidence of an association between 12-month exposure to $PM_{2.5}$ and mortality in this analysis.

1 However, in response, Pope and Burnett (2007) point out that such use of long-term time trends as the

2 primary source of exposure variability has been avoided in most other air pollution epidemiology studies

3 because of such concerns about potential confounding of such time-trend associations.

4 By linking monitoring data to the U.S. Medicare system by county of residence, Zeger et al. (2007)

5 analyzed Medicare mortality records, comprising over 20 million enrollees in the 250 largest counties

6 during 2000-2002. The authors estimated log-linear regression models having as outcome the age-specific

7 county level mortality rates and, as the main predictor, the average $PM_{2.5}$ pollution level in each county

8 during 2000. Area-level covariates were used to adjust for socio-economic status and smoking. The

9 authors reported results under several degrees of adjustment for spatial confounding and with

10 stratification into eastern, central and western U.S. counties. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated

11 with a 7.6% increase in mortality (95% CI: 4.4-10.8). When adjusted for spatial confounding, the

12 estimated log-relative risks dropped by 50%. Zeger et al. (2007) found a stronger association in the

13 eastern counties than nationally, with no evidence of an association in western counties.

## 7.6.3. $PM_{10-2.5}$

14 In the original analyses of the Six Cities and ACS cohort studies, no associations were found

15 between long-term exposure to $PM_{10-2.5}$ and mortality, while the extended and follow-up analyses that are

16 discussed above did not evaluate potential associations with $PM_{10-2.5}$. Two recent reports from the

17 AHSMOG and Veterans study cohorts have, however, provided some limited evidence for associations

18 between long-term exposure to $PM_{10-2.5}$ and mortality, as summarized below.

19 **AHSMOG:** As was found with fine particles, a positive association with coronary heart disease

20 mortality was reported for females (RR = 1.38 [95% CI: 0.97-1.95] per 10 $\mu g/m^3$ $PM_{10-2.5}$), but not for

21 males (RR = 0.92 [95% CI: 0.66-1.29] per 10 $\mu g/m^3$ $PM_{10-2.5}$); associations were strongest in the subset of

22 postmenopausal women (80 deaths) (Chen et al., 2005a).

23 **Veterans cohort:** In this study (Lipfert et al., 2006a), a significant association was reported

24 between long-term exposure to $PM_{10-2.5}$ and total mortality in a single-pollutant model (RR = 1.07, 95%

25 CI 1.01-1.12 per 10 $\mu g/m^3$ $PM_{10-2.5}$). However, the association became negative and not statistically

26 significant in a model that included traffic density. As it would be expected that traffic would contribute to

27 the thoracic coarse particle concentrations, it is difficult to interpret the results of these multipollutant

28 analyses.

## 7.6.4. $PM_{10}$

1    The original analyses of the AHSMOG cohort study found positive associations between long-term

2    concentrations of $PM_{10}$ and 15-year mortality due to natural causes and lung cancer (Abbey et al., 1999).

3    McDonnell et al. (2000) reanalyzed these data and concluded that previously observed association of

4    long-term ambient $PM_{10}$ concentrations with mortality for males were best explained by a relationship of

5    mortality with the fine fraction of $PM_{10}$ rather than the coarse fraction of $PM_{10}$. Recent reports from the

6    AHSMOG study cohort, as well as the Nurses' Health Study, the U.S. Cystic Fibrosis cohort and a cohort

7    of women in Germany have, however, provided some evidence for associations between long-term

8    exposure to $PM_{10}$ and mortality among women, as summarized below.

9    **AHSMOG:** As was found with fine particles, a positive association with coronary heart disease

10   mortality was reported for females (RR = 1.22 [95% CI: 1.01-1.47] per 10 $\mu g/m^3$ $PM_{10}$), but not for males

11   (RR = 0.94 [95% CI: 0.82-1.08] per 10 $\mu g/m^3$ $PM_{10}$); associations were strongest in the subset of

12   postmenopausal women (80 deaths) (Chen et al., 2005a).

13   **Nurses' Health Study Cohort:** The Nurses' Health Study (Puett et al., 2008) is an ongoing

14   prospective cohort study examining the relation of chronic particulate exposures with all-cause mortality

15   and incident and fatal coronary heart disease consisting of 66,250 female nurses in MSAs in the

16   northeastern region of the U.S. All cause mortality was statistically significantly associated with average

17   $PM_{10}$ exposures in the time period 3-48 months. The association was strongest with average $PM_{10}$

18   exposure in the 24 months prior to death (hazard ratio 1.16 [95% CI: 1.05-1.28]) and weakest with

19   exposure in the month prior to death (hazard ratio 1.04 [95% CI: 0.98-1.11]). The association with fatal

20   CHD occurred with the greatest magnitude with mean exposure in the 24 months prior to death (hazard

21   ratio 1.42 [95% CI: 1.11-1.81]).

22   **U.S. Cystic Fibrosis Cohort:** No clear significant association was reported in this cohort that

23   primarily focused on evidence of exacerbation of respiratory symptoms (Goss et al., 2004). However,

24   only 200 deaths had occurred in the cohort of over 11,000 people (average age in cohort was 18.4 years),

25   so the power of this study to detect associations was low.

26   **German Cohort:** The North Rhine-Westphalia State Environment Agency (LUA NRW) initiated a

27   cohort of approximately 4800 women, and assessed whether long-term exposure to air pollution

28   originating from motorized traffic and industrial sources was associated with total and cause-specific

29   mortality (Gehring et al., 2006). They found that cardiopulmonary mortality was associated with $PM_{10}$

30   (RR = 1.52 [95% CI: 1.09-2.15] per 10 $\mu g/m^3$ $PM_{10}$).

## 7.6.5. Composition and Source-Oriented Analyses of PM

1    As discussed in the 2004 PM AQCD, only a very limited number of the chronic exposure cohort

2    studies have included direct measurements of chemical-specific constituents, or assessments of source-

3    oriented effects, of PM in their analyses. One exception is the Veterans Study, which looked at

4    associations with some constituents, and traffic.

5    **Veterans Cohort:** A recent reanalysis of the Veterans cohort data focused on exposure to traffic-

6    related air pollution (traffic density based on traffic flow rate data and road segment length) reported a

7    stronger relationship between mortality with long-term exposure to traffic than with $PM_{2.5}$ mass (Lipfert

8    et al., 2000). A significant association was reported between total mortality and $PM_{2.5}$ in single-pollutant

9    models (RR = 1.12 [95% CI: 1.04-1.20] per 10 $\mu g/m^3$ $PM_{2.5}$). The authors observe that this risk estimate

10   is larger than results reported in a previous study of this cohort. In multipollutant models including traffic

11   density, the association with $PM_{2.5}$ was reduced and lost statistical significance. Traffic emissions

12   contribute to $PM_{2.5}$ so it would be expected that the two would be highly correlated, and, thus, these

13   multipollutant model results should be interpretted with caution. In a companion study, Lipfert et al.

14   (2006b) used data from EPA's fine particle speciation network, and reported findings for $PM_{2.5}$ were

15   similar to those reported by Lipfert et al. (2006a). A positive association also was reported for mortality

16   with sulfates using the more recent data, but was not statistically significant. Using 2002 data from the

17   fine particle speciation network, significant associations were found between mortality and long-term

18   exposures to nitrates, EC, Ni and V, as well as traffic density and peak ozone concentrations. In

19   multipollutant models, associations with traffic density remained significant, as did nitrates, Ni and V in

20   some models.

21   **Netherlands Study:** Beelen et al. (2008a) studied the association between long-term exposure to

22   traffic-related air pollution and mortality in a Dutch cohort. They used data from an ongoing cohort study

23   on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. Exposure to BS, $NO_2$,

24   $SO_2$, and $PM_{2.5}$, as well as various exposure variables related to traffic, were estimated at the home

25   address. Cox analyses were conducted in the full cohort, adjusting for age, sex, smoking, and area-level

26   socioeconomic status. Traffic intensity on the nearest road was independently associated with mortality.

27   Relative risks (95% confidence intervals) for a 10 $\mu g/m^3$ increase in BS concentrations (difference

28   between 5th and 95th percentile) were 1.05 (95% CI: 1.00-1.11) for natural cause, 1.04 (95% CI:

29   0.95-1.13) for cardiovascular, 1.22 (95% CI: 0.99-1.50) for respiratory, 1.03 (95% CI: 0.88-1.20) for lung

30   cancer, and 1.04 (95% CI: 0.97-1.12) for mortality other than cardiovascular, respiratory, or lung cancer.

31   Results were similar for $NO_2$ and $PM_{2.5}$, but no associations were found for $SO_2$. The authors concluded

32   that traffic-related air pollution and several traffic exposure variables were associated with mortality in

1    the full cohort, although the relative risks were generally small. Associations between natural-cause and

2    respiratory mortality were statistically significant for $NO_2$ and BS. These results add to the evidence that

3    long-term exposure to traffic-related particulate ambient air pollution is associated with increased

4    mortality.

5        Given the general dearth of published source-oriented studies of the mortality impacts of long-term

6    PM exposure components, and given that the recent Medicare Cohort study now indicates that such

7    ecological cross-sectional studies can be useful for evaluating time trends and/or comparisons across

8    pollution components, it may well be that examining past cross-sectional studies comparing source-

9    oriented components of PM may be informative. In particular, Ozkaynak and Thurston (1987), utilized

10   the chemical speciation conducted in the Inhalable Particle (IP) Network to conduct a chemical

11   constituent and source-oriented evaluation on long-term PM exposure and mortality in the U.S. They

12   analyzed the 1980 U.S. vital statistics and available ambient air pollution data bases for sulfates and fine,

13   inhalable, and TSP mass. Using multiple regression analyses, they conducted a cross-sectional analysis of

14   the association between various particle measures and total mortality. Results from the various analyses

15   indicated the importance of considering particle size, composition, and source information in modeling of

16   particle pollution health effects. Of the independent mortality predictors considered, particle exposure

17   measures most related to the respirable fraction of the aerosols, such as fine particles and sulfates, were

18   most consistently and significantly associated with the reported SMSA-specific total annual mortality

19   rates. On the other hand, particle mass measures that included thoracic coarse particles (e.g., total

20   suspended particles and inhalable particles) were often found to be non-significant predictors of total

21   mortality. Furthermore, based on the application of fine particle source apportionment, particles from

22   industrial sources and from coal combustion were indicated to be more significant contributors to human

23   mortality than fine soil-derived particles.

## 7.6.6. Within-City Effects of PM Exposure

24       Much of the exposure gradient in the national-scale cohort studies was due to city-to-city

25   differences in regional air pollution, raising the possibility that some or all of the original PM-survival

26   associations may have been driven instead by city-to-city differences in some unknown (non-pollution)

27   confounder variable. This has been evaluated by two recent studies.

28       **ACS, Los Angeles:** To investigate this issue, a new analysis using ACS data focused on

29   neighborhood-to-neighborhood differences in urban air pollutants, using data from 23 $PM_{2.5}$ monitoring

30   stations in the Los Angeles area, and applying interpolation methods to assign exposure levels to study

31   individuals (Jerrett et al., 2005b). This resulted in both improved exposure assessment and an increased

1    focus on local sources of fine particle pollution. Significant associations between $PM_{2.5}$ and mortality

2    from all causes and cardiopulmonary diseases were reported with the magnitude of the relative risks being

3    greater than those reported in previous assessments (after adjustment for potential confounders including

4    traffic, RR for cardiovascular diseases = 1.17 [95% CI: 1.05-1.31], per 10 $\mu g/m^3$ $PM_{2.5}$; RR for ischemic

5    heart disease = 1.38 [95% CI: 1.11-1.72] per 10 $\mu g/m^3$ $PM_{2.5}$). This indicates that city-to-city confounding

6    was not the cause of the associations found in the earlier ACS Cohort studies. The authors also suggest

7    that reducing exposure error can result in even stronger associations between $PM_{2.5}$ and mortality than

8    generally observed in broader studies having less exposure detail.

9        **WHI Study:** This study also investigated the within- vs. between-city effects in its cities. As shown

10   in Figure 7-9, similar effects for both the within and between-city analyses demonstrate that this

11   association is not due to some other (non-pollution) confounder differing between the various cities,

12   strengthening confidence in the pollution-effect estimates.
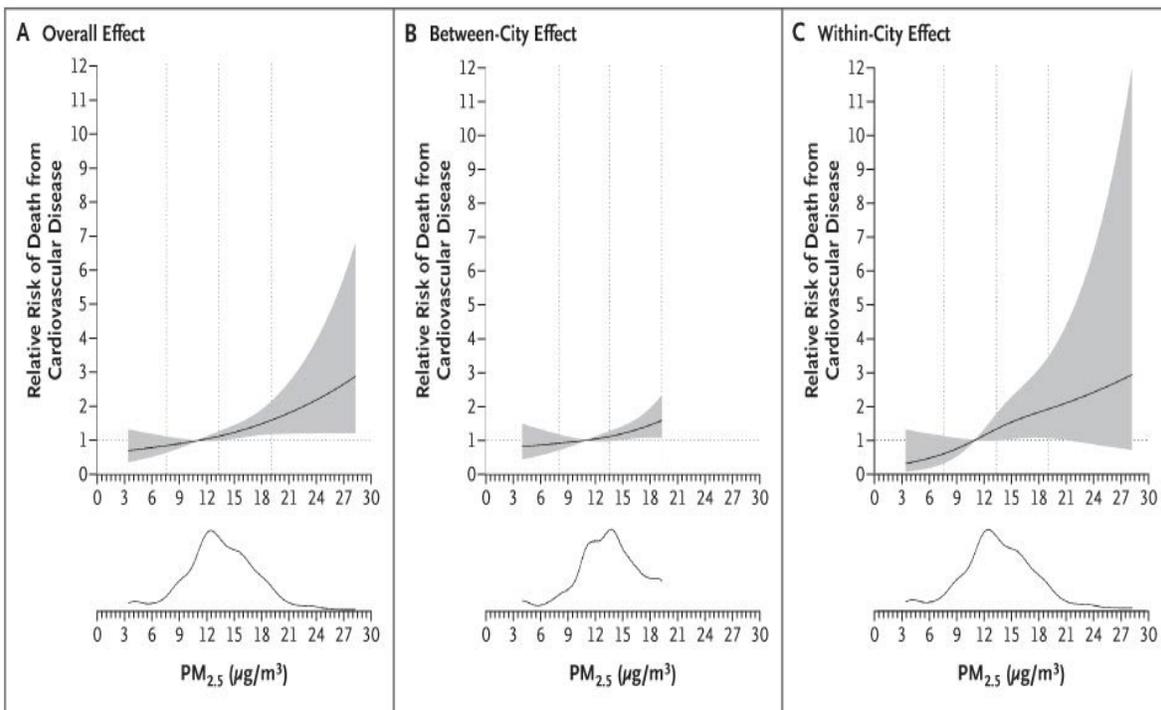


Source: Miller et al. (2007b)

Figure 7-9.    **Plots of the relative risk of death from cardiovascular disease from the Women's Health Initiative study displaying the between-city and within-city contributions to the overall association between $PM_{2.5}$ and cardiovascular mortality windows of exposure-effects.**

# 7.6.7. Effects of Different Long-term Exposure Windows

1      The delay between changes in exposure and changes in health has important policy implications.

2      Schwartz et al. (2008) investigated this issue using an extended follow-up of the Harvard Six Cities Study.

3      Cox proportional hazards models were fit controlling for smoking, body mass index, and other covariates.

4      Penalized splines were fit in a flexible functional form to the concentration response to examine its shape,

5      and the degrees of freedom for the curve were selected based on Akaike's information criterion. They also

6      used model averaging as an alternative approach, where multiple models are fit explicitly and averaged,

7      weighted by their probability of being correct given the data. The lag relationship by model was averaged

8      across a range of unconstrained distributed lag models (i.e., same year, year prior, two years prior, etc.).

9      Results of the lag comparison are shown in Figure 7-10 indicating that the effects of changes in exposure

10     on mortality are seen within two years. The authors also noted that the concentration-response curve was

11     linear, clearly continuing below the level of the current U.S. air quality standard of 15 µg/m$^3$.
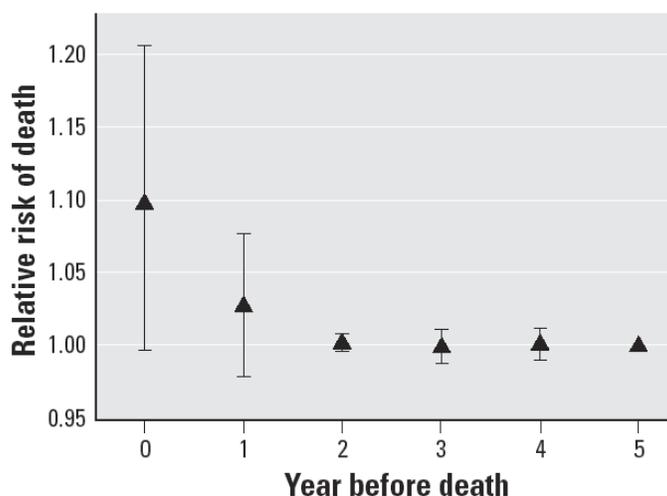


Source: Schwartz et al. (2008)

**Figure 7-10.**   **The model-averaged estimated effect of a 10- µg/m$^3$ increase in PM$_{2.5}$ on all-cause mortality at different lags (in years) between exposure and death. Each lag is estimated independently of the others. Also shown are the pointwise 95% CIs for each lag, based on jacknife estimates.**

12     Röösli et al. (2005) took an alternative approach to determining the window over which the

13     mortality effects of long-term pollution exposures occurred. They fit the model shown in Figure 7-11

14     using k = 0.5 based on the Utah Steel Strike (Pope, 1989) and the Ireland coal ban study (Clancy et al.,

15     2002). They found that roughly 75% of health benefits are observed in the first 5 years, as shown in

1    Table 7-9. This suggests that the most recent years of exposure are most important to mortality, consistent

2    with the findings of Schwartz et al. (2008).
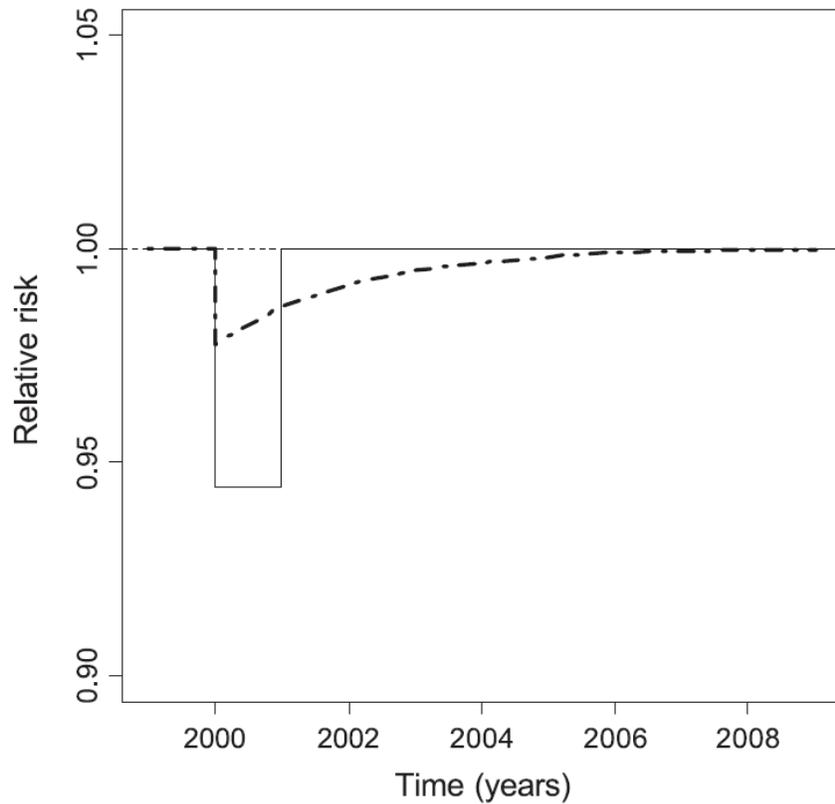
**Figure 7-11.  Time course of relative risk of death after a sudden decrease in air pollution exposure during the year 2000, assuming a steady state model (solid line) and a dynamic model (bold dashed line). The thin dashed line refers to the reference scenario.**

3    Puett et al. (2008) also compared different long-term lags, with exposure periods ranging from 1

4    month to 48 months prior to death. They found statistically significant associations with average $PM_{10}$

5    exposures in the time period 3-48 months prior to death, with the strongest associations in the 24 months

6    prior to death and the weakest with exposure in the 1 month prior to death. These results indicate a

7    developing coherence of the air pollution mortality literature, and the mortality risk benefits from

8    reducing air pollution would be expected within a few years of intervention.

**Table 7-9.** Distribution of the effect of a hypothetical reduction of 10 μg/m³ PM₁₀ in 2000 on all-cause mortality 2000-2009 in Switzerland.

| Year | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|------|------|------|------|------|------|------|------|------|------|------|------|
| Proportion of total effect (%) | - | 39.3 | 23.9 | 14.5 | 8.8 | 5.3 | 3.2 | 2.0 | 1.2 | 0.7 | 0.4 |
| Relative risk (per 10 μg/m³ reduction in PM₁₀) | 1.0 | 0.9775 | 0.9863 | 0.9917 | 0.9950 | 0.9969 | 0.9981 | 0.9989 | 0.9993 | 0.9996 | 0.9997 |

Relative risk and proportion of total effect in each year are shown, assuming a time constant k of 0.5
Source: Röösli et al. (2005)

## 7.6.8. Summary and Causal Determinations

1   The recent evidence is largely consistent with past studies, further supporting the evidence of

2   associations between long-term $PM_{2.5}$ exposure and increased risk of human mortality in areas with mean

3   concentrations from 14 to 29 μg/m³ (Figure 7-8). New evidence from the Six Cities cohort study shows a

4   relatively large risk estimate for reduced mortality risk with decreases in $PM_{2.5}$ (Laden et al., 2006). The

5   results of new analyses from the Six Cities cohort and the ACS study in Los Angeles suggest that

6   previous and current studies may have underestimated the magnitude of the association (Jerrett et al.,

7   2005b). With regard to mortality by cause-of-death, the most recent ACS analysis (Pope et al., 2004b)

8   indicates that cardiac mortality primarily accounts for the total mortality association with $PM_{2.5}$ among

9   adults, and not respiratory mortality. The recent WHI cohort study shows even higher cardiac risks

10  per μg/m³ than found in the ACS study, but this is likely due to the fact that the study included only

11  women without pre-existing cardiovascular disease. Furthermore, the WHI study also considered within

12  vs. between city mortality, as well as morbidity co-associations with $PM_{2.5}$ in the same population. The

13  first showed that the results are not due to between city confounding, and the morbidity analyses show the

14  coherence of the mortality association across health endpoints, supporting the biological plausibility of

15  the air pollution-mortality associations found in these studies.

16      The findings from a multiyear expert judgment study that comprehensively characterizes the size

17  and uncertainty in estimates of mortality reductions associated with decreases in $PM_{2.5}$ in the U.S

18  provides additional support for an association between long-term exposure to $PM_{2.5}$ and mortality (Roman

19  et al., 2008). This study applied state-of-the-art expert judgment elicitation techniques to develop

20  probabilistic uncertainty distributions that reflect the broader array of uncertainties in the concentration-

21  response relationship. This study followed best standard practices for expert elicitations based on the

22  body of literature accumulated over the past two decades, including: explicit criteria for expert selection,

23  a detailed interview protocol, briefing materials provided to experts in advance of the interview, and

24  workshops prior to and following the PM expert elicitation. The main goal of the protocol was to answer

1  the following question: "What is your estimate of the true percent change in annual, all-cause mortality in

2  the adult U.S. population resulting from a permanent 1 µg/m³ reduction in annual average ambient PM$_{2.5}$

3  across the U.S.?" The resulting PM$_{2.5}$ effect estimate distributions, elicited from 12 of the world's leading

4  experts on this issue, are shown in Figure 7-12. They indicate both larger central estimates of mortality

5  reductions for decreases in long-term PM$_{2.5}$ exposure in the U.S. (averaging almost 1% per µg/m³ PM$_{2.5}$)

6  than reported (for example) by the ACS Study (i.e., 0.6% per µg/m³ PM$_{2.5}$ in (2002), and a wider

7  distribution of uncertainty by each expert than provided by any one of the PM$_{2.5}$ epidemiologic studies.

8  However, a composite uncertainty range of the overall mean effect estimate (i.e., based upon all 12

9  experts' estimates, but not provided in Figure 7-12) would be much narrower, and closer to that derived

10  from the ACS study than indicated for any one expert shown in Figure 7-12.
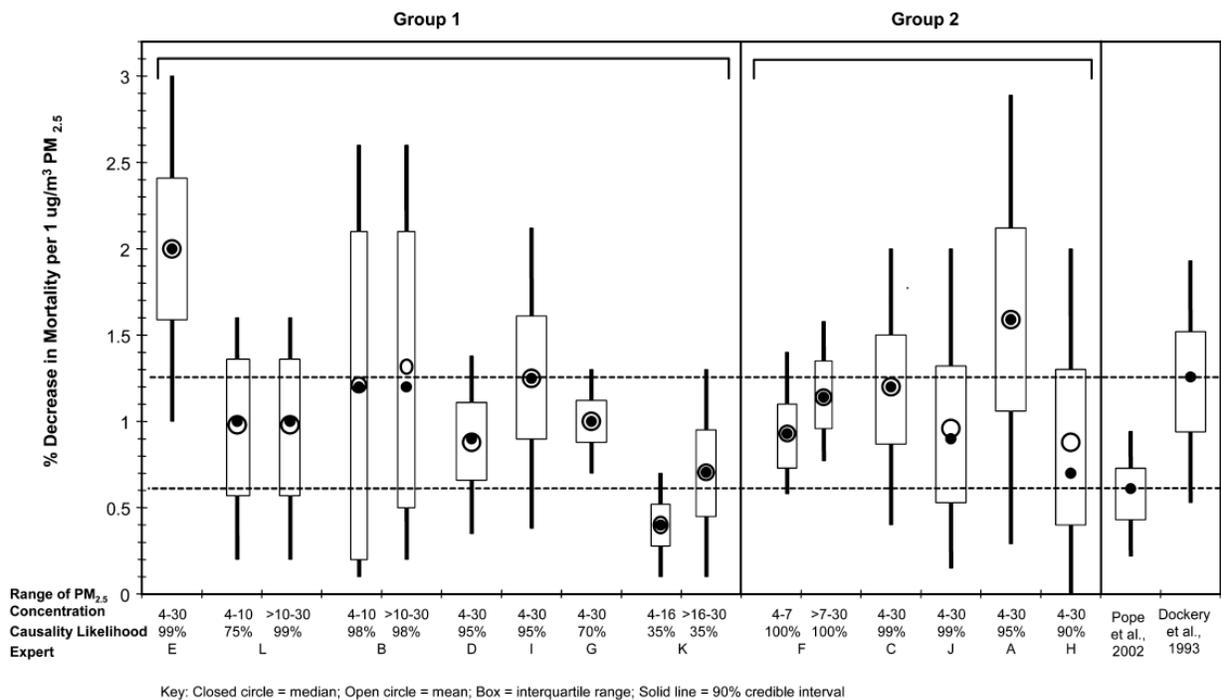


Source: Roman et al. (2008)

**Figure 7-12.  Experts' mean effect estimates and uncertainty distributions for the PM$_{2.5}$ mortality concentration-response coefficient for a 1 µg/m³ change in annual average PM$_{2.5}$**

11  In the 2004 PM AQCD, results from the ACS and Six Cities study analyses indicated that thoracic

12  coarse particles were not associated with mortality. The new findings from AHSMOG and Veterans cohort

13  studies provide limited evidence of associations between long-term exposure to PM$_{10-2.5}$ and mortality in

14  areas with mean concentrations from 16 to 25 µg/m³.

1    Overall, recent evidence supports the strong evidence reported in the 2004 PM AQCD that long-

2    term exposure to $PM_{2.5}$ is associated with an increased risk of human mortality, though evidence is still

3    lacking to adequately characterize the association between $PM_{10-2.5}$ and PM sources and/or components.

4    Collectively, the evidence is **sufficient to conclude that the relationship between long-term PM$_{2.5}$**

5    **exposures and mortality is likely to be causal.** When looking at the cause of death, the strongest

6    evidence comes from mortality due to cardiovascular disease, with additional evidence supporting an

7    association between $PM_{2.5}$ and lung cancer mortality (Figure 7-8). There is little new evidence that

8    supports an association between $PM_{2.5}$ exposure and respiratory mortality (Figure 7-8), though the

9    existing evidence from the Harvard Six Cities and ACS studies show a strong relationship with

10   cardiopulmonary mortality (Figure 7-7). These findings are consistent and coherent with the evidence

11   from epidemiologic, human clinical and animal toxicological evidence for the effects of short-term

12   exposure on cardiovascular morbidity presented in Section 6.2., short- and long-term exposures on

13   respiratory morbidity (Sections 6.3. and 7.3, respectively), and infant mortality presented in Section 7.5.

14   Additionally, the evidence for short-term cardiovascular morbidity and short- and long-term respiratory

15   morbidity provide biological plausibility for mortality due to cardiovascular or respiratory disease. **The**

16   **evidence for PM$_{10}$ is suggestive of a causal relationship between long-term exposures and**

17   **mortality.** The most recent evidence for this association is particularly strong for women. **The evidence**

18   **for PM$_{10-2.5}$ is inadequate to determine if a causal relationship exists between long-term exposures**

19   **and mortality.**

# Chapter 8. Public Health Impacts

1    This section addresses several issues relating to the broader public health impact from exposure to
2    ambient PM through a discussion on: (1) the shape of the concentration-response (C-R) relationship for
3    PM, with an evaluation of the new evidence available to assess a population threshold value for health
4    effects; and (2) the identification of subpopulations which may experience increased risks from PM
5    exposures, through either enhanced susceptibility (e.g., as a result of pre-existing disease, genetic factors,
6    age) and/or vulnerability associated with differential exposure (e.g., close proximity to sources,
7    activities).


## 8.1. Concentration-Response Relationship

8    An important consideration in characterizing the overall public health impacts associated with PM
9    exposure is whether the C-R relationship is linear across the full concentration range that is encountered
10   or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). The 2004
11   PM AQCD found, through the examination of multi-city studies (primarily those conducted using
12   NMMAPS data) that the linear model adequately represented the PM C-R relationship. In this ISA
13   additional studies have been identified that attempt to characterize the shape of the PM C-R curve. During
14   the evaluation of these studies particular interest is given to the shape of the C-R curve at and below the
15   current $PM_{10}$ and $PM_{2.5}$ NAAQS daily level ($PM_{10}$: 150 $\mu g/m^3$ and $PM_{2.5}$: 35 $\mu g/m^3$) and annual level
16   ($PM_{2.5}$: 15 $\mu g/m^3$).
17   In addition to examining the shape of the C-R relationship studies have also attempted to
18   identifying possible PM "thresholds" (i.e., levels which PM concentrations must exceed in order to elicit
19   a health response). An evaluation of multi-city studies in the 2004 PM AQCD found no evidence for the
20   presence of a threshold whereas, single-city studies did provide some suggestive evidence, but not in a
21   statistically clear manner. Overall, a multitude of factors have been identified that complicate the ability
22   to determine the shape of the PM C-R curve and the potential presence of a threshold including:
23   interindividual variability; additivity of pollutant-induced effects to naturally occurring background
24   disease processes; exposure error; response error; and low data density in the lower concentration range.
25   With consideration of these limitations, epidemiologic studies that examined the shape of the C-R curve
26   and the potential presence of a threshold for different exposure durations are presented below. The
27   discussion focuses on mortality effects associated with short- and long-term exposure to PM for which the
28   most in-depth analysis of the C-R relationship has occurred.

## 8.1.1. Mortality Associated with Short-Term Exposure to PM

1        Although studies have consistently found that the C-R relationship between PM exposure and

2    mortality is linear and does not suggest the presence of a threshold, novel and more complex statistical

3    analyses continue to be developed to further analyze both the PM C-R curve and whether a threshold

4    exists. In an analysis of the PM-mortality C-R relationship for short-term exposure to $PM_{10}$, Daniels et al.

5    (2004) constructed three different models (i.e., (1) log-linear model, (2) spline model, and (3) threshold

6    model) to investigate the shape of the curve and whether a threshold exists. In their analysis the spline

7    model, which would allow for departures from linearity, showed a linear relationship without indicating a

8    threshold for both total (non-accidental) and cardiorespiratory mortality for each 10 µg/m$^3$ increase in

9    $PM_{10}$, but the authors did find evidence for a threshold at 50 µg/m$^3$ for other-cause mortality (i.e., total

10   minus cardiorespiratory mortality). Further analysis of these models using AIC suggest that the log-linear

11   model is appropriate when describing the $PM_{10}$-mortality relationship. However, it must be noted, as

12   stated by the HEI review committee, that AIC was not developed to assess scientific theories of etiology

13   and, therefore, the results obtained from this analysis, although consistent with the findings from previous

14   C-R relationship analyses, must be viewed with caution.

15       Schwartz (2004b) used a different technique to examine the C-R relationship, the inclusion of

16   indicator variables for days in which the $PM_{10}$ concentration was between 15 and 25 µg/m$^3$, 25 and

17   34 µg/m$^3$, 35 and 44 µg/m$^3$, and above 45 µg/m$^3$. In this analysis the authors did not find any evidence for

18   deviations from linearity when combining estimates across 14 cities. Schwartz (2004b) did not analyze

19   city-specific thresholds, but Samoli et al. (2005), in the analysis of the C-R relationship in 22 European

20   cities observed heterogeneity in the shape of the C-R curve across cities. Therefore, although the

21   combined analysis conducted by Samoli et al. (2005) supports a log-linear association between $PM_{10}$ and

22   mortality, the heterogeneity observed between cities complicates the biological explanation for the

23   combined and city-specific results. Overall, the aforementioned studies all support the use of a

24   no-threshold log-linear model, but additional issues such as the influence of heterogeneity in estimates

25   between cities, and the effect of seasonal and regional differences in PM on the C-R relationship still

26   require further investigation.

## 8.1.2. Mortality Associated with Long-Term Exposure to PM

27       In addition to examining the C-R relationship between short-term exposure to PM and mortality,

28   one study conducted an analysis of the shape of the C-R relationship associated with long-term exposure

29   to PM. Schwartz et al. (2008) examined the C-R relationship between long-term exposure to $PM_{2.5}$ and

1    mortality using data from the Harvard Six Cities Study. The authors used two approaches both of which

2    involved Cox proportional hazards models. The first method used penalized splines, which fit a flexible

3    functional form that allowed for analysis of the C-R, while the second approach used Bayesian model

4    averaging (BMA) to combine the results of multiple models. In addition, the BMA approach used

5    piecewise linear functions to examine slope changes at various $PM_{2.5}$ concentrations (i.e., 10, 15, 20, 25,

6    and 30 μg/m$^3$). Using both approaches, the C-R curve was found to be indistinguishable from linear, and,

7    therefore, little evidence was observed to suggest that a threshold exists in the association between

8    long-term exposure to $PM_{2.5}$ and the risk of death (Schwartz et al., 2008).

9    To date, the majority of studies that examined the C-R relationship between long-term exposure to

10   PM and mortality have assumed a no-threshold log-linear model; however, uncertainty still exists

11   surrounding the shape of the C-R curve. To further evaluate this uncertainty, EPA conducted an expert

12   elicitation (Roman et al., 2008) to develop probabilistic uncertainty distributions in an attempt to

13   characterize the array of uncertainties in the C-R relationship. During this process 12 experts were asked

14   to provide their judgment on the true shape of the C-R curve for annual average $PM_{2.5}$ concentrations

15   ranging from 4 to 30 μg/m$^3$. Eight of the 12 experts specified that the existing data is consistent with a

16   log-linear C-R curve. The remaining four experts all proposed non-linear functions that used two log-

17   linear segments. These experts suggested the use of a piece-wise function in order to account for the

18   uncertainty in mortality effects at low $PM_{2.5}$ concentrations. Of the four experts that selected a non-linear

19   curve only one expert believed a threshold existed, even though the remaining experts agreed that,

20   collectively, the epidemiologic data did not provide evidence of a population threshold.

## 8.1.3. Summary of Concentration-Response Relationship

21   The examination of the PM C-R curve has primarily occurred in studies that have analyzed the

22   association between short- and long-term exposure to PM and mortality. These studies have used various

23   statistical methods, but overall have consistently found that a no-threshold log-linear model adequately

24   portrays the PM-mortality C-R relationship in multi-city analyses. At this time, uncertainty still exists

25   surrounding the PM-mortality C-R relationship on a city-to-city basis due to heterogeneity in the shape of

26   the C-R curve across cities.

# 8.2. Potentially Susceptible and Vulnerable Subpopulations

27   Interindividual variation in human responses to air pollutants indicates that not all individuals

28   exposed to pollutants respond similarly. That is, some subpopulations are at increased risk to the

1     detrimental effects of pollutant exposure. The NAAQS are intended to provide an adequate margin of

2     safety for both general populations and sensitive subpopulations, or those subgroups potentially at

3     increased risk for ambient air pollution health effects. For the purposes of this document, a susceptible

4     subpopulation is defined as one that might exhibit an adverse health effect to a pollutant at concentrations

5     lower than those needed to elicit the same response in the general population or elicit a more adverse

6     effect to the same concentration. A vulnerable subpopulation is one that might be differentially exposed to

7     higher concentrations of a pollutant than the general population, regardless of the health outcome. The

8     previous review of the PM NAAQS identified certain groups within the population that may be more

9     susceptible to the effects of PM exposure, including infants, older adults, asthmatics, individuals with

10     COPD or cardiovascular disease, diabetics, and individuals with certain genetic polymorphisms. Other

11     subgroups considered to be somewhat vulnerable in the previous review include individuals that

12     encompass particular socioeconomic status (SES) groups and education levels; exercising individuals;

13     and those living near roadways. Table 8-1 provides an overview of the characteristics that contribute to

14     susceptible/vulnerable subpopulations, which have been observed in the examination of the NAAQS for

15     all criteria pollutants. Those characteristics of susceptible/vulnerable subpopulations exposed specifically

16     to PM, as mentioned in the literature that encompasses this ISA, are discussed below.

**Table 8-1.**     **Characteristics of susceptible/vulnerable subpopulations.**

| Susceptibility Characteristics[1] | Vulnerability Characteristics[2] |
|---|---|
| Age: Children, Older Adults (65+) | Education Level |
| Infants: Premature, Low Birth Weight | Air Conditioning Use |
| Pregnancy | Proximity to Roadways |
| Birth Defects | Geographic Location (West vs. East) |
| Gender | Level of Exercise |
| Race/Ethnicity | Work Environment (e.g., outdoor workers) |
| Genetic Factors | Socioeconomic Status |
| Pre-existing disease: Obesity, Diabetes, Respiratory diseases (e.g., asthma), Cardiovascular diseases | |
| Nutritional status | |

[1] Susceptible (i.e., intrinsic) refers to biological characteristics of an individual, which can include life stage, genetics, and pre-existing disease.
[2] Vulnerable (i.e., extrinsic) refers to non-biological variables associated with an individual that can result in a health effect.

# 8.2.1. Susceptibility Characteristics

## 8.2.1.1. Age

1    The 2004 PM AQCD found evidence that age modifies the health effects associated with exposure

2    to PM. Depending on the health effect under investigation, children and older adults (i.e., $\geq$ 65 years)

3    have been identified as the two most susceptible subpopulations. Most studies that age-stratify results

4    have typically reported associations between PM and respiratory-related health effects for children,

5    specifically asthma, and associations for cardiovascular-related disease in older adults (U.S. EPA, 2004).

6    As the demographics of the U.S. population shift over the next 20 years with a larger percentage of the

7    population (i.e., 13% of the population in 2011 and a projected 20% in 2030) encompassing individuals

8    over the age of 65, an increase in the number of PM-related health effects could occur

9    (U.S. Census Bureau, 2000).

10    The recent epidemiologic, human clinical, and toxicological literature has examined the role of age

11    on the health effects observed upon exposure to PM. Overall, the results from epidemiologic studies vary,

12    depending on the health outcome of interest, in regards to which ages are most susceptible to PM

13    exposure. Studies that examined the effect of short-term exposure to PM on cardiovascular morbidity,

14    specifically, hospital admissions were found to exhibit a greater degree of variability in the estimates

15    reported between studies depending on the study location (i.e., U.S. or Europe). The majority of studies

16    conducted in Europe that present age-stratified results found that age (i.e., $\geq$ 65) modifies the PM risk

17    associated with cardiovascular hospital admissions. Le Terte et al. (2002b) found in the European

18    APHEA2 study that the excess risk of hospitalization for IHD attributable to $PM_{10}$ was approximately

19    twice as large in patients aged $\geq$ 65 years as compared to those aged < 65 years. Barnett et al. (2006)

20    analyzed data from several cities across Australia and New Zealand and found that the excess risk of

21    hospitalizations for cardiac diseases, congestive heart failure, IHD, MI, and all CVD was greater among

22    patients aged $\geq$ 65 as compared to those individuals <65 years upon exposure to $PM_{2.5}$. The French PSAS

23    program also found that the excess risk of hospitalization for all CVD, cardiac diseases, and IHD

24    attributable to $PM_{10}$, $PM_{2.5}$, and $PM_{10-2.5}$ was consistently greater among patients aged $\geq$ 65 years than in

25    all ages combined (Host et al., 2007; Larrieu et al., 2007) In many cases, the $PM_{10}$ effects were only

26    significant among older adults; however, formal tests of heterogeneity were commonly not reported in

27    these studies. A detailed evaluation of the U.S.-based studies that examined the association between

28    short-term exposure to PM and cardiovascular morbidity did not find consistent results across studies.

29    Only Zanobetti and Schwartz (2002) in their analysis of the effect of $PM_{10}$ on cardiac hospital admissions

30    among Medicare beneficiaries in 4 cities found that age (i.e., >75 compared to individuals 65-75)

31    modified the PM risk. In addition, two studies that examined the association between short-term exposure

1 to $PM_{10}$ and hospitalizations for MI found no evidence of effect modification by age (Zanobetti and

2 Schwartz, 2005) among Medixare beneficiaries in 21 cities and Metzger et al. 2004 in the Atlanta-based

3 SOPHIA study).

4      Although epidemiologic studies did not consistently find that age modified PM risk estimates for

5 cardiovascular morbidity, data from human clinical studies provide support for an increase in

6 cardiovascular effect in older adults. Human clinical studies that exposed individuals to CAPs have found

7 evidence of increased cardiovascular responses in older subjects. Devlin et al. (2003) found that older

8 subjects exposed to fine particulate CAPs experienced significant decreases in HRV (both in time and

9 frequency) immediately following exposure, when compared to data in healthy young subjects. In

10 addition, Gong et al. (2004b) found that older subjects showed significant decreases in HRV when

11 exposed to CAPs, but this study did not compare the response in older subjects to those elicited by young,

12 healthy individuals. Although cardiovascular morbidity epidemiologic studies were unable to consistently

13 suggest that older adults are more susceptible to PM, decreased HRV in older individuals has been shown

14 to predict increased risk of cardiovascular morbidity. (Brook et al., 2004).

15      Animal models have also been developed that mimic the physiologic conditions associated with

16 older individuals in order to examine PM-related health effects. For example, Nadziejko et al. (Nadziejko

17 et al., 2004) observed arrhythmias in older, but not younger, rats exposed to fine CAPs. In addition,

18 another study (Tankersley et al., 2004) that used a mouse model of terminal senescence observed various

19 cardiovascular-related responses including: altered baseline autonomic tone in response to carbon black

20 exposure which may affect the quality and severity of cardiovascular responses (Tankersley et al., 2007).

21 Reductions in cardiac fractional shortening and significant pulmonary vascular congestion upon exposure

22 to carbon black were also reported in old mice (Tankersley et al., 2008). Overall, these studies do provide

23 some biological plausibility for the increase in cardiovascular effects in older adults observed in the

24 human clinical studies.

25      Epidemiologic studies that examined the association between exposure to PM and respiratory

26 morbidity, and whether age modifies the effects observed, found evidence that supports the findings of the

27 2004 PM AQCD, which suggested that children are more susceptible to respiratory-related health effects

28 (Barnett et al., 2005; Mar et al., 2004; Peel et al., 2005). Mar et al. (2004) found that children exposed to

29 various PM size fractions were at an increased risk of developing lower respiratory symptoms in Spokane,

30 Washington. In addition, Peel et al. (2005) and Barnett et al. (2005) both observed that children were

31 more susceptible to respiratory-related hospital admissions upon exposure to $PM_{10}$. The literature has not

32 consistently found an association between short-term exposure to PM and respiratory-related health

33 effects in older adults, but some studies have reported an increase in respiratory hospital admissions

34 (Andersen et al., 2007b; Fung et al., 2006). The results from dosimetry studies have shown a depression

1   of PM clearance throughout the respiratory tract with increasing age from young to adulthood in humans

2   and laboratory animals, which could lend support to older adults also being susceptible to PM-related

3   respiratory health effects although this has not yet been supported by the human clinical or epidemiologic

4   literature (Section 4.3.4.1).

5       The new epidemiologic studies that examine the effect of short-term exposure to PM on mortality

6   have found that individuals over the age of 65 are more susceptible to all-cause (non-accidental) mortality

7   upon exposure to both $PM_{10}$ (Zeka et al., 2006a) and $PM_{2.5}$ (Franklin et al., 2007; Ostro et al., 2006),

8   which is consistent with the findings of the 2004 PM AQCD. However, Ostro et al. (2006) only observed

9   a slight increase in mortality for older adults, but they did observe that the inclusion of gaseous

10  copollutants (i.e., CO and $NO_2$) in the older adults model did not affect the $PM_{2.5}$ coefficient, unlike the

11  all-age model whose effect estimate was attenuated upon the inclusion of CO and $NO_2$ (Ostro et al.,

12  2006). Therefore, the results obtained by Ostro et al. (2006) further suggest that older adults are more

13  susceptible to PM exposures even though the overall effect estimate does not differ significantly from the

14  estimate obtained from the all-ages model. Studies that examined the effects of long-term exposure to PM

15  have found results contradictory to those obtained for mortality attributed to short-term exposures.

16  Villeneuve et al. (2002) found that individuals < 60 f had the greatest risk of PM-related mortality;

17  whereas, Lipfert et al. (2002) observed evidence that suggested that $PM_{2.5}$ disproportionately affects

18  individuals < 65 years while individuals > 65 years are more susceptible to $PM_{10}$.

## 8.2.1.2. Pregnancy

19      Pregnant women may be a susceptible subpopulation primarily due to the potential effect of

20  environmental contaminants on the developing fetus. In the case of exposure to PM, adverse health

21  effects in the offspring are mediated by a health response in the pregnant woman. Fedulov et al. (2008)

22  used an animal model to examine the effect of DEPs along with an immunologically "inert" particle

23  (titanium dioxide [$TiO_2$]) on pregnant mice. The authors found that pregnant mice exhibited a local and

24  systemic inflammatory response when exposed to both DEP and $TiO_2$, which was not observed in control,

25  non-pregnant mice. In addition, the offspring of exposed pregnant mice developed AHR and allergic

26  inflammation. The importance of this finding is that an inflammatory response leads to the differential

27  activation of multiple genes involved in immune response and regulation, cell metabolism, and

28  proliferation (2008).

29      In an additional study Hamada et al. (2007) also observed allergic responses in the offspring of

30  dams exposed to ROFA prior to delivery. The offspring responded to OVA immunization and aerosol

31  challenge with AHR and increased antigen-specific IgE and IgG1 antibodies. Overall, these studies

1    suggest that exposure to PM and even relatively inert particles during pregnancy can potentially lead to

2    increased allergic susceptibility in offspring, specifically, asthma.

### 8.2.1.3. Gender

3        Although the 2004 PM AQCD did not find consistent evidence to support a difference in health

4    effects by gender, there does appear to be gender differences in the localization of particles upon

5    deposition and the deposition rate (U.S. EPA, 2004). The recent epidemiologic studies that examine the

6    association between exposure to PM and mortality and morbidity provide inconclusive results as to

7    whether PM disproportionately affects males or females. Both Zanobetti and Schwartz (2005) and

8    Wellenius et al. (2006b) did not find gender to be a significant effect modifier of the risk estimates

9    associated with cardiovascular hospital admissions, but Pope et al. (2006) did observe a slightly larger,

10   non-significant, association between $PM_{2.5}$ and hospitalization for acute IHD events in males. In the

11   examination of the association between short-term exposure to $PM_{10}$ and respiratory hospitalization,

12   Luginaah et al. used both a time-series and case-crossover design and found similar effects for both

13   males and females. Boezen et al. (2005) did observe differential effects for males and females depending

14   on the endpoint examined (i.e., slightly larger association for upper respiratory symptoms in males and

15   cough in females) during their analysis of the $PM_{10}$-respiratory morbidity relationship. However, the

16   authors hypothesized that these differences could potentially be due to the differential daily exposure to

17   traffic exhaust experienced by men compared to women. Variable results were also observed in those

18   studies that examined the effect of short-term exposure to PM on mortality. Epidemiologic studies that

19   examined the relationship between short-term exposure to $PM_{10}$ and mortality did not observe any effect

20   modification when stratifying by gender (Zeka et al., 2006a), while some $PM_{2.5}$ studies (Franklin et al.,

21   2007; Ostro et al., 2006) did observe slightly larger, but non-significant, estimates in females compared to

22   males. Similar analyses were also conducted when examining the association between long-term exposure

23   to PM and mortality, but unlike the results presented above for short-term exposure studies, each study

24   consistently found that $PM_{2.5}$ and/or $PM_{10}$ mortality risk estimates for females were slightly larger,

25   although not significantly so, than those for males (Chen et al., 2005a; Naess et al., 2007a; Zanobetti and

26   Schwartz, 2007).

### 8.2.1.4. Race/Ethnicity

27       Epidemiologic studies that examined the effect of race and ethnicity on morbidity and mortality

28   obtained largely inconsistent results. Wellenius et al. (2006b) and Zanobetti and Schwartz (2005) both

29   observed that race did not significantly modify the association between short-term exposure to $PM_{10}$ and

CHF hospitalizations and MI hospitalizations, respectively. In the analysis of the $PM_{10}$-mortality relationship, Zeka et al. (2006a) did not observe any difference in mortality effect estimates when stratifying by race (i.e., black and white) upon short-term exposure to $PM_{10}$. However, Ostro et al. (2006) when performing a similar analysis, but also including ethnicity, observed a positive and significant effect for whites and Hispanics, but not for blacks in response to short-term exposure to $PM_{2.5}$. An additional analysis performed by Ostro et al. (2006) using $PM_{2.5}$ and various $PM_{2.5}$ species as the pollutants of interest, also observed a significant association between mortality, specifically cardiovascular mortality, and Hispanic ethnicity (Ostro et al., 2008). Overall, although significant associations have been observed between various PM size fractions and race and/or ethnicity it remains unclear if either increases the susceptibility of individuals to PM-related health effects.

### 8.2.1.5. Gene-Environment Interaction

A consensus now exists that gene-environment interactions merit serious consideration during the examination of the relationship between ambient exposures to air pollutants and the development of health effects (Gilliland et al., 1999; Kauffmann, 2004). Inter-individual variation in human responses to air pollutants suggests that some subpopulations are at increased risk of detrimental effects due to pollutant exposure, and it has become clear that the genetic makeup of an individual is an important susceptibility factor (Kleeberger and Ohtsuka, 2005). Gene-environment interactions can result in health effects due to either: (1) genetic polymorphisms, which result in the lack of a protein or a change that makes a dysfunctional protein that is needed to maintain homeostasis in the body (e.g., scavenging of ROS by glutathione-S-transferase [GST] genes), or (2) genetic damage in response to an exposure which potentially leads to a health response (e.g., formation of benzo [a] pyrene DNA adducts in response to PM exposure). To date, the majority of studies examine gene-environment interactions due to genetic polymorphisms. In order to establish useful links between polymorphisms in candidate genes and adverse health effects several criteria must be satisfied: (1) the product of the candidate gene must be significantly involved in the pathogenesis of the adverse effect of interest; (2) polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein; and (3) the issue of confounding by other environmental exposures must be carefully considered (U.S. EPA, 2008d).

It has been hypothesized that the cardiovascular and respiratory health effects that occur in response to short-term exposure to PM are mediated by oxidative stress (see Section 4.3). Research has examined this hypothesis by primarily focusing on the GST genes because they have common, functionally important polymorphic alleles that significantly affect antioxidant defense function in the lung (e.g., homozygosity for the null allele at the GSTM1 and GSTT1 loci, homozygosity for the A105G allele at the GSTP1 locus). Exposure to radicals and oxidants in air pollution leads to a cascade of events,

1    which can result in a reduction in glutathione (GSH), and an increase in the transcription of GSTs.

2    Individuals with genotypes that result in reduced or absent enzymatic activity are likely to have reduced

3    antioxidant defenses and potentially increased susceptibility to inhaled oxidants and radicals.

4        Numerous studies have examined the role of genetic polymorphisms on PM-related cardiovascular

5    health effects using the Normative Aging Study cohort. Schwartz et al. (2005b) and Chahine et al. (2007)

6    both found that individuals with null GSTM1 alleles had a larger decrease in HRV upon exposure to $PM_{2.5}$

7    compared to individuals with at least one allele. Polymorphisms in the heme oxygenase-1 (HO-1)

8    promoter resulted in different responses in HRV upon exposure to $PM_{2.5}$ depending on whether the

9    individual had the long or short repeat polymorphism (only those individuals with the long repeat

10    polymorphism had a decline in HRV) (Chahine et al., 2007). These results taken together suggest that

11    individuals with null alleles or specific polymorphisms in genes that mediate the antioxidant response to

12    oxidative stress are more susceptible to PM exposure. However, in some cases genetic polymorphisms

13    may actually reduce an individual's susceptibility to PM-related health effects. For example, Park et al.

14    (2006) found that individuals with 2 hemochromatosis (HFE) polymorphisms, which result in an increase

15    in iron uptake, had smaller reductions in HRV upon exposure to $PM_{2.5}$.

16        Additional studies have also examined whether genetic polymorphisms increase the susceptibility

17    of individuals to respiratory morbidity in response to PM exposure. Gilliland et al. (2004) examined the

18    effect of allergens and DEPs on individuals with either null genotypes for GSTM1 and GSTT1 or GSTP1

19    codon 105 variants. They found that individuals with the GSTM1 null or the GSTP1 I105 wildtype

20    genotypes were more susceptible to allergic inflammation upon exposure to allergen and DEPs.

21        Although some of the aforementioned studies have observed associations between exposure to PM

22    and various genetic polymorphisms, multiple factors besides the specific polymorphism under

23    investigation may be causing the response observed. Overall, additional research is required to further

24    substantiate the influence of gene-environment interactions on susceptibility to health effects in response

25    to PM exposure.

## 8.2.1.6. Pre-Existing Disease

26        In 2004, the National Research Council (NRC) published a report that emphasized the need to

27    evaluate the effect of air pollution on susceptible groups, including those with respiratory illnesses and

28    cardiovascular diseases (NRC, 2004). The 2004 PM AQCD found epidemiologic evidence suggesting that

29    individuals with pre-existing heart and lung diseases, and diabetes may be more susceptible to PM

30    exposure. In addition, toxicological studies that used animal models of cardiopulmonary diseases and

31    heightened allergic sensitivity also found evidence of enhanced susceptibility. Since the previous PM

32    AQCD epidemiologic, toxicological, and human clinical studies have constructed models or directly

1   examined the effect of PM on individuals with pre-existing diseases to identify whether exposure to PM

2   disproportionately effects certain subpopulations. A significant percentage of the U.S. population has

3   cardiovascular diseases and respiratory illnesses (see Table 8-2). In addition, diabetes and obesity, two

4   conditions linked to chronic inflammation, have recently been found to potentially facilitate PM-mediated

5   health effects. The large prevalence of diabetes in the U.S. population and the increasing percent of

6   individuals defined as overweight or obese (BMI $\geq$ 25.0) (56%-65% between NHANES III and NHANES

7   [1999-2002)]), in combination with those individuals defined as having a pre-existing cardiovascular or

8   respiratory disease, constitute an extremely large percent of the U.S. population that may be susceptible to

9   PM-related health effects (NCHS, 2007).

## 8.2.1.7. Cardiovascular Diseases

10  The effect of underlying cardiovascular diseases on PM-related health effects was also examined

11  using epidemiologic and human clinical studies, along with toxicological studies that use models to

12  mimic the physiologic conditions associated with various cardiovascular diseases (e.g., MI, angina, and

13  atherosclerosis). Epidemiologic studies have observed cardiovascular health outcomes in individuals with

14  underlying cardiovascular diseases upon exposure to PM. An increase in risk estimates for associations

15  between $PM_{10}$ and mortality have been observed in individuals with underlying stroke (Zeka et al., 2006b)

16  and congestive heart failure (Bateson and Schwartz, 2004). In addition, studies that have focused on

17  morbidity outcomes have found an increase in emergency department (ED) visits for individuals with

18  various cardiovascular conditions. Metzger et al. (2007), in Atlanta, observed that exposure to $PM_{10}$

19  resulted in an increase in ED visits for arrhythmias and CHF in individuals with underlying hypertension,

20  along with an increase in IHD ED visits for individuals with pre-existing arrhythmia; however, CHF did

21  not contribute to an increase in IHD ED visits. An additional study conducted in Atlanta, Peel et al. (Peel

22  et al., 2007), presented results consistent with those reported by Metzger et al. (2007) – secondary

23  hypertension increased the risk of CHF and arrhythmia ED visits upon exposure to $PM_{10}$. In contrast,

24  Pope et al. (2006) observed no association between secondary hypertension and IHD ED visits in Utah,

25  but they did find an increase in hospital admissions for acute IHD in individuals with underlying CHF

26  with exposure to $PM_{2.5}$. Two additional studies also observed no effect modification during an analysis of

27  underlying cardiovascular diseases. Zanobetti and Schwartz (2005) did not find an increase in MI hospital

28  admissions for exposure to $PM_{10}$ in individuals with secondary atrial fibrillation or CHF in a cohort of

29  more than 300,000 hospital admissions. Wellenius et al. (2006b) also found no effect modification

30  between CHF hospital admissions and acute MI or arrhythmia in 7 U.S. cities in response to exposure to

31  $PM_{10}$, such asHRV, . When looking at specific cardiac measurements, such as HRV upon exposure to

32  $PM_{2.5}$, pre-existing cardiovascular conditions (i.e., hypertension and IHD) have been found to contribute

1 to a reduction in the HF parameter (Park et al., 2005b). Overall, the epidemiologic evidence reports

2 inconsistent findings regarding the effect of pre-existing cardiovascular diseases on cardiovascular

3 hospital admissions and ED visits in response to exposure to PM.

4      Human clinical and toxicological studies have attempted to decipher the role of underlying

5 cardiovascular conditions on PM-related health effects by either designing studies that include subjects

6 with pre-existing cardiovascular diseases or employing animal models of a specific cardiovascular

7 disease. The effects of PM on rats that experienced a MI were analyzed by Anselme et al. (2007) and

8 Wellenius et al. (2006b) using two different models. Wellenius et al. (2006b) found, using the

9 post-myocardium sensitivity model (acute MI), that exposure to CAPs decreased spontaneous

10 supraventricular arrhythmias. In contrast, the MI model of chronic heart failure (rats that experienced an

11 MI 3 months prior to exposure), demonstrated a prominent increase in the incidence of premature

12 ventricular contraction when exposed to DE and this response was not observed in healthy rats (2007).

13 The discrepancies in effects could be due to differences in MI model or exposure atmosphere.

14      Wellenius et al. (2003) examined the effects of PM on angina using myocardial ischemic

15 preconditioning in dogs, which mimics the effects associated with IHD. In this study heart rate variability

16 was examined in response to exposure to fine particulate CAPs. The authors found that exposure to fine

17 particulate CAPs via tracheostomy prior to preconditioning increased integrated ST-segment elevation,

18 indicating ischemia.

19      The majority of the toxicology studies that examined the association between PM and pre-existing

20 cardiovascular diseases used a model of oxidative stress, the ApoE$^{-/-}$ mouse model. Each of these studies

21 observed physiologic alterations in response to both short- and long-term exposure to various PM size

22 fractions. Campen et al. (2005; 2006) both examined the effects of short-term exposure to PM on ApoE$^{-/-}$

23 mice. Campen et al. (2005) found that DE induced dramatic bradycardia and T-wave depression, while

24 Campen et al. (2006) found that whole gasoline emissions induced T-wave alterations.

25      In analyses that focused on the health effects associated with long-term exposure to PM on ApoE$^{-/-}$

26 mice, relatively consistent physiologic effects were observed across studies. Araujo et al. (2008) in a

27 exposed mice to ultrafine CAPs and found that long-term exposure to PM enhanced the size of aortic

28 lesions. Similarly, Chen and Nadziejko (2005) and Sun et al. (2005; 2008) exposed mice to $PM_{2.5}$ CAPs

29 with the same results. Additional long-term exposure studies observed a decreasing trend in heart rate,

30 physical activity, and temperature along with biphasic responses in HRV (SDNN and rMSSD) (Hwang et

31 al., 2005) upon exposure to CAPs.

32      Human clinical studies have also examined the effect of pre-existing diseases on the health effects

33 associated with exposure to PM. Mills et al. (2007; 2008) investigated the effects of dilute diesel-exhaust,

34 and fine and ultrafine CAPs, respectively, on subjects with chronic heart disease (CHD). Exposure to

1   dilute diesel-exhaust was found to promote exercise-induced myocardial ischemia and inhibit endogenous

2   fibrinolytic capacity (Mills et al., 2007), while fine and ultrafine CAPs, which were low in combustion

3   products, were not found to exhibit any significant effects on vascular function. An additional study

4   conducted by Carlsten et al. (2008), which also examined cardiovascular effects, found that DE did not

5   elicit any prothrombotic effects in subjects with metabolic syndrome.

## 8.2.1.8. Respiratory Illnesses

6      Investigators have examined the effect of pre-existing respiratory illnesses on multiple health

7   outcomes (e.g., mortality, asthma symptoms, congestive heart failure, etc.) in response to exposure to

8   ambient levels of PM. In some cases animal models have been developed and/or human clinical studies

9   conducted in order to substantiate the results obtained from epidemiologic studies. Unlike the analyses

10  conducted for pre-existing cardiovascular diseases, which examined the progression of only

11  cardiovascular conditions in response to PM exposure, the studies that examined the effect of pre-existing

12  respiratory diseases on PM-related health effects examined both respiratory and cardiovascular health

13  outcomes.

14      The majority of epidemiologic studies examined the effect of various pre-existing respiratory

15  illnesses on PM-related health effects, specifically in individuals with asthma or COPD. Although each

16  epidemiologic study was conducted in a different location, using (in some cases) different averaging times

17  and/or lags, an increase in respiratory effects in individuals with pre-existing asthma was consistently

18  observed in response to short-term exposure to size-fractionated PM. Individuals with pre-existing asthma

19  were found to have an increase in: medication use (Rabinovitch et al., 2006), respiratory symptoms

20  (i.e., asthma symptoms, cough, shortness of breath, and chest tightness (Gent et al., 2003), and asthma

21  symptoms (Delfino et al., 2002; Delfino et al., 2003a) when exposed to $PM_{2.5}$; and morning symptoms

22  (Mortimer et al., 2002); and asthma attacks (Desqueyroux et al., 2002a) when exposed to $PM_{10}$. The

23  results of epidemiologic studies that focused on individuals with pre-existing COPD are less consistent

24  than those reported for studies that examined the effect of short-term exposure to PM on individuals with

25  pre-existing asthma. Both Silkoff et al. (2005) and (Desqueyroux et al., 2002b) did not find an increase in

26  the exacerbation of COPD in response to short-term exposure to $PM_{2.5}$. However, Trenga et al. (2006) and

27  Lagorio et al. (2006) did observe declines in lung function $FEV_1$ and $FEV_1$ and FVC, respectively in

28  response to $PM_{10}$ and/or $PM_{2.5}$.

29      Collectively, human clinical studies that examined the health effects associated with pre-existing

30  respiratory diseases (i.e., asthma and COPD) did not find an increase in respiratory effects upon exposure

31  to PM. Gong et al. (2003a; Gong et al., 2008) found that healthy and asthmatic subjects exposed to fine

32  and ultrafine CAPs, exhibited similar respiratory responses. In addition, Gong et al. (2004a) found no

1     significant difference in respiratory effects between healthy and COPD inflicted individuals upon

2     exposure to fine CAPs. However, the results from dosimetry studies, which have shown that mucociliary

3     clearance is impaired in patients with COPD relative to healthy controls, suggest that individuals with

4     preexisting COPD are potentially at a greater risk of COPD exacerbations (see Section 4.3.4.3), but this

5     has not yet been confirmed in human clinical or epidemiologic studies

6            Toxicological studies have examined the effect of pre-existing allergy on PM-related health effects

7     through the use of the ovalbumin-induced allergic airway disease model. Morishita et al. (2004) used this

8     model to assess the health effects of $PM_{2.5}$ components. Using CAPs from Detroit, an area with pediatric

9     asthma rates three times the national average, rats with induced allergic airway disease were found to

10     preferentially retain PM derived from identified local combustion sources in association with eosinophil

11     influx and BALF protein content after a short-term exposure (Morishita et al., 2004). These findings

12     suggest that individuals with allergic airways conditions are more susceptible to allergic airways

13     responses upon exposure to $PM_{2.5}$, which may be attributed to increased pulmonary deposition and

14     localization of particles in the respiratory tract (Morishita et al., 2004). This conclusion is supported by a

15     series of human clinical studies which have shown that exposure to DEPs increases the allergic

16     inflammatory response in atopic individuals (Bastain et al., 2003; Diaz-Sanchez et al., 1997; Nordenhall

17     et al., 2001).

18            Of the studies that focused on the association between short- and long-term exposure to PM and

19     mortality, only a few further refined their analysis to examine the effect of pre-existing respiratory

20     illnesses on the PM-mortality relationship. Using different pre-existing respiratory illnesses, Zeka et al.

21     (2006a) (examined pneumonia) and De Leon et al. (2003) (all respiratory illesses) found that short-term

22     exposure to $PM_{10}$ along with: (1) pneumonia increased the risk of non-accidental mortality, and (2)

23     respiratory illnesses increased the risk of circulatory mortality, respectively. Additionally, Zanobetti et al.

24     (2008) observed an association between long-term exposure to $PM_{10}$ and mortality in individuals that had

25     previously been hospitalized for COPD.

## 8.2.1.9. Respiratory Contributions to CV Effects

26            Although the majority of health effects observed in individuals with pre-existing respiratory

27     illnesses were associated with respiratory illness exacerbations, studies also examined whether underlying

28     respiratory illnesses can lead to cardiovascular effects upon PM exposure. The epidemiologic studies that

29     examined this association did not observe an increase in hospital admission or emergency department

30     visits for a variety of cardiovascular effects (e.g., ischemic heart disease, arrhythmias, congestive heart

31     failure, myocardial infarction) for individuals with underlying respiratory infection (Wellenius et al.,

32     2006b), pneumonia (Zanobetti and Schwartz, 2005), and COPD (Peel et al., 2007; Wellenius et al.,

1　2005a). However, human clinical and toxicological studies did observe some cardiovascular effects in

2　individuals with pre-existing respiratory illnesses. Gong et al. (2003a) observed signs of acute responses

3　in the cardiovascular system, systemic circulation, and central-airway cell populations in asthmatic

4　individuals exposure to fine CAPs. Batalha et al. (2002), using a chronic bronchitis animal model, found

5　that the pulmonary artery lumen-to-wall ratio was decreased in chronic bronchitis rats exposed to both

6　filtered air and CAPs. Normal rats were also found to have a reduced pulmonary artery lumen-to-wall

7　ratio, but only when exposed to $PM_{2.5}$ CAPs. Overall, it is unclear if underlying respiratory illnesses result

8　in increased susceptibility to cardiovascular health effects.

## 8.2.1.10. Inflammatory Conditions: Diabetes and Obesity

9　An increasing number of studies have been conducted since the 2004 PM AQCD to examine the

10　effects of short-term exposure to PM on individuals with chronic inflammatory conditions, such as

11　diabetes and obesity. As the percent of the population with each condition (i.e. diabetes and obesity)

12　continues to increase these subpopulations could represent a large number of individuals that are

13　susceptible to the health effects associated with exposure to PM. Although a few studies have found that

14　individuals with diabetes are at increased risk of mortality upon exposure to $PM_{10}$ (Goldberg et al., 2006;

15　Zeka et al., 2006a), the majority of the literature focuses on cardiovascular health effects in these

16　individuals.

17　It has been hypothesized that the systemic inflammatory cascade leads to an increase in

18　cardiovascular risk (Dubowsky et al., 2006). To examine the potential increase in risk associated with

19　short-term exposure to $PM_{10}$ in diabetics, human clinical studies have been conducted to determine the

20　physiologic changes that occur in individuals with diabetes in response to PM exposure. These studies

21　examine both changes in inflammatory markers along with specific physiologic changes in the

22　cardiovascular system. Liu et al. (2007b) observed an increase in end-diastolic FMD and end-systolic

23　FMD, but decreases in end-diastolic basal diameter and end-systolic basal diameter in diabetics upon

24　exposure to $PM_{10}$. The authors also observed positive associations with FMD and blood pressure in

25　diabetic individuals. An examination of biomarkers found mixed results, with Liao et al. (2005) observing

26　an increase in vWF; Liu et al. (2007b) observing an increase in TBARS, but not CRP or TNF-α; and

27　Dubowsky et al. (2006) observing an increase in CRP and WBC s. Overall, it is unclear how differences

28　in each of the aforementioned biomarkers contribute to the potential overall cardiovascular effect

29　observed in diabetic individuals; however, an increase in inflammation, oxidative stress, and acute phase

30　response may contribute to cardiovascular effects.

31　Further examination of the potential effect of underlying diabetes in individuals exposed to PM

32　through epidemiologic studies has found some evidence, which supports an increase in

1  cardiovascular-related ED visits and hospital admissions. Multicity studies have found upwards of 75%

2  greater risk of hospitalization for cardiac diseases in individuals with diabetes upon exposure to $PM_{10}$

3  (Zanobetti and Schwartz, 2002). Additional single-city analyses have also found an increase in risk for

4  ED visits for IHD, arrhythmias, and CHF in response to $PM_{10}$ exposure in diabetics (Metzger et al., 2007;

5  Peel et al., 2007). However, some studies (both multicity and single-city) have not observed an

6  association between cardiovascular ED visits and hospital admissions in response to exposure to $PM_{10}$ in

7  diabetics (Pope et al., 2006; Wellenius et al., 2006b; Zanobetti and Schwartz, 2005). Overall, although

8  studies have reported health effects associated with PM in a study population of diabetics, further work is

9  needed to confirm these associations, and to investigate by which pathophysiological pathway(s) diabetics

10  may have a greater response to PM.

**Table 8-2.  Percent of the U.S. population inflicted with respiratory diseases, cardiovascular diseases, and diabetes.**

| Chronic Condition/ Disease | Adults (18+)* Number (x 10$^6$) | Adults (18+)* % | Age 18-44 % | Age 45-64 % | Age 65-74 % | Age 75+ % | Regional NE % | Regional MW % | Regional S % | Regional W % |
|---|---|---|---|---|---|---|---|---|---|---|
| *RESPIRATORY DISEASES* | | | | | | | | | | |
| Asthma* | 24.2 | 11.0 | 11.5 | 10.5 | 11.7 | 9.3 | 11.7 | 11.5 | 10.5 | 10.8 |
| Asthma (< 18 years) | 6.8* | 9.3* | — | — | — | — | — | — | — | — |
| *COPD* | | | | | | | | | | |
| Chronic bronchitis | 9.5 | 4.3 | 2.9 | 5.5 | 5.6 | 6.7 | 3.8 | 4.4 | 4.9 | 3.5 |
| Emphysema | 4.1 | 1.8 | 0.3 | 2.4 | 5.0 | 6.4 | 1.4 | 2.3 | 1.9 | 1.6 |
| *CARDIOVASCULAR DISEASES* | | | | | | | | | | |
| All heart disease | 24.1 | 10.9 | 3.6 | 12.3 | 26.1 | 36.3 | 10.8 | 12.7 | 10.9 | 9.2 |
| Coronary heart disease | 14.1 | 6.4 | 0.9 | 7.2 | 18.4 | 25.5 | 6.4 | 7.6 | 6.6 | 4.7 |
| Hypertension | 51.6 | 23.4 | 7.7 | 32.4 | 52.7 | 53.5 | 22.2 | 23.7 | 25.3 | 20.6 |
| Stroke | 5.6 | 2.6 | 0.5 | 2.4 | 7.6 | 11.2 | 2.1 | 2.8 | 2.9 | 2.2 |
| Diabetes | 17.1 | 7.8 | 2.6 | 10.4 | 18.2 | 17.9 | 7.2 | 8.1 | 8.0 | 7.4 |

* All data for adults except asthma prevalence data for children under 18 years of age, from CDC (2008a, b). For adults prevalence data based off adults responding to "ever told had asthma."
Source: Pleis and Lethbridge-Çejku (2007); CDC (2008a, b)

11      In addition to diabetes, obesity has been examined as a health condition, which could potentially

12  lead to an increase in PM-related health effects. Although Schwartz et al. (2005a) found an adverse

13  modification of HRV in obese individuals and Dubowsky et al. (2006) observed an increase in

1    inflammatory markers (i.e., CRP, IL-6, and WBC) in response to short-term exposure to $PM_{2.5}$, it remains

2    unclear if obese individuals are more susceptible to PM-related health effects.

## 8.2.2. Vulnerability Characteristics

3        Epidemiologic studies have examined characteristics that potentially increase the vulnerability of

4    subpopulations to PM-related health effects by analyzing potential effect modification of the association

5    between health outcomes and PM exposure. In most cases those individuals vulnerable to PM-related

6    health effects do not have underlying conditions that result in increased susceptibility to PM exposure, but

7    instead are disproportionately exposed to PM.

## 8.2.3. Urban Environment

8        Zeka et al. (2005) in their analysis of 20 U.S. cities found that exposure to $PM_{10}$ increased in

9    mortality as population density increased and as the percent of primary $PM_{10}$ from traffic increased across

10   cities. Both of these factors taken together represent the urban environment, and support the hypothesis

11   that as density of the urban environment increases so does the percent of the primary $PM_{10}$ from traffic

12   sources (Zeka et al., 2005). Likewise, Wilson et al. (2007b) found that the most urban environment had

13   the highest mortality risk estimate when stratifying Phoenix into central, middle, and outer rings of

14   varying urban density. Although urban density and traffic-related PM contribute to the vulnerability of

15   individuals that reside in urban environments, other factors (e.g., socioecominic status (SES) and

16   education level) are known to highly influence the overall health of a population and may also be

17   contributing to the effects associated with an urban environment.

## 8.2.4. Socioeconomic Status

18       Based on data from the 2000 U.S. census, from among commonly-used indicators of SES, about

19   12% of individuals and 9% of families are below the poverty level, and 20% of the U.S. population does

20   not have a high school or higher level of education (U.S. Census). These individuals classified as having a

21   lower SES and/or education level than the general population tend to reside in low-income areas, which

22   are sometimes located in urban environments. Laurent et al. (2008) and O'Neill et al. (2003) noted that

23   there has not been a consistently-observed trend that characterizes the impact of SES on exposure to PM

24   (sometimes including BC or sulfate aerosols) or other air pollutants. Laurent et al. (2008) argued that the

1    spatial scale of the study and the number and nature of selected SES variables and within-variable factors

2    clearly impacts their influence in epidemiologic models (see Section 3.7.4).

3        SES and education level have been shown in some studies (e.g., Filleul et al., 2004; Finkelstein et

4    al., 2003) to modify health outcomes of PM exposure for a population and may also be contributing to the

5    effects associated with an urban environment. For instance, Franklin et al. (2008) noted an increased risk

6    in mortality upon exposure to $PM_{2.5}$ and its components for individuals of low SES. Additional analyses

7    stratified by education level have also observed consistent trends of increased risk in mortality for all

8    PM-size fractions for individuals with low educational attainment (Ostro et al., 2006; 2008; Zeka et al.,

9    2006). However, other factors associated with low SES and educational attainment that were not

10    examined in any of the aforementioned studies, which may increase these individuals sensitivity to

11    PM-related health effects include: higher prevalence of pre-existing diseases; inadequate medical

12    treatment; and limited access to fresh foods leading to a reduced intake of antioxidant polyunsaturated

13    fatty acids and vitamins (Kan et al., 2008). It should be noted that in some other studies (e.g., Filleul et

14    al., 2005; Tolbert et al., 2000), no effect of SES on health outcome was demonstrated.

15        Air conditioning use, although not a direct measure of SES, has been found to reduce personal

16    exposure to PM. Barn et al. (2008) and Baxter et al. (2007b). Both noted that window opening was an

17    important variable for determining PM infiltration factors. Franklin et al. (2007), in an examination of

18    27 cities, observed a marked decrease in mortality as the percentage of homes using air conditioning

19    increased, with "the effect of $PM_{2.5}$ disappear[ing] in communities with high central air conditioning

20    prevalence and summer peaking particle concentrations." However, the results from epidemiologic

21    studies have not overwhelmingly concluded that air conditioning use significantly reduces the

22    PM-mortality association. Zeka et al. (2005) in a multicity analysis only observed a slight decline in

23    $PM_{10}$-mortality association as the percentage of the population with air conditioning increased. A more

24    recent analysis by Franklin et al. (2008) did not analyze air conditioning use individually because they

25    believed using air conditioning alone in a model did not adequately account for the differences in building

26    ventilation rates, which differ by season and community. Therefore, by using temperature as a surrogate

27    of ventilation, Franklin et al. (2008) found that at times when temperatures are extremely low or high the

28    $PM_{2.5}$ mortality association was reduced potentially because of a reduction in building ventilation rates.

29    Although consistency has not been observed uniformly across studies regarding the effect of air

30    conditioning use on PM-related health effects, the evidence suggests that individuals with access to air

31    conditioning, and more than likely with a higher SES, could potentially be less vulnerable to PM-related

32    health effects.

## 8.2.5. Geographic Location

1    In addition to the previously mentioned, economic and societal factors that could potentially

2    increase the vulnerability of an individual to PM-related health effects, numerous studies have also

3    continued to examine the geographic heterogeneity in PM-related health effects. All of the studies

4    identified in the current PM ISA that have examined the PM-mortality relationship, in regards to

5    geographic location within the U.S., have concluded that the effects are greater in the East compared to

6    the West. Although the definition of East versus West varies from study to study the effects observed are

7    fairly consistent regardless of the PM-size fraction analyzed. Dominici et al. (2007b) and Peng et al.

8    (2005) both found that the East exhibited a larger percent increase in all-cause (non-accidental) mortality

9    compared to the West when examining $PM_{10}$-mortality effects. However, in addition to an all season

10   analysis, Peng et al. (2005) conducted seasonal analyses and observed the same pattern of effects, with

11   the greatest effects occurring in the Northeast during the summer along with some indication of a summer

12   effect in the industrial Midwest. In the examination of the $PM_{2.5}$ -mortality relationship by geographic

13   location Franklin et al. (2007) and Franklin et al. (2008) found results consistent with those reported in

14   the $PM_{10}$ analyses. Franklin et al. (2007) observed greater effects in the East compared to the West;

15   whereas, Franklin et al. (2008) found similar results, but compared effects observed in the East and

16   Central U.S. to those in the West. Overall, the epidemiologic literature suggests that individuals residing

17   in the Eastern U.S. are more vulnerable to PM-related health effects.

# Chapter 9. Ecosystem and Welfare Effects

## 9.1. Introduction

1    This chapter is a concise synthesis and evaluation of the most policy-relevant science used to help
2    form the scientific foundation for review of the secondary (welfare-based) NAAQS aimed at protecting
3    against welfare effects of ambient airborne PM. Specifically, Chapter 9 assesses the effects of
4    atmospheric PM on the environment, including: (a) effects on visibility, (b) effects on individual
5    organisms, (c) direct and indirect effects on ecosystem, (d) effects on materials, and (e) effects on climate.
6    As discussed in chapter 1, the effects of particulate $NO_X$ and SOx have recently been evaluated in the *ISA*
7    *for Oxides of Nitrogen and Sulfur – Ecological Criteria* (U.S. EPA, 2008e). That ISA focused on the
8    effects of deposition of $NO_X$ and SOx (both gas- and particle-phase) related to acidifying deposition and
9    nutrient enrichment, as well as the potential for increased mercury methylation. Thus, in conjunction with
10    the ISA for $NO_X$ and SOx, emphasis here is placed on the effects of airborne PM on visibility and climate,
11    and on the effects of deposition of PM constituents other than $NO_X$ and SOx, primarily metals and
12    carbonaceous compounds.
13    Section 9.2 of this chapter provides the summary and conclusions for the major welfare and
14    ecological effects evaluated. EPA's framework for causality, described in Chapter 1, is applied throughout
15    the evaluation and the causal conclusions are highlighted in this first section. The evidence for each of
16    these major effects is evaluated in more detail in Sections 9.3 through 9.8. These sections initially
17    highlight the conclusions from the 2004 PM AQCD (U.S. EPA, 2004), followed by an evaluation of
18    recent publications and assessment of the expanded body of evidence. In some sections, few new
19    publications are available, and the discussion is primarily a brief overview of the key conclusions from
20    the previous review.

## 9.2. Summary and Conclusions

### 9.2.1. Summary of Effects on Visibility

21    **The evidence is sufficient to infer a causal relationship between ambient PM and visibility**
22    **impairment.** Visibility impairment is caused by light scattering and absorption by suspended particles and
23    gases. $NO_2$ is the only commonly occurring atmospheric pollutant gas that absorbs visible spectrum

1    radiation, though in most situations the amount of light absorption by $NO_2$ is overwhelmed by the higher

2    levels of particulate light extinction (i.e. the combination of scattering and absorption) usually

3    accompanying high $NO_2$ concentrations. Light scattering by gases in a pollutant-free atmosphere provides

4    a limit to visibility in pristine conditions and is a major contributor to the total light extinction during the

5    least visibility-impaired periods in remote regions of the western U.S. PM is the overwhelming source of

6    visibility impairment. EC and some crustal minerals are the only commonly occurring airborne particle

7    components that absorb light. All particles scatter light, and generally light scattering is the largest of the

8    four light extinction components. While larger particles scatter more light than similarly shaped smaller

9    particles of the same composition, the light scattered per unit of mass concentration is greatest for

10    particles with diameters from about 0.3 to 1.0 μm.

11    For special studies where detailed particle composition by size data are available, accurate

12    calculations of light extinction can be made. However, routinely available PM speciation data can be used

13    to make reasonable estimates of light extinction using relatively simple algorithms that multiply the

14    concentrations of each of the major PM species by its dry extinction efficiency and by a water growth

15    term that accounts for particle size change as a function of relative humidity for hygroscopic species (i.e.

16    sulfate, nitrate and sea salt). This permits the visibility impairment associated with each of the major PM

17    components to be separately estimated from PM speciation monitoring data. There are six major PM

18    components: $PM_{2.5}$ sulfate usually assumed to be ammonium sulfate, $PM_{2.5}$ nitrate usually assumed to be

19    ammonium nitrate, $PM_{2.5}$ organic carbon compound, $PM_{2.5}$ EC, $PM_{2.5}$ crustal material (call fine soil), and

20    $PM_{10-2.5}$ or coarse mass.

21    Particulate sulfate and nitrate are produced in the atmosphere from gaseous precursors, making

22    them secondary PM species. They both have comparable light extinction efficiencies (haze impacts per

23    unit mass concentration) at any relative humidity level, their light scattering per unit mass concentration

24    increases with increasing relative humidity, and at sufficiently high humidity levels (RH>85%) they are

25    the most efficient particulate species contributing to haze. Particulate sulfate is the dominate source of

26    regional haze in the eastern U.S. (>50% of the particulate light extinction) and an important contributor to

27    haze elsewhere in the country (>20% of particulate light extinction).

28    Particulate nitrate is a minor component of remote-area regional haze in the non-California western

29    and eastern U.S., but an important contributor in most of California and in the upper Midwestern U.S.

30    especially during winter when it is the dominant contributor to particulate light extinction. While both

31    nitric acid (a reaction product of $NO_X$ emissions) and ammonia are needed to form ammonium nitrate, the

32    apparent reason for the Midwest nitrate bulge is an abundance of atmospheric ammonia in this region

33    principally from agricultural emissions. There is evidence that transport from the Midwest nitrate bulge

34    region is responsible for some of the ammonium nitrate episodes experienced in downwind regions far to

1 the east. Urban particulate nitrate concentrations are significantly elevated above surrounding remote-area

2 background concentrations with the largest urban contributions in the western U.S. Particulate ammonium

3 nitrate concentrations in California and the Midwestern nitrate bulge region are an order of magnitude

4 greater than estimated natural levels of ammonium nitrate. Thermodynamic and air quality simulation

5 modeling shows that particulate nitrate concentrations are sensitive to changes in either $NO_X$ emissions

6 (from a combination of mobile and point sources) and ammonia emissions (principally from agricultural

7 sources), with the responsiveness of particulate nitrate to emissions changes depending on the relative

8 abundance of ammonia and nitric acid in the atmosphere.

9 EC and organic compound species (i.e. carbonaceous components of PM) have the highest dry

10 extinction efficiencies of the major PM species and are responsible for a large fraction of the haze

11 especially in the Northwestern U.S., though absolute concentrations are as high in the eastern U.S. Both

12 are a product of incomplete combustion of fuels, including those used in internal combustion processes

13 (gasoline and diesel emissions) and open biomass burning (smoke from wild and prescribed fire). Organic

14 compound PM species are also produced by atmospheric transformation of precursor gaseous emissions.

15 Smoke plume impacts from large wildfires dominate many of the worst haze periods in the western U.S.

16 Carbonaceous PM is generally the largest component of urban excess $PM_{2.5}$. western urban areas have

17 more than twice the average concentrations of carbonaceous PM than remote areas sites in the same

18 region. In eastern urban areas $PM_{2.5}$ is dominated by about equal concentrations of carbonaceous and

19 sulfate components, though the usually high relative humidity in the East causes the hydrated sulfate

20 particles to be responsible for about twice as much of the urban haze as that caused by the carbonaceous

21 PM.

22 Radiocarbon dating of carbonaceous PM from twelve sites (eight in the West, two of which are

23 urban) showed that about half of the urban area carbonaceous PM is from contemporary as opposed to

24 fossil sources, while in remote areas the fraction that is contemporary ranges from 82%-100%. Summer

25 urban excess carbonaceous PM is dominated by fossil carbon for the two western urban areas (Phoenix,

26 AZ and Seattle, WA), but nearly half of the winter urban excess for these two urban areas are from

27 contemporary carbon sources (e.g. residential wood combustion). An empirical relationship between the

28 radiocarbon analysis results and the more widely measured elemental and organic carbon data set was

29 used to estimate the fraction of contemporary carbon at about 150 monitoring locations nationwide. The

30 highest fraction of contemporary carbon is for the western remote areas sites during the summer (>90%

31 contemporary) and the least was for eastern urban areas during the summer (< 45% contemporary).

32 Winter tended to have less extreme fractions of contemporary carbon for both remote and urban areas. A

33 lower bound estimate of 40% of the contemporary and 35% of the fossil carbon is from secondary

34 conversion of gaseous precursor during the summer at the twelve radiocarbon monitoring sites,

1  suggesting that primary carbonaceous PM whether from fossil or contemporary sources represent less

2  than two thirds of the total carbonaceous PM.

3  PM$_{2.5}$ crustal material (referred to as fine soil) and coarse mass (i.e., PM$_{10}$ minus PM$_{2.5}$) are

4  significant contributors to haze in the arid Southwestern U.S. where they contribute a quarter to a third of

5  the haze, with coarse mass usually contributing twice that of fine soil. Coarse mass concentrations are as

6  high in the Central Great Plains as in the Southwestern deserts though there are no corresponding high

7  concentrations of fine soil as in the Southwest. Also, the relative contribution to haze by the high coarse

8  mass in the Great Plains is much smaller because of the generally higher haze levels caused by the high

9  concentrations of sulfate and nitrate PM in that region.

10  A comprehensive assessment of the 610 worst haze sample periods over a three year period in the

11  western U.S. where dust is the major contributor categorized each site/sampler period into four causal

12  groups: Asian dust, local windblown dust, transported regional windblown dust, and undetermined dust

13  (i.e. not in one of the three other groups). Most dust days occurred at sites in Arizona, New Mexico,

14  Colorado, western Texas, and southern California, and these were dominated by local and regionally

15  transported wind-blown dust. Asian dust caused only a few of the worst dust days during the 3-year

16  assessment period, though it is an important source of dust for the more northerly regions of the West

17  (responsible for 10%-40% of their worst dust periods) were there is rarely any windblown dust probably

18  due to the greater ground cover. The frequency of worst dust events classified as undetermined was

19  greatest for sites in the vicinity of large urban and agricultural areas such as those in California and

20  Southern Arizona.

21  Urban visibility has been examined in two types of studies directly relevant to this review process:

22  urban visibility preference studies and urban visibility valuation studies. Both types of studies are

23  designed to evaluate individuals' desire for good VAQ where they live, using different metrics. Urban

24  visibility preference studies examine individuals' preference by investigating the basic question "what

25  level of visibility degradation is unacceptable," while economic studies examine preference by

26  investigating "how much would you be willing to pay to improve visibility."

27  There are three completed urban visibility research projects focused on identifying preferences for

28  urban VAQ, and one additional pilot study (designed as a survey instrument development project) that

29  provided additional information. The completed studies were conducted in Denver, Colorado (Ely et al.,

30  1993), two cities in British Columbia, Canada (1996), and Phoenix, Arizona

31  (BBC Research & Consulting, 2002). The pilot study was conducted in Washington, DC (ABT, 2001).

32  One notable finding of the three visibility preference studies and the one pilot study is the general degree

33  of consistency in the median preferences for an acceptable level of visibility degradation. The range of

34  median acceptable preference level from the four studies is 19 to 25 deciviews (DV), the preferred

1 measure of visibility impairment. Measured in terms of visual range (VR), these median acceptable levels

2 are between 30 and 55 km.

3 The economic importance of urban visibility has been examined by a number of studies designed to

4 quantify the benefits (or willingness to pay) associated with potential improvements in urban visibility.

5 Urban visibility valuation research prior to 1997 was summarized in Chestnut and Dennis (1997), and

6 was also described in the 2004 PM AQCD (U.S. EPA, 2004) and the 2005 OAQPS PM NAAQS Staff

7 Paper (U.S. EPA, 2005b). Since the mid 1990s, little new information has become available regarding

8 urban visibility valuation.

## 9.2.2. Summary of Effects on Individual Organisms and Ecosystems

9 **The evidence is sufficient to infer a causal relationship between ambient PM and effects on**

10 **individual organisms and ecosystems, based on information from the previous review and limited**

11 **new findings in this review.** However, our ability to quantify relationships between ambient

12 concentrations of PM and ecosystem response is hampered by significant data gaps and uncertainties.

13 The PM deposition that can affect individual organisms and ecosystems is not a single pollutant.

14 Rather, PM deposition comprises a heterogeneous mixture of particles differing in origin, size, and

15 chemical composition. The effects of exposure to a given mass concentration of PM of a particular size

16 may, depending on the mix of deposited particles, lead to widely differing phytotoxic responses and

17 ecosystem effects.

18 The deposition of PM onto vegetation and soil, depending on its chemical composition, can

19 produce direct or indirect responses within an ecosystem. The ecosystem response to pollutant deposition

20 is a direct function of the level of sensitivity of the ecosystem and its ability to ameliorate resulting

21 change.

22 Upon entering the soil environment, PM pollutants can alter ecological processes of energy flow

23 and nutrient cycling, inhibit nutrient uptake, change ecosystem structure, and affect ecosystem

24 biodiversity. Many of the most important effects occur in the soil. The soil environment is one of the most

25 dynamic sites of biological interaction in nature. It is inhabited by microbial communities of bacteria,

26 fungi, and actinomycetes. These organisms are essential participants in the nutrient cycles that make

27 elements available for plant uptake. Changes in the soil environment that influence the role of the bacteria

28 and fungi in nutrient cycling determine plant and ultimately ecosystem response.

29 Changes in the soil can result from the deposition of heavy metals. Exposures to heavy metals are

30 highly variable, depending on whether deposition is by wet or dry processes. Few metals (e.g., Cu, Ni,

31 Zn) have been documented to cause direct phytoxicity under field conditions. Exposure to coarse particles

1 of natural origin and elements such as Fe and Mg are more likely to occur via dry deposition, while fine

2 particles of atmospheric origin are more likely to contain elements such as Ca, Cr, Pb, N, and V.

3 Ecosystems immediately downwind of major emissions sources such as power generating, industrial, or

4 urban complexes can receive locally heavy deposition inputs. By negatively affecting litter

5 decomposition, heavy-metal accumulation can adversely influence nutrient cycling (U.S. EPA, 2004).

6 Phytochelatins produced by plants as a response to sublethal concentrations of heavy metals are

7 indicators of metal stress to plants. The increasing concentrations of phytochelatins across regions and at

8 greater elevation associated with gradients in levels of forest injury implicate them in forest decline

9 (U.S. EPA, 2004).

10 The amount of PM entering the immediate plant environment and deposited onto the plant surfaces

11 or soil in the vicinity of the roots, determines the biological effect. Three major routes are involved during

12 the wet and dry deposition processes: (1) precipitation scavenging in which particles are deposited in rain

13 and snow; (2) occult (fog, cloud water, and mist interception) deposition; and (3) dry deposition.

14 Deposition of PM on the surfaces of above-ground plant parts can have physical and/or chemical

15 effects. Particles transferred from the atmosphere to plant surfaces may cause direct effects if they reside

16 on the leaf, twig, or bark surface for an extended period; are taken up through the leaf surface; or are

17 removed from the plant via resuspension to the atmosphere, washing by rainfall, or litter-fall with

18 subsequent transfer to the soil.

19 An important characteristic of fine particles is their ability to affect the flux of solar radiation

20 passing through the atmosphere directly, by scattering and absorbing solar radiation, and, indirectly, by

21 acting as cloud condensation nuclei (CCN) that, in turn, influence the optical properties of clouds.

22 Regional haze has been estimated to diminish surface solar visible radiation by approximately 8%. Crop

23 yields can be sensitive to the amount of sunlight received, and crop losses have been attributed to

24 increased airborne particle levels in some areas of the world.

## 9.2.3. Summary of Effects on Materials

25 **The evidence is sufficient to infer a causal relationship between ambient PM and effects on**

26 **materials.** Building materials (metals, stones, cements, and paints) undergo natural weathering processes

27 from exposure to environmental elements (wind, moisture, temperature fluctuations, sunlight, etc.).

28 Metals form a protective film of oxidized metal (e.g., rust) that slows environmentally induced corrosion.

29 However, the natural process of metal corrosion is enhanced by exposure to anthropogenic pollutants.

30 A significant detrimental effect of particle pollution is the soiling of painted surfaces and other

31 building materials. Soiling changes the reflectance of opaque materials and reduces the transmission of

light through transparent materials. Soiling is a degradation process that requires remediation by cleaning or washing, and, depending on the soiled surface, repainting. Particulate deposition can result in increased cleaning frequency of the exposed surface and may reduce the usefulness of the soiled material. Attempts have been made to quantify the pollutant exposure levels at which materials damage and soiling have been perceived. However, to date, insufficient data are available to advance our knowledge regarding perception thresholds with respect to pollutant concentration, particle size, and chemical composition.

## 9.2.4. Summary of Effects on Climate

**The evidence is sufficient to infer a causal relationship between ambient PM and effects on climate, including both direct effects on radiative forcing and indirect effects that involve cloud feedbacks that influence precipitation formation and cloud lifetimes.** Direct effects are relatively better understood than indirect effects. Aerosol PM can contribute to both atmospheric warming (especially BC) and cooling (most other PM constituents); but the overall net effect is cooling, and this partially counteracts the warming caused by greenhouse gasses. It also appears that PM can result in precipitation suppression downwind of urban pollution sources. Orographic precipitation is disproportionately affected, and this effect is believed to reduce orographic precipitation by up to 25% at some locations in the western U.S.

# 9.3. Effects on Visibility

## 9.3.1. Introduction

In recent years, most visibility research involved characterizing visibility levels and trends, improving our understanding of the atmospheric processes and pollutants responsible for the impacts, and attribution of visibility-impairing pollutants to emission sources, source types, and regions. The motivation for much of this work has come from the visibility protection provisions of the 1977 Clean Air Act Amendments (CAAA) that called for the development of regulations to address reduction of regional haze in 156 national parks and wilderness areas to natural levels, and from the subsequent Regional Haze Rule (RHR) promulgated in 1999 by EPA in response to the CAA mandate. Implementation of the RHR entails planned emissions reductions to reach natural haze levels by 2064 in six ten-year planning steps.

Haze levels caused solely by PM from natural sources are generally much lower than contemporary levels, with the largest difference being between the inorganic salts ammonium sulfate and ammonium

1    nitrate taken to be just a few tenths of a microgram per cubic meter each (Trijonis et al., 1990), while

2    current levels of both over large regions of the country are an order of magnitude or more larger (DeBell,

3    2006). However, natural source PM can be substantial on an episodic basis for crustal mineral PM

4    components during high windblown dust conditions and for carbonaceous PM from biogenic combustion

5    during wildfire and prescribed burning episodes. The need for information to generate RHR

6    implementation plans has resulted in extensive use of continental-scale air quality simulation modeling

7    and assessment of expanded ambient monitoring data sets.

8        Aside from the remote-area visibility investigations conducted in response to the RHR, relatively

9    little work on visibility effects has been done in recent years. However, the relationship between PM and

10   haze levels permits use of routine filter-based PM chemical speciation data collected in numerous urban

11   areas (Jayanty, 2003), as well as high time- and size-resolved PM speciation data available in several

12   cities such as those in the PM Supersites program (Solomon and Hopke, 2008) to improve our

13   understanding of urban visibility. Comparisons between urban and remote areas data in the same region

14   affords the opportunity to differentiate between regional and local visibility impacts. Better size and time

15   resolution PM composition data compared to that available from the routine monitoring programs reduce

16   the number of simplifying assumptions required to estimate visibility levels, thereby reducing the

17   uncertainty of the estimates.

18       There has been relatively little new research on the optical and human perceptual aspects of

19   atmospheric visibility over the last decade or more. These topics have been the subjects of numerous

20   earlier investigations that have been summarized in detail elsewhere (Middleton, 1952; Tombach and

21   McDonald, 2004; Trijonis et al., 1990; U.S. EPA, 1979, 1980; Watson et al., 2002), including past criteria

22   documents on PM, $SO_2$ and $NO_X$ (U.S. EPA, 1982, 1993, 2004).

23       The background section below contains an overview of long-available information to help provide

24   context to the more recently published literature summarized in subsequent sections.

## 9.3.2. Background

25       Air pollution-induced visibility impairment is caused by the loss of image-forming light (i.e.

26   signal) and the addition of non-imaging forming light (i.e. noise) between an observer and the object

27   being viewed. These changes to the light reaching the observer are a result of light being scattered and

28   absorbed by particles and gases in the sight path (see the schematic in Figure 9-1). Electromagnetic theory

29   developed to characterize the interaction of light with matter (Mie, 1908) permits the calculation of light

30   scattering and absorption by particles and gas molecules where the index of refraction and shape of

31   particles by size are known (van de Hulst, 1981).

1    The ability of human observers to visually detect distant objects or identify changes in their

2    appearance depends on the apparent contrast of the object against its background. The apparent contrast is

3    affected by changes in the transparency of the atmosphere caused by air pollution as well as factors not

4    related to air quality such as length of the sight path, scenic lighting and the physical characteristics of the

5    viewed object and other elements of the scene. To rigorously determine the perceived visual effects of

6    changes in the optical properties of the atmosphere requires the use of radiative transfer modeling to

7    determine changes in light from the field of view experienced by the observer, followed by the use of

8    psychophysical modeling to determine the response to the light by the eye-brain system. The complexity

9    of such an approach discourages its common use.
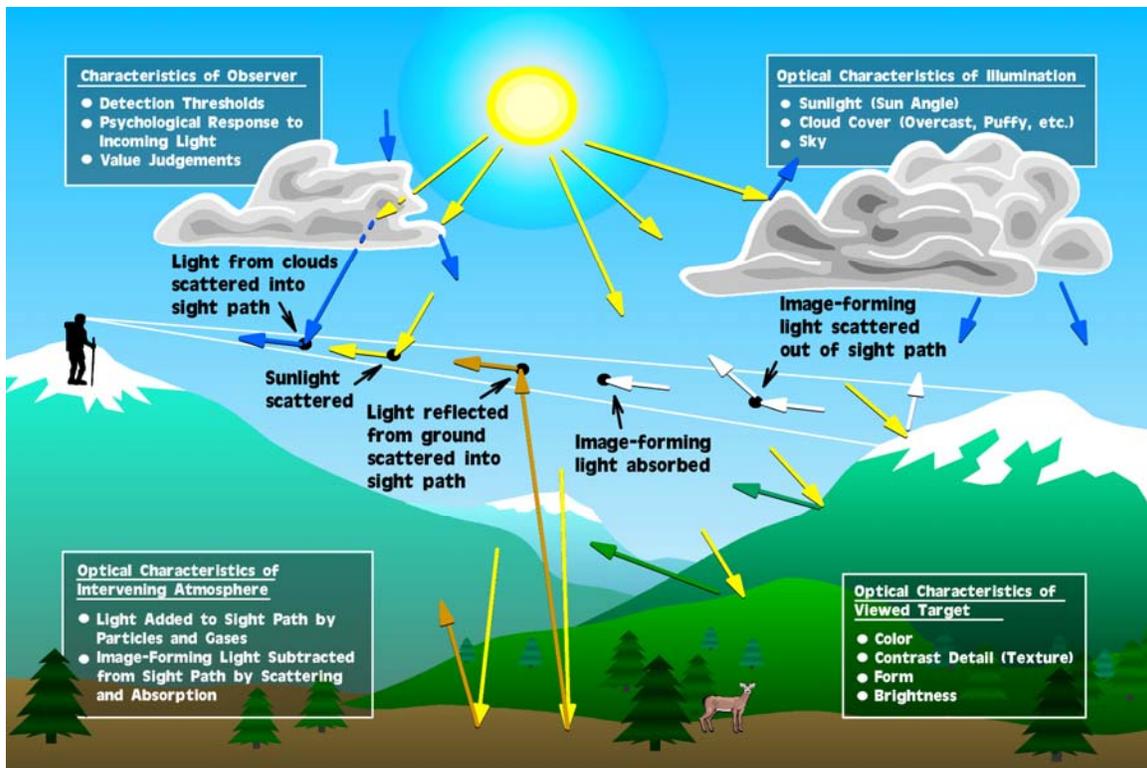


Source: Malm (1983)

**Figure 9-1.    Important factors involved in seeing a scenic vista are outlined. Image-forming information from an object is reduced (scattered and absorbed) as it passes through the atmosphere to the human observer.  Air light is also added to the sight path by scattering processes. Sunlight, light from clouds, and ground-reflected light all impinge on and scatter from particulates located in the sight path. Some of this scattered light remains in the sight path, and at times it can become so bright that the image essentially disappears. A final important factor in seeing and appreciating a scenic vista are the characteristics of the human observer.**

1    Atmospheric light extinction is a fundamental atmospheric optics metric used to characterize air

2    pollution impacts on visibility. It is the fractional loss of intensity in a light beam per unit distance due to

3    scattering and absorption by the gases and particles in the air. Light extinction ($b_{ext}$) can be expressed as

4    the sum of light scattering by particles ($b_{s,p}$), scattering by gases ($b_{s,g}$), absorption by particles ($b_{a,p}$) and

5    absorption by gases ($b_{a,g}$). Light extinction and its components are expressed in units of inverse length,

6    typically either inverse kilometers (km$^{-1}$) or, as will be the convention in this document, inverse

7    megameters (Mm$^{-1}$). Traditionally, for visibility-protection applications, the most sensitive portion of the

8    spectrum for human vision (550 nm) has been used to characterize light extinction and its components.

9    A parametric analysis has shown that a constant fractional change in light extinction results in a

10   similar perceptual change regardless of baseline conditions (Pitchford et al., 1990). From this assessment,

11   the deciview haze index, which is a log transformation of light extinction, similar in many ways to the

12   decibel index for acoustic measurements, was developed (Pitchford and Malm, 1994). A one deciview

13   (1dv) change is about a 10% change in light extinction, which is a small change that is detectable for

14   sensitive viewing situations. The haze index in deciview units is an appropriate metric for expressing the

15   extent of haze changes where the perceptibility of the change is at issue. The regional haze rule has

16   adopted the deciview haze index as the metric for tracking long-term haze trends of visibility-protected

17   federal lands (U.S. EPA, 2001). Light extinction and it components are more useful metrics for

18   characterizing the apportionment of haze to its pollutant components due to the approximately linear

19   relationship between pollutant species concentrations and their contributions to light extinction.

20   Daytime visibility has dominated the perspective taken by those who have studied the visibility

21   effects of air pollution, though nighttime visibility is also know to be impacted by air pollution.

22   Stargazing is a popular human activity in urban and remote settings. The reduction in visibility of the

23   night sky is primarily dependent on the addition of a light into the sight path, the brightness of the night

24   sky, and the reduction in contrast of stars against the background (see the schematic in Figure 9-2). These

25   are controlled by the addition of PM, which enhances scattering, and the addition of anthropogenic light.

26   Scattering of anthropogenic light contributes to the "skyglow" within and over populated areas, adding to

27   the total sky brightness. The visual result is a reduction of the number of visible stars and the

28   disappearance of diffuse or subtle phenomena such as the Milky Way. The extinction of starlight is a

29   secondary and minor effect also caused by increased scattering. Anthropogenic light sources include

30   artificial outdoor lighting, which varies dramatically across space. Natural sources include the Moon,

31   planets, and stars that have a predictable rhythm across time.
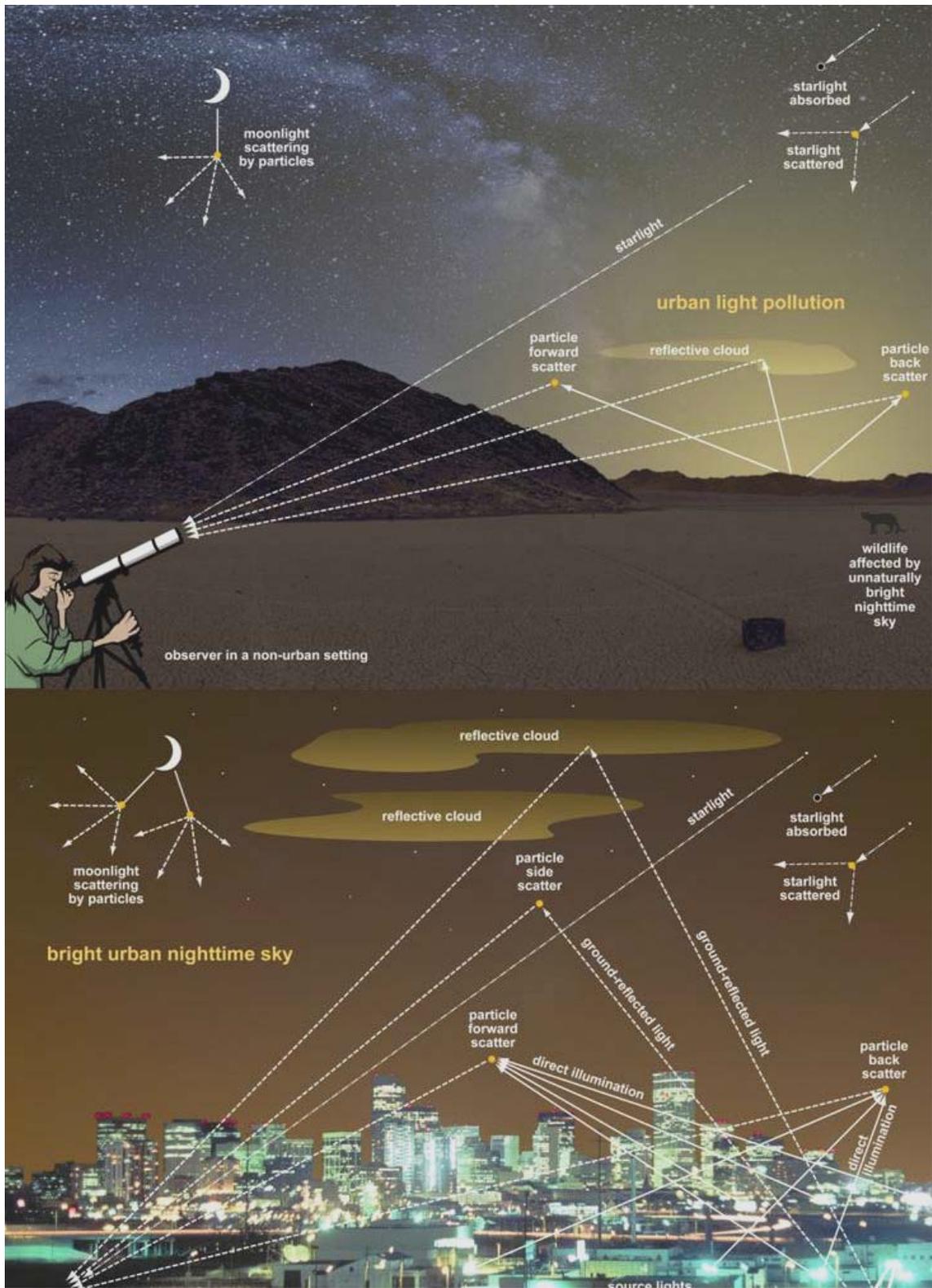
**Figure 9-2.** Schematic of remote-area (top) and urban (bottom) nighttime sky visibility showing the effects of PM and light pollution.

1    The nighttime visual environment has some important differences to note. Light sources and
2    ambient conditions are typically five to seven orders of magnitude dimmer at night than in sunlight.
3    Moonlight, like sunlight, introduces light throughout an observer's sight path at a constant angle. On the
4    other hand, dim starlight emanates from all over the celestial hemisphere while artificial lights are
5    concentrated in cities and illuminate the atmosphere from below. Sight paths are often inclined upward at
6    night as targets may be nearby terrain features or celestial phenomena. Extinction behaves the same at
7    night as during the day, lowering the contrast of scenes through scattering and absorption; nevertheless
8    the different light sources will yield variable changes in visibility as compared to what has been
9    established for the daytime scenario. Little research has been conducted on nighttime visibility. Even if
10   the air quality–visibility interactions are shown to be similar between day and night settings, the human
11   psychophysical response at night is expected to differ. Recent advances in the ability to instrument and
12   quantify nighttime scenes (Duriscoe et al., 2007) can be utilized to evaluate and help establish standards
13   for nocturnal visibility. The remainder of this document focuses exclusively on daytime visibility.

## 9.3.2.1. Non-PM Visibility Effects

14   Light extinction due to the gaseous components of the atmosphere are relatively well understood
15   and well estimated for any atmospheric conditions. Absorption of visible light by gases in the atmosphere
16   is primarily by $NO_2$, and can be directly and accurately estimated from $NO_2$ concentrations by
17   multiplying by the absorption efficiency. Scattering by gases is described by the Rayleigh scattering
18   theory. Rayleigh scattering occurs in a pollution-free atmosphere as a result of light scattering by the gas
19   molecules that compose the atmosphere (i.e. $N_2$, $O_2$, $CO_2$, etc.) and depends on only on the density of the
20   atmosphere, with highest values at sea level (~12 $Mm^{-1}$) and diminishing with elevation (8 $Mm^{-1}$ at ~4
21   km), and varies somewhat at any elevation due to atmospheric temperature and pressure variations.
22   Rayleigh scattering can be accurately determined for any elevation and meteorological conditions.
23       $NO_2$ absorbs more light in the short wavelength blue portion of the spectrum than at longer
24   wavelengths. For this reason a plume or layer of $NO_2$ remove more of the blue light from the scene
25   viewed through the layer giving a yellow or brown appearance to the layer or plume. This filtering of blue
26   light by $NO_2$ can deepen the brown appearance of hazes over urban areas, although it is not the sole cause
27   of such discoloration (U.S. EPA, 1993). The photopic-weighted absorption efficiency at the 550 nm
28   wavelength is incorporated into the revised version of the algorithm for estimating light extinction from
29   aerosol data that is used for implementing the RHR (Pitchford et al., 2007). However, $NO_2$ is not
30   routinely measured at any of the monitoring sites representing visibility protected areas where its impacts
31   are assumed to be inconsequential compared to those of PM. At background concentrations $NO_2$
32   absorption is generally less than five percent of the light scattering by clean air (Rayleigh scattering),

1   making it unperceivable. Plume visibility models are available to assess both achromatic and

2   discoloration associated with $NO_2$ light absorption, for point source emissions (Seigneur et al., 1984;

3   U.S. EPA, 1980).

## 9.3.2.2. PM Visibility Effects

4   Particle light extinction is more complex than that caused by gaseous components. PM is

5   responsible for most visibility impairment except under near-pristine conditions, where Rayleigh

6   scattering is the largest contributor to light extinction or in plumes of combustion sources that are

7   well-controlled for particulate emissions (e.g. coal-fired power plants with bag houses), where light

8   absorption by $NO_2$ may dominate the light extinction.

9   Light-absorbing carbon (e.g., diesel exhaust soot and smoke) and some crustal minerals are the

10  only commonly occurring airborne particle components that absorb light. All particles scatter light, and

11  generally particle light scattering is the largest of the four light extinction components. While a larger

12  particle scatters more light than a similar shaped smaller particle of the same composition, the light

13  scattered per unit of mass concentration [i.e. mass scattering efficiency in units of $Mm^{-1}/(\mu g/m^3)$ which

14  reduces to $m^2/g$] is greatest for particles with diameters from about 0.3 to 1.0 μm. If the index of

15  refraction, particle shape and concentration as a function of particle size are well characterized, Mie

16  theory can be used to accurately calculate the light scattering and absorption by those particles. However,

17  it is rare that these particle properties are known, so assumptions are used in place of missing information

18  to develop a simplified calculation scheme that provides an estimate of the particle light extinction from

19  available data sets.

20  Particles composed of water soluble inorganic salts (i.e. ammoniated sulfate, ammonium nitrate,

21  sodium chloride, etc.) are hygroscopic in that they absorb water as a function of relative humidity to form

22  liquid solution droplet. Aside from the chemical consequences of this water growth, the droplets become

23  larger when relative humidity increases resulting in increased light scattering, hence the same PM dry

24  concentration produces greater haze levels. Figure 9-3 shows the effect of water growth as a function of

25  relative humidity on light scattering for two size distributions of ammonium nitrate and ammonium

26  sulfate particles as well as for internal and external mixtures (i.e. mixed within the same particle and in

27  separate particles respectively) of the two components. This figure illustrates a number of important

28  points. The water growth effect is substantial with an increase in light scattering by about a factor of ten

29  between 40% and 97% relative humidity for the same dry particle concentrations. The amount of

30  scattering is significantly dependent on the dry particle size distribution. However the growth curves for

31  ammonium sulfate, ammonium nitrate and mixtures of the two components are similar at any of

1    the dry particle size distributions. Water growth curves are also available for sodium chloride, the major

2    component in sea salt, which is an important PM component at coastal locations.
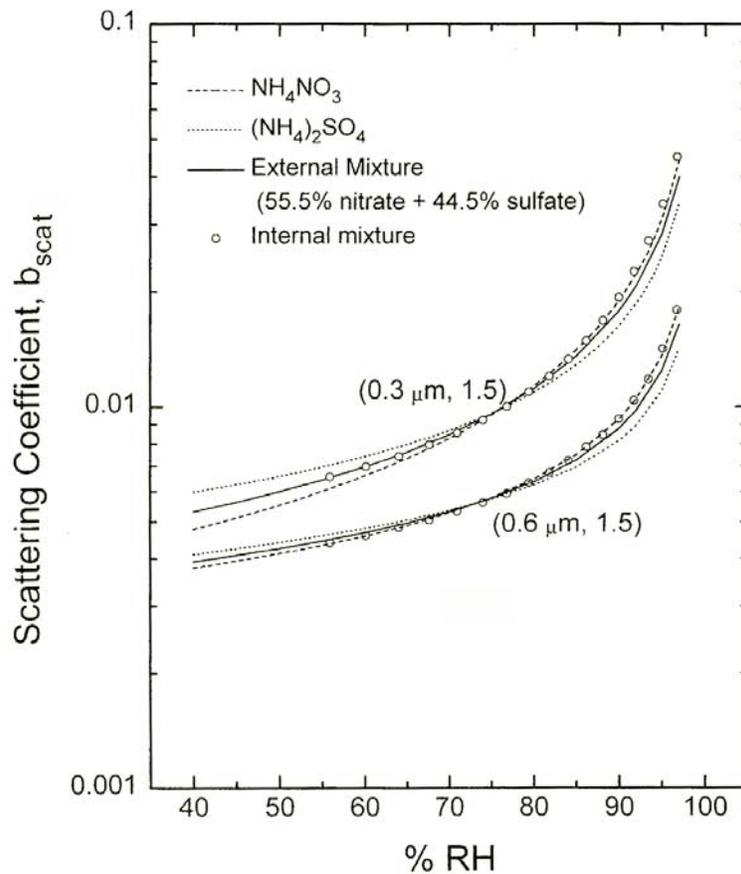


Source: Tang (1996)

**Figure 9-3.**    **Effect of relative humidity on light scattering by mixtures of ammonium nitrate and ammonium sulfate.**

3        PM light scattering can be accurately calculated for any relative humidity if the chemical

4    composition as a function of dry particle size is known (Malm et al., 2007). However, most routinely

5    available ambient monitoring programs do not include data with sufficient detail to make such

6    calculations. The IMPROVE network with its greater than 150 remote area monitoring sites (DeBell,

7    2006) and the CSN (Jayanty, 2003) with its greater than 150 urban area monitoring sites collect 24-h

8    duration fine particle samples ($PM_{2.5}$) that are analyzed for the major components including sulfate and

9    nitrate by ion chromatography. CSN also analyzes for ammonium ion, but does not monitor coarse mass

10   ($PM_{10-2.5}$), while IMPROVE measures coarse mass but does not analyze for ammonium ion. Neither data

11   set has sufficient size resolution to make theoretical calculations of light extinction, nor does either

1    program routinely monitor $NO_2$ concentrations, which would be required to calculate its contribution to

2    light extinction by absorption.

3         A simple algorithm is frequently used to estimate light extinction from the concentrations of the

4    major components. The concentration of each of the major aerosol components is multiplied by a dry

5    extinction efficiency value and for the hygroscopic components (e.g. ammoniated sulfate and ammonium

6    nitrate) an additional multiplicative term to account for the water growth to estimate that components

7    contribution to light extinction. Both the dry extinction efficiency and water growth terms are developed

8    by some combination of empirical assessment and theoretical calculation using typical particle size

9    distributions associated with each of the major aerosol components, and they are evaluated by comparing

10   the algorithm estimates of light extinction with coincident optical measurements. Summing the

11   contribution of each component gives the estimate of total light extinction. The most commonly used of

12   these is referred to as the IMPROVE algorithm because it was developed specifically to use the

13   IMPROVE aerosol monitoring data and was evaluated using IMPROVE optical measurements at the

14   subset of sites that make those measurements (Sisler et al., 1996). The formula for the traditional

15   IMPROVE algorithm is shown below.

$$
\begin{aligned}
b_{ext} \approx\ &3 \times f(RH) \times [Sulfate] \\
&+ 3 \times f(RH) \times [Nitrate] \\
&+ 4 \times [Organic\ Mass] \\
&+ 10 \times [Elemental\ Carbon] \\
&+ 1 \times [Fine\ Soil] \\
&+ 0.6 \times [Coarse\ Mass] \\
&+ 10
\end{aligned}
$$

(9-1)

16   Light extinction ($b_{ext}$) is in units of $Mm^{-1}$, the mass concentrations of the components indicated in

17   brackets are in $\mu g/m^3$, and $f(RH)$ is the unitless water growth term that depends on relative humidity.

18   Since IMPROVE doesn't include ammonium ion monitoring, the assumption is made that all sulfate is

19   fully neutralized ammonium sulfate and all nitrate is assumed to be ammonium nitrate. Though often

20   reasonable, neither assumption is always true. In the eastern U.S. during the summer there is insufficient

21   ammonia in the atmosphere to neutralize the sulfate fully. Fine particle nitrates can include sodium or

22   calcium nitrate, which are the fine particle fraction of generally much coarser particles due to nitric acid

23   interactions with sea salt at near-coastal areas (sodium nitrate) or nitric acid interactions with calcium

24   carbonate in crustal aerosol (calcium nitrate) (Lee et al., 2008; Malm and Hand, 2007). Despite the

25   simplicity of the algorithm, it performs reasonably well and permits the contributions to light extinction

1    from each of the major components (including the water associated with the sulfate and nitrate

2    compounds) to be separately estimated.

3         The *f(RH)* term inflate the particulate sulfate and nitrate light scattering for high relative humidity

4    conditions. For relative humidity below 40% the *f(RH)* value is 1, but it increases to 2 at ~66%, 3 at

5    ~83%, 4 at ~90%, 5 at ~93% and 6 at ~95% relative humidity. The result is that both particulate sulfate

6    and nitrate are more efficient per unit mass than any other aerosol component for relative humidity above

7    ~85% where its total light extinction efficiency exceeds the $10m^2/g$ associated with EC. Based on this

8    algorithm, particulate sulfate and nitrate are estimated to have comparable light extinction efficiencies

9    (i.e. the same dry extinction efficiency and *f(RH)* water growth terms), so on a per unit mass

10   concentration basis at any specific relative humidity they are treated as equally effective contributors to

11   visibility impacts.

## 9.3.3. Effects on Visibility

## 9.3.4. Monitoring and Assessment

12        Monitoring and the assessment of monitoring data serve a number of goals with regard to the

13   visibility effects of PM, including improving our understanding of the physio/chemical/optical properties

14   of the aerosol, characterizing spatial and temporal air quality patterns, and assessing the causes

15   (i.e. pollution sources and atmospheric processes) that are responsible for visibility impairment.

16   Information generated by special studies employing sophisticated instrumentation are typically needed to

17   advance our understanding of aerosol properties, while characterizing trends is the product of analyzing

18   routine monitoring data, whereas assessing the causes of haze usually involves a weight-of-evidence

19   approach applied to special study and/or routine monitoring data sets plus the use of air quality simulation

20   modeling. This section summarizes recently available information that is based on monitoring data.

### 9.3.4.1. Aerosol Properties

21        Particle size is the most influential physical property of aerosol with respect to their dry light

22   extinction efficiency. Chemical composition by size is used to ascertain density (needed to convert

23   aerodynamic to physical size) and to identify the water growth characteristics of the aerosol (needed to

24   calculate the particle size at ambient RH). To characterize aerosol properties of interest for visibility

25   effects, field monitoring programs typically include particle size distribution monitoring, high size

26   resolution particle sampling with subsequent compositional analysis, and optical monitoring. These

1   generate data that permit optical closure assessments where the light scattering and/or light extinction

2   estimates from the aerosol data are compared to corresponding optical data. Since component

3   contributions to visibility are generally assessed by applying the IMPROVE or some similar algorithm to

4   measured or modeled aerosol concentration data, this section will include recent investigations that

5   evaluate or address various assumptions inherent in the use of these simple algorithms.

6       One component of the Big Bend Regional Aerosol and Visibility Observational (BRAVO) Study,

7   conducted at Big Bend National Park, TX in the summer and fall of 1999, entailed use of detailed

8   measurements of aerosol chemical composition, size distribution, water growth, and optical properties to

9   characterize the aerosol and assess the relationship between aerosol physical, chemical and optical

10  properties (Schichtel et al., 2004). Fine ammoniated sulfate during the BRAVO Study was about half the

11  fine particle mass concentration and was shown to be responsible for about 35% of the light extinction.

12  Rayleigh scattering was the second largest contributor at about 25%, followed by coarse particle (about

13  18%), and organic compounds (about 13%). There was little fine particle nitrate (less than 5% of the mass

14  concentration) and most of it is apparently in the form of sodium nitrate and two thirds of it was found in

15  the coarse mode where it comprises about 8% of the coarse particle mass concentration. Both the

16  composition of the nitrate and the fact of much of it being in the coarse size mode (2.5 μm >D>10 μm)

17  are inconsistent with the implied assumptions of the IMPROVE algorithm.

18      A year-long special study of coarse particle speciation was conducted at nine IMPROVE remote

19  area monitoring sites during 2003 to 2004 to provide additional information about the geographic and

20  seasonal variations in coarse particle composition (Malm et al., 2007). The same sampling and analytical

21  methodologies procedures were used for the $PM_{10}$ samples as are routinely used on the IMPROVE $PM_{2.5}$

22  samples. The IMPROVE coarse particle speciation study did not include ammonium analysis, so sulfate

23  and nitrate ions were assumed to be ammonium sulfate and ammonium nitrate. As expected crustal

24  minerals were the largest contributors to coarse mass overall (about 60%), though at Mt. Rainier the

25  fraction of coarse PM that was organic exceeded the crustal mineral by nearly two to one (i.e. 59.2%

26  compared to 33.5%) On average across sites the organic particulate contributed significantly at about one

27  quarter of the coarse mass, while ammonium nitrate was the third largest contributor to coarse mass

28  (about 8%). Seas salt was negligible overall, but high at the one coastal site (i.e. 12% at Brigantine, NJ).

29  The sites with the highest coarse nitrate concentrations are the two in California (San Gorgonio,

30  0.74 μg/m$^3$ and Sequoia, 0.69 μg/m$^3$) where fine nitrates are also high on average (2.66 μg/m$^3$ and

31  2.14 μg/m$^3$ respectively). Brigantine, a coastal site in New Jersey had the highest fraction of total nitrate

32  in the coarse size range (36%). The authors speculate that Brigantine's particulate nitrate is likely sodium

33  nitrate, the result of nitric acid reactions with sodium chloride. The nine-site average fraction of total

1    nitrate in the coarse size range is 26%. By contrast, coarse sulfate concentrations are small with only

2    about ~1% of the total sulfate in the coarse fraction.

3        Routine IMPROVE monitoring data include the mass concentration, but not the composition of the

4    coarse PM fraction, so the algorithm used to estimate light extinction doesn't include any provision for

5    varied coarse PM composition as shown in this study. This study shows that about 10% of the coarse

6    mass across the nine monitoring sites is composed of hygroscopic materials (i.e. ammonium sulfate,

7    ammonium nitrate and sea salt), which during high humidity conditions will scatter more light than

8    estimated by the current algorithm (e.g. ~20% bias at ~90% relative humidity). However, at coastal sites

9    such as the Brigantine, NJ, IMPROVE site where the combined concentration of the inorganic salts (i.e.

10   sea salt, nitrate and sulfate) constitute a significant fraction (~24% on average) of the coarse mass

11   concentration, the IMPROVE algorithm underestimation of light extinction by coarse PM can be

12   significant for high relative humidity conditions (~60% at ~90% relative humidity). The resulting

13   underestimation of total light extinction is typically much smaller since fine particle light extinction

14   generally exceeds that contributed by coarse particles. Another issue with regard to estimating light

15   extinction from coarse PM concentration when the composition is not crustal minerals, as has been

16   assumed, has to do with the lower average density of the coarse mode particles that results in greater

17   particle numbers and/or larger particles and therefore a greater light extinction efficiency (Malm and

18   Hand, 2007).

19       Special studies with more complete, higher time resolution and size resolved particulate inorganic

20   ion species chemistry and precursor gases were conducted at seven of the nine sites with IMPROVE

21   coarse particle speciation monitoring (Lee et al., 2008). This work confirmed the presence of sodium and

22   calcium nitrate (referred to as mineral nitrate) primarily in the coarse particle size range in addition to fine

23   particle ammonium nitrate where low temperatures, high humidity and excess ammonium (beyond that

24   required to neutralize the particulate sulfate) favored particle phase equilibrium. Figure 9-4 is a map

25   showing the locations and sample times and estimated composition of the total particulate nitrate for the

26   seven locations for this special study. Sites with a high fraction of ammonium nitrate (e.g. San Gorgonio,

27   Bondville, and Brigantine) have the highest nitrate contributions to total mass concentration and haze

28   levels, whereas sites with high mineral nitrates tend to have low total nitrate contributions. This work

29   shows that the common assumption that particulate nitrate are in the fine particle size range and consists

30   principally of ammonium nitrate is not necessarily true.
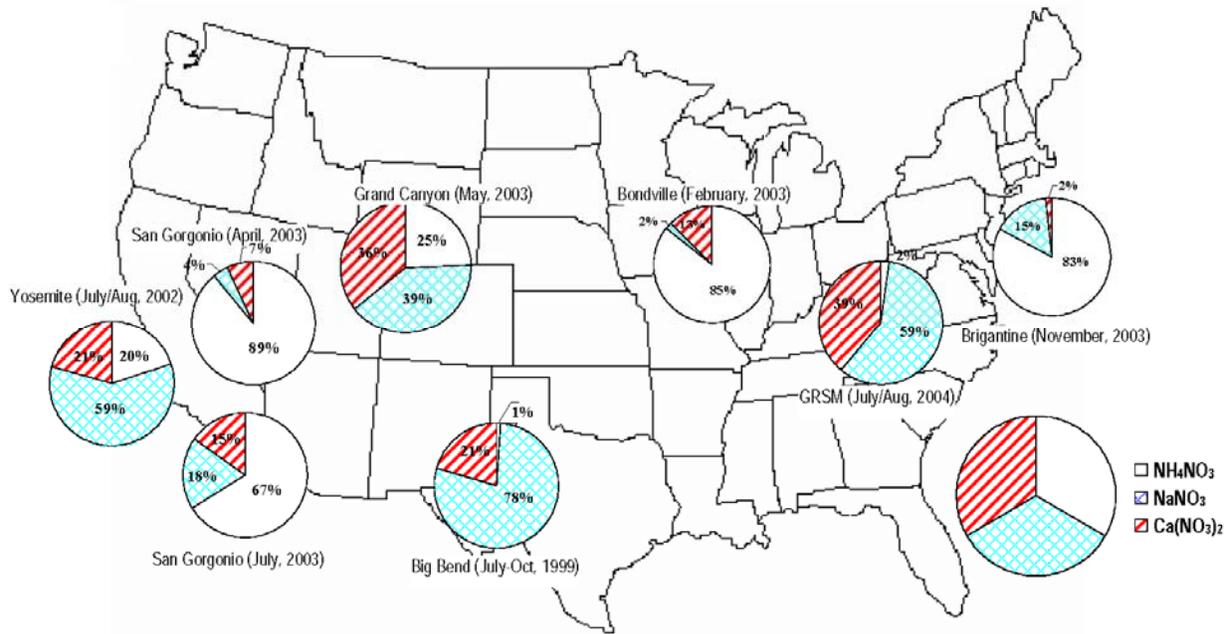
**Figure 9-4.** **Estimated fractions of total particulate nitrate during each field campaign comprised of ammonium nitrate, reacted sea salt nitrate (shown as NaNO$_3$), and reacted soil dust nitrate (shown as Ca(NO$_3$)$_2$).**

1    Extinction efficiencies for individual particle species can be theoretically calculated from

2    sized-resolved aerosol measurements and can be inferred using multiple linear regression applied to

3    aerosol composition and light extinction measurement data. In a recent publication, Hand and Malm

4    (2007) reviewed the literature since 1990 in which aerosol mass scattering efficiency values were

5    calculated or inferred. From these they have compiled normalized dry scattering efficiency values for the

6    individual species. Based on 93 separate determinations including marine, remote continental and urban

7    areas data sets, the average dry mass scattering efficiency for ammonium sulfate is $2.5 \pm 0.6$ m$^2$/g.

8    Average values tended to be somewhat lower for the marine aerosol ($\sim$2 m$^2$/g) than for remote continental

9    ($\sim$2.7 m$^2$/g) and urban (2.6 m$^2$/g) areas, and values also tended to be lower for fairly clean arid locations

10    compared with more humid polluted areas.

11    Based on 48 separate determinations including remote area and urban area data sets, the average

12    dry mass scattering efficiency for ammonium nitrate is $2.7 \pm 0.5$ m$^2$/g (Hand and Malm, 2007). Average

13    values were higher in remote locations ($2.8 \pm 0.5$ m$^2$/g) compared to urban locations ($2.2 \pm 0.5$ m$^2$/g)

14    though this might be accounted for by the predominate use of multiple linear regression for the remote

15    areas, which can be biased high, compared to the use of theoretical calculations for the urban data sets.

1      Organic fine PM extinction efficiency of 3.9+1.5 m2/g is based on 58 separate determinations,

2      though much higher values (~6 $m^2$/g) resulted for locations influenced by industrial and biomass

3      combustion sources (Hand and Malm, 2007). These organic fine PM extinction efficiency values were

4      adjusted to use a consistent ratio of organic mass to organic carbon of 1.8 for each determination of the

5      mass concentration. This value is generally associated with aged organic PM, while for more freshly

6      emitted PM, such as in an urban environment, a smaller ratio (e.g. 1.4) would be more appropriate. This

7      could explain the discrepancy between two approaches used to estimate the organic PM light extinction

8      efficiency for Phoenix (Hand and Malm, 2006), which resulted in a significantly lower value where a site

9      specific regression method was used compared to the value obtained from a method optimized for

10     remote-area monitoring (2.47$m^2$/g compared to 3.71 $m^2$/g). However in Fresno both the mass balance and

11     light scattering balance was improved by using a ratio of 1.8 instead of 1.4 to estimate the organic

12     compound mass (Watson et al., 2007). Another possible or partial factor with respect to urban light

13     extinction efficiency for organic PM may be that the size distribution of freshly emitted organic PM in

14     urban areas extends significantly into the ultra-fine particle size range (Demerjian and Mohnen, 2008)

15     that is less efficient per mass concentration at light scattering than the generally larger-sized aged organic

16     PM such as from a distant forest fire as was measured at the Baltimore Supersite.

17      Hand and Malm (2007) also reviewed and made recommendation for extinction efficiencies for the

18     other components PM components including for mixed coarse mode (1.0 ± 0.9 $m^2$/g based on 51

19     determinations) and fine mode dust or soil (3.3 ± 0.6 $m^2$/g based on 23 determinations, but recommending

20     1.0 $m^2$/g for use with data from realistic collection efficiency samplers) and fine sea salt (4.5 ± 0.9 $m^2$/g

21     based on 25 determinations, but recommending 1.0 $m^2$/g to 1.3 $m^2$/g for use with data from realistic

22     collection efficiency samplers). This work did not address light absorption efficiency of elemental (or

23     black) carbon or crustal PM.

24      The Hand and Malm (2007) average dry mass light scattering efficiency values are generally

25     consistent with the values for the IMPROVE algorithm (as shown in equation 9-1). However the adoption

26     of the IMPROVE algorithm by EPA for calculating the haze metric used to track trends and assess the

27     nominal pace of progress for the Regional Haze Rule (U.S. EPA, 2001) resulted in much greater scrutiny

28     of its performance in estimating extinction (Lowenthal and Kumar, 2003; Malm and Hand, 2007; Ryan et

29     al., 2005). Among the issues raised is that the algorithm tended to underestimate the light extinction for

30     the haziest conditions that occur principally during the summer in the southeastern U.S. and overestimate

31     for near pristine conditions that tend to occur most often in the arid western U.S. Furthermore they

32     showed the lack of mass or light scattering closure at coastal sites due to sea salt that was not accounted

33     for by the IMPROVE algorithm. These assessments used mass concentration and light extinction closure

34     and regression analysis methods to infer that the dry extinction efficiency for the major fine particle

1   components would need to vary in order to avoid the biased estimates of light extinction at the extremes.

2   Theoretical calculations of sulfate dry extinction efficiencies for 41 days of size-resolved chemical

3   composition data for Big Bend, Texas as part of the BRAVO Study produced a range of results from ~2.4

4   m$^2$/g to ~4.1 m$^2$/g, with the larger dry extinction efficiency values tending to be associated with higher

5   ammonium sulfate mass concentration and narrower size distributions (Schichtel et al., 2004).

6          In response to the technical concerns raised about the performance of the IMPROVE algorithm, a

7   revised algorithm was developed (Pitchford et al., 2007). The revised version of the algorithm differs

8   from the original algorithm by including a fine sea salt term related to the measured chloride ion

9   concentration, increases by about 30% the mass concentration of the organic aerosol component by

10  changing the ratio of organic compound mass to organic carbon mass from 1.4 to 1.8, uses site elevation

11  dependent Rayleigh scattering in place of 10Mm$^{-1}$ that had been used at every site, added a $NO_2$ light

12  absorption term and employs a split component model for the secondary particulate components (i.e.

13  sulfate, nitrate and organic species) with new water growth terms to better estimate their extinction at the

14  high and low extremes of the range. The revised algorithm is displayed below in equation 9-2 where bold

15  type face indicates terms that differ from the original IMPROVE algorithm (equation 9-1).

$$
\begin{aligned}
b_{ext} \approx\ & 2.2 \times f_s(RH) \times [\textit{Small Sulfate}] + 4.8 \times \mathbf{f_L(RH)} \times [\textbf{\textit{Large Sulfate}}] \\
& + 2.4 \times f_s(RH) \times [\textit{Small Nitrate}] + 5.1 \times \mathbf{f_L(RH)} \times [\textbf{\textit{Large Nitrate}}] \\
& + 2.8 \times [\textit{Small Organic Mass}] + 6.1 \times [\textbf{\textit{Large Organic Mass}}] \\
& + 10 \times [\textit{Elemental Carbon}] \\
& + 1 \times [\textit{Fine Soil}] \\
& + 1.7 \times \mathbf{f_{ss}(RH)} \times [\textbf{\textit{Sea Salt}}] \\
& + 0.6 \times [\textit{Coarse Mass}] \\
& + \textit{Rayleigh Scattering} \ (\textbf{\textit{Site Specific}}) \\
& + \mathbf{0.33 \times [NO_2\ (ppb)]}
\end{aligned}
$$

<div align="right">(9-2)</div>

16         Small and large sulfate, nitrate and organic mass are used to refer to the splitting of the

17  concentrations of each of those three species into two size distributions. This approach accounts for

18  increased light extinction efficiency with mass by using a simple mixing model that assume that each of

19  these three components are comprised of an external mixture of small and large particle size modes.

20  Conceptually, the large mode particles represent aged or cloud-processed aerosol, while the small mode

21  particles represent relatively newly generated particles from the gas phase precursors. The former are

22  more likely to be associated with high concentrations while the latter are likely to be at relatively low

23  concentration.

1    The geometric mean diameter and standard deviations assumed for these two size modes are

2    0.5 μm and 1.5 for the large mode particles and 0.2 μm and 2.2 for the small mode particles. Mie theory

3    applied to these size distributions for the three species results in dry extinction efficiencies for the small

4    and large mode ammonium sulfate (2.2 m$^2$/g and 4.8 m$^2$/g), ammonium nitrate (2.4 m$^2$/g and 5.1 m$^2$/g)

5    and organic mass (2.8 m$^2$/g and 6.1 m$^2$/g). Water growth terms specifically derived for the small and large

6    size distribution using the upper branch of the hygroscopic growth curves for ammonium sulfate are

7    applied to both the sulfate and nitrate PM. No water growth is assumed for organic PM.

8    A simple empirically developed apportionment approach that was evaluated by testing the new

9    algorithms estimated light scattering at the 21 IMPROVE sites that have nephelometer-measured light

10    scattering data. The fraction of the fine particle component (sulfate, nitrate, or organic mass) that is in the

11    large mode is calculated by dividing the total concentration of the component by 20 μg/m$^3$ (e.g. if the total

12    fine particle nitrate concentration is 4 μg/m$^3$, the large mode concentration is 1/5 of 4 μg/m$^3$ or 0.8 μg/m$^3$,

13    leaving 3.2 μg/m$^3$ in the small mode). If the total concentration of a component exceeds 20 μg/m$^3$, all of it

14    is assumed to be in the large mode.

15    The performance of the original and revised IMPROVE algorithms was evaluated using the data

16    for 21 IMPROVE remote-area monitoring sites that also have nephelometer monitoring of particle light

17    scattering. Figures 9-5 and 9-6 are scatterplots of the estimated versus measured light scattering for the

18    two algorithms. The revised algorithm has noticeably reduced bias at the upper and lower extremes.

19    However, the new algorithm estimates have somewhat reduced precision (i.e., the points are more broadly

20    scattered). States have adopted the new algorithm for the technical assessments that support their

21    Regional Haze Rule State Implementation Plans, but the revised algorithm was too recently developed to

22    be incorporated into any of the peer-reviewed technical literature reported on below. In general the

23    differences resulting from use of the original versus the revised IMPROVE algorithm in identifying best

24    and worst haze conditions and the apportionment of the various PM components are small with exception

25    of coastal locations where sea salt may be a significant contributor.
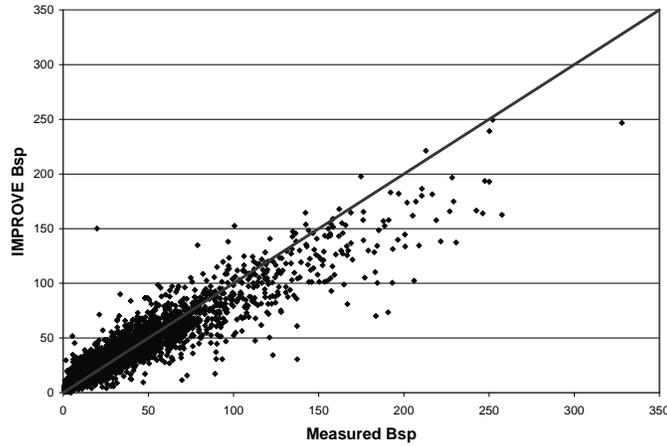
**Figure 9-5.    A scatter plot of the original IMPROVE algorithm estimated particle light scattering versus measured particle light scattering.**
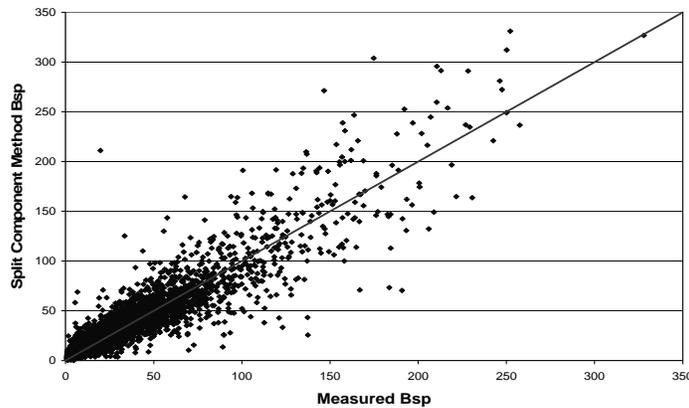
**Figure 9-6.    Scatter plot of the revised algorithm estimates of light scattering versus measured light scattering.**

## 9.3.4.2. Spatial Patterns

1    The IMPROVE network is the basis for much of what is known about particulate species spatial

2    and temporal patterns for remote areas of the U.S. Though IMPROVE includes some urban monitoring

3    sites, most of what is known about urban particle speciation trends is based on the EPA Speciation Trend

4    Network (STN) and other similarly operated state particle speciation sites jointly referred to as the

5    Chemical Speciation Network (CSN) (Jayanty, 2003). The number of IMPROVE network sites has

6    increased considerably beginning in 2000, first to increase its ability to generate data representative of the

7    156 visibility-protected national parks and wilderness areas, then later as the states in the central U.S.

1    requested additional remote-area monitoring to better understand their contributions to regional haze. The

2    expansion of the network into the central U.S. significantly improved our understanding of spatial trends

3    in a region of the country that had little speciation monitoring. Except as otherwise noted most of the

4    information in this section was from the IMPROVE Report IV (DeBell, 2006) and displays of data that

5    are readily generated using the Visibility Information Exchange Web Site (VIEWS). VIEWS, the ambient

6    monitoring data system, is one of several websites (as described in Table 9-1) sponsored by the Regional

7    Planning Organizations (RPO) that documents substantial, though often otherwise unpublished, technical

8    information generated to support implementation of the Regional Haze Rule.

**Table 9-1.    Regional Planning Organization websites with visibility characterization and source attribution assessment information.**

| Type of Information | Name and Web Address | RPO | Information Content and Comments |
|---|---|---|---|
| RPO Home Pages | Western Regional Air Partnership http://www.wrapair.org/ | WRAP | Organizational structure, plans, projects, reports and links to other sites with additional information. |
| | Central Regional Air Planning Association http://www.cenrap.org/ | CENRAP | MANE-VU works in close cooperation with Northeast States for Coordinated Air Use Management (NESCAUM) and Mid-Atlantic Regional Air Management Association (MARAMA) to develop the technical information for Regional Haze Rule in the Northeast. All three web sites contain unique technical support information. |
| | Midwest Regional Planning Organization http://64.27.125.175/mrpo.html | MRPO | |
| | Visibility Improvement State and Tribal Association of the Southeast http://www.vistas-sesarm.org/ | VISTAS | |
| | Mid-Atlantic/Northeast Visibility Union http://www.manevu.org/ http://www.nescaum.org/topics/regional-haze http://www.marama.org/visibility/ | MANE-VU NESCAUM MARAMA | |
| Visibility - Air Quality Monitoring Data | Visibility Information Exchange Web Site http://vista.cira.colostate.edu/views/ | All RPOs | All IMPROVE and most other PM speciation data, RHR compatible derived parameters, and user-friendly tools to summarize and display data. |
| Emission Inventory Data | Emissions Data Management System http://www.wrapedms.org/default_login.asp | WRAP | WRAP emission inventory data warehouse and tools that provides a consistent approach to regional emissions tracking |
| Monitoring Data Assessment | Causes of Haze Assessment http://www.coha.dri.edu/ | WRAP CENRAP | Monitoring site-specific descriptive characterizations and maps, seasonal and trends analysis, air flow analysis, & receptor modeling. |
| Visibility Modeling | U. of California-Riverside Modeling Center http://pah.cert.ucr.edu/aqm/308/ http://pah.cert.ucr.edu/aqm/cenrap/index.shtml http://pah.cert.ucr.edu/vistas/ | WRAP CENRAP VISTAS | Descriptions of input data, performance, and results of regional scale modeling (CMAQ & CAMx) & source attribution for base and future year regional haze. |
| Integrated Information to Support RHR SIP Preparations | Technical Support System http://matar.cira.colostate.edu/tss/ | WRAP | Provides access and common formats to display and summarize emissions inventory information, monitoring data/ assessment and regional haze modeling result to aid state and tribal analyst prepare RHR implementation plans. |

1    Figure 9-7 shows maps of remote area light extinction estimates from PM speciation data for two

2    years selected to demonstrate the additional information available due to the expansion of the IMPROVE

3    network into the central U.S. The locations of monitoring sites supplying the data shown as color contours

4    are shown as dot on the maps. Users of such contour maps are usually cautioned that the contours are only

5    there to guide the eye to sites with similar measurements and that nothing should be implied about spatial

6    patterns where there are no monitoring sites. Certainly these plots give proof to the wisdom of such

7    warnings. Prior to 2001 there were no IMPROVE or any other remote-area aerosol speciation monitoring

8    sites in the central states between northern Minnesota and Michigan to the north and Arkansas and

9    Kentucky to the south. The lack of monitoring over such a large region in the center of the country hid the

10   presence of high average regional haze levels over the Midwestern U.S. Smaller scale differences are seen

11   in the rest of the country and some of those are due to interannual variations as well as to better spatial

12   resolution made possible by a more dense monitoring network.
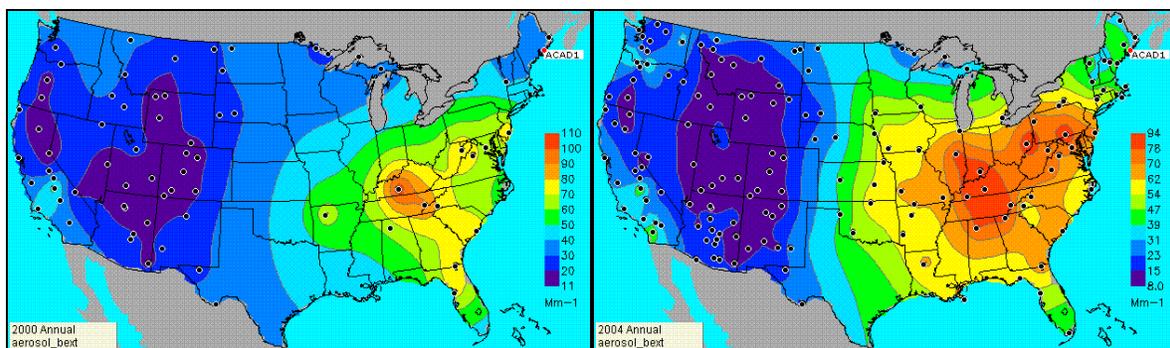


Source: VIEWS (http://vista.cira.colostate.edu/views/)

**Figure 9-7.    IMPROVE network PM species estimated light extinction for 2000 (left) and for 2004 (right).**

13   Figure 9-8 shows the seasonal pattern of PM species estimated light extinction using maps of mean

14   values for each of the calendar quarter for 2004. The first quarter has the highest region of haze centered

15   in the Midwestern U.S.; the warmer second and third quarters have the region of highest haze over the

16   Ohio River Valley; and the fourth quarter is a composite with high haze in both the Midwest and Ohio

17   River Valley. Smaller regions of haze show up in the Columbia River Valley (border between Washington

18   and Oregon) in the colder first and fourth quarters and in Southern California in the warmer second and
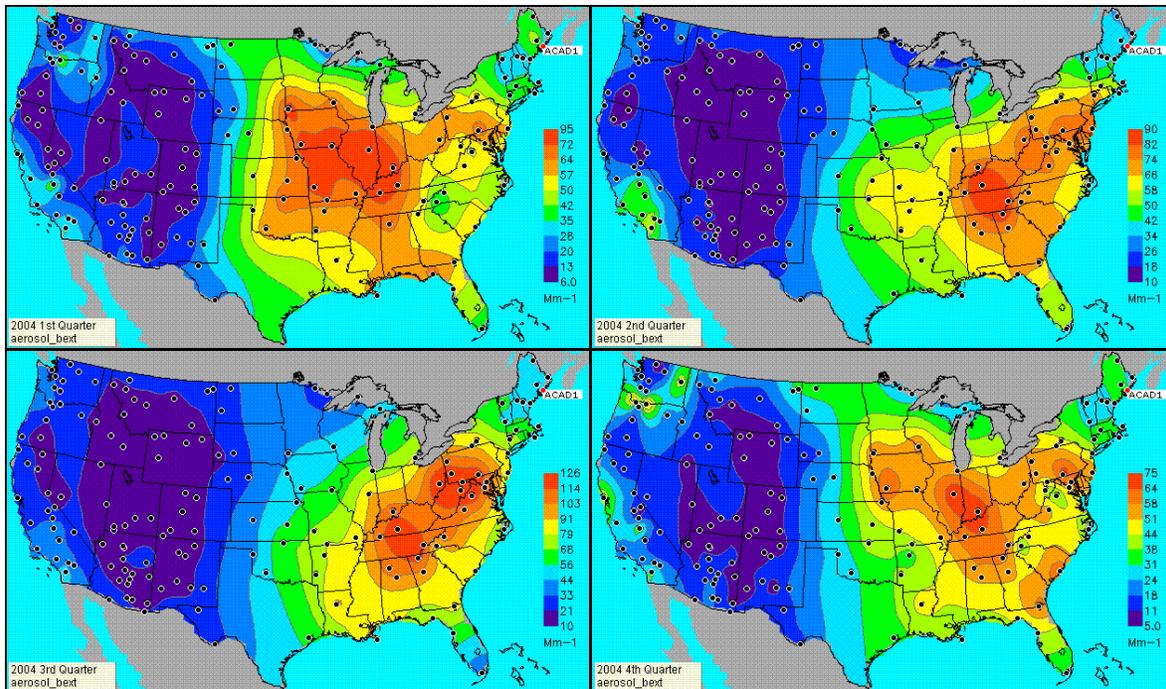
19   third quarters.

**Figure 9-8.    Mean estimated light extinction from PM speciation measurements for the first (top left), second (top right), third (bottom left), and fourth (bottom right) calendar quarters of 2004.**

1    The IMPROVE algorithm permits each PM component contribution to light extinction to be
2    separately estimated. Figures 9-9, 9-10 and 9-11 display the seasonal variation of the percent contribution
3    to aerosol light extinction by the various component-estimates. Figure 9-9 shows the contributions by
4    sulfate and nitrate particulate including the haze enhancement caused by the absorbed water in humid
5    conditions. As shown in Figures 9-9, a large regional pattern of high contribution to haze by nitrate PM is
6    centered in the Midwest, and during the cooler months the nitrate PM is the dominant cause of haze in the
7    region responsible for a third to a half of the particulate light extinction. Midwestern particulate nitrate is
8    responsible for the regional pattern of the highest haze levels shifting from the Ohio River Valley during
9    summer to the Midwest in the winter as shown in Figure 9-8. Particulate nitrate is also a significant
10   contributor to particulate light extinction year-around in California, where is generally contributes
11   20%-40%. The Pacific Northwest, parts of Idaho and Utah experience large contributions to particulate
12   light extinction by nitrates during the colder seasons, with contributions of 20%-30%.
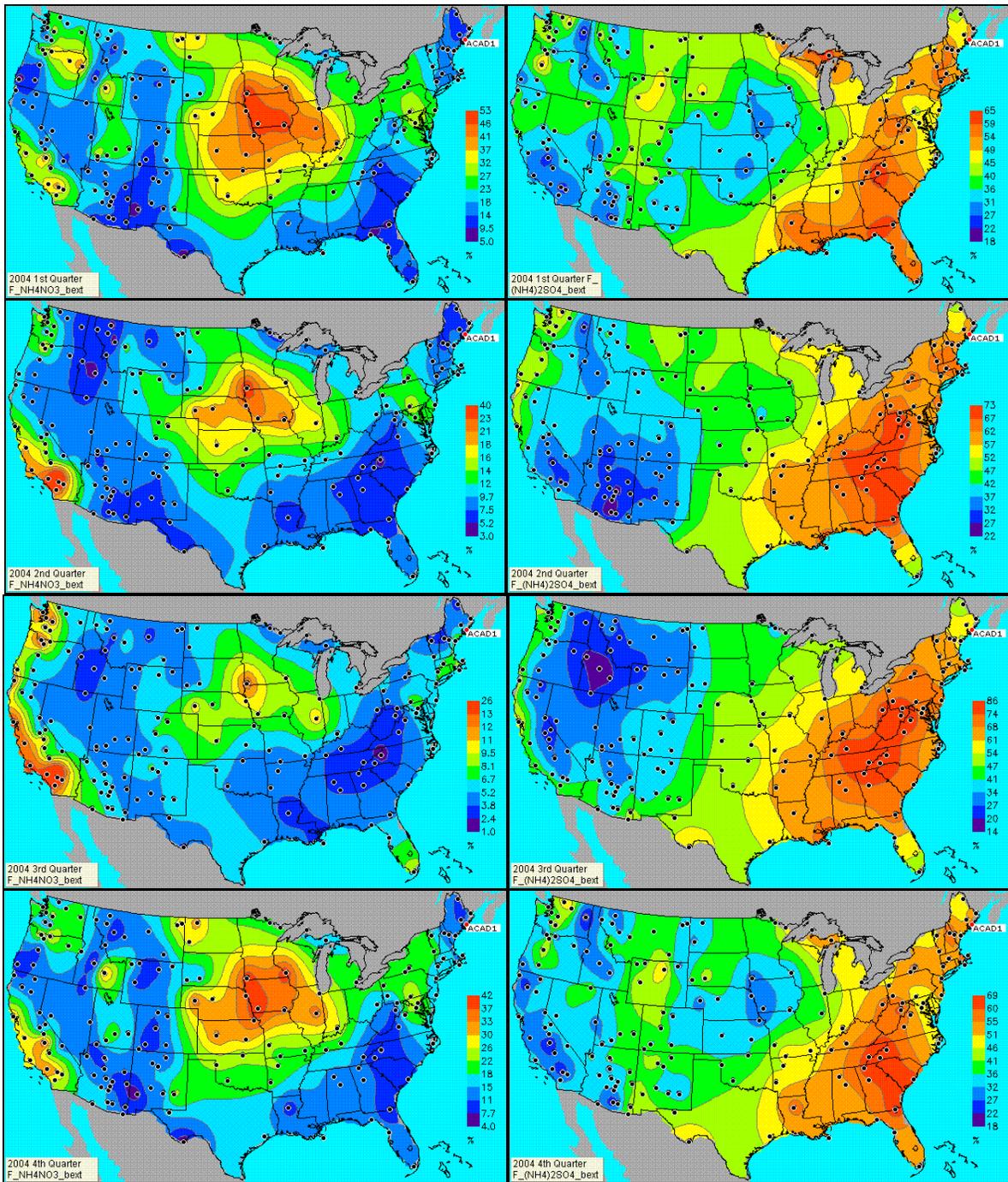
**Figure 9-9.    Percent contributions of ammonium nitrate (left column) and ammonium sulfate (right column) to particulate light extinction for each calendar quarter of 2004 (first through fourth quarter arranged from top to bottom).  Note that the color scales are different for each map.**

1    Figure 9-9 also shows that particulate sulfate is the predominate contributor in the eastern U.S.,

2    where it contributes 40% or more on average and during the summer months up to three quarters of the

3    particulate light extinction over much of the East. In the western U.S. particulate sulfate generally

4    contribute 20%-50% of the particle light extinction. Regions of the lowest fractional contributions by

5    particulate sulfate and nitrate for any calendar quarter are generally in the western U.S., and as are shown

6    in the subsequent two figures have significant contributions by crustal PM components (i.e. coarse mass

7    and fine soil) and by carbonaceous PM (i.e., organic mass and EC).

8    Figure 9-10 shows the contributions to haze by the carbonaceous PM components (i.e. organic

9    mass and EC). They show broadly similar patterns with the greatest contributions in the western U.S

10   especially during the warmer months of the year. For the most part this spatial pattern results from the

11   dominate contributions to haze by sulfate and nitrate PM in the eastern half of the U.S., leaving relatively

12   little for other component contributions. The fractional contribution to haze by organic PM is generally

13   two to five times that of EC. In absolute terms, both carbonaceous components tend to have two to three

14   times higher concentrations in the eastern U.S. than in the non-coastal western states.

15   Figure 9-11 shows the contributions to haze by coarse mass and fine soil components. As with the

16   carbonaceous components, these crustal dominated components have a similar spatial pattern with regions

17   of highest contribution to haze in the western U.S., and just as for the carbonaceous PM, the explanation

18   for low contributions in the eastern U.S. is the dominate contributions to haze by sulfate and nitrate PM

19   leaving relatively little for other components. The crustal components contribute more to haze in the arid

20   regions of the west including the southwestern deserts. In absolute terms, coarse mass concentrations are

21   as high in the rural areas of the center of the country (including Oklahoma, Arkansas, Kansas, Missouri,

22   and Iowa) as they are in the Desert Southwest. Typically coarse mass contributions to haze exceed those

23   of fine mass by a factor of 2 to 4.
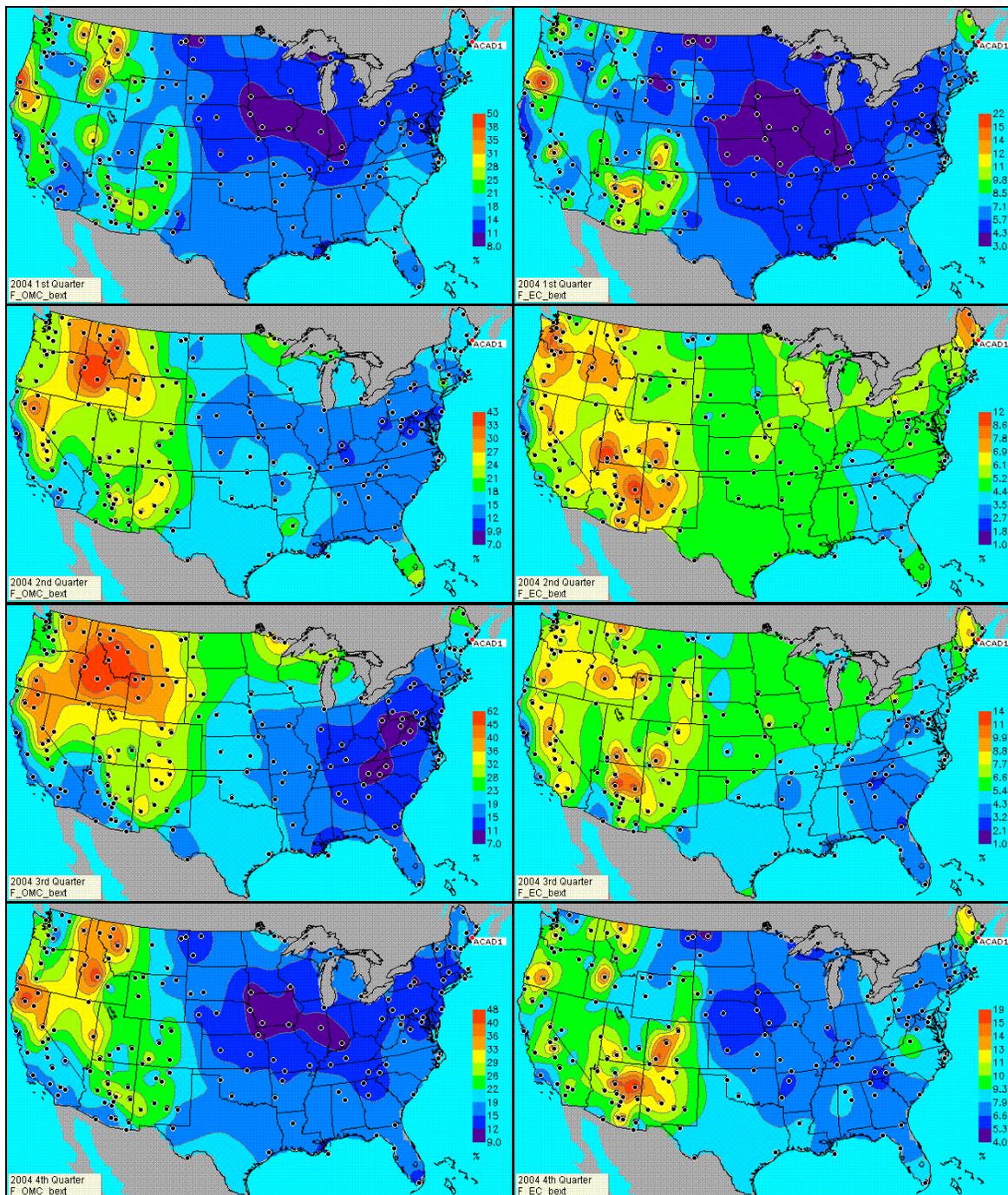
**Figure 9-10.  Percent contributions of organic mass (left column) and EC (right column) to particulate light extinction for each calendar quarter of 2004 (first through fourth quarter arranged from top to bottom).  Note that the color scales are different for each map.**
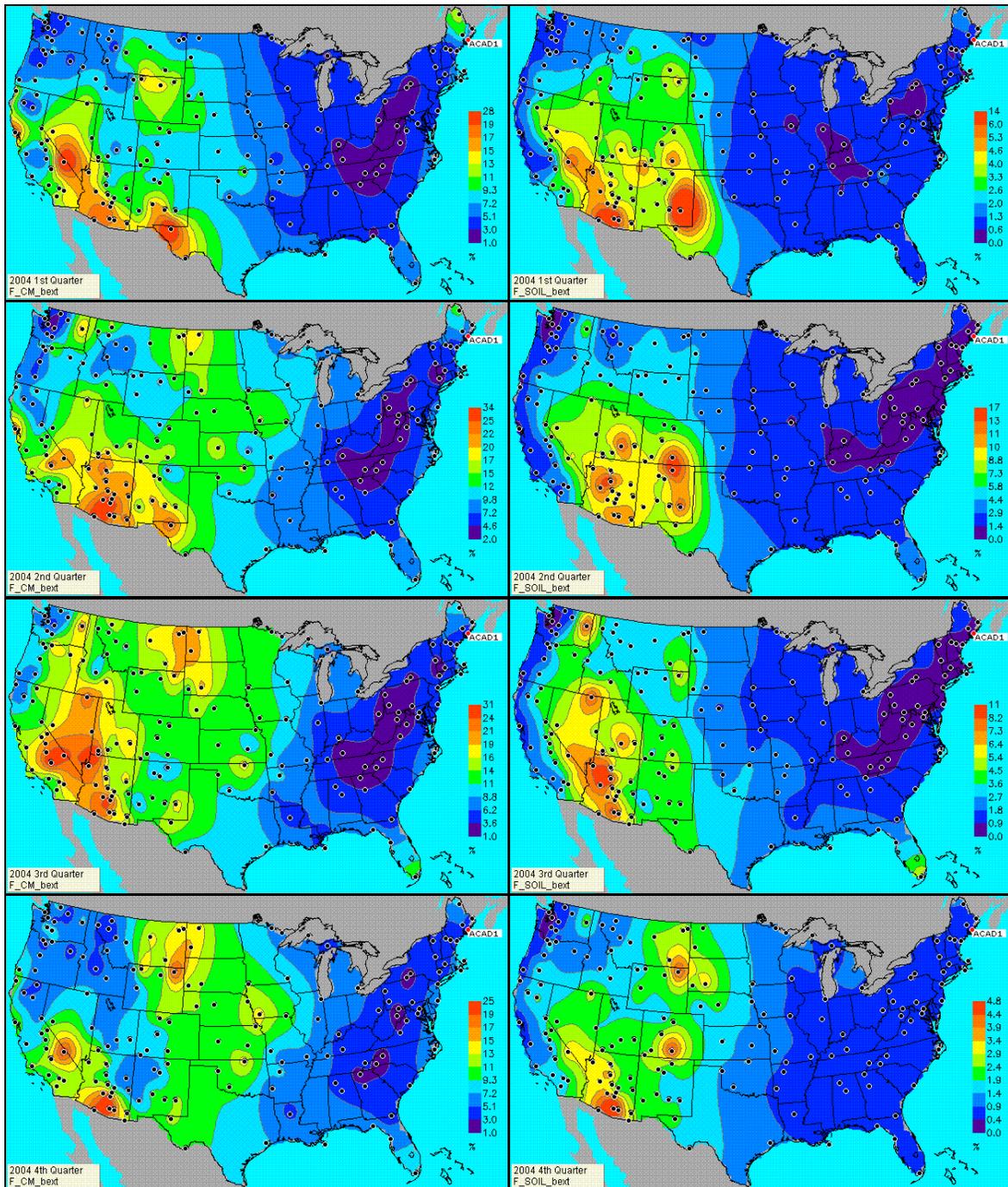
**Figure 9-11.** **Percent contributions of coarse mass (left column) and fine soil (right column) to particulate light extinction for each calendar quarter of 2004 (first through fourth quarter arranged from top to bottom). Note that the color scales are different for each map.**

### 9.3.4.3. Urban and Regional Patterns

1    Using a combination of IMPROVE and CSN data, it is possible to compare urban $PM_{2.5}$

2    concentrations and composition to corresponding remote-area regional values. These are shown as paired

3    color contours maps for IMPROVE and IMPROVE plus CSN (see Figures 9-12 to 9-17) (U.S. EPA,

4    2004) used the pairing of IMPROVE and CSN monitoring sites at 13 selected urban areas to separate

5    local and regional contributions of three major $PM_{2.5}$ components as shown in Figure 9-24. In Figures

6    9-12 and 9-13 we see that urban $PM_{2.5}$ concentrations are systematically higher than those in the

7    surrounding non-urban regions. The urban excess is generally much higher in the western U.S. than in the

8    East (e.g. there are five contour intervals separating Salt Lake City from its remote regional area

9    compared to only two for Indianapolis). This implies that eastern and western urban $PM_{2.5}$ concentrations

10   and resulting visibility levels are less different than the eastern and western regional concentrations and

11   visibility levels.
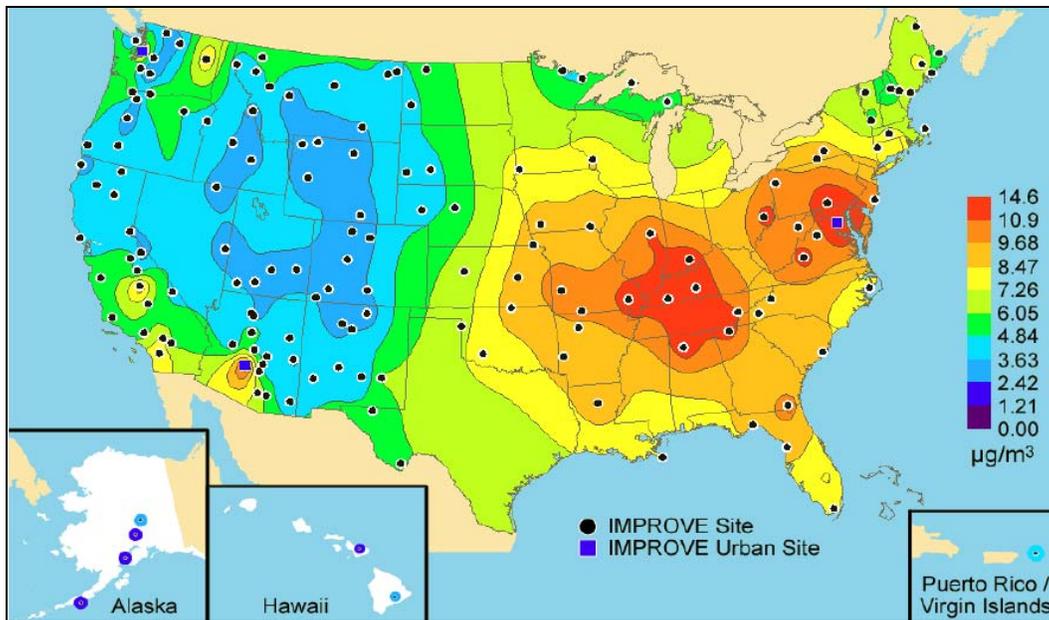


Source: DeBell et al. (2006).

**Figure 9-12.   IMPROVE Mean $PM_{2.5}$ mass concentration determined by summing the major components for the 2000 through 2004.**
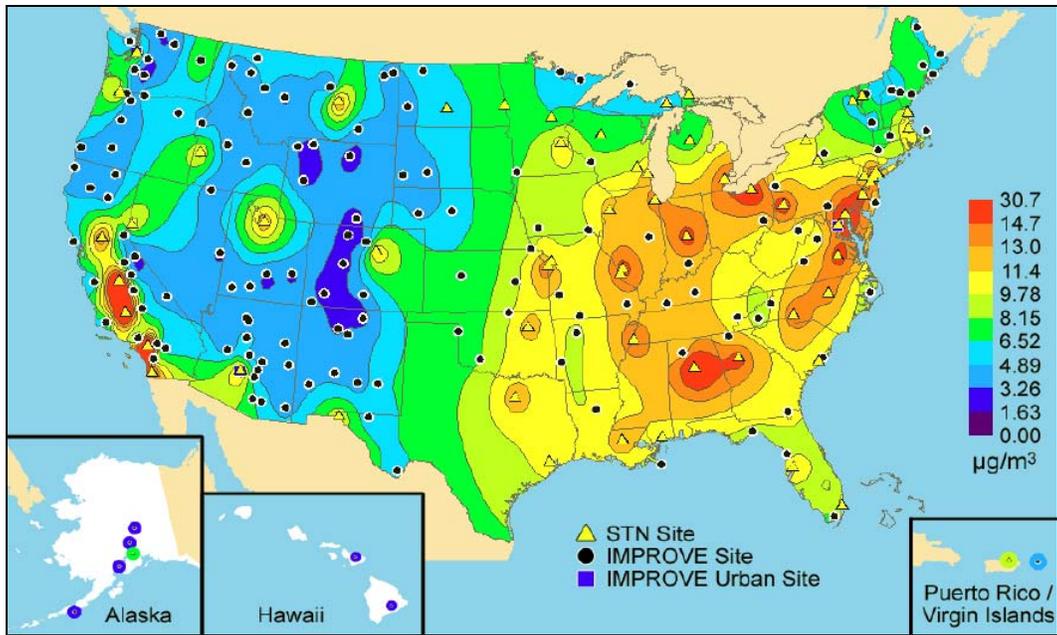
**Figure 9-13.  IMPROVE and CSN (STN) mean PM$_{2.5}$ mass concentration determined by summing the major components for 2000 through 2004**
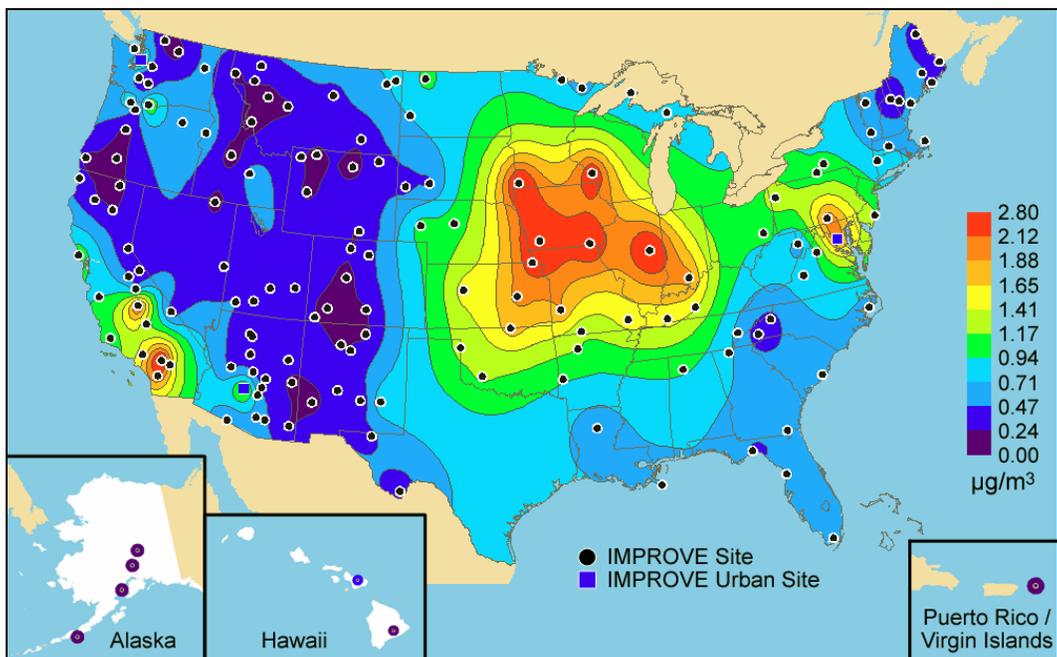
**Figure 9-14.  IMPROVE mean ammonium nitrate concentrations for 2000 through 2004.**
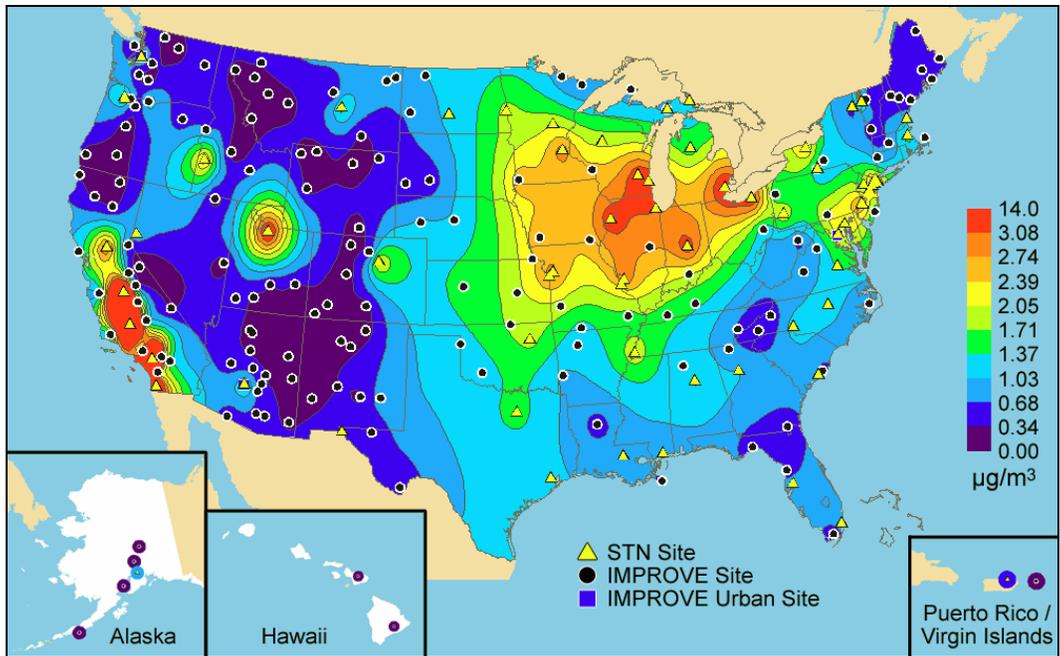
Source: DeBell et al. (2006).

**Figure 9-15.   IMPROVE and CSN (STN) mean ammonium nitrate concentrations for 2000 through 2004.**
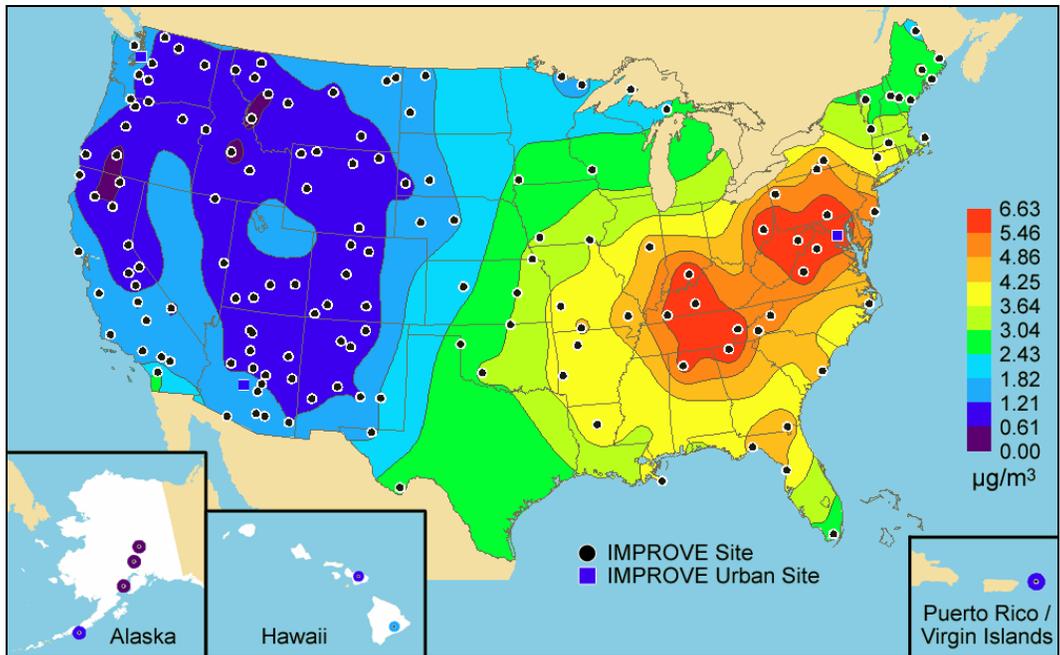


Source: DeBell et al. (2006).

**Figure 9-16.   IMPROVE mean ammonium sulfate concentrations for 2000 through 2004.**
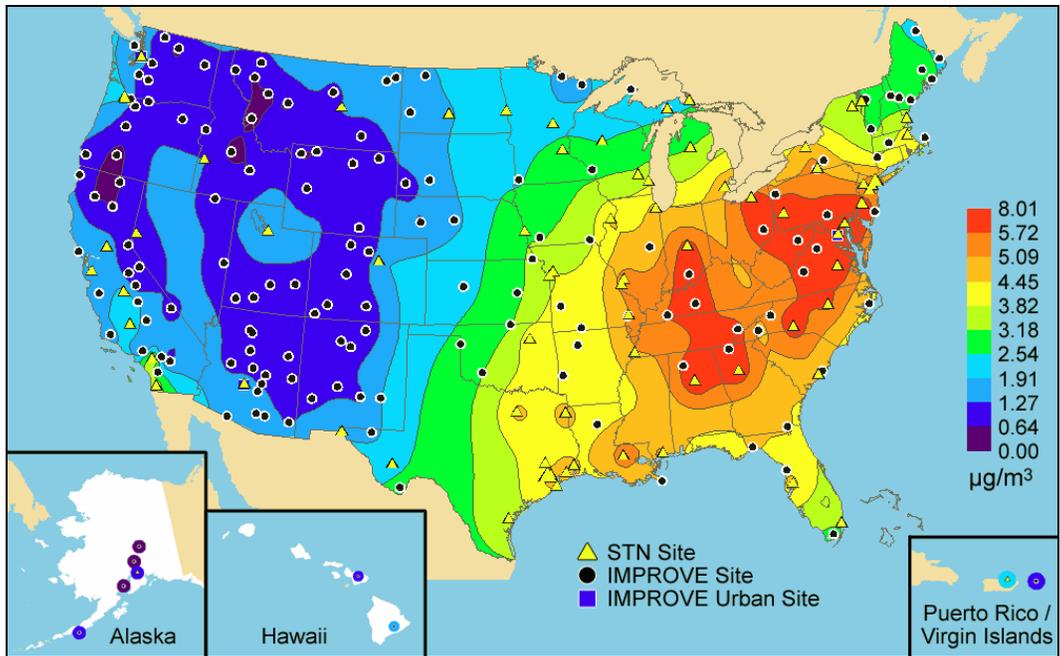
**Figure 9-17.   IMPROVE and CSN (STN) mean ammonium sulfate concentrations for 2000 through 2004.**

1    Figures 9-14, 9-15, and 9-24 show the PM$_{2.5}$ nitrate in remote and urban areas. Here the western

2    states have urban particulate nitrate concentrations that far exceed twice the remote area regional

3    concentrations. For the Central Valley of California and Los Angeles areas, the urban excess of

4    ammonium nitrate exceeds regional concentrations by from 2 μg/m$^3$ to 12 μg/m$^3$. In the region of the

5    Midwest nitrate bulge, the urban concentrations were less than twice the regional concentrations for an

6    annual urban excess of about 1 μg/m$^3$. Northeast and southeast of the Midwest nitrate bulge, annual urban

7    particulate nitrate concentrations are several tenths to about one microgram per cubic meter above the

8    remote area regional concentrations, with warmer southern locations tending to have the smaller

9    concentrations of both regional and urban excess particulate nitrate.

10    As shown in Figures 9-16, 9-17, and 9-24, annual-averaged urban particulate sulfate concentrations

11    are generally not much higher than the regional values, with urban excess generally of less than about a

12    half microgram per cubic meter. The exceptions apparent by comparing Figures 9-16 and 9-17 are in

13    Texas and Louisiana where urban excess particulate sulfate are greater than 1 μg/m$^3$, perhaps caused by

14    local emissions (e.g. from oil refineries). Urban contributions are a larger fraction of the total particulate

15    sulfate concentrations in the western U.S. because the regional levels are much lower than in the East.

16    The modest additional particulate sulfate concentrations associated with urban areas suggests that most

17    particulate sulfate is regionally distributed, and that IMPROVE and CSN monitoring sites can be used

1    together to enhance our ability to delineate particulate sulfate spatial distributions. For example, note that

2    the additional data from urban sites shown in Figure 9-17 extends to the north and south the apparent

3    distribution of the high particulate sulfate loading shown in Figure 9-16 over Tennessee and Kentucky, as

4    well as the high loadings over southern Pennsylvania, eastern West Virginia and northern Virginia. (The

5    color-contour suggested dip in concentrations between the two eastern particulate sulfate high

6    concentrations regions may not exist in the atmosphere, but this cannot be verified without speciation

7    monitoring sites in southern Ohio, the boarder of Kentucky and West Virginia and western Virginia.)

8        Urban and remote area carbonaceous $PM_{2.5}$ are displayed in Figures 9-18 and 9-19 (organic mass),

9    9-20 and 9-21 EC, and 9-22 and 9-23 (total carbon = organic + EC concentration). Just as with particulate

10   nitrate both organic mass and EC concentrations are more than twice the remote-area background

11   concentrations for western urban monitoring locations. One of the more interesting pairing of sites is for

12   the Virgin Islands compared to the urban site at San Juan Puerto Rico (see the map cutout Figures 9-18

13   through 9-21). The San Juan urban excess organic carbon is moderate, while the EC value is among the

14   most extreme inferred in this manner. For eastern urban areas, approximately half the total carbon is local

15   with the other half is regional. In eastern urban areas, carbonaceous and sulfate particulate are the two

16   major components of $PM_{2.5}$, with roughly equal contributions, and account for over 80% of the mass

17   concentration. Edgerton et al. (2004) showed that carbonaceous $PM_{2.5}$ is responsible for most of the urban

18   excess above regional concentrations at four urban/rural paired SEARCH monitoring sites in the

19   southeastern U.S. However, the higher overall light extinction efficiency for sulfate resulting from its

20   hydrophilicity gives it ~ 2: 1 dominance in responsibility for eastern urban light extinction.

21       Urban and remote area fine soil $PM_{2.5}$ concentrations are displayed in Figures 9-22 and 9-23. Urban

22   fine soil levels are at most a few tenths of a microgram per cubic meter higher than the regional

23   background levels and in some regions they are much less. Just as with carbonaceous $PM_{2.5}$, the Virgin

24   Island, San Juan, Puerto Rico pair are interesting for fine soil. In this case the interesting feature is that

25   both of these island monitoring sites have high concentrations of fine soil, which is caused to their being

26   in the trans-Atlantic transport path of dust from Africa (Prospero, 1996).

27       No urban – remote pair of coarse mass concentration maps is available because CSN does not

28   monitor coarse mass. Malm et al. (2004) contains a map of annual mean coarse mass concentration for

29   2003 which includes the values for IMPROVE urban sites, including two in the western U.S. with much

30   more coarse mass than the nearby remote areas monitoring sites (i.e., ~24 $\mu g/m^3$ compared to ~9 $\mu g/m^3$

31   for Phoenix, and ~6 $\mu g/m^3$ compared to ~2 $\mu g/m^3$ for Puget Sound) and one eastern IMPROVE site at

32   Washington, DC with less coarse mass than the surrounding remote area values (~2 $\mu g/m^3$ compared to

33   ~4 $\mu g/m^3$).
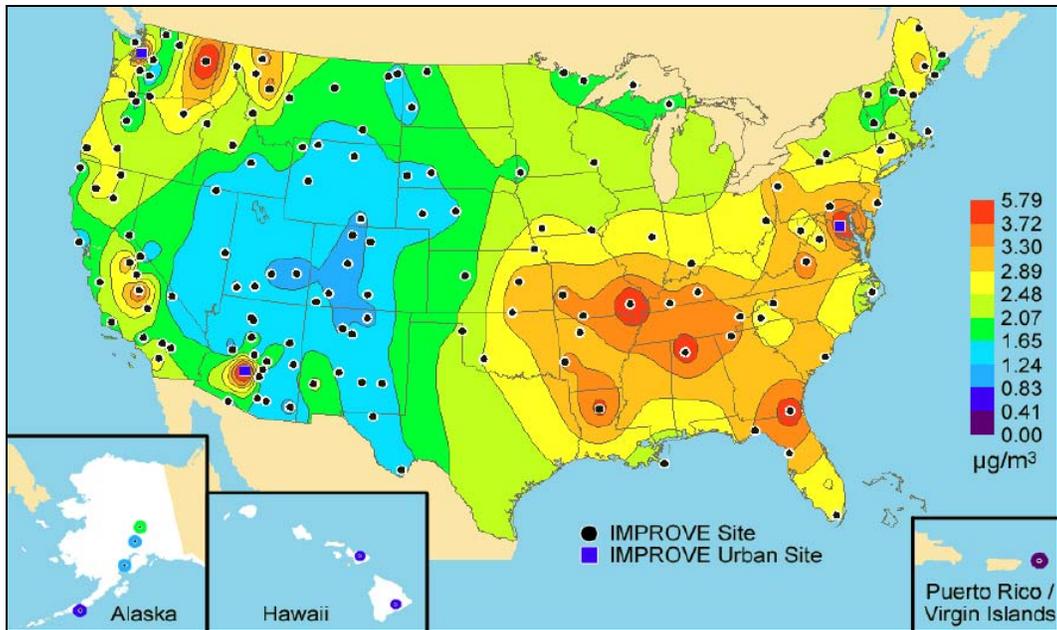
Source: DeBell et al. (2006).

**Figure 9-18.   IMPROVE monitored mean organic mass concentrations for 2000 through 2004.**
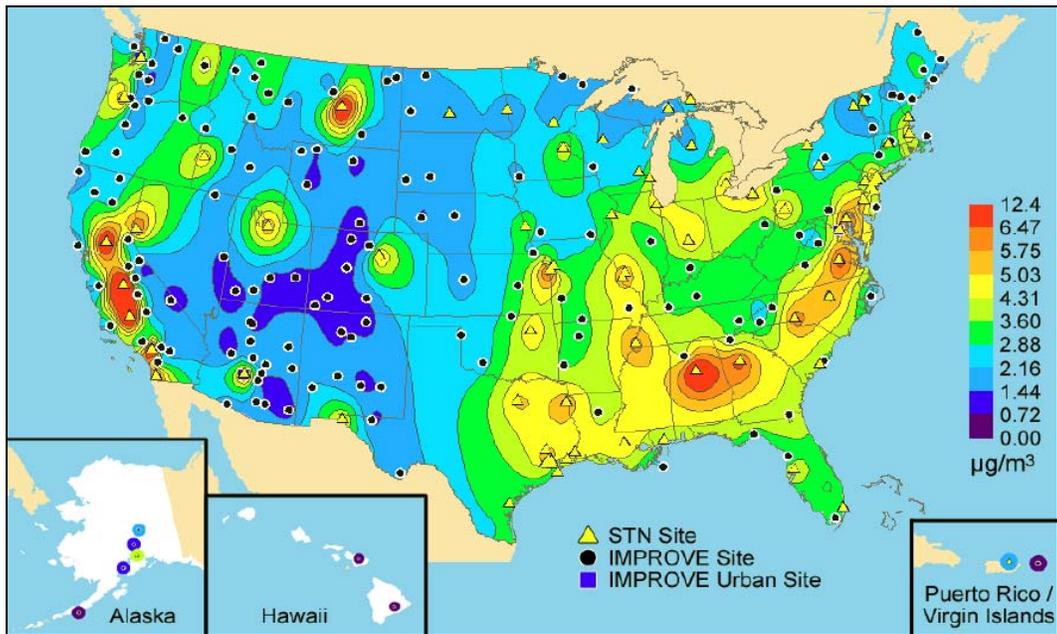


Source: DeBell et al. (2006).

**Figure 9-19.   IMPROVE and CSN (STN) mean organic mass concentrations for 2000 through 2004.**
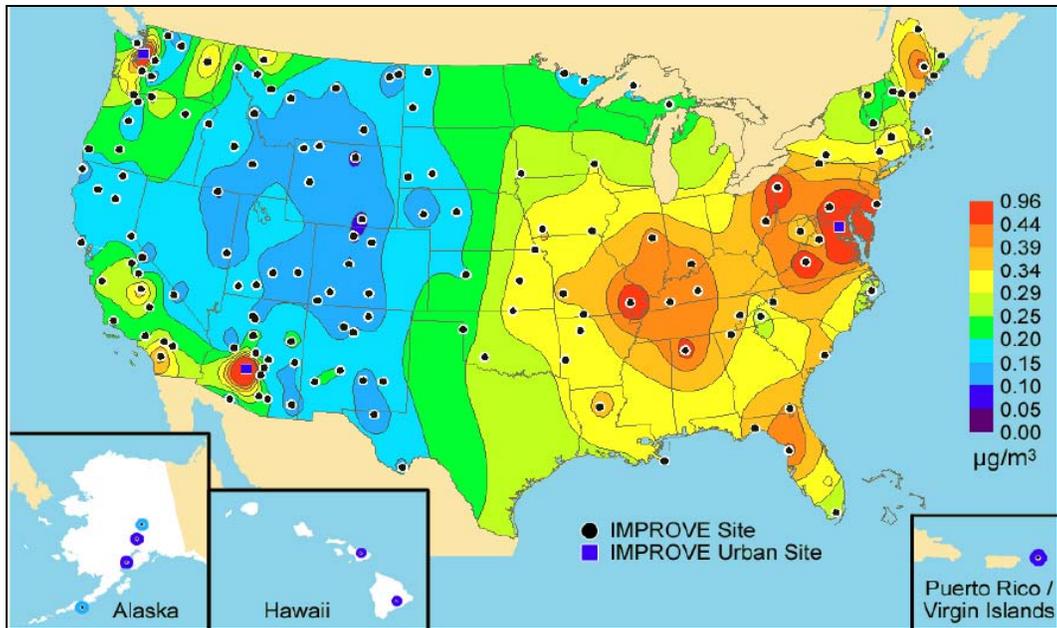
**Figure 9-20.  IMPROVE mean EC concentrations for 2000 through 2004.**
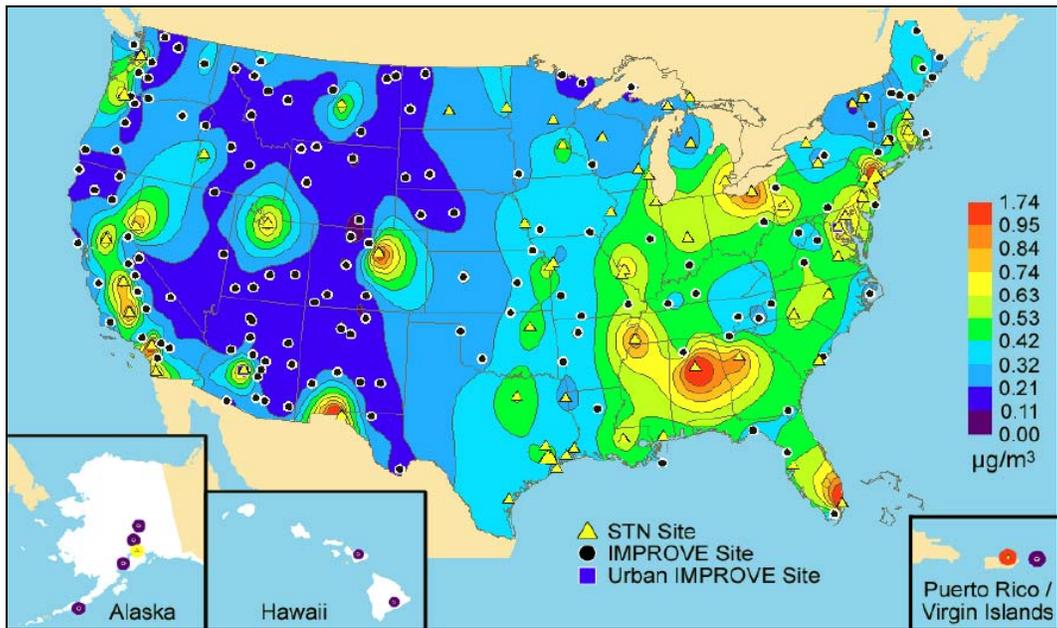
**Figure 9-21.  IMPROVE and CSN (STN) mean EC concentrations for 2000 through 2004.**
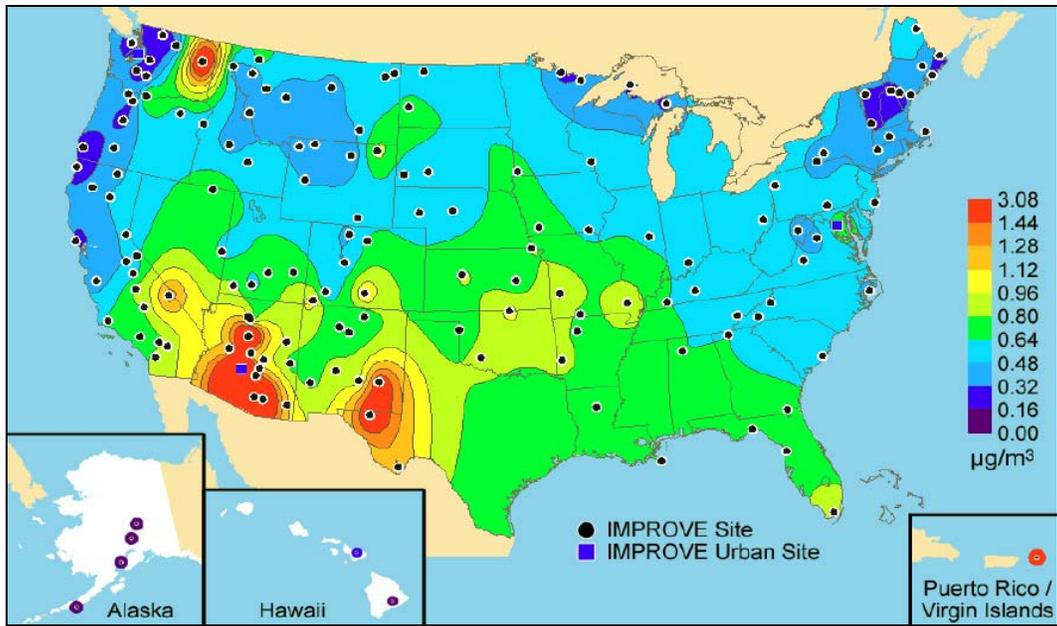
**Figure 9-22.   IMPROVE mean fine soil concentrations for 2000 through 2004.**
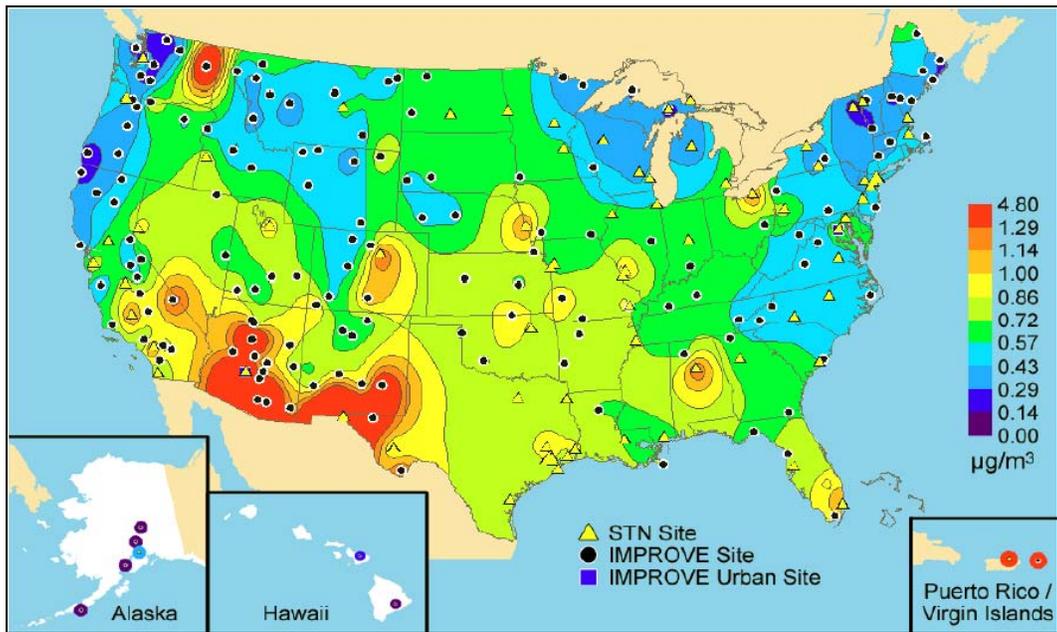
**Figure 9-23.   IMPROVE and CSN (STN) fine soil concentrations, 2000 through 2004.**
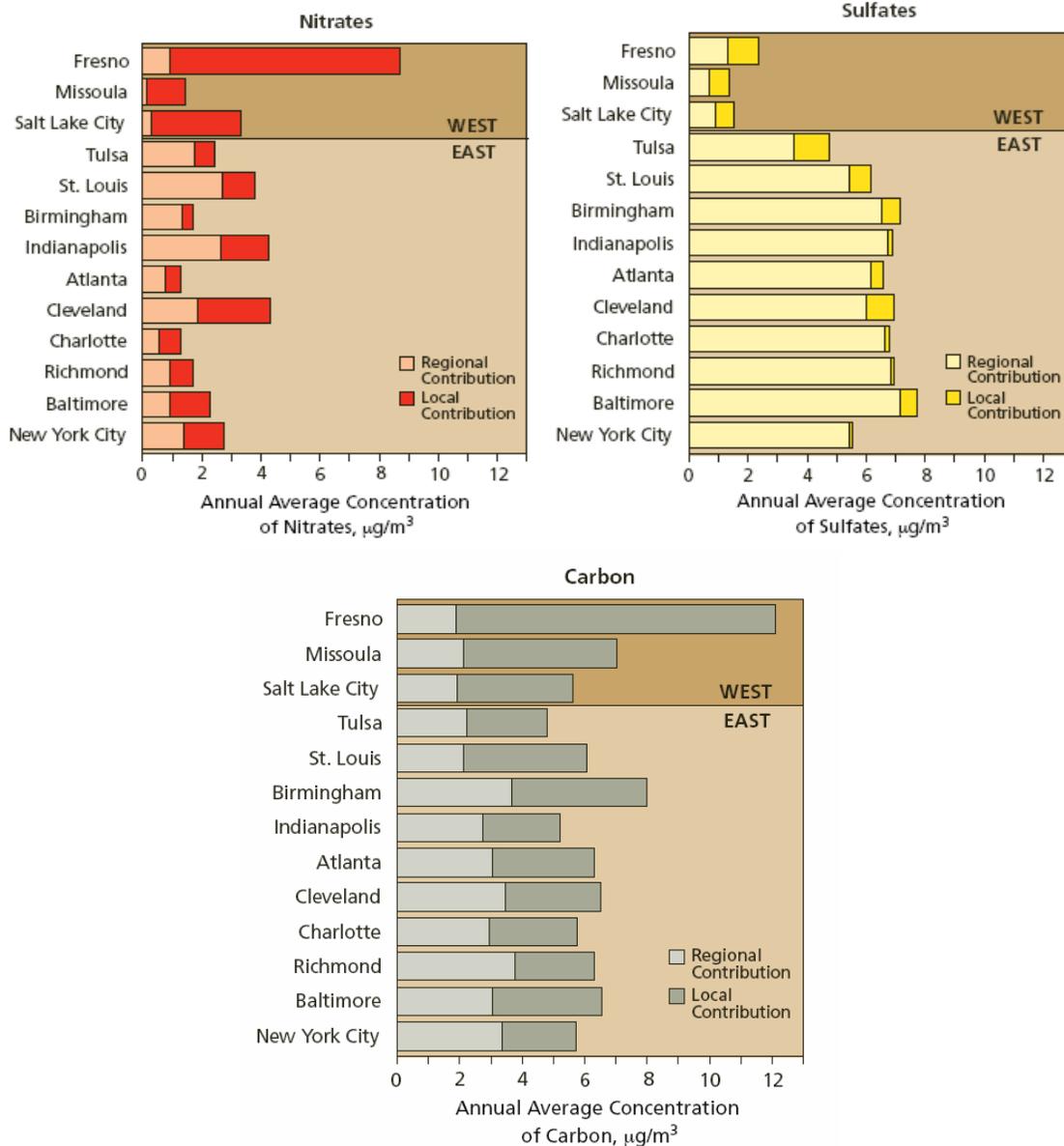
Source: U.S. EPA (2004)

**Figure 9-24. Regional and local contributions to annual average PM$_{2.5}$ by particulate sulfate, nitrate and total carbon (i.e. organic plus EC) for select urban areas based on paired IMPROVE and CSN monitoring sites.**
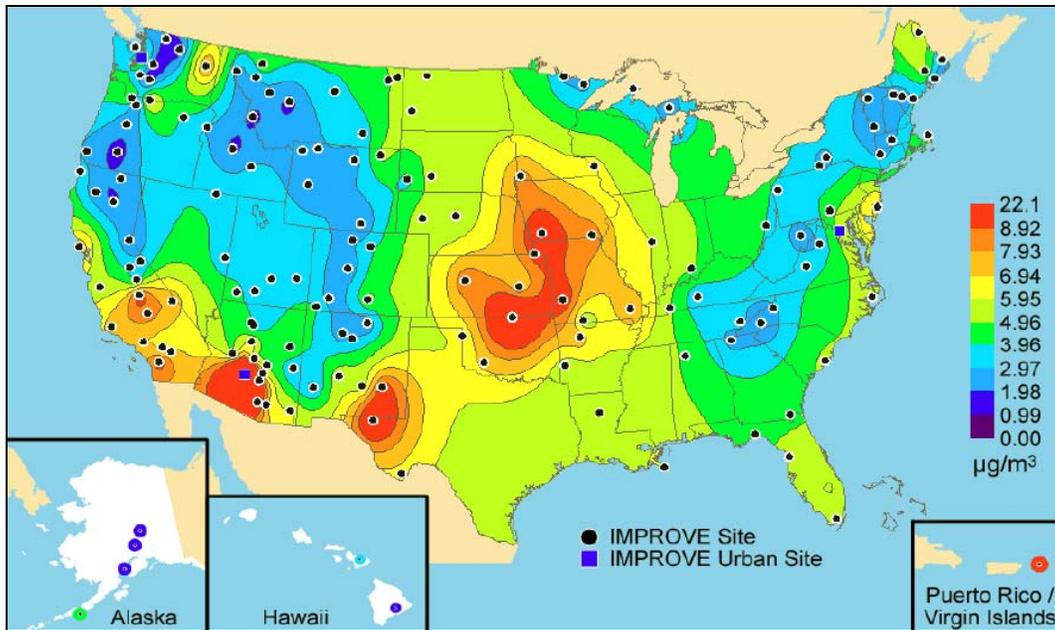
**Figure 9-25.   IMPROVE mean coarse mass concentrations for 2000 through 2004.**

1    Figure 9-25 shows the remote area coarse mass concentrations as measured by the IMPROVE

2  network. The pattern of high coarse mass concentrations from Oklahoma to Iowa is comparable to the

3  high concentration levels in the desert southwest, though as shown in Figure 9-11 it contributes a smaller

4  relative share of the light extinction because of the higher contributions to haze by particulate nitrate and

5  sulfate in this agricultural region of the country. Comparing Figures 9-22 and 9-25 shows that the coarse

6  mass and fine soil concentration patterns are similar for the desert southwest but there is a much lower

7  fine soil to coarse mass concentration ratio for the agricultural center of the country, suggesting a regional

8  difference in the size distribution of suspendable soil materials.

## 9.3.4.4. Temporal Trends

9    Visibility trend analysis requires relatively long data records to avoid having meteorologically

10  driven interannual variability obscure more meaningful emissions-driven air quality trends. A requirement

11  for long-term data limits the number of monitoring sites useful for trend analysis. Maps that show haze

12  trends for IMPROVE sites for the 10-year period from 1995 through 2004 for the mean of the 20% best

13  and the 20% worst haze days where sites are required to have a minimum of six complete years of data

14  during the ten-year period is shown in Figures 9-26 and 9-27, respectively. The best haze days have

15  improving haze at most sites (32 of 47), no trend at several sites (10 of 47) and degrading visibility at just

1    one site (Great Sand Dunes, CO). The worst haze days have improving haze conditions at several sites

2    (13 of 47), no trend at most sites (30 of 47) and degrading visibility at a few western sites (4 of 47).

3          Eight- ten- and sixteen-year trends analysis conducted for the Western Regional Air Partnership

4    (WRAP) as part of the Causes of Haze Assessment (http://www.wrapair.or) show that improving trends

5    for the 20% best haze levels for the sites in the western U.S. generally correspond to improving trends for

6    all of the major components with the exception of particulate nitrate. Trends assessment for the worst

7    haze days at western sites show consistent reductions in particulate sulfate, but otherwise have mixed

8    increasing and decreasing haze component trends, many of which are not statistically significant.

9    Edgerton, et al. (2004) showed a decreasing trend in $PM_{2.5}$ of about 18% (corresponding to 1 μg/m$^3$ to

10   2 μg/m$^3$) for four urban – rural paired SEARCH sites in the Southeastern U.S. corresponding to similar

11   reductions in sulfate and carbonaceous particulate.
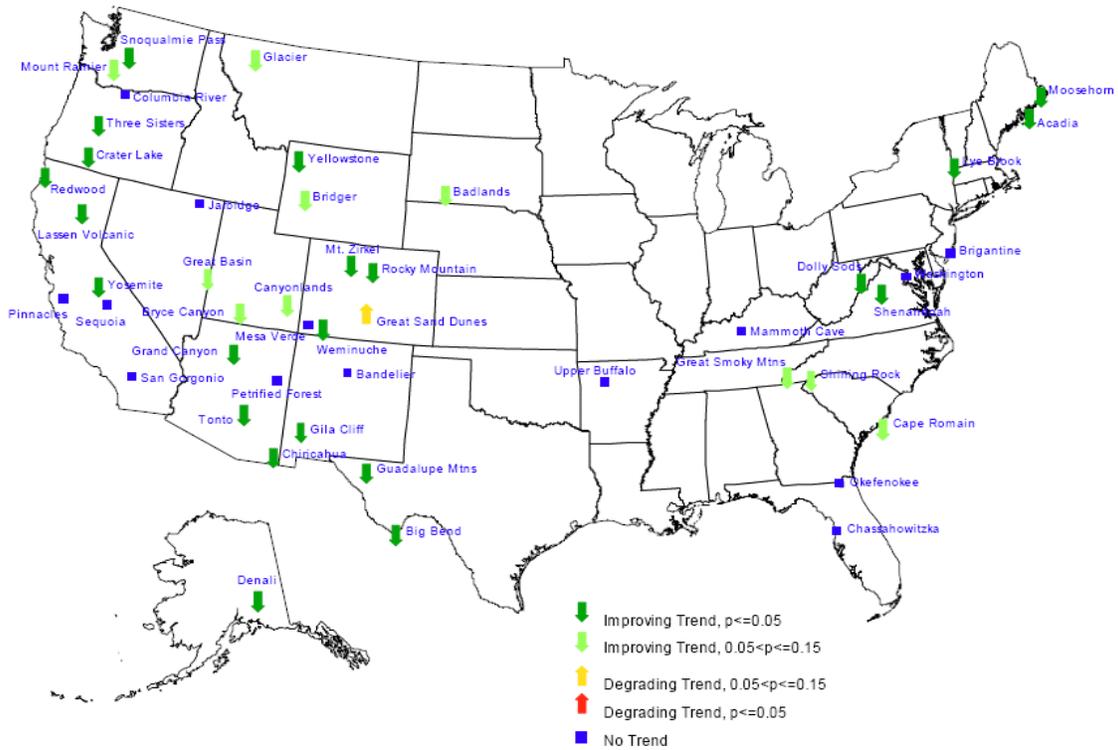


Source: DeBell et al. (2006)

**Figure 9-26.  Ten-year (1995-2004) haze trends for the mean of the 20% best annual haze conditions.**
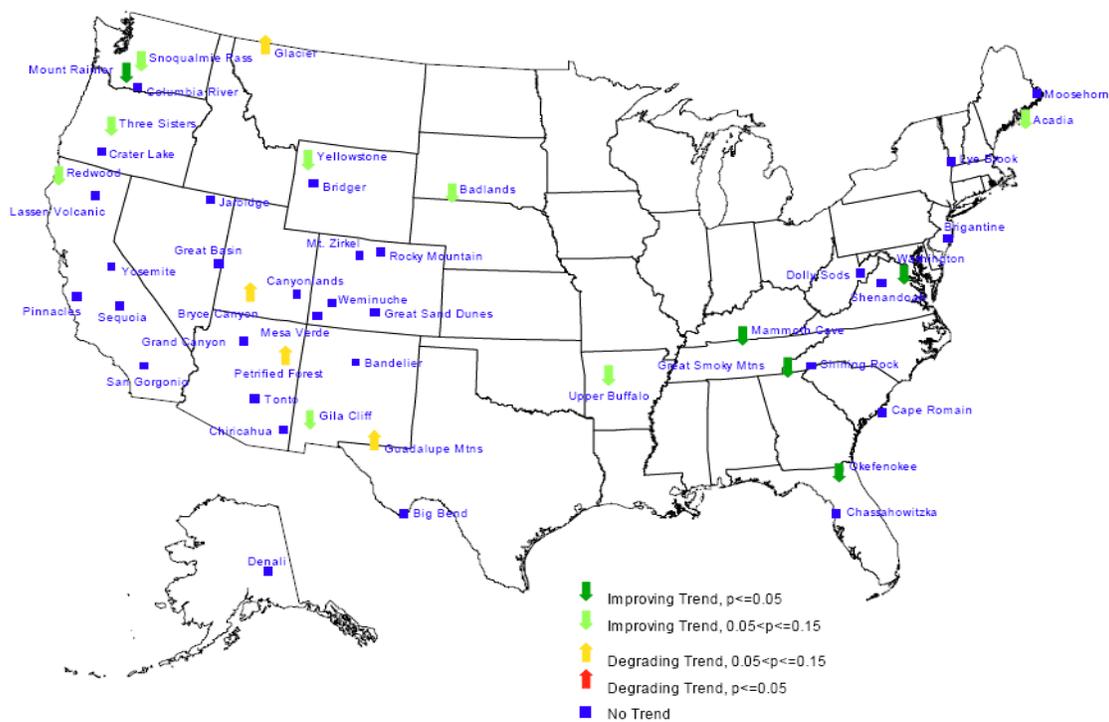
**Figure 9-27.  Ten-year (1995-2004) haze trends for the mean of the 20% worst annual haze conditions.**

1    Malm et al. (2002) conducted 10-year (1988 to 1998) trends analyses on the combination of

2    IMPROVE and CASTNET (Clean Air Status and Trends Network) (Baumgardner et al., 1999) particulate

3    sulfate concentration datasets, which were shown to produce comparable sulfate concentrations at 23 co-

4    located monitoring sites. Figure 9-28 show time plots of 80th percentile particulate sulfate concentrations

5    and annual average $SO_2$ emissions from the National Emissions Trends (EPA, 2000) database for four

6    regions of the U.S. Note that the concentration and emissions scales on the plots are each a factor of three,

7    so that an equal percentage change in particulate sulfate and $SO_2$ emissions slope in any plot will have the

8    same trend line slope. Each plot shows a strong correspondence between 80th percentile particulate

9    sulfate and $SO_2$ emissions trends. The western U.S. had steadily declining trends in both, for an overall

10    decrease of about 15%. The northeastern U.S. had a decrease of about 27% over the ten year period with

11    the largest one year decrease of about 20% between 1994 and 1995 as a result of the Phase I

12    implementation of the Acid Rain Program. The southwestern U.S. (Texas, New Mexico and Colorado)

13    had about a 15% increase in particulate sulfate and $SO_2$ emissions over the ten-year period. The

14    southeastern U.S. had a declining trend for the early 1990s followed be an increasing trend for the later

15    half of the decade, with a net decrease over the decade of less than 10%. Others have shown similar

1 decreasing particulate sulfate concentration trends and a correspondence in trends between $SO_2$ emissions

2 and particulate sulfate concentration by region (Holland et al., 1999; U.S. EPA, 2004).
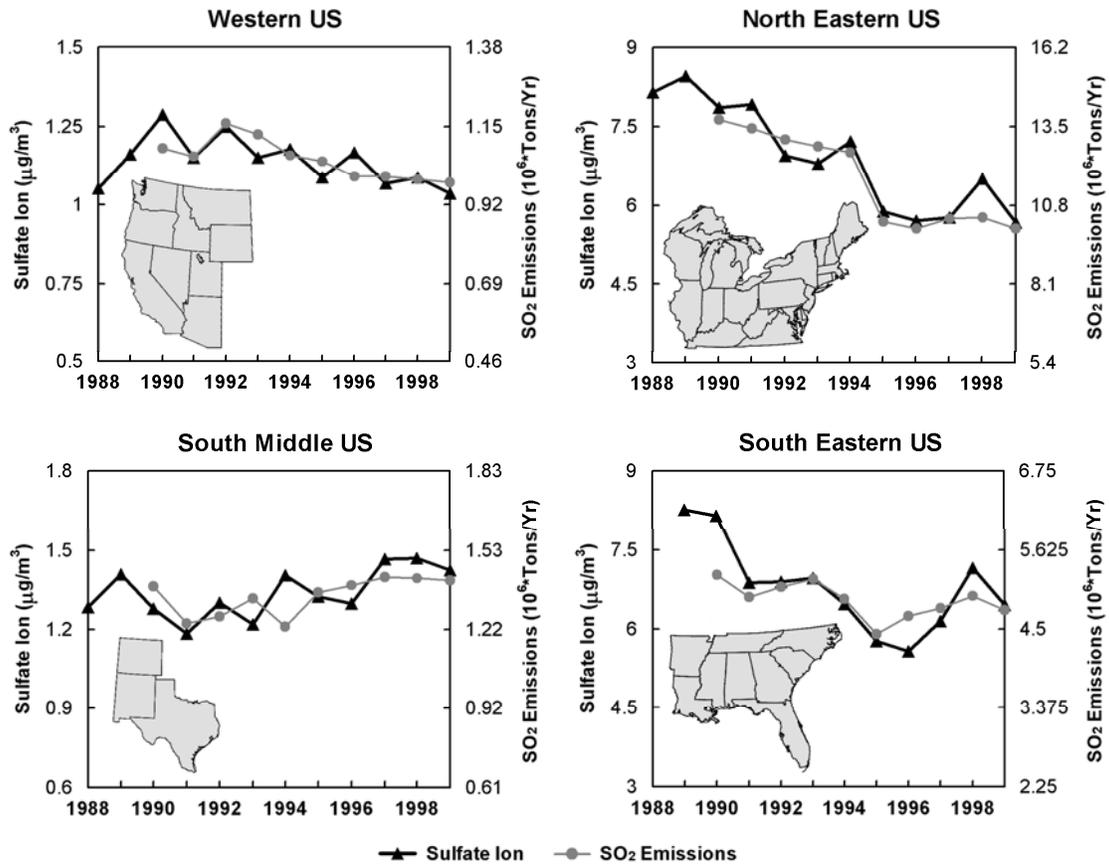
**Figure 9-28. Ten-year trends in the 80th percentile particulate sulfate concentration based on IMPROVE and CASTNet monitoring and net $SO_2$ emissions from the National Emissions Trends (NET) data base by region of the U.S.**

3 Holland et al. (1999) developed and compared $NO_X$ emissions trends from 1989 to 1995 to

4 corresponding trends in total nitrogen concentration (defined as particulate nitrate plus gaseous nitric

5 acid) for the eastern U.S. (states between Louisiana to Minnesota and further east) based on data from 34

6 rural CASTNet dry deposition monitoring sites. They found a decrease in nitrogen median values of about

7 8% associated with a decrease of 5.4% in non-biogenic $NO_X$ emissions. Trends in haze associated with

8 particulate sulfate and nitrate concentrations should correspond fairly well with trends in their

9 concentration due to the simple relationship between concentration and light extinction at any relative

10 humidity. However, nitrogen as defined in the Holland et al. (1999) trend analysis includes the nitrogen

1    from particulate nitrate and gaseous nitric acid, but nitric acid does not contribute to light extinction. For

2    situations with limited atmospheric ammonia or elevated temperatures, trends in nitrogen may be

3    principally in nitric acid with no net change in nitrate light extinction. Alternately with abundant ammonia

4    and low temperatures the trend in nitrogen may be principally in particulate nitrate and the nitrate

5    component of haze.

6         Ten-year trends (1994-2003) of particulate nitrate contribution to light extinction during the 20%

7    worst haze conditions conducted as part of the Causes of Haze Assessment (see the link in Table 9-1) are

8    shown in Figure 9-29. This indicates that haze from particulate nitrates is increasing across the western

9    U.S. at a rate of several $Mm^{-1}$ per year in parts of California and at a rate of several tenths of an $Mm^{-1}$

10   across the Four-Corners states. While statistically significant, these trends are influenced by an

11   unexplained nationwide period of depressed nitrate concentrations measured by the IMPROVE network

12   during a four year period from the winter of 1996-97 through the winter of 2000-01. Extensive

13   examinations of plausible monitoring methodological explanations have failed to offer any evidence that

14   the data are invalid (McDade, 2006), but no satisfactory atmospheric or emissions-related explanation has

15   been offered to account for this four-year depression of nitrate. Similar analyses of particulate nitrate haze

16   trends are not available for the rest of the country.

17        Maps of remote-area 8-, 10-, and 16-year trends for carbonaceous and crustal PM species based on

18   IMPROVE monitoring are available for the western U.S. conducted as part of the Causes of Haze

19   Assessment. Generally these show a broad range of results (i.e., a mixture of statistically significant

20   upward or downward trends and insignificant trends often with neighboring sites having opposing trends)

21   that vary considerably depending on the number of years selected (i.e. 8, 10, or 16) and whether trends are

22   for the best, worst, or middle of the haze distribution data. The scatter in these results is undoubtedly due

23   to the high interannual variability and varying locations of wildfire and wind-suspended dust emissions

24   that dominate the remote-area concentrations of the carbonaceous and crustal PM species in the western

25   U.S.
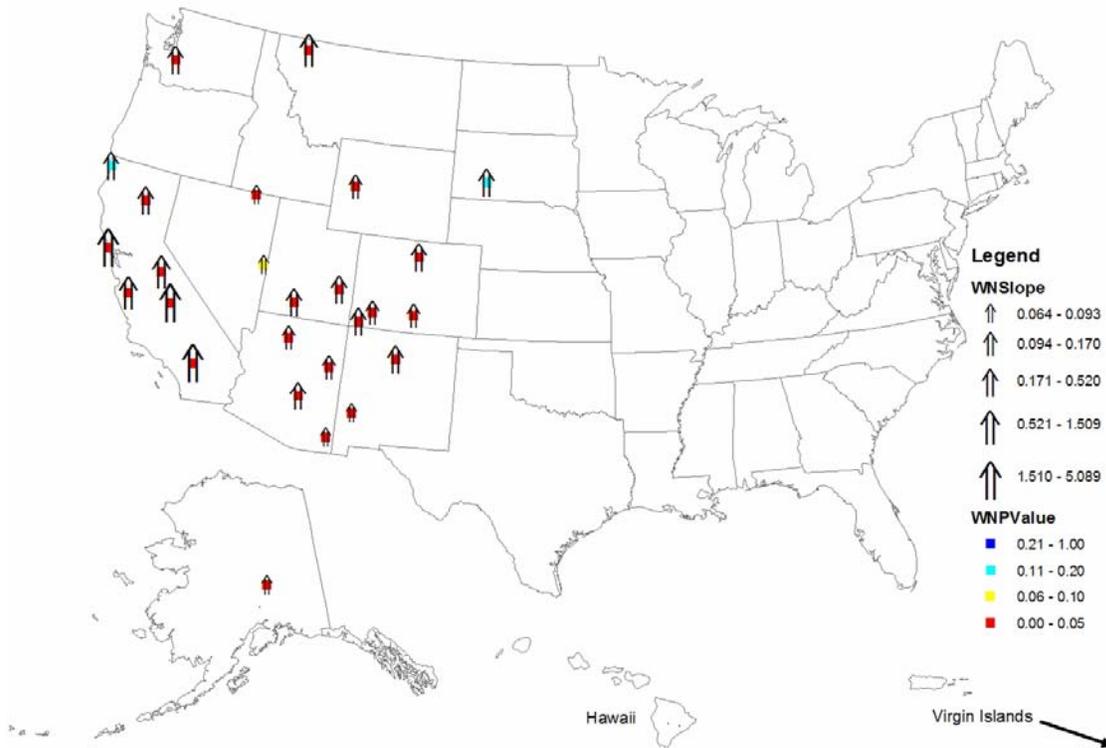
**Figure 9-29. Map of 10-year trends (1994-2003) in haze by particulate nitrate contribution to haze for the worst 20% annual haze periods. The orientation, size and color of the arrows indicate the direction, magnitude and statistical level of significance of the trends. These consistent upward trends may be a misleading result due to an unexplained sampling issue (see text for additional information).**

### 9.3.4.5. Causes of Haze

1      As indicated above, estimates of haze levels contributed by particulate species are proportional to

2      their concentrations at any relative humidity. However, in order to attribute haze to emissions from

3      individual sources, source types, or source regions, scientists generally apply any of a number of receptor

4      and air quality simulation modeling approaches and when using multiple approaches they reconcile the

5      results of each using a weight-of-evidence methodology. Commonly this methodology has been applied to

6      the extensive datasets generated by special studies designed to estimate source-receptor relationships for a

7      few receptor locations or for individual emission sources (Pitchford et al., 1999; 2005; Schichtel et al.,

8      2005). More recently the Regional Planning Organizations (RPOs) have sponsored extensive regional

9      haze source attribution assessments using weight-of-evidence methodologies to reconcile attribution

10     results for virtually all of the remote-area IMPROVE sites to support the development of State

11     Implementation Plans for the Regional Haze Rule. Additionally, a number of recent urban special studies,

1  including those sponsored by EPA PM Supersites program (Solomon and Hopke, 2008), have addressed

2  the causes of and sources contributing to urban excess haze above region levels.

3      The relative importance of the PM species that contribute to haze varies by region of the U.S. and

4  time of year as seen in Figures 9-9, 9-10 and 9-11, above. Generally haze in the western half of the U.S. is

5  not dominated by any one or two PM species. In the eastern half of the U.S., nitrate, especially during

6  summer and winter in the Midwest, and sulfate are the dominate haze species. As described above, urban

7  haze can be viewed as a composite of the regional and local contributions where local contributions seem

8  to be dominated by carbonaceous and to a lesser extent nitrate and crustal PM components. There have

9  been far fewer urban investigations that explicitly consider visibility impacts, though there are numerous

10  studies of urban PM source attribution. The order of discussion below on the cause of haze is by region

11  beginning in the western U.S. and proceeding to the east, analogous to dominate air flow patterns across

12  the lower 48 states and will include information from urban studies along side those of remote-area haze

13  investigations.

14      Based on modeling of an episode (Sept. 23 to 25, 1996) in the California South Coast Air Basin

15  (SCAB) and another episode (Jan. 4 to 6, 1996) in the Jan Joaquin Valley (SJV) by Ying and Kleeman

16  (2006), about 80% of the particulate sulfate for both regions are from upwind sources, with most of the

17  remaining associated with diesel and high-sulfur fuel combustion. Kleeman et al. (1999), using a

18  combination of measurements and modeling, showed that the upwind particulate sulfate source region for

19  the SCAB was over the Pacific Ocean (confirmed by measurements on Santa Catalina Island) and that

20  these particles subsequently grew with accumulation of additional secondary aerosol material, principally

21  ammonium nitrate as they traversed the SCAB. The majority of the nitric acid that forms particulate

22  nitrate in the SCAB is from diesel and gasoline combustion (~63%), while much of the ammonia is from

23  agricultural sources (~40%) and catalyst equipped gasoline combustion (~16%) and upwind sources

24  (~18%). The majority of the organic carbon found in SCAB was attributed in this study to primary

25  emissions by transportation-related sources including diesel (~13%) and gasoline (~44%) engines and

26  paved road dust (~12%). At the Fullerton site in the middle of the SCAB the concentration of locally

27  generated organics is roughly double that of the locally generated nitrates (~5.6 $\mu g/m^3$ compared to

28  ~2.4 $\mu g/m^3$), while at Riverside on the east edge of the SCAB and near the large agricultural sources of

29  ammonia emissions, the particulate nitrate concentrations are nearly double that of organic PM

30  (~17 $\mu g/m^3$ compared to ~10 $\mu g/m^3$).

31      Ying and Kleeman (2006) showed that during the winter 1996 episode in the SJV most of the nitric

32  acid that forms particulate nitrate is from upwind sources (~57%) with diesel and gasoline combustion

33  contributing most of the rest (30%), while much of the ammonia is from upwind sources (~39%) and a

34  combination of area, soil and fertilizer sources (~52%). In an assessment of PM particle size and

composition in the SJV during the winter of 2000-2001, Herner, et al. (2006) showed that fresh emissions of carbonaceous PM from combustion sources in urban locations (Sacramento, Modesto, and Bakersfield, CA) move quickly from ultrafine particle size (i.e. diameter ~0.1 μm) to accumulation mode by condensation with accumulation mode (i.e., diameter ~0.5 μm) particles, and that secondary nitrate particle formation occurs preferentially on the surface of hydrated ammonium sulfate particles during the afternoon when gas-phase nitric acid is at peak photo-chemical production from $NO_X$. Given the abundance of ammonia emissions and low ambient temperatures, particulate nitrate production in this way is only limited by the availability of nitric acid. Due to the cool winter conditions there was little secondary organic aerosol production during this study. Sea salt was shown to dominate the larger coarse particle mode during on-shore wind at the background coastal monitoring site at Bodega Bay, north of San Francisco, CA.

Using a regression analysis to find the dependence of particulate sulfate concentration measured over a three year period (2000–2002) at 84 western IMPROVE monitoring sites on the modeled transport trajectories to the sites for each sample period, Xu et al. (2006) were able to infer the source regions that supplied particulate sulfate in the western U.S. Among the source regions included in this analysis were the near coastal Pacific Ocean (i.e. a 300 km zone off the coast of California, Oregon, and Washington). Up to half of the particulate sulfate measured at Southern California monitoring sites was associated with this source region. As shown in Figure 9-30 the zone of impact from this source region included large regions of California, Arizona, and Nevada. The authors made the case that high sulfur content fuel used in marine shipping and port emissions may be largely responsible. As a result, the Western Regional Air Partnership (WRAP) RPO emissions inventory was modified to include marine shipping and a Pacific Offshore source region was added to source attribution by air quality simulation modeling.

The sulfate attribution results of the WRAP air quality modeling (results available on the Technical Support System (TSS) website, see Table 9-1 for the web-link) credit the Pacific offshore source region with somewhat smaller contributions than those from the trajectory regression work by Xu, with concentrations at the peak impact site in California that are about 45% compared to 50% by regressions and even greater differences for more distant monitoring sites. Based on the modeling attribution the Pacific offshore source region was responsible for 10%-20% of the nitrate measured in Southern California.
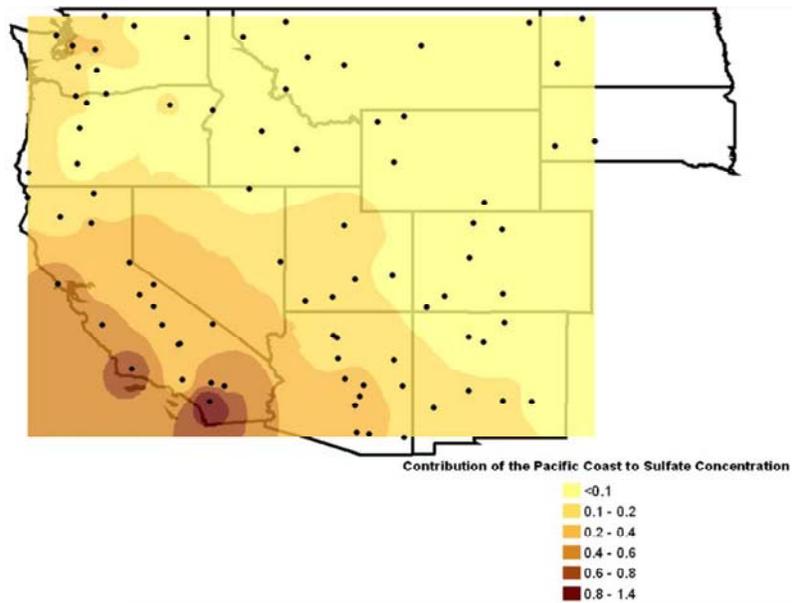
Source: Xu et al. (2006).

**Figure 9-30. Contributions of the Pacific Coast area to the ammonium sulfate (µg/m³) at 84 remote-area monitoring sites in western U.S. based on trajectory regression (dots denote locations of the IMPROVE aerosol monitoring sites).**

1    A coordinated effort by federal, state, and county air quality organizations to determine the causes

2    of haze in the Columbia River Gorge (a deep and narrow gap in the Cascade Mountains on the

3    Washington/Oregon border) through extensive multiyear measurements and high spatial resolution air

4    quality modeling of typical episodes demonstrated the multitude of emission sources that contribute to its

5    impairment (Pitchford et al., 2007). During the summer, Gorge winds are generally from the west and

6    relatively dry. More than half of the haze during a typical summer episode is from a combination of

7    international and other distant sources (~22% at the western end of the Gorge) and regional natural

8    sources including wildfire and secondary (~39% at the western end of the Gorge) organic PM from

9    biogenic emissions. The Portland/Vancouver metropolitan area was responsible for a significant amount

10   of the haze during the summer (~20% on in the western end of the Gorge, while sources within the Gorge

11   were responsible for a moderate amount of haze (~6% and ~9% at the western and eastern ends of the

12   Gorge). The wind is much more often from the east during the winter. The highest haze levels in the

13   Gorge are during the winter and are associated with fog conditions that rapidly convert precursor gaseous

14   emissions of $NO_X$ and $SO_2$ from local and regional combustion sources and $NH_4$ from local and regional

15   agricultural activities to secondary nitrate and sulfate PM that persist as a post-fog intense haze.

16   Contributions by these sources east of the Gorge contribute ~57% of the haze on the eastern end of the

17   Gorge, with half of the nitrate and sulfate particulate from electric utility emissions and most of the rest

18   from transportation sources. Other sources contributing during the winter haze at the eastern end of the

1   Gorge are from sources outside the modeling domain (i.e. most of Washington and Oregon) and within

2   the Gorge (~23% and ~10% respectively).

3       An assessment of concurrent measurements at the nearby Mt. Hood IMPROVE monitoring site

4   (45 km south of the Columbia River at 1531m ASL), show that Columbia River Gorge haze levels and

5   especially the wintertime high nitrate/sulfate contributions to haze are not typical of the generally higher

6   elevation remote areas of the region (Pitchford et al., 2007). However the Gorge's high wintertime nitrate

7   and sulfate are found at the Hells Canyon IMPROVE site, which is similarly situated in a narrow canyon

8   of the Snake River almost 400 km east of the Gorge (from the VIEWS web site, see Table 9-1).
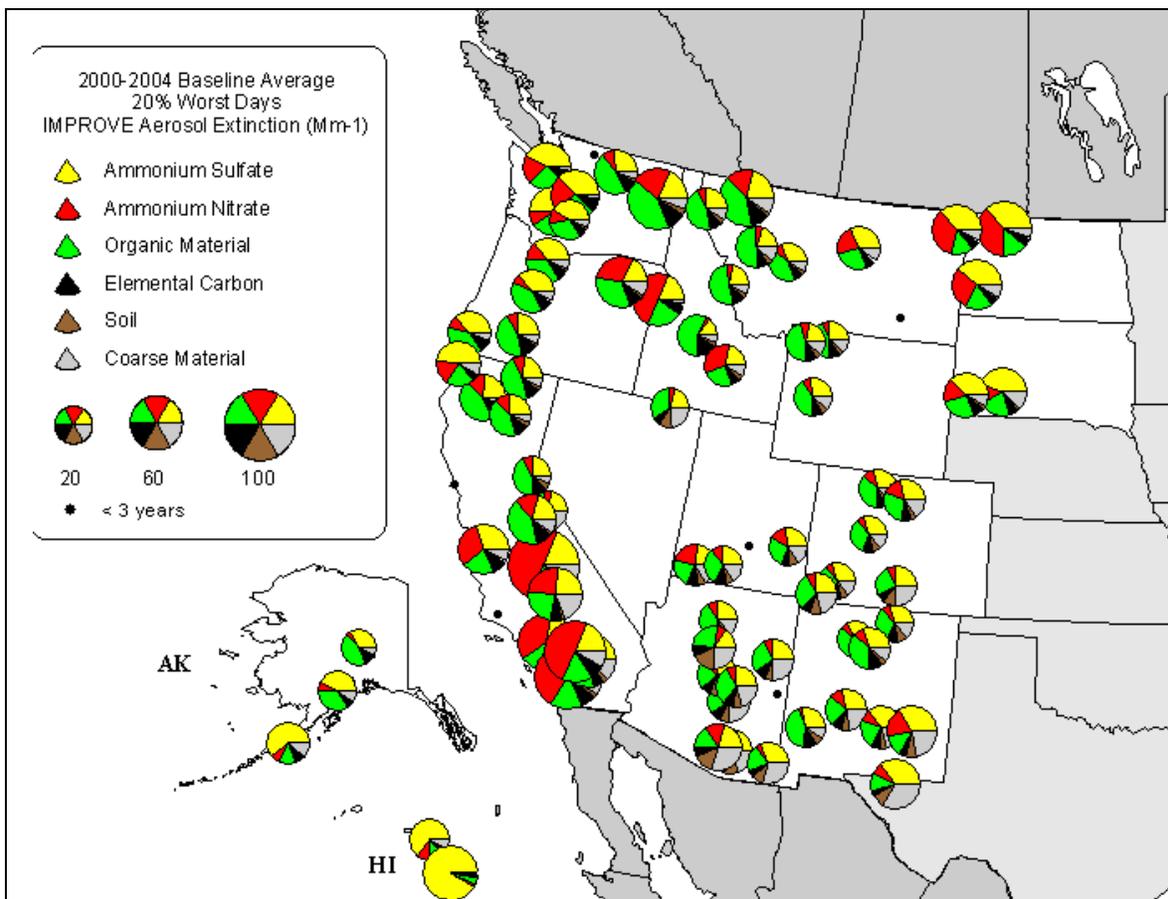


Source: From the TSS web site.

**Figure 9-31.  Shows the IMPROVE monitoring sites in the WRAP region with at least three years of valid data and identifies the six sites selected to demonstrate the apportionment tools.  Pie diagrams show the composition for the mean of the 20% worst haze conditions.**

1      Several example monitoring locations distributed across the northern and southern portions of the

2      western U.S. have been selected to illustrate the attribution results from the WRAP-sponsored attribution

3      analysis tools that estimate the relative responsibility for haze of the various PM species by source region

4      and source type. The selected sites include Olympic National Park (NP), WA; Yellowstone NP, WY; and

5      Badlands NP, SD across the north, and San Gorgonio Wilderness (W), CA; Grand Canyon NP, AZ and

6      Salt Creek W, NM across the south as shown in Figure 9-31.

7      WRAP-sponsored CMAQ modeling used virtual tracers of $SO_2$ and $NO_X$ emissions that tracked the

8      source region and category through the transport and transformation processes to particulate sulfate and

9      nitrate. This was used to produce pie diagrams of particulate sulfate and nitrate attribution results by

10    source region for each of these sites as shown in Figure 9-32 (produced using the TSS, see Table 9-1).

11    Based on these sites, over half of the particulate sulfate in remote areas of the Pacific coastal states is

12    from outside of the U.S. (Pacific offshore and outside of the domain). The outside of the domain values

13    were derived by simulating the fate of the boundary condition concentrations, which for the WRAP air

14    quality modeling were obtained using output from the GEOS-CHEM global air quality model (Fiore et

15    al., 2003). The sulfate fraction from the region labeled outside of domain was approximately uniform

16    throughout the western U.S. with site-to-site variation in the fraction caused mostly by variations in total

17    sulfate concentration. The more northerly sites have impacts from Canadian emissions, while the southern

18    sites have impacts from Mexican emissions. Half of the Salt Creek, New Mexico sulfate is from the

19    domestic source emissions further to the east, which also contribute about 20%-Badlands particulate

20    sulfate concentrations. A breakout of the emission sources from within the WRAP region by source type

21    (not shown) has most of the emissions from point sources, with the combination of motor vehicle, area

22    and wildfire emissions contributing from a few percent at the furthest eastern sites to about half at San

23    Gorgonio.

24      By comparison, the particulate nitrate is much more from domestic regional emission sources, with

25    ~60%-~80% being from emissions within the WRAP region. For the west coast sites about 25% of the

26    nitrate is from a combination of Pacific offshore emissions (i.e. marine shipping) and outside domain

27    regions. Canadian emissions are responsible for about 10%-30% of the particulate nitrate for the three

28    northern sites, but Mexican emissions do not contribute appreciably to particulate nitrate for the three

29    southern sites. Motor vehicles are the largest contributing $NO_X$ source category responsible for particulate

30    nitrate for these six WRAP sites, with a combination of point, area and wildfire source categories also

31    contributing from about 10%-50% of the WRAP regional emissions.

32
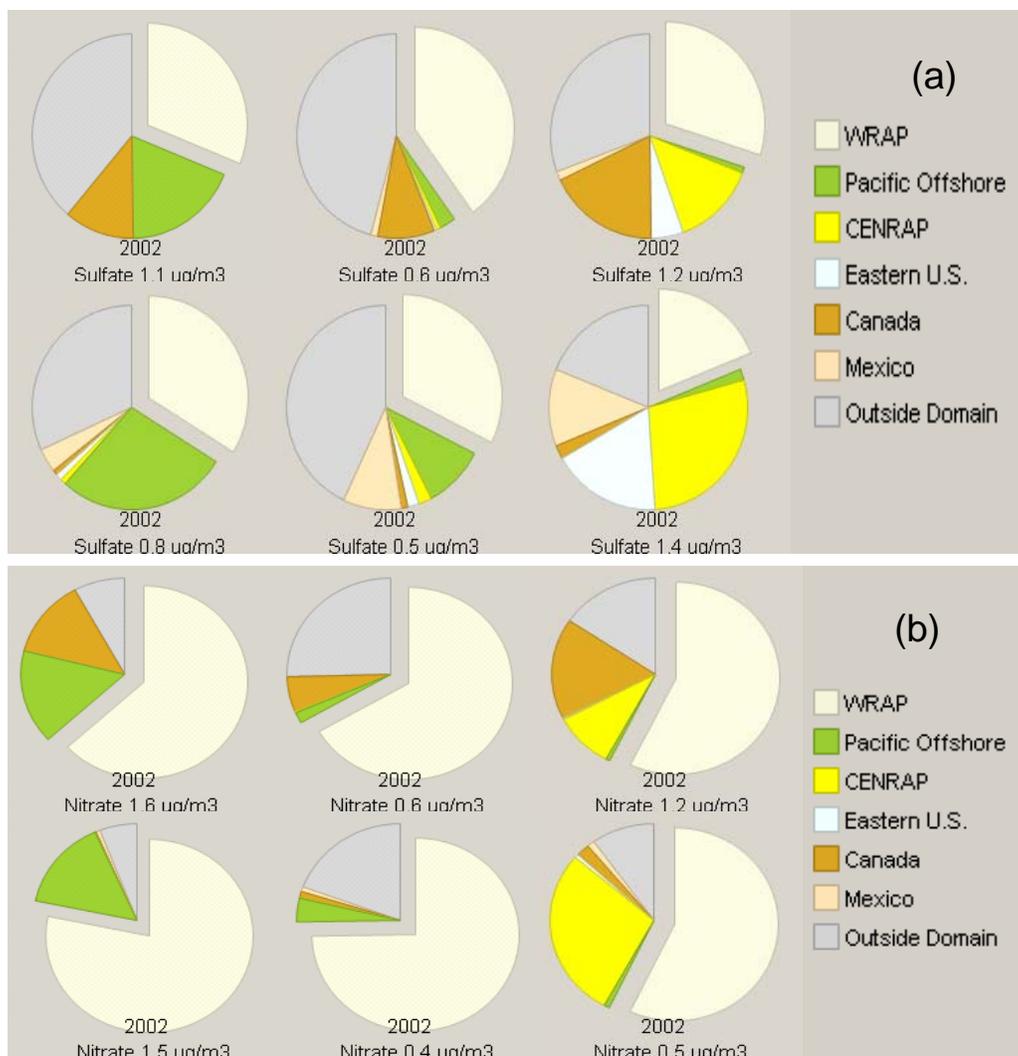
**Figure 9-32.** **Particulate sulfate (a) and nitrate (b) source attribution by region using CAMx modeling for six western remote area monitoring sites: top left to right Olympic NP, WA; Yellowstone NP, WY; Badlands NP, SD; bottom left to right San Gorgonio W, CA; Grand Canyon NP, AZ; and Salt Creek W, NM. WRAP includes ND, SD, WY, CO, NM and all states further west. CENRAP includes all states east of WRAP and west of the Mississippi River including MN. eastern U.S. includes all states east of CENRAP. The Pacific Offshore extends 300km to the west of CA, OR, and WA. Outside Domain refers to the modeling domain, which extend hundreds of kilometer into the Pacific and Atlantic Oceans and from Hudson Bay Canada to just north of Mexico City. This figure was assembled from site-specific diagrams produced on the TSS web site (see Table 9-1).**

1      WRAP only used the virtual tracer approach to investigate source locations and categories for $SO_2$

2  and $NO_X$ emissions. A different type of virtual tracer modeling tool was used to track various the organic

3  carbon compounds and sort them into three groups. The first group labeled primary organics includes all

4  of the organics that are emitted directly as PM from any source type and location. The second group

1    labeled anthropogenic secondary organics is PM produced in the atmosphere by aromatic VOCs. The

2    third category labeled biogenic secondary organics is PM produced in the atmosphere by biogenic VOCs.

3    Organic PM in the biogenic secondary category includes those that would functionally be considered

4    man-made emissions (e.g. those from agricultural crops and urban landscapes), though in most remote

5    areas of the west these man-made VOC emissions are small compared to those of the natural biogenic

6    sources. Figures 9-33, 9-34 and 9-35 show the monthly averaged apportionment of organic PM for the six

7    selected monitoring locations.
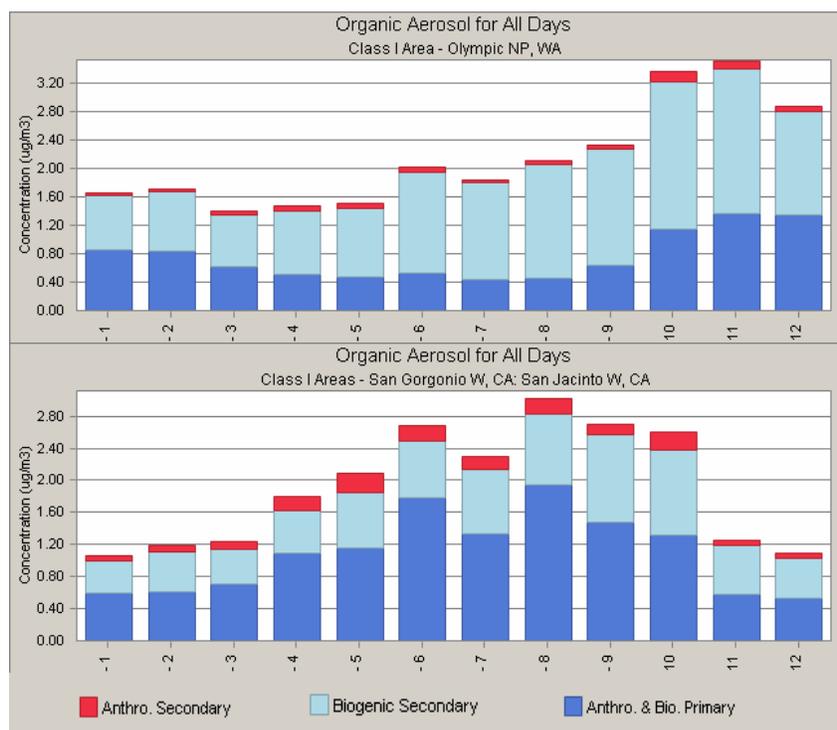


**Figure 9-33.   Monthly averaged model predicted organic mass concentration apportioned into primary and anthropogenic and biogenic secondary PM categories for the Olympic National Park (top) and San Gorgonio Wilderness (bottom) monitoring sites. From the TSS web site, see Table 9-1.**

8        Based on the modeling results for these six sites and confirmed by measurements (see, e.g. Figure

9    9-10), a west to east decreasing gradient of organic mass exists with annual concentrations from ~2 μg/m$^3$

10   for the coastal state sites to ~1 μg/m$^3$ for the intermountain west sites to less than 1 μg/m$^3$ for the sites just

11   east of the Rocky Mountains, discounting the large fire impacts for July at Yellowstone N.P. which raised

12   its annual mean to ~2 μg/m$^3$. At all of these remote-area sites anthropogenic secondary PM is estimated to

13   be a small fraction of the organic mass, with the largest fractional contribution at the San Gorgonio

1     monitoring site immediately downwind of the major Southern California urban areas, yet having less than

2     10% of the monthly mean organic mass from anthropogenic secondary PM. Of the six selected

3     monitoring sites, San Gorgonio has the highest fraction of the organic PM from primary emissions

4     (~57%), followed by Yellowstone (~55%), then the two eastern-most sites (Badlands ~42% and Salt

5     Creek 41%), and with Grand Canyon and Olympic national parks the lowest fraction by primary

6     emissions (~37%). Yellowstone N.P. would have had the lowest fraction of organic PM by primary

7     emissions had it not been for the month of July (the 11 month mean is 29%) when wild fire smoke

8     contributed.
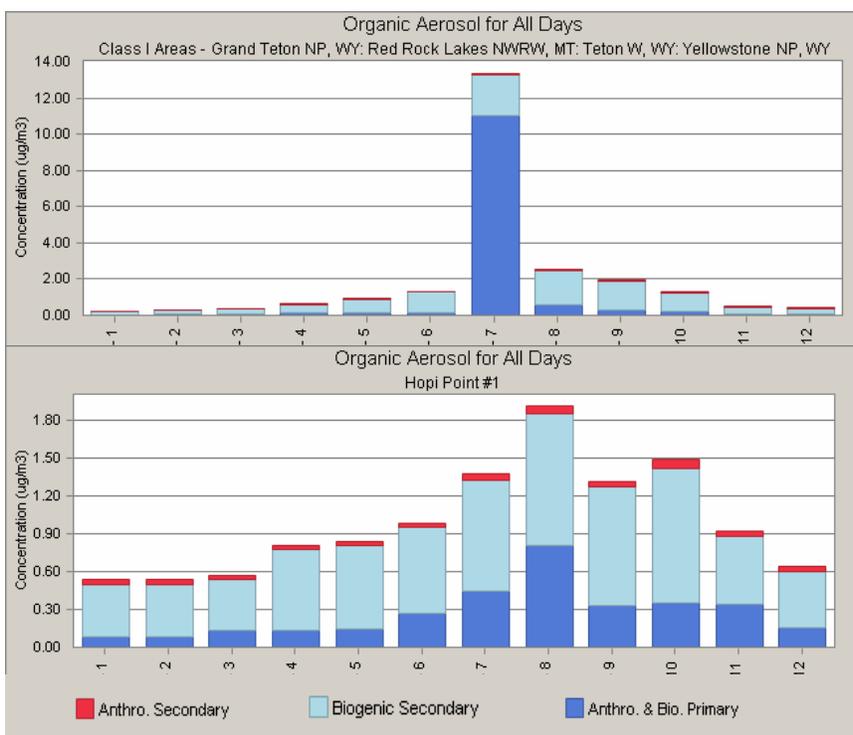


**Figure 9-34. Monthly averaged model predicted organic mass concentration apportioned into primary and anthropogenic and biogenic secondary PM categories for the Yellowstone National Park (top) and Grand Canyon (Hopi Point) (bottom) monitoring sites. From the TSS web site, see Table 9-1.**
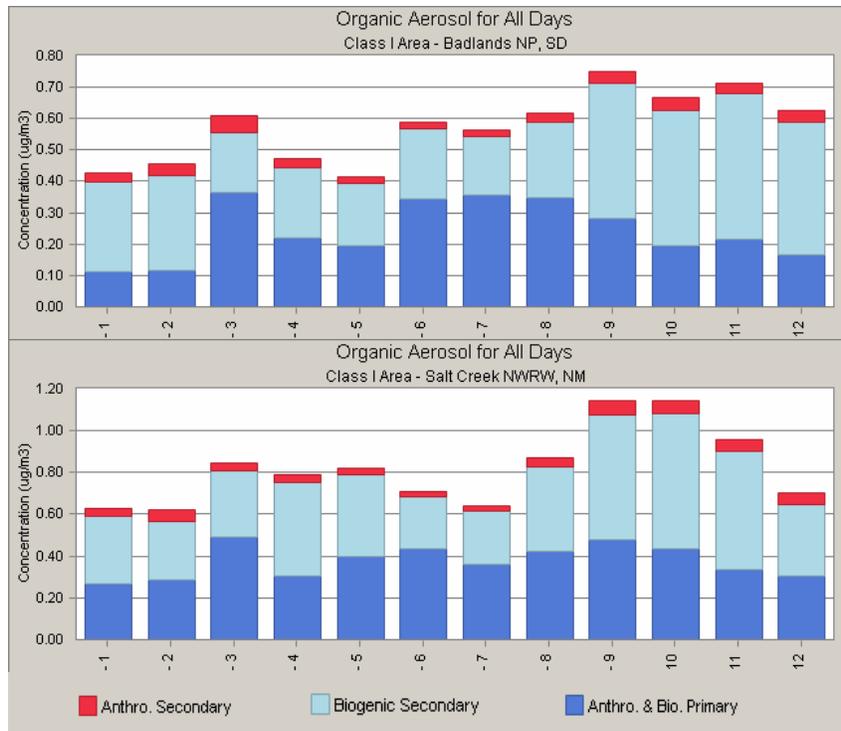
**Figure 9-35. Monthly averaged model predicted organic mass concentration apportioned into primary and anthropogenic and biogenic secondary PM categories for the Badland National Park (top) and Salt Creek Wilderness (bottom) monitoring sites. From the TSS web site, see Table 9-1.**

1        Radiocarbon ($^{14}$C) dating techniques were used to group ambient PM carbon into fossil and

2    contemporary source categories at 12 IMPROVE monitoring sites across the U.S., 8 of which are in the

3    WRAP region (Schichtel et al., 2008). Results of this work showed that contemporary carbon accounts for

4    about half the carbon in urban areas, 70%-97% in near-urban areas (i.e., San Gorgonio) and 82%-100% in

5    remote areas. Comparing these radiocarbon dating results with the WRAP virtual tracer modeling results

6    for organic aerosol (above), and presuming that the modeled anthropogenic secondary organic is fossil

7    carbon and the biogenic secondary is contemporary carbon, suggests that a large fraction of the model-

8    determined regional primary organic PM is from contemporary carbon sources (e.g. smoke from

9    wildfires).

10       Schichtel, et al. (2008) compared radiocarbon measurements at two sets of urban/rural paired sites

11    in the west (Mount Rainer/Seattle, and Tonto/Phoenix). Figure 9-36 shows that most of total carbon urban

12    excess (i.e. urban site concentration minus the regional site concentration) in the summer is from fossil

13    carbon sources (87% and 79% respectively), while in the winter there is a surprisingly high fraction of the

14    urban excess at both sites that is from contemporary carbon sources (41% and 47% respectively). This

15    implies that urban, and therefore anthropogenic, activities generate almost as much $PM_{2.5}$ carbon from

1  contemporary sources (e.g. residential wood combustion) as from the fossil sources during the winter for

2  these two western urban areas.



**Figure 9-36.  Comparison of carbon concentrations between Seattle (Puget Sound site) and Mt. Rainer (left) and between Phoenix and Tonto (right) showing the background site concentration (gray) and the urban excess concentration (black) for total, fossil and contemporary carbon during the summer and winter studies.**
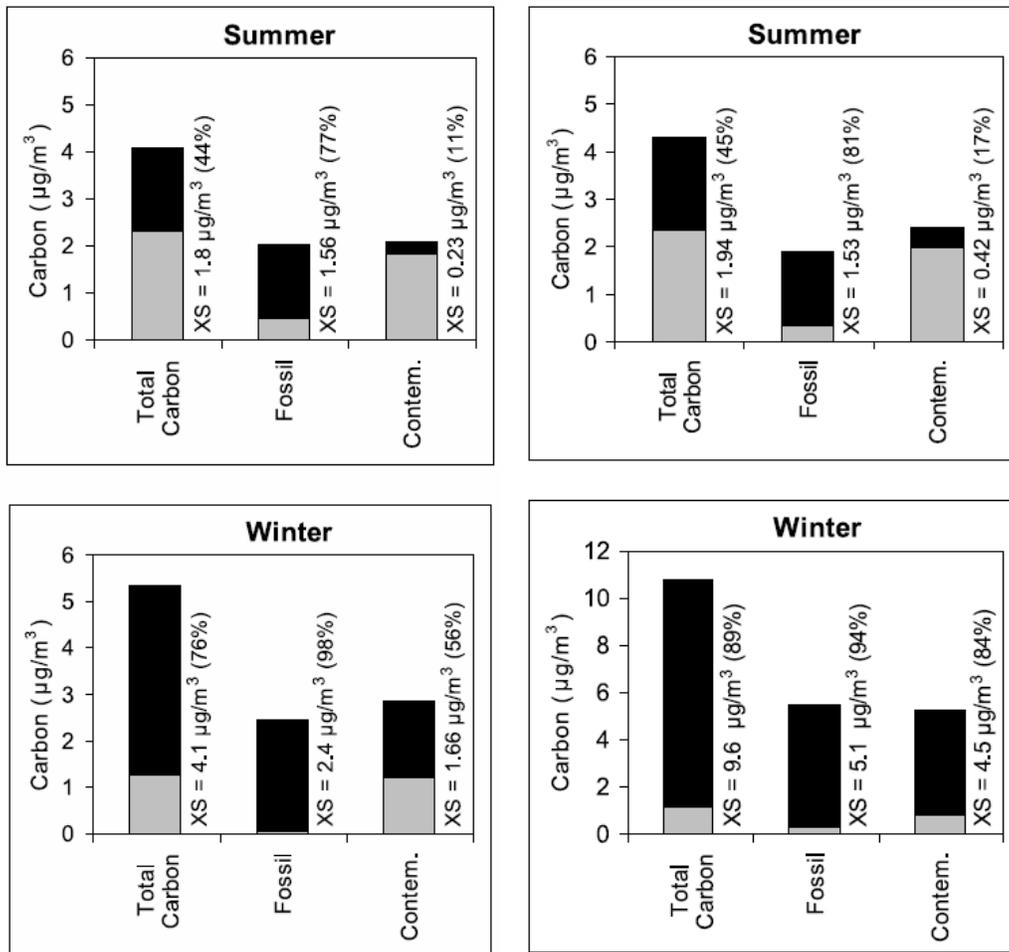
Source: (Schichtel et al., 2008)

3        Contemporary carbon estimates for all of the IMPROVE network monitoring sites for data from

4  two summer seasons (June, July and August, 2004/2005) and two winter seasons (December, 2004/2005,

5  January and February, 2005/2006) were calculated from the measured EC/TC ratios using the 12-site

6  empirical relationship between radiocarbon determined contemporary carbon fraction and IMPROVE

7  measured EC/TC ratio (Schichtel et al., 2008). The results are displayed in color contour maps in Figure

8  9-37, which also shows the radiocarbon determined contemporary carbon for the 12 sites. The lowest

1      contemporary carbon estimates (< 60%) in both seasons are for urban areas. In the rural West, most of the

2      sites have over 90% of their PM carbon from contemporary carbon sources during the summer and from

3      60%-over 90% during the winter. In the rural East, most of the sites have 45%-90% of their PM carbon

4      from contemporary carbon sources during the summer and from 60%-over 90% in the winter.
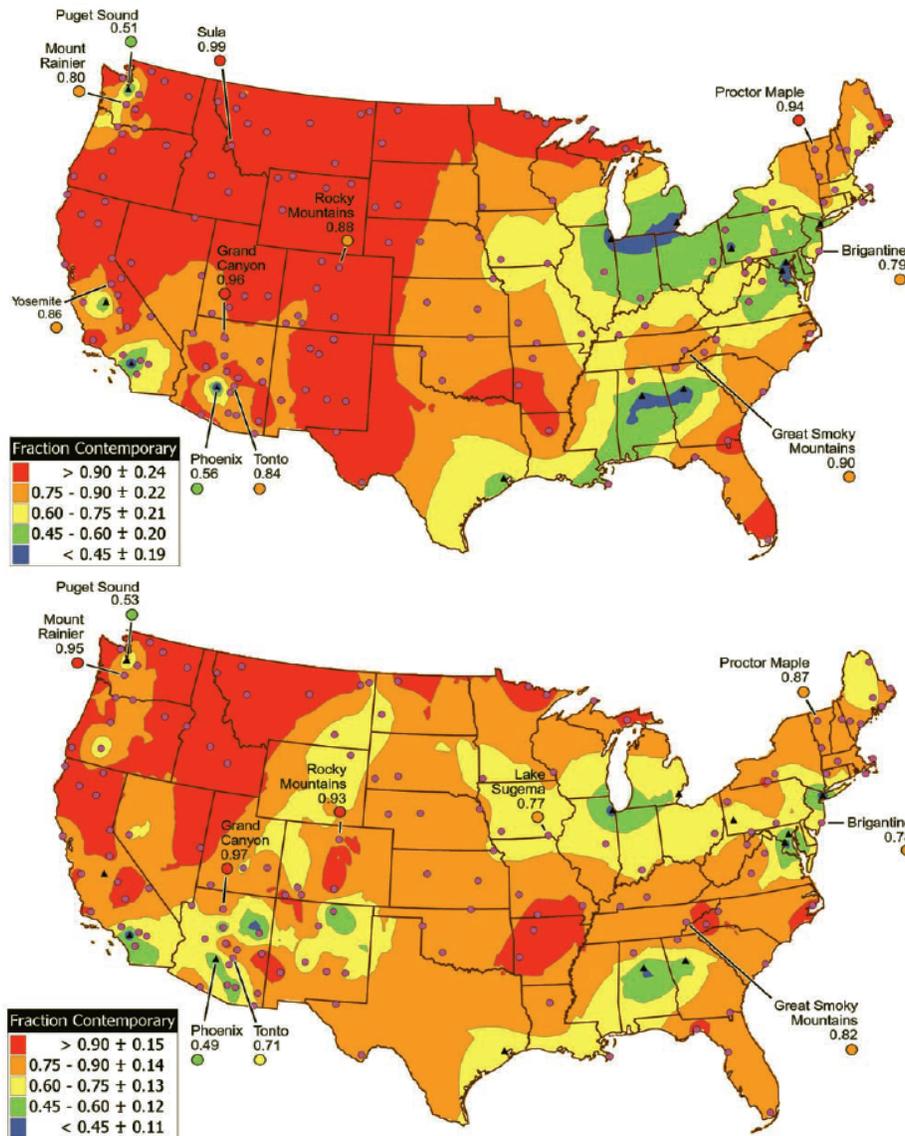


**Figure 9-37.** **Average contemporary fraction of PM$_{2.5}$ carbon for the summer (top) and winter (bottom), estimated from IMPROVE monitoring data (6/04 to 2/06) based on EC/TC ratios. The contemporary values from radiocarbon dating for the 12 monitoring sites are indicated in by colored circles with the site names. Color contours are shown to aid in showing sites with similar values. Site locations are indicated by circles for remote area sites and triangles for urban sites.**

1    Schichtel, et al. (2008) showed a strong relationship between the site-averaged ratios of EC to total

2    carbon (EC/TC) and the site-averaged fraction of fossil carbon separately for the summer and winter data

3    sets (i.e. $R^2$ of 0.71 and 0.87 respectively). Using regression analysis they estimated that the summer and

4    winter EC/TC ratios associated with purely fossil carbon were $0.35 \pm 0.039$ and $0.46 \pm 0.028$ respectively

5    and for purely contemporary carbon the EC/TC ratios were $0.12 \pm 0.011$ and $0.19 \pm 0.0095$. These ratios

6    are shown to be consistent with corresponding ratios from the literature for source testing primary fossil

7    and contemporary combustion sources respectively. They are also shown to be consistent with the 90

8    percentile value of the EC/TC ratio from the urban IMPROVE monitoring sites (0.41 and 0.44 for

9    summer and winter) and the 10th percentile values of the EC/TC ratio for remote areas IMPROVE

10   monitoring sites (0.07 and 0.16 for summer and winter), which they argue are dominated by fossil and

11   contemporary carbon respectively.

12   The largest sources of contemporary carbon are primary emissions from biomass burning and

13   secondary organic aerosol from biogenic precursor gases (e.g. terpenes from conifer forests). Schichtel, et

14   al. (2008) estimated the 12-site overall contribution by secondary organic PM to the summer

15   contemporary carbon fraction as $36 \pm 6.4\%$ by assuming the EC/TC ratio for contemporary carbon during

16   the winter represented the ratio of primary emissions only (i.e. no secondary organic PM formation in the

17   winter) and that the EC/TC ratio for primary emissions is independent of seasons. The same method

18   applied to the fossil carbon fraction yielded an estimate of $23 \pm 10\%$ of the fossil carbon PM from

19   secondary organic formation in the atmosphere during the summer. These estimates correspond to over

20   40% of the contemporary and over 35% of the fossil organic carbon being from secondary PM formation.

21   WRAP applied a weighted emissions potential analysis tool that combined gridded emissions data

22   with back-trajectory analysis that simulated the transport pathway to the various monitoring sites to infer

23   likely source region and emission categories for the 20% best and 20% worst haze conditions for each of

24   the IMPROVE PM speciation monitoring location in the West. Unlike the virtual tracer approach that

25   uses a full regional air quality simulation model, this method does not explicitly account for chemistry or

26   removal processes and it does not incorporate the sophisticated dispersion estimates (i.e., it uses one over

27   distance weighting for dispersion), so it should be considered a screening tool that has been found to be

28   helpful in identifying the likely sources contributing to haze. Primary organic and EC PM species results

29   from the weighted emissions potential tool for the worst 20% haze days using the 2000 to 2004 base years

30   emissions and trajectories, and the same trajectories with 2018-projected emissions for each of the six

31   selected western monitoring locations are shown in Figures 9-38 through 9-43.
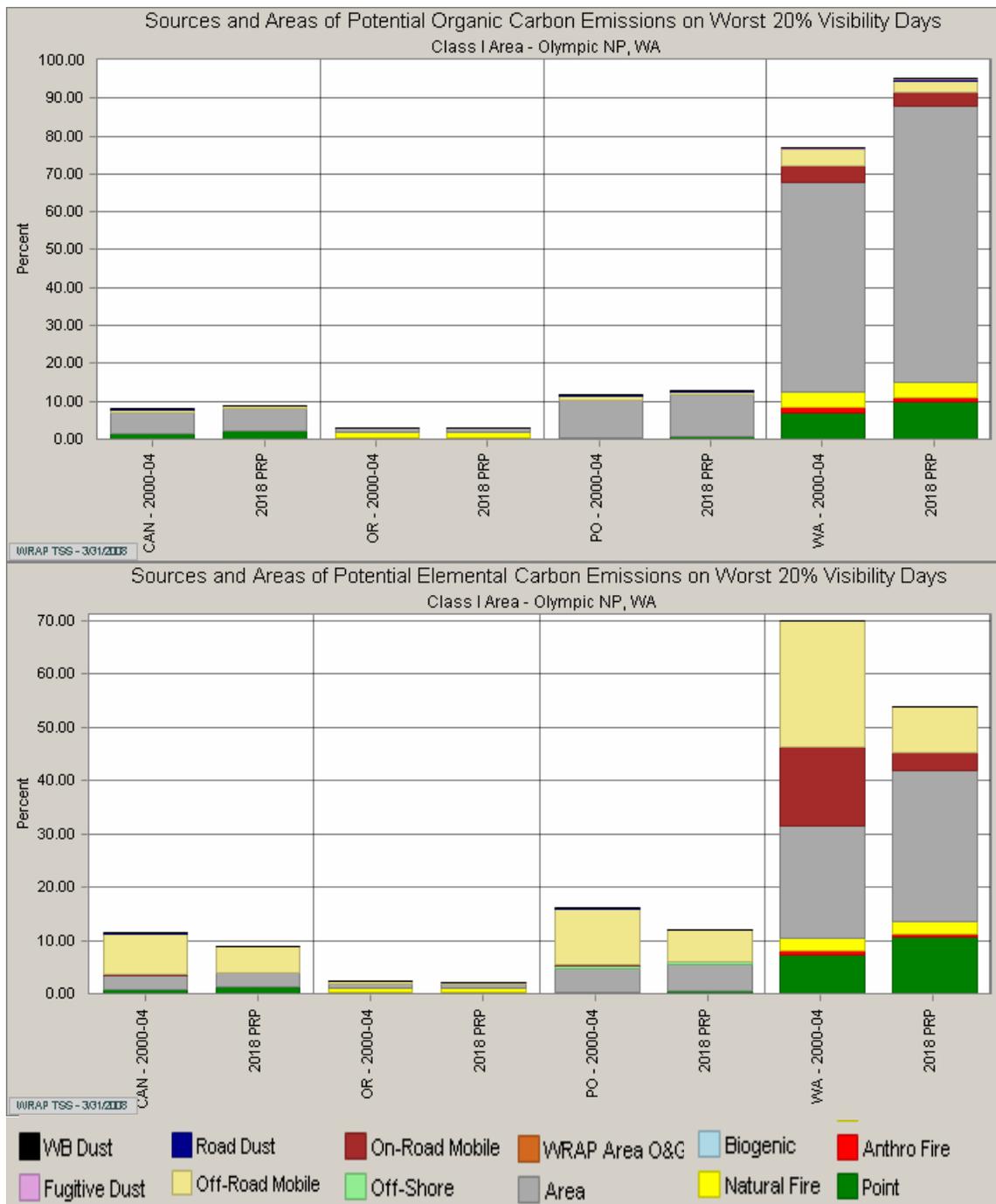
**Figure 9-38. Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for Olympic N.P. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., Canada, Oregon, Pacific Off-Shore, and Washington from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**
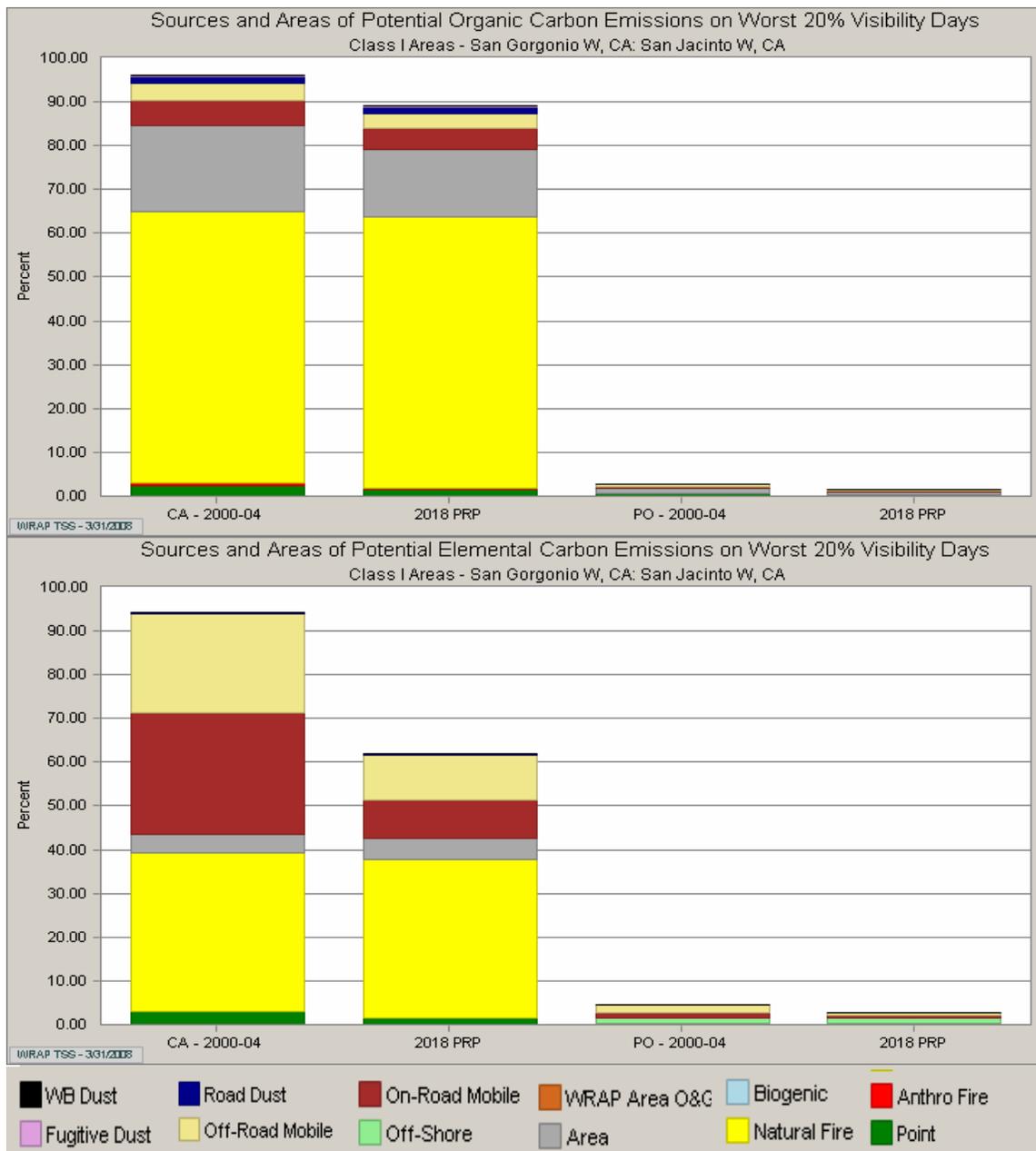
**Figure 9-39.** **Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for San Gorgonio W. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., California and Pacific Off-Shore from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**

1    For Olympic N.P. (Figure 9-38), most of the primary organic as well as most of the EC PM is likely
2    to be from the state of Washington during the worst haze days. This is because the multi-day trajectories

1   that transport emissions on its worst days tend to be short (within 200 km based on maps available on

2   TSS, see Table 9-1). Area sources, which include emissions from residential wood heating, watercraft,

3   non-mobile urban and other sources too small to be labeled as point sources, are the big contributors to

4   primary organic, while on- and off-road mobile emissions plus area sources are large contributors to the

5   EC at Olympic N.P. The 2018 projected growth in area sources and decrease in emissions of mobile

6   source emissions is anticipated to increase the haze by primary organic while reducing the haze by EC at

7   Olympic N.P. The same analysis applied to San Gorgonio (Figure 9-39), is similar in that the majority of

8   the emissions with the potential to contribute to primary organic and EC PM is from the home state,

9   California in this case. However, the likely importance of natural fire emissions for carbonaceous PM

10  species sites is substantially greater at San Gorgonio W. than it was for Olympic N.P.

11       The weighted emissions potential results applied to Yellowstone N.P. and Grand Canyon N.P.

12  (Figures 9-40 and 9-41) show the likely dominance of natural fire emissions in the intermountain western

13  U.S. to primary organic and EC PM. during worst haze conditions for these two locations. Numerous

14  states have emissions that have the potential to contribute noticeably to these carbonaceous species, due to

15  relatively long multi-day trajectories (500 km to 1000 km) on worst haze days, though for both sites the

16  home state has the greatest potential based on this inverse distance weighting approach. On- and off-road

17  mobile sources in Arizona and California have significant potential to contribute to Grand Canyon

18  carbonaceous particles, especially EC concentrations, probably due to some of the trajectories being over

19  the populated areas of these two states to the south and southwest of Grand Canyon.

20       For the most easterly of the selected WRAP sites, Badlands N.P. and Salt Creek, the weighted

21  emissions potential results for primary organic and EC (Figures 9-42 and 9-43) show potential

22  contributions from a greater number of states and multi-state regions than for selected sites further to the

23  west. This may be due in part to trajectories associated with worst haze conditions for these two sites

24  being moderately long (~500 km) and in multiple directions. Natural fire emissions have the greatest

25  potential to contribute to organic species PM at Badlands N.P., but are less likely to be dominant at Salt

26  Creek, or at either site in its contribution to EC PM concentrations. The contributions by emissions from

27  area and mobile sources from the home states and states to the east (Central States Regional Air

28  Partnership states are labeled CEN in the figures) are potentially greater than by natural fire; this is

29  especially true for contributions to EC PM.
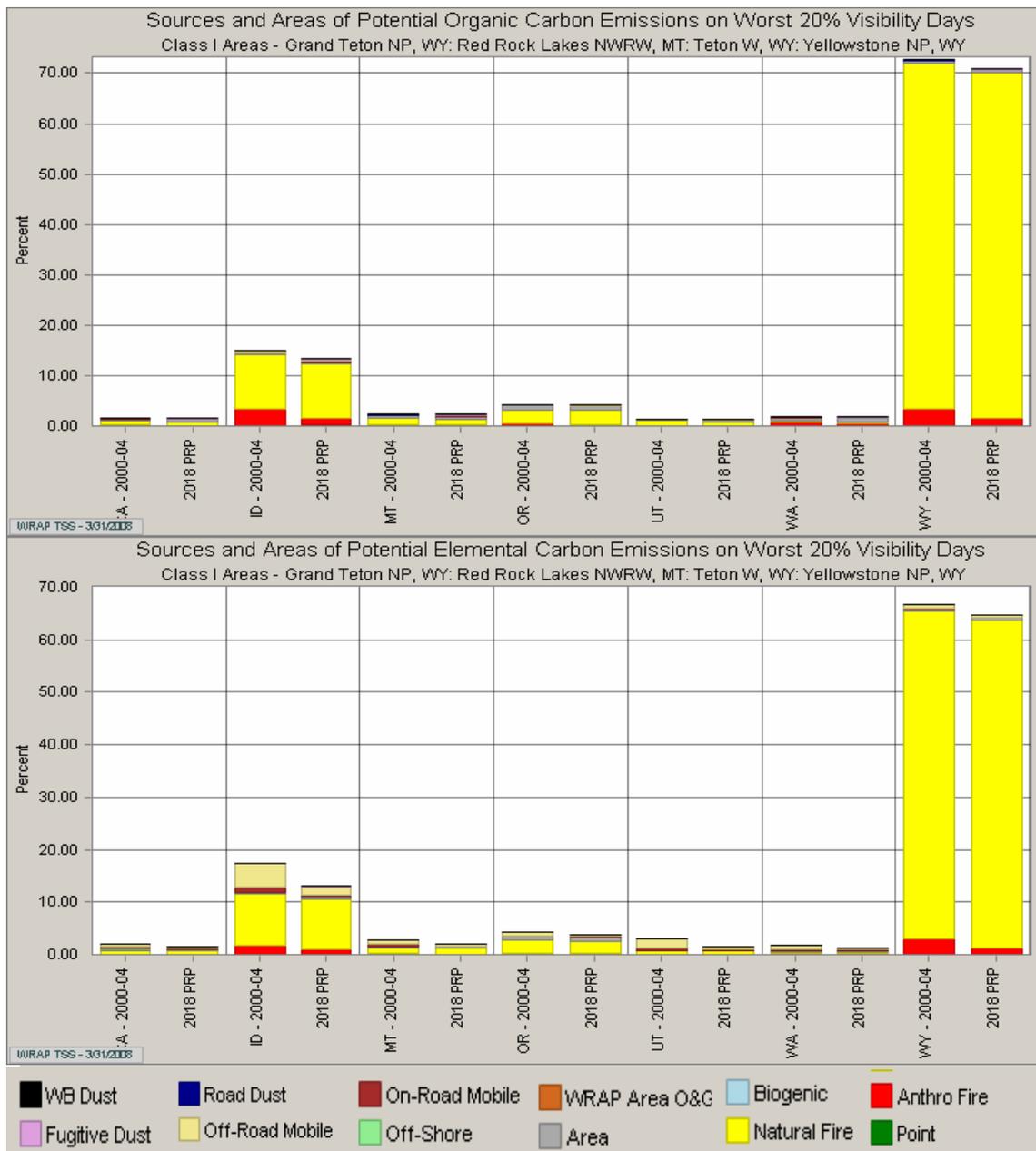
**Figure 9-40. Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for Yellowstone N.P. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., California, Idaho, Montana, Oregon, Utah, Washington, and Wyoming from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**
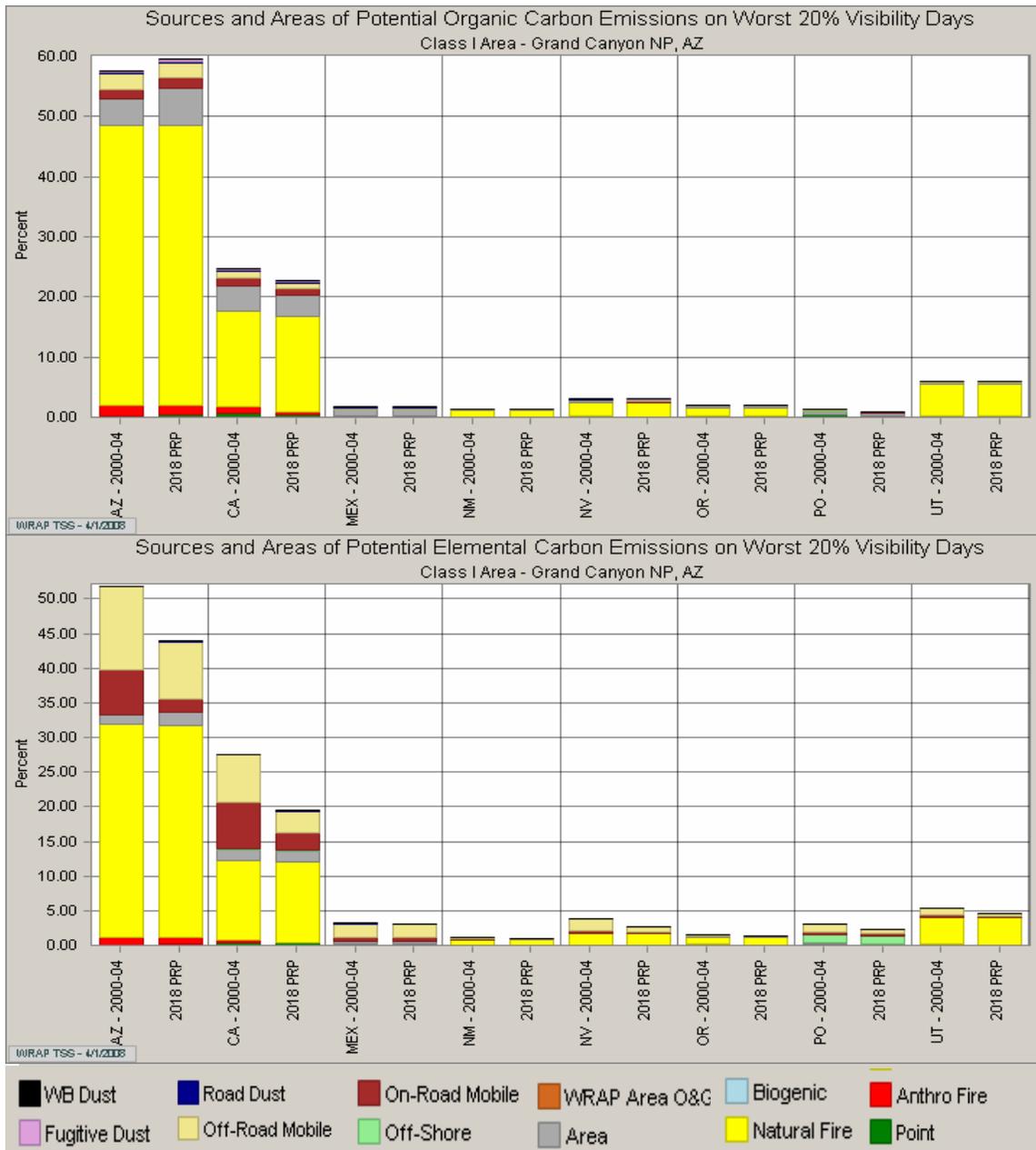
**Figure 9-41.** **Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for Grand Canyon N.P. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., Arizona, California, Mexico, New Mexico, Nevada, Oregon, Pacific Off-shore and Utah from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**
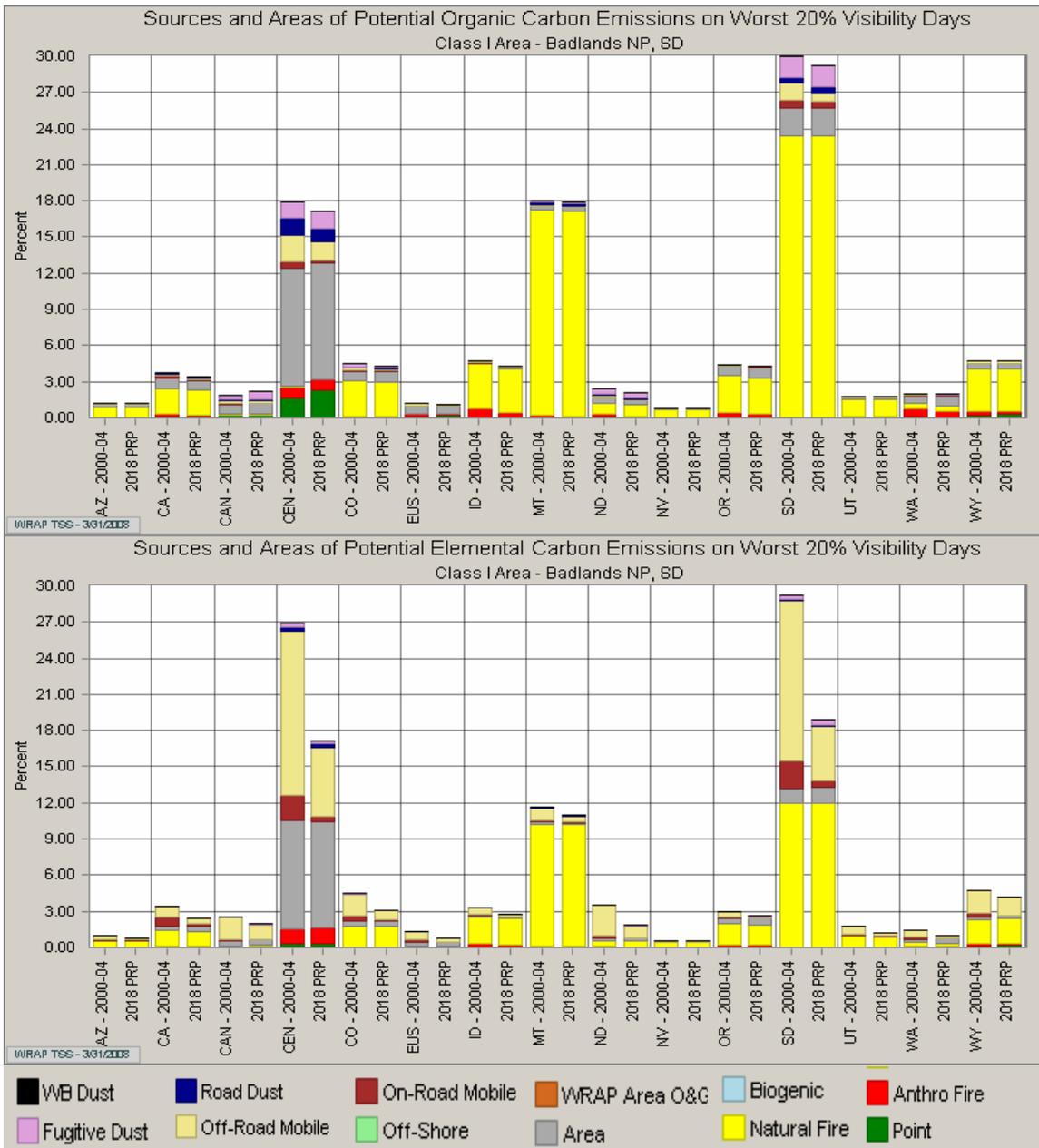
**Figure 9-42. Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for Badlands N.P. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., Arizona, California, Canada, CenRAP, Colorado, eastern U.S., Idaho, Montana, North Dakota, Nevada, Oregon, South Dakota, Utah, Washington, and Wyoming from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**
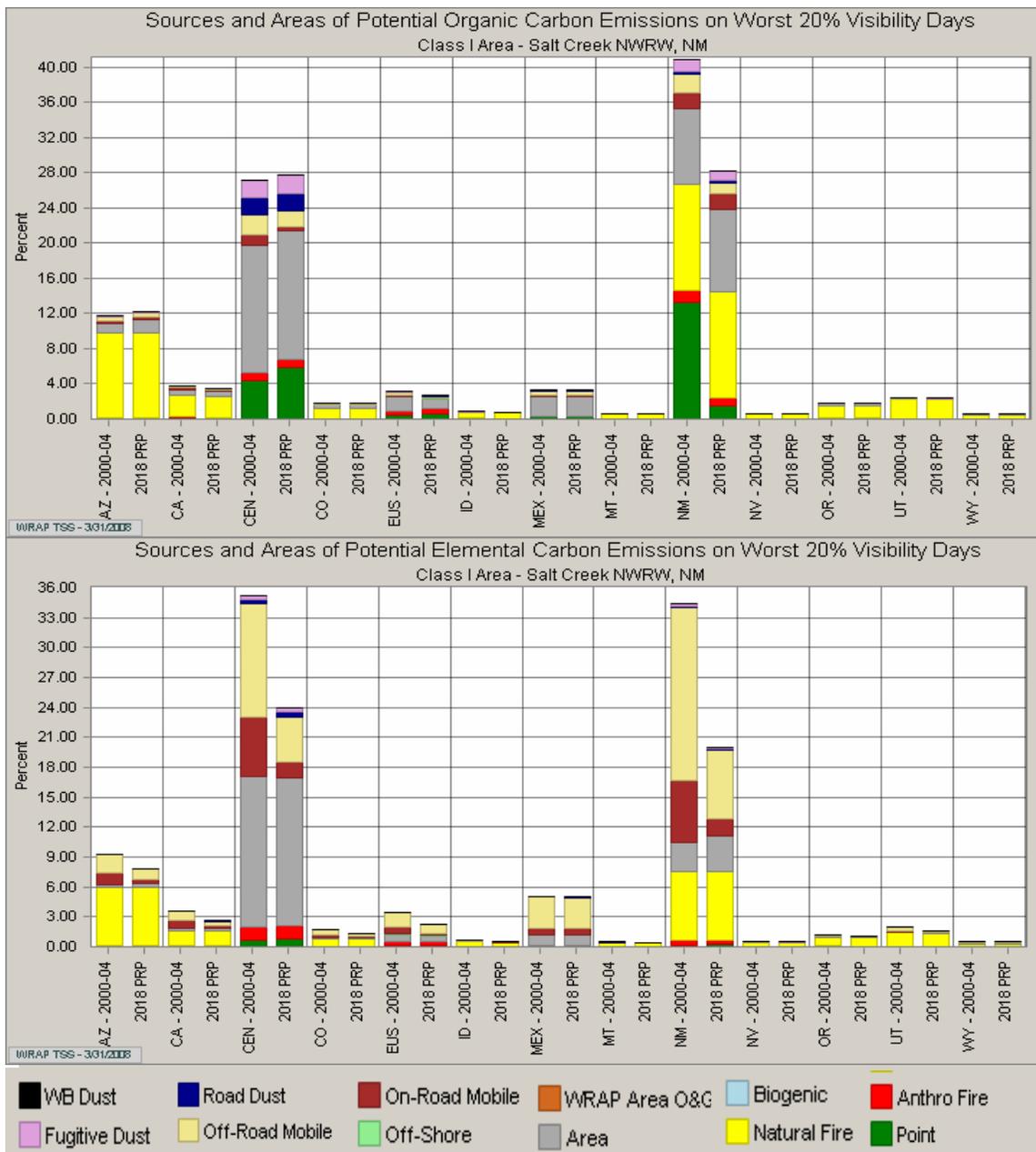
**Figure 9-43. Results of the weighted emissions potential tool applied to primary organic carbon emissions (top) and EC emissions (bottom) for the baseline and projected 2018 emissions inventories for Salt Creek W. Only source regions (WRAP states and other regions) with the largest estimated contributions are shown (i.e., Arizona, California, CenRAP, Colorado, eastern U.S., Idaho, Mexico, Montana, New Mexico, Nevada, Oregon, Utah, and Wyoming from left to right). The scale is normalized (i.e., unitless) one over distance weighted emissions multiplied by trajectory residence time. From the TSS web site (see Table 9-1).**

1    WRAP applied the weighted emissions potential tool to assess likely source types and regions

2    contributing to coarse mass concentrations. The results for the six selected monitoring sites (not shown)

3    are as follows. Most dust at Olympic N.P. is likely to be from fugitive dust sources in Washington state,

4    while at San Gorgonio it is likely more from road dust with smaller amounts from fugitive dust sources.

5    The amount from wind-blown dust is small for both of these far westerly sites. Wind-blown dust is likely

6    the largest source contributing to coarse mass at Grand Canyon N.P., Badlands N.P. and Salt Creek

7    Wilderness with most of it originating in the home-state for those sites. The weighted emissions potential

8    results for coarse mass at Yellowstone are different from those of the other five selected sites in that Idaho

9    and Montana each have a higher potential to contribute to coarse mass on the worst haze days than the

10   home state (Wyoming), and that wind-blown and road dust both contribute to substantially as does

11   fugitive dust and natural fire.

12       In another WRAP-sponsored effort to better understand the causes of remote area haze in the

13   western U.S., each of the worst haze days for all western IMPROVE monitoring sites where dust (defined

14   as the sum of coarse mass and fine soil PM) was the largest contributor to light extinction was separately

15   assessed to categorize the most likely dust source (Kavouras et al., 2007) 2008 and the Causes of Haze

16   Website – see Table 9-1). Elemental composition was used to assess the likelihood that the dust was

17   associated with long-range transport from Asia. A regression analyses at each site between dust

18   concentrations and coincident local wind speed was used to generate site-specific estimates of local

19   windblown dust for each sample period. Finally, back trajectory analysis combined with maps constructed

20   of wind erosion potential (i.e., developed by combining soil types and land cover classifications) are used

21   in a manner similar to the weighted emissions potential analysis to identify the likelihood of regionally

22   transported wind-blown dust as the source. These assessments were conducted on each of the 610

23   so-called "worst dust haze days" at 70 monitoring sites for data from 2001 through 2003 to classify each

24   day by its likely contributions from Asian dust, local windblown dust, upwind transport and

25   undetermined. The undetermined category includes those sample periods that failed to be classified into

26   one of the other three source categories suggesting that mechanically suspended dust activities (e.g.

27   unpaved road dust, agricultural, construction and mining activities) may be responsible.

28       Of the 610 "worst dust haze days" at the 70 WRAP monitoring sites, 55 sample periods are

29   classified as Asian dust influenced, almost exclusively in the spring; 201 sample period are classified as

30   local windblown dust, mostly in the spring but some in all seasons; 240 sample periods are classified as

31   upwind transported dust, with a broader seasonal distribution centered on summer and few instances

32   during winter; and 114 are in the undetermined category with most seasonally distributed with most in

33   summer and least in winter. Most dust days occurred in the deserts of Arizona, New Mexico, Colorado,

34   western Texas and southern California, and these were dominated by local and regionally transported

1    wind-blown dust (e.g. 84% for Salt Creek W.). Asian dust caused only a few of the worst dust days during

2    the 3-year assessment period, though it is an important source (i.e., 10% - 40% of the worst dust days) for

3    sites in the more northern regions of the West with greater vegetative land-cover where local and

4    regionally transported wind-blown dust was infrequent. The frequency of worst dust events classified as

5    undetermined was greatest for sites in the vicinity of large urban and agricultural areas such as those in

6    California and southern Arizona.

7         Source attribution of the particulate sulfate contribution to haze at Big Bend NP, TX was a primary

8    motivation for the BRAVO Study. Schichtel, et al. (2005) showed that during the four-month field

9    monitoring study (July through October, 1999) $SO_2$ emissions sources in the U.S. and Mexico were

10   responsible for ~55% and ~38% of the particulate sulfate respectively. Among U.S. source regions, TX

11   was responsible for ~16%, eastern U.S. ~ 30%, and the western U.S. ~9%. A large coal fired power plant,

12   the Carbón facility in Mexico, just south of Eagle Pass, TX, was responsible for about ~19%, making it

13   the largest single contributor. Pitchford et al. (2005) put these results into the context of other component

14   contributions to regional haze, plus seasonal and longer-term variations in haze by particulate

15   components. Figure 9-44 shows the temporal variation of the contributions by the various $SO_2$ emissions

16   source regions plus the Carbón facility during the BRAVO Study period. The largest particulate sulfate

17   peak haze periods are dominated by infrequent large contribution by emission sources in TX and eastern

18   U.S., while Mexican sources including the Carbón facility are more frequent contributors to haze, but at

19   generally lower light extinction levels. Particulate nitrate contributions to haze at Big Bend NP are among

20   the lowest measured in the U.S. (~3% of light extinction on average and for worst haze episodes).
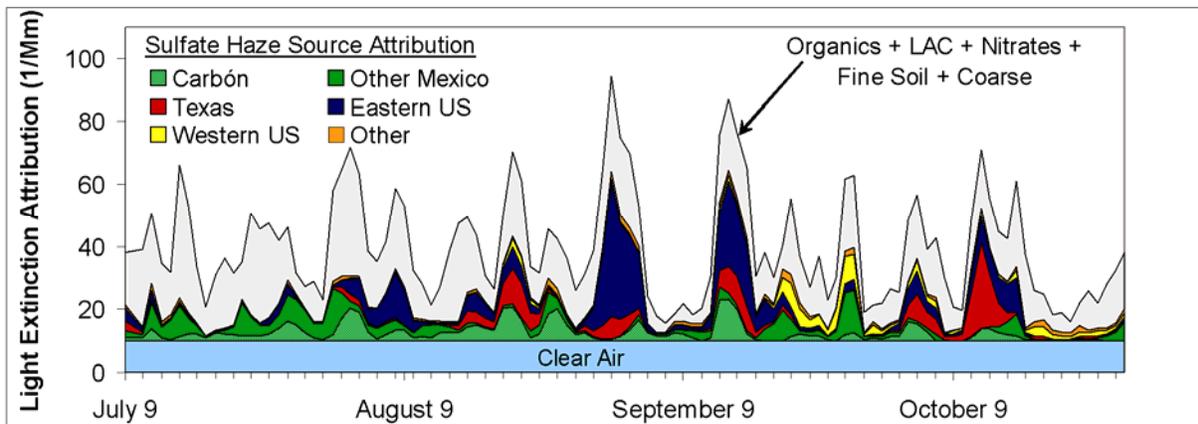


Source: Pitchford et al. (2005)

**Figure 9-44.   BRAVO Study haze contributions for Big Bend National Park, TX during a four-month period in 1999. Shown are impacts by various particulate sulfate sources, as well as the total light extinction level (black line) and Rayleigh or clear air light scattering.**
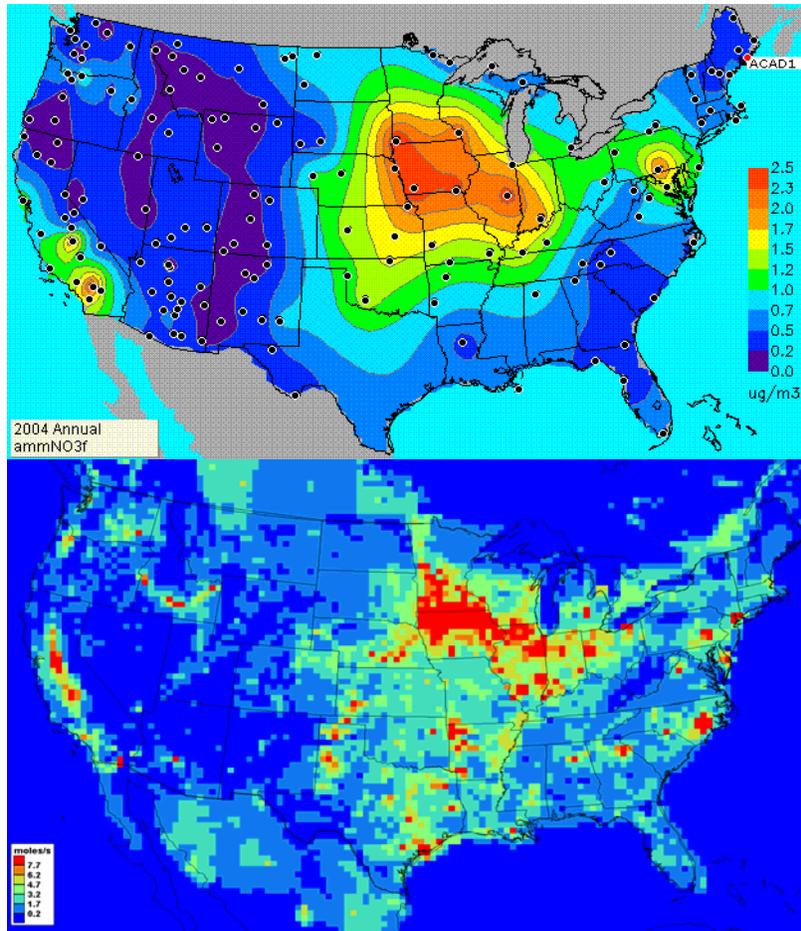
**Figure 9-45.** Maps of spatial patterns for average annual particulate nitrate measurements (top), and for ammonia emissions for April 2002 from the WRAP emissions inventory (bottom).
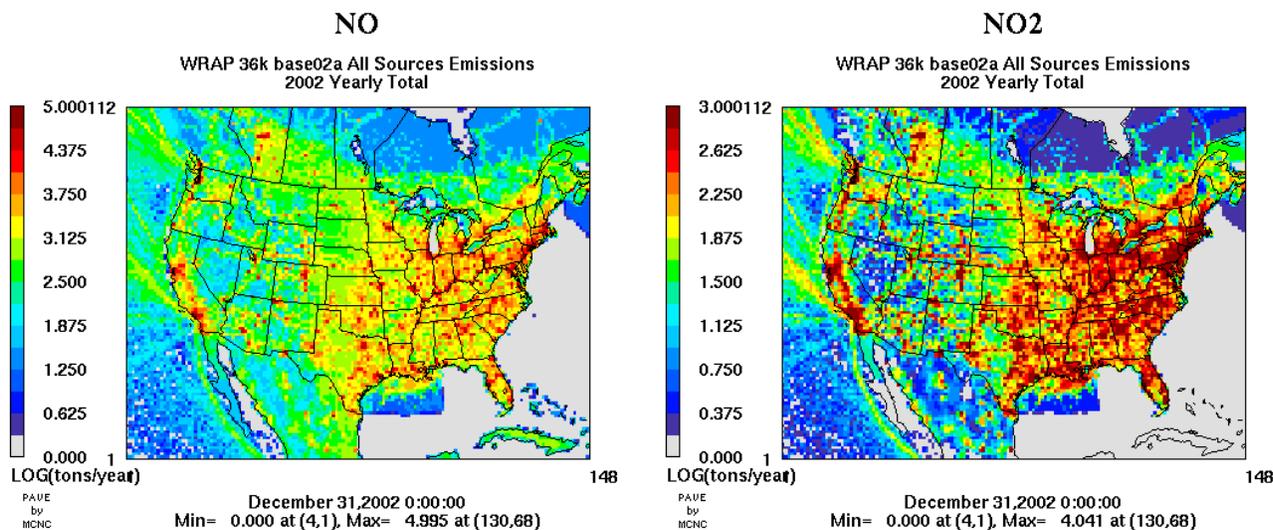
**Figure 9-46.** Maps of spatial patterns of annual NO (left) and NO$_2$ (right) emissions for 2002 from the WRAP emissions inventory.

1      Nitrate concentrations are a significant contributor to light extinction further to the north of Texas

2      in the center of the country. While sulfate can be in particulate form though not fully neutralized by

3      ammonia, nitric acid from NO$_X$ emissions requires neutralization by ammonium to become particulate

4      ammonium nitrate. One way to explore the causes of the Midwest nitrate bulge is to compare its spatial

5      distribution with the spatial distributions of NO$_X$ and ammonia emissions. Figure 9-45 shows a map of the

6      annual average particulate nitrate concentrations (top) with a map of ammonia emissions directly below

7      it. Animal agriculture is responsible for most of the ammonia emissions in the Midwest. The striking

8      similarity between the ambient particulate nitrate concentration and the ammonia emissions spatial

9      patterns with regional maximum centered on Iowa is in contrast to the NO$_X$ (i.e., NO + NO$_2$) emissions

10      spatial patterns, shown in Figure 9-46. NO$_X$ emissions are high over a broad region of the country

11      associated with the larger population densities and greater numbers of fossil fuel electric generation plant

12      generally to the east of the Midwest nitrate bulge. While both ammonia and nitric acid are needed to form

13      particulate ammonium nitrate, the maps suggest the Midwest nitrate bulge is due primarily to the

14      abundance of free ammonia (i.e. the amount beyond what is required to neutralize the acidic particulate

15      sulfate). By contrast the region to the east of the Midwest nitrate bulge should have plenty of nitric acid

16      given the higher emissions of NO$_X$, but apparently has a deficiency of free ammonia. The few eastern

17      monitoring sites with locally high particulate nitrate (near southeastern PA) are located within a small

18      region of high density animal agricultural that shows up as a high ammonia emissions region in Figure 9-

19      45. Note that California's South Coast and Central Valley have both high ammonia and high NO$_X$

20      emissions, explaining the high particulate nitrate contribution to haze there.

1        To better understand the role of ammonia in the formation of the Midwest nitrate bulge, the

2    Midwest RPO and Central States Regional Air Partnership deployed a measurement program from late

3    2003 through early 2005 at 10 locations (9 rural and 1 urban) in the region (see Figure 9-47) to monitor

4    particulate sulfate, nitrate, and ammonium ions, plus the precursor gases sulfur dioxide, nitric acid, and

5    ammonia (Kenski, et al., 2004, Sweet, et al., 2005). These data have been used as input for

6    thermodynamic equilibrium modeling to assess the changes in PM levels that would result from changes

7    to precursor concentrations (Blanchard and Tanenbaum, 2005, Blanchard et al., 2007). Blanchard and

8    Tanenbaum (2005) and Blanchard et al. (2007) conclude that the current conditions at nine of the ten sites

9    are near the point of transition between the precursor species (nitric acid and ammonia) that limits the

10    formation of particulate nitrate. If excess ammonia increases, either by greater ammonia emissions or by

11    anticipated decreases in $SO_2$ emissions, then nitric acid levels would need to be reduced (via lower $NO_X$

12    emissions) in order to reduce the particulate nitrate levels.

13        Given the comparability of particulate sulfate and nitrate with regard to their light extinction

14    efficiencies, their visibility impacts are proportional to the sum of their mass concentrations. A reduction

15    in sulfate caused by $SO_2$ emission reductions would reduce the particulate sulfate concentration, though

16    according to the thermodynamic equilibrium modeling for these sites the particulate nitrate concentration

17    will be increase somewhat. However the total particulate sulfate plus nitrate concentration would be

18    reduced so visibility impacts would be decreased. At current ammonium levels the predicted response of

19    changes to sulfate and nitric acid concentrations (i.e. $SO_2$ and $NO_X$ emissions changes) are similar in

20    respect to the resulting magnitude of changes to the total particulate sulfate plus nitrate concentrations. At

21    all but two sites the total particulate sulfate plus nitrate concentrations would decrease if either ammonia

22    or nitric acid where reduced.
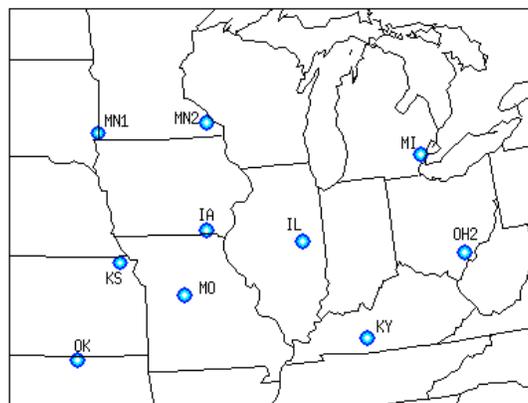


Kenski et al., 2004

**Figure 9-47.   Midwest ammonia monitoring network.**

1      A further level of complications in understanding the response of particulate nitrate to changes in

2    precursor concentrations results from the temperature and humidity dependence of the partition between

3    particulate ammonium nitrate and the disassociated gaseous nitric acid and ammonia. This dependence

4    causes seasonal and even diurnal differences in the expected responses of particulate nitrate

5    concentrations to changes in precursor concentrations. As expected during the colder times of the year the

6    total particulate concentrations are more sensitive to changes in ammonia and nitric acid levels than

7    during the warmer seasons when sulfate levels are greater.

8      As shown in Figure 9-48, results of an air transport assessment to identify emission source areas

9    associated with high particulate nitrate at five monitoring locations in the East (four remote-area sites and

10   Toronto, Canada) implicate the high ammonia emissions region of the Midwest as a common source

11   region (Canada-U.S. Air Committee, 2004). This assessment does not preclude local sources of the

12   precursor gases responsible for particulate ammonium nitrate, but does suggest that long-range transport

13   of particulate nitrate or ammonia from the high emissions region of the Midwest is also contributing to

14   eastern nitrate episodes.
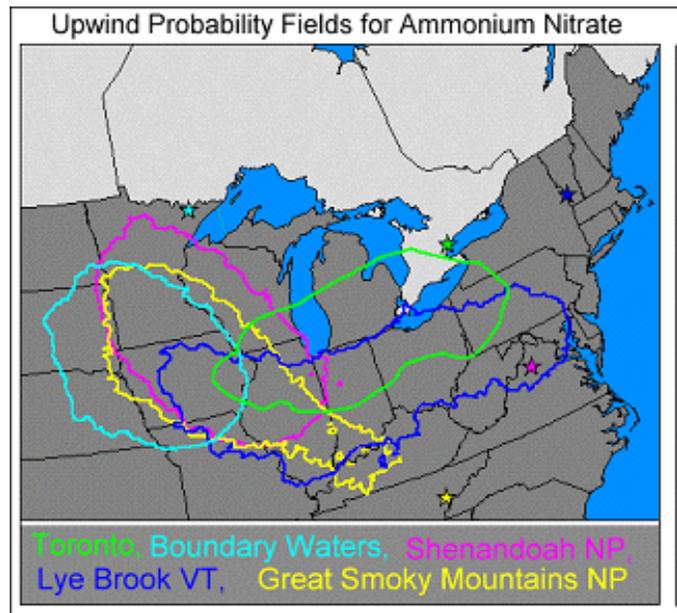


From Canada-U.S. Air Committee, 2004.

**Figure 9-48. Upwind transport probability fields associated with high particulate nitrate concentrations measured at Toronto, Canada; Boundary Water Canoe Area, MN; Shenandoah National Park, VA; Lye Brook, VT; and Great Smoky Mountains National Park, TN.**

1        In a similar air transport assessment for measurements at Underhill, VT and at Brigantine, NJ,

2    Hopke et al. (2005) identified separate regions associated with particulate sulfate accompanied by trace

3    particulate components associated with coal burning (e.g. selenium) and accompanied by trace particulate

4    components associated with oil burning (e.g. vanadium). As shown in Figure 9-49, the coal-burning

5    related particulate sulfate for these two monitoring sites is associated with long-range transport from the

6    Ohio River Valley, while oil-burning related particulate sulfate is from more nearby emissions in the high

7    population region of coastal New York, New Jersey, Massachusetts, and Connecticut.
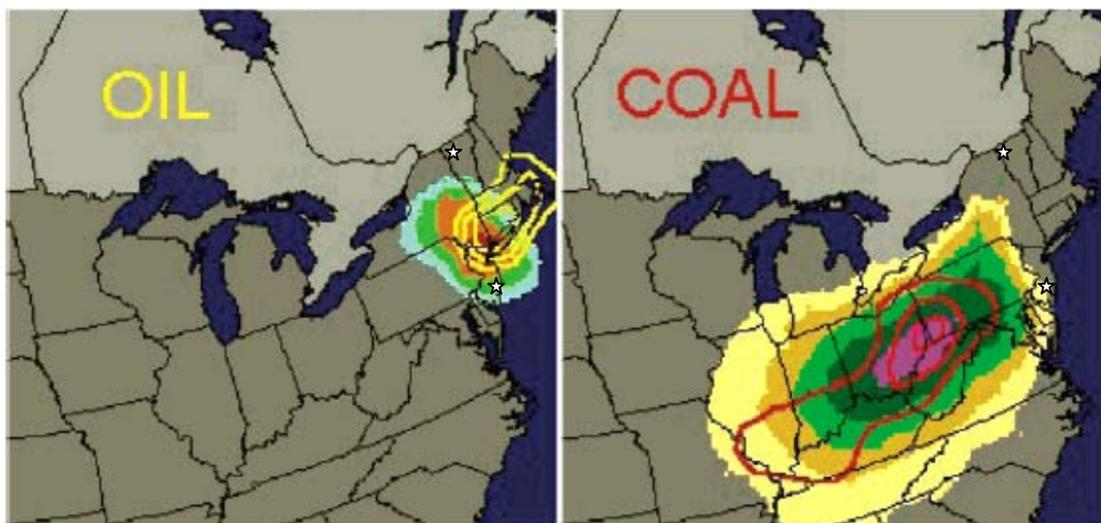


Hopke, et al. (2005).

**Figure 9-49.** **Trajectory probability fields for periods with high particulate sulfate measured at Underhill, VT and Brigantine, NJ (shown as white stars) associated with oil-burning trace components (left) and with coal-burning trace components (right). Shown for comparison are the interpolated $SO_2$ emissions areal density contours for oil combustion sources (emissions times 10) and coal combustion sources, displayed as yellow and red contour lines respectively.**

8        The Regional Aerosol Intensive Network (RAIN) was established by MANE-VU to generate

9    enhanced continuous visibility, plus fine particle mass and composition monitoring data at a string of

10   three monitoring locations along the transport path from the Ohio River Valley to coastal Maine

11   (NESCAUM, 2006). The dominant role of particulate sulfate in the northeast is well demonstrated by a

12   scatter plot of RAIN data that shows the relationship between particulate sulfate extinction, calculated

13   using the IMPROVE algorithm plotted against directly measured particle light scattering for hourly data

14   over a eight month period beginning in July 2004 at the Acadia National Park, ME monitoring site (see

15   Figure 9-50). Particulate sulfate explains 90% of the variance in particulate light scattering even though it

1    is responsible for only about 64% of the total light extinction (annual averaged value from the VIEWS

2    web site). Adding the contribution by the second-largest regional contributor to light extinction,

3    particulate organic carbon with about 14%, does not improve the variance explained, but does increase

4    the slope to 0.78. The noticeable difference between these two plots is that the particulate sulfate alone

5    underestimates light scattering during low haze periods (points on the plot are below the regression line

6    for light scattering < 70Mm$^{-1}$), while the agreement is improved with the addition of particulate organic

7    carbon contributions to haze (regression slope is nearer to one and reduced bias for low haze periods).

8    Particulate nitrate contribution to light extinction at Acadia is about 10% on average.
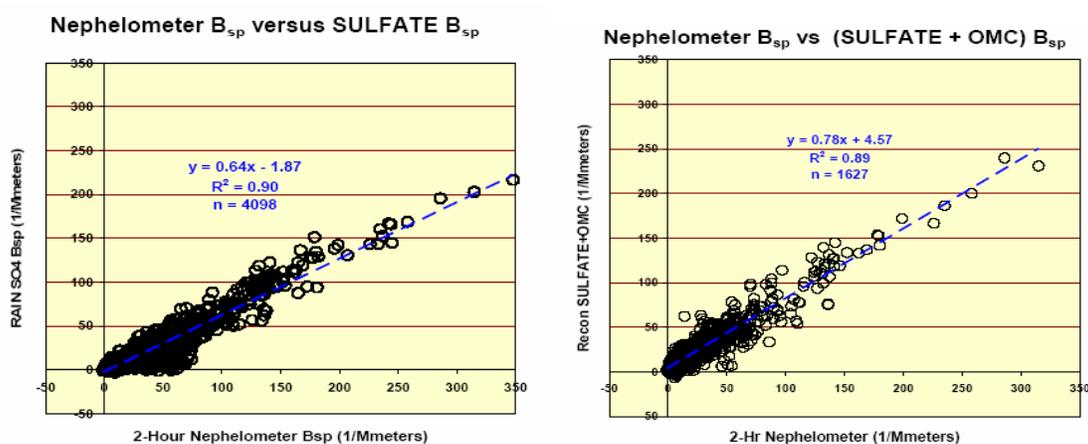


Source: RAIN Preliminary Data Analysis Report, NESCAUM, 2006.

**Figure 9-50.   Scatter plots of particulate sulfate (left) and particulate nitrate and organic mass (right) versus nephelometer measured particle light scattering for Acadia National Park, ME.**

9        Particulate nitrate levels are considerably lower in the sulfate-dominated warmer southeastern U.S.

10    than in the Northeast and upper Midwest. Blanchard, et al. (2007) conducted thermodynamic equilibrium

11    modeling on data from the eight Southeastern Aerosol Research and Characterization (SEARCH)

12    monitoring sites and found that total particulate nitrate plus sulfate is much more responsive to changes in

13    sulfate concentrations than to changes in nitric acid concentrations, which in turn is more responsive than

14    changes in ammonia concentrations.
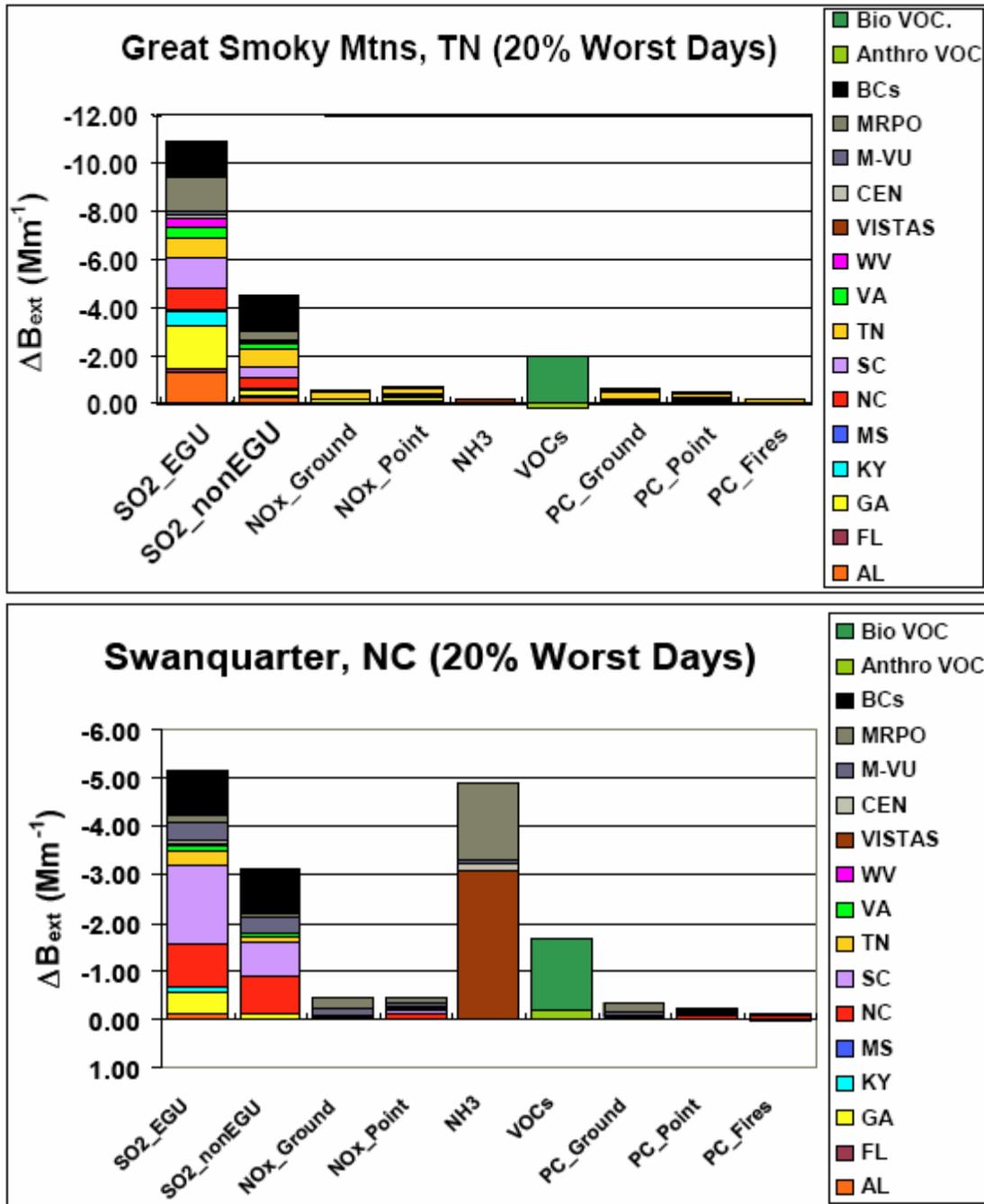
**Figure 9-51.** CMAQ air quality modeling projections of visibility responses on the 20% worst haze days at Great Smoke National Park, NC (top) and Swanquarter Wilderness, NC (bottom) to 30% reductions from a projected 2009 emission inventory of visibility-reducing pollutants by source category and geographic areas.

1    The VISTAS RPO commissioned an emissions sensitivity study using CMAQ modeling on winter

2    and summer 2009 emissions projected from the 2002 emissions inventory (NCDENR, 2007). Figure 9-51

1  contains bar plots for two North Carolina class I areas that indicate projected changes in light extinction

2  for the worst haze day due to 30% emissions reductions by particulate species, source types and location

3  across the Southeastern states modeling domain (i.e. as far west as Texas, as far north as Pennsylvania, as

4  far south as the Florida Keys and as far east as ~300 km from the North Carolina coast). Great Smoky

5  Mountains, in the southern Appalachian Mountains has the greatest sensitivity to changes by $SO_2$

6  emissions from electrical generation units (EGU) and to a lesser extent other $SO_2$ emission sources in the

7  region. Reductions of $NO_X$ emissions from ground or point sources are not nearly as effective as $SO_2$

8  reductions in reducing the light extinction levels at Great Smoky Mountains. This is due principally to the

9  worst days at Great Smoky Mountains occurring during the summer, when temperatures are too high to

10  support high particulate nitrate concentrations. For the same reason, ammonia emission reductions are

11  also ineffective. Swanquarter Wilderness, NC is a coastal location where some of the worst haze days are

12  during the winter and include contributions from particulate ammonium nitrate. Both $SO_2$ and ammonia

13  emissions reductions would be effective at reducing worst haze days at the Swanquarter Wilderness,

14  though $NO_X$ emissions are not as effective presumably because the atmosphere is ammonia-limited for

15  particulate nitrate production.

## 9.3.5. Urban Visibility Valuation and Preference

16  The Clean Air Act §302(h) defines public welfare to include the effects of air pollution on

17  "…visibility, … and personal comfort and wellbeing. " Though good visibility conditions in Class I (e.g.

18  National Parks) and wilderness areas have long been recognized as important to the public welfare (see

19  discussions in EPA (2004 and 2005) and Chestnut and Dennis (1997), visibility conditions in urban areas

20  also contribute to the public welfare. Visibility impairment may be caused by either natural or manmade

21  conditions (or both), but it is only impairment that occurs as a result of air pollution (either alone or in

22  combination with water vapor or other atmospheric conditions) that can be mitigated by regulations such

23  as the Regional Haze Rule (40 CFR 51.300 through 309) or the Secondary National Ambient Air Quality

24  Standards (NAAQS). Visibility impairment resulting from air pollution is referred to as visual air quality

25  (VAQ).

26  Visibly poor air quality causes people to be concerned about substantive health risks, but degraded

27  VAQ adversely affects people in additional ways. These include the aesthetic benefits of better visibility,

28  improved road and air safety, and enhanced recreation in activities like hiking and bicycling. Because the

29  human health impacts of air pollution are regulated under the Primary NAAQS, it is necessary to separate

30  out the aesthetic and wellbeing components associated with the visibility condition produced by a given

31  level of air pollution when assessing the need for additional regulation to protect the public welfare effect

1    of visibility under the Secondary NAAQS. The degree to which previous human preference and valuation

2    studies for VAQ have adequately made this distinction and separation is an important issue in applying

3    results from available studies in a Secondary NAAQS (or benefits estimation for any policy effecting

4    VAQ) context. The remainder of this discussion is focused on those aesthetic and wellbeing qualities

5    associated with a given VAQ in urban areas.

6        The term "urban visibility" is used to refer to VAQ throughout a city or metropolitan area. Urban

7    visibility includes the VAQ conditions in all locations that people experience in their daily lives, including

8    scenes such as residential streets and neighborhood parks, commercial and industrial areas, highway and

9    commuting corridors, central downtown areas, and views from elevated locations providing a broad

10   overlook of the metropolitan area. Thus urban visibility, which is sometimes referred to as 'residential

11   visibility,' encompasses more than the visibility conditions only at an individual's specific place of

12   residence, but all the VAQ they see on a regular basis. Urban visibility includes not only major cities, but

13   VAQ conditions in smaller towns and cities. The key distinction is between visibility conditions in urban

14   and suburban locations and visibility in rural or wilderness settings such as the Class 1 areas defined by

15   the Clean Air Act, which include National Parks and similar natural settings.

16       Visibility has direct significance to people's enjoyment of daily activities and their overall

17   wellbeing. Visibility conditions can be described both as an aesthetic quality as well as a scientifically

18   measurable set of atmospheric conditions. Due to the subjective nature of aesthetics, people's preferences

19   with respect to visibility are difficult to express or quantify, but people have expressed in many different

20   ways that they enjoy and value a clear view. A number of social science disciplines have undertaken to

21   link perceived urban visibility to an array of effects reflecting the overall desire for good VAQ, and the

22   benefits of improving currently degraded VAQ. This wide range of diverse studies have identified types of

23   benefits of good VAQ in addition to those directly connected with air-pollution related health effects such

24   as respiratory diseases and premature mortality.

25       For example, psychological research has demonstrated that people are emotionally affected by

26   VAQ such that their overall sense of wellbeing is diminished (e.g., Bickerstaff and Walker, 2001).

27   Researchers have also shown that perception of pollution is correlated with stress, annoyance, and

28   symptoms of depression (Bickerstaff and Walker, 2001; Evans and Jacobs, 1982; Jacobs et al., 1984).

29   Sociological research has demonstrated that VAQ is deeply intertwined with a "sense of place," effecting

30   people's sense of the desirability of a neighborhood quite apart from the actual physical conditions of the

31   area (e.g., ABT, 2002; Day, 2007; Elliott et al., 1999; Howel et al., 2002). Public policy research finds that

32   people think it is important to protect visibility, and accept the concept of setting standards to protect

33   visibility (e.g., ABT, 2001; BBC Research & Consulting, 2002; Ely et al., 1993; Pryor, 1996). Finally,

34   economic valuation research has measured the amount of money that people are willing to pay to protect

1  or improve both urban visibility (e.g., summary review in Beron et al., 2001; Chestnut and Dennis, 1997)

2  and natural locations such as National Parks and other locations defined by the Clean Air Act as Class I

3  visibility areas (e.g., summary review in Chestnut and Dennis, 1997).

4  The purpose of the remainder of this section is to review four urban preference studies, as well as

5  one new urban visibility valuation study not previously discussed in an EPA Criteria Document or

6  OAQPS Staff Paper. This literature is relevant to the review of a Secondary NAAQS standard concerning

7  VAQ, as well as a review of potentially including urban visibility valuation in a damage function

8  approach (separately estimating individual effect categories) an economic benefit analysis.

9  Urban visibility has been examined in two types of studies directly relevant to the NAAQS review

10  process: urban visibility preference studies and urban visibility valuation studies. Both types of studies are

11  designed to evaluate individuals' desire (or demand) for good VAQ where they live, using different

12  metrics to evaluate demand. Urban visibility preference studies examine individuals' demand by

13  investigating the basic question "what level of visibility degradation is unacceptable," while economic

14  studies examine demand by investigating "how much would you be willing to pay to improve visibility."

## 9.3.5.1. Urban Visibility Preference Studies

15  One group of urban visibility research projects focused on identifying preferences for urban VAQ

16  without necessarily estimating the economic value of improving visibility. This group of preference

17  studies used a common focus group method to estimate the level of visibility impairment that respondents

18  described as "acceptable." The specific definition of acceptable was largely left to each individual

19  respondent, allowing each to identify their own preferences.

20  There are three completed studies that used this method, and one additional pilot study (designed as

21  a survey instrument development project) that provided additional information (Table 9-2). The

22  completed studies were conducted in Denver, Colorado (Ely et al., 1991), two cities in British Columbia,

23  Canada (Pryor, 1996), and Phoenix, Arizona (BBC Research & Consulting, 2002). The pilot study was

24  conducted in Washington, DC (ABT, 2001).

25  Each study collected information in a focus group setting, presenting slides depicting various

26  visibility conditions. All four studies used photographs of a single scene from the study's city; each photo

27  included images of the broad downtown area and spreading out to the hills or mountains composing the

28  scene's backdrop. The maximum sight distance under good conditions varied by city, ranging from 8

29  kilometers in Washington, DC to mountains hundreds of kilometers away in Denver. Multiple photos of

30  the same scene were used to present approximately 20 different levels of visibility impairment. The

31  Denver and British Columbia studies used actual photographs taken in the same location to depict various

32  visibility conditions. The Phoenix and Washington, DC pilot study used photographs prepared using the

1    WinHaze software from Air Resource Specialists (ARS). WinHaze is a computer-imaging software

2    program that simulates visual air quality differences of various scenes, allowing the user to "degrade" an

3    original near-pristine visibility condition photograph to create a photograph of each desired VAQ level.

**Table 9-2.    Summary of urban visibility preference studies.**

|  | Denver, CO | Phoenix, AZ | 2 British Columbia cities | Washington, DC (pilot) |
|---|---|---|---|---|
| Report Date | 1991 | 2003 | 1996 | 2001 |
| Duration of session |  | 45 min | 50 mins | 2 h |
| Compensation | None (civic groups) | $50 | None (class room exercise) | $50 |
| # focus group sessions | 17 | 27 total at 6 locations, Including 3 in Spanish | 4 | 1 |
| # participants | 214 | 385 | 180 | 9 |
| Age range | adults | 18-65+ | University students | 27-58 |
| Annual or seasonal | Wintertime | Annual | Summertime | Annual |
| # total scenes presented | Single scene of downtown with mountains in background | Single scene of downtown and mountains, 42 km maximum distance | Single scene from each city | Single scene of DC Mall and downtown, 8 km maximum sight |
| # of total visibility conditions presented | 20 levels (+ 5 duplicates) | 21 levels (+ 4 duplicates) | 20 levels (10 each from each city) | 20 levels (+ 5 duplicates) |
| Source of slides | Actual photos taken between 9am and 3pm | WinHaze | Actual photos taken at 1pm or 4pm | WinHaze |
| Medium of presentation | Slide projection | Slide projection | Slide projection | Slide projection |
| Ranking scale used | 7 point scale | 7 point scale | 7 point scale | 7 point scale |
| Visibility range presented | 11 to 40 dV | 15 to 35 dV | 13 to 25 dV (Chilliwack) 13.5 to 31.5 dV (Abbotsford) | 9 to 38 dV |
| Health issue directions | Ignore potential health impacts; visibility only | Judge solely on visibility, do not consider health | Judge solely on visibility, do not consider health | Health never mentioned, "Focus only on visibility" |
| Key Questions asked | a) Rank VAQ (1-7 scale) | a) Rank VAQ (1-7 scale) | a) Rank VAQ (1-7 scale) | a) Rank VAQ (1-7 scale) |
|  | b) Is each slide "acceptable" | b) Is each slide "acceptable" | b) Is each slide "acceptable" | b) Is each slide "acceptable" |
|  | c) "How much haze is too much?" | c) How many days a year would this picture be "acceptable" |  | c) if this hazy, how many hours would it be acceptable (3 slides only) |
|  |  |  |  | d) valuation question |
| Mean dV found "acceptable" | 20.3 dV | 23 to 25 dV | ~23 dV(Chilliwack), ~19 dV(Abbotsford) | ~20 dV (range 20-25) |

4    A common characteristic of the three visibility preference studies was that each were conducted in

5    the West where distant mountains were shown in the photograph used to elicit local participant responses

6    about visibility. Among other issues, the Washington D.C. pilot study was the first step in a process to

7    expand the results to other regions where typical scenes may have different sensitivity to perceived

1  visibility changes in PM air quality and where participants may have different acceptable visibility

2  preference levels.

3      One notable finding of the three visibility preference studies and the one pilot study is the general

4  degree of consistency in the median preferences for an acceptable level of visibility degradation. The

5  range of median acceptable preference level from the four studies is 19 to 25 deciviews (dV), the

6  preferred measure of visibility impairment. Measured in terms of visual range (VR), these median

7  acceptable levels are between 30 and 55 km.

## 9.3.5.2. Denver, Colorado Urban Visibility Preference Study

8      The Denver urban visibility preference study (Ely et al., 1993) was conducted on behalf of the

9  Colorado Department of Public Health and Environment (CDPHE). The study conducted a series of focus

10  group sessions with 17 civic and community groups in which a total of 214 individuals were asked to rate

11  slides. The slides depicted varying levels of VAQ for a well-known Denver vista, including a broad view

12  of downtown Denver with the mountains to the west composing the scene's background. The participants

13  were instructed to base their judgments on three factors:

14      1.  the standard was for an urban area, not a pristine national park area where the standards might
15          be more strict;

16      2.  the level of an urban visibility standard violation should be set at a VAQ level considered to
17          be unreasonable, objectionable, and unacceptable visually; and

18      3.  judgments of standards violations should be based on visibility only, not on health effects.

19      Participants were shown 25 randomly ordered slides of actual photographs. The visibility

20  conditions presented in the slides ranged from 11 to 40 dV, approximating the 10th to 90th percentile of

21  wintertime visibility conditions in Denver. The participants rated the 25 slides based on a scale of 1 (poor)

22  to 7 (excellent), with 5 duplicates included. They were then asked to judge whether the slide would

23  violate what they would consider to be an appropriate urban visibility standard (i.e., whether the level of

24  impairment was "acceptable" or "unacceptable"). The individual's judgment of a slide's VAQ and

25  whether the slide violated a visibility standard were highly correlated (Pearson correlation coefficient

26  greater than 80%), as were the VAQ ratings and the yes/no "acceptable" response. The participant's

27  median response was that a visibility level of 20.3 dV (extinction coefficient $b_{ext}$ = 0.76/km, or VR ~ 51

28  km) was judged as "acceptable." The CDPHE subsequently established a Denver visibility standard at

29  this level (defined as $b_{ext}$ = 0.76/km), based on the median 50% acceptability findings from the study.

## 9.3.5.3. Phoenix, Arizona Urban Visibility Preference Study

1    The Phoenix urban visibility preference study (BBC Research & Consulting, 2002) was conducted

2    on behalf of the Arizona Department of Environmental Quality. The Phoenix study patterned its focus

3    group survey process after the Denver study. The study included 385 participants in 27 separate focus

4    group sessions. Participants were recruited using random digit dialing to obtain a sample group designed

5    to be demographically representative of the larger Phoenix population. Focus group sessions were held at

6    six neighborhood locations throughout the metropolitan area to improve the participation rate. Three

7    sessions were held in Spanish in one region of the city with a large Hispanic population (25%), although

8    the final overall participation of native Spanish speakers (18%) in the study was modestly below the

9    targeted level. Participants received $50 as an inducement to participate.

10    Participants were shown a series of 25 images of the same vista of downtown Phoenix, with South

11    Mountain in the background at a distance of about 40 km. Photographic slides of the images were

12    developed using WinHaze. The visibility impairment levels ranged from 15 to 35 dV (the extinction

13    coefficient, $b_{ext}$, range was approximately 45/km to 3.5/km, or a visual range of 87 to 12 km). Participants

14    first individually rated the randomly shown slides on a VAQ scale of 1 (unacceptable) to 7 (excellent).

15    Participants were instructed to rate the photographs solely on visibility, and to not base their decisions on

16    either health concerns or what it would cost to have better visibility. Next, the participants individually

17    rated the randomly ordered slides as "acceptable" or "unacceptable," defined as whether the visibility in

18    the slide is unreasonable or objectionable. Better visibility conditions (15 dV and 20 dV) were judged

19    "acceptable" by 90 percent of all participants. At 24 dV nearly half of all participants thought the VAQ

20    was "unacceptable," with almost three-quarters judging 26 dV as unacceptable.

21    The Phoenix urban visibility study formed the basis of the decision of the Phoenix Visibility Index

22    Oversight Committee for a visibility index for the Phoenix Metropolitan Area (Arizona Department of

23    Environmental Quality, 2003). The Phoenix Visibility Index establishes an indexed system with 5

24    categories of visibility conditions, ranging from "Excellent" (14 dV or less) to "Very Poor" (29 dV or

25    greater). The "Good" range is 15 to 20 dV. The environmental goal of the Phoenix urban visibility

26    program is to achieve continued progress through 2018 by moving the number of days in lower quality

27    categories into better quality categories.

## 9.3.5.4. British Columbia, Canada Urban Visibility Preference Study

28    The British Columbia urban visibility preference study (Pryor, 1996) was conducted on behalf of

29    the Ministry of Environment. The study conducted focus group sessions that were also developed

30    following the methods used in the Denver study. Participants were students at the University of British

1   Columbia, who participated in one of four focus group sessions with between 7 and 95 participants. A

2   total of 180 respondents completed surveys (29 did not complete the survey).

3       Participants in the study were shown slides of two suburban locations in British Columbia:

4   Chilliwack and Abbotsford. Using the same general protocol as the Denver study, Pryor found that

5   responses from this study found the acceptable level of visibility was 23 dV in Chilliwack and 19 dV in

6   Abbotsford. Pryor (1996) discusses some possible reasons for the variation in standard visibility

7   judgments between the two locations. Factors discussed include the relative complexity of the scenes,

8   potential bias of the sample population (only University students participated), and the different levels of

9   development at each location. Abbotsford (population 130,000) is an ethnically diverse suburb adjacent to

10  the Vancouver Metro area, while Chilliwack (population 70,000) is an agricultural community 100 km

11  east Vancouver in the Frazier Valley.

12      The British Columbia urban visibility preference study is being considered by the B.C. Ministry of

13  the Environment as a part of establishing urban and wilderness visibility goals in British Columbia.

## 9.3.5.5. Washington, DC Urban Visibility Pilot Preference Study

14      The Washington, DC urban visibility pilot study (Abt Associates 2001) was conducted on behalf of

15  the EPA, and was designed to be a pilot focus group study, an initial developmental trial run of a larger

16  study. The intent of the pilot study was to study both focus group method design and potential survey

17  questions. Due to funding limitations, only a single focus group session was held, consisting of one

18  extended session with 9 participants. No further urban visibility focus group sessions were held in

19  Washington, DC.

20      Due to the small number of participants, it is not possible to make statistical inferences about the

21  opinions of the general population. The study does, however, provide additional useful information about

22  urban visibility studies, potentially helping to both better understand previous studies as well as design

23  future studies.

24      The study also adopted the general Denver study method, modifying it as appropriate to be

25  applicable in an eastern urban setting which has substantially different visibility conditions than any of

26  the three western locations of the other preference studies. Washington's (and the entire East) visibility is

27  typically substantially worse than western cities, and has different characteristics. Washington's visibility

28  impairment is primarily a uniform whitish haze dominated by sulfates, relative humidity levels are higher,

29  the low lying terrain provides substantially shorter maximum sight distances, and many residents are not

30  well informed that anthropogenic emissions impairs visibility on hazy days.

31      The Washington focus group session included questions on valuation, as well as on preferences.

32  The focus group was asked to state their preferences measured in an increase in the general cost of living

for certain levels of improvement in visibility on a typical summer day. A general cost of living approach is one payment vehicle approach that can be used in willingness to pay studies, especially for environmental issues arising from multiple diverse emission sources (e.g., transportation, electricity generation, industry, etc.) making a specific price increase potentially misleading.

The first part of the focus group session was designed to be an hour long, and was comparable to the focus group sessions in the Denver and Phoenix studies. A single scene was used; a panoramic shot of the Potomac River, Washington mall and downtown Washington, DC. In the first part of the session people were asked to rate the VAQ of 25 photographs (prepared using WinHaze, and projected on a large screen), judge the acceptability of visibility level in each slide, and answer the valuation questions. The second half of the session, however, was a moderated discussion session about the format and content of the first phase of the session. In this moderated discussion, participants were asked about their understanding of each question asked in the first half of the session. Particular issues in designing a focus group session were also explored. Important participant comments included:

1. Participants had been asked how they reacted to the initial direction to base their answers only on visibility, but health was never explicitly mentioned by the focus group moderator. Participants strongly agreed with the decision to not mention that health effects are associated with visibility impairment. They understood the directions as meaning they should ignore health issues, and said their answers would have been different if they included health as well as visibility in their judgments.

2. Differentiating between haze and weather conditions was difficult. Weather was not discussed in the focus group session, and the photographs were WinHaze altered photos with identical weather conditions. Participants mentioned they were still confused about the role of weather and humidity in the different visibility conditions presented in the photos.

3. Questions about how many hours an impairment level would be acceptable were confusing. Most participants were normally indoors during most of the day, so questions about duration of outdoor conditions were difficult to answer.

4. Participants strongly agreed that not mentioning the purpose of the study, or the sponsor, until the very end (after all the questions were answered) was viewed as very important. Most felt this information would have influenced their answers.

### 9.3.5.6. Urban Visibility Valuation Studies

1    The economic importance of urban visibility has been examined by a number of studies designed to

2    quantify the benefits (or willingness to pay) associated with potential improvements in urban visibility.

3    Urban visibility valuation research prior to 1997 was summarized in Chestnut and Dennis (1997), and

4    was also described in the 2004 Air Quality for PM (p. 4-186 to 4-190, (U.S. EPA, 2004) and the 2005

5    OAQPS PM NAAQS Staff Paper (EPA, 2005). These reviews summarize 34 estimates (based on different

6    cities or model specifications) from six different studies. Since the mid 1990s, however, only one new

7    valuation study of urban visibility has been published.

8    One urban visibility benefit assessment not included in those reviews is "The Benefits of Visibility

9    Improvement: New Evidence from the Los Angeles Metropolitan Area" (Beron et al., 2001). Rather than

10   a contingent valuation method (CVM) technique used in the majority of other urban visibility valuation

11   studies, Beron et al. used a housing market hedonic technique. The housing hedonic methods were used in

12   previous urban visibility studies by Murdoch and Thayer, 1988, and Trijonis et al., 1985. A housing

13   market hedonic study views a housing unit as composed of a bundle of attributes, and uses housing sale

14   price data from a large number of units in a metropolitan area to estimate the value of each component.

15   Hedonic pricing has been used to estimate economic values for environmental effects that have a direct

16   effect on housing market values. It relies on the measurement of differentials in property values under

17   various environmental quality conditions including air pollution, visibility and other environmental

18   amenities such as access to nearby beaches and parks, as well as by physical attributes of the house and

19   attributes of the neighborhood.

20   Beron et al. (2001) obtained data on approximately 840,000 owner-occupied, single family housing

21   sales between 1980 and 1995 from the California South Coast Air Basin (composed of Los Angeles and

22   Orange Counties, and the portions of Riverside and San Bernardino Counties in the greater metropolitan

23   area). The real estate data included information on the sale price of the house, 13 housing attributes

24   (square footage, number of bathrooms, etc.), 9 neighborhood attributes (percent poverty, school quality,

25   FBI crime index, etc.), and three air pollution variables: ozone, particulates (measured by total suspended

26   particulates, or TSP), and visibility. Visibility was measured as the annual average of visual range,

27   measured in miles, and was obtained from seven airports within the study region. The visibility range was

28   from 12.4 miles (Los Angeles International Airport, 1991) to 31.9 miles (Palm Springs Airport, 1995).

29   Ozone data (39 monitors) and TSP data (40 monitors) were obtained from the South Coast Air Quality

30   Management District. Annual mean values for each year were calculated for ozone and TSP.

31   Beron et al. (2001) presented results for a hypothetical basin-wide 20% visibility improvement, or

32   an increase from 15.3 to 18.4 miles, which is equivalent to approximately 27.6 deciViews (dV, a preferred

33   measure of visibility) to 25.8 dV. The initial results reflect the change in the purchase price of a house

1    associated with this difference in VAQ, which can be interpreted as a present value of a stream of annual

2    values over the lifetime of the house. The authors therefore selected a time horizon (30 years) and an

3    interest rate (8%) to calculate an annual per household benefit per dV ranging from $484 to $1,756. The

4    Beron results are higher than the CVM-based values summarized in Chestnut and Dennis (1997), which

5    ranged from $12 to $132 per dV. It should be noted that the $132 CVM values cited by Chestnut and

6    Dennis (1997) is from a study in the Los Angeles area (Brookshire, 1979). The Beron et al. (2001) results

7    are also higher than the Trijonis et al. (1990) hedonic study in the Los Angeles area, which had a range of

8    $134 to $360 per dV. All values reported here are in terms of 1994 prices.

9          A critical question for all urban visibility valuation studies is the extent to which the estimated

10   values strictly reflect preferences for visibility, and do not include a component of preferences for

11   reducing health risk from air pollution. The ability to isolate the value of visibility from within the

12   collection of intertwined benefits from visual air quality, which is inherently multi-attributed, is a

13   challenge for all visibility valuation studies. Each study attempts to isolate visibility from other effect

14   categories, but different studies take different approaches.

15         Beron et al. (2001) include two measures of air pollution directly related to health effects in their

16   housing market hedonic study, ozone and particulates (using TSP as the metric for particulates), as well as

17   visibility. They argue that the presence of the two health-related pollution levels results in a estimated

18   hedonic demand function for visibility that successfully separates the health component of demand for

19   overall air quality from the visibility component. An alternative interpretation is that the estimated

20   visibility function still includes a component of health risk because the housing market data does not

21   support completely isolating the demand for visibility (due to correlated variables, omitted variables,

22   measurement error, model specification error, etc.) from demand for health risk reductions measured by

23   the two health related air quality metrics.

24         A key issue in interpreting the Beron et al. (2001) results is whether the objective measures of air

25   quality characteristics (e.g., visibility, PM concentrations, etc.) capture people's perceptions of the

26   different aspects of air quality in a given location. To the extent the people simultaneously use what they

27   see regarding VAQ as an indicator of the overall air quality including potential health risks, then including

28   all the measures in the equation is not necessarily sufficient to isolate one effect from the other.

## 9.4. Deposition of PM

29         Airborne particles, their gas-pahse precursors, and their transformation products are removed from

30   the atmosphere by wet and dry deposition processes. These deposition processes transfer PM pollutants to

1  other environmental media where they can alter the structure, function, diversity, and sustainability of

2  complex ecosystems.

# 9.4.1. Forms of Deposition

## 9.4.1.1. Fine vs. Coarse PM

3  Research summarized by the previous NAAQS PM assessment illustrated the complexity of

4  deposition processes in patchy forested landscapes and the effects of vertical stratification within

5  canopies. There are also differences in the deposition behavior of fine and coarse particles. Coarse

6  particles generally settle nearer their site of formation than do fine particles. In addition, the chemical

7  constitution of individual particles is correlated with size. For example, much of the base cation and

8  heavy metal burden is present on coarse particles.

9  Fine PM may act as a carrier for materials such as herbicides that are phytotoxic. Fine PM provides

10  much of the surface area of particles suspended in the atmosphere, whereas coarse PM provides much of

11  the mass of airborne particles. Surface area can influence ecological effects associated with the oxidizing

12  capacity of fine particles, their interactions with other pollutants, and their adsorption of phytoactive

13  organic compounds. Fine and coarse particles also respond to changes in atmospheric humidity,

14  precipitation, and wind, and these can alter their deposition characteristics.

15  Fine PM is often a secondary pollutant that forms within the atmosphere, rather than being directly

16  emitted from a pollution source. It derives from atmospheric gas-to-particle conversion reactions

17  involving nucleation, condensation, and coagulation, and from evaporation of water from contaminated

18  fog and cloud droplets. Fine PM may also contain condensates of volatile organic compounds, volatilized

19  metals, and products of incomplete combustion, including polycyclic aromatic hydrocarbons (PAH) and

20  BC (soot) (U.S. EPA, 2004).

21  Coarse PM is mainly a primary pollutant, having been emitted from pollution sources as fully

22  formed particles derived from abrasion and crushing processes, soil disturbances, desiccation of marine

23  aerosol emitted from bursting bubbles, hygroscopic fine PM expanding with humidity to coarse mode,

24  and/or gas condensation directly onto preexisting coarse particles. Suspended primary coarse PM may

25  contain iron, silica, aluminum, and base cations from soil, plant and insect fragments, pollen, fungal

26  spores, bacteria, and viruses, as well as fly ash, brake lining particulates, debris, and automobile tire

27  fragments. Coarse mode particles can be altered by chemical reactions and/or physical interactions with

28  gaseous or liquid contaminants.

1    Direct and indirect radiative effects of atmospheric particulates influence local and regional

2    climate. In particular, dust derived from wind erosion can be lifted to high altitude and be transported long

3    distances from the source location (Mahowald et al., 2002). This process is most pronounced in desert

4    regions. Desert dust is the main atmospheric aerosol component in many arid and semi-arid regions,

5    especially the Sahara and the desert regions of central Asia (Zakey et al., 2006b). In recent years, a

6    number of efforts have been made to simulate the desert dust cycle in global climate models (c.f., Cakmur

7    et al., 2004; Cakmur et al., 2006; Miller et al., 2004; Zakey et al., 2006a; Zender et al., 2004).

8    Exposure to a given mass concentration of PM may lead to widely differing phytotoxic and other

9    environmental outcomes depending upon the particular mix of PM constituents involved. Especially

10    important in this regard are S and N components of PM, which are addressed in the Integrated Science

11    Assessment for Oxides of Nitrogen and Sulfur ($NO_XSO_X$ ISA), and effects of particulate heavy metals

12    and organic contaminants. This variability has not been characterized adequately. Though effects of

13    specific chemical fractions of PM have been described to some extent, there has been relatively little

14    research aimed at defining the effects of unspeciated PM on plants or ecosystems.

### 9.4.1.2. Deposition Modes

#### *Wet Deposition*

15    Wet deposition results from the incorporation of atmospheric particles and gases into cloud droplets

16    and their subsequent precipitation as rain or snow, or from the scavenging of particles and gases by

17    raindrops or snowflakes as they fall (Lovett, 1994). Wet deposition depends on precipitation amount and

18    ambient pollutant concentrations. Receptor (i.e., vegetation) surface properties have little effect on wet

19    deposition, although leaves can retain liquid and solubilized PM. In terrain containing extensive

20    vegetative canopies, any material deposited via precipitation to the upper stratum of foliage is likely to be

21    intercepted by several foliar surfaces before reaching the soil. This allows such processes as foliar uptake,

22    chemical transformation, and re-suspension into the atmosphere to occur.

23    Landscape characteristics can affect wet deposition via orographic effects and by the closer

24    aerodynamic coupling to the atmosphere of tall forest canopies as compared to the shorter shrub and

25    herbaceous canopies. Following wet deposition, humidity and temperature conditions further affect the

26    extent of drying versus concentrating of solutions on foliar surfaces, which influence the rate of metabolic

27    uptake of surface solutes (Swietlik and Faust, 1984). The net consequence of these factors on direct

28    physical effects of wet deposited PM on leaves is not known (U.S. EPA, 2004).

29    Rainfall introduces new wet deposition and also redistributes throughout the canopy previously

30    dry-deposited PM (Peters and Eiden, 1992). Both effects contribute to the relationships between canopy

1   leaf area and foliar contact and influence the potential direct PM effects on vegetation. The concentrations
2   of suspended and dissolved materials are typically highest at the onset of precipitation and decline with
3   duration of individual precipitation events (Hansen et al., 1994). Sustained rainfall removes much of the
4   accumulation of dry-deposited PM from foliar surfaces, reducing direct foliar effects and combining the
5   associated chemical burden with the wet deposited material (Lovett, 1994) for transfer to the soil. Intense
6   rainfall may contribute substantial total particulate inputs to the soil, but it also removes bioavailable or
7   injurious pollutants from foliar surfaces. This washing effect, combined with differential foliar uptake and
8   foliar leaching of different chemical constituents of PM, alters the composition of the rainwater that
9   reaches the soil and the pollutant burden that is taken up by plants. Once in the soil, chemical particle
10  constituents may affect biogeochemical cycles of major, minor, and trace elements. Low intensity
11  precipitation events, in contrast, may deposit significantly more particulate pollutants to foliar-surfaces
12  than high intensity precipitation events. Additionally, low-intensity events may enhance foliar uptake
13  through the hydrating of some previously dry-deposited particles (U.S. EPA, 2004).

## Dry Deposition

14  Dry particulate deposition, especially of heavy metals, base cations, and organic contaminants, is a
15  complex, poorly characterized process. It appears to be controlled primarily by such variables as
16  atmospheric stability, macro- and micro-surface roughness, particle diameter, and surface characteristics
17  (Hosker and Lindberg, 1982). The range of particle sizes, the diversity of canopy surfaces, and the variety
18  of chemical constituents in airborne PM have made it difficult to predict and to estimate dry particulate
19  deposition (U.S. EPA, 2004).

20  Dry deposition of atmospheric particles to plant and soil surfaces affects all exposed surfaces.
21  Larger particles >5 μm diameter are dry deposited mainly by gravitational sedimentation and inertial
22  impaction. Smaller particles, especially those with diameters between 0.2 and 2 μm, are not readily
23  dry-deposited and may travel long distances in the atmosphere until their eventual deposition, most often
24  via precipitation. Plant parts of all types, along with exposed soil and water surfaces, receive steady
25  deposits of dry dusts, EC, and heterogeneous secondary particles formed from gaseous precursors
26  (U.S. EPA, 1982).

27  Estimates of regional particulate dry deposition infer fluxes from the product of variable and
28  uncertain particulate concentrations in the atmosphere and even more variable and uncertain measured or
29  modeled estimates of dry $V_d$ parameterized for a variety of specific surfaces (e.g., Brook et al., 1999).
30  Even for specific sites and well defined particles, uncertainties are large. Modeling the dry deposition of
31  particles to vegetation is at a relatively early stage of development, and it is not currently possible to
32  identify a best or most generally applicable modeling approach (U.S. EPA, 2004).

*Occult Deposition*

1    The occurrence of occult deposition tends to be more restricted geographically, mainly to coastal

2    and high mountain areas. Several factors make occult deposition particularly effective, where it occurs,

3    for the delivery of dissolved and suspended particulates to vegetation. Concentrations of

4    particulate-derived materials are often many-fold higher in cloud or fog water than in precipitation or

5    ambient air due to orographic effects and gas-liquid partitioning. In addition, fog and cloud water deliver

6    chemical particle constituents in a bioavailable hydrated form to foliar surfaces. This enhances deposition

7    by sedimentation and impaction of submicron aerosol particles that exhibit low $V_d$ prior to fog droplet

8    formation (Fowler et al., 1989). Deposition to vegetation in fog droplets is proportional to wind speed,

9    droplet size, concentration, and fog density. In some areas, typically along foggy coastlines or at high

10   elevations, occult deposition represents a substantial fraction of total deposition to foliar surfaces (Fowler

11   et al., 1991).

# 9.4.2. Methods for Estimating Dry Deposition

12   Methods for estimating dry deposition of particles are more restricted than for gaseous species and

13   fall into two major categories: surface analysis methods, which include all types of measurements that

14   examine contaminant accumulation on surfaces of interest; and atmospheric deposition rate methods,

15   which measure contaminants in the atmosphere and on surfaces from which one may estimate the

16   deposition rate (Davidson and Wu, 1990). Surface extraction or washing methods characterize the

17   accumulation of particles on natural receptor surfaces of interest or on experimental surrogate surfaces.

18   These techniques rely on methods designed specifically to remove only surface-deposited material. Total

19   surface rinsate may be equated to accumulated deposition or to the difference in concentrations in rinsate

20   between exposed and control (sheltered) surfaces and may be used to refine estimates of deposition.

21   Foliar extraction techniques may underestimate deposition to leaves because of uptake and translocation

22   processes that remove pollutants from the leaf surface (Garten and Hanson, 1990; Taylor Jr. et al., 1988).

23   Foliar extraction methods also cannot distinguish gas- from particle-phase sources (Bytnerowicz et al.,

24   1987a; Bytnerowicz et al., 1987b; Dasch, 1987; Lindberg and Lovett, 1985; Van Aalst, 1982).

25   The National Dry Deposition Network (NDDN) was established in 1986 to document the

26   magnitude, spatial variability, and trends in dry deposition across the U.S. Currently, the network operates

27   as a component of the Clean Air Status and Trends Network (CASTNet) (Clarke et al., 1997). A

28   significant limitation on current capacity to estimate regional effects of PM is inadequate knowledge of

29   the mechanisms and factors governing particle dry deposition to diverse surfaces (U.S. EPA, 2004).

1     Dry deposition can not be directly measured. Deposition rates and totals are often calculated as the

2    product of measured ambient concentration and a modeled deposition velocity. This method is widely

3    used because atmospheric concentrations are easier to measure than are dry deposition rates, and models

4    have been developed to estimate deposition velocities. Ambient pollutant concentrations and

5    meteorological conditions required for application of inferential models are routinely collected at

6    CASTNet dry deposition sites. Monitored chemical species are limited to ozone, sulfate, nitrate,

7    ammonium, sulfur dioxide, and nitric acid. The temporal resolution for the ambient concentration

8    measurements and dry deposition flux calculations is hourly for ozone and weekly for the other chemical

9    substances (Clarke et al., 1997).

10     Collection and analysis of stem flow and throughfall can also provide useful estimates of

11    particulate deposition when compared to directly sampled precipitation. The method is most precise for

12    PM deposition when gaseous deposition is a small component of the total dry deposition and when

13    leaching or uptake of compounds of interest out of or into the foliage is not a significant fraction of the

14    depositional flux total because these lead to positive and negative affects in the calculated totals.

15     Foliar washing, whether using precipitation or experimental lavage, is one of the best available

16    methods to determine dry deposition of PM to vegetated ecosystems. Major limitations include the site

17    specificity of the measurements and the restriction to elements that are largely conserved within the

18    vegetative system. Surrogate surfaces have not been found that can adequately replicate essential features

19    of natural surfaces; and therefore do not produce reliable estimates of particle deposition to the landscape.

20     Micrometeorological methods employ eddy covariance, eddy accumulation, or flux gradient

21    protocols for quantifying dry deposition. These techniques require measurements of PM concentrations

22    and of atmospheric transport processes. They are currently well developed for ideal conditions of flat,

23    homogeneous, and extensive landscapes and for chemical species for which accurate and rapid sensors

24    are available. Additional studies are needed to extend these techniques to more complex terrain and more

25    chemical species.

26     The eddy covariance technique measures vertical fluxes of gases and fine particles from

27    calculations of the mean covariance between the vertical component of wind velocity and pollutant

28    concentration (Wesely et al., 1982). This technique is limited by its requirement for sensors capable of

29    acquiring concentration data at 5 to 20 Hz. For the flux gradient or profile techniques, vertical fluxes are

30    calculated from a concentration difference and an eddy exchange coefficient determined at discrete

31    heights (Erisman et al., 1988; Huebert et al., 1988). Most measurements of eddy transport of PM have

32    used chemical sensors (rather than mass or particle counting) to focus on specific PM components. These

33    techniques have not been well developed for generalized particles and may be less suitable for coarse

34    particles that are transported efficiently in high frequency eddies (Gallagher et al., 1988).

1　　　Emissions of PM and deposition are generally highest in urban areas as a result of industrial

2　processes, vehicular traffic and home heating (Lu et al., 2003; Rocher et al., 2004). Urban settings

3　therefore continue to be a major focus of atmospheric particulate research. Previous work tended to focus

4　on the size of particles as a consequence of epidemiologic studies that found strong associations between

5　particle size and respiratory illness. More recent studies have also assessed the chemical composition of

6　particles and processes involved in their formation. Gilli et al. (2008) found that concentrations of

7　secondary particles, those formed in the atmosphere from gaseous phase pollutants or resulting from

8　adsorption of elements to emitted or resuspended particles, could comprise up to 45% of $PM_{10}$ in Italian

9　cities, but that this percentage could vary considerably depending on local conditions such as surrounding

10　landscape, climate, meteorological conditions, and characteristics of urban development. The most

11　important secondary components were $NO_3^-$ and $SO_4^{2-}$, although $Cl^-$ was also important in coastal

12　settings. Secondary components tend to be more important constituents of the small fractions of PM (less

13　than 10 μm) than the larger fractions. This characteristic is relevant to abatement strategies because the

14　small fraction of PM will often increase the most during high pollution episodes (van Dingenen et al.,

15　2004). In the cities studied by Gilli et al. (2007) the $PM_{2.5}$ fraction comprised about 60% of the total $PM_{10}$.

**Table 9-3.　Factors potentially important in estimating mercury exposure and how they are addressed in this study.**

| Factor | Importance and Possible Effect on Mercury Exposure |
|---|---|
| Type of anthropogenic source of mercury | Different combustion and industrial process sources are anticipated to have different local scale impacts due to physical source characteristics (e.g., stack height), the method of waste generation (e.g., incineration or mass burn) or mercury control devices and their effectiveness. |
| Mercury emission rates from stack | Increased emissions will result in a greater chance of adverse impacts on environment. |
| Mercury species emitted from stack | More soluble species will tend to deposit closer to the source. |
| Form of mercury emitted from stack | Transport properties can be highly dependent on form. |
| Deposition differences between vapor and particulate-bound mercury | Vapor-phase forms may deposit significantly faster than particulate-bound forms. |
| Transformations of mercury after emission from source | Relatively nontoxic forms emitted from source may be transformed into more toxic compounds. |
| Transformation of mercury in watershed soil | Reduction and revolatilization of mercury in soil limits the buildup of concentration. |
| Transport of mercury from watershed soils to water body | Mercury in watershed soils can be a significant source to water bodies and subsequently to fish. |
| Transformation of mercury in water body | Reduction, methylation, and demethylation of mercury in water bodies affect the overall concentration and the MHg fraction, which is bioaccumulated in fish. |
| Facility locations | Effects of meteorology and terrain may be significant. |
| Location relative to local mercury source | Receptors located downwind are more likely to have higher exposures. Influence of distance depends on source type. |
| Contribution from non-local sources of mercury | Important to keep predicted impacts of local sources in perspective. |
| Uncertainty | Reduces confidence in ability to estimate exposure accurately. |

Source: Modified from U.S. EPA (1997)

1    The most useful records of long-term atmospheric metal deposition are recorded as accumulations

2    in ice, snow, peat, and lake sediment. Case studies presented by Norton (2007) focused on three elements

3    (Cd, Pb, Hg), which are biologically active, have negative consequences for ecosystem and human health,

4    and are dominated by atmospheric inputs. Sedimentary pollution records suggest that atmospheric

5    deposition of these elements in the U.S. peaked in about the period 1965 to 1975, but subsequently

6    declined by 75% or more. High concentrations still reside in soil in some areas, but the flux through

7    aquatic ecosystems has decreased in recent years (Norton, 2007).

8    Few studies in the past have reconstructed, from lake sediment records, the atmospheric

9    depositional history of trace metals and PAHs in lakes adjacent to coal-fired power plants. However,

10   Donahue et al. (2006) analyzed sediment from Wababun Lake, which is located in Alberta, Canada in

11   proximity (within 35 km) to four power plants built since 1950. Trace metal concentrations of Hg, Cu, Pb,

12   As, and Se in lake sediment increased by 1.2- to 4-fold. The total PAH flux to surface sediments was 730

13   to 1100 $\mu g/m^2/yr$, which was two to five times higher than in two lakes situated 20 km to the north and 70

14   km to the south.

15   The U.S. EPA (1997) compiled an assessment of the sources and environmental effects of Hg in the

16   U.S. A variety of factors were found to influence Hg deposition, fate and transport (Table 9-3).

## 9.4.3. Factors Affecting Dry Deposition

17   In the size range ~0.1 to 1.0 $\mu m$, where $V_d$ is relatively independent of particle diameter (Figure 9-

18   52), particulate deposition is controlled by roughness of the surface and by the stability and turbulence of

19   the atmospheric surface layer. Impaction and interception dominate over diffusion as dry deposition

20   processes, and the $V_d$ is considerably lower than for particles that are either smaller or larger than this size

21   range (Shinn, 1978).

22   Deposition of particles between 1 and 10 $\mu m$ diameter is strongly dependent on particle size

23   (Shinn, 1978). Larger particles within this size range are collected more efficiently at typical wind speeds

24   than are smaller particles (Clough, 1975), suggesting the importance of impaction. Impaction is related to

25   wind speed, the square of particle diameter, and the inverse of receptor diameter as a depositing particle

26   fails to follow the streamlines of the air in which it is suspended around the receptor. When particle

27   trajectory favors a collision, increasing either wind speed or the ratio of particle size to receptor cross

28   section increases the probability of collision.
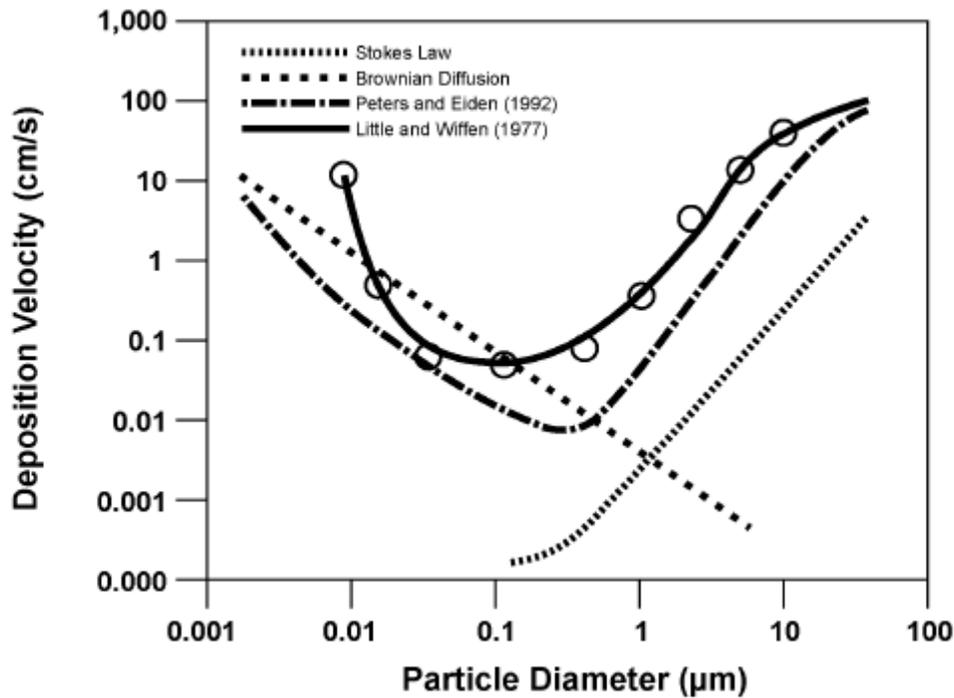
Source: U.S. EPA (2004).

**Figure 9-52.** **The relationship between particle diameter and deposition velocity for particles. Values measured in wind tunnels by Little and Wiffen (1977) over short grass with wind speed of 2.5 m/s closely approximate the theoretical distribution determined by Peters and Eiden (1992) for a tall spruce forest. These distributions reflect the interaction of Brownian diffusivity (descending dashed line), which decreases with particle size and sedimentation velocity (ascending dotted line from Stokes Law), which increases with particle size. Intermediate-sized particles (0.1 to 1.0 μm) are influenced strongly by both particle size and sedimentation velocity, and deposition is independent of size.**

1    Empirical measurements of $V_d$ for fine particles under wind tunnel and field conditions have often

2    been several-fold greater than predicted by available theory (Unsworth and Wilshaw, 1989). A large

3    number of transport phenomena, including streamlining of foliar obstacles, turbulence structure near

4    surfaces, and various phoretic transport mechanisms are not well characterized (U.S. EPA, 2004). The

5    discrepancy between measured and predicted values of $V_d$ may reflect model limitations or experimental

6    limitations in the specification of the effective size and number of receptor obstacles. Available reviews

7    (e.g., U.S. EPA, 1996, 2004) suggest the following generalizations: (1) particles >10 μm exhibit variable

8    $V_d$ between 0.5 and 1.1 cm/s depending on friction velocities, whereas a minimum particle $V_d$ of 0.03

9    cm/s exists for particles in the size range 0.1 to 1.0 μm; (2) the $V_d$ of particles is approximately a linear

1    function of friction velocity; and (3) deposition of particles from the atmosphere to a forest canopy is

2    from 2 to 16 times greater than deposition in adjacent open terrain like grasslands or other low vegetation.

## 9.4.3.1. Leaf Surface Effects on Deposition Velocity

3    The chemical composition of PM is not usually considered to be a primary determinant of $V_d$.

4    Rather, the plant leaf surface has an important influence on the $V_d$ of particles, and therefore on the rate

5    and total of dry deposition to the terrestrial environment. Relevant leaf surface properties include

6    stickiness, microscale roughness, and cross-sectional area. These properties affect the probability of

7    impaction and particle bounce. The efficiency of deposition to vegetation also varies with leaf shape.

8    Particles impact more frequently on the adaxial (upper surface) surface than on the abaxial (lower

9    surface). Most particles accumulate in the midvein, central portion of leaves. The greatest particle loading

10   on dicotyledonous leaves is frequently on the adaxial surface at the base of the blade, just above the

11   petiole junction. Precipitation washing probably plays an important role in this distribution pattern

12   (U.S. EPA, 2004).

13   Lead particles have been shown to accumulate to a greater extent on older than younger needles

14   and twigs of white pine, suggesting that wind and rain may be insufficient to fully wash the foliage.

15   Fungal mycelia (derived from windborne spores) were frequently observed in intimate contact with other

16   particles on leaves, which may reflect minimal re-entrainment of the spore due to shelter by the particles,

17   mycelia development near sources of soluble nutrients provided by the particles, or simply co-deposition

18   (Smith and Staskawicz, 1977).

19   Leaves with complex shapes tend to collect more particles than do those with more regular shapes.

20   Conifer needles are more efficient than broad leaves in collecting particles by impaction, reflecting the

21   small cross section of the needles relative to the larger leaf laminae of broadleaves and the greater

22   penetration of wind into conifer canopies than broadleaf ones (U.S. EPA, 2004).

## 9.4.3.2. Canopy Surface Effects on Deposition Velocity

23   Surface roughness increases particulate deposition, and $V_d$ is usually greater for a forest than for an

24   nonforested area and greater for a field than for a water surface. Different size particles have different

25   transport properties and $V_d$. The upwind leading edges of forests, hedge rows, and individual plants are

26   primary sites of coarse particle deposition. Impaction at high wind speed and the sedimentation that

27   follows the reduction in wind speed and carrying capacity of the air in these areas lead to preferential

28   deposition of larger particles (U.S. EPA, 2004).

1  Air movement is slowed in proximity to vegetated surfaces. Canopies of uneven age or with a

2  diversity of species are typically aerodynamically rougher and receive larger inputs of dry-deposited

3  pollutants than do smooth, low, or monoculture vegetation (Garner et al., 1989; U.S. EPA, 2004).

4  Canopies on slopes facing the prevailing winds receive larger inputs of pollutants than more sheltered,

5  interior canopy regions.

6  All foliar surfaces within a forest canopy are not equally exposed to particle deposition. Upper

7  canopy foliage tends to receive maximum exposure to coarse and fine particles, but foliage within the

8  canopy tends to receive primarily fine aerosol exposures. The dry deposition of fine-mode particles and

9  unreactive gases tends to be more evenly distributed throughout the canopy.

10  Both uptake and release of PM constituents can occur within the canopy. The leaf surface is a

11  region of leaching and uptake. Exchange also occurs with epiphytic organisms and bark and through

12  solubilization of previously dry deposited PM. Vegetation emits a variety of particles and particulate

13  precursor materials.

## 9.4.4. Magnitude of Dry Deposition

14  Dry deposition of PM is most effective for coarse particles. These include primary geologic

15  materials and elements such as iron and manganese. By contrast, wet deposition is more effective for fine

16  particles of secondary atmospheric origin and elements such as cadmium, chromium, lead, nickel, and

17  vanadium (Reisinger, 1990; Smith, 1990; U.S. EPA, 2004). The relative magnitudes of the different

18  deposition modes varies with ecosystem type, location, elevation, and chemical burden of the atmosphere

19  (U.S. EPA, 2004).

20  High-elevation forests generally receive larger particulate deposition loadings than equivalent low

21  elevation sites. Higher wind speeds at high elevation enhance the rate of aerosol impaction. Orographic

22  effects enhance rainfall intensity and composition and increase the duration of occult deposition.

23  High-elevation forests are often dominated by coniferous species with needle-shaped leaves that enhance

24  impaction and retention of PM delivered by all three deposition modes.

25  Urban stormwater can be rich in heavy metals and other contaminants derived from atmospheric

26  deposition, and can be a major source of pollutant inputs to water bodies in urban settings. Urban

27  stormwater runoff can also be toxic to aquatic biota, partly due to trace metal concentrations (Greenstein

28  et al., 2004; Sabin et al., 2005; Schiff et al., 2002). These processes are largely a function of the

29  impervious nature of much of the ground surface in urban areas (i.e., buildings, roads, sidewalks, parking

30  lots, construction sites). Dry-deposited pollutants can build up, especially in arid and semi-arid

31  environments, and then be washed into surface waters with the first precipitation event.

## 9.4.4.1. Using Vegetation for Estimating Atmospheric Deposition

1         Whereas direct real-time measurement of deposition or air concentrations of atmospheric

2   contaminants is desirable, it is not always practical (Howe et al., 2004). Instead, passive time-integrative

3   methods are frequently used. These can involve analysis of vegetative tissues as a record of pollutant

4   exposure, or analysis of lake sediment cores or ice cores to determine changes in pollutant input over

5   time. There is a general assumption that the concentration of an analyte in vegetation reflects the

6   time-integrated concentration of that analyte in the air. The development of deposition layers in sediment

7   or ice cores allows the possibility of determining the effects of changes in the atmospheric concentration

8   over periods of years, decades, or longer.

9         Biomonitoring methods are important in air pollution assessment and provide a complement for

10   more typical instrumental analyses. It is well know that mosses can accumulate heavy metals to high

11   levels in response to atmospheric deposition. The effects of deposited metals on the mosses have been less

12   well studied. Tremper et al. (2004) exposed mosses of two species to roadside conditions and sampled

13   them over a period of three months. Under field conditions, chlorophyll concentrations in moss tissue

14   were not affected by metal contamination and accumulation.

15         Because mosses accumulate dissolved and PM deposited from the atmosphere, they have been used

16   extensively in Europe as surrogate collectors for estimating bulk (wet plus dry) deposition of metals. The

17   ease and low cost of this method has enabled regional assessments to be conducted throughout Europe.

18         Despite its wide use, however, several papers have pointed out complications in the use of mosses

19   to quantify metal deposition rates. Zechmeister (1998) found that the uptake efficiency for 12 heavy

20   metals in 3 species of moss was similar, but that uptake efficiency in a fourth species was uncorrelated

21   with the other species for about half the metals considered. Zechmeister (1998) also showed that

22   productivity of an individual species can vary greatly among sites. To calculate atmospheric deposition of

23   metals from accumulation in mosses, both the metal concentration and the rate of biomass production is

24   needed. Further complication was shown in the study of Shakya et al. (2008), which revealed that

25   accumulation of Cu, Zn and Pb decreased chlorophyll content. Sites with higher deposition levels may

26   therefore have lower rates of productivity than cleaner sites.

27         Differences in uptake efficiencies among species and productivity among sites has led to the use of

28   a single moss species placed in mesh bags that can be distributed to areas where that species of moss does

29   not grow naturally. Studies to standardize this passive deposition monitoring approach have been limited.

30   Adamo et al. (2007) evaluated the effects of washing with water, oven drying, and acid washing as

31   preteatments and found little difference in uptake efficiencies, although the ratio of the collecting surface

32   area to mass was found to be a key factor in uptake efficiency.

1    Couto et al. (2004) investigated dry versus bulk deposition of metals using transplanted moss bags.

2    This study showed that at some sites dry deposition exceeded bulk deposition, a likely outcome of

3    wash-off of dry deposited particles. This study also documented intercationic displacement and leaching

4    as a result of acidic precipitation. The authors concluded that the accumulated metal concentration

5    represented an unstable equilibrium between inputs and outputs of elements that were a function of the

6    local environment and weather during the exposure period. They also concluded that it was not possible

7    to extrapolate calibrations between metal accumulation in moss and atmospheric deposition of metals to

8    areas with different weather conditions, precipitation pH, and air contaminant concentrations.

9    Zechmeister et al. (2003) also presented results demonstrating the problems with dry deposited particles

10   that can be washed off by rain. These studies indicate that moss is not a completely effective collector of

11   total particle deposition. Deposition estimates from moss accumulation probably represent values that fall

12   between wet deposition and total deposition.

13       A European moss biomonitoring network has been in place since 1990 (Harmens et al., 2007).

14   Sampling surveys are repeated every five years. The survey conducted in 2005/2006 occurred in 32

15   countries at over 7000 sites. The network reports metal concentrations associated with live moss tissue.

16   Trends analysis of these data showed statistically significant decreases over time in moss concentrations

17   for As, Cu, V, and Zn. Trends were not observed for Cr, Fe, or Ni. Results for individual countries

18   participating in the survey have also been published. In Hungary, major pollution sources were readily

19   detected by moss sampling (Ötvös et al., 2003). Somewhat higher metal concentrations in mosses in 1997

20   than in other European countries were attributed to the use of a different moss species in the Hungarian

21   survey (Ötvös et al., 2003). Similar sampling in Romania showed regions with contamination that were

22   among the highest in Europe. These results were consistent with known air quality problems in Romania

23   (Lucaciu et al., 2004). Because particulate deposition is not well characterized using this method, spatial

24   patterns and temporal trends for particulate metal deposition in Europe only provide crude estimates of

25   relative deposition patterns.

26       The use of moss to assess heavy metal deposition has received much less attention in the U.S. than

27   in Europe. A study conducted in the Blue Ridge Mountains, VA, found that metal concentrations in moss

28   were related to elevation and canopy species at some sites (Schilling and Lehman, 2002). However, metal

29   concentrations in moss were not related to concentrations in the O horizon of the soil. Other measurement

30   methods for trace metal deposition were not available to compare with moss concentrations.

31       Epiphytic lichens have also been used to evaluate heavy metal accumulation. Helena et al. (2004)

32   found substantially increased concentrations of metals in lichens transplanted from a relatively clean

33   region to an area in proximity to a metal smelter. The presence of specific species of bryophyte or lichen

34   can serve as an effective bioindicator of metal contamination (Cuny et al., 2004). In some studies, tree

1　bark has been used as a biomonitor for atmospheric deposition of heavy metals (Baptista et al., 2008;

2　Pacheco and Freitas, 2004; Rusu et al., 2006).

3　　　Biomonitoring using mosses, lichens, or other types of vegetation has been well established as a

4　means of identiff spatial patterns in the atmospheric deposition of heavy metals in relation to power

5　plants, industry, and other point and regional emissions sources. More recently, a number of studies

6　(López Alonso et al., 2002; 2003a; 2003b) have used cattle reared predominantly on local forage as a

7　means of monitoring atmospheric inputs of Cu, Ar, Zn, and Hg. For example, Hg emissions from coal

8　fired power plants in Spain had a substantial effect on Hg accumulation by calves (López Alonso et al.,

9　2003a). Accumulation of Hg by cattle extended to about 140 to 200 km downwind from the source.

10　　　Yang et al. (2007a) investigated the effectiveness of pine needles as passive air samplers for

11　semi-volatile organic compounds (SOCs), such as PAHs, that are partially or completely

12　particle-associated in the atmosphere. PAH distribution patterns are complicated by their properties,

13　which span a broad range of octanol-air partition coefficients. This allows them to be present in both

14　vapor and particle phases. In addition, the air-plant partitioning of PAHs is affected by air temperature and

15　atmospheric stability (2007a). DeNicola et al. (2005) documented the suitability of a Mediterranean

16　evergreen oak (*Quercus ilex*) to serve as a passive biomonitor for atmospheric contamination with PAH in

17　Italy.

## 9.4.4.2. Deposition to Canopies

18　　　Tree canopies have been shown to increase dry deposition from the atmosphere, including

19　deposition of PM. Dry deposition rates in the canopy are commonly estimated by the difference between

20　throughfall deposition and deposition measured by an open collector, although the use of this approach to

21　specifically quantify particulate deposition is complicated by gaseous deposition to leaf surfaces and, for

22　some elements, leaching and uptake. Avila and Rodrigo (2004) found that trace metal deposition in

23　throughfall in a Spanish oak forest were higher than bulk deposition for Cu, Pb, Mn, V, and Ni, but not for

24　Cd and Zn. This study also found that dry deposition of Cu, Pb, Zn, Cd and V occurred, but that canopy

25　uptake of Zn and Cd also occurred. Leaching of Mn and Ni from the foliage was observed as well.

26　Leaching of Ni, Cu, Mn, Rb, and Sr from a red spruce-balsam fir canopy by acidic cloud water was also

27　measured in a study by Lawson et al. (2003). These studies suggest that leaching of trace metals from

28　forest canopies varies with tree species and the acidity of precipitation. Throughfall therefore cannot be

29　assumed to represent total deposition of heavy metals without evaluating uptake and leaching at the

30　specific study site.

31　　　Physical models have provided an alternative to estimating dry deposition to canopies with

32　throughfall measurements. Recently, Pryor (1996) and Binkowski (2004) identified an additional

1 complication in that models typically hold particle size constant. Nevertheless, there may be significant

2 modification of particle size distributions during the deposition process. Condensation processes in the

3 vicinity of the canopy can increase particle size and may explain discrepancies between observations and

4 modeled dry deposition that is based on air sampling of particulates above the canopy.

5     The use of pine and oak canopies as bioindicators of atmospheric trace metal pollution was

6 investigated by Aboal et al. (2004). Metal concentrations in leaves were found to be one to three orders of

7 magnitude lower than in mosses collected in this study. As an ecosystem pool, metals in leaves were

8 likely to be much more important than those in mosses. The authors concluded, however, that these tree

9 species were not effective bioindicators of atmospheric deposition of heavy metals.

10     The effectiveness of tree canopies in capturing particulates was investigated as a method for

11 improving air quality by Freer-Smith et al. (2004). This study showed that with consideration of planting

12 design, location of pollution source, and tree species, planting of trees can be affective at reducing

13 particulate air pollution. However, this approach does not address the possible effects of the captured

14 pollution on trees, soils and surface waters.

15     An important aspect of global Hg cycling is the extent to which the Hg stored in forest vegetation

16 originates from the soil or the atmosphere. In other words, do plants recycle Hg by uptake from the soil

17 and then return it to the soil in litterfall, or do plants directly capture atmospheric Hg and then deliver it to

18 the soil as an external source? The question was addressed in a mesocosm experiment by Ericksen et al.

19 (2003). Aspen trees were grown in gas-exchange chambers in Hg-enriched soil ($12.3 \pm 1.3$ µg/g) and the

20 Hg content in the foliage was analyzed. Foliar Hg increased with leaf age for two to three months and

21 then stabilized at leaf concentrations near 150 ng/g. About 80% of the Hg found in above-ground biomass

22 was present in the leaves. The concentration of Hg in trees grown in the same mesocosms in containers of

23 low Hg soil ($0.03 \pm 0.01$ µg/g) exhibited foliar Hg concentrations that were similar to those of trees grown

24 in Hg-enriched soil. Almost all of the foliar Hg originated from the atmosphere. Clearly, plant foliage can

25 be a major sink for airborne Hg, which can subsequently enter the soil after litterfall (Ericksen et al.,

26 2003). However, this study did not determine the extent to which atmospheric Hg was dry-deposited on

27 the foliage, as opposed to gaseous uptake through the stomata.

## 9.4.4.3. Deposition to Soil

28     As with mosses, accumulation of heavy metals in surface soils provides a general reflection of the

29 spatial distribution of industrial pollution. In the study of Romic and Romic (2003), relationships were

30 found between urban activities and concentrations of metals in soils in developed areas surrounding

31 Zagreb, Croatia. Goodarzi et al. (2002) compared deposition estimated by moss bags to concentrations of

32 metals in A-horizon soils in the vicinity of a large smelter. Statistically significant correlations were

observed between the moss bag deposition estimates and the soil metal concentrations for Cd, Pb, Zn, and in some cases also Cu. These correlations suggested that atmospheric deposition of metals caused elevated metal concentrations in the uppermineral horizon of these soils. No correlations were found for Hg or As in this study.

Studies have also looked at metal accumulation in peat because of the tendency of most metals to be immobilized through binding with organic matter. Steinnes et al. (2005) presented geographical patterns of metal concentrations in surface peat throughout Norway that corresponded to pollution sources, although the peat samples were collected in 1979. Zaccone et al. (2008) found that variations of metal concentrations with depth in a single Swiss peat core corresponded with the depositional history that would be expected from the industrial revolution, although $Cs^{137}$ activity exhibited a distribution in the profile that was not fully consistent with the Chernobyl nuclear reactor accident. A detailed study of Finish peat showed that relationships between depth profiles of metal concentrations and deposition history can match well for some metals at some sites, but not well for the same metals at other sites (Rausch et al., 2005). They also found that Zn and Cd accumulation rates were independent of deposition history at each of three study sites.

Metal deposition to soil is also a significant concern adjacent to roadways. The concentrations of Cd, Ca, Cu, Pb, and Zn in road runoff were found to be significantly higher during winter in Sweden. This seasonal pattern was attributed to the intense wearing of the pavement that occurred during winter due to the use of studded tires in combination with chemical effects of deicing salts (Bäckström et al., 2003).

## 9.4.5. Components of Deposition

### 9.4.5.1. Trace Metals

Atmospheric deposition can be the primary source of some metals to some watersheds. Metal inputs can include the primary crustal elements (Al, Ca, K. Fe, Mg, Si, Ti) and the primary anthropogenic elements (Cu, Zn, Cd, Cr, Mn, Pb, V). The crustal elements are derived largely from weathering and erosion, whereas the anthropogenic elements are derived from combustion, industrial sources, and other man-made sources (Goforth and Christoforou, 2006).

There are a number of natural geologic sources of Hg emissions to the atmosphere. These include geothermal and volcanic activity, geologic metal deposits, and organic-rich sedimentary rocks. These natural emissions combine with anthropogenic emissions from such sources as power plants, landfills, sewage sludge, mine waste, and incineration (Gustin, 2003; Schroeder and Munthe, 1998). Emissions

1   from natural sources are controlled by geologic features, including substrate Hg content, rock type, the

2   degree of hydrothermal activity, and the presence of heat sources (Gustin, 2003).

3       The significance of natural Hg sources relative to anthropogenic sources varies geographically. For

4   example, Nevada occurs within a global mercuriferous belt, with area emissions about three times higher

5   than the value assumed for global modeling (Gustin, 2003). In Nevada, natural and anthropogenic Hg

6   emissions are approximately equal (Gustin, 2003).

7       Heavy metal deposition to forested sites depends on forest location as well as upwind emissions

8   source strength. The deposition velocity tends to be dependent on particle size and chemical species.

9   Larger particles deposit more efficiently than smaller particles. Heavy metals preferentially associate with

10  fine particles. Fine particles also have the longest atmospheric residence times. Depending on climate and

11  topography, fine particles may remain airborne for days to months and may be transported thousands of

12  kilometers from their source.

13      Ecosystems immediately downwind of major heavy metal emissions sources may receive locally

14  heavy dry deposition. Trace element investigations conducted in roadside, industrial, and urban

15  environments have also shown that substantial amounts of particulate heavy metals can accumulate on

16  vegetative surfaces.

17      The distribution of toxic elements in urban soils has been an important area of study (cf., Madrid et

18  al., 2002; Markiewicz Patkowska et al., 2005). Generally, Cu, Pb, Zn, and Ni have accumulated in urban

19  soils compared with their rural counterparts (Yuangen et al., 2006). Effects on soil microbiology have not

20  been well studied but can include effects on microbial biomass, microbial utilization of C, and other

21  indicators of the health and functioning of urban soils. Yuangen et al. (2006) found that urban soil basal

22  respiration rates were positively correlated with soil acetic acid-extractable Cd, Cu, Ni, and Zn. The soil

23  microbial biomass was negatively correlated with the concentrations of Pb fractions, but not with other

24  metals. Overall microbial biomass was lower for urban soils as compared with rural soils (Yuangen et al.,

25  2006).

26      There is concern that Pb contamination of forest soil could move into groundwater. This would be

27  an important issue in view of the large quantity of Pb deposited from the atmosphere in the 1960s and

28  1970s in response to combustion of leaded gasoline. This issue was investigated by Watmough et al.

29  (2004) who applied a stable isotope ($^{207}$Pb) to the forest floors of white pine (*Pinus strobus*) and sugar

30  maple (*Acer saccharum*) stands. Added Pb was rapidly lost from the forest floor, likely due to high litter

31  turnover in these forest types. However, Pb concentrations in the upper 30 cm of mineral soil were

32  strongly correlated with soil OM, suggesting that Pb does not readily move down the soil profile to the

33  ground water, but rather is associated with the organic content of the upper soil layers (Watmough et al.,

34  2004).

1    Karar et al. (2006) used factor analysis to identify possible sources contributing to $PM_{10}$ deposition

2    at two urban sites in India: one residential and one industrial. At both sites, vehicular traffic and road dust

3    were identified as potential sources. In addition, solid waste dumping and soil dust were identified at the

4    residential site, and the galvanizing, electroplating, and tanning industries were identified at the industrial

5    site.

6       Azimi et al. (2003) found in rural and urban areas of France that dry deposition comprised 40, 60

7    and 80% of total deposition for Cd, Cu and Pb, although total concentrations were lower at the rural sites

8    than at the urban sites for most metals. Additional work by this group (Azimi et al., 2005) showed that

9    total deposition of these metals decreased from 1994 to 2002. Sabin et al. (2006a) presented literature

10   values of heavy metal dry deposition that showed urban areas to have deposition levels approximately an

11   order of magnitude higher than rural areas. Tasdamir et al. (2006) also reported deposition fluxes in dry

12   deposition for trace metals (Cu, Pb, Mn, Cr, Ni, Co, and Cd) in a Turkish urban environment. Fluxes were

13   of similar magnitude to those previously reported for urban industrialized areas, although the highest

14   particulate fluxes were for crustal elements (Ca, Mg, Fe and Mn) associated with coarse particles.

15      Information on atmospheric transport and deposition of heavy metals was provided by analysis of

16   snow chemistry radiating away from a metal smelter in an isolated region in Quebec (Telmer et al., 2004).

17   Transport of 27 metals was found to exceed 50 km. Wet deposition was distinguished from dry deposition

18   by filtering melted snow samples. Deposition beyond 50 km was found to be largely in soluble forms,

19   although significant particle deposition occurred beyond this distance. Partitioning between soluble and

20   insoluble forms varied by element. Elements that were most readily wet deposited included Pb and Cu,

21   and elements with the largest fraction in particles were Ti and Sb.

22      Detailed modeling results obtained by Lu et al. (2003) for the Los Angeles basin showed that the

23   majority (approximately 80%) of local metal deposition was associated with particles larger than 10 μm,

24   and as a result, 35-45% of metal emissions were deposited locally. However, this study also indicated that

25   most of the remaining metals not deposited locally within the basin (65-75%) are transported over

26   continental to global scales. These authors further concluded that routine air monitoring for PM in the 2.5

27   and 10 mm size fractions is not adequate for measuring urban trace metal deposition. The importance of

28   large particle deposition was also demonstrated by Tasdemir et al. (2004) in Chicago, where the

29   deposition of polychlorinated biphenyls (PCBs) was associated with particles of about 25 μm. Because

30   there are few point sources of PCBs, the gaseous phase of these molecules is expected to be in

31   equilibrium with PM-associated PCBs. The relatively high air concentrations and deposition velocities of

32   coarse particles in urban settings therefore lead to higher PCB deposition than in rural environments.

33      Much of the urban $PM_{10}$ emissions total is from non-exhaust traffic emissions (Hussein et al.,

34   2008). Studded tires cause higher $PM_{10}$ emissions than summer tires. Friction wear is small compared to

1    suspension of accumulated road dust in contributing to the total $PM_{10}$ emissions of traffic. Deposition of

2    heavy metals may be particularly high along freeways and other heavily traveled roads. Sabin et al.

3    (2006b) found that deposition rates in the vicinity of a large Los Angeles freeway were considerably

4    higher than urban background rates 10 to 150 m away from the freeway, particularly for Cu, Pb and Zn.

5    This was explained by a combination of vehicle emissions and resuspension of coarse particles (>6 μm)

6    by rapidly moving traffic that provided PM to which the metals can adsorb. Similar results were observed

7    in Australia, where road-deposited sediments were found to have high concentrations of Zn, Fe, Pb, Cd,

8    Cu, Cr, Al and Mn (Herngren et al., 2006). However, this study found maximum metal concentrations

9    associated with particles in the 0.45 to 75 μm range, which is somewhat smaller than those reported by

10   Sabin et al. (2006a). Herngren et al. (2006) also pointed out that the PM size class of 0.45 to 75 μm was

11   much smaller than the minimum size of 250 μm removed by street cleaning practices.

12       Because PM deposited along roadsides is prone to being washed into storm drains and ditches that

13   empty into nearby surface waters, the high deposition of trace metals associated with roads represents a

14   significant metal loading to surface waters (Herngren et al., 2006; Sabin et al., 2006a; 2006b) This has

15   also been shown in two studies of roof wash-off in urban areas. In Paris, France, Rocher et al. (2004)

16   found that wash-off from roofs was a significant input to surface waters for heavy metals and

17   hydrocarbons. They found that metal deposition did not have a strong seasonal signal, but that incomplete

18   combustion of heating fuels resulted in the highest hydrocarbon deposition during the heating season. A

19   similar study in Austin, TX showed high concentrations of Zn, Pb, Cd, and PAH in roof wash-off (Van

20   Metre and Mahler, 2003). In both the studies of Rocher et al. (2004) and Van Metre et al. (2003), roofing

21   materials had the largest effect on Zn concentrations in wash-off, but concentrations of Cu and Pb were

22   also elevated by roof materials.

## 9.4.5.2. Mercury

23       The most important factors involved in the atmospheric fate and transport of Hg include:

24   (1) emissions; (2) atmospheric transformation and transport; (3) deposition to the Earth surface; and

25   (4) re-emission to the atmosphere (U.S. EPA, 1997).

26       There are both anthropogenic and natural sources of Hg emission to the atmosphere. Natural

27   processes include volatilization from marine and fresh water aquatic ecosystems, degassing from soils and

28   geologic materials, and volcanic emissions (U.S. EPA, 1997). Most anthropogenic emissions are from

29   combustion sources and industrial processes. Particulate Hg emissions are mainly in oxidized form due to

30   the relatively high vapor pressure of elemental Hg (U.S. EPA, 1997).

31       The residence time of Hg in the atmosphere depends on its chemical form. Hg(0) has an average

32   atmospheric residence time of about a year, and is therefore transported long distances. Oxidized Hg

1   (Hg(II)) has a residence time of hours to months and is prone to rapid deposition via wet and dry

2   deposition processes. However, some Hg(II) is associated with fine particles, and therefore can have an

3   atmospheric residence time that is more similar to that of Hg(0) (U.S. EPA, 1997). Fluxes of Hg(0) from

4   geologic sources, and anthropogenic emissions from combustion and industrial sources all contribute to

5   the global atmospheric reservoir of Hg, which has a residence time of up to a couple of years (U.S. EPA,

6   1997).

7       The divalent species of Hg are more readily removed from the atmospheric than is elemental Hg.

8   Dry deposition transfers both particulate and gaseous divalent Hg from the atmosphere to the Earth

9   surface at locations where substantial amounts of atmospheric divalent Hg occurs. In addition, particulate

10  Hg is readily wet deposited due to cloud scavenging processes and precipitation. The divalent species

11  have much lower Henry's Law constants than does elemental Hg and therefore partition readily to the

12  aqueous phase. This is especially true for the gas phase divalent Hg (U.S. EPA, 1997).

13      Most of the Hg emitted to the atmosphere deposits as Hg(II). The deposited Hg(II) can revolatilize

14  back to the atmosphere, be methylated in the soil, or be transported to a water body via runoff and

15  leaching. Methylation can also occur within the water body, and either Hg(II) or methyl Hg can be

16  reintroduced from the water back to the atmosphere.

17      Atmospheric Hg deposition has increased with industrialization. For example, Steinnes et al.

18  (2005) found that Hg concentrations in dated peat samples were about 15 times higher in the last 100

19  years than in pre-industrial times. However, the complexities of atmospheric Hg chemistry and typically

20  low atmospheric concentrations make quantification of particulate Hg deposition a challenging process

21  (Lynam and Keeler, 2005). Gaseous divalent Hg (Hg(II)) is highly soluble, and therefore can be

22  wet-deposited, but also can become associated with various types of PM that will control its deposition

23  characteristics. Gaseous elemental Hg (Hg(0)) is relatively insoluble, but can be oxidized in the

24  atmosphere to Hg(II) (Seigneur et al., 2003). Collection of PM Hg is typically done through air filtration

25  that requires extended sampling times as a result of low air concentrations. Lynam et al. (2005) found that

26  oxidation of Hg(0) may occur if sampling is done during high $O_3$ events, resulting in artificially high

27  measurements of PM Hg concentrations. The complexities of Hg deposition were also shown by Graydon

28  et al. (2006) who found that a portion of wet deposited Hg(II) to forest canopies may be photo-reduced to

29  gaseous Hg(0) that is then reemitted to the atmosphere. This canopy effect suggests that throughfall may

30  underestimate total deposition. Net deposition of Hg to soil surfaces was evaluated by Gustin et al.

31  (2006). This study showed that reemission of deposited Hg from soil is affected by environmental

32  conditions including soil moisture, temperature, light, atmospheric oxidants and Hg concentrations in air.

33  Further work is needed to constrain estimates of deposition to soils under varying conditions.

1    Modeling approaches have been developed from assumptions regarding Hg deposition processes.

2    Without measurement data for evaluation, these results have an unknown level of uncertainty. However,

3    detailed Hg emissions inventories have been developed for some regions, such as the Great Lakes

4    (Murray and Holmes, 2004), which have been useful for deposition modeling. Using this approach,

5    Landis and Keeler (2002) estimated that dry deposition to Lake Michigan approximately equaled wet

6    deposition, and that atmospheric deposition to the lake was the primary Hg input. Several other studies

7    have developed deposition estimates for the Great Lakes through modeling. These include Gbor et al.

8    (2007), in which particulate Hg(II) was estimated to be only 7% of dry deposited gaseous Hg(II), and 2%

9    of total deposition to Lake Michigan.

10    Similar modeling approaches have been used in efforts to distinguish among deposition of locally

11    and regionally emitted Hg and the deposition of Hg that has resulted from intercontinental transport.

12    Seigneur et al. (2003) estimated that U.S. emissions other than from New York contributed 25 to 49% of

13    total Hg deposition in the U.S. This study also estimated that particulate Hg(II) comprised 1-2% of total

14    deposition in New York State, although dry deposition of gaseous Hg(II) was estimated to comprise about

15    30% of total Hg deposition.

16    Hg deposition measurements at Mace Head, Ireland, considered a global background site, were

17    reported by Seigneur et al. (2003) to be 14-94 pg/m$^3$ for wet and gaseous deposition of Hg(II) and 5-115

18    pg/m$^3$ for particulate Hg(II) deposition. A similar modeling exercise by Travnikov (2005) estimated that

19    for the Northern Hemisphere in general, the contribution of total Hg deposition from intercontinental

20    transport was about the same as that from regional pollution sources, although the Travnikov (2005)

21    article did not report the fraction of dry or particulate deposition. This literature suggests that particulate

22    Hg deposition is a small fraction of total Hg deposition, but the measurement difficulties and limited

23    available data coupled with the complexities of atmospheric Hg speciation indicate that further research is

24    needed to ascertain the environmental relevance of particulate Hg.

### 9.4.5.3. Organics

25    Most persistent organic pollutants (POPs) enter the biosphere via human activities, including

26    synthetic pesticide application, output of polychlorinated dibenzo dioxins (PCDD) from incinerators, and

27    accidental release of PCBs from transformers (Lee et al., 2003d). Once they are introduced into the

28    environment, their accumulation and magnification in biological systems are determined by

29    physiochemical properties and environmental conditions. Uptake by plants can occur at the soil/plant

30    interface and at the air/plant interface. For lipophilic POPs, such as PCDDs and PCBs, the air/plant

31    response route generally dominates (Lee et al., 2003d; Thomas et al., 1998), but uptake through

1   above-ground plant tissue also occurs. In a study of zucchini (*Cucurbita pepo*), Lee et al. (2003d) found

2   chlordane pesticide components in all vegetation tissues examined: root, stem, leaves, fruits.

3       Organic compounds partition between gas and particle phases, and organic particulate deposition

4   depends largely on the particle sizes available for adsorption (U.S. EPA, 2004). Dry deposition of organic

5   materials is often dominated by the coarse fraction. Gas-particle phase interconversions are important in

6   determining the amount of dry deposition.

7       Many pesticides are carcinogenic or estrogenic and pose potential threats to aquatic and terrestrial

8   biota. Although deposition of semi-volatile organic compounds (SOC) was previously reported for the

9   Sierra Nevada Mountains in California and the Rocky Mountains in Colorado, little was previously

10  known about the occurrence, distribution, or sources of SOC in alpine, sub-Arctic, and Arctic ecosystems

11  in the western U.S. The snowpack is efficient at scavenging of both particulate and gas phase pesticides

12  from the atmosphere (Halsall, 2004; Lei and Wania, 2004).

13      Analysis of pesticides in snowpack samples from seven national parks in the western U.S. by

14  Hageman et al. (2006) illustrated the deposition and fate of 47 pesticides and their degradation products.

15  Correlation analysis with latitude, temperature, elevation, PM, and two indicators of regional pesticide

16  use suggested that regional patterns in historic and current agricultural practices are largely responsible

17  for the distribution of pesticides in the national parks. Pesticide deposition to parks in Alaska was

18  attributed to long-range atmospheric transport.

19      Deposition and fate of PAH has been an important area of research. Because they are carcinogenic,

20  PAHs are important environmental contaminants. Root-soil behavior of PAHs is an area of active study.

21  Soil-bound PAHs are associated with soil organic matter and are therefore generally not easily available

22  for root uptake. PAHs are readily adsorbed to root surfaces but there seems to be little movement to the

23  interior of the root or movement up to the shoots (Gao and Zhu, 2004).

24      Paddy rice is the main food crop planted in China. As an aquatic plant having aerial roots, the

25  movement of PAHs into rice roots may be different than their movement into more widely studied

26  land-grown food crops. PAH concentrations in the rice roots were more correlated with the water and air

27  compartments than with the soil (Jiao et al., 2007).

28      The group PAH contaminant group includes known carcinogens, such as benzo[a]pyrene (B[a]P)

29  and substances thought to be toxic. They are common air pollutants in metropolitan areas, derived from

30  vehicular traffic and other urban sources. Especially high concentrations have been found near Söderberg

31  aluminum production industries and areas where wood heating during winter is common. Other sources,

32  in addition to gasoline and diesel engines, include forest fires and various forms of fossil fuel combustion

33  (Sanderson and Farant, 2004).

1    PAHs include hundreds of different compounds that are characterized by possessing two or more

2    fused benzene rings. They are widespread contaminants in the environment, and are formed by

3    incomplete combustion of fossil fuels and other organic materials. Eight PAHs are considered

4    carcinogenic and 16 are classified by EPA as priority pollutants. The behavior of PAHs is strongly

5    determined by their chemical characteristics, especially their nonpolarity and hydrophobicity. They

6    readily adsorb to particulates in the air and to sediments in water. Srogi (2007e) provided a thorough

7    review of PAH concentrations in various environmental compartments and their use for assessing

8    environmental risks and possible effects on ecosystems and human health.

9    The total PAH concentration in grasses adjacent to a highway have been measured to be about eight

10   times higher than in grasses from reference sites not close to a highway (Crépineau et al., 2003). Howe et

11   al. (2004) found that concentrations of PAHs and hexachlorobenzene (HCB) in spruce (*Picea* spp.)

12   needles at 36 sites in eastern Alaska varied by an order of magnitude. Samples collected near the city of

13   Fairbanks generally had higher concentrations than samples collected from rural areas. The relative

14   importance of combustion sources versus petrogenic sources was highest in the near-coastal areas, as

15   reflected in variation in the concentration of ratios of isomeric PAHs.

## 9.4.5.4. Base Cations

16   With respect to ecosystem effects from PM deposition, the inclusion of base cations (especially Ca,

17   Mg, and K) in atmospheric deposition is generally considered to be a positive effect. Base cations are

18   important plant nutrients that are in some locations present in short supply and that are further depleted by

19   the acidic components of deposition. Increased base cation deposition can help to ameliorate adverse

20   effects of acidification of soils and surface waters and reduce the toxicity of inorganic Al to plant roots

21   and aquatic biota. These topics are covered in detail in the recent $NO_XSO_X$ ISA (2008c).

22   Calcium supply is also well known to be important for breeding success in passerine bird species.

23   Eggshell thickness, egg size, clutch size, and hatchability of pied flycatcher (*Ficedula hypoleuca*) were

24   found to be depressed near the Cu smelter at Harjavalta, SW Finland (Eeva and Lehikoinen, 2004).

25   Availability of Ca-rich food to the birds was estimated by counting snail shells in the nests postfledging.

26   The number of snail shells correlated positively with the Ca concentration of nestling feces and adult

27   breeding success. In addition, the negative impact of Cu on the number of fledglings was stronger at

28   locations where Ca concentration was low (Eeva and Lehikoinen, 2004).

29   Although the effects of base cation deposition inputs to terrestrial ecosystems are most commonly

30   considered to be positive, under very high base cation deposition levels, plant health can be adversely

31   affected. Dust that is high in base cations can settle on leaves and other plant structures and remain for

32   extended periods of time. This is especially likely in arid environments because rainfall can serve to wash

1    dry deposited materials off the foliage. Extended dust coverage can result in a variety of adverse impacts

2    on plant physiology (Grantz et al., 2003). For example, van Heerden et al. (2007) documented decreased

3    chlorophyll content, inhibition of $CO_2$ assimilation, and uncoupling of the oxygen-evolving complex in

4    desert shrubs exposed to high limestone dust deposition near a limestone quarry in Namibia.

5            Based on the IFS data, the U.S. EPA (2004) concluded that particulate deposition has a greater

6    effect on base cation inputs to soils than on base cation losses associated with the inputs of sulfur,

7    nitrogen, and $H^+$. These atmospheric inputs of base cations have considerable significance, not only to the

8    base cation status of these ecosystems, but also to the potential of incoming precipitation to acidify or

9    alkalize the soils in these ecosystems. This topic is discussed in detail in the recent $NO_X SO_X$ ISA (2008e).

# 9.5. Effects on Individual Organisms

10           Deposition of PM from the atmosphere to the soil or plant surface is required before most

11   biological effects on plants or ecosystems can occur. Exposure to a given amount of airborne PM may

12   lead to differing responses, depending on the particular mix of deposited particles. PM is not a single

13   pollutant, but rather a heterogeneous mixture of particles differing in size, origin, and chemical

14   composition. Atmospheric PM has been defined, for regulatory purposes, mainly by size fractions and

15   less clearly so in terms of chemical nature, structure, or source. PM size classes do not necessarily relate

16   to effects (U.S. EPA, 1996). Both fine and coarse-mode particles may affect plants and other organisms.

17   Much of the burden of sulfates ($SO_4^{2-}$), nitrates ($NO_3^-$), ammonium salts ($NH_4^+$), and hydrogen ions ($H^+$)

18   resides in the atmosphere either dissolved in fog water or as liquid or solid aerosols. Assessment of

19   atmospheric deposition effects of S and N particles overlaps substantially with material covered in the

20   recent $NO_X SO_X$ ISA (2008e). Therefore, effects of acidifying particulate deposition are not covered in this

21   assessment.

## 9.5.1. Effects on Plants

22           Exposure to airborne PM can lead to differing phytotoxic responses, depending on the particular

23   mix of deposited particles. This was well-known at the time of the previous PM criteria assessment, as

24   summarized below. Effects of particulate deposition on individual plants or ecosystems are difficult to

25   characterize because of the complex interactions among biological, physicochemical, and climatic factors.

26   Most direct effects occur in severely polluted areas surrounding industrial point sources, such as

27   limestone quarries, cement kilns, and metal smelting facilities (U.S. EPA, 2006b). Experimental

28   application of PM constituents to foliage typically elicits little response at the more common ambient

1    exposure concentrations. The diverse chemistry and size characteristics of ambient PM and the lack of

2    clear distinction between effects attributed to phytotoxic particles and to other air pollutants further

3    confound understanding of the direct effects on foliar surfaces. The majority of the documented toxic

4    effects of particles on vegetation reflect their chemical content (e.g., acid/base, trace metal, nutrient),

5    surface properties, or salinity (U.S. EPA, 2004).

6          Studies of the direct effects of particles on vegetation have not yet advanced to the stage of

7    reproducible exposure experiments. In general, phytotoxic gases are deposited more readily, assimilated

8    more rapidly, and lead to greater direct injury of vegetation as compared with most common particulate

9    materials. The dose-response functions obtained in early experiments following the exposure of plants to

10   phytotoxic gases generally have not been observed following the application of particles (U.S. EPA,

11   2004).

12         Atmospheric PM may affect vegetation directly following deposition on foliar surfaces or

13   indirectly by changing the soil chemistry or by changing the amount of radiation reaching the Earth's

14   surface through PM-induced climate change processes. Indirect effects acting through the soil are often

15   thought to be most significant because they can alter nutrient cycling and inhibit plant nutrient uptake

16   (U.S. EPA, 2004).

17         Particles can be deposited from the atmosphere to surfaces of the leaf, twig, or bark. Subsequently,

18   those particles can be taken up by the plant through the leaf surface, or be removed from the plant via

19   resuspension to the atmosphere, washing by rainfall, or litter-fall with subsequent transfer to the soil. Any

20   PM deposited on above-ground plant parts can have physical or chemical effects on the plant. The U.S.

21   EPA (2004) reported that the effects of "inert" PM are mainly physical; whereas those of toxic particles

22   can be both chemical and physical.

23         Since publication of EPA's 2004 PM criteria assessment, additional research has been conducted on

24   the effects of PM on plants. For example, windblown PM affects physical, chemical, and biological

25   attributes of both plants and animals (c.f., Englert, 2004; Gleason et al., 2007; Kappos et al., 2004).

26   Experiments by Gleason et al. (2007) suggest that most direct effects on plants of windblown PM

27   originating on road surfaces occur within 40 m of the source. Windblown PM from roads or agriculture

28   can cover plant photosynthetic structures (Sharifi et al., 1999), cause impact damage (Armbrust and Retta,

29   2002), or interfere with physiological mechanisms (Burkhardt et al., 2002).

30         The atmospheric deposition of PM into the ocean has important implications for primary

31   productivity and carbon sequestration. This is because metals in PM deposition limit phytoplankton

32   growth in parts of the ocean (Crawford et al., 2003). In particular, Fe and Zn can influence the

33   productivity of algae that are involved in $CaCO_3$ production. The production of both particulate organic C

34   and $CaCO_3$ drive the ocean's biological carbon pump (Shulz et al., 2004). Thus, in oceanic areas of trace

1   metal limitation, changes in trace metal atmospheric deposition can affect biogenic calcification, with

2   potential consequences for $CO_2$ partitioning between the ocean and atmosphere.

3       A study by Sheesley et al. (2004) illustrated the value of bioassay procedures to provide an initial

4   screening of ambient PM toxicity. They used two species of green algae and two extraction methods to

5   compare the toxicities of atmospheric PM collected at two urban/industrial sites and one rural site near the

6   southern shore of Lake Michigan. Toxicities varied by site, by extraction solvent, and by bioassay. Results

7   suggested that toxicity was not related to the total mass of PM in the extract, but to the chemical

8   components of the PM. It is noteworthy that the concentrations of PAHs and other contaminants in PM in

9   this type of short-term and acute toxicity testing are much higher than would be found in the natural

10  environment. Thus, the purpose of this type of testing is to provide an initial screening-level comparison

11  of relative toxicities of atmospheric PM from different source areas. It does not provide the data that

12  would be needed to assess risk (Sheesley et al., 2004).

13      Some plant species have good ability to extract heavy metals from soil, thereby offering potential

14  for phytoremediation. For example, several species of willow (*Salix* spp.) accumulate high levels of Zn

15  and Cd in aboveground biomass (Lunácková et al., 2003; Meers et al., 2007; Rosselli et al., 2003). A first

16  estimation of the order of magnitude of potential metal removal by willow was 2 to 27 kg/ha/yr of Zn and

17  0.25 to 0.65 kg/ha/yr for Cd (Meers et al., 2007).

18      Otnyukova (2007) demonstrated vertical gradients within a coniferous forest canopy in the

19  fruticose lichen genus *Usnea* with respect to lichen thallus morphology and heavy metal concentration.

20  Abnormal thalli at the tree-top level contained higher concentrations of Al, Fe, Zn, F, Sr, and Pb. This

21  vertical pattern within the tree canopy is in general accordance with known deposition of PM to plants

22  (Otnyukova, 2007).

## 9.5.1.1. Direct Effects of Coarse-mode Particles

23      The current state-of-scientific knowledge regarding the direct effects of coarse PM on plants has

24  not changed since publication of the previous PM criteria assessment (U.S. EPA, 2004). The summary

25  provided here is taken from that report. In many rural areas and some urban areas, the majority of the

26  mass in the coarse particle mode derives from the elements silicon, aluminum, calcium, and iron,

27  suggesting a crustal origin as fugitive dust from disturbed land, roadways, agriculture tillage, or

28  construction activities. Rapid sedimentation of coarse particles tends to restrict their direct effects on

29  vegetation largely to roadsides and forest edges, which often receive the greatest deposition (U.S. EPA,

30  2004).

31      Dust can cause both physical and chemical effects. Deposition of inert PM on above-ground plant

32  organs sufficient to coat them with a layer of dust may result in changes in radiation received, a rise in

1    leaf temperature, and the blockage of stomata. Crust formation can reduce photosynthesis and the

2    formation of carbohydrates needed for normal growth, induce premature leaf-fall, damage leaf tissues,

3    inhibit growth of new tissue, and reduce starch storage. Dust may decrease photosynthesis, respiration,

4    and transpiration; and it may result in the condensation and reactivity of gaseous pollutants with PM,

5    thereby causing visible injury symptoms and decreased productivity (U.S. EPA, 2004).

6        The chemical composition of PM is usually the key phytotoxic factor leading to plant injury. For

7    example, cement-kiln dust liberates calcium hydroxide on hydration. It can then penetrate the epidermis

8    and enter the mesophyll, causing an increase in leaf surface pH.

9        Sea-salt particles can serve as nuclei for the absorption and subsequent reaction of other gaseous

10   and particulate air pollutants. Direct effects on vegetation reflect these inputs and salt injury caused by the

11   sodium and chloride that constitute the bulk of these particles. Foliar injury from salt deposition can

12   influence plant species composition in coastal environments. It appears that, to cause injury, salt deposited

13   on leaf surfaces must dissolve and be absorbed into leaf tissue. Therefore, if RH remains below about

14   70%, even heavy deposition of salt may not induce injury to some plant species (U.S. EPA, 2004).

15   Little salt is taken up by plant roots; rather, most enters through the aerial organs. Mechanical

16   injury resulting from leaves and twigs beating against each another in the wind at coastal locations causes

17   the formation of small lesions through which salt can enter. After entry into the plant, chloride can be

18   translocated to the leaves and twigs where it can accumulate to concentrations that kill a portion of the

19   plant. Deposition and translocation of chloride results in death of the seaward leaves and twigs. The result

20   is the continued growth of the uninjured branches in an inland direction. As a result, the canopy angle

21   varies with the intensity of salt spray (U.S. EPA, 2004).

22   Injury to vegetation from the application of deicing salt is caused by salt spray blown or drifting

23   from the highways (Viskari and Kärenlampi, 2000). The most severe injury is often observed nearest the

24   highway. Conifers planted near roadway margins in the eastern U.S. often exhibit foliar injury due to

25   toxic levels of saline aerosols deposited from deicing solutions (U.S. EPA, 2004).

## 9.5.1.2. Effects of Fine-mode Particles

### *Trace Elements*

26   Effects of fine particle trace elements were described by the U.S. EPA (2004), and some additional

27   more recent research has also been conducted, especially on the topic of vegetative uptake of trace

28   elements from the soil. The state of scientific understanding as presented by the U.S. EPA (2004) is

29   summarized below, followed by discussion of more recent research findings. All but 10 of the 90 elements

30   that comprise the inorganic fraction of the soil occur at concentrations of < 0.1% (1000 µg/g) and are

1    termed "trace" elements or trace metals. Trace metals with a density greater than 6 g/cm$^3$, referred to as

2    "heavy metals," are of particular interest because of their potential toxicity to plants and animals.

3    Although some trace metals are essential for vegetative growth or animal health, they are all toxic in large

4    quantities. Most trace elements exist in the atmosphere in particulate form as metal oxides (Ormrod,

5    1984). Aerosols containing trace elements derive predominantly from industrial activities. Generally, only

6    the heavy metals Cd, Cr, Ni, and Hg are released from stacks in the vapor phase (McGowan et al., 1993).

7    Deposition of trace elements along roadsides and in industrial and urban environments can cause

8    accumulation of particulate heavy metals on vegetative surfaces. Foliar uptake of metals can cause

9    adverse effects in aboveground plant tissues. Low solubility limits foliar uptake and direct heavy metal

10    toxicity because trace metals must be brought into solution before they can enter into the leaves or bark of

11    vascular plants. In those instances when trace metals are absorbed, they are frequently bound in leaf tissue

12    and are lost when the leaf drops off (Hughes, 1981).

13    Direct effects of trace elements on vegetation can result from their deposition and residence on

14    foliar surfaces. Low solubility limits entry into plant tissue. Trace metals absorbed into leaf tissue are

15    eventually transferred to the soil litter layer where they can affect litter decomposition, an important

16    source of soil nutrients. Fungi and microorganisms living on leaves aid in leaf decomposition after leaves

17    are dropped to the forest floor. Changes in litter decomposition processes in response to metal toxicity can

18    influence nutrient cycling in the soil and limit the supply of essential nutrients.

19    Trace metals, particularly heavy metals (e.g., Cd, Cu, Pb, Cr, Hg, Ni, Zn) can influence forest

20    growth. Growth suppression of foliar microflora has been shown to result from Fe, Al, and Zn. These

21    three metals can also inhibit fungal spore formation, as can Cd, Cr, Mg, and Ni (see Smith, 1990). The

22    greatest injury to vegetation occurs from pollution near mining, smelting, and other industrial sources.

23    Direct metal phytotoxicity can occur only if the metal can move from the surface into the leaf or directly

24    from the soil into the root.

25    Trace metals are found in small amounts in soils, ground water, and vegetation. Many are essential

26    micronutrients required for growth by plants and animals. Naturally occurring mineralization can produce

27    metal concentrations in soils and vegetation that are high compared to atmospheric sources. Many metals

28    are bound by chemical processes in the soil, reducing their availability to biota. However, epiphytic or

29    parasitic root colonizing microorganisms can solubilize and transport metals for toot uptake (cf., Lingua

30    et al., 2008).

31    Heavy metals deposited from the atmosphere to forests accumulate either in the organic forest floor

32    or in the upper mineral soil layers. These are the areas that have the greatest root development. Metal

33    concentration tends to decrease with soil depth. Shallow-rooted plant species are most likely to take up

34    metals from the soil (Martin and Coughtrey, 1981). Though all heavy metals can be directly toxic at

1    sufficiently high levels, only Cu, Ni, and Zn have been documented as frequently being toxic to plants

2    (U.S. EPA, 2004). Toxicity due to Cd, Co, and Pb has been seen only under unusual conditions (Smith,

3    1990). Chronic exposure at lower concentrations have the potential to interfere with nutrient-cycling

4    processes if mycorrhizal function is impaired. The potential pathways of accumulation of trace metals in

5    terrestrial ecosystems, as well as the possible consequences of trace metal deposition on ecosystem

6    functions, are summarized in Figure 9-53 (U.S. EPA, 2004).
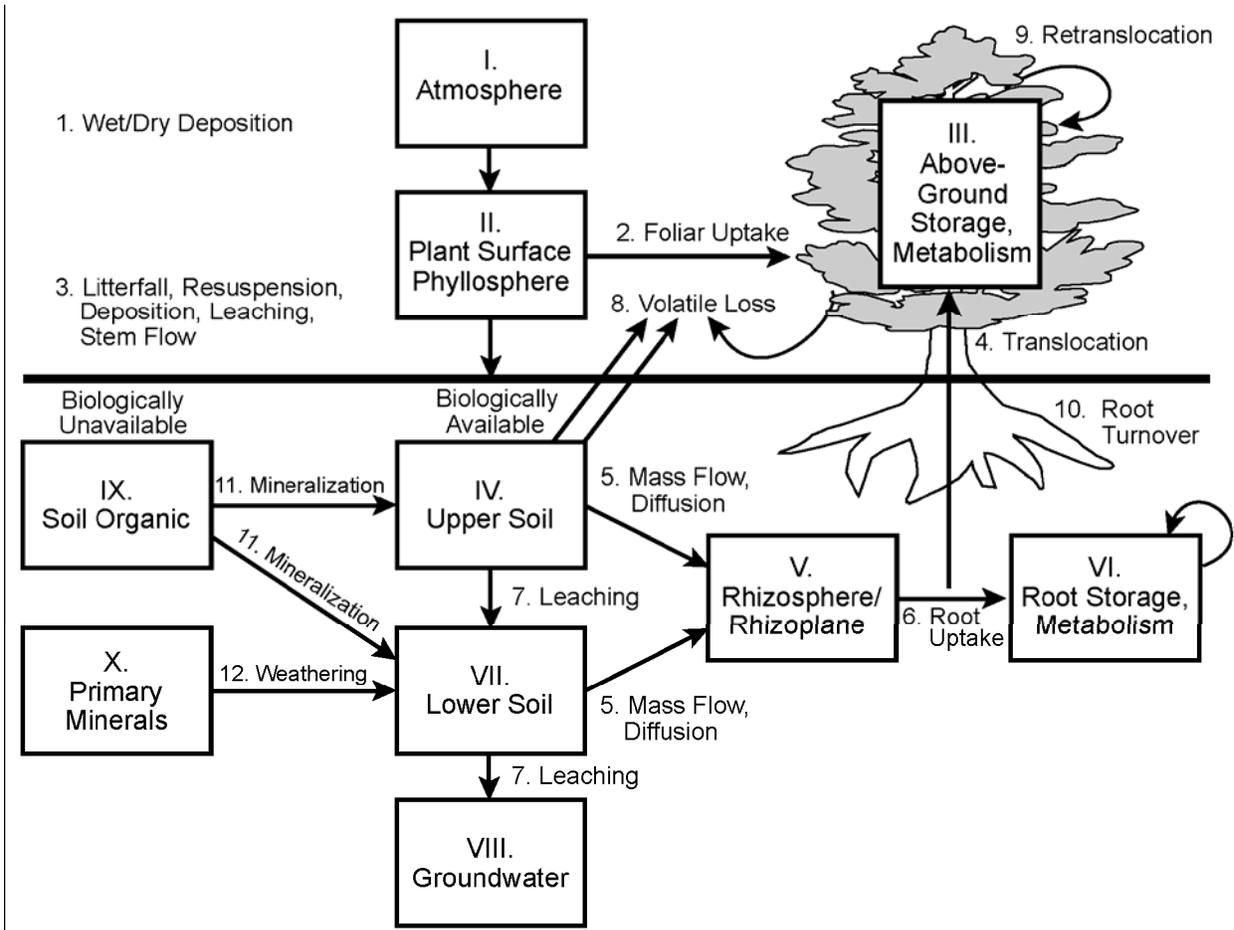


Source: U.S. EPA, (2004)

**Figure 9-53. Relationship of plant nutrients and trace metals with vegetation. Compartments (roman numerals) represent potential storage sites; whereas arrows (Arabic numerals) represent potential transfer routes.**

7    The effects of Pb on ecosystems are discussed in the 2006 Pb AQCD (U.S. EPA, 2006b), which

8    concluded that, due to the deposition of Pb from past practices (e.g., leaded gasoline, ore smelting) and

9    the long residence time of Pb in many aquatic and terrestrial ecosystems, a legacy of environmental Pb

10   burden exists, over which is superimposed much lower contemporary Pb loadings. The potential for

1   ecological effects of the combined legacy and contemporary Pb burden to occur is a function of the

2   bioavailability or bioaccessibility of the Pb, which, in turn, is highly dependent upon numerous site

3   factors (e.g., soil organic carbon content, pH, water hardness). However, while the more localized

4   ecosystem impacts observed around smelters are often striking, it was found that the effects could not be

5   attributed solely to Pb, recognizing the presence of many other stressors (e.g., other heavy metals, oxides

6   of sulfur and nitrogen) that can also act singly or in concert with Pb to cause such notable environmental

7   impacts. (U.S. EPA, 2004, 2008e).

8      At the time of the most recent air quality criteria report for PM (U.S. EPA, 2004), trace metal

9   toxicity of lichens had been demonstrated in relatively few cases. Nash (1975) documented Zn toxicity in

10  the vicinity of a Zn smelter near Palmerton, PA. Experimental data had suggested that lichen tolerance to

11  Zn and Cd generally ranges between 200 and 600 ppm (Nash, 1975).

12     Phytochelatins are intracellular metal-binding peptides that act as specific indicators of metal

13  stress. Because they are produced by plants as a response to sublethal concentrations of heavy metals,

14  they can indicate that heavy metals play a role in forest decline (Gawel et al., 1996). Phytochelatin

15  concentrations have previously been measured in coniferous trees in the northeastern U.S. The U.S. EPA

16  (2004) summarized studies indicating that both the number of dead red spruce trees and phytochelatin

17  concentrations increased sharply with elevation in the northeastern U.S. Red spruce stands showing

18  varying degrees of decline indicated a systematic and significant increase in phytochelatin concentrations

19  associated with the extent of tree injury. The U.S. EPA (2004) interpreted these data as indicating that

20  metal stress causes tree injury and contributes to forest decline in the northeastern U.S.

21     Mercury in vegetation is derived almost exclusively from the atmosphere (Grigal, 2003). Mercury

22  uptake from soil is limited, partly because roots adsorb Hg but transport it to foliage very poorly (Grigal,

23  2002). Grigal (2003a) provided a thorough review of the sequestration of Hg in forest and peatland

24  ecosystems. A fundamental aspect of Hg cycling is its strong relationship to organic matter. For that

25  reason, peatlands sequester much larger quantities of Hg than would be expected on the basis of their land

26  area. Thus, if global climate change affects C storage, it may indirectly affect Hg storage because of the

27  strong relationship between Hg and organic matter (Grigal, 2003).

28     The accumulation of heavy metals in soils is determined by a variety of soil characteristics,

29  including pH, Fe and Al oxide content, amount of clay and organic material, and CEC (Hernandez et al.,

30  2003). Thus, the pattern of distribution of heavy metals in soils depends on the soil characteristics and on

31  the metal characteristics.

32     Small roots (< 2 mm diameter) provide the major uptake and transport system to the above-ground

33  plant and generally contain a large proportion of the total metals found in plants (Gordon and Jackson,

34  2000). Atmospherically-deposited metals accumulate in upper soil horizons where fine roots are most

1    developed. Surface litter decomposition is reduced in soils having high metal concentrations. This is

2    likely due to the sensitivity to metals of microbial decomposers and reduced palatability of plant litter

3    having high metal concentration (Johnson and Hale, 2008). Root decomposition is a key component of

4    nutrient cycling. Johnson and Hale (2008) measured in situ fine root decomposition at Sudbury, Ontario

5    and Rouyn-Noranda, Quebec. Elevated soil metal concentrations (Cu, Ni, Pb, Zn) did not necessarily

6    reduce fine root decomposition. Only at sites having high concentrations of metals did decomposing roots

7    show increased metal concentrations over time.

8          The availability for plant uptake of metals in soil depends on metal speciation and soil pH. In

9    addition, metal binding to dissolved organic matter (DOM) reduces bioavailability (Sauvé, 2001).

10    Because OM typically decreases with soil depth, the affinity of metals for OM can influence metal

11    bioavailability at different soil depths.

12          Heavy metal particles are important constituents of tire dust. These particles accumulate on the

13    road surface as part of brake linings, road paint, tire debris, DE, road construction materials, and catalyst

14    materials. Tire dust can be suspended in the atmosphere and contribute metals to soil, air, and urban

15    runoff (Adachi and Tainosho, 2004; Davis et al., 2001; Smolders and Degryse, 2002). In particular, Zn

16    oxide comprises 0.4 to 4.3% of tire tread (Smolders and Degryse, 2002) and tire dust is a substantial

17    source of environmental Zn pollution. Adachi and Tainosho (2004) used a field emission screening

18    electron microscope equipped with an energy dispersive x-ray spectrometer to characterize heavy metal

19    particles embedded in tire dust. Samples were classified into four likely source categories, based on

20    cluster analysis. Based on morphology and chemical composition, the samples were identified as having

21    derived from brake dust (rich in Fe, with traces of Cu, Sb, Ba), yellow paint ($CrPbO_4$ particles), brake

22    dust (particulate Ti, Fe, Cu, Sb, Zr, Ba and heavy minerals [Y, Zr, La, Ce]), and tire tread (Zn oxide).

23          Build-up of high concentrations of trace metals in soil is difficult to remediate because of the long

24    residence times of metals in the environment. Plants that survive on heavy metal contaminated soils are of

25    particular interest because of the mechanisms that allow them to tolerate such conditions and interactions

26    between soil contamination and vegetation composition (Becker and Brändel, 2007; Hall et al., 2002).

27          Burt et al. (2003b) investigated the concentrations and chemical forms of trace metals in

28    smelter-contaminated soils collected in the Anaconda and Deer Lodge Valley area of Montana, one of the

29    major mining districts of the world for over a century (1864 to 1983). The relative distributions of trace

30    metals within the more soluble soil extraction forms were similar to their respective total concentrations.

31    This suggested a relationship between the concentrations of total trace elements and concentrations of

32    soluble mobile fractions.

33          Sequential extractions do not provide direct characterization of trace metal speciation, but rather an

34    indication of chemical reactivity (Burt et al., 2003b; Ramos et al., 1994). Soluble and exchangeable forms

1  are considered readily mobile and bioavailable. Those bound to clay minerals or organic matter are

2  considered generally unavailable.

3  There are substantial differences among plant species in their response to heavy metal exposure.

4  These differences can be attributed to differential uptake and excretion rates, increased storage capability,

5  and various physiological changes to compensate for metal stress. Toxicity response is also dependent on

6  the nutritional status of the plant and the development of mycorrhizae (Strandberg et al., 2006).

7  Under high atmospheric pollution levels, the abundance of most plant species tends to decrease

8  with increasing heavy metal concentrations in plant tissues. Salemaa et al. (2004) investigated heavy

9  metal concentrations in understory plant species growing at varying distances from the Harjavalta Cu-Ni

10  smelter. Heavy metal concentrations (except Mn) were highest in bryophytes, followed by lichens, and

11  were lowest in vascular plants. Vascular plants are generally able to restrict the uptake of toxic elements,

12  and therefore grew closer to the smelter than lichens. A pioneer moss (*Pohlia nutans*) was unusual in that

13  it survived close to the smelter despite its accumulation of high levels of Cu and Ni.

14  Contamination of stream sediments by heavy metals can impact adjacent terrestrial ecosystems

15  when high flows cause resuspension of sediment particles. For example, Ozdilek et al. (2007) showed that

16  metal concentrations in vegetation along the Blackstone River in Massachusetts and Rhode Island were

17  generally inversely related to the distance from the riverbank, with higher metal concentrations in plant

18  tissues located near the river.

19  Plants respond to high concentrations of metals in soil through a variety of mechanisms. These can

20  include exclusion, adaptation, compartmentalization, and chelation with phytochelatins, which are

21  peptides synthesized from glutathione.

22  It can be difficult to assess the extent to which observed metal concentrations in soil are of

23  anthropogenic origin. This is because soil parent material, pedogenesis, and anthropogenic inputs all

24  influence the amounts and distribution of trace elements in soil. Trace element concentrations in some

25  natural soils that are remote from air pollution can be higher than soils derived from other parent material

26  that receive anthropogenic inputs (Burt et al., 2003a).

## *Organic Compounds*

27  Volatile organic compounds in the atmosphere are partitioned between the gas and particle phases.

28  As described by the U.S. EPA (2004), the partitioning depends on vapor pressure, temperature, surface

29  area of the particles, and the nature of the particles and of the chemical being adsorbed. A wide variety of

30  organic contaminants are deposited from the atmosphere. These include chemicals such as DDT, PCBs,

31  and PAHs.

1    Below is a summary of the findings of the U.S. EPA (2004), followed by discussion of more recent

2    research findings. Plants may be used as passive monitors to compare the deposition of organic

3    compounds between sites. Vegetation can be used semi-quantitatively to indicate organic pollutant levels

4    if the mechanism of accumulation is considered. Organic compounds can enter the plant via the roots or

5    be deposited as a particle onto the leaves and be taken up through the cuticle or stomata. The pathways

6    depend on the chemical and physical properties of the pollutant. These include, for example, lipophilicity,

7    water solubility, vapor pressure, and Henry's law constant. Environmental conditions can also be

8    important, including temperature and organic content of soil; plant species, and the foliar surface area and

9    lipid content.

10    Organic particulates in the atmosphere are diverse in their makeup and sources. Vegetation itself is

11    an important source of hydrocarbon aerosols. Terpenes, particularly α-pinene, β-pinene, and limonene,

12    released from tree foliage may react in the atmosphere to form submicron particles. These naturally

13    generated organic particles contribute significantly to the blue haze aerosols formed naturally over

14    forested areas (Geron et al., 2000; U.S. EPA, 2004). The low water solubility with high lipo-affinity of

15    many organic xenobiotics control their interaction with the vegetative components of natural ecosystems.

16    Foliar surfaces are covered with a waxy cuticle layer that helps reduce moisture loss and short-wave

17    radiation stress. This epicuticular wax consists largely of long-chain esters, polyesters, and paraffins.

18    These accumulate lipophilic compounds. Organic air contaminants in the particulate or vapor phase can

19    be absorbed to, and accumulate in, the epicuticular wax of leaf surfaces. Direct uptake of organic

20    contaminants through the cuticle and the vapor-phase uptake through the stomata are not well

21    characterized for most trace organics.

22    The leaves of *Quercus ilex* have been shown to readily accumulate PAHs in situ. Young leaves

23    accumulated PAHs within three weeks of bud break. Mature leaves showed seasonality, with higher PAH

24    concentrations during winter (Alfani et al., 2005). Plants also vary in the extent to which they take up

25    heavy metals from the soil. Variability has been shown to occur in response to different plant species and

26    different metals. For example, Szabó and Fodor (2006) exposed winter wheat (*Triticum aestivum*), maize

27    (*Zea mays*) and sunflower (*Helianthus annuus*) to a variety of micro-pollutants. Cadmium accumulation

28    was significant in both vegetative and reproductive plant parts. Vegetative winter wheat accumulated

29    substantial amounts of Hg, but the other species did not. Lead, Cu, and Zn showed only moderate

30    enrichment in crops (Szabó and Fodor, 2006).

31    Topographic and vegetative characteristics exert different influence on deposition modes. In

32    general, dry deposition is most affected by plant morphology (Grantz et al., 2003). The potential effects of

33    PM on vegetation include the full range of biological organization, with exposures occurring through the

34    soil and through vegetative surfaces. In general, soil-mediated exposure is thought to be more significant

1    (Grantz et al., 2003). Soil acts as an important storage compartment for POPs, including PCBs and PAHs.

2    There is a continuous process of partitioning between the soil pool and the atmosphere, and this controls

3    the regional and global transport of these compounds (Backe et al., 2004; Wania and Mackay, 1993). Over

4    time, POPs move towards equilibrium between the environmental compartments, and this process can be

5    described using the fugacity concept (Backe et al., 2004; Mackay, 1991). Fugacity reflects the tendency of

6    a chemical constituent to escape one environmental compartment and move to another. When an

7    equilibrium distribution is achieved, the fugacity quotient values in each compartment will be equal.

8    Soil/air partitioning is controlled by a variety of factors. These include soil properties, such as OM

9    content, moisture, porosity, texture, and structure, as well as the physiochemical properties of the

10   pollutant, including vapor pressure and water solubility.

## 9.5.2. Effects on Animals

11        Some amphibian ecotoxicological research has focused on heavy metal exposure. Contaminant

12   uptake can occur by oral, pulmonary, and dermal exposure (c.f., James et al., 2004; Johnson et al., 1999;

13   Lambert, 1997). This is potentially important because of documented declines in amphibian populations

14   in the U.S. and elsewhere in recent decades (c.f., Houlahan et al., 2000). Toads were shown to be fairly

15   tolerant of Cd exposure (James et al., 2004). It is not clear whether current levels of terrestrial metal

16   contamination pose an increased risk to amphibians in general.

17        Bioindicator organisms can be especially useful for monitoring PM effects over geographical and

18   temporal scales. Terrestrial invertebrates have been used to monitor contaminants in both air and soil.

19   Snails (*Helix* spp.) accumulate trace metals and agrochemicals, and can be used as effective biomonitors

20   for urban air pollution (Beeby and Richmond, 2002; Regoli et al., 2006; Viard et al., 2004). Demonstrated

21   biological effects include growth inhibition, impairment of reproduction, and induction of

22   metallothioneins that are involved in metal detoxification (Gomot-de Vaufleury and Kerhoas, 2000;

23   Regoli et al., 2006). The use of sentinel species to detect the effects of complex mixtures of air pollutants

24   is of particular value because the chemical constituents are difficult to characterize, exhibit varying

25   bioavailability, and are subject to various synergistic effects.

26        Regoli et al. (2006) caged land snails (*Helix aspersa*) at five locations in the urban areas of Ancona,

27   Italy. After four weeks of exposure to ambient air pollution levels, the snails were analyzed for trace

28   metals and PAHs. Biomarkers were measured that correlated with contaminant accumulation, including

29   levels of metallothioneins, activity of biotransformation enzymes, and peroxisomal proliferation. In

30   addition, indicators of oxidative stress were measured, such as oxyradical scavenging capacity, onset of

31   cellular damage, and loss of DNA integrity. Results documented substantial accumulation of metals and

PAHs in snail digestive tissues in urban areas having high traffic congestion. Cellular reactivity was also found, suggesting that this species is an effective bioindicator for multipollutant air quality and PM monitoring.

Earthworms are considered to be relatively sensitive indicators of soil metal contamination. They are continuously exposed to the soil via dermal contact and also ingest large quantities of soil. In addition, earthworms often constitute a large percentage of soil animal biomass. Massicotte et al. (2003) compared the cell viability and phagocytic potential of three earthworm species (*Lumbricus terrestris*, *Eisenia andrei*, and *Aporrectodea tuberculata*) in response to atmospheric emissions of metals from a cement factory in Quebec, Canada. Cell viability actually increased in proximity (0.5 km) to the cement factory for *A. tuberculata*, and this might have been due to beneficial effects of increased Ca deposition. There were no significant differences observed for the other two species (Massicotte et al., 2003).

## 9.5.3. Effects on Microbes and Fungi

Accumulation of heavy metals in litter can interfere with nutrient cycling. Microorganisms are responsible for decomposition of organic matter, which contributes to soil fertility. Toxic effects on the microflora can be caused by Zn, Cd, and Cu. The U.S. EPA (2004) judged that addition of only a few mg/kg of soil of Zn can inhibit sensitive microbial processes. Enzymes involved in the cycling of N, P, and S (especially arylsulfatase and phosphatase) seem to be most affected (Kandeler et al., 1996).

It is believed that increased accumulation of litter in metal-contaminated areas is due to the effects of metal toxicity on microorganisms. Smith (1991) reported the effects of Cd, Cu, Ni, and Zn on the symbiotic activity of fungi, bacteria, and actinomycetes. In particular, the formation of mycorrhizae has been shown to be reduced when Zn, Cu, Ni, and Cd were added to the soil.

Most studies of the effects of heavy metals on soils have been conducted under laboratory conditions. However, Oliveira and Pampulha (2006) performed a field study to evaluate long-term changes in soil microbiological characteristics in response to heavy metal contamination. Dehydrogenase activity, soil ATP content, and enumeration of major soil microbial groups illustrated the effects of contamination. There was a marked decrease in total culturable numbers of the different microbial groups. In particular, asymbiotic nitrogen-fixers and heterotrophic bacteria were found to be sensitive. Dehydrogenase activity was confirmed to be a good assay for determining the effect of heavy metals on physiologically active soil microbial biomass.

The toxic effects of heavy metals on soil microorganisms are well known. However, less is known about the relative sensitivity of different types of soil microorganisms (Rajapaksha et al., 2004). Vaisvalavicius et al. (2006) assessed the toxicity of high concentrations of Pb (839 mg/kg), Zn (844

mg/kg), and Cu (773 mg/kg) in the upper 0 to 0.1 m soil layer. Microbial abundance of all groups was reduced and enzymatic activity was lower than for uncontaminated soil. In particular, actinomycetes, oligonitrophobic and mineral N assimilating bacteria were most affected.

Effects of heavy metals in soil on microbes depends on soil pH, organic content, and the type of heavy metal exposure (Kucharski and Wyszkowska, 2004). Some studies have shown that heavy metals inhibit microbial activity in soil (Šmejkalová et al., 2003; Vasundhara et al., 2004). However, Wyszhowska et al. (2008) showed that heavy metals can either inhibit or stimulate the growth of soil microbes. Populations of *Azotobacter* spp. decreased, but populations of oligotrophic and copiotrophic bacteria, actinomyces, and fungi increased in response to heavy metal exposure. Acute metal stress causes a decrease in microbial biomass as metal-sensitive microbes are inhibited (Joynt et al., 2006).

Soil OM cycling is known to be sensitive to disturbance due to heavy metal pollution. This can cause increased litter accumulation at sites close to metal emissions point sources. The relative importance of the various processes that might be responsible for this observation is poorly known. Boucher et al. (2005) conducted $CO_2$ evolution studies in microcosms having metal-rich and metal-poor plant materials. Their results suggested that there was a pool of less readily decomposable C that appeared to be preferentially preserved in the presence of high metal (Zn, Pb, Cd) concentrations in the leaves of the metallophyte *Arabidopsis halleri*. An additional possibility is that increased lignification of the cell walls increased the amount of insoluble C (cf., Mayo et al., 1992).

Studies of the impacts of metal stress on the microbial community composition in soil have generally been based on microbial culturing techniques that can select only a subset of the natural soil population of microbes. More recent culture-independent studies have been conducted using phospholipids or nucleic acid biomarkers to reveal information regarding changes in microbial community structure (c.f., Joynt et al., 2006). Using this approach, Joynt et al. (2006) demonstrated that soils contaminated with both metals (Pb, Cr) and organic solvent compounds over a period of several decades had undergone changes in community composition, but still contained a phytogenetically diverse group of bacteria. This may reflect adaptation to the potentially toxic conditions through such processes as natural selection, gene exchange, and immigration.

Comparison between a severely contaminated soil with a similar soil that had much lower levels of contamination showed considerably lower microbial diversity in the contaminated soil, particularly for asymbiotic nitrogen fixers and heterotrophic bacteria (Oliveira and Pampulha, 2006).

Arbuscular mycorrhizal (AM) fungi can play important roles in mitigating toxicity of heavy metals in plants. For example, AM symbiosis is known to be involved in plant adaptation to As-contaminated soils. Higher plants that are adapted to As contaminated soils are generally associated with mycorrhizal fungi (Gonzalez-Chavez et al., 2002). It has also been shown that AM symbioses can influence plant

coexistence and community diversity (O'Connor et al., 2002). Some plants associated with AM fungi can
successfully colonize sites that are heavily contaminated by heavy metals (Pennisi, 2004).

Dong et al. (2008) cultivated white clover (*Trifolium repens*) and ryegrass (*Lolium perenne*) in
As-contaminated soil (water extractable As 82.7 mg/kg). The growth and P nutrition of both species
largely depended on AM symbiosis. The AM-inoculated plants showed selective uptake and transfer of P
over As.

# 9.6. Effects on Ecosystems

Because PM is heterogeneous with respect to chemical composition and size, it can cause a variety
of ecological effects, which were described by the U.S. EPA (2004) and by Grantz et al. (2003). These
effects are summarized below, based on those publications. Physical effects of particle deposition on
vegetation may include abrasion and radiative heating. Chemical effects may be more significant,
particularly from acidic particles associated with sulfate and nitrate (U.S. EPA, 2008e).

The effects of airborne particles are manifested via physical and chemical effects at the individual
organism (i.e., plant, microbe) level. However, individual organisms are interconnected within
populations, communities, and ecosystems. Ecosystems respond to stresses through their constituent
organisms. The responses of species and populations to atmospheric PM are determined by changes in
their physical and chemical environment that apply selection pressures on individual organisms. The most
common response in a vegetation community under stress is the elimination of the more sensitive
individuals and populations and an increase in abundance of those species that tolerate or are favored by
that particular stress.

Ecosystem response to pollutant deposition is a function of the ecosystem's ability to ameliorate
effects on individual plants and other organisms. At least three levels of biological interaction are
involved: (1) the individual organism and its environment, (2) the population and its environment, and (3)
the biological community composed of many species and its environment (Billings, 1978). Individual
organisms within a population vary in their ability to withstand the stress of environmental change. The
response of individual organisms within a population is based on their genetic constitution, stage of
growth at time of exposure to stress, and the microhabitat in which they are growing (Levin, 1998). The
range within which organisms can exist and function determines the ability of the population to survive.
Those able to cope with the stresses survive and reproduce. Competition among different species results
in succession (community change over time) and, ultimately, produces ecosystems composed of
populations of species that have the capability to tolerate the stresses (Guderian, 1985; Rapport and
Whitford, 1999).

1     Ecosystems are subject to natural periodic stresses, such as drought, flooding, fire, and attacks by

2   biotic pathogens (e.g., fungi, insects). Natural perturbations return succession to an earlier stage; reduce

3   ecosystem structure and function; disrupt the plant processes of photosynthesis and nutrient uptake,

4   carbon allocation, and transformation that are directly related to energy flow and nutrient cycling; disrupt

5   food webs; and reduce the total nutrient inventory (Odum, 1993). Such transformations set the stage for

6   recovery and allow perturbed ecosystems to adapt to changing environments (Holling, 1986). Recovery

7   from natural perturbations can be rapid (Odum, 1993).

8     In contrast, anthropogenic stresses can result in damaged ecosystems that do not recover readily

9   (Odum, 1993; Rapport and Whitford, 1999). Ecosystems sometimes lack the capacity to adapt to

10   anthropogenic stresses and maintain their normal structure and functions unless the stressor is removed

11   (Rapport and Whitford, 1999). These stresses result in a process of ecosystem degradation marked by a

12   decrease in biodiversity, reduced primary and secondary production, and a lower capacity to recover and

13   return to its original state. In addition, there can be an increased prevalence of disease, reduced nutrient

14   cycling, increased dominance of exotic species, and increased dominance by smaller, short-lived

15   opportunistic species (Odum, 1985; Rapport and Whitford, 1999).

16     The possible effects of particulate (and other) air pollutants on ecosystems have been categorized

17   by Guderian (1977) as follows:

18        ▪   accumulation of pollutants in plants and other ecosystem components (such as soil and
19             surface- and groundwater),

20        ▪   damage to consumers as a result of pollutant accumulation,

21        ▪   changes in species diversity because of shifts in competition,

22        ▪   disruption of biogeochemical cycles,

23        ▪   disruption of stability and reduction in the ability to self-regulate,

24        ▪   breakdown of stands and associations, and

25        ▪   expansion of denuded zones.

26     Ecosystem response to stress can be difficult to determine because the changes are often subtle.

27   This is particularly true of responses to atmospheric particles (U.S. EPA, 2004). Changes in the soil may

28   not be observed until pollutant deposition has occurred for many decades, except in the most severely

29   polluted areas around heavily industrialized point sources. The presence of co-occurring pollutants

30   generally makes it difficult to attribute ecological effects to PM alone or to one constituent in the

31   deposited PM. In other words, the potential for alteration of ecosystem function and structure exists but

can be difficult to quantify except in cases of extreme levels of deposition, especially when there are other

pollutants present in the ambient air that may produce additive or synergistic responses.

## 9.6.1. Biogeochemical Processes

Atmospherically deposited PM can interact with a variety of biogeochemical processes. Conclusions from the U.S. EPA (2004) are summarized here. In addition, there have been some more recent modeling and mass balance studies that have attempted to quantify some of these linkages.

Atmospheric PM can affect ambient radiation, which can be considered in both its direct and diffuse components. Foliar interception by canopy elements occurs for both up- and down-welling radiation. Therefore, the effect of atmospheric PM on atmospheric turbidity influences canopy processes both by radiation attenuation and by changing the efficiency of radiation interception in the canopy through conversion of direct to diffuse radiation (Hoyt, 1978). Diffuse radiation is more uniformly distributed throughout the canopy and increases canopy photosynthetic productivity by distributing radiation to lower leaves. The enrichment in photosynthetically active radiation (PAR) present in diffuse radiation appears to offset a portion of the effect of an increased atmospheric albedo due to atmospheric particles.

The effects of regional haze on the yield of crops because of reduction in solar radiation were examined by Chameides et al. (1999) in China, where regional haze is especially severe. They estimated that approximately 70% of crops were being depressed by at least 3 to 5% by regional scale air pollution and its associated haze (Chameides et al., 1999; U.S. EPA, 2004).

The ability of plants to take up metals from soil is an important part of metal cycling in the environment. This uptake process allows the metals to enter the food web, where they might exert mutagenic, carcinogenic, and teratogenic effects (Hunaiti et al., 2007). Some metals, including Cu, Co, Ni, and Zn, are essential micronutrients needed for plant growth. Others, including Hg, Cd, and Pb are not essential for plants. Kim et al. (2003) found decreased concentration of K in needles and Ca in stems of *Pinus sylvestris* seedlings exposed to Cd addition. This response suggests a disturbance of nutrition in response to Cd.

Pollutant-caused needle loss can reduce the interception of pollutants from the atmosphere, and therefore reduce their concentrations in stemflow. This may be responsible for the observation that species diversity of lichens is sometimes higher on trees affected by die-back (Hauck, 2003). This is an example of pollution effects on trees actually reducing the extent of pollution effects on the lichens attached to those trees.

1    A number of mass balance approaches (Macleod et al., 2005; Toose and Mackay, 2004), and metal

2    speciation and transport models (c.f. Bhavsar et al., 2004a; 2004b; Gandhi et al., 2007) have been

3    developed in recent years.

## 9.6.2. Bioaccumulation

### 9.6.2.1. Metals

4    Biomagnification is the progressive accumulation of chemicals with increasing trophic level

5    (LeBlanc, 1995). Organic Hg is the most likely metal to biomagnify, in part because organisms can

6    efficient assimilate methylmercury and it is slowly eliminated (Croteau et al., 2005; Reinfelder et al.,

7    1998). In general, however, it has been assumed that metal biomagnification in aquatic ecosystems is an

8    exception rather than the rule (Gray, 2002). More recent research has demonstrated aquatic

9    biomagnification of certain metals. For example, (Stewart et al., 2004) used stable isotopes of C and N to

10   show biomagnification of Se in San Francisco Bay food webs. Croteau et al. (2005) identified trophic

11   position of estuarine organisms and food web structure in the delta of San Francisco Bay to document Cd

12   biomagnification in invertebrates that live on macrophytes and also in fish. Concentrations of Cd were

13   biomagnified 15 times within two trophic links in each food web. In contrast, no tendency towards

14   biomagnification was observed for Cu.

15   The study of trophic transfer and biomagnification is limited by the difficulty in discriminating

16   food webs and the uncertainty associated with assignment of trophic position to individual species

17   (Croteau et al., 2005). Use of stable isotopes can help to establish linkages. However, it is difficult to

18   determine the extent to which biomagnification occurs in a given ecosystem without thoroughly

19   investigating physiological biodynamics, habitat, food web structure, and trophic position of relevant

20   species. Thus, development of an understanding of ecosystem complexity is necessary to determine what

21   species might be at greatest risk from toxic metal exposure (Croteau et al., 2005).

22   Chlorinated POPs can be transported as particles through the atmosphere from industrial and

23   agricultural sources and deposited in remote regions. They have been detected in all levels of the Arctic

24   food web (Oehme et al., 1995). The polar bear is the top predator in the Arctic and feeds preferentially on

25   ringed seals and, to a lesser extent, on other seal species. Bioconcentration of organochlorines has been

26   shown in the Arctic food web, including fish, seals, and polar bears (Oehme et al., 1995).

27   Bioaccumulation of heavy metals can occur through the plant-herbivore and litter-detrivore food

28   webs. The U.S. EPA (2004) concluded that Cd and Zn can bioaccumulate in earthworms. Other

1   invertebrates inhabiting soil litter may also accumulate metals. Although food web accumulation of a

2   metal may not result in mortality, it might reduce breeding potential.

3       Metal accumulation in litter can be found mainly around brass works and Pb and Zn smelters.

4   Organisms that feed on earthworms living in soils with elevated metal concentrations may also

5   accumulate Pb and Zn. Increased concentrations of heavy metals have been found in a variety of

6   mammals living in areas with elevated heavy metal concentrations in the soils.

7       Estuarine salt marshes are often located close to urban and industrial areas and receive elevated

8   levels of point and nonpoint (including atmospheric deposition) sources of trace metal contaminants.

9   Vegetation is important in the retention and accumulation of heavy metals in salt marshes. Soil

10  microorganisms, especially arbuscular mycorrhizal fungi (AMF), provide a key physical link between the

11  soil environment and plant roots. Carvalho et al. (2006) conducted experiments on the effects of AMF on

12  the uptake of Cd and Cu by *Aster tripolium*, a common plant species in polluted salt marshes and a host of

13  AMF. Carvalho et al. (2006) found that AMF colonization increased metal accumulation in the root

14  system of *Aster tripolium* without enhancing translocation to the shoot. By trapping toxic metals in the

15  roots, this plant species may reduce the extent of vegetative stress caused by metal exposure and act as an

16  effective sink for these metals.

17      Marine bivalve mollusks bioaccumulate trace metals and other contaminants (LaBrecque et al.,

18  2004) and therefore may be used as bioindicators of contamination. In addition, they constitute an

19  important link to human health by virtue of their importance as a food source (Cheggour et al., 2005; Li et

20  al., 2006).

21      There is not a standard method available for quantifying the bioavailability of heavy metals in soil.

22  A variety of models, isotopic studies, and sequential extraction methods have been used (c.f., Collins et

23  al., 2003; Feng et al., 2005; Shan et al., 2003). Total metal concentration in soil does not give a good

24  indication of potential biological effects because soils vary in their ability to bind metals in forms that are

25  not bioavailable. There are various methods available for assessing what is bioavailable, but soils are

26  heterogeneous and there is no ideal method for evaluating what conditions the soil biota experience.

27  Almås et al. (2004) argued that the actual measurement of biological effects is the best criterion for

28  determining bioavailability. In particular, the replacement of metal-sensitive microorganisms by

29  metal-tolerant organisms within each functional group may be one of the most sensitive indicators of

30  metal exposure. An increase in microbial trace metal tolerance per se would not be problematic if it was

31  not for the fact that this increase in tolerance is generally accompanied by a decrease in microbial

32  diversity (Almås et al., 2004; Lakzian et al., 2002).

33      Once metals accumulate to high concentrations in soils it is difficult to remove them. This is

34  because they are persistent and do not degrade. However, there are a variety of microbial and plant

1 species that are known to accumulate high concentrations of metals when grown in metal-contaminated

2 soil (Prasad and De Oliveira Freitas, 2003). Plants that hyperaccumulate metals have potential for

3 remediation of metal-contaminated sites. About 400 species have been reported. Brassicaceae has the

4 largest numbers of taxa, with 11 genera and 87 species known to hyperaccumulate one or more metal

5 contaminants (Prasad and De Oliveira Freitas, 2003).

6      In aquatic ecosystems, biomagnification of trace metals does not necessarily occur. Nguyen et al.

7 (2005) found biodiminution for most metals in Lake Balaton, Hungary, with the exception of slight

8 enrichment of Zn from PM to zooplankton and of Cd from sediment to mussel.

9      Once transported to aquatic ecosystems, trace metals often preferentially bind to sediment particles.

10 Some of these sediment-bound metals may be unavailable to biota; in contrast, metals bound to sediment

11 organic matter may exhibit varying degrees of bioavailability (Di Toro et al., 2005). Piol et al. (2006)

12 studied the bioavailability of sediment-bound Cd to the freshwater oligochaete *Lumbriculus variegatus*.

13 They found that Cd uptake depended on the amount of free dissolved Cd(II), and the Cd contribution

14 from sedimentary particles to biological uptake was negligible.

## 9.6.2.2. Organics

15      The accumulation of PAHs in vegetation, due to their lipophilic nature, could contribute to human

16 and other animal exposure via food consumption. As a result, plant uptake of PAHs has been an important

17 area of research (Gao and Zhu, 2004). Most bioaccumulation of PAHs by plants occurs by leaf uptake

18 (Tao et al., 2006). Root uptake also occurs. It appears that roots preferentially accumulate the lower

19 molecular weight PAHs due to their greater water solubility (Wild and Jones, 1992).

20      Various models have been developed to simulate plant uptake of organic contaminants. The simple

21 partition-limited model of Chiou et al. (2001) has been further expanded to increase complexity and to

22 include root uptake pathways (e.g., Fryer and Collins, 2003; Yang and Zhu, 2007; Zhu et al., 2004).

23      In evaluating receptor choice for studies of contaminant exposure to plants, and also remediation

24 potential, it is important to consider differences among species. For example, Parrish et al. (2006)

25 assessed the bioavailability of PAHs in soil. During the first growing season, zucchini (*Cucurbita pepo*

26 ssp. *pepo*) accumulated significantly more PAHs than did other related plant species, including up to three

27 orders of magnitude greater levels of the six-ring PAHs. Parrish et al. (2006) also noted differences in

28 PAH uptake by two different species of earthworm.

29      Previously, there was relatively little information available regarding incorporation of

30 atmospherically deposited PAHs into aquatic food webs. It is known that PAHs can be transferred to

31 higher trophic levels, including fish, and that this transfer can be mediated by aquatic invertebrates, which

32 generally comprise an important part of fish diets. High mountain lakes offer an effective receptor for

1 quantification of biomagnification in aquatic ecosystems from atmospheric PM deposition. There are

2 typically no sources of organic contaminants in their watersheds, and atmospheric inputs dominate as

3 sources of contamination. In addition, such lakes tend to have relatively simple food webs. Vives et al.

4 (2005) investigated PAH content of brown trout (*Salmo trutta*) and their food items. Total PAH

5 concentrations tended to be highest in organisms that occupy littoral habitats, and lowest in pelagic

6 organisms. This may reflect more efficient transfer of PAHs to underlying sediments in shallower water

7 and associated degradation within the water column.

8 It is difficult to discriminate between PAHs that are adsorbed to plant root surfaces as opposed to

9 those that are actually taken up by the roots. In general, soil bound PAHs are associated with soil OM and

10 are therefore not readily available for root uptake (Fismes et al., 2002; Jiao et al., 2007). Wild et al. (2005)

11 used two-photon excitation microscopy to visualize the uptake and transport of two PAHs (anthracene and

12 phenanthrene) from a contaminated soil into living wheat and maize roots. Jiao et al. (2007) developed a

13 sequential extraction method to discriminate between PAH adsorption in rice roots.

14 Maize roots and tops of plants have been shown to directly accumulate PAHs from aqueous

15 solution and from air in proportion to exposure levels. Root concentration factors are log-linear functions

16 of log-based octanol-water partition coefficients (log $K_{ow}$); similarly, leaf concentration factors are

17 log-linear functions of log-based octanol-air partition coefficients (log $K_{oa}$) (Lin et al., 2007). Although

18 the bulk concentrations of PAHs in various plant tissues can differ greatly, the observed differences

19 disappear after they are normalized to lipid content (Lin et al., 2007). This suggests that the lipid content

20 of different plant tissues may influence PAH distribution within the plant.

## 9.6.3. Nutrient Cycling

21 Upon entering the soil environment, PM pollutants can alter ecological processes of energy flow

22 and nutrient cycling, inhibit nutrient uptake, change ecosystem structure, and affect ecosystem

23 biodiversity. Many of the most important effects occur in the soil. The soil environment is one of the most

24 dynamic sites of biological interaction in nature. It is inhabited by microbial communities of bacteria,

25 fungi, and actinomycetes. These organisms are essential participants in the nutrient cycles that make

26 elements available for plant uptake. Changes in the soil environment that influence the role of the bacteria

27 and fungi in nutrient cycling determine plant and ultimately ecosystem response.

28 Many of the major indirect plant responses to PM deposition are chiefly soil-mediated and depend

29 on the chemical composition of the individual components of deposited PM. Effects may result in

30 changes in biota and in soil conditions that affect ecological processes, such as nutrient cycling and

31 uptake by plants.

The soil environment is rich in biota. Bacteria and fungi are usually most abundant in the rhizosphere, the soil around plant roots that all mineral nutrients must pass through. Bacteria and fungi benefit from the nutrients that are present in root exudates and make mineral nutrients available for plant uptake. The soil-mediated ecosystem impacts of PM are largely determined by effects on the growth of bacteria and mycorrhizal fungi that are involved in nutrient cycling and plant nutrient uptake.

## 9.6.4. Ecosystem Structure and Function

Ecosystems are often subjected to multiple stressors, of which atmospheric PM deposition is only one. Additional stressors are also important, including $O_3$ exposure, climatic variation, natural and human disturbance, the occurrence of invasive non-native plants, native and non-native insect pests, disease, acidification, and eutrophication. PM deposition interacts with these other stressors to affect ecosystem patterns and processes in ways that we are only beginning to understand.

Kiikkilä (2003) investigated the effects of heavy metal pollution in proximity to a Cu-Ni smelter at Harjavalta, Finland. The deposition of heavy metals increased within 30 km of the smelter. Only slight changes in the understory vegetation were observed at distances greater than 8 km from the smelter. At 4 km distance, species composition of vegetation, insects, birds, and soil microbiota changed and tree growth was reduced. Within about 1 km, only the most resistant organisms were surviving.

The Harjavalta region is one of the most intensively studied heavy metal polluted areas in the world. Kiikkilä et al. (2003) reviewed available data on heavy metal deposition and environmental effects in this area. Emissions from the smelter were as high as 1100 t/yr of dust, 140 t/yr Cu, 96 t/yr Ni, 162 t/yr Zn, and 94 t/yr Pb in 1987. Deposition levels decreased substantially after 1990, to only a few percent of the amounts that occurred during the 1980s.

Tree growth (Scots pine) has been poor (Mälkönen et al., 1999) and most vegetation was absent within 0.5 km of the smelter. Effects on plant species occurrence close to the smelter were almost entirely negative. In contrast, some animal species responded positively, including a leaf miner, three species of aphid, and some ants, beetles, and spiders.

Inhibition of nutrient cycling and displacement by Cu and Ni of base cations from cation exchange sites on the soil resulted in a decrease in base cation concentrations in the organic soil layer (Derome and Lindroos, 1998; Kiikkilä, 2003) close to the Harjavalta smelter. In addition, Mg, Ca, and Mn concentrations in Scots pine needles were low, and this was attributed by Kiikkilä (2003) to the toxic effects of Cu and Ni to plant fine roots and also to ectomycorrhizal root tips (c.f., Helmisaari et al., 1999). Nutrient translocation during autumn was also affected close to the smelter; as a consequence needle concentrations of K were relatively high (Nieminen et al., 1999).

1    The number of soil animals clearly decreased and their community structure was altered close to

2    the Harjavalta smelter (Kiikkilä, 2003). However, this effect was only pronounced within about 2 km of

3    the smelter. This suggests that the soil microfauna is relatively resistant to metal pollution effects.

4    Soil microbial activity decreased close to the Harjavalta smelter (Kiikkilä, 2003), as reflected by

5    microbial respiration, distribution of species within physiological groups, and microbial and fungal

6    biomass. The fungi appeared to be more sensitive to metal contamination than the bacteria (c.f., Pennanen

7    et al., 1996). The rate of litter decomposition decreased, causing an accumulation of needle litter on top of

8    the forest floor near the smelter (c.f., Fritze et al., 1989).

9    Changes in breeding success of cavity-nesting passerine birds close to the Harjavalta smelter were

10   attributed by Kiikkilä (2003) to habitat changes in response to metal toxicity. In particular, there was an

11   apparent decrease in the proportion of green insect larvae in the diet of nestlings. In addition, pollution

12   stress was inferred from increased heavy metals and decreased Ca in the diet of the pied fly catcher

13   (*Ficedula hypoleuca*) (Eeva et al., 2000).

14   As pollution levels increase, it is expected that the more sensitive species will be lost and the more

15   tolerant species remain. This gives rise to the concept of pollution-induced community tolerance (PICT),

16   which has been demonstrated for populations of bacteria and fungi (Davis et al., 2004). They assessed the

17   effects of long-term Zn exposure on the metabolic diversity and tolerance to Zn of a soil microbial

18   community across a gradient of Zn pollution. PICT was found to correlate better with total soil Zn than

19   with the concentration of Zn in soil pore water.

20   The toxicity of mixtures of metals is more difficult to determine than is the toxicity of a single

21   metal. The toxicity of the mixture might be approximately equal to the sum of the toxicities of individual

22   components. Alternatively, synergistic or antagonistic interactions can cause the toxicity of the mixture to

23   be lower or higher than the sum of the individual toxicities (Ince et al., 1999). There are a variety of

24   available approaches to assess the toxicity of mixtures of metals. For example, a toxic unit can be defined,

25   and the toxic units of individual contaminants summed, accounting for synergism and antagonism. The

26   toxic effect of a mixture can be described empirically as a polynomial function of individual toxic

27   concentrations, including cross terms. Alternatively, the attenuation of bioluminescence of a test

28   organism, such as *Vibrio fischeri*, can be measured (Utgikar et al., 2004).

# 9.7. Effects on Materials

29   Effects of air pollution on materials are related to both aesthetic appeal and physical damage.

30   Deposited particles, primarily carbonaceous compounds, cause soiling of building materials and culturally

31   important items, such as statues and works of art. Physical damage from dry deposition of PM also can

1    accelerate natural weathering processes. The major deterioration phenomenon affecting building materials

2    in response to atmospheric deposition is probably sulphation, leading to secondary salt crystallization

3    which forms gypsum (Marinoni et al., 2003).

4        This section (a) summarizes information on exposure-related effects on materials associated with

5    particulate pollutants as addressed in the 2004 PM AQCD (U.S. EPA, 2004) and (b) presents relevant

6    information derived from very limited research conducted and published since completion of that

7    document. Most recent work on this topic has been conducted outside the U.S.

8        There are a variety of factors that contribute to the deterioration of monuments and buildings of

9    cultural significance. They include: (1) biodeterioration processes; (2) weathering of materials exposed to

10   the air; and (3) air pollution from both anthropogenic and natural sources (Herrera and Videla, 2004).

11   Because of the diversity in climate, proximity to marine aerosol sources, and pollution of various types,

12   the magnitude and relative importance of these causal agents vary by location.

13       Much existing literature on damage to structural materials of cultural heritage has not seriously

14   considered the importance of biodeterioration process and the relationship that often exists between

15   environmental characteristics and the microbial communities that colonize monuments and buildings. In

16   general, high humidity, high temperature, and air pollution often enhance the biodeterioration hazard.

17   Herrera and Videla (2004) concluded that heterotrophic bacteria, fungi, and cyanobacteria were the main

18   microbial colonizers of buildings that they investigated in Latin America. Their analyses suggested that

19   the major deterioration mechanism of limestone at the Mayan site of Uxmal in a non-polluted rural

20   environment was biosolubilization induced by metabolic acids produced by bacteria and fungi. The rock

21   decay at Tulum, near the seashore, was mainly attributed to the marine influence. At Medellin, it appeared

22   that biodeterioration effects from microbes synergistically enhanced the effects of atmospheric factors on

23   material decay. Deterioration of structural material in the Cathedral of La Plata, located in a mixed

24   urban/industrial environment, was attributed mainly to atmospheric pollutants (Herrera and Videla, 2004).

25       Ambient particles can cause soiling of man-made surfaces. Soiling generally is considered an

26   optical effect. Soiling changes the reflectance from opaque materials and reduces the transmission of light

27   through transparent materials. Soiling can represent a significant detrimental effect, requiring increased

28   frequency of cleaning of glass windows and concrete structures, washing and repainting of structures,

29   and, in some cases, reducing the useful life of the object. Particles, especially carbon, may also help

30   catalyze chemical reactions that result in the deterioration of materials during exposure (U.S. EPA, 2004).

31       Soiling is dependent on atmospheric particle concentration, particle size distribution, deposition

32   rate, and the horizontal or vertical orientation and texture of the exposed surface (Haynie, 1986). The

33   chemical composition and morphology of the particles and the optical properties of the surface being

1 soiled will determine the time at which soiling is perceived by human observers (Nazaroff and Cass,

2 1991).

3      Ferm et al. (2006) reported development of a simple passive particle collector for estimating dry

4 deposition to objects of cultural heritage. The observed mass of deposited particles mainly belonged to the

5 coarse particulate mode. The sampler collects particles from all directions. It replicates at least some of

6 the complexity of particle deposition to actual objects, and is easier to analyze than a precious object

7 (Ferm et al., 2006).

8      Soiling of urban buildings constitutes a visual nuisance that leads to the loss of architectural value.

9 Soiling can include reversible darkening of the building surfaces and also irreversible damage. Water

10 runoff patterns on the building surfaces are influenced by the type of surface material, architectural

11 elements, and climate. Therefore, soiling does not occur uniformly across the building. Public perception

12 of soiling entails complex interactions between the extent of soiling, architecture, and aesthetics (Grossi

13 and Brimblecombe, 2004).

14      One of the most significant air pollution damage features affecting urban buildings and monuments

15 is the formation of black crusts. Quantification of different forms of carbon in black crusts is difficult.

16 There is often a carbonate component which is derived from the building material, plus organic carbon

17 and EC, derived from air pollution. Elemental C is considered to be a tracer for combustion sources,

18 whereas organic C may derive from multiple sources, including atmospheric deposition of primary and

19 secondary pollutants, and the decay of protective organic treatments (Bonazza et al., 2005). Bonazza et al.

20 (2005) quantified organic and elemental C in damage layers on European cultural heritage structures.

21 Organic C predominated over elemental C at almost all locations investigated. Traffic appeared to be the

22 major source of fine carbonaceous particles, with organic matter as the main component (Putaud et al.,

23 2004). Viles and Gorbushina (2003) found that soiling in Oxford, UK showed a relationship with traffic

24 and $NO_2$ concentrations.

25      In addition to the soiling effects of BC, much soiling appears to be largely of microbiological origin

26 (Viles and Gorbushina, 2003). Microbial biofilms, composed mainly of fungi, can stain exposed rock

27 surfaces with yellow, orange, brown, gray, or black colors. Microorganisms may be able to trap PM more

28 efficiently than the stone surface itself. In addition, microbial growth may be stimulated by organic or

29 nutrient constituents in PM deposition.

30      Viles et al. (2002) investigated the nature of soiling on limestone tablets in relation to ambient air

31 pollution and climate at three contrasting sites in Great Britain over periods of one to eight years.

32 Spectrophotometer and microscope observations suggested that there were not consistent trends in soiling

33 over time at the study sites. Each site behaved differently in terms of the temporal development of soiling

1  and the differences between sheltered and exposed limestone tablets. In addition, organisms played

2  important roles in the soiling response, even at the highly polluted site.

3      Some work has been conducted on public perception regarding the lightness of historic buildings

4  and the aesthetic need for cleaning subsequent to soiling by air pollution. Brimblecombe and Grossi

5  (2005) found a strong relationship between the perceived lightness of a building and the opinion that it

6  was dirty. This relationship was used to establish levels of blackening that might be publicly acceptable.

7      Recently, the importance of organic contaminant deposition to the overall air pollution damage to

8  building materials has been recognized. Low molecular weight organic anions such as formate, acetate,

9  and oxalate are ubiquitous in black crusts in damage layers on stones and mortars sampled from

10  monuments and buildings throughout Europe (Sabbioni et al., 2003). This has been observed at urban,

11  suburban, and rural sites.

## 9.7.1. Effects on Paint

12      Studies have evaluated the soiling effects of particles on painted surfaces (U.S. EPA, 2004).

13  Particles composed of EC, acids, and various other constituents are responsible for the soiling of

14  structural painted surfaces. Coarse-mode particles (>2.5 μm) initially contribute more soiling of

15  horizontal and vertical painted surfaces than do fine-mode particles (< 2.5 μm), but are more easily

16  removed by rain (Haynie and Lemmons, 1990). Rain interacts with coarse particles, dissolving the

17  particle and leaving stains on the painted surface (Creighton et al., 1990; Haynie and Lemmons, 1990).

18  Particle deposition contributes to increased frequency of cleaning of painted surfaces and physical

19  damage to the painted surface. Air pollution affects the durability of paint finishes by promoting

20  discoloration, chalking, loss of gloss, erosion, blistering, and peeling (U.S. EPA, 2004). There have been

21  no new developments in this field subsequent to the review of the U.S. EPA (2004).

## 9.7.2. Effects on Metal Surfaces

22      Metals undergo natural weathering processes. The effects of air pollutants on natural weathering

23  processes depend on the nature of the pollutant(s), the deposition rate, and the presence of moisture

24  (U.S. EPA, 2004). Pollutant effects on metal surfaces are governed by such factors as the presence of

25  protective corrosion films and surface electrolytes, the orientation of the metal surface, and surface

26  moisture. Surface moisture facilitates particulate deposition and promotes corrosive reactions. Formation

27  of hygroscopic salts increases the duration of surface wetness and enhances corrosion.

1     A corrosion film, such as for example the rust layer on a metal surface, provides some protection

2     against further corrosion. Its effectiveness in retarding the corrosion process is affected by the solubility

3     of the corrosion layer and the pollutant exposure. Other than the effects of acidifying compounds, there

4     has not been additional research conducted in recent years on the effects of PM deposition on metal

5     corrosion.

## 9.7.3. Effects on Stone

6     Air pollutants can enhance the natural weathering processes on building stone. The development of

7     crusts on stone monuments has been attributed to the interaction of the stone's surface with pollutants,

8     wet or dry deposition of atmospheric particles, and dry deposition of gypsum particles. Because of a

9     greater porosity and specific surface, mortars have a high potential for reacting with environmental

10    pollutants (Zappia et al., 1998).

11    Most research evaluating the effects of air pollutants on stone structures has concentrated on

12    gaseous pollutants (U.S. EPA, 2004). The dark color of gypsum is attributed to soiling by carbonaceous

13    particles. A lighter gray colored crust is attributed to soil dust and metal deposits (Ausset et al., 1998;

14    Camuffo, 1995; Lorusso et al., 1997; Moropoulou et al., 1998). Lorusso et al. (1997) attributed the need

15    for frequent cleaning and restoration of historic monuments in Rome to exposure to total suspended

16    particulates.

17    Grossi et al. (2003) investigated the black soiling rates of building granite, marble, and limestone in

18    two urban environments with different climates. Horizontal specimens were exposed, both sheltered and

19    unsheltered from rainfall. Limestone showed soiling proportional to the square root of the time of

20    exposure, but granite and marble did not.

21    Black soiling is caused mainly by particulate EC (PEC). For that reason, it is most prevalent in

22    urban environments due to the formation of carbonaceous fine particles from the incomplete combustion

23    of fossil fuels. Traffic emissions, especially from diesel engines, and wood burning are important sources

24    of PEC (Grossi et al., 2003).

25    Kamh et al. (2005) studied the effects of weathering on Conway Castle, an historical structure in

26    Great Britain built about 1289 AC. The weathering was identified as honeycomb, blackcrust, exfoliation,

27    and discoloration, with white salt efflorescence at some parts. These features are diagnostic for salt

28    weathering (Goudie et al., 2002), and this was confirmed by laboratory analyses, including scanning

29    electron microscopy and x-ray diffraction. The authors concluded that the salt was derived from three

30    sources: sea spray, chemical alteration of the carbonate in mortar into sulfate salts by acidic deposition,

31    and wet deposition of air pollutants on the stone surface. The salt content on the rock surface fills the rock

1    pores and then exerts high pressure on the rock texture due to hydration of the salt in the cold humid

2    environment. In particular, $CaSO_4$ and $Na_2SO_4$ exert enough pressure on hydration as to deteriorate

3    construction rock at both the micro- and macroscale (Moses and Smith, 1994).


# 9.8. Effects on Climate

4        The Intergovernmental Panel on Climate Change (IPCC) summary documents *Climate Change*

5    *2007* provided substantial background information on the effects of PM on climate. Much of the material

6    presented in this section is taken from these documents, especially from Chapter 2 (Changes in

7    Atmospheric Constituents and in Radiative Forcing) of the Working Group I Report, *The Physical Science*

8    *Basis* (IPCC, 2007). The reader is referred to these reports for more detailed discussion of the topics

9    summarized here.

10        Ecosystems across the Earth are tightly interconnected. Changes in one compartment can affect the

11    state of another. Feedbacks between compartments can amplify or mitigate changes (Grannas et al.,

12    2007). Such connections apply to the climate system. PM in the atmosphere adsorbs and scatters solar

13    radiation, interacts with water, and changes cloud properties. Therefore, atmospheric PM can affect

14    multiple aspects of climate (Seinfeld and Pankow, 2003). Fine-mode aerosols have sizes close to the

15    wavelengths of visible light, and therefore are expected to have a stronger effect on climate than larger

16    particles. Also, fine-mode particles can be transported far from their source region and therefore

17    contribute to spatially diffuse effects (Kanakidou et al., 2005).

18        The radiative forcing of climate by most anthropogenic aerosols has long been known to be

19    opposite in sign to effects from greenhouse gases(GHG) (Mahlman, 1997). The major aerosol

20    components include sulfates and other inorganic species and carbonaceous species (Park, 2005 #4735).

21    The carbonaceous species include complex mixtures of organic compounds plus BC or soot though the

22    composition of the mix of organic compounds is poorly characterized.

23        PM has long been known to have important effects that directly and indirectly modifying the

24    climate system (Aunan et al., 2006; Hansen and Sato, 2001; Heywood and Shine, 1995). Atmospheric

25    particles like $SO_4^{2-}$ and organic carbon cool the atmosphere through scattering of shortwave radiation;

26    others like BC warm the atmosphere through absorption of shortwave radiation. In addition, PM can

27    influence climate by affecting clouds and the albedo of snow and ice (Aunan et al., 2006). Such effects

28    appear to be especially pronounced in the developing world. For example, Menon et al. (2004) suggested

29    that the observed trend towards increased summer floods in southern China and drought in northern China

30    might be linked to radiation-absorbing atmospheric particles.

1    The review of Pöschl (2005) provided an overview of the current state of knowledge, major

2    uncertainties, and research perspectives on the properties and interactions of atmospheric aerosols and

3    their effects on climate. Airborne PM undergoes a variety of physical and chemical interactions and

4    transformations that result in changes in particle size, structure, and composition (Figure 9-54). Clouds

5    are formed by condensation of water vapor on pre-existing aerosol particles (cloud condensation nuclei

6    [CCN] and ice nuclei [IN]). Most clouds re-evaporate, releasing the aerosol particles back into the

7    atmosphere. If the cloud particles form precipitation, the aerosol particles, including CCN, are scavenged

8    from the atmosphere. Depending on aerosol properties and meteorological conditions, the lifetime of

9    aerosol PM in the atmosphere ranges from hours to weeks (Pöschl, 2005). There is substantial uncertainty

10   in the magnitude of the aerosol effects, and much of this uncertainty concerns changes in cloud properties.
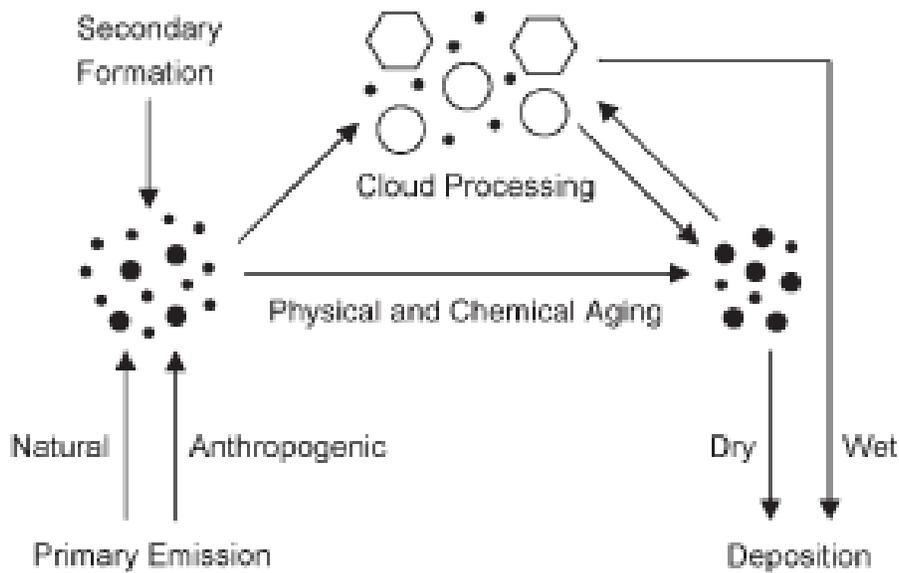
Source: Pöschl (2005)

**Figure 9-54.  Atmospheric cycling of aerosols.**

11       There is a complex interdependence of composition, composition-dependent properties,

12   atmospheric interactions and transformations, climate effects, and aerosol sources (Figure 9-55) (Figure

13   E&S-7, Pöschl, 2005). The associated feedback loops constitute areas of intense research central to

14   climate science.
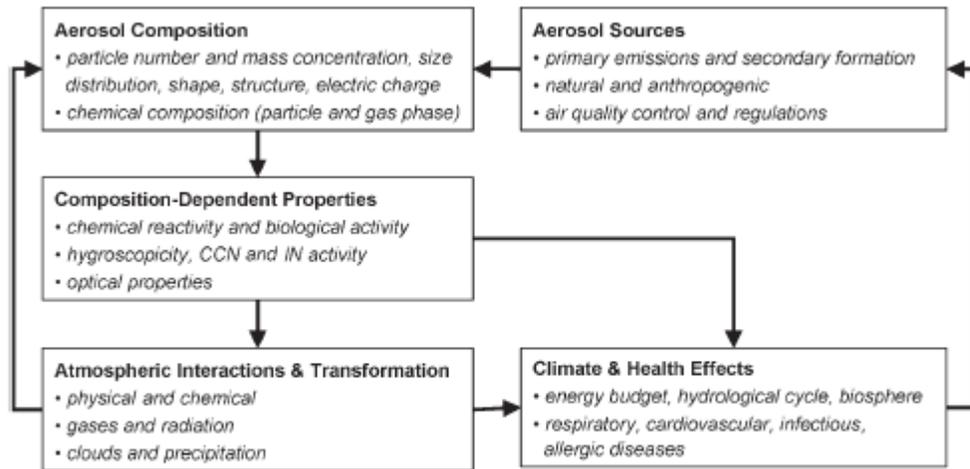
Figure 3. Interdependence and feedback between atmospheric aerosol composition, properties, interactions and transformation, climate and health effects, and sources.

Source: Pöschl (2005).

**Figure 9-55.** **Interdependence and feedback between atmospheric aerosol composition, properties, interactions and transformation, climate and health effects, and sources.**

1       The IPCC Third Assessment Report (IPCC, 2001) categorized radiative forcings (RFs) from

2   aerosols into direct and indirect effects (see Figure 9-56). The direct effect involves scattering and

3   absorption of shortwave and longwave radiation, directly altering the radiative balance of the

4   Earth-atmosphere system. Multiple aerosol components contribute to this direct effect, including sulfate,

5   fossil fuel organic C, fossil fuel black C, biomass burning, and mineral dusts (Menon et al. 2002; Wang

6   2007). Scattering aerosols exert a net negative (cooling) RF. Partially absorbing aerosols can exert a net

7   negative top-of-the-atmosphere (TOA) RF over dark surfaces like oceans and dark forests, or a net

8   positive TOA RF over bright surfaces, such as desert, snow, ice, or cloud fields (Chylek and Wong, 1995;

9   Forster et al., 2007; Haywood and Shine, 1997).

10      The indirect effects involve modification of the radiative properties, amount, and lifetime of clouds.

11   They are determined by the effectiveness of aerosol particles to act as CCN (Forster et al., 2007; Penner,

12   2001). The component of the indirect effect that pertains to the cloud droplet number concentration and

13   cloud droplet size is called the "first indirect effect" or "cloud albedo effect." The component that pertains

14   to cloud liquid water content, cloud height, and lifetime is called the "second indirect effect" or the "cloud

15   lifetime effect" (Forster et al., 2007; Lohman and Feichter, 2005; Ramaswamy et al., 2001).
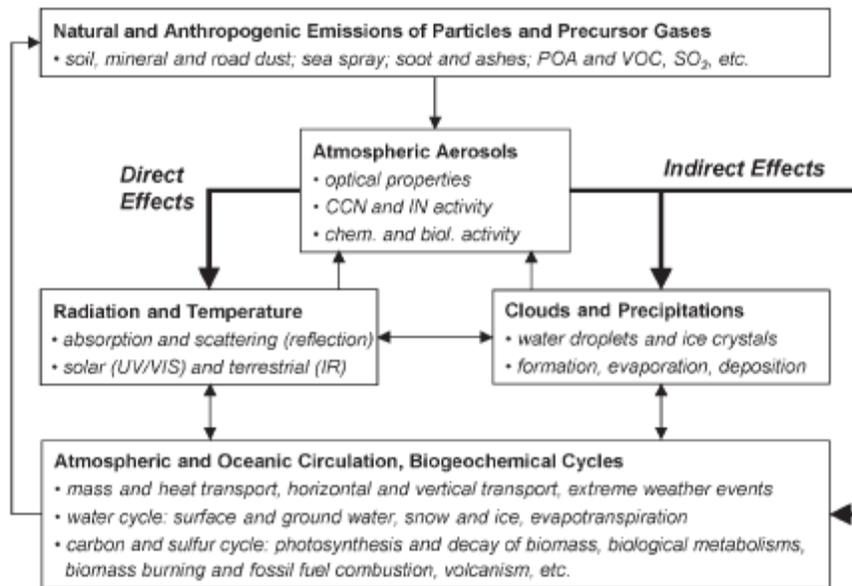
**Figure 9-56.  Direct and indirect aerosol effects and major feedback loops in the climate system.**

1    Figure 9-56 illustrates these effects and some of the major feedback loops. The key feedback loops

2    involve various interactions of atmospheric aerosols with solar and terrestrial radiation, clouds and

3    precipitation, general circulation, hydrological cycle, and with natural and anthropogenic aerosol sources.

4    Each of the interactions shown in Figure 9-56 comprises a wide range of poorly understood processes

5    which are not well quantified. Moreover, the actual climate system responses are highly variable and

6    uncertain. In many cases, even the sign or direction of the effect is not known. For example, increased

7    $CO_2$ is expected to increase photosynthesis, biogenic emissions of VOC, and the formation of SOA

8    particles which can serve as CCN, increase cloudiness, and cause cooling (Kanakidou et al., 2005). On

9    the other hand, this effect could be countered by temperature-related biological stress, eutrophication,

10   decreased photosynthesis, decreased VOC emissions and secondary organic aerosol formation and

11   cloudiness, and enhanced warming (Pöschl, 2005). Such complexities are among the most important

12   reasons for the uncertainty of climate sensitivity and for the moderately wide range of projected global

13   mean surface temperature increases over the next century (Kanakidou et al., 2005; Lohman and Feichter,

14   2005; Pöschl, 2005).

# 9.8.1. Direct Effects

## 9.8.1.1. Radiation Budget

1      RF is quantified as the rate of energy change per unit area of the earth as measured at the top of the

2  atmosphere in units of watts per square meter ($W/m^2$). This allows quantitative comparison of various

3  natural and anthropogenic climate drivers. The total direct aerosol RF estimated by models and

4  observations is on the order of -0.5 (± 0.4) $W/m^2$, with a medium-low level of scientific understanding

5  (Forster et al., 2007). The negative sign indicates an overall direct cooling effect from aerosols. The direct

6  RF of individual aerosol species including sulfate, fossil fuel OC, BC, biomass burning, nitrate, and

7  mineral dust are less certain than the estimated total direct aerosol RF. The estimated direct RF of -0.5

8  $W/m^2$ for total aerosols compares with an RF of +1.66 $W/m^2$ for $CO_2$ and +0.48 $W/m^2$ for $CH_4$ (Forster et

9  al., 2007).

10     Atmospheric PM can alter the characteristics and net receipt of solar radiation. The characteristics

11  and amounts of environmental radiation in turn are important in determining rates of photosynthesis and

12  water cycling. Atmospheric turbidity describes the degree of scattering occurring in the atmosphere due to

13  particles and gases. Total particle-based extinction, however, is the sum of both scattering and absorption.

14  Absorption of short-wavelength solar radiation reduces the amount of radiation reaching the Earth's

15  surface and leads to atmospheric heating (U.S. EPA, 2004). If the absorbing particles re-radiate in the

16  infrared range, some of this energy is lost as long-wave re-radiation to space. The balance of this energy is

17  captured at the surface as down-welling infrared radiation. Canopy temperature and transpirational water

18  use by vegetation are particularly sensitive to long-wave, infrared radiation. Atmospheric heating caused

19  by particles in the atmosphere reduces vertical temperature gradients, and this could reduce the intensity

20  of atmospheric turbulent mixing. The magnitude of such potential effects on turbulent transport is

21  unknown.

22     Atmospheric turbidity increases the intensity of diffuse (sky) radiation. In a clear atmosphere,

23  diffuse radiation may be on the order of 10% of total solar radiation, whereas under highly turbid humid

24  conditions this fraction will be higher. The ratio is highest at solar noon and lowest near dawn or dusk

25  when the path length through the atmosphere is longest. The wavelength dependence of particle scattering

26  induces an enrichment of photosynthetically active radiation (PAR) with respect to total or direct beam

27  radiation (U.S. EPA, 2004).

28     Aerosols produced by incomplete combustion, including those produced by forest fire and fuel

29  combustion, contain significant fractions of BC which absorbs across the solar and terrestrial radiation

30  spectra. The presence of absorbing aerosols reduces the ratio of PAR to total radiation received at the

31  surface, potentially reducing photosynthetic water uptake efficiency. The net effect of aerosol absorption

1    on the surface depends on the relative magnitudes of the particulate absorption coefficients in the visible

2    and infrared area and on the albedo of the Earth's surface (U.S. EPA, 2004).

3         The largest effects of atmospheric PM on visibility and atmospheric turbidity are due to light

4    scattering. Non-absorbing, scattering aerosols raise the overall albedo of the atmosphere and reduce the

5    amount of radiation reaching the Earth's surface by the amount reflected or scattered back into space.

6    U.S. EPA (2004) reported the results of analysis of data collected by a global network of thermopile

7    pyranometers operated by the World Meteorological Organization indicating a 50-year global reduction of

8    2.7% per decade in the amount of solar radiation reaching the Earth's surface. This has been associated

9    with an increasing global albedo caused by an increasing abundance of atmospheric particles.

10        The absorption of solar radiation by atmospheric particles, together with the trapping of infrared

11   radiation emitted by the Earth's surface by certain gases, enhances the heating of the Earth's surface and

12   lower atmosphere. It is generally believed that greenhouse gas emissions caused most of the global mean

13   warming observed during the 20th century and that $SO_4^{2-}$ and other aerosols counteracted this warming to

14   some extent by reflecting solar radiation to space and therefore cooling the lower atmosphere and the

15   Earth's surface. The role of BC in absorbing incoming shortwave radiation and thereby heating the lower

16   atmosphere may have been underestimated (Hansen and Sato, 2001; Novakov et al., 2003). However, a

17   detection and attribution analysis by Jones et al. (2005), with recent Hadley Centre simulations (Roberts

18   and Jones, 2004), examined the sensitivity of the effects of greenhouse gas variations on climate with the

19   inclusion of BC. They found that the $SO_4^{2-}$ pattern was too similar to the inverse of the BC pattern to be

20   able to deduce the contribution to warming over the past 100 years due to BC. There was no evidence that

21   BC counteracted to any substantial degree the cooling effect of $SO_4^{2-}$ aerosol.

22        The principal aerosols that can influence climate are listed in Table 9-4, along with their primary

23   sources and the estimated ranges of contribution computed using different models (Haywood and

24   Boucher, 2000; IPCC, 2001). OC aerosols are mostly reflective. BC aerosols are mostly absorbing in the

25   visible and UV regions, and this causes BC to counteract the cooling caused by other aerosols. The

26   amount of BC emitted by a combustion source depends on the burning efficiency of the fuel as well as the

27   mass of fuel burned. The mass of BC emitted per unit mass of fuel burned (emission factor) depends on

28   fuel type (i.e., coal, biomass, diesel) (i.e., coal, biomass, diesel; Menon, 2004). For example, coal burning

29   in an inefficient stove or furnace produces orders of magnitude more BC than the same fuel burned in a

30   modern electric power plant (Menon, 2004).

31        Smoke particles that originate from fires affect climate primarily by scattering and absorbing solar

32   radiation. This direct radiative forcing reduces the net solar radiation that reaches the Earth's surface

33   (Davison et al., 2004; Kobayashi et al., 2004). In addition, soot aerosols increase air temperature, reduce

34   relative humidity, and reduce cloud cover (Liu, 2005). McConnell et al. (2007) investigated the deposition

1   history of BC in Greenland ice cores and found that deposition peaked during the industrial revolution,

2   resulting in climate forcing of 3 $W/m^2$ from 1906 to 1910. The estimated median surface radiative forcing

3   in early summer based on the ice coring was 0.42 $W/m^2$ before 1850, 1.13$W/m^2$ during the period from

4   1850 to 1951, and 0.59 $W/m^2$ after 1951.

**Table 9-4.**    **Range in estimated source strength (Tg aerosol/year).**

| Type | Source Strength |
|---|---|
| *SULFATE* | |
| Industrial | 65-92.4 |
| Ocean | 10.7-23.7 |
| Aircraft | 0.04 |
| Biomass burning | 2.0-3.0 |
| *ORGANIC CARBON* | |
| Fossil fuel | 10-20 |
| Biomass | 30-45 |
| *BLACK CARBON* | |
| Fossil fuel | 5.8-6.6 |
| Biomass | 6.0-17.2 |
| *NITRATES* | |
| Fossil fuel | 0.3 |
| Biomass | 5.7 |
| Other (human, soils, animal, agriculture) | 74.5 |
| *SEA SALT* | |
| < 2 μm | 82 |
| >2 μm | 2583 |
| *DUST* | |
| < 2 μm | 243 |
| >2 μm | 4859 |

Source: Menon (2004)

5        Much interest has developed in defining more precisely the role of pyrogenic C in the boreal C

6   cycle. This is due to: (1) the resistance of pyrogenic C to decomposition; (2) its influence on soil

7   processes; and (3) the absorption of solar radiation by soot aerosols (Preston and Schmidt, 2006).

8   Preston and Schmidt (2006) reviewed the current state of knowledge regarding atmospheric emissions of

9   pyrogenic C in the boreal zone. They considered chemical structures, analytical methods, formation,

10   characteristics in soil, loss mechanisms, and longevity. Biomass is largely converted to gaseous forms

1   during burning, but up to several percent is converted to pyrogenic C, and this includes charcoal and BC.

2   Charcoal is defined visually; BC is defined chemically by its resistance to oxidation in the laboratory.

3       Andreae and Gelencsér (2006) reviewed a different category of light-absorbing carbon, referred to

4   as brown carbon. Operational methods used to measure all light-absorbing carbon are estimated to have a

5   factor-of-2 at present.

6       Within the boreal zone, fire is a critical driver of ecosystem process and nutrient cycling (Hicke et

7   al., 2003). For example, Bachelet et al. (2005) estimated that 61% of the C gained in Alaska by primary

8   production of boreal forests between 1922 and 1996 was lost to fire.

9       An updated modeling effort to evaluate the radiative effects of aerosols was presented by Stier et al.

10  (2007). Inclusion of refractive indices recommended by Bond and Bergstrom (2005) significantly

11  increased aerosol RF and resulted in better agreement with sun-photometer estimates. Although this stage

12  of climate modeling improved the representation of aerosols, large uncertainties remain regarding the

13  effects of aerosol mixing and aerosol-cloud interactions. Furthermore, Stier et al. (2007) emphasized that

14  these types of modeling efforts are dependent upon emission estimates that are likely to vary by a factor

15  of 2 or more.

16      One important reason for the acknowledged uncertainty in estimating global emissions of

17  carbonaceous aerosols is the influence of intermittent fires that can occur at scales large enough to affect

18  hemispheric aerosol concentrations. To better quantify the effects of large-scale fire, Generoso et al.

19  (2007) used satellite observations of boreal fires in Russia in 2003 to evaluate the performance of a global

20  chemistry and transport model in simulating aerosol optical thickness, transport, and deposition.

21  Emissions estimates of BC and OC were adjusted in the model to better match satellite observations of

22  pollutant transport over the North Pacific. This resulted in an increase in optical thickness and BC

23  deposition by a factor of 2. The adjusted model estimated that the fires contributed 16-33% of the optical

24  thickness and 40-56% of BC deposition north of $75^{o}$ N in the spring and summer of 2003.

25      Large fires also occurred over the Iberian Peninsula and Mediterranean coast during 2003. A

26  meso-scale atmospheric transport model was used with ground-based measurements and satellite optical

27  measurements to characterize the dispersion of emitted smoke particles and quantify radiative effects

28  across Europe (Hodzic et al., 2007). The modeled wildfire emissions resulted in increases in $PM_{2.5}$

29  concentrations from 20 to 200%. The increased aerosol concentration was estimated to increase radiative

30  forcing by 10-35 W/m$^2$ during the period of strong fire influence. Absorption of radiation by BC was also

31  estimated to decrease rates of photolysis by 30%. In this simulation, all particles were assumed to be

32  internally mixed, and secondary aerosol formation was not considered. Meteorological conditions in

33  Europe during the exceptionally hot summer of 2003 were linked to enhanced photochemically derived

1 pollutants, increased wild fires, and elevated aerosol concentrations in an analysis by Vautard et al.

2 (2007a).

3      In addition to incidental fires, routine biomass burning, usually associated with agriculture in

4 eastern Europe, also has been shown to contribute to hemispheric concentrations of carbonaceous

5 aerosols. In the spring of 2006, the most severe air pollution levels in the Arctic to date were recorded

6 (Stohl et al., 2007). Atmospheric transport modeling coupled with satellite fire detection data identified

7 biomass burning for agriculture as the primary cause of the high pollution levels. Concentrations of $PM_{2.5}$

8 peaked during the pollution episode at values of an order of magnitude greater than those recorded prior

9 to the episode. The increased transport of pollution into the Arctic during 2006 was attributed to weather

10 conditions that delayed preparations for crop planting into May. Weather patterns favorable for pollutant

11 transport into the Arctic were related to unusually warm weather in late April and May, when the majority

12 of agricultural biomass burning took place that year.

13      In the summer of 2004, 2.7 million ha were burned by wildfire in Alaska and 3.1 million ha were

14 burned in Canada. Effects on atmospheric air quality were measured throughout the Arctic, although the

15 concentrations of particulates varied considerably. Aerosol optical depths were also increased at all

16 measurement stations, which indicated that the fires were likely to have had a significant effect on the

17 atmospheric radiation budget for the Arctic (Stohl et al., 2006). At one site, a pronounced drop in albedo

18 was observed due presumably to high deposition of light absorbing particulates on the snow surface by

19 the North American fires in 2004.

20      Investigations of the effects of large fires on climate forcing have typically focused on the

21 absorptive effects of BC. However, these fires also release large amounts of $CO_2$ and $CH_4$, as well as light

22 scattering compounds such as OC, and can enhance cloud formation. These fires also increase radiative

23 surface absorption through BC deposition on snow and ice, and alter surface albedo and ecosystem energy

24 budgets within the burn perimeter. Randerson et al. (2006) estimated the net climate forcing of

25 greenhouse gases, aerosols, BC deposition on snow and ice and changes in albedo for the year subsequent

26 to a fire and for 80 years in the future in interior Alaska. The net effect of the fire in the first year was an

27 increase in radiative forcing, but over the 80-year recovery period, average net annual radiative forcing

28 was decreased by the fire.

29      International shipping has been identified as an additional source of carbonaceous aerosols.

30 Simulations with a climate model that included aerosol effects and 3 different emissions inventories

31 showed that shipping contributed 2.3-3.6% of the total sulfate atmospheric aerosol content and 0.4-1.4%

32 of the total BC atmospheric aerosol content, based on global means in 2000. This modeling also showed

33 that aerosol optical thickness over the Indian Ocean, the Gulf of Mexico, and the northeastern Pacific

34 Ocean varied by 8 to 10%. The corresponding all-sky (that includes both cloudy and clear skies) direct

1    radiative forcings ranged from −0.011 W/m$^2$ to −0.013 W/m$^2$. The greatest effect of aerosols emitted from

2    global shipping is likely to be an increase in cloud formation and the resulting change in reflectivity of

3    shortwave radiation. Aerosols from shipping were estimated to contribute 17-39% of the total

4    anthropogenic aerosol radiation forcing effect.

## 9.8.1.2. Temperature

5    BC is the main component of soot in the atmosphere and it changes the temperature of the air in

6    three ways (Jacobson, 2004): Daytime warming of the atmosphere and cooling of the ground surface

7    immediately below the BC PM. This atmospheric warming is caused by absorption of solar radiation by

8    the soot particles. Because this radiation does not reach the ground, the ground is cooled; Nighttime

9    warming of both the atmosphere and the ground due to absorption of the Earth's thermal-infrared

10   radiation, a portion of which is redirected back to the ground. This warming also occurs primarily locally,

11   in the vicinity of the soot particles; Large-scale daytime and nighttime warming of the air by advected

12   molecules in the atmosphere that had previously been heated by the soot. These warmed molecules can

13   have long lifetimes and be transported large distances remote from the soot PM that initiated the

14   warming.

15   When BC is deposited to the surface of ice or snow, solar absorption and heating occur at the

16   surface. This can melt additional snow or ice at the surface and the reflectivity of the surface can change.

17   Both factors affect aspects of climate. Jacobson (Jacobson, 2003a, 2004) and Jacobsen et al. (Jacobson,

18   2003c) estimated the warming due to fossil fuel BC and organic matter using the Gas, Aerosol, Transport,

19   Radiation, General Circulation, Mesoscale and Ocean Model (GATOR-GCMOM). The modeling effort

20   included consideration of the BC cycle, accounting for emissions, transport, aerosol coagulation, aerosol

21   growth, cloud activation, aerosol-cloud coagulation, cloud-cloud coagulation, rainout, washout, dry

22   deposition, and processes of precipitated and dry-deposited BC in snow and sea ice. Results suggested

23   that BC absorption in snow and sea ice increased near-surface temperatures over a 10-year simulation by

24   about 0.06$^o$K (Jacobson, 2003c).

25   BC soot is a potentially important agent of climate warming in the Arctic, and northern boreal

26   wildfires may contribute substantially to this effect. Soot is approximately twice as effective as $CO_2$ in

27   altering surface air temperature, and can reduce sea ice formation and snow albedo (Hansen and

28   Nazarenko, 2004).

29   Kim et al. (2005c) investigated the relationships between northern boreal wildfires and reductions

30   in Arctic sea ice and glacial coverage. They modeled the FROSTFIRE boreal forest control burn

31   (Hinzman et al., 2003) with respect to BC aerosol transport, dispersion, and deposition. Model results

32   suggested that boreal wildfires could be a major source of BC soot to sea ice and glaciers in Alaska. This

1    may exacerbate summer melting of sea ice and reduce recruitment of first year ice into multi-year ice,

2    thereby leading to an overall reduction in sea ice. Similarly, increased BC soot on glaciers would be

3    expected to increase summer melting and lead to an overall reduction in glacial coverage (Kim et al.,

4    2005c).

5        Jacobson (2002b) proposed, based on model simulations with 12 identifiable effects of aerosol

6    particles on climate, emission reductions of fossil fuel particulate BC and associated organic matter could

7    potentially slow warming for a specific period more than reduction of $CO_2$ or $CH_4$ for a specific period.

8    Jacobson's (2006) calculations suggested that fossil fuel BC plus organic matter emissions reductions

9    could eliminate 8 to 18% of total anthropogenic warming, and 20 to 45% of net warming after accounting

10   for aerosol cooling, within a period of three to five years. (Chock et al., 2003; See also conflicting

11   discussions in papers by Feichter et al., 2003; Jacobson, 2003b; see further responses by Jacobson, 2003c,

12   d; Penner, 2003; Penner et al., 2003).

13       Bond and Sun (2005) reviewed published data regarding the warming potential of BC, compared

14   with $CO_2$ and other GHG. Climatic effects of GHG are generally compared on the basis of

15   top-of-the-atmosphere, globally averaged changes in radiative balance. On that basis, BC is one of the

16   largest individual warming agents, after $CO_2$ and perhaps $CH_4$ (Bond and Sun, 2005; Jacobson, 2000;

17   Sato et al., 2003b).

18       Reddy and Boucher (2007) conducted an analysis that provided regional estimates of BC emissions

19   from fossil fuels and biofuels. These estimates indicated that East and Southeast Asia contributed over

20   50% of the global BC burden and its associated direct radiative forcing. Europe was found to be the

21   largest BC contributor in the northern latitudes. The indirect effect of BC deposition on snow was also

22   estimated to be highest for Europe.

23       To improve understanding of the role of aerosols in climate forcing, Chung and Seinfeld (2002)

24   estimated the global distribution of BC, primary organic particles (those directly emitted from

25   combustion), secondary organic particles (primary organic compounds partially oxidized in the

26   atmosphere), and sulfate aerosols to model the overall radiative forcing of these groups of compounds.

27   The model was run with the assumption that the BC particles do not combine with organic carbon or

28   sulfate particles (termed an external mixture), and with the assumption that the particles are represented

29   by a core of BC surrounded by a shell of light scattering aerosols. Modeling results suggested an overall

30   radiative cooling effect from aerosols ranging from -0.39 to -0.78 $W/m^2$.

31       Roberts and Jones (2008) used a climate modeling approach to compare possible effects of BC on

32   climate warming to those attributable to emissions from greenhouse gases. Results suggested that the

33   warming effect from atmospheric BC aerosols may not be large relative to that from greenhouse gases. A

34   different modeling approach by Roeckner et al. (2006) evaluated the effects of BC and primary organic

carbon on climate under two scenarios of carbonaceous aerosol emissions. In the first scenario, BC and

primary OC emissions decreased over Europe and China, but increased at lower latitudes. In the second

scenario, emissions were frozen at 2000 levels. The effects of both scenarios on mean global temperature

were found to be small, but higher aerosol emissions at low latitudes did result in atmospheric heating and

corresponding land surface cooling that led to increased precipitation and runoff in this simulation.

### 9.8.1.3. Precipitation

Study of BC effects in tropical climates was undertaken by Wang (2007). Substantial effects of

direct radiative forcing by BC on the tropical Pacific were shown in model results that were similar to the

El Niño Southern Oscillation activities both in the nature and scale of effects with enhancement of the

Indian monsoon circulation. The model suggested that atmospheric heating by radiation absorption by BC

can form temperature and pressure anomalies that favor propagation of convection from western to

central and eastern Pacific. More work will be needed to distinguish between the aerosol signal and

natural factors in controlling tropical precipitation in this region.

### 9.8.1.4. Magnitude of Overall Direct Effects

Satellite estimates of the magnitude of the solar direct radiative effects (DRE) include effects due to

both natural aerosols and anthropogenic aerosols. In recent years, satellite estimates of the global

clear-sky DRE over oceans have advanced due to development of improved aerosol instrumentation and

algorithms (Forster et al., 2007; Penner, 2001; Yu, 2006). Kaufman et al. (2005) estimated the

anthropogenic component of the clear sky RF over ocean of -1.4 W/m$^2$. Christopher et al. (2006)

estimated an identical number using a combination of the Moderate Resolution Imaging Spectrometer

(MODIS) instrument and the Clouds and the Earth's Radiant Energy System (CERES) broadband TOA

fluxes.

There have also been significant recent advancements in development and deployment of

surface-based remote sensing sun-photometer sites such as AERONET (Holben et al., 1998) and networks

of aerosol lidar-systems (Matthias, 2004; Murayama, 2001; Welton et al., 2001). A climatology of the

aerosol DRE was developed by Zhou et al. (2005) based on the AERONET data.

There have been recent advances in modeling the aerosol direct effect, with development of more

complete aerosol modules and their inclusion in a larger number of global atmospheric models (Forster et

al., 2007). The more complex models like those of Adams (2002), Easter (2004) and Stier (2005) now

include dynamic aerosol size distributions and changes over aerosol lifetime, and also consider mixing of

1   the aerosol components in a more physically realistic way than was available at the time of the Third

2   IPCC Assessment (Forster et al., 2007).

3       Progress has also been made in comparing aerosol model simulations. These include the Global

4   Aerosol Model Intercomparison (AeroCom) initiative (Kinne, 2006; Schulz et al., 2004; Textor, 2006).

5   These intercomparisons help to illustrate the aspects of aerosol dynamics that are poorly constrained in

6   the models. For example, coarse aerosol fractions are largely responsible for variation in natural aerosol

7   emissions (e.g., dust and sea salt). Source strength is also strongly dependent on wind speed, adding to the

8   complexity of modeling natural aerosols (Forster et al., 2007). As a result, model estimates of dust

9   emissions for the same time period can vary by more than a factor of two depending on dust

10  parameterization values in the models (Balkanski et al., 2003; Luo et al., 2003; Timmreck and Shulz,

11  2004; Zender et al., 2004).

12      Global estimates of aerosol direct RF were summarized by Forster et al. (2007) as global annual

13  mean values at TOA, inclusive of the effects of clouds. Individual estimates, and their uncertainties, were

14  provided for each of the major aerosol components. Current estimates, as summarized by Forster et al.

15  (2007) are:

16      - sulfate, -0.4 (± 0.2) $W/m^2$

17      - organic C from fossil fuels, -0.05 (± 0.05) $W/m^2$

18      - black C from fossil fuels, +0.20 (± 0.15) $W/m^2$

19      - biomass burning, +0.03 (± 0.12) $W/m^2$

20      - nitrate, -0.10 (± 0.10) $W/m^2$

21      - mineral dust, -0.1 (± 0.2) $W/m^2$

22      Forster et al. (2007) presented a combined model-based estimate of the cumulative aerosol direct

23  RF from all components based on multiple models and adding separate estimates for nitrate and

24  anthropogenic mineral dust (which are missing from most global model simulations). The overall

25  model-derived aerosol direct RF was estimated as -0.4 $W/m^2$, with a 90% confidence interval of 0 to -0.8

26  $W/m^2$. Three satellite-based measurement estimates suggest a stronger aerosol direct RF than the model

27  simulations of approximately -0.55 $W/m^2$ (Bellouin et al., 2005; Chung et al., 2005; Yu, 2006).

# 9.8.2. Indirect Effects

1    Aerosols can interact with clouds and precipitation in a variety of ways with processes outlined by

2    IPCC (Denman et al., 2007) and summarized in Tables 9-5 and 9-6. Such cloud feedbacks remain the

3    largest source of uncertainty in climate estimates.

4    Because clouds form with the aid of hygroscopic aerosols, anthropogenic PM can have indirect

5    effects on climate by altering cloud microphysical processes. Indirect effects of aerosols on climate relate

6    in part to perturbation of the albedo of clouds. The first indirect effect from increased cloud condensation

7    nuclei refers to increased cloud droplet concentrations, smaller droplet radii, and more reflective clouds.

8    The second indirect effect refers to the observation that decreased cloud droplet effective radii can cause

9    lower coalescence rates, reduced precipitation, longer cloud lifetime, and greater cloud spatial extent

10   (Kanakidou et al., 2005). Even small changes in cloud properties over global scales can have substantial

11   effects on the amount of solar radiation absorbed by the Earth, and therefore have an important effect on

12   climate. Much of the uncertainty associated with predicting effects on cloud radiative properties is due to

13   variability in cloud droplet number as influenced by aerosol characteristics. Model simulations reported

14   by Kristjánsson (2002) suggested that BC PM contributes only marginally to these indirect effects.

**Table 9-5.    Overview of the different aerosol indirect effects and their sign of the net radiative flux change at the top of the atmosphere (TOA).**

| Effect | Cloud Types Affected | Process | Sign of Change in TOA Radiation | Potential Magnitude | Scientific Understanding |
|---|---|---|---|---|---|
| Cloud albedo effect | All clouds | For the same cloud water or ice content more but smaller cloud particles reflect more solar radiation | Negative | Medium | Low |
| Cloud lifetime effect | All clouds | Smaller cloud particles decrease the precipitation efficiency thereby presumably prolonging cloud lifetime | Negative | Medium | Very low |
| Semi-direct effect | All clouds | Absorption of solar radiation by absorbing aerosols affects static stability and the surface energy budget, and may lead to an evaporation of cloud particles | Positive or Negative | Small | Very low |
| Glaciation indirect effect | Mixed-phase clouds | An increase in IN increases the precipitation efficiency | Positive | Medium | Very low |
| Thermodynamic effect | Mixed-phase clouds | Smaller cloud droplets delay freezing causing super-cooled clouds to extend to colder temperatures | Positive or Negative | Medium | Very low |

Source: Denman (2007)

**Table 9-6.** Overview of the different aerosol indirect effects and their implications for the global mean net shortwave radiation of the surface Fsfc (columns 2-4) and for precipitation (columns 5-7).

| Effect | Sign of Change in Fsfc | Potential Magnitude | Scientific Understanding | Sign of Change in Precipitation | Potential Magnitude | Scientific Understanding |
|---|---|---|---|---|---|---|
| Cloud albedo effect | Negative | Medium | Low | n.a. | n.a. | n.a. |
| Cloud lifetime effect | Negative | Medium | Very low | Negative | Small | Very low |
| Semi-direct effect | Negative | Large | Very low | Negative | Large | Very low |
| Glaciation indirect effect | Positive | Medium | Very low | Positive | Medium | Very low |
| Thermodynamic effect | Positive or Negative | Medium | Very low | Positive or Negative | Medium | Very low |

Source: Denman (2007)

## 9.8.2.1. First Indirect Effect: Cloud Albedo

1    The best characterized indirect effects included in climate models is the increase in cloud droplets

2    (Lohman and Feichter, 2005). This occurs if the aerosol concentration increases without a change in the

3    moisture content of the cloud. The size and number of droplets decreases, thereby increasing the albedo of

4    the cloud and the reflection of radiation back into space. This process also can suppress precipitation,

5    which increases cloud life and reduces aerosol washout.

6    The effects of PM on cloud formation and cloud processes are magnified by the multitude of

7    linkages between clouds and the overall climate system. In particular, clouds affect solar and terrestrial

8    radiation and precipitation formation. Interactions between aerosols and clouds are complex, sometimes

9    non-linear, and not well quantified (Ramaswamy et al., 2001). On average, clouds have a cooling effects

10    on the present climate of the earth (Quante, 2004); however, a small change in the amount and

11    distribution of cloud cover could have an important effect on the total energy budget of the planet.

12    Estimates of current simulations of the magnitude of the cloud albedo effect were summarized by

13    Forster et al. (2007). Increased concentrations of CCN or ice nuclei (IN) due to human activities can

14    modify the properties of clouds and affect climate by increasing the albedo of clouds (Jacob et al., 2005;

15    Penner, 2001; Ramanathan et al., 2001).
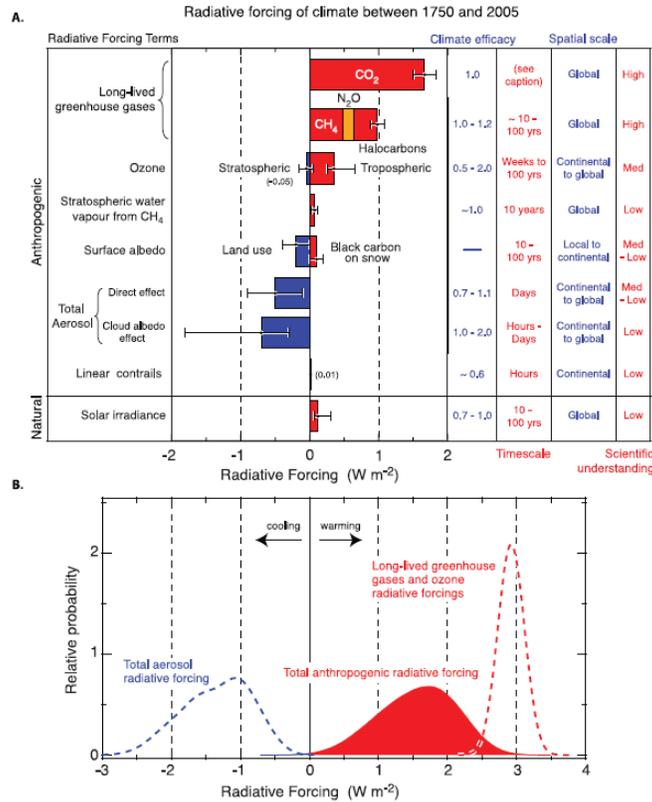
Source: Forster et al. (2007)

**Figure 9-57.** **(A) Global mean RFs from the agents and mechanisms discussed in Forster et al. (2007) grouped by agent type. Anthropogenic RFs and the natural direct solar RF are shown. Columns indicate other characteristics of the RF; efficacies are not used to modify the RFs shown. Time scales represent the length of time that a given RF term would persist in the atmosphere after the associated emissions and changes ceased. No $CO_2$ time scale is given, as its removal from the atmosphere involves a range of processes that can span long time scales, and thus cannot be expressed accurately with a narrow range of lifetime values. (B) Probability distribution functions (PDFs) generated by combining human-caused RFs given above in panel A. Three cases are shown: the total of all anthropogenic RF terms (block filled red curve); LLGHGs and ozone RFs only (dashed red curve); and aerosol direct and cloud albedo RFs only (dashed blue curve). Surface albedo, contrails and stratospheric water vapor RFs are included in the total curve but not in the others. For all of the contributing forcing agents, the uncertainty is assumed to be represented by a normal distribution (and 90% confidence intervals) with the following exceptions: contrails, for which a lognormal distribution is assumed to account for the fact that the uncertainty is quoted as a factor of three; and tropospheric ozone, the direct aerosol RF (sulfate, fossil fuel organic and BC, biomass burning aerosols) and the cloud albedo RF, for which discrete values are randomly sampled. Additional normal distributions are included in the direct aerosol effect for nitrate and mineral dust. A one-million point Monte Carlo simulation was performed to derive the PDFs (Boucher and Haywood, 2001). Natural RFs (solar and volcanic) are not included in these three PDFs. Climate efficacies are not accounted for in forming the PDFs.**
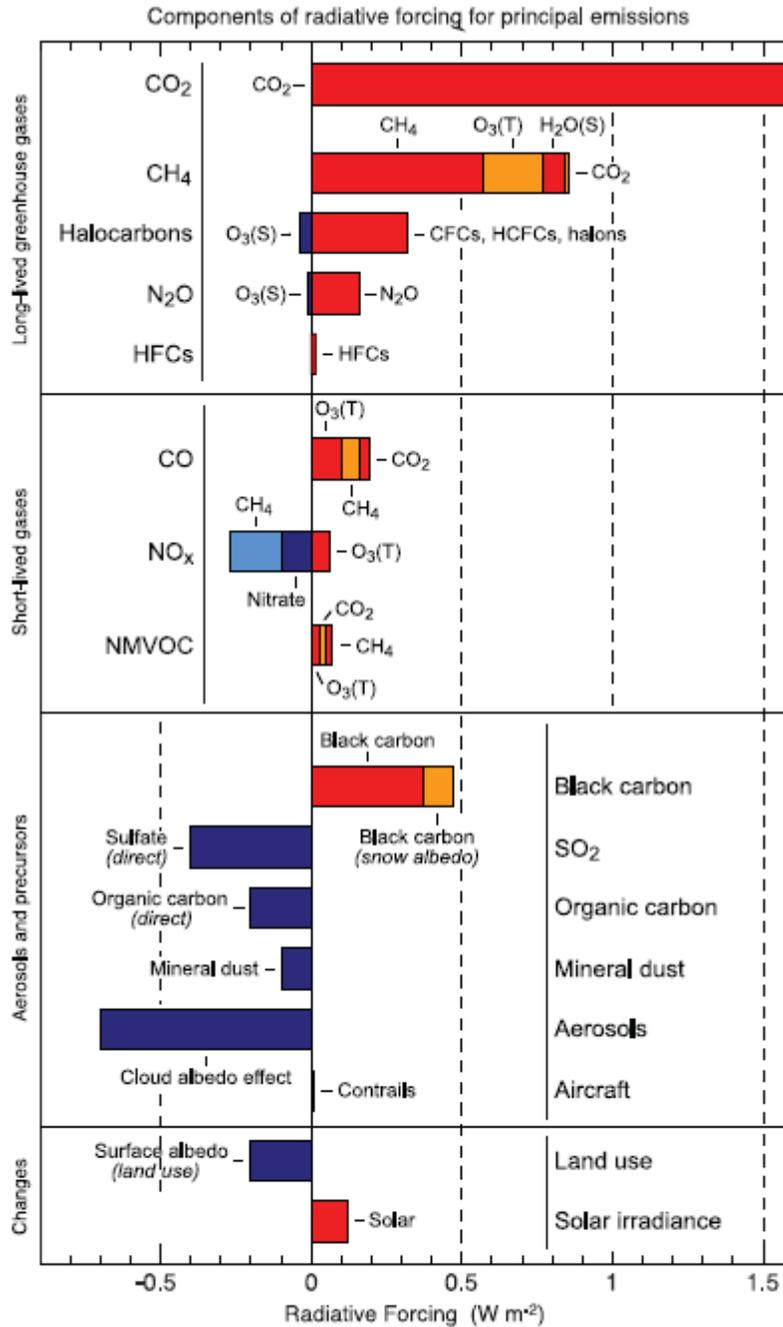
Source: Forster et al. (2007).

**Figure 9-58.** **Components of RF for emissions of principal gases, aerosols and aerosol precursors and other changes. Values represent RF in 2005 due to emissions and changes since 1750. (S) and (T) next to gas species represent stratospheric and tropospheric changes, respectively.**

1    Regional studies have illustrated links between forest fire smoke and cloud properties. In the

2    Amazon Basin, smoke caused increased cloud droplet number concentrations and reduced cloud droplet

1    sizes (Andreae et al., 2004; Mircea, 2005). The ability of a given particle to act as effective CCN may be

2    more strongly controlled by the size of the particle, rather than particle composition (Dusek et al., 2006).

3    Numerous difficulties remain, however, in quantifying such effects (cf. Forster et al., 2007; McFiggans

4    and Midgley, 2001).

5        Atmospheric models estimate a negative global mean RF due to the cloud albedo effect from PM,

6    with substantial variation among the estimates of the magnitude of this effect, from -0.22 to -1.85 W/m$^2$

7    (Forster et al., 2007). Variation in these estimates stems largely from differences among model treatment

8    of aerosol, cloud processes, and aerosol-cloud interaction processes (Forster et al., 2007). The effect is

9    generally larger over land than oceans, and the model estimates are more variable (and uncertain) over

10   land (Lohman and Feichter, 2005). Forster et al. (2007) provided a best estimate for the cloud albedo RF

11   of -0.7 W/m$^2$, with a 90% confidence range (5%-95% uncertainty range) of -0.3 to -1.8 W/m$^2$.

12       The RFs discussed by Forster et al. (cf. 2007) and summarized here are illustrated in Figure 9-57

13   along with their uncertainty ranges. This helps put the estimates of RF from aerosol particles into the

14   context of RF estimates from long lived greenhouse gasses and other agents of warming. The combined

15   aerosol direct effect and cloud albedo indirect effect exert an RF that is estimated to be about -1.3 W/m$^2$,

16   with a 90% confidence range of -22 to -0.5 W/m$^2$. A breakdown of the estimated RF for each of the

17   principal gas- and aerosol-phase emissions components is given in Figure 9-58. The estimated indirect

18   cloud albedo effect is larger than any of the individual component direct effects. Among the aerosol

19   components, only BC is believed to exert a positive RF.

20       Precipitation suppression by PM has been known for several decades and has been quantified in

21   recent studies. It is believed to result primarily from the cloud albedo indirect effect. Increases in CCN

22   concentrations downwind of field burning sites were investigated by Warner and Twomey (1967) and

23   Warner (1968). Albrecht (1989) hypothesized that higher water droplet concentrations in ship-track trails,

24   due to the high CCN concentration and consequent formation of more small cloud droplets, would reduce

25   drizzle drop formation. Aircraft observations showed that ship-track clouds do actually contain higher

26   cloud droplet concentrations than surrounding clouds, smaller droplet sizes, and only 10% of the number

27   of drizzle drops as the surrounding clouds (Radke et al., 1989). Rosenfeld (1999, 2000) identified

28   pollution tracks downwind of pollution sources comprised of highly reflective cloud droplets. These

29   pollution-track clouds have smaller effective cloud particle size than clouds in surrounding less polluted

30   areas, resulting in precipitation suppression. More recently, Borys et al. (2003) found that winter

31   orographic precipitation can be reduced by up to 50% by decreased riming efficiency of ice crystals when

32   pollution aerosols contribute to smaller cloud droplets.

33       The effects of aerosols on cloud processes over land have been shown to vary compared with those

34   over the ocean. Rosenfeld et al. (2002) found that increased concentrations of aerosol pollutants over the

1  ocean suppressed precipitation to a much lesser degree than over land. This difference was explained by

2  the tendency of sea salt nuclei to initiate formation of droplets that can readily combine with pollutant

3  particles. This process also results in a lower atmospheric residence time for pollutant aerosols over

4  oceans than over land, thus contributing to the cloud lifetime effect described below.

## 9.8.2.2. Second Indirect Effect: Cloud Lifetime

5  As discussed by Denman et al. (2008), the cloud albedo effect cannot be easily separated from

6  other effects, especially from the cloud lifetime effect. The processes that decrease cloud droplet size per

7  given liquid water content also decrease the formation of precipitation, and therefore presumably prolong

8  cloud lifetime. An increase in cloud lifetime would be expected to feed back to cloud albedo.

9  To estimate or model the radiative effects of aerosols, it is important to determine the dependence

10  of aerosol optical properties on relative humidity (RH). Such information is needed to quantify the

11  influence of atmospheric aerosols on climate. Relative humidity controls the water content of atmospheric

12  particles, and the magnitude of the RH influence depends on aerosol size and composition (Baynard et al.,

13  2006). Water uptake properties of particulate OM must also be simplified and approximated (Kanakidou

14  et al., 2005; Quinn et al., 2005) in order to more fully characterize the RH dependence of light scattering

15  by PM.

16  Representations of aerosol-cloud and convection-cloud interactions in climate models are crude

17  (Lohman and Feichter, 2005). Cloud cover is variable and inhomogeneous (2007). Models do not

18  consistently provide accurate estimates of the amounts of cloud liquid and ice water content, and GCMs

19  do not resolve the small scales at which aerosol-cloud interactions occur. In addition, differences in the

20  horizontal and vertical resolution of cloud occurrence limit accurate representation of the shallow warm

21  cloud layers over the oceans most susceptible to changes due to anthropogenic aerosol particles (2007).

22  One important aspect of the cloud albedo effect involves effects on local and regional precipitation

23  budgets. The suppression of precipitation by PM pollution is supported by a large body of recent research.

24  Small atmospheric particles slow precipitation formation in clouds. For orographic clouds, which are

25  shallow and short-lived, there is a net decrease in precipitation amount. As a further consequence of the

26  decrease in precipitation, cloud lifetime is extended, with additional feedback to albedo and other climate

27  impacts. Increased cloud lifetime and extent results in a further increase in the reflection of solar radiation

28  (Ramanathan et al., 2001).

29  The complexities of aerosol effects on cloud processes under varying relative humidity were

30  investigated by Fan et al. (2008). This study showed that aerosol effects on cloud microphysical

31  properties and precipitation were negligible at a relative humidity of 40%, but were significant at a

32  relative humidity of 60-70%. Effects were also shown to vary between continental clouds and marine

1    clouds, as well as with composition and concentration of aerosols. Additional information on aerosol

2    effects on meteorological relationships were shown by Massie et al. (2007), who reported that aerosol

3    indirect effects were a function of the atmospheric pressure at the top of clouds. This information was

4    useful in improving model results that simulate increases in cloud reflectance from non absorbing

5    aerosols.

6         Atmospheric soot particles up to 10 μm can influence climate processes by altering the radiation

7    balance through cloud formation. In addition, soot particles can act as condensation nuclei to change

8    precipitation patterns ((Hansen and Nazarenko, 2004; Sato et al., 2003b).

9         The effects of low solubility organic aerosols on droplet formation rates relative to levels of

10   inorganic pollutant aerosols were investigated by Shantz et al. (2003). Less soluble organic acid particles

11   were found to delay droplet formation relative to more soluble $(NH_4)_2SO_4$. Results also suggested that

12   internal mixing of relatively insoluble organic compounds with $(NH_4)_2SO_4$ also delayed droplet formation

13   relative to the inorganic particle. Overall delay in droplet formation from low-solubility organics was

14   estimated to reduce droplet numbers in clouds by up to 85%. Particle solubility was indicated as a

15   potentially important factor in the precipitation efficiency of clouds.

16        One aspect of carbonaceous aerosol is its capacity to provide CCN. These PM constituents were

17   previously thought to be hydrophobic and therefore not involved in cloud formation. More recent research

18   has suggested that these particles are largely hydrophobic at the time of emission, but that they acquire

19   hydrophilic characteristics with ageing (Alves et al., 2006). During long-range transport, the organic

20   compounds in the aerosol phase are oxidized into secondary products and largely transfer to the

21   particulate phase that is much less volatile and more water soluble (Atkinson, 1994). At remote sites, the

22   organic aerosol may be the main source of CCN; even in less remote regions, one-third to one-half of the

23   total organic mass can be water soluble (Alves et al., 2006).

24        More comprehensive modeling efforts have recently added formulations to combine direct

25   radiative absorption with the indirect climate forcing from effects of aerosols on cloud processes in

26   climate models. Kristjánsson et al. (2005) modeled the relative effects of direct and indirect radiative

27   forcing by a suite of aerosols that are prevalent in the atmosphere. This modeling exercise indicated that

28   the indirect cooling effect was much stronger than the warming effect from direct absorption, but that the

29   uncertainly was large. In fact, these authors stated that the uncertainly was so large that it could be

30   possible that indirect cooling is presently offsetting much of the current $CO_2$ warming effect. Jacobson

31   (2006) modeled emissions and effects of BC on both direct radiative forcing and indirect effects of

32   hydrometeor particle formation (cloud droplets that incorporate BC) to determine the climate effect of

33   BC. The heat generated from radiative absorption by BC within the cloud was found to increase water

34   vapor and decrease precipitation. The increase in water vapor at the expense of precipitation contributed

1  to warming beyond that caused by BC absorption within clouds. This result contrasts with the increase in

2  albedo and associated cooling attributed to increased concentrations of non-absorbing aerosols that

3  decrease droplet size and increase the reflectiveness of clouds.

4      First-principle approaches have been developed in which cloud droplet number is computed for

5  each GCM grid cell (e.g., Jacobson, 2003a, 2004). The indirect effects of carbonaceous aerosols are

6  believed to be of only minor importance (Jacobson, 2003c).

7      Uncertainty in model results stems in part from a lack of atmospheric measurements. Recently,

8  Kaufman (2006) was able to produce the first measurement-based estimates of the anthropogenic aerosol

9  fraction and of the impact of aerosol on the cloud cover and height with MODIS (Moderate Resolution

10  Imaging Spectroradiometer) satellite imagery. Further work of this type is necessary to evaluate the wide

11  range of modeling results.

## 9.8.3. Other Effects

12      There are several other kinds of climate effects from aerosol PM. None is well understood or well

13  quantified. The semi-direct effect, which involves absorption of solar radiation by soot particles followed

14  by re-emission as thermal radiation, is expected to heat the air mass and increase its static stability relative

15  to the surface. The semi-direct effect can also cause evaporation of cloud droplets, thereby partially

16  offsetting the cloud albedo indirect effect. The glaciation effect involves an increase in IN, which is

17  expected to cause rapid glaciation of a super-cooled liquid water cloud due to the differences in vapor

18  pressure over ice and water. Unlike cloud droplets, these ice crystals can quickly reach precipitation size,

19  with the potential to turn a non-precipitating cloud into a precipitating cloud. The thermodynamic effect

20  involves a delay in freezing by the smaller cloud droplets, which can cause super cooled clouds to occur

21  under colder temperatures. The possible consequences to radiative flux of all of the processes are outlined

22  in Table 9-5 (top of the atmosphere effects) and Table 9-6 (surface radiative and precipitation effects;

23  Denman et al., 2007), though significant uncertainties remain. Nevertheless, the individual processes

24  cannot be considered in isolation because of the numerous feedbacks, and because atmospheric aerosol

25  concentrations and climate are intimately coupled (Denman et al., 2007; Dentener, 2006).

## 9.8.4. Effects on Local and Regional Climate

26      Most effects of PM on climate, as assessed by IPCC (c.f., Stohl et al., 2007) and summarized in this

27  assessment, focus on global-scale processes and responses. In addition, it is also possible that PM

28  emissions contribute to local and regional climate changes. These might include short-term cycles in

1    rainfall or temperature and rainfall suppression, especially near cities and for orographic precipitation.

2    Rainfall suppression, in particular, is believed to exacerbate water supply problems which are substantial

3    in many regions, especially in the western U.S.

4         Aerosol particles, directly and through cloud enhancement, may reduce near-surface wind speeds

5    locally. Slower winds, in turn, reduce evaporation. The overall impact can be a reduction in local

6    precipitation. Jacobson and Kaufman (2006) investigated the effects of PM on spatially-distributed wind

7    speeds and resulting feedbacks to precipitation using the GATOR-GCMOM (Jacobson, 2001) and

8    supporting evidence from satellite data. The study focused on the South Coast Air Basin (SCAB) in

9    California during February and August, 2002-2004. The modeled precipitation decrease over land in

10   California was 2% of the baseline 1.5 mm/day due to emissions of anthropogenic aerosol particle and

11   precursor gasses in the SCAB domain. However, the reduction over much of the Sierra Nevada, where

12   most precipitation falls, was up to 0.5 mm/day, or 4 to 5% of the baseline 10 to 13 mm/day in that

13   mountainous region (Jacobson and Kaufman, 2006). The probable mechanism was described as follows.

14   Aerosol particles and aerosol-enhanced clouds reduce wind speeds below them by stabilizing the air,

15   reducing the vertical transport of horizontal momentum. In turn, the reduced wind speeds, and associated

16   reduced evaporation and increased cloud lifetime, contributes to reduced local and regional precipitation

17   (Jacobson and Kaufman, 2006).

18        Effects of air pollution on regional precipitation were quantified by Givati and Rosenfeld (2004).

19   They found a 15 to 25% reduction in the orographic component of precipitation downwind of major

20   coastal urban areas during the 20th century. Their study focused on orographically-forced clouds because

21   these short-lived, shallow clouds are expected to exhibit the largest effect of air pollution on precipitation.

22   Substantially larger precipitation suppression due to aerosol particulate pollution was found between

23   Fresno and Sacramento in California by Givati (2004). Precipitation losses over topographical barriers in

24   the Sierra Nevada amounted to 15%-25% of the annual precipitation at elevations less than 2,000 m. This

25   precipitation suppression occurred mainly in the relatively shallow orographic clouds within the cold air

26   mass of cyclones. The suppression that occurred on the upslope side of the mountains was coupled with

27   similar percentage (but lower absolute volume) enhancement on the drier downslope eastern side (Givati

28   and Rosenfeld, 2004). Similar results were found in studies by Griffith et al. (2005), Jirak and Cotton

29   (Jirak and Cotton, 2006), Rosenfeld and Givati (2006), and Rosenfeld et al. (2007). At all of these study

30   locations (California, Israel, Utah, Colorado, China), orographic precipitation decreased by 15 to 30%

31   downwind of pollution sources, likely due to creation of more and smaller cloud droplets and resulting

32   suppression of precipitation.

33        The study of Givati and Rosenfeld (2004) was the first to quantify the microphysical effect of

34   mesoscale precipitation. Following the findings of Givati and Rosenfeld (2004), the effects of aerosol air

1   pollution on precipitation at high elevation sites in the Front Range of Colorado adjacent to urban areas

2   were investigated by Jirak and Cotton (2006). Examination of precipitation trends showed that the ratio of

3   upslope precipitation during easterly flows at high elevation west of Denver and Colorado Springs to the

4   upwind urban sites decreased by about 30% over the past half century. These results provide further

5   support for the hypothesis that aerosol pollution suppresses orographic precipitation downwind of

6   pollution source areas.

7       Griffith et al. (2005) found similar reductions in mountainous precipitation in Utah, downwind of

8   Salt Lake City and Provo. The ratio of precipitation at mountain stations located in rural settings in Utah

9   and Nevada remained stable, supporting the hypothesis that air pollution decreases Ro (the ratio of

10  precipitation at the downwind site to precipitation at the upwind pollution source) over the mountains to

11  the east of Salt Lake City.

12      Rosenfeld and Givati (2006) extended the investigation of the suppression of precipitation by

13  aerosol pollutants to a larger scale by examining the ratio between precipitation amounts over the hills to

14  precipitation over upwind lowland areas throughout the western U.S. from the Pacific Coast to the Rocky

15  Mountains. They found in these paired analyses a pattern of decreasing precipitation by as much as 24%

16  from the Mexican border to central California, with no decrease in northern California and Oregon and

17  smaller decrease of 14% in Washington east of Seattle and Puget Sound. Similar decreases were found

18  over Arizona and New Mexico (Rosenfeld and Givati, 2006), Utah (Griffith et al., 2005), and the east

19  slope of the Colorado Rockies (Jirak and Cotton, 2006).

20      Suppression of winter orographic precipitation appears to occur up to hundreds of kilometers

21  inland of coastal urban areas (Rosenfeld and Givati, 2006). Decreases in this precipitation ratio occurred

22  during winter orographic precipitation, but not during convective summer precipitation over the same

23  mountain ranges. This finding agrees with the expectation that aerosol-induced changes in the rate of

24  precipitation formation would cause a decrease in precipitation from shallow and short-lived orographic

25  clouds, but not necessarily from deeper and longer-lived thermally-driven convective clouds.

26      Results of these studies of aerosol effects on orographic precipitation suggest that human-caused

27  air pollution, and fine particles in particular, have had a large effect on precipitation well beyond the local

28  scales of the pollution sources (Rosenfeld and Givati, 2006).

## 9.8.5. Glaciers and Snowpack

29      Organic compounds are incorporated into snow by wet and dry deposition processes (Lei and

30  Wania, 2004; Roth et al., 2004). Atmospherically deposited organics appear to be ubiquitous in

31  snowpacks at appreciable concentrations (Grannas et al., 2007). Examples include PAHs, phthalates,

1  alkanes, phenols, low molecular weight carbonyls, POPs, and low molecular weight organic acids (cf.,

2  Halsall, 2004; Nakamura et al., 2000; Villa et al., 2003). Humic-like substances found in the snowpack

3  may release VOCs into the atmosphere via photo-oxidation (Grannas et al., 2004; Grannas et al., 2007).

4  Several thousand organic species were identified by Grannas et al. (2006), based on molecular weight,

5  from a single ice core collected in Russia. Little information is available, however, regarding the chemical

6  properties of these chemical constituents. In addition to the diversity of chemicals that are deposited into

7  the snowpack, there are also biological organisms, including bacteria and algae. Their role in influencing

8  snow chemistry and volatilization processes are not understood (Grannas et al., 2007).

9      Recent research has explored connections between the atmosphere and the cryosphere (land or sea

10  covered by snow or ice). A seasonal maximum of 40% of the Earth's land surface is covered by snow or

11  ice, as well as several percent of the oceans. Particulate deposition to snow and ice surfaces can affect

12  melting rates. Deposition of PM to glacial ice surfaces can affect the subsequent rate of melting. A thin

13  cover of debris contributes to accelerated melting. A thicker cover of debris, such as may result from a

14  volcanic eruption, retards melting. The difference is due to the changing balance between enhanced

15  absorption of shortwave radiation by PM and conductive heat flow (insulation) through a buildup of

16  material having low heat conduction (Kirkbride and Dugmore, 2003).This issue is particularly important

17  for deposition of large quantities of volcanic material. To a lesser extent, however, the same principles

18  apply to PM deposition derived from air pollution. Under a thin layer of debris, ablation rates are higher

19  than for clean ice. However, as the thickness of the debris layer increases, ablation rates systematically

20  decline (Nicholson and Benn, 2006). The threshold debris thickness that separates ablation increase from

21  decrease is site specific and depends on local climate and the nature of the debris particles. Nicholson and

22  Benn (2006) presented a surface energy balance model to calculate ice melt beneath a surface debris

23  layer, based on meteorological data and basic debris characteristics. Modeled melting rates matched

24  observed rates, suggesting that the model produced useful results.

25      Long-range atmospheric transport of PM delivers a large fraction of the total input of POPs to the

26  Arctic region (Halsall, 2004). These contaminants can accumulate in Arctic food webs and have become

27  the focus of international research and concern. Nevertheless, fate and transport of POPs within terrestrial

28  and marine Arctic ecosystems are not well understood and are strongly affected by the presence of snow

29  and ice. Sea ice provides a barrier to air-water exchange, and this hinders volatilization and re-emission of

30  previously deposited contaminants (Halsall, 2004). Thus, the effects of greenhouse gasses and PM on

31  climate in the Arctic region have feedbacks to POP fate, transport, and toxicity. The transfer of POPs

32  among the major abiotic environmental compartments in the Arctic are summarized in Figure 9-59 from

33  Halsall (2004). Recent studies detailing rate and transport of POPs are summarized in Table 9-7.

**Table 9-7.** Recent studies highlighting POP occurrence and fate in the major arctic compartments.

| | **Atmosphere** | |
|---|---|---|
| 1 | Annual time-series of OC and PCB concentrations in the Norwegian Arctic | Oehme et al. (1996) |
| 2 | Long-term analysis of the chlordane-group and their input to the Arctic with changing sources | Bidleman et al. (2002) |
| 3 | PAH occurrence at monitoring sites across the Arctic, seasonality and gas/particle partitioning | Halsall et al. (1997) |
| 4 | PCB occurrence at monitoring sites across the Arctic, spatial differences and seasonality | Stern et al. (1997) |
| 5 | Long-term analysis of PCB and OC trends in the Canadian Arctic and seasonal patterns | Hung et al. (2001; 2002) |
| 6 | Trans-Pacific LRAT and impact of Asian sources on the western Canadian Arctic | Bailey et al. (2000) |
| | *FRESHWATER* | |
| 7 | Annual average water concentrations in major Russian rivers for selected OC pesticides | Alexeeva et al. (2001) |
| 8 | Long-term (decades) PCB deposition profile in Arctic lake sediments | Muir et al. (1996) |
| 9 | Mass balance of selected OCs in Canadian Arctic lake conducted with data collected over 3 years | Helm et al. (2002) |
| 10 | Examining the biodegradation of HCHs in Canadian Arctic watersheds | Helm et al. (2000) |
| | *MARINE* | |
| 11 | Transport and entry of β-HCH into western Arctic Ocean via Pacific surface waters | Li et al. (2002) |
| 12 | Occurrence of current use pesticides in air, fog and surface seawater in the western Arctic Ocean | Chermyak et al. (1996) |
| 13 | Resolving petrogenic and anthropogenic PAH input to marine sediments in coastal Arctic seas | Yunker et al. (1996) |
| 14 | Quantifying abiotic and biotic degradation of HCHs in the Arctic Ocean water column | Harner et al. (2000) |
| 15 | PCBs and OCs in surface ocean water—Bering and Chukchi seas | Strachan et al. (2001) |
| 16 | Spatial patterns of HCHs and toxaphene in Arctic Ocean surface water | Jantunen and Bidleman (1998) |
| | *SNOW/AIR-FRESHWATER* | |
| 17 | PAHs (and inorganics) in surface snow layers (snowpit) at Summit, Greenland | Masclet et al. (2000) |
| 18 | PAHs measured in snow and firn layers on Agassiz ice-cap, Ellesmere Island, Canada | Peters et al. (1995) |
| 19 | Modelling OC behaviour and fate in the surface seasonal snow pack at Amituk Lake, Canada | Wania et al. (1998) |
| 20 | OCs, PCBs and PAHs in snow and ice of the Ob-Yenisey watershed of the Russian Arctic | Melnikov et al. (2003) |
| | *OCEAN/AIR* | |
| 21 | Transfer of α-HCH across the air/water interface in the western Arctic ocean | Jantunen and Bidleman (1996) |
| 22 | Calculated seasonality of OC air/water fluxes in the Canadian high Arctic | Hargrave et al. (1997) |
| | *OCEAN/ICE* | |
| 23 | Transport potential of contaminants across the Arctic ocean via sea-ice drift | Pfirman et al. (1997) |
| 24 | The importance of eastern Arctic sea-ice drift as a source of contaminants to the Norwegian sea | Korsnes et al. (Korsnes et al., 2002) |

Source: Halsall (2004)
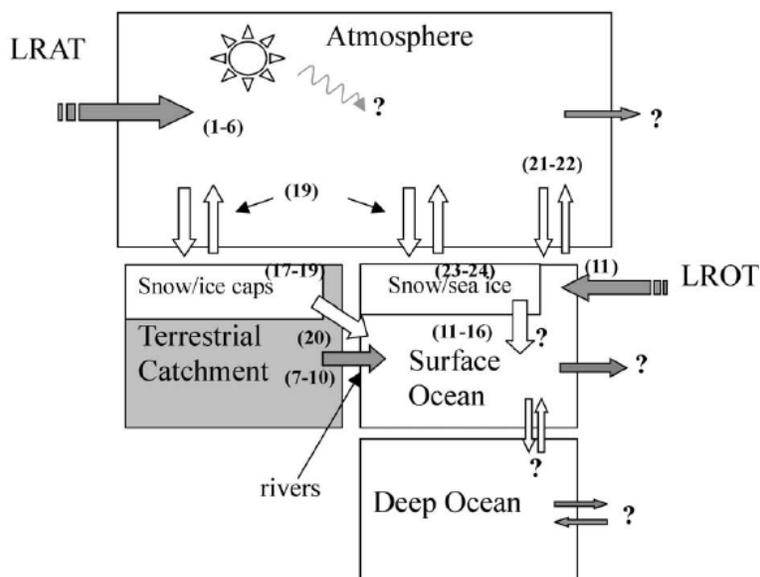
**Figure 9-59.** **The transfer of POPs between the major abiotic compartments of the Arctic. Shaded arrows represent inputs/outputs of POPs to the Arctic. The numbers refer to selected studies detailing the occurrence and behavior of POPs, and are listed in Table 9-7. Question marks represent those areas that are least well understood. LRAT-long range atmospheric transport; LROT – long range oceanic transport.**

## 9.8.6. Global Warming Potentials

1    One approach to making comparisons of effects from the many and varied contributors to climate

2    warming involves use of global warming potentials (GWPs) defined as the integral of the radiative

3    forcing caused by the pulse emission of 1 kg of a chemical species of a time horizon T, which results in a

4    unit of W m$^2$/kg/yr (Boucher and Reddy, 2008). It depends on both the radiative efficiency of the

5    chemical species and its decay time.

6    Bond and Sun (2005) estimated that BC has a high GWP of 680 even though it has a short lifetime

7    in the atmosphere. Reddy and Boucher (2007) found that the direct GWP for BC depends on its source

8    region. Such regional differences reflect differences in atmospheric lifetime, which are largely due to the

9    regional efficacy of wet deposition as a process that removes PM from the atmosphere. The GWP of BC

10   is still highly uncertain (Boucher and Reddy, 2008).

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