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Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure

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Executive Summary

In the proposed rule on the National Ambient Air Quality Standards for particulate matter (PM), EPA committed to conduct a review and assessment of the numerous studies relevant to assessing the health effects of PM that were published too recently to be included in the 2004 PM Air Quality Criteria Document (AQCD). This report presents the findings of EPA's survey and provisional assessment of such studies. EPA has screened and surveyed the recent literature and developed a provisional assessment that places those studies of potentially greatest relevance in the context of the findings of the 2004 PM AQCD. The focus is on: (a) epidemiologic studies that used $PM_{2.5}$ or $PM_{10-2.5}$ and were conducted in the U.S. or Canada, and (b) toxicology or epidemiologic studies that compared effects of PM from different sources, PM components, or size fractions. Given the limited time available, the provisional assessment presented here does not attempt to critically review individual studies or to provide the kind of full integration found in a typical AQCD.

This survey and assessment finds that that the new studies expand the scientific information and provide important insights on the relationships between PM exposure and health effects of PM. Taken in context, however, the new information and findings do not materially change any of the broad scientific conclusions regarding the health effects of PM exposure made in the 2004 PM AQCD. In brief, this report finds the following:

- Recent epidemiologic studies, most of which are follow-ups or extensions of earlier work, continue to find that *long-term exposure to fine particles* is associated with both mortality and morbidity, as was stated in the 2004 PM AQCD. Notably, a follow-up to the Six Cities study shows that an overall reduction in $PM_{2.5}$ levels results in reduced long-term mortality risk. Both this study and the analysis of the ACS cohort data in Los Angeles suggest that previous studies may have underestimated the magnitude of mortality risks. Some studies provide more mixed results, including the suggestion that higher traffic density may be an important factor. In addition, the California Children's Health Study reported that measures of $PM_{2.5}$ exposure and PM components and gases were associated with reduction in lung function growth in children, increasing the evidence for increased susceptibility early in life, as was suggested in the 2004 PM AQCD. The results of recent epidemiologic and toxicology studies have also reported new evidence linking long-term exposure to fine particles with a measure of atherosclerosis development and, in a cohort of individuals with cystic fibrosis, respiratory exacerbations.

- Recent epidemiologic studies have also continued to report associations between *acute exposure to fine particles* and mortality and morbidity health endpoints. These include three multi-city analyses, the largest of which (in 204 counties) shows a significant association between acute fine PM exposures and hospitalization for cardiovascular and respiratory diseases, and suggestions of differential cardiovascular effects in eastern U.S. as opposed to western U.S. locations. The new studies support previous conclusions that short-term exposure to fine PM is associated with both mortality and morbidity, including a substantial number of studies reporting associations with cardiovascular and respiratory health outcomes such as changes in heart rhythm or increases in exhaled NO.

- New toxicology and epidemiologic studies have continued to link health outcomes with a range of *fine particle sources and components.* Several new epidemiologic analyses and toxicology studies have included source apportionment techniques, and the results indicated that fine PM from numerous sources, including traffic-related pollution, regional sulfate pollution, combustion sources, resuspended soil or road dust, are associated with various health outcomes. Toxicology studies continue to indicate that various components, including metals, sulfates, and elemental and organic carbon, are linked with health outcomes, albeit at generally high concentrations. Recent epidemiologic studies have also linked different fine PM components with a range of health outcomes; new studies indicate effects of the organic and elemental carbon fractions of fine PM that were generally not evaluated in earlier analyses.

- The recent epidemiologic studies greatly expand the more limited literature on health effects of *acute exposure to thoracic coarse particles ($PM_{10-2.5}$)*. The 2004 PM AQCD conclusion that $PM_{10-2.5}$ exposure was associated with respiratory morbidity is substantially strengthened with these new studies; several epidemiologic studies, in fact, report stronger evidence of associations with $PM_{10-2.5}$ than for $PM_{2.5}$. In two new case-crossover studies, associations with thoracic coarse particles are robust to the inclusion of gaseous copollutants. For mortality, many studies do not report statistically significant associations, though one new analysis reports a significant association with cardiovascular mortality in Vancouver, Canada.

- Evidence of associations between *long-term exposure to thoracic coarse particles* and either mortality or morbidity remains limited.

- New toxicology studies have demonstrated that exposure to *thoracic coarse particles*, or PM sources generally representative of this size fraction (e.g., road dust), can result in inflammation and other health responses. Clinical exposure of healthy and asthmatic humans to concentrated ambient air particles comprised mostly of $PM_{10-2.5}$ showed changes in heart rate and heart rate variability measures. The results are still too limited to draw conclusions about specific thoracic coarse particle components and health outcomes, but it appears that endotoxin and metals may play a role in the observed responses. Two studies comparing toxicity of dust from soils and road surfaces found variable toxic responses from both urban and rural locations.

- Significant associations between improvements in health and reductions in PM and other air pollutants have been reported in intervention studies or "found experiments." One new study reported reduced mortality risk with reduced $PM_{2.5}$ concentrations. In addition, several studies, largely outside the U.S., reported reduced respiratory morbidity with lowered air pollutant concentrations, providing further support for the epidemiological evidence that links PM exposure to adverse health effects.

Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure

1. INTRODUCTION AND METHODOLOGY

EPA is currently in the final stages of the review of the national ambient air quality standards (NAAQS) for particulate matter (PM). As described in more detail in the Federal Register Notice of EPA's proposed rule on the PM NAAQS (71 FR 2620), EPA has prepared the *Air Quality Criteria for Particulate Matter* (hereafter 2004 PM AQCD) that reviewed, summarized and integrated the results of studies on PM (EPA, 2004). As noted in the PM proposal[1], EPA is aware that numerous studies potentially relevant to assessing the health effects of ambient PM have been published recently that were not included in the 2004 PM AQCD. The proposal notice also indicates the Agency's intent to conduct a review and assessment of these new studies before a final decision is made on the PM NAAQS. This report presents the findings of EPA's survey and provisional assessment of potentially relevant recent studies on the health effects of PM exposure. As outlined below, EPA has 1) screened the recently available literature to identify potentially relevant studies, 2) surveyed those studies to summarize the key findings, and 3) developed a preliminary assessment that places those of potentially greatest relevance in the context of the findings of the 2004 AQCD. Given the limited time available, the provisional assessment presented here does not attempt to critically review individual studies or to provide the kind of full integration found in a typical AQCD.

The literature search and submissions from public commenters found that hundreds of studies have been published in the last few years on the health effects of particulate matter. In an initial screen of the literature, more than 700 studies were identified as being potentially relevant to this review. In surveying these studies, EPA emphasized studies more likely to be relevant to considerations for the PM NAAQS decision. The specific criteria focused on (a) epidemiologic studies that used $PM_{2.5}$ or $PM_{10-2.5}$ and were conducted in the U.S. or Canada, and (b) toxicology or epidemiologic studies that compared effects of PM from different sources, PM components, or size fractions. These criteria resulted in a list of over 200 studies that are summarized in tables in this report that provide descriptive and quantitative information. The most significant studies are discussed in the assessment, and where feasible, quantitative results are compared to those from the 2004 PM AQCD. Bibliographies have been attached for studies identified as being potentially relevant through the survey effort but not discussed in detail in this report.

[1] As stated in the PM NAAQS proposal notice: "The EPA is aware that a number of new scientific studies on the health effects of PM have been published since the 2002 cutoff date for inclusion in the Criteria Document. As in the last PM NAAQS review, EPA intends to conduct a review and assessment of any significant new studies published since the close of the Criteria Document, including studies submitted during the public comment period in order to ensure that, before making a final decision, the Administrator is fully aware of the new science that has developed since 2002. In this assessment, EPA will examine these new studies in light of the literature evaluated in the Criteria Document. This assessment and a summary of the key conclusions will be placed in the rulemaking docket." (71 FR 2625)

The overview in the main body of this report is organized into three main sections: (1) epidemiologic studies on effects associated with long-term exposure to PM, focusing on U.S. and Canadian studies with measurements of $PM_{2.5}$ or $PM_{10-2.5}$; (2) results from time-series epidemiologic studies, again focusing on U.S. and Canadian studies with measurements of $PM_{2.5}$ or $PM_{10-2.5}$; and (3) results of recent toxicology and epidemiologic studies that have evaluated health effects with exposure to PM from different sources. This last section includes results of studies that assessed the effects of a range of sources or components in the same study. Most studies have focused on components or sources of fine particles, but information related to sources of thoracic coarse particles was also included to the extent available.

2. OVERVIEW OF RECENT HEALTH STUDY RESULTS

2.1 Epidemiologic Studies of Long-Term Exposure

2.1.1 Mortality

An extensive discussion of prospective cohort studies was included in Section 8.2.3 of the 2004 PM AQCD. These discussions emphasized the results of four U.S. prospective cohort studies. The greatest weight was placed on the findings of the American Cancer Society (ACS) and the Harvard Six Cities studies which had undergone extensive, independent reanalysis and were based on cohorts that were broadly representative of the U.S. population. These studies provided strong evidence that long-term exposure to fine particles and sulfates was associated with mortality. In addition, results from the Seventh-Day Adventist (AHSMOG) cohort provided some suggestive but less conclusive evidence for associations, and results from the Veterans Cohort provided inconsistent evidence for associations between long-term exposures to $PM_{2.5}$ and mortality. Overall, the 2004 PM AQCD concluded that there was strong epidemiologic evidence for associations between long-term exposures to $PM_{2.5}$ and mortality (p. 9-46).

In the 2004 PM AQCD, no association was observed between mortality and long-term exposure to $PM_{10-2.5}$ in the ACS study (Pope et al., 2002), and a positive but nonsignificant association was reported in males in the AHSMOG cohort (McDonnell et al., 2000). Thus, the 2004 PM AQCD concluded that there was insufficient evidence for associations between long-term exposure to thoracic coarse particles and mortality.

Fine Particles:

Recent studies include results of new analyses for the ACS and Harvard Six Cities studies; as highlighted below, the new findings strengthen the evidence linking long-term exposure to $PM_{2.5}$ and mortality. Recent reports have also included analyses from the AHSMOG and Veterans study cohorts, as well as a Cystic Fibrosis cohort and a subset of the ACS for California. These results, along with those from studies available in the 2004 PM AQCD, are shown in Figure 1. The risk estimates and PM concentrations reported in the studies are summarized in Table 1, along with results available in the 2004 PM AQCD; further details on the studies are presented in Appendix A, Table A1.

Table 1. Mortality and Morbidity Effect Estimates and PM Concentrations from U.S. and Canadian Studies with Long-Term Exposures to $PM_{2.5}$ and $PM_{10-2.5}$. Adapted from Appendix 3B of the 2005 OAQPS Staff Paper. Shaded rows present results from recent studies that were not available in the 2004 PM Criteria Document.

Study	Indicator	Relative Risk (95% CI)	Study Concentrations ($\mu g/m^3$) *
Increased Total Mortality in Adults			
Six Cities[A]	$PM_{2.5}$	1.13 (1.04, 1.23)	NR (11, 30)
	SO_4^{2-} (15 $\mu g/m^3$)	1.54 (1.15, 2.07)	NR (5, 13)
Six Cities[B]	$PM_{15-2.5}$	1.43 (0.83, 2.48)	
Six Cities Reanalysis[D]	$PM_{2.5}$	1.14 (1.05, 1.23)	NR (11, 30)
Six Cities Follow-up[AA]	$PM_{2.5}$	1.16 (1.07, 1.26)	NR (10.2, 22)
ACS Study[C]	$PM_{2.5}$	1.07 (1.04, 1.10)	18[1] (9, 34)
	SO_4^{2-} (15 $\mu g/m^3$)	1.11 (1.06, 1.16)	11[1] (4, 24)
ACS Study Reanalysis[D]	$PM_{2.5}$	1.07 (1.04, 1.10)	20 (10, 38)
	$PM_{15-2.5}$	1.00 (0.99, 1.02)	7.1 (9, 42)
ACS Study Extended Analyses[E]	$PM_{2.5}$ (1979-83) $PM_{2.5}$ (1999-00) $PM_{2.5}$ (average)	1.04 (1.01, 1.08) 1.06 (1.02, 1.10) 1.06 (1.02, 1.11)	21 (9, 34) 14 (5, 20) 18 (7.5, 30)
ACS Los Angeles[BB]	$PM_{2.5}$	1.17 (1.05, 1.30)	NR (9, 27)
AHSMOG[H]	$PM_{2.5}$	1.09 (0.98, 1.21) (males)	32 (17, 45)
	$PM_{10-2.5}$	1.05 (0.92, 1.21) (males)	27 (4, 44)
Veterans Cohort[G]	$PM_{2.5}$ (1979-81)	0.90 (0.85, 0.95) (males)	24 (6, 42)
Veterans Cohort[CC]	$PM_{2.5}$ (1999-2001)	1.12 (1.04, 1.20) (males)	14.6 (SD 3.1)
Veterans Cohort[CC]	$PM_{10-2.5}$ (1989-96)	1.07 (1.01, 1.12) (males)	16.0 (SD 5.1)
California Cancer Prevention Study[DD]	$PM_{2.5}$ (1979-83)	1.04 (1.01, 1.07) (deaths 1973-1982) 1.00 (0.98, 1.02) (deaths 1983-2002)	23.4 (10.6-42.0)
U.S. Cystic Fibrosis[EE]	$PM_{2.5}$	1.32 (0.91, 1.93)	13.7 (11.8, 15.9)
Increased Cardiopulmonary Mortality in Adults			
Six Cities[A]	$PM_{2.5}$	1.18 (1.06, 1.32)	NR (11, 30)
Six Cities Reanalysis[D]	$PM_{2.5}$	1.19 (1.07, 1.33)	NR (11, 30)

Table 1. Mortality and Morbidity Effect Estimates and PM Concentrations from U.S. and Canadian Studies with Long-Term Exposures to $PM_{2.5}$ and $PM_{10-2.5}$. Adapted from Appendix 3B of the 2005 OAQPS Staff Paper. Shaded rows present results from recent studies that were not available in the 2004 PM Criteria Document.

Study	Indicator	Relative Risk (95% CI)	Study Concentrations ($\mu g/m^3$) *
Six Cities Follow-up[AA]	$PM_{2.5}$	1.28 (1.13-1.44) (Cardiovascular) 1.08 (0.79-1.49) (Respiratory)	NR (10.2, 22)
ACS Study[C]	$PM_{2.5}$	1.12 (1.07, 1.17)	18[1] (9, 34)
ACS Study Reanalysis[D]	$PM_{2.5}$	1.12 (1.07, 1.17)	20 (10, 38)
	$PM_{15-2.5}$	1.00 (0.98, 1.03)	7.1 (9, 42)
ACS Study Extended Analyses[E]	$PM_{2.5}$ (1979-83) $PM_{2.5}$ (1999-00) $PM_{2.5}$ (average)	1.06 (1.02, 1.10) 1.08 (1.02, 1.14) 1.09 (1.03, 1.16)	21 (9, 34) 14 (5, 20) 18 (7.5, 30)
ACS Cause-specific[FF]: All cardiovascular Ischemic heart disease Dysrhythmia, et al. Hypertensive Other atherosclerosis Cerebrovascular disease Diabetes Other cardiovascular All Respiratory COPD Pneumonia Other respiratory	$PM_{2.5}$ (average)	 1.12 (1.08, 1.15) 1.18 (1.14, 1.23) 1.13 (1.05, 1.21) 1.07 (0.90, 1.26) 1.04 (0.89, 1.21) 1.02 (0.95, 1.10) 0.99 (0.86, 1.14) 0.84 (0.71, 0.99) 0.92 (0.86, 0.98) 0.84 (0.77, 0.93) 1.07 (0.95, 1.20) 0.86 (0.73, 1.02)	17.1 (7.5, 30)
ACS Los Angeles:[BB] Ischemic heart disease Cardiopulmonary	$PM_{2.5}$	 1.39 (1.12, 1.73) 1.12 (0.97, 1.30)	NR (9, 27)
AHSMOG[H]	$PM_{2.5}$	1.23 (0.97, 1.55) (males)	32 (17, 45)
	$PM_{10-2.5}$	1.20 (0.87, 1.64) (males)	27 (4, 44)
AHSMOG[GG] Fatal coronary heart disease	$PM_{2.5}$	1.42 (1.06, 1.90) (females) 1.49 (1.17, 1.89) (postmenopausal) 0.90 (0.76, 1.05) (males)	29 (SD 9.8)
	$PM_{10-2.5}$	1.38 (0.97, 1.95) (females) 1.61 (1.12, 2.33) (postmenopausal) 0.92 (0.66, 1.29) (males)	25.4 (SD 8.5)
Increased Lung Cancer Mortality in Adults			
Six Cities[A]	$PM_{2.5}$	1.18 (0.89, 1.57)	NR (11, 30)

Table 1. Mortality and Morbidity Effect Estimates and PM Concentrations from U.S. and Canadian Studies with Long-Term Exposures to $PM_{2.5}$ and $PM_{10-2.5}$. Adapted from Appendix 3B of the 2005 OAQPS Staff Paper. Shaded rows present results from recent studies that were not available in the 2004 PM Criteria Document.

Study	Indicator	Relative Risk (95% CI)	Study Concentrations ($\mu g/m^3$) *
Six Cities Reanalysis[D]	$PM_{2.5}$	1.21 (0.92, 1.60)	NR (11, 30)
Six Cities Follow-up[AA]	$PM_{2.5}$	1.27 (0.96, 1.69)	NR (10.2, 22)
ACS Study[C]	$PM_{2.5}$	1.01 (0.91, 1.12)	18[U] (9, 34)
ACS Study Reanalysis[D]	$PM_{2.5}$	1.01 (0.91, 1.11)	20 (10, 38)
	$PM_{15-2.5}$	0.99 (0.93, 1.05)	7.1 (9, 42)
ACS Study Extended Analyses[E]	$PM_{2.5}$ (1979-83) $PM_{2.5}$ (1999-00) $PM_{2.5}$ (average)	1.08 (1.01, 1.16) 1.13 (1.04, 1.22) 1.14 (1.05, 1.24)	21 (9, 34) 14 (5, 20) 18 (7.5, 30)
ACS Los Angeles[BB]	$PM_{2.5}$	1.44 (0.98, 2.11)	NR (9, 27)
AHSMOG[H]	$PM_{2.5}$	1.39 (0.79, 2.50) (males)	32 (17, 45)
	$M_{10-2.5}$	1.26 (0.62, 2.55) (males)	27 (4, 44)
Increased Bronchitis in Children			
Six Cities[I]	$PM_{2.5}$	1.3 (0.9, 2.0)	NR (12, 37)
24 Cities[J]	SO_4^{2-} (15 $\mu g/m^3$) $PM_{2.1}$	3.02 (1.28, 7.03) 1.31 (0.94, 1.84)	4.7 (0.7, 7.4) 14.5 (5.8, 20.7)
AHSMOG[K]	SO_4^{2-} (15 $\mu g/m^3$)	1.39 (0.99, 1.92)	—
12 Southern California communities[M] (children with asthma)	$PM_{2.5}$	1.3 (0.9, 1.7)	15.3 (6.7, 31.5)
12 Southern California communities[HH] (children with asthma)	$PM_{2.5}$ $PM_{10-2.5}$	1.34 (1.11, 1.63) 1.10 (0.82, 1.49) (between communities)	13.8 (5.5, 28.5) 17.0 (10.2, 35.0)
12 Southern California communities[HH] (children with asthma)	$PM_{2.5}$ $PM_{10-2.5}$	2.37 (1.13, 4.94) 1.21 (0.59, 2.54) (within community change)	13.8 (5.5, 28.5) 17.0 (10.2, 35.0)
Increased Cough in Children			
12 Southern California communities[M] (children with asthma)	$PM_{2.5}$	1.2 (0.8, 1.8)	15.3 (6.7, 31.5)
Increased Pulmonary Exacerbations in Cystic Fibrosis Patients			
U.S. Cystic Fibrosis[EE]	$PM_{2.5}$	1.21 (1.07, 1.33)	13.7 (11.8, 15.9)

Table 1. Mortality and Morbidity Effect Estimates and PM Concentrations from U.S. and Canadian Studies with Long-Term Exposures to $PM_{2.5}$ and $PM_{10-2.5}$. Adapted from Appendix 3B of the 2005 OAQPS Staff Paper. Shaded rows present results from recent studies that were not available in the 2004 PM Criteria Document.

Study	Indicator	Relative Risk (95% CI)	Study Concentrations ($\mu g/m^3$) *
Decreased Lung Function in Children			
24 City[J]	SO_4^{2-} (15 $\mu g/m^3$)	−6.56% (-9.64, -3.43) FVC	4.7 (0.7, 7.4)
	$PM_{2.1}$	−2.15% (-3.34, -0.95) FVC	14.5 (5.8, 20.7)
12 Southern California communities[Q] (4^{th} grade cohort)	$PM_{2.5}$	−0.18 (-0.36, 0.0) FVC % growth	NR (10, 35)[3]
		−0.4 (-0.75, -0.04) MMEF % growth	NR
	$PM_{10-2.5}$	−0.22 (-0.47, 0.02) FVC % growth	
		−0.54 (-1.0, -0.06) MMEF % growth	
12 Southern California communities[Q] (second 4^{th} grade cohort)	$PM_{2.5}$	−0.06 (-0.30, 0.18) FVC % growth	NR (5, 30)[4]
		−0.42 (-0.84, 0.0) MMEF % growth	
		−0.20 (-0.64, 0.25) PEFR % growth	
12 Southern California communities[II] (first 4^{th} grade cohort, 8-yr follow-up)	$PM_{2.5}$	-26.4 (-72.9, 20.1) FVC growth -35.0 (-67.1, -2.8) FEV_1 growth -74.1 (-151.5, 3.4) MMEF growth	NR (5, 28)
Lung Function Changes in Adults			
AHSMOG[T] (% predicted FEV_1, males)	SO_4^{2-} (1.6 $\mu g/m^3$)	−1.5% (-2.9, -0.1) FEV_1	7.3 (2.0, 10.1)

* Note: Effect estimates presented using standardized increments of 10 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$. Concentrations are presented as mean (min, max), or mean (±SD); NS Changes = No significant changes (no quantitative results reported); NR = not reported.

[1] Median
[2] Results only for smoking category subgroups.
[3] Estimated from Figure 1, Gauderman et al. (2000)
[4] Estimated from figures available in online data supplement to Gauderman et al. (2002)

References:

[A] Dockery et al. (1993)
[B] EPA (1996a)
[C] Pope et al. (1995)
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[F] Abbey et al. (1999)
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[H] McDonnell et al. (2000)
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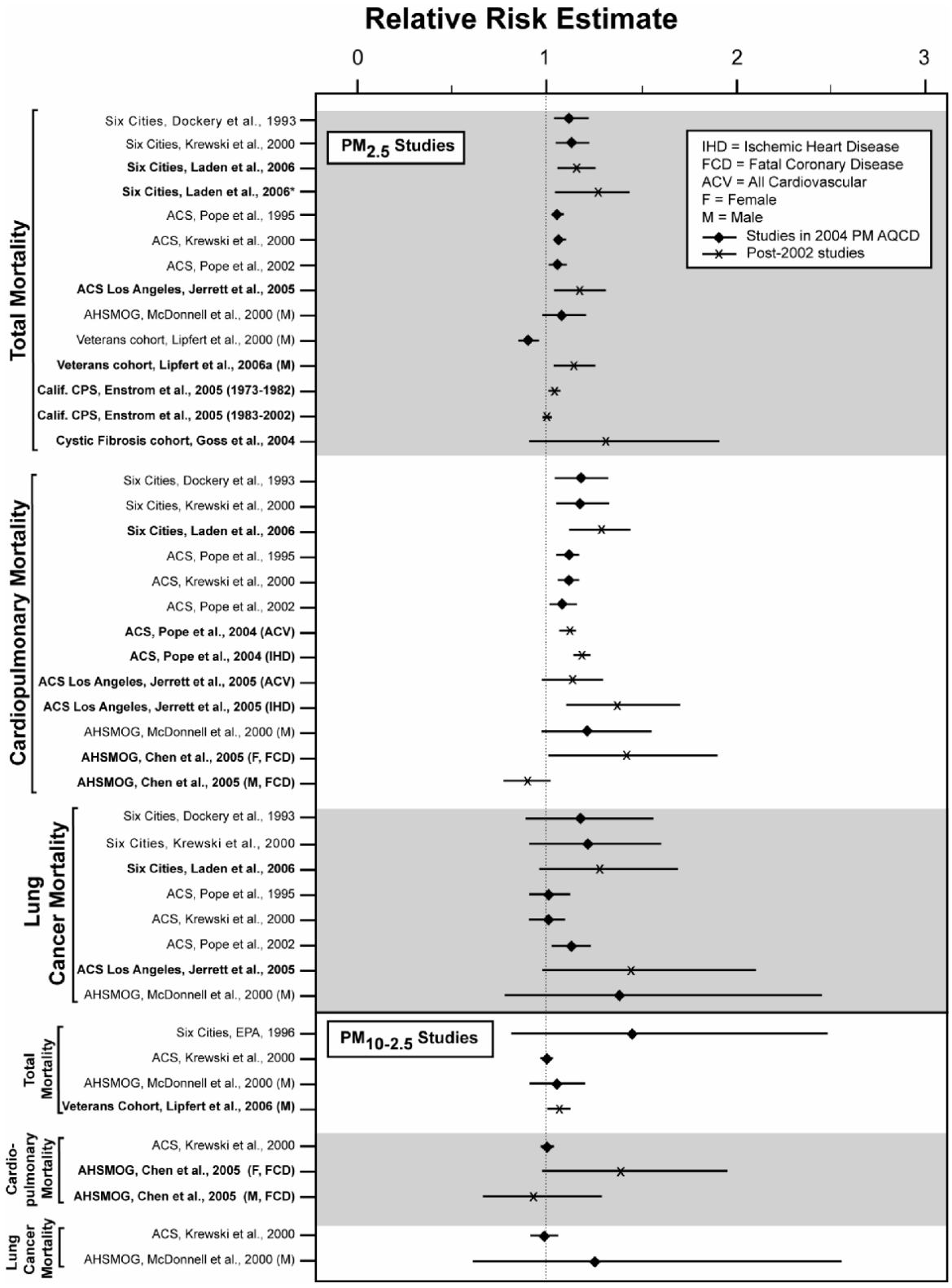

Figure 1. Relative risk estimates (and 95% confidence intervals) for associations between long-term exposure to PM (per 10 $PM_{10-2.5}$) and mortality. *Note: The second result presented for Laden et al. (2006) is for the intervention study results.

Harvard Six Cities: A new study has used updated air pollution and mortality data; an additional 1,368 deaths occurred during the follow-up period (1990-1998) and 1,364 deaths occurred in the original study period (1974-1989). Statistically significant associations are reported between long-term exposure to $PM_{2.5}$ and mortality for data for the two periods (RR = 1.16, 95% CI 1.07-1.26 per 10 $\mu g/m^3$ $PM_{2.5}$). Of note, however, a statistically significant *reduction* in mortality risk is reported with *reduced* long-term fine particle concentrations (RR = 0.73, 95% CI 0.57-0.95 per 10 $\mu g/m^3$ $PM_{2.5}$). This is equivalent to an RR of 1.27 for reduced mortality risk, suggesting a larger effect than in the cross-sectional analysis. This reduced mortality risk was observed for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths. Mean $PM_{2.5}$ concentrations from the follow-up period range from 10.2 to 22.0 $\mu g/m^3$ in the six cities. The means across the six cities were 18 $\mu g/m^3$ in the first period and 14.8 $\mu g/m^3$ in the follow-up period. The $PM_{2.5}$ concentrations for recent years were estimated from visibility data which introduces uncertainty in interpreting the results of this study (Laden et al., 2006). Coupled with the results of the original analysis (Dockery et al., 1993), this study strongly suggests that reduction in fine PM pollution has yielded positive health benefits.

ACS Extended Analyses: One new analysis further evaluated associations between long-term $PM_{2.5}$ and sulfate exposures in 50 U.S. cities and mortality, adding new information about deaths from specific cardiovascular and respiratory causes. Significant associations were reported with deaths from specific cardiovascular diseases, particularly ischemic heart disease, and a group of cardiac conditions including dysrhythmia, heart failure and cardiac arrest (RR for cardiovascular mortality = 1.12, 95% CI 1.08-1.15 per 10 $\mu g/m^3$ $PM_{2.5}$); no associations were reported with respiratory mortality. The mean $PM_{2.5}$ concentration (1979-1983 and 1999-2000) was 17.1 $\mu g/m^3$ (Pope et al., 2004).

ACS, Los Angeles: Much of the exposure gradient in the national-scale ACS studies was due to city-to-city differences in regional air pollution. A new analysis using ACS data focused on neighborhood-to-neighborhood differences in urban air pollutants, on data from 23 $PM_{2.5}$ monitoring stations in the Los Angeles area and using interpolation methods to assign exposure levels to individuals (Jerrett et al., 2005). This resulted in both improved exposure assessment and an increased focus on local sources of fine particle pollution. Significant associations between $PM_{2.5}$ and mortality from all causes and cardiopulmonary diseases were reported with the magnitude of the relative risks being greater than those reported in previous assessments (after adjustment for potential confounders including 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 heart disease = 1.38, 95% CI 1.11-1.72 per 10 $\mu g/m^3$ $PM_{2.5}$). The authors suggest that reducing exposure error can result in stronger associations between $PM_{2.5}$ and mortality than generally observed in broader studies having less exposure detail.

California cancer prevention study: In a cohort of elderly people in 11 California counties (mean age 73 years in 1983), an association was reported for long-term $PM_{2.5}$ exposure with all-cause deaths in 1973-1982 (RR = 1.04, 95% CI 1.01-1.07 per 10 $\mu g/m^3$ $PM_{2.5}$). No significant associations were reported with deaths in later time periods

(1983-2002) (RR = 1.00, 95% CI 0.98-1.02 per 10 μg/m^3 $PM_{2.5}$) when $PM_{2.5}$ levels had decreased in the most polluted counties. The $PM_{2.5}$ data are from the EPA's Inhalation Particle Network, and represent a subset of data used in the 50-city ACS study (Pope et al., 1995). The use of average values for California counties as exposure surrogates likely leads to significant exposure error as many California counties are large and quite topographically variable. The mean $PM_{2.5}$ concentration (1979-1983) was 23.4 μg/m^3 (Enstrom, 2005).

AHSMOG: In this analysis for the Seventh-Day Adventist cohort in California, positive, statistically significant association with coronary heart disease mortality was reported for 92 deaths among females (RR = 1.42, 95% CI 1.06-1.90 per 10 μg/m^3 $PM_{2.5}$), but not for 53 deaths among males (RR = 0.90, 95% CI 0.76-1.05 per 10 μg/m^3 $PM_{2.5}$). Associations were strongest in the subset of postmenopausal women (80 deaths; RR=1.49, 95% CI 1.17, 1.89 per 10 μg/m^3 $PM_{2.5}$). The authors speculated that females may be more sensitive to air pollution-related effects based on differences between males and females in dosimetry and exposure, along with the generally lower blood cell levels in females. The mean $PM_{2.5}$ concentration averaged over 1973-1998 was 29.0 μg/m^3 (Chen et al., 2005).

Veterans cohort: A recent analysis of the Veterans cohort data focused on exposure to traffic-related air pollution (traffic density based on traffic flow rate data and road segment length) reported a stronger relationship between mortality with long-term exposure to traffic than with $PM_{2.5}$ mass. A significant association was reported between total mortality and $PM_{2.5}$ in single-pollutant models (RR = 1.12, 95% CI 1.04-1.20 per 10 μg/m^3 $PM_{2.5}$); the author observes that this risk estimate is larger than results reported in a previous study (Lipfert et al., 2000). In multi-pollutant models including traffic density, the association with $PM_{2.5}$ was reduced and lost statistical significance. Traffic emissions contribute to $PM_{2.5}$ so it would be expected that the two would be highly correlated, and thus these multi-pollutant model results should viewed with caution. The mean $PM_{2.5}$ level was 14.6 μg/m^3 using data from 1997-2001 (Lipfert et al., 2006a).

In a companion study, Lipfert et al. (2006b, in press) used data from EPA's fine particle speciation network, and reported findings for $PM_{2.5}$ were similar to those reported in the Lipfert et al., 2006a. A positive association was also reported for mortality with sulfates using the more recent data, but was not statistically significant. Using 2002 data from the fine particle speciation network, significant associations were found between mortality and nitrates, EC, Ni and V, as well as traffic density and peak ozone concentrations. In multi-pollutant models, associations with traffic density remained significant, as did nitrates, Ni and V in some models. The mean $PM_{2.5}$ level was 13.2 μg/m^3 using data from 2002 (Lipfert et al., 2006b, in press).

U.S. Cystic Fibrosis cohort: A positive, but not statistically significant, association was reported in this cohort (RR = 1.32, 95% CI 0.91-1.93 per 10 μg/m^3 $PM_{2.5}$) in a study that primarily focused on evidence of exacerbation of respiratory symptoms (as discussed in the following section). Only 200 deaths had occurred in the cohort of over 11,000 people

(average age in cohort was 18.4 years) thus the power of the study to detect associations is limited. The mean $PM_{2.5}$ concentration was 13.7 $\mu g/m^3$ (Goss et al., 2004).

Infant mortality: A new study in California has reported statistically significant associations between mortality from respiratory causes with exposure to $PM_{2.5}$, using $PM_{2.5}$ levels averaged over the time between the infant's birth and death (RR 1.07, 95% CI 0.93-1.24 per 10 $\mu g/m^3$ $PM_{2.5}$ for overall mortality and 2.13, 95% CI 1.12-4.05 for respiratory mortality). The mean $PM_{2.5}$ exposure concentrations ranged from 17.3 to 19.8 $\mu g/m^3$ (Woodruff et al., 2006).

Thoracic coarse particles:

In the original analyses of the Six Cities and ACS cohort studies, no associations were found between long-term exposure to $PM_{10-2.5}$ and mortality; the extended and follow-up analyses that are discussed above for fine particles did not evaluate potential associations with $PM_{10-2.5}$. Two recent reports from the AHSMOG and Veterans study cohorts have provided some limited suggestive evidence for associations between long-term exposure to $PM_{10-2.5}$ and mortality, as summarized below.

AHSMOG: As was found with fine particles, a positive association with coronary heart disease mortality was reported for females (RR = 1.38, 95% CI 0.97-1.95 per 10 $\mu g/m^3$ $PM_{2.5}$), but not for males (RR = 0.92, 95% CI 0.66-1.29 per 10 $\mu g/m^3$ $PM_{2.5}$); associations were strongest in the subset of postmenopausal women (80 deaths). The mean $PM_{10-2.5}$ concentration over 1973-1998 was 25.4 $\mu g/m^3$ (Chen et al., 2005).

Veterans cohort: A significant association was reported between long-term exposure to $PM_{10-2.5}$ and total mortality in a single-pollutant model (RR = 1.07, 95% CI 1.01-1.12 per 10 $\mu g/m^3$ $PM_{2.5}$), but the association became negative and not statistically significant in a model that included traffic density. As it would be expected that traffic would contribute to thoracic coarse particle concentrations, it is difficult to interpret the results of these multi-pollutant analyses. The average $PM_{10-2.5}$ concentration over 1989-1996 was 16.0 $\mu g/m^3$ (Lipfert et al., 2006).

Conclusions

As shown in Figure 1, the pattern of results from the new studies for both fine and thoracic coarse particles is generally similar to those available previously. Overall, the recent evidence supports associations between long-term $PM_{2.5}$ exposure and mortality, with key new evidence from the Six Cities cohort study showing a relatively large risk estimate for reduced mortality risk with decreases in $PM_{2.5}$ (Laden et al., 2006). The results of new analyses from the Six Cities cohort and the ACS study in Los Angeles suggest that previous and current studies may underestimate the magnitude of the association (Jerrett et al., 2005). In addition, exposure to $PM_{2.5}$ was associated with increased respiratory mortality in infants in a new study in California (Woodruff et al., 2006). New evidence from the Veterans cohort study report associations with $PM_{2.5}$ in single-pollutant models, though the authors report that traffic density is a stronger predictor of mortality than $PM_{2.5}$ (Lipfert et al., 2006a). There is also suggestive

evidence for an association with mortality in the analysis of the Cystic Fibrosis cohort data. The new study using Cancer Prevention Study cohort data in Los Angeles, however, indicates no association with $PM_{2.5}$ except when using the first time period in the study (Enstrom et al., 2005).

In the 2004 PM AQCD, results from the ACS and Six Cities study analyses indicated that thoracic coarse particles were not associated with mortality. The new findings from AHSMOG and Veterans cohort studies provide some suggestive evidence of associations between long-term exposure to $PM_{10-2.5}$ and mortality in areas with mean concentrations from 16 to 25 $\mu g/m^3$. The 2004 PM AQCD placed greatest weight on the ACS and Six Cities study findings; further evidence will need to be evaluated in the next review of the PM NAAQS on whether long-term exposure to thoracic coarse particles is associated with mortality.

2.1.2 Morbidity

The 2004 PM AQCD (Section 8.3.3.2) included results from two U.S. and Canadian children's cohort studies that had been available in the 1996 PM AQCD—the Harvard Six Cities and Harvard 24-cities studies—that reported significant associations between respiratory symptoms and decreased lung function with long-term exposure to fine particles and acid aerosols. More recent studies were available, using data from the Children's Health Study in southern California; these studies also indicated that long-term exposure to fine particles was associated with decreased lung function growth[2] in children. The results from analyses of data from the AHSMOG showed suggestive, but inconsistent findings between long-term exposure to PM and respiratory morbidity in adults. Overall, the 2004 PM AQCD concluded that long-term exposure to PM, especially fine particles, was associated with respiratory morbidity (2004 PM AQCD, p. 8-343). Limited and inconsistent evidence was available on associations between long-term exposure to $PM_{10-2.5}$ and respiratory morbidity.

Among the recently published studies are longer follow-up analyses of respiratory morbidity using data from the Children's Health Study, as well as a study based on data from the U.S. Cystic Fibrosis Cohort. The quantitative results of these studies are included in Table 1, and further details presented in Appendix A, Table A1.

Fine particles:

> *Children's Health Study*: Significant associations are reported between long-term exposure to fine particles, as well as acid vapor and NO_2, and reduced lung function growth (Gauderman et al., 2004) and increased risk of bronchitic symptoms, prevalence of chronic cough, or bronchitis (McConnell et al., 2003). These results expand upon the findings available in the 2004 PM AQCD, including assessment of lung function measurements in children over an 8-year follow-up period (Gauderman et al., 2004). In addition, McConnell et al. (2003) measured respiratory symptom prevalence over a

[2] In these studies, lung function measurements were repeated several years apart. Increases in lung function measures over this time period are referred to as lung function growth by the authors, with "decreased lung function growth" indicating smaller increases in lung function measurements for the children with higher air pollution exposure.

4-year period, and reported larger effect estimates with changes in $PM_{2.5}$ concentration over time within the communities than with changes in $PM_{2.5}$ between communities. The mean $PM_{2.5}$ concentration for the 12 California communities in 1994-2000 was 13.8 $\mu g/m^3$ (McConnell et al., 2003; mean concentrations range from 5 to 28 $\mu g/m^3$ in Gauderman et al., 2004). One additional analysis, based on monthly prevalence of respiratory symptoms, reports no significant associations with $PM_{2.5}$ (Millstein et al., 2004).

U.S. Cystic Fibrosis cohort: The risk of experiencing pulmonary exacerbations was significantly increased with long-term exposure to $PM_{2.5}$ (Goss et al., 2004). The mean $PM_{2.5}$ concentration in 2000 was 13.7 $\mu g/m^3$.

Cardiovascular clinical studies: One new study has provided insight into the potential effect of long-term exposure to $PM_{2.5}$ on the development of cardiovascular disease; no such studies were available in the 2004 PM AQCD. Using data from two clinical trials conducted in the Los Angeles area, the authors reported a significant association between long-term exposure to $PM_{2.5}$ and carotid intima-media thickness, a measure of atherosclerosis development. The mean $PM_{2.5}$ concentration was 20.6 $\mu g/m^3$ (Kunzli et al., 2005).

Thoracic coarse particles:

Two reports from the Children's Health Study included results for *thoracic coarse particles*. A significant association was observed between monthly prevalence of wheeze and $PM_{10-2.5}$ during March-August in one new study, but no association was seen in other parts of the year (Millstein et al., 2004). No significant associations were reported between long-term exposure to $PM_{10-2.5}$ and incidence of bronchitic symptoms in another report in which the mean $PM_{10-2.5}$ concentration was 17.0 $\mu g/m^3$ (McConnell et al., 2003).

The recent findings from the southern California Children's Health Study add support to previous conclusions that long-term fine particle exposure is associated with increased incidence of respiratory symptoms and decreased lung function growth in children. The new evidence from the Cystic Fibrosis Cohort provides additional evidence for associations with pulmonary exacerbations, particularly in a cohort of likely more susceptible individuals. These new studies also report associations with fine particle concentrations that are somewhat lower than those from studies available in the 2004 PM AQCD. These recent findings, however, do not show associations between respiratory morbidity and long-term exposure to $PM_{10-2.5}$; in contrast, one earlier analysis from the Children's Health Study in California had suggested such associations.

No studies available in the 2004 PM AQCD had assessed associations between long-term PM exposure and cardiovascular morbidity. A new analysis shows an association between long-term $PM_{2.5}$ exposure and a measure of atherosclerosis development (Kunzli et al., 2005).

2.2 Epidemiologic Short-Term Exposure Study Results

The 2004 PM AQCD included the results of many new epidemiologic studies reporting associations between short-term exposure to PM and a range of health outcomes. The larger body of evidence from studies of PM_{10} and other PM indicators provided strong evidence for associations between short-term PM exposure and both mortality and morbidity (2004 PM AQCD, p. 8-337).

The 2004 PM AQCD concluded that there was strong epidemiological evidence linking short-term exposures to $PM_{2.5}$ with cardiovascular and respiratory mortality and morbidity. Positive, often statistically significant associations were observed between $PM_{2.5}$ and these various health endpoints (2004 PM AQCD, p. 9-46). The epidemiological evidence was found to support likely causal associations between $PM_{2.5}$ and both mortality and morbidity from cardiovascular and respiratory diseases, based on an assessment of strength, robustness, and consistency in results (2004 PM AQCD, p. 9-48).

Fewer studies were available to assess associations between $PM_{10-2.5}$ and health outcomes. The magnitude of the effect estimates for associations between $PM_{10-2.5}$ and mortality and morbidity effects (especially respiratory morbidity) was found to be similar to that for $PM_{2.5}$, but the strength of the evidence for $PM_{10-2.5}$ effects was reduced due to lower precision (AQCD, p. 9-46). Despite the reduced strength, the associations were found to be generally robust to alternative modeling strategies or consideration of potential confounding by co-pollutants. The collective evidence was found to be suggestive of associations for morbidity with short-term changes in $PM_{10-2.5}$ (2004 PM AQCD, p. 9-48).

Sections 2.2.1 and 2.2.2 highlight results from recent time-series epidemiologic studies. Tables A2 through A12 (Appendix A) summarize results of recent epidemiologic studies that evaluated relationships between health effects and short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$. The discussions below emphasize results of studies conducted in the U.S. and Canada; however, some results are also presented from additional international studies or studies using indicators, such as PM_{10}, that assess key issues or questions highlighted in the 2004 PM AQCD.

The 2004 PM AQCD included a particular focus on results of multicity studies due to their evaluation of a wide range of PM exposures and large numbers of observations, which lead to generally more precise effects estimates than most smaller scale independent studies of single cities. The multicity studies also allowed investigation of homogeneity or heterogeneity of PM-health relationships, evaluation of confounding by co-pollutants across communities with different air pollution mixtures, and assessment of potential effect modifiers. Numerous multicity analyses have been published in recent years. Most of the recent multi-city studies report statistically significant associations between short-term exposure to PM_{10} and mortality or morbidity and these study results are briefly summarized in Section 2.2.3 as being particularly relevant to help address key methodological questions. In addition, 3 new multi-city studies have evaluated associations with $PM_{2.5}$, one of which included $PM_{10-2.5}$, and these studies are highlighted in the following sections.

2.2.1 Mortality

Results from multi- and single-city epidemiologic studies on mortality were presented in Figure 9-4 of the 2004 PM AQCD. Associations were mostly positive and of similar magnitude for both $PM_{2.5}$ and $PM_{10-2.5}$. A number of the associations between mortality and short-term $PM_{2.5}$ exposure were statistically significant, while few associations with $PM_{10-2.5}$ reached statistical significance, possibly due to increased measurement error in estimating $PM_{10-2.5}$ exposure (2004 PM AQCD, p. 9-28). Several recent studies have reported associations between mortality and short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$. These findings are included with those available from the 2004 PM AQCD in Figure 2, where it can be seen that the new study results are generally quite similar to those previously available. Note that Figure 2 presents results from single-pollutant models for purposes of comparing results across studies that included different mixes of copollutants, as done in the 2004 PM AQCD.

2.2.1.1 Associations Between Acute Exposure to Fine Particles and Mortality

A number of recent studies have evaluated associations between fine particles and mortality, including two multicity studies (Appendix A; Table A2). Evidence for associations between short-term exposure to $PM_{2.5}$ and all-cause, cardiovascular, and respiratory mortality comes from the multi-site study by Ostro et al. (2006) conducted in nine California counties that had mean $PM_{2.5}$ concentrations ranging from 14 to 29 $\mu g/m^3$. Significant associations were reported in single-pollutant models for all-cause, cardiovascular and respiratory mortality for all ages, as well as a significant association with all-cause mortality for those aged >65 years. The authors observed that in multipollutant models, the $PM_{2.5}$ effect estimate was attenuated when highly correlated pollutants (NO_2 and CO) were added to the model, but was not affected by the inclusion of O_3. However, in those aged >65 yr (who generally experienced stronger associations with mortality), adjusting for gaseous pollutants did not affect the $PM_{2.5}$ coefficient.

Burnett et al. (2004) evaluated the relationship between NO_2 and mortality in 12 Canadian cities during the period 1981 to 1999. While the focus of this analysis was on associations with NO_2, the analysis included other pollutants as well. $PM_{2.5}$ data were available only on 12% of days with mortality data, compared to the other gaseous pollutants that had >90% data available, and for most of the study time period, $PM_{2.5}$ was measured every 6th day. In analyses using these data, the association between $PM_{2.5}$ and all-cause mortality was marginally significant (as shown in Figure 2). In two-pollutant models with NO_2, the effect estimate for $PM_{2.5}$ became negative (not significant), while the estimate for NO_2 remained robust. NO_2 concentrations were found to be correlated with $PM_{2.5}$ concentrations ($r = 0.48$).

Burnett and colleagues (2004) also report results from a separate analysis using more recent data with daily $PM_{2.5}$ measurements (1998-2000). The authors state that a positive association was found between mortality and $PM_{2.5}$ in this additional analysis (presumably significant, but confidence intervals were not provided). In this case, the NO_2 association was reduced considerably after adjustment for $PM_{2.5}$, whereas the $PM_{2.5}$ association remained fairly robust with NO_2 adjustment. These findings emphasize the difficulty of working with data collected every 6th day. The mean $PM_{2.5}$ concentration for all 12 cities was 12.8 $\mu g/m^3$ with city-specific means ranging from 8.1 $\mu g/m^3$ in St. John to 16.7 $\mu g/m^3$ in Windsor.

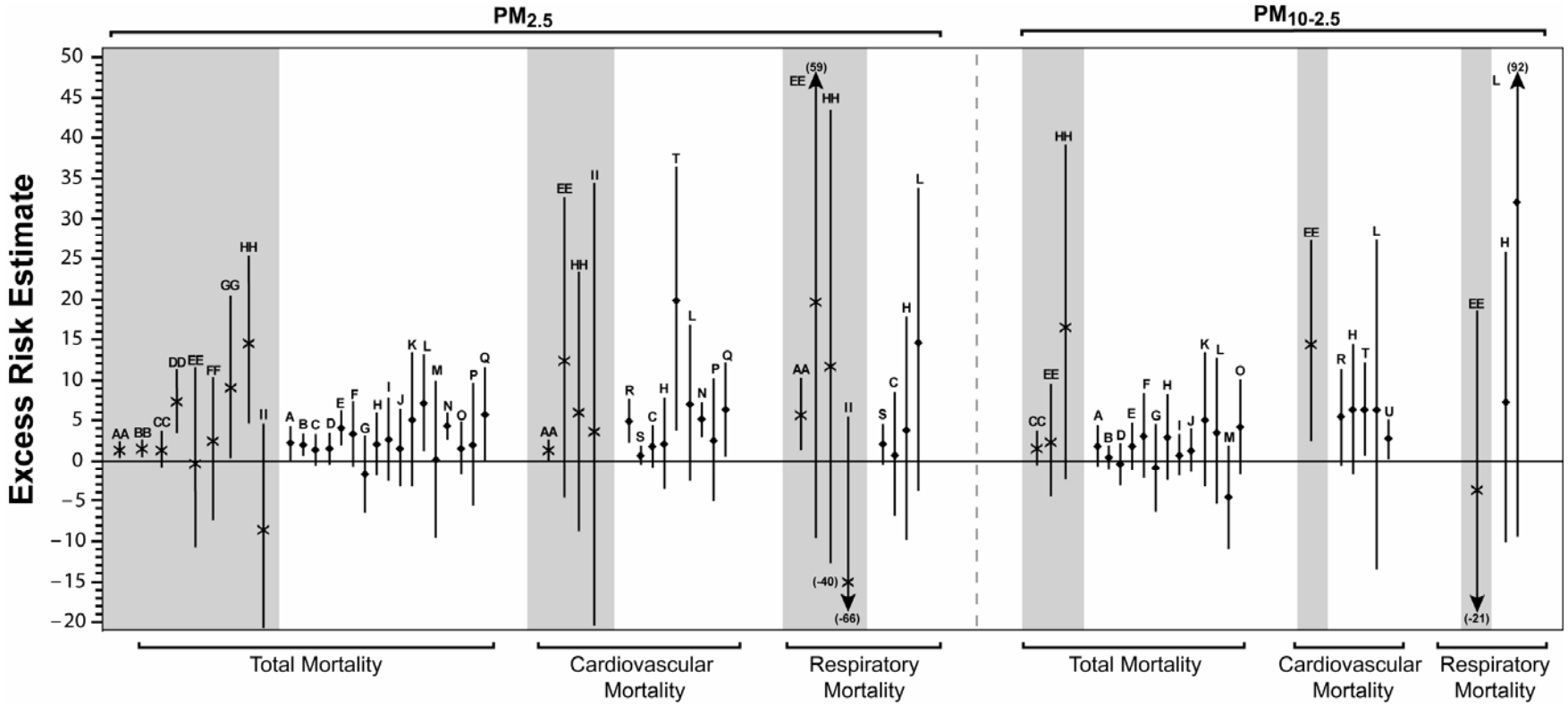

Figure 2. Excess risk estimates for total nonaccidental, cardiovascular, and respiratory mortality in single-pollutant models for U.S. and Canadian studies, including aggregate results from multicity studies (denoted in bold print below). PM increment used for standardization was 25 μg/m^3 for both $PM_{2.5}$ and $PM_{10-2.5}$. Results presented in the 2004 PM AQCD are marked as ♦ in the figure (studies A through T). Results from recent studies are shaded in grey and marked as × in the figure (studies AA through HH).

A. **Burnett and Goldberg (2003), 8 Canadian cities**
B. Klemm and Mason (2003), 6 U.S. cities
C. Moolgavkar (2003), Los Angeles
D. Klemm and Mason (2003), St. Louis
E. Klemm and Mason (2003), Boston
F. Klemm and Mason (2003), Kingston-Harriman
G. Klemm and Mason (2003), Portage
H. Ito (2003), Detroit
I. Chock et al. (2003) Pittsburgh (age <75 yr)
J. Chock et al. (2003) Pittsburgh (age 75+ yr)
K. Klemm and Mason (2000), Atlanta
L. Fairley (2003), Santa Clara County
M. Klemm and Mason (2003), Topeka
N. Tsai et al. (2000), Newark
O. Klemm and Mason (2003), Steubenville
P. Tsai et al. (2000), Elizabeth
Q. Tsai et al (2000), Camden
R. Lipfert et al. (2000), Philadelphia
S. Ostro et al. (1995), Southern California
T. Mar et al. (2003), Phoenix
U. Ostro et al. (2003), Coachella Valley
AA. Ostro et al. (2006), 9 counties in CA
BB. Ostro et al. (2006), 9 counties in CA (age >65 yr)
CC. Burnett et al. (2004), 12 Canadian cities
DD. Ito et al. (in press), Washington, DC
EE. Villeneuve et al. (2003), Vancouver, Canada
FF. Slaughter et al. (2005), Spokane
GG. Goldberg et al. (2006), Montreal, Canada (age 65+ yr)
HH. Klemm et al. (2004), Atlanta (age 65+ yr)
II. Klemm et al. (2004), Atlanta (age <65 yr)

Several single-city studies have also been published. Evidence for associations between fine particles and mortality was seen in studies in Montreal (Goldberg et al., 2006) and Atlanta (Klemm et al., 2004), as well as in studies that focused on source apportionment in Phoenix (Mar et al., 2006) and Washington, DC (Ito et al., 2006). No associations were reported in studies in Vancouver (Villeneuve et al., 2003) and Spokane (Slaughter et al., 2005); these studies reported low $PM_{2.5}$ concentrations. Finally, one new analysis reports no evidence for associations between short-term exposure and death due to sudden infant death syndrome (Dales et al., 2004). The mean $PM_{2.5}$ concentrations in locations where statistically significant associations were reported ranged from about 12 to greater than 20 $\mu g/m^3$.

In Figure 2, the results of the recent time-series studies are presented alongside the findings available in the 2004 PM AQCD. In this figure, it can be seen that the results of the larger multicity studies are quite consistent with those in earlier studies. The studies have been presented in order of decreasing statistical power (based on number of days and number of health events per day) from left to right for each group of studies. Some of the recent studies have fairly low statistical power which is reflected in the large confidence intervals and more variable effect estimate sizes shown in Figure 2. These results, while imprecise, are also generally consistent with earlier study results. Collectively, evidence regarding the $PM_{2.5}$-mortality association from the most recent literature appears to be consistent with that available from the 2004 PM AQCD.

2.2.1.2 Associations Between Acute Exposure to Thoracic Coarse Particles and Mortality

Several new studies examined the association between $PM_{10-2.5}$ and mortality in the U.S. and Canada (Appendix A; Table A3). The multicity study by Burnett et al. (2004), aimed primarily at NO_2, also examined the association between $PM_{10-2.5}$ and all-cause, nonaccidental mortality for lag day 1 (i.e., previous day) using data from 12 Canadian cities. The association with $PM_{10-2.5}$ was positive but not significant; there was a significant association with PM_{10} that lost significance with adjustment for NO_2. However, particle data were available only on 12% of days in this study, as discussed above. The mean $PM_{10-2.5}$ concentration in this study was 11.4 $\mu g/m^3$ (12 city means range from 5.5 to 15.9 $\mu g/m^3$).

Figure 2 includes results from the recent single-pollutant studies and those available in the 2004 PM AQCD. Looking across all studies, it can be seen that associations between $PM_{10-2.5}$ and total and cardiovascular mortality are generally positive and a number are statistically significant, particularly for cardiovascular mortality. As discussed in the 2004 PM AQCD, some studies indicated stronger associations between acute $PM_{10-2.5}$ exposure and cardiovascular mortality than for all-cause mortality. One recent study in Vancouver, Canada, also observed a statistically significant relationship with cardiovascular mortality on lag day 0 (i.e., same day) but not on lag day 1 or 2 or the 3-day average lag periods (i.e., 24-hour average concentrations measured 1-, 2- or 3-days prior) (Villeneuve et al., 2003). No associations were found for all-cause, respiratory, or cancer mortality in this study. The mean $PM_{10-2.5}$ concentration in this study was 6.1 $\mu g/m^3$ (range 0 to 72 $\mu g/m^3$).

Other recent studies did not report statistically significant associations between $PM_{10-2.5}$ and total mortality. Slaughter et al. (2005) did not find a significant relationship for $PM_{10-2.5}$ with all-cause, nonaccidental mortality in Spokane, WA, which likely had higher $PM_{10-2.5}$ concentrations than Vancouver, Canada (data not shown). Neither Slaughter et al. (2005) nor Burnett et al. (2004) investigated the relationship with cardiovascular mortality. A recent PM_{10} study in El Paso (Staniswalis et al., 2005) supports the hypothesis that wind-blown dust coming from non-urban areas during high wind speeds (assumed largely coarse-fraction particles) is less toxic than particles generated within the urban area. Finally, Klemm and colleagues (2004) reported a positive, but not statistically significant association between $PM_{10-2.5}$ and mortality in Atlanta. The mean $PM_{10-2.5}$ concentration in this study was 9.7 $\mu g/m^3$ (range 1.7 to 25.2 $\mu g/m^3$).

2.2.2 Morbidity

Results from epidemiologic studies on hospital admissions were presented in Figure 9-5 of the PM AQCD. Associations were all positive and of similar magnitude for both $PM_{2.5}$ and $PM_{10-2.5}$. Many of the associations with short-term $PM_{2.5}$ exposure were statistically significant, especially for respiratory diseases. Likely due to increased measurement error, some, but not all, of the associations with $PM_{10-2.5}$ reached statistical significance (2004 PM AQCD, p. 9-29). Several recent studies have reported associations between short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and hospitalization or emergency department visits for cardiovascular and respiratory diseases. These findings are included with those available from the 2004 PM AQCD in Figure 3.

2.2.2.1 Associations Between Acute Exposure to Fine Particles and Morbidity

These new studies substantially expand the evidence for associations between $PM_{2.5}$ and effects on the cardiovascular system (Appendix A; Tables A4, A6 and A8). These include a powerful new multi-city study by Dominici et al. (2006) that used data from the Medicare National Claims History Files for 11.5 million people living in 204 urban counties in the U.S.; the average $PM_{2.5}$ concentration for 1999-2000 was 13.4 $\mu g/m^3$. There was only limited consideration of other pollutants in this analysis. Hospital admission rates for cause-specific cardiovascular and respiratory diseases were significantly associated with short-term $PM_{2.5}$ exposure in individuals aged >65 yr. The largest association was reported with heart failure. Significant associations were also found between short-term $PM_{2.5}$ exposure and hospital admissions for cerebrovascular disease, and positive though not statistically significant associations were seen with peripheral vascular disease, ischemic heart disease, and cardiac rhythm. When evaluated on a region-specific basis, positive associations with cardiovascular disease hospitalization were seen in the Midwest, Northeast, and Southern regions; the authors suggest that differences in the sources and composition of fine particles contributes to the geographic differences seen in effect estimates.

One recent study reports significant associations between short-term exposure to $PM_{2.5}$ and emergency department visits for all cardiovascular diseases, congestive heart failure and peripheral vascular and cerebrovascular disease in Atlanta (Metzger et al., 2004). Another study reports no evidence of associations with cardiovascular visits in Spokane, where the $PM_{2.5}$ concentrations were low (authors report that 90% of concentrations ranged between 4.2 and 20.2 $\mu g/m^3$) (Slaughter et al., 2005).

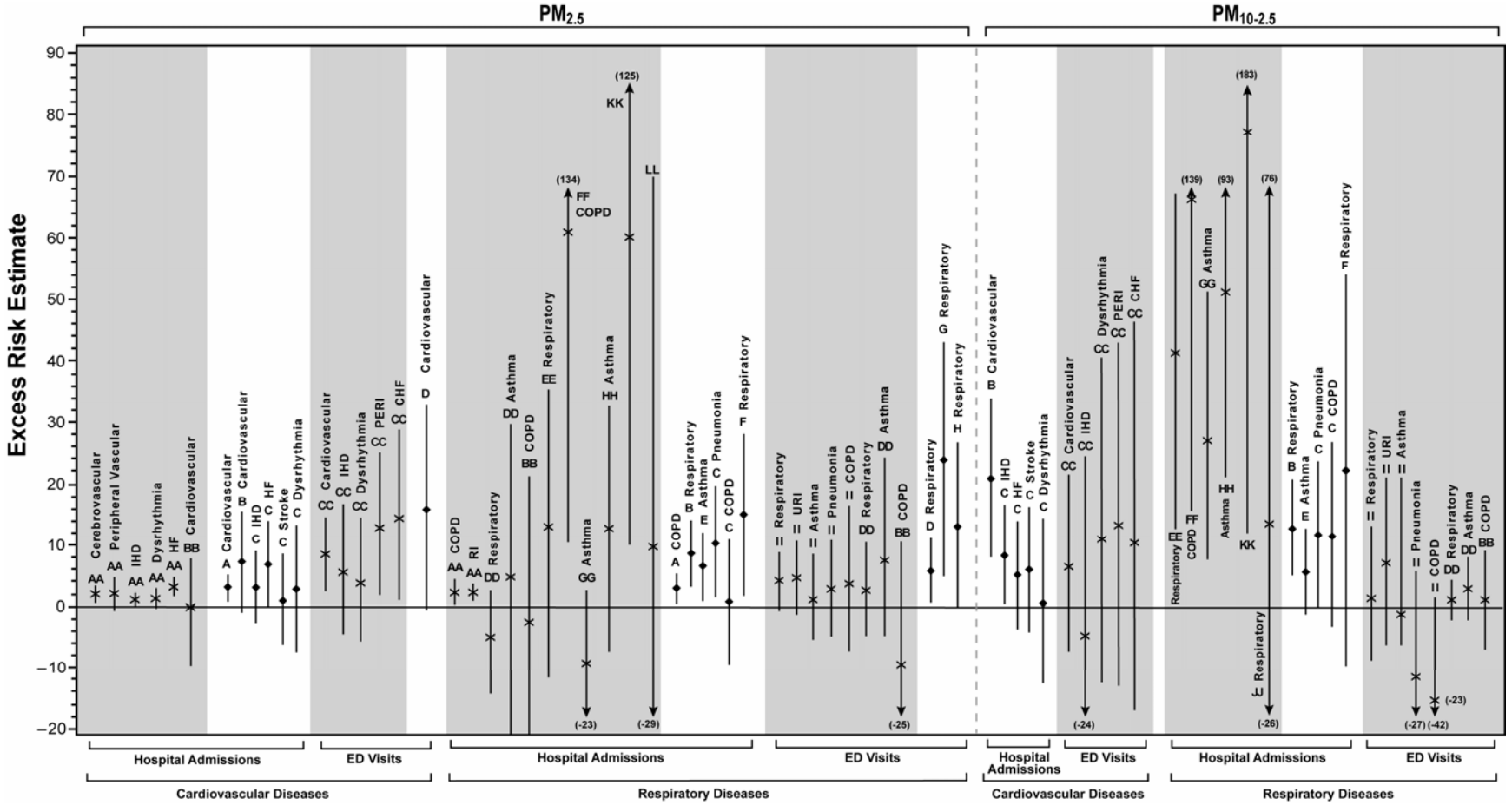

Figure 3. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models for U.S. and Canadian studies, including aggregate results from a multicity study (denoted in bold print below). PM increment used for standardization was 25 μg/m^3 for both $PM_{2.5}$ and $PM_{10-2.5}$. Results presented in the 2004 PM AQCD are marked as ♦, in the figure (studies A through H). Results from recent studies are shaded in grey and marked as × in the figure (studies AA through JJ). (CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HF = heart failure; IHD = ischemic heart disease; PERI = peripheral vascular and cerebrovascular disease; RI = respiratory infection; URI = upper respiratory infection).

A. Moolgavkar (2003), Los Angeles
B. Burnett et al. (1997), Toronto
C. Ito (2003), Detroit
D. Stieb et al. (2000), St. John
E. Sheppard (2003), Seattle
F. Thurston et al. (1994), Toronto
G. Delfino et al. (1997), Montreal
H. Delfino et al. (1998), Montreal

AA. Dominici et al. (2006), 204 U.S. counties (age >65 yr)
BB. Slaughter et al. (2005), Spokane (age 15+ yr)
CC. Metzger et al. (2004), Atlanta
DD. Slaughter et al. (2005), Atlanta
EE. Chen et al. (2005), Vancouver, Canada (age 65+ yr)
FF. Chen et al. (2004), Vancouver, Canada (age 65+ yr)

GG. Lin et al. (2002), Toronto, Canada (age 6-12 yr, boys)
HH. Lin et al. (2002), Toronto, Canada (age 6-12 yr, girls)
II. Peel et al. (2005), Atlanta
JJ. Yang et al. (2004), Vancouver, Canada (age >3 yr)
KK. Lin et al. (2005), Toronto, Canada (age <16 yr, boys)
LL. Lin et al. (2005), Toronto, Canada (age <16 yr, boys)

Numerous new studies have reported associations between ambient $PM_{2.5}$ and subtle cardiovascular effects such as changes in cardiac rhythm or heart rate variability (Appendix A; Table A8). In the 2004 PM AQCD, the data base was characterized as having some studies with conflicting results and a note of caution was raised in regard to drawing conclusions relating $PM_{2.5}$ and heart rate variability and other measures of cardiovascular pathophysiological alterations. Of about 10 new studies evaluating associations between acute $PM_{2.5}$ exposure and heart rate variability, most reported statistically significant associations with $PM_{2.5}$. . Two new studies showed associations for $PM_{2.5}$ with ST segment depressions, an indicator of myocardial ischemia (Gold et al., 2005). One new study examined $PM_{2.5}$ effects on bronchial artery reactivity (a marker for cardiovascular disease risk) and reported a significant association (O'Neill et al., 2005). Noting that many of these studies were conducted over shorter time periods, nevertheless, it is reported that mean or median $PM_{2.5}$ concentrations in a number of studies were in the range of 10-11 $\mu g/m^3$, with maximum levels ranging from about 40 to 60 $\mu g/m^3$.

For respiratory effects, Dominici et al. (2006) report significant associations between $PM_{2.5}$ and hospitalization for chronic obstructive pulmonary disease (COPD) and respiratory infection in the study of 204 U.S. counties mentioned above (Appendix A; Table A4). Less regional variation was seen for respiratory hospitalization than for cardiovascular hospital admissions; in contrast with the results for cardiovascular diseases, effect estimates for both COPD and respiratory infections admissions were larger for the western U.S. than the eastern U.S.

There are also several single-city studies that were conducted in Canada that show no associations between hospitalization and acute exposure to $PM_{2.5}$ (Lin et al., 2002; Lin et al., 2005; Yang et al., 2004; Chen et al., 2004; Chen et al., 2005). All were studies of hospitalization for respiratory diseases, though studies differed in age group and respiratory endpoint, and the mean $PM_{2.5}$ concentrations in the studies ranged from 7.7 to 18 $\mu g/m^3$. Another recent study reports positive associations with respiratory emergency department visits, although none are statistically significant (Peel et al., 2005) (mean concentration of 19.2 $\mu g/m^3$). Finally, there was no evidence of associations with respiratory visits in Spokane, where the $PM_{2.5}$ concentrations were low (90^{th} percentile was 20.2 $\mu g/m^3$) (Slaughter et al., 2005).

There are numerous new studies that examined various respiratory outcomes in relation to $PM_{2.5}$ exposure (Appendix A; Table A10), including one new multicity study that reported a significant association between respiratory symptoms and short-term $PM_{2.5}$ exposure (Gent et al., 2003) (mean concentration of 13.1 $\mu g/m^3$); however, the effect estimate is reduced and not statistically significant with adjustment for ozone. Associations have also been reported between acute $PM_{2.5}$ exposure and a new endpoint not previously reported, FE_{NO} (fractional exhaled nitric oxide, a marker of airway inflammation), in three studies conducted in Seattle, WA (Jansen et al., 2005; Koenig et al., 2005; Mar et al., 2005) and one in Steubenville, OH (Adamkiewicz et al., 2004). In addition, a study in Seattle reports statistically significant associations with lower respiratory symptoms in children with asthma (Mar et al., 2004). One study in Atlanta reported no positive associations between $PM_{2.5}$ and medical visits for various respiratory conditions—in fact, some associations were negative in direction—but positive associations were reported for several components of $PM_{2.5}$ (Sinclair and Tolsma, 2004).

2.2.2.2 Associations Between Acute Exposure to Thoracic Coarse Particles and Morbidity

A number of new epidemiologic studies are available for assessing associations between short-term $PM_{10-2.5}$ exposure and various morbidity health outcomes, especially related to respiratory morbidity (Appendix A; Tables A5, A7, A9, and A11). As shown in Figure 3, a number of recent reports have shown significant associations between respiratory hospitalization and acute exposure to $PM_{10-2.5}$. These include associations with hospitalization in Vancouver for respiratory illness in children <3 years of age (Yang et al., 2004), COPD in the elderly, (Chen et al., 2004) and respiratory illness in the elderly (Chen et al., 2005). Associations were also reported with hospitalization for asthma in children (Lin et al., 2002) and respiratory illness in children (Lin et al., 2005) in Toronto. These associations with hospital admissions for respiratory disease were observed for $PM_{10-2.5}$ in both time-series and case-crossover analyses, and the associations remained significant with adjustment for gaseous co-pollutants in four of the five studies (except Chen et al., 2005). The effect estimate increased with longer averaging times up to 4-7 days. Slaughter et al. (2005) did not observe significant associations between $PM_{10-2.5}$ and hospitals admissions or emergency room visits in Spokane, WA for all ages taken together. Overall, these studies provide evidence for associations between acute $PM_{10-2.5}$ exposure and respiratory morbidity in locations where reported mean concentrations range from 5.6 to 12.2 $\mu g/m^3$, and maximum concentrations from 24.6 to 68 $\mu g/m^3$.

One new panel study in Spokane indicated that exposure was associated with several upper respiratory tract symptoms in children with asthma, but no association was reported in adults (Mar et al., 2004). Peel et al. (2005) reported no significant associations between $PM_{10-2.5}$ and respiratory emergency department visits in Atlanta; however in another Atlanta study, significant associations were reported between acute $PM_{10-2.5}$ exposure and outpatient medical visits for several respiratory conditions (Sinclair and Tolsma, 2004).

Little evidence was available on associations between cardiovascular morbidity and $PM_{10-2.5}$ in the 2004 PM AQCD. In Atlanta, no significant associations were found between acute exposure and cardiovascular emergency department visits (Metzger et al., 2004). However, one recent study in Coachella Valley, CA reported significant associations between decreases in heart rate variability with short-term exposure to $PM_{10-2.5}$, but not with $PM_{2.5}$ (Lipsett et al., 2006). In addition, a panel study in Vancouver (Ebelt, et al., 2005) found significant associations between estimates of personal exposure to ambient particles, and to a lesser extent, ambient concentrations with decreased FEV_1 and increases in systolic blood pressure and supraventricular ectopy. However, associations were not significant with measures of heart rate variability. No associations were reported with estimates of personal exposure to nonambient particles. The mean $PM_{10-2.5}$ concentrations in the Coachella Valley and Vancouver studies range from about 10 to over 20 $\mu g/m^3$ At the low end of reported concentrations is Vancouver, where $PM_{10-2.5}$ means were 6-7 $\mu g/m^3$ and maxima were about 25 $\mu g/m^3$. Of note, correlations reported between $PM_{10-2.5}$ and combustion-related gaseous co-pollutants (CO, NO_2, SO_2) are generally higher than those reported between $PM_{2.5}$ and the gases in Vancouver. At the high end is Coachella Valley, where PM_{10} concentrations were quite high, with peak levels exceeding the current PM_{10} standard level.

Taken together, there is a substantial new body of evidence linking acute exposure to $PM_{10-2.5}$ with morbidity, including associations with respiratory hospitalization, respiratory

symptoms, and cardiovascular health outcomes. Of note, several recent studies have reported associations for several indicators of morbidity with $PM_{10-2.5}$, but not with $PM_{2.5}$. In addition, some new studies have used case-crossover methods and reported little evidence for confounding by co-pollutants. A key research question that has been identified during the current PM NAAQS review is to better understand the sources and components of $PM_{10-2.5}$ that may be responsible for different health effects, and these findings continue to support that research need.

2.2.3 Issues for Interpretation of Epidemiologic Study Results

More than 20 new multicity studies have been published in recent years. Three of these studies have included measurements of $PM_{2.5}$ and one included $PM_{10-2.5}$ and these studies are summarized in more detail above (Burnett et al., 2004; Dominici et al., 2006; Ostro et al., 2006). The remaining studies used PM_{10}; the results are summarized briefly in an annotated bibliography (Appendix B). Most of these recent studies continue to report associations between short-term exposure to PM_{10} and mortality or morbidity.

Methodological Issues: The results of the PM_{10} multicity studies are briefly highlighted here due to the importance of multicity studies in being able to evaluate issues that are not readily addressed in single-city analyses. The studies are grouped in Appendix B by the general issues being evaluated in the analyses. These studies address a range of questions and uncertainties that remained in the 2004 PM AQCD, including:

- Several recent multicity studies reported that associations between PM_{10} and mortality are not likely to be confounded by weather or influenza epidemics (Schwartz 2004a; Welty and Zeger, 2005; Analitis et al., 2006; Touloumi et al., 2005). As observed in the 2004 PM AQCD, assessments of copollutant confounding are complicated when the air pollutants are closely correlated, such as pollutants generated from common sources. Results from single-pollutant models may overestimate effects from that pollutant; however, multi-pollutant model results may be misleading when reporting results for correlated pollutants. One new multi-city study used case-crossover design and reported no evidence of confounding between PM_{10} and gaseous co-pollutants in associations with mortality in 14 U.S. cities (Schwartz et al., 2004b). Using more traditional time-series methods, Ostro et al. (2006) reported attenuation of associations between $PM_{2.5}$and mortality with highly-correlated gaseous pollutants in adults <65 years of age, but not in analyses for the elderly. In 12 Canadian studies, $PM_{2.5}$ and $PM_{10-2.5}$ were robust to adjustment for NO_2 in models using only data from the time period when daily PM data were available, but effect estimates were not statistically significant in models using data from the full time period (Burnett et al., 2004). Dominici et al. (2006) report little evidence of effect modification by ozone concentrations in the relationship between $PM_{2.5}$ and hospitalization.

- Daniels et al. (2004) reported that there was no evidence for a threshold level in the PM_{10}-mortality association in analyses of data from the National Morbidity, Mortality and Air Pollution Study.

- The recent multicity studies continue to report somewhat stronger associations with the use of a distributed lag model (Analitis et al., 2006; Zanobetti et al., 2003; Zeka et al., 2005). In addition, one new analysis shows little evidence that the associations are unlikely to represent advancement of death by only a few days (Dominici et al., 2003).

- The recent studies also report findings that are robust to the use of different analytical methods (Roberts and Martin, 2006) and assess the influence of measurement error in underestimation of the PM_{10}-mortality association (Zeka and Schwartz, 2004).

Variation in effects between locations: Numerous new multicity analyses in Europe and the U.S. have studied the variation of PM-health associations between locations, and assessed factors that may influence heterogeneity in PM-related health effects (Dominici et al., 2003; Medina-Ramon et al., 2006; Samoli et al., 2005; Le Tertre et al., 2005; Zeka et al., 2005; Zeka et al., 2006). Consistent with the findings available in the 2004 PM AQCD, the recent studies highlight exposure differences (e.g., air conditioning use) and the influence of traffic as potentially associated with larger effects of PM_{10}. Some recent studies also suggest that variability in climate and a number of preexisting health conditions may modify the effects of PM.

New health outcomes: New multicity analyses have also reported associations between PM_{10} and new health outcomes, including emergency admissions for myocardial infarction (Zanobetti and Schwartz, 2005), readmission to the hospital for cardiac causes (Von Klot et al., 2005) and potential changes in physiological cardiac indicators (Ibald-Mulli et al., 2004; Timonen et al., 2006)Numerous recent single-city studies also expand of the health endpoints that are reported to be associated with PM, generally focusing on $PM_{2.5}$ exposures. These newly reported health endpoints include: (1) indicators of the development of atherosclerosis with long-term PM exposure; (2) indicators of changes in cardiac rhythm, including arrhythmia or ST-segment changes; (3) effects on developing children and infants; (4) markers of inflammation such as exhaled NO; and (5) effects on organ systems outside the cardiopulmonary systems. Numerous new epidemiologic studies have reported associations between PM, primarily using $PM_{2.5}$, and cardiovascular health outcomes such as cardiac arrhythmia, ST segment depression, and decreased heart rate variability. New toxicology reports suggest that the brain may be affected by exposure to PM, including reports of increases in inflammatory biomarkers and neurodegeneration following exposure to CAPs (Campbell et al., 2005; Veronesi et al., 2005).

Potentially susceptible or vulnerable subpopulations: In the 2004 PM AQCD, people with preexisting heart or lung disease, children, and older adults were considered likely to be more susceptible to PM-related effects. Recent studies provide increasing evidence that pre-existing diseases, particularly diabetes, may increase susceptibility to the cardiovascular effects of PM. Goldberg et al. (2006) reported significant associations between $PM_{2.5}$ and diabetes deaths, as well as total mortality in people with previous diagnoses of diabetes. One new toxicology study has suggested mechanistic evidence for diabetes-related susceptibility (Proctor et al., 2006). Additional research utilizing susceptible animal models of vascular conditions (e.g., the Spontaneously Hypertensive rat and the apolipoprotein deficient mouse) have demonstrated that exposure to CAPs or surrogate PM can exacerbate symptoms, compromise function and potentiate disease states.

2.3 Intervention Studies

The 2004 PM AQCD highlighted the results of several new "intervention" studies or "found experiments" that reported associations between reductions in air pollution and improvements in public health (2004 PM AQCD, Sections 8.2.3.4 and 9.2.2.6). While few in number, these studies were found to provide important support to the epidemiologic evidence linking air pollution exposure with adverse health effects.

One new study reported evidence for reduced mortality risk when ambient pollution was decreased (Laden et al., 2006). As discussed briefly above, the authors report a statistically significant reduction in mortality risk with reduced long-term fine particle concentrations (RR 0.73, 95% CI 0.57-0.95, per 10 $\mu g/m^3$ $PM_{2.5}$).

Several recent intervention studies have evaluated changes in respiratory health outcomes associated with decreased pollution levels; the results of these studies are summarized in Table A13 (Appendix A). One U.S. study reported reductions in respiratory medical visits with decreased traffic volume that resulted from closure of the Peace Bridge in Buffalo, NY, following September 11, 2001 (Lwebuga-Mukasa et al., 2003). Studies conducted in Switzerland and East and West Germany have also reported reductions in respiratory symptoms or improved lung function with decreases in ambient PM concentrations measured as TSP or PM_{10} (Bayer-Oglesby et al., 2005; Sugiri et al., 2006; Frye et al., 2003; Heinrich et al., 2002). In addition, Burr et al. (2003) reported associations between reduced respiratory symptoms and reductions in traffic volume. Overall, this group of studies indicates that declining concentrations of PM and other pollutants is associated with reduced mortality risk and improved respiratory health and thus add substantial support to the evidence available in the 2004 PM AQCD.

2.4 Health Effects Related to Sources or Components of PM

The current PM NAAQS have been established using $PM_{2.5}$ and PM_{10} mass as the indicators, as opposed to singling out any particular component or class of particles. This decision was based on evidence from epidemiologic studies that reported significant associations between various PM components or characteristics, evidence that PM was associated with health effects in numerous areas that had differing components or sources of PM, and evidence from animal toxicology and controlled human exposure studies that had reported health effects associations with high concentrations of numerous fine particle components (e.g., sulfates, nitrates, transition metals, organic compounds).

In the 2004 PM AQCD, epidemiologic and toxicology studies provided evidence for effects associated with various fine particle components or size-differentiated subsets of fine particles. Toxicology studies reported effects with exposure to different sources or components of PM (generally at high levels), such as metals, diesel particles, acid aerosols, and bioaerosols (Chapter 7 of the 2004 PM AQCD). The findings of these studies indicated that, for a given health response, some fine particle components were more closely linked with that response than other components. However, the evidence did not suggest that any component could be singled out as potentially the sole contributor to toxicity, or as having no toxic effects.

Chapter 8 of the 2004 PM AQCD included a discussion of three new epidemiologic studies that reported associations between various health outcomes and different PM components. Three new studies that had conducted source-oriented evaluation of PM provided new insights into the relationship between fine particles from different sources and mortality. While few in number and somewhat preliminary in nature, these studies suggested that a number of source types were associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning; no associations were reported with the crustal factor from fine particles (2004 PM AQCD, Section 8.2.2.5).Considered together, the 2004 PM AQCD concluded: "These studies suggest that many different chemical components of fine particles and a variety of different types of source categories are all associated with, and probably contribute to, mortality, either independently or in combinations" (p. 9-31). Conversely, there was no basis to conclude that any individual fine particle component cannot be associated with adverse health effects.

Many new studies have been published in recent years that provide interesting new insights into the effects of different sources or types of PM. For the purposes of this provisional assessment of new literature published since the release of the 2004 PM AQCD, emphasis has been placed on studies that investigated the health effects related to PM sources or comparisons of various PM components. To highlight the scientific content of the recent literature while focusing on key PM study categories, this section focuses on results of studies that evaluated the effects of a range of sources or components. This includes studies that used source apportionment, or that compared effects for a range of PM components. Thus, the discussion includes: (1) recent epidemiologic studies using source apportionment; (2) epidemiologic evidence on effects with PM components; (3) results of new toxicology studies using source apportionment with exposures to concentrated ambient particles (CAPs) to provide insight into potential effects related to PM from different sources, and comparative toxicology studies using fine particle components; and (4) toxicology study results for different surrogates and size fractions of PM, including thoracic coarse PM ($PM_{10-2.5}$). In addition, numerous epidemiologic and/or toxicology studies have reported effects of several sources, components, or characteristics as discussed in the 2004 PM AQCD. Specific findings for these PM characteristics are not discussed in detail; instead, the available new studies are included in reference lists for the following categories:

- ultrafine PM;
- metals (including residual oil fly ash);
- traffic;
- woodsmoke; and
- endotoxin.

2.4.1 Epidemiologic Studies Using Source Apportionment

Some recent epidemiologic studies have employed statistical approaches of source contributions from source apportionment analyses in evaluating associations of health effects with particular source categories of PM. Since source apportionment analysis is based on finding independent groupings of chemical components, the source categories should not confound each other.

A workshop was held in May 2003 during which several groups determined source category contributions (using multiple techniques) using ambient PM chemical concentration data from Washington, D.C. (U.S. Park Service, IMPROVE) and from Phoenix (U.S. EPA). An intercomparison of the source apportionment results was also published (Hopke et al., 2006). The statistical associations of these source category contributions with total (non-accidental) and cardiovascular mortality were then determined by Ito et al. (2006) for Washington and Mar et al. (2006) for Phoenix. The results from different groups varied, in part depending on the participants' experience and expertise with source apportionment and time-series epidemiologic analyses (Appendix A; Table A14). Although several groups separated the traffic source into diesel and gasoline, for the reported analyses, all traffic-related source categories were summed into a "traffic" source category. For Washington, DC, the correlations of daily contributions of source categories across the various investigators/techniques were fair for crustal, secondary sulfate, secondary nitrate, primary residual oil combustion, and incinerator, but poor for traffic, wood burning, and salt (correlation not reported for primary coal combustion). In Phoenix, AZ, the correlations of daily contributions across the various investigators and analysis techniques were high for traffic, secondary sulfate, and sea salt, and low for biomass burning, metals, and primary coal burning.

In Washington, DC, secondary sulfate and primary coal combustion were statistically significant with total mortality on lag day 3. $PM_{2.5}$ had a statistically significant relationship with total mortality on lag day 1 and 3 before controlling for temperature, but only on lag day 3 after controlling for temperature. For cardiovascular mortality, no source categories were statistically significant across all investigators/techniques. However, for one or more analyses, statistically significant results were found for soil (lag 2, 3, and 4), traffic (lag 3), secondary sulfate (lag 0 and 3), residual oil (lag 0), wood smoke (lag 3), and primary coal burning (lag 3). The Washington, DC samples were collected on Saturday and Thursday only; so, each lag has a different set of mortality days which may introduce some uncertainty into the lag structure.

In Phoenix, only sea salt (lag 5) was statistically significant with total mortality for all analyses, while 3/5 data sets gave statistically significant results for Cu smelter (lag 0) and 1/8 for sulfate (lag 0). For cardiovascular mortality, most data sets gave statistically significant (or nearly so) associations for traffic (lag 1, 6/9), secondary sulfate (lag 0, 6/8), sea salt (lag 5, 6/6), and Cu smelter (lag 0, 3/5). Data sets from both cities show secondary sulfate as the source category with the highest statistically significant relative risk (5-95th percentile increments), although the lag days and mortality categories differ by city (lag 0 for cardiovascular mortality in Phoenix, AZ, and lag 3 for total mortality in Washington, DC, with some Washington, DC, data sets reporting lags 0 and 3 for cardiovascular mortality). A generalized traffic source is implicated for cardiovascular mortality at lag 1 in Phoenix, AZ and lag 3 in Washington, DC.

One study used source apportionment techniques to assess relationships between cardiovascular morbidity and acute fine particle exposure in a panel of healthy young male patrol officers in Wake County, NC. Riediker et al. (2004) reported the strongest associations between a "speed change" factor (Cu, S, and aldehydes) and a number of cardiovascular health indicators. There were suggested associations with a gasoline combustion factor, and there was limited evidence for associations with fine particles of crustal origin.

Taken together, the results of these new studies are consistent with previously-available evidence that link health outcomes with fine particles from a range of sources, including motor vehicles and combustion of oil or coal. The use of source categories in community time-series epidemiology shows promise but additional work is needed in characterizing the various sources, understanding the spatial variability of the different source categories, and obtaining daily composition and concentration data for periods of several years in additional cities.

2.4.2 Epidemiologic Studies on Effects of Fine Particle Components

As summarized in Section 8.2.2.5 of the 2004 PM AQCD, epidemiologic studies have reported generally positive, often statistically significant associations between various fine particle components and mortality. Numerous studies have reported associations between short-term sulfate exposures and mortality and morbidity; the effect estimates reported for mortality range from about 1 to 9% increases in mortality per 5 $\mu g/m^3$ increase in ambient sulfate concentration (as shown in Figure 8-6 of the 2004 PM AQCD). Associations have also been reported with other PM components, including carbonaceous components (elemental carbon, organic carbon, and coefficient of haze), nitrates, and metals.

Associations between mortality and long-term exposure to ambient sulfates was reported in prospective cohort studies, with effect estimates reported in the range of 11 to 50% increases in mortality per 15 $\mu g/m^3$ increase in sulfates (2004 PM AQCD, Table 8-15). Prospective cohort studies have also reported associations between long-term exposure to sulfates and respiratory effects, such as prevalence of chronic bronchitis (2004 PM AQCD, section 8.3.3.2).

Several recent epidemiologic studies have evaluated associations between *short-term exposure* to fine particle components and various health outcomes, as shown in Table A15 (Appendix A). Overall, this group of studies reports associations between mortality and morbidity with several fine particle components. A number of studies report associations with sulfates that are generally consistent with those in earlier reports. Several recent studies have also shown associations with the organic carbon and elemental carbon components of fine particles.

- For mortality, significant associations were reported with sulfates in a new study in Montreal (Goldberg et al., 2006), and a positive, borderline significant, association with sulfates was reported in a study of 12 Canadian cities (Burnett et al., 2004). Positive, but not statistically significant, associations between mortality and fine particle sulfates was reported in Vancouver (Villeneuve et al., 2003). A study in Atlanta also evaluated associations with other fine particle components, and reported positive but not significant associations between mortality and sulfates and EC, OC, and not association with nitrates (Klemm et al., 2004).

- For emergency department visits, two reports from the ARIES study in Atlanta evaluated associations between short-term fine particle component exposures and visits for cardiovascular or respiratory diseases (Metzger et al., 2004; Peel et al., 2005). Both studies report no significant associations for short-term exposures to either sulfates or water-soluble metals with visits for cardiovascular or respiratory diseases. Significant

associations were reported between OC and EC and emergency department visits for all cardiovascular diseases and congestive heart disease (Metzger et al., 2004). No significant associations were reported between any component and respiratory visits, except for an association between OC and emergency department visits for pneumonia (Peel et al., 2005).

- For cardiovascular health outcomes, one study that was conducted in Boston, MA reported a significant association between short-term sulfate exposure and percent change in brachial artery diameter, an indicator of vascular reactivity (O'Neill et al., 2005); other components were not evaluated.

- For respiratory health outcomes, medical visits for asthma in children and lower respiratory infections (all ages) were associated with the EC and OC components of fine particles in Atlanta, but no associations were reported with sulfates or acidity (Sinclair and Tolsma, 2004). Metals were positively associated with medical visits for lower respiratory infection, but not for other outcomes. For adult asthma and upper respiratory infections, there were no significant positive associations with any of the fine PM components; however, sulfates were negatively associated with upper respiratory infection visits (Sinclair and Tolsma, 2004). In a panel study of Hispanic children, OC and EC (measured in PM_{10}) were significantly associated with asthma symptoms; other PM components were not included in this study (Delfino et al. 2003).

In addition, one recently published epidemiologic study has also assessed associations between mortality and *long-term exposure* to fine particle components (see Table 1). Mortality was significantly associated with long-term exposure to four fine particle components (EC, nitrates, nickel, and vanadium), and a positive but not statistically significant association was reported with sulfates using the Veterans cohort (Lipfert et al., 2006b, in press).

2.4.3 Toxicology Studies—Source Apportionment and Fine Particle Components

There were nine studies in the 2004 PM AQCD that investigated the effects of fine particle CAPs exposure in humans and laboratory animals (Sections 7.2.2 and 7.3.1). The results of these studies generally showed associations between the CAPs exposure and cardiovascular parameters. Effects on the respiratory system were largely absent for pulmonary function, but were present for markers of inflammation. Source apportionment was largely absent in the previous CAPs studies, although some evidence linked transition metal components in ambient PM with lung injury. Additionally, as CAPs composition varies day-to-day, it is difficult to establish clear relationships between individual components and adverse health effects. The 2004 PM AQCD pointed to a "critical need for the systematic conduct of studies in the potential respiratory effects of major components of PM from different regions of the U.S., in recognition that PM of different composition and from different sources can vary markedly in its potency for producing different respiratory effects" (2004 PM AQCD, p. 7-85).

Toxicological studies employing CAPs offer a relevant surrogate for atmospheric PM. As ambient PM is just one component of a complex mixture that interacts with gases and other aerosols, CAPs systems provide a method of exposing subjects to the particle phase. Gases

(such as O_3 and SO_2) are not concentrated and organic PM components in CAPs likely differ from components in ambient PM, particularly for ultrafine CAPs systems (Su et al., 2006). Similarly, thoracic coarse PM is not enriched (except for the coarse particle concentrator) and only certain systems are capable of concentrating ultrafine PM.

There are three main CAPs exposure systems currently in use. The Harvard Air Particle Concentrator (HAPC) uses virtual impactor technology to concentrate particles from 0.15 to 2.5 μm (Sioutas et al., 1997). The versatile aerosol concentration enrichment system (VACES) is also based on virtual impactor technology and concentrates ultrafine particles, as well as those in the fine particle range (Sioutas et al., 1999). It is important to note that both ultrafine systems (HAPC and VACES) do not uniformly concentrate particles across all size fractions and that the enrichment factor has been shown to decrease for PM sized <75 nm (Su et al., 2006). The centrifugal concentrator most efficiently concentrates particles in the 0.5–2.5 μm size range (Gordon et al., 1998). For the purposes of this provisional assessment, CAPs studies have been grouped into those that conducted source apportionment analyses or those that linked PM components to health outcomes. Additional CAPs studies that reported linkages between mass and toxicity are presented in a subsequent section.

Among the recent toxicology studies are 27 new studies reporting effects of CAPs exposure. These include several reports from a large study of subchronic exposure to CAPs that was carried out using three different mice strains. Four of the acute and one subchronic study (with an additional *in vitro* study) performed complex source apportionment or factor analyses. Eight (three human and five animal studies) used regression approaches to estimate the relationship between health effects and the concentration of individual PM constituents. Additional exposure details, endpoints, and results for all of the CAPs studies are provided in Appendix A (Tables A16–A18); the tables present only those findings that were positive in the "Results" column.

Source Apportionment Studies

Table 2 shows those endpoints which were associated with various source categories from humans exposed to Chapel Hill, NC, CAPs (Huang et al., 2003b) and mice exposed subchronically to Tuxedo, NY, CAPs (Lippman et al., 2005b). Increases in blood fibrinogen levels in healthy humans were correlated with a Cu-Zn-V factor (stated by the authors to be linked to combustion, including oil combustion) in the acute exposure study (Huang *et al.*, 2003b). In addition, elevated polymorphonuclear leukocytes in bronchoalveolar lavage fluid (BALF) were observed with CAPs, and this increase was associated with a Fe-Se-sulfate factor; the authors considered this factor to represent sulfurous smog and photochemical air pollution. There were no other identifiable CAPs factors that were linked to any health outcome.

Using mouse models, Lippmann et al. (2005b) reported post-exposure decreases in heart rate variability (HRV) parameters in subchronic exposures to CAPs for three factors—secondary sulfate, residual oil, and motor vehicles—but an increase in HRV parameters with a CAPs factor representing resuspended soil. Similar findings were reported for heart rate, with slight increases and decreases being observed for different source categories at one interval or another.

Table 2. CAPs Sources and Associated Endpoints: Acute and Subchronic Exposures

Source Category	Endpoint Affected	Time	Species	Reference
Zn-Cu-V	↑ blood fibrinogen	18 hr post-exposure	Human	Huang, Y-C.T (2003)
Fe-Se-sulfate	↑ BALF PMN	18 hr post-exposure	Human	Huang, Y-C.T (2003)
Secondary sulfate (S, Si, OC)	↓ HR ↓ SDNN, ↓ RMSSD	Afternoon post-exposure Night post-exposure	$ApoE^{-/-}$ mouse	Lippmann et al. (2005b)
Resuspended soil (Ca, Fe, Al, Si)	↓ HR ↑ HR ↑ SDNN, ↑ RMSSD	During exposure Afternoon post-exposure Night post-exposure	$ApoE^{-/-}$ mouse	Lippmann et al. (2005b)
Residual oil (V, Ni, Se)	↓ SDNN, ↓ RMSSD	Afternoon post-exposure	$ApoE^{-/-}$ mouse	Lippmann et al. (2005b)
Motor vehicle/other	↓ RMSSD	Afternoon post-exposure	C57 mouse	Lippmann et al. (2005b)

As shown in Table 2, not all source categories were linked to HR or HRV parameters at any given time during or after exposure.

One *in vivo* study employed rats and mice (Steerenberg et al., 2006) which were exposed to one of five PM types collected from Europe. The traffic, industry/combustion/incinerator, and wood smoke source clusters were associated with the adjuvant activity for respiratory allergy, whereas the secondary inorganic/long range cluster correlated with systemic allergy (Steerenberg et al., 2006). The crustal material and sea spray sources were linked to acute inflammation, although the endotoxin content also correlated with some of these biomarkers (Steerenberg et al., 2006).

In the remaining CAPs studies that included source apportionment, Batalha et al. (2002) reported changes in lumen/wall ratio, an indicator of vasoconstriction, with sulfate and Si (suggested to be an indicator of road dust) in normal rats and with OC in chronic bronchitic rats. Wellenius et al. (2003) also linked a cardiovascular response, ST-segment elevation, with Si and other crustal elements derived from Boston CAPs. In the latter study, there were a number of tracer elements that were not associated with any electrocardiogram measure, including Ni, S, and carbon black.

Studies of fine particle components in CAPs

In addition, six CAPs studies have reported associations between observed cardiovascular or respiratory endpoints and specific PM constituents. Table 3 presents more specific results, and the overall findings are briefly summarized below:

Table 3. CAPs Components and Associated Endpoints for Acute Studies

Component	Endpoint Affected	Species	Reference
Al	lipid peroxidation oxidative stress (heart)	rat rat	Rhoden et al. (2004) Gurgueira et al. (2002)
Si	lipid peroxidation oxidative stress (heart) lumen/wall ratio ST-segment elevation	rat rat rat dog	Rhoden et al. (2004) Gurgueira et al. (2002) Batalha et al. (2002) Wellenius et al. (2003)
Fe	lipid peroxidation oxidative stress (lung) oxidative stress (heart)	rat rat rat	Rhoden et al. (2004) Gurgueira et al. (2002) Gurgueira et al. (2002)
Zn	oxidative stress (lung) plasma fibrinogen	rat rat	Gurgueira et al. (2002) Kodavanti et al. (2005)
Mn	oxidative stress (lung)	rat	Gurgueira et al. (2002)
Cu	oxidative stress (lung)	rat	Gurgueira et al. (2002)
Ti	oxidative stress (heart)	rat	Gurgueira et al. (2002)
Sulfate	FEV_1 decrements FVC decrements lumen/wall ratio	human ($+NO_2$) human ($+NO_2$) rat	Gong et al. (2005) Gong et al. (2005) Batalha et al. (2002)
OC	brachial arterial diameter diastolic blood pressure lumen/wall ratio	human human rat	Urch et al. (2004) Urch et al. (2005) Batalha et al. (2002)
EC	brachial arterial diameter lumen/wall ratio	human rat	Urch et al. (2004) Batalha et al. (2002)
Pb	lumen/wall ratio	rat	Batalha et al. (2002)

- Si—oxidative stress and cardiovascular endpoints;
- Fe—oxidative stress;
- OC and EC—cardiovascular effects;
- Zn—oxidative stress and fibrinogen; and
- Sulfate—pulmonary and cardiovascular effects.

Fine Particle CAPs Studies Without Source Apportionment or Identified Components

Effects on the cardiovascular system have been reported in a number of human studies. Markers of cardiovascular function, such as brachial arterial diameter and blood pressure, have been shown to decrease with CAPs exposure (Urch et al., 2004, 2005). Increased occurrence of ectopic and abnormal beats has also been reported in healthy and COPD subjects with exposure to CAPs (Devlin et al., 2003). Similar to studies cited in the 2004 PM AQCD, elevated blood fibrinogen levels were observed in volunteers exposed for two hours to Chapel Hill, NC CAPs

(Ghio et al., 2003). Hematological alterations, including increased peripheral basophils (Gong et al., 2004a) and decreased white blood cell counts (Ghio et al., 2003), have also been reported. Two recent studies measuring heart rate (HR) and heart rate variability (HRV) have demonstrated that a single two-hour exposure to CAPs from Los Angeles, CA, or Chapel Hill, NC, can result in decreased HRV in human volunteers (Devlin et al., 2003; Gong et al., 2004a). Interestingly, in the Los Angeles studies, healthy subjects were reported to have greater decreases in HRV compared to compromised individuals with COPD (Gong et al., 2004a).

In addition, a few studies have reported some associations with respiratory health endpoints. Arterial oxygen saturation decreased in healthy and COPD patients exposed for two hours to $PM_{2.5}$ Los Angeles CAPs (Gong et al., 2005). Elevated polymorphonuclear leukocytes in bronchioalveolar lavage fluid were observed in healthy volunteers at 18-hr post-exposure to Chapel Hill, NC, CAPs (Ghio et al., 2003). Of the two recent fine CAPs studies that measured pulmonary function, only one showed decreased maximal mid-expiratory flow, forced expiratory volume and forced vital capacity and the latter two responses were only observed with co-exposure to NO_2 (Gong et al., 2005); the other study did not report any changes in spirometry or respiratory symptoms (Gong et al., 2004a).

To date, the CAPs animal studies reported in the scientific literature have been of relatively short duration (i.e., four weeks or less). There is one large subchronic PM inhalation study in the recent literature on toxicological effects of repeated exposures to ambient particles in mice exposed to Tuxedo, NY, CAPs for five or six months during the spring and summer of 2003 (Lippmann et al., 2005a; Sun et al., 2005). Following CAPs exposure, mice models of aortic and/or coronary atherosclerosis had altered HR and HRV (Chen and Hwang, 2005; Hwang et al., 2005; Lippmann et al., 2005b), advanced plaque deposits and lesions in the aorta and heart (Chen and Nadziejko, 2005), and changes in vasomotor tone (Sun et al., 2005). Additional molecular and biochemical analyses demonstrated altered gene expression post-exposure, including those genes involved in the regulation of circadian rhythm, heat shock, inflammation, and signal transduction (Gunnison and Chen, 2005). CAPs exposure also induced neurodegeneration in the substantia nigra nucleus compacta of $ApoE^{-/-}$ mice (Veronesi et al., 2005). Interestingly, subchronic CAPs-exposure did not appear to cause pulmonary effects in any mouse strain.

Finally, three reports do not specifically link PM components to health endpoints, but two draw inferences that relate the effects seen with a heavy industrial source located near the study site (Dvonch et al. 2004; Morishita et al., 2004). One additional study of mice exposed to fine CAPs in Los Angeles, downwind of heavily trafficked highways, demonstrated effects on biomarkers of inflammation in the brain (Campbell et al., 2005). Additionally, in the one *in vitro* study that applied factor analysis to CAPs for cytokine release, the oil-fired power plant emission source (comprised of V, Ni, and Se) was linked to the response, but not the regional secondary sulfate or resuspended soil factors (Maciejczyk and Chen, 2005). Considered as a group, these new studies suggest that many fine particle components can adversely affect health, and that PM-associated cardiovascular and respiratory effects may be linked to resuspended soil, regionally transported air pollution, and combustion or industrial sources.

2.4.4 Toxicology Studies—Thoracic Coarse Particles

Few studies examined the effects of thoracic coarse PM on cellular responses prior to the release of the 2004 PM AQCD. When considered together, the four *in vitro* studies discussed in Chapter 7 of the 2004 PM AQCD document provided some evidence that exposure to thoracic coarse PM may result in proinflammatory effects, as well as cytotoxicity and oxidant generation (Section 7.4.2). However, as little data was available at that time on thoracic coarse PM toxicity, a very limited evaluation of the literature was conducted. Recent publications include sixteen new studies (one human, six *in vivo*, and nine *in vitro*) that have specifically focused on the thoracic coarse fraction of PM, with the majority of these providing direct comparisons with smaller size fractions (i.e., fine and ultrafine).

In one important new study, healthy and asthmatic humans were exposed to CAPs via a high concentration efficiency coarse particle concentrator, in which 80% of the PM mass was comprised of the thoracic coarse fraction (Gong et al., 2004b). Exposure to thoracic coarse CAPs from Los Angeles also caused lowered HR and HRV. Asthmatics exposed to thoracic coarse Los Angeles CAPs had no changes in arterial oxygen saturation (Gong et al., 2004b). Healthy subjects were reported to have greater decreases in HRV compared to compromised individuals with COPD (Gong et al., 2004b).

Two *in vitro* studies evaluated cytokine release and cell viability following exposure to $PM_{2.5}$ soil dusts from a variety of southwestern U.S. locations (Veranth et al., 2004, 2006). The responses were quite variable and did not appear to be attributable to sample location category (e.g., urban/rural, road surface/open land, military/civilian) or endotoxin content. A multivariate analysis of the findings demonstrated a handful of correlations with soil dust constituents (Veranth et al., 2006).

The *in vivo* rodent studies provide evidence that the observed effects from exposure (via non-inhalation routes) to thoracic coarse or fine PM are related to the endotoxin or allergen levels, which were often associated with sampling location. These effects included elevated cytokine release (Nygaard et al., 2005; Schins et al., 2004) and adjuvant activity (Steerenberg et al., 2005). Schins et al. (2004) reported differences between thoracic coarse PM from rural and urban areas in The Netherlands, with greater responses for elevated neutrophils and tumor necrosis factor-α in BALF from rural PM, but greater induction of macrophage inflammatory protein-2 *in vitro* from urban PM (both PM types contained relatively high levels of endotoxin). Otherwise, the thoracic coarse fraction tended to induce similar toxic responses as that observed with the fine fraction. In the one study that employed coal fly ash, no differences in effects were reported for the thoracic coarse fraction compared to saline control animals (Gilmour et al., 2004).

Similar to the *in vivo* research with surrogate and size-fractionated PM, *in vitro* studies have also shown associations between the induction of inflammatory mediators and PM endotoxin content (Huang et al., 2003a; Pozzi et al., 2003), whereas others have found seasonal relationships with thoracic coarse PM effects (Becker et al., 2005b; Hetland et al., 2005; Li et al., 2002). The latter finding could be partially attributable to microbial products or their interactions with metals (Hetland et al., 2005). Becker et al. (2005b) further examined possible associations between cellular responses and PM components using principal component analysis

and reported a Cr/Al/Si/Ti/Fe/Cu factor correlating with IL-6 and IL-8 release. Examination of IL-6 induction in alveolar macrophages and IL-8 release in normal human bronchial epithelial cells following thoracic coarse PM exposure showed associations with Toll-like receptor (TLR) 4 and TLR2 gene expression, respectively (Becker et al., 2005a). Generation of hydroxyl radicals has also been recently observed with thoracic coarse PM (Shi et al., 2003). In contrast, some studies have also demonstrated greater effects with the fine or ultrafine size fraction compared to thoracic coarse PM (Li et al., 2002; Li et al., 2003; Gilmour et al., 2004).

2.4.5 Toxicology Studies—Comparison of Ambient PM

There were numerous studies included in the 2004 PM AQCD that employed ambient particles collected on filters. These included extracts of collected or stored PM and the majority of studies utilized Ottawa (EHC-93) or Provo, Utah PM_{10}. Generally, animals exposed to these particles had elevated biomarkers of pulmonary injury and inflammation, as well as systemic and cardiovascular responses (Chapter 7). The 2004 PM AQCD stated that studies using collected urban PM "have provided evidence indicating that the chemical composition of ambient particles can have a major influence on toxicity" (Section 7.10.2.1, pg 7-127). The results of research published since 2002 have largely supported and expanded the findings of previous studies cited in the 2004 PM AQCD. Five studies are highlighted which evaluated the toxicity of urban PM or that collected on filters (one human, two *in vivo*, and two *in vitro*). Further details on these studies are included in Table A19 (Appendix A).

Two recent studies investigated the effects of urban (Hettstedt) and rural (Zerbst) particles ($PM_{2.5}$) on lung inflammation and pulmonary function in humans and rodents (Gavett et al., 2003; Schaumann et al., 2004). In healthy human volunteers, instillation of either PM induced airway inflammation, whereas Hettstedt PM resulted in greater influxes of BALF monocytes and increased oxidant radical generation compared Zerbst PM (Schaumann et al., 2004). In allergic mice, exposure to either PM type induced lung injury and proinflammatory cytokines (Gavett et al., 2003). However, aspiration of Hettstedt PM caused heightened airway responsiveness and elevated lung inflammatory cells in sensitized mice exposed before allergen challenge (Gavett et al., 2003). The endotoxin content was below 0.32 EU/mg in both PM samples.

Two other *in vivo* toxicology studies examined the cardiovascular and cytogenetic effects of urban PM exposure (Rhoden et al., 2005; Soares et al., 2003). Rhoden et al. (2005) compared autonomic nervous system (ANS) effects between Boston CAPs (via inhalation) and SRM 1649 (via intratracheal instillation). Both particles altered ANS function and these changes preceded and were required for increased cardiac reactive oxygen species generation (Rhoden et al., 2005). Soares et al. (2003) measured micronuclei (MN) in peripheral erythrocytes of mice exposed to urban air of Sao Paulo or Atibaia, Brazil (with the latter being a rural location) and reported that there were significant increases in MN frequency for mice exposed to the Sao Paulo atmosphere.

The results of recent studies assessing effects of different components from different particle samples or size classes are summarized in Table 4, along with other studies that attempted to link *in vitro* effects with PM components (discussed in the preceding section).

Table 4. PM Components, Size Fractions, and Associated *In Vitro* Toxicity

Component	Endpoint Affected	Size Fraction	Cell Type	Reference
Br	IL-8	Fine	BEAS-2B	Veranth et al. (2006)
Cr	IL-8 IL-8 TNF-α	Fine, ultrafine Fine Ultrafine	NHBE BEAS-2B RAW 264.7	Becker et al. (2005b) Huang et al. (2003a) Huang et al. (2003a)
Cu	Hydroxyl radical 8-OHdG formation	Coarse Coarse	A549 A549	Shi et al. (2003) Shi et al. (2003)
Si	IL-6	Coarse	Human AM	Becker et al. (2005b)
Fe	IL-6 TNF-α	Coarse, fine Ultrafine	Human AM RAW 264.7	Becker et al. (2005b) Huang et al. (2003a)
Mn	IL-8 Cell viability	Fine Fine	BEAS-2B BEAS-2B	Huang et al. (2003a) Veranth et al. (2006)
Ni	IL-6	Fine	BEAS-2B	Veranth et al. (2006)
OC	Lipid peroxidation IL-6 Hydroxyl radical	Fine Fine Ultrafine	BEAS-2B BEAS-2B BEAS-2B	Huang et al. (2003a) Veranth et al. (2006) Li et al. (2003)
EC	Lipid peroxidation IL-6	Fine Fine	BEAS-2B BEAS-2B	Huang et al. (2003a) Veranth et al. (2006)

These recent studies continue to show that exposure to different types of surrogate fine PM is associated with a range of health outcomes, particularly those related to the cardiovascular system. These findings also expand upon the body of evidence related to the effects of thoracic coarse particles and PM composition. Exposure to thoracic coarse particles has been linked with a number of effects, including inflammatory mediator release and reactive oxygen species generation. The results are still too limited to draw conclusions about specific thoracic coarse particle components and health outcomes, but it appears that endotoxin and metals potentially play roles in the observed responses. While these studies provide interesting new insight into potential links between different types of particles and observed effects, it is much too early to distinguish any PM components as being primarily responsible for any specific effect or conversely, as not involved in any toxicological response.

2.4.6 Studies of Specific Fine Particle Components or Characteristics

Toxicological evidence on the effects of different types of particles or particle components was discussed in Section 7.10.2 of the 2004 PM AQCD. The particle characteristics or sources discussed included acid aerosols, metals, diesel exhaust particles, organic components, ultrafine particles and bioaerosols. In addition to the discussions above, EPA observes that numerous recent individual toxicology studies have investigated the effects of exposure to these particle components or characteristics. For this provisional assessment, EPA has not critically reviewed the large number of studies that have assessed effects of

individual components, but will highlight below the general nature of the new findings. Bibliographies for these groups of particle types or characteristics are included in Attachment B.

The main overarching conclusion from these groups of studies is that the recent studies generally substantiate and support conclusions drawn from earlier work. For example, numerous studies had suggested that metals (e.g., transition metals such as V or Ni) contributed to the toxic effects observed with PM exposures (albeit at generally high exposure levels). Recently-published studies provide more evidence that metal constituents of particles may play important roles in PM-related toxicity.

Ultrafine Particles: The 2004 PM AQCD had an extensive discussion of the physical and chemical properties and behavior of ultrafine particles (diameter <0.1 μm). A growing body of evidence from toxicology studies indicated that ultrafine particles were linked with a number of health outcomes; however, there was very limited information on the health effects of ultrafine particles from epidemiologic studies. The 2004 PM AQCD observed that acute exposures to ultrafine particles were associated with slight increases in blood viscosity and with respiratory symptoms or decreased lung function, and one study had reported associations with mortality. Toxicological studies used various types of ultrafine model particles (e.g., carbon black), and reported greater inflammatory responses when compared at the same mass of fine particles of the same chemical composition at similar mass doses (2004 PM AQCD, p. 7-221). Hence, in the ambient environment where fine particle mass greatly exceeds ultrafine mass, it remains to be determined whether this relative difference in potency is reflected in real world exposures.

Since April 2002, about 60 recent studies have evaluated effects of ultrafine particles, and over 150 have assessed effects associated with diesel exhaust or traffic-related PM (see Attachment B). Diesel and other forms of traffic are considered to be major sources of atmospheric ultrafine PM. Recent toxicology studies continue to indicate that ultrafine particles have effects and many toxicology studies indicate that, on a mass basis, ultrafine particles are more toxic than fine particles. Ultrafine particles have been observed to translocate from the olfactory mucosa to the brain and from the lungs to the liver and the systemic circulation. However, a number of uncertainties remain regarding the extent of ultrafine particle extrapulmonary translocation, including clearance rates and routes (e.g., lymphatic system or gastrointestinal tract). Ultrafine particles appear to enter cells and cause mitochondrial damage, based on evidence from *in vitro* studies. Most studies using laboratory-generated carbon particles do not demonstrate lung inflammation, but report cardiac and vascular effects. Additionally, exposure to ambient ultrafine PM causes lung inflammation that is associated with organic carbon carried by the ultrafine particles. A few epidemiologic studies have associated health effects with particle number, particle surface area, or active surface area, all variables that are thought to be associated more with ultrafine than fine particles. As was true in the 2004 PM AQCD, the epidemiologic studies generally do not indicate that ultrafine PM is more strongly associated with health effects than fine PM. In general, studies report associations between both fine and ultrafine particles, and in a number of cases the associations are reported to be stronger for fine than for ultrafine PM. Thus, further evaluation is needed on effects of ultrafine particles in the next review of the PM NAAQS.

Sulfates and Acid Aerosols: As stated in the 2004 PM AQCD, there is "little new information on the effects of acid aerosols." There was a much more extensive discussion on the toxicity of sulfates in Section 11.2 of the previous PM AQCD (U.S. EPA 1996), which concluded that human and animal toxicology studies indicated that acid aerosols are associated with small changes in pulmonary function, but generally at concentrations greater than those measured in ambient air. The results of four recent acid aerosol toxicological studies generally agree with conclusions in the 2004 PM AQCD. Three of these studies involve controlled human and animal exposures to acid aerosols with or without gaseous co-pollutants such as ozone (O_3). One study employed *in vitro* techniques to assess the toxic effects of sulfate on different cell types, including alveolar macrophages and blood polymorphonuclear leukocytes. As shown in Table A20 the recent studies reported limited evidence for effects with exposure to sulfuric acid or sulfate aerosols. One study found that there was some suggestion for interactive effects with ozone (Kleinman et al., 2003). There were no new toxicological studies published in the last four years that utilized nitrate aerosols (i.e., ammonium nitrate or nitric acid) to examine health outcomes.

Diesel exhaust particles: This source of particles has been the subject of numerous studies; the 2004 PM AQCD highlighted findings from the Diesel Health Assessment Document along with some additional studies. There are a number of new studies which have investigated the toxicity of diesel exhaust by eliminating the particle or gas portion of the exposure atmosphere or by separating the organic constituents from the carbonaceous core. Some studies have suggested that the gases, organic particle compounds, or particle core are responsible for the observed effects, and it is likely that all exhaust components contribute to toxicity. Comparison of these results across laboratories or studies is difficult, as the composition of diesel exhaust is highly dependent upon the generation method.

Traffic-related particles: A large body of literature is accumulating on a range of health effects that may be associated with exposure to traffic. These exposures include both particulate and gaseous pollutants and the reported findings include cardiovascular responses, inflammatory changes, allergenic effects, and mutagenicity. Toxicology studies and a partially annotated bibliography of epidemiologic studies are included in Attachment B.

Organic compounds: Little evidence was available on effects of particulate organic compounds in the 2004 PM AQCD (Section 7.10.2.5). A number of the recently published studies have used fine particle speciation data, along with factor analysis methods, to assess potential effects of the organic component of fine PM. Previous studies indicated that PM organic compounds (e.g., PAHs) can be mutagenic. However, few studies had provided information on potential associations with other health endpoints. Recent study results suggest that organic constituents of ambient PM can be linked to a number of biomarker and physiological responses, such as lipid peroxidation and oxidative stress generation, cytokine release, elevated plasma fibrinogen, and decreased diastolic blood pressure and vessel diameter.

Metals: As stated in Section 7.10.2.3 in the 2004 PM AQCD, the effects of metals leached from ambient filter extracts or residual oil fly ash have been shown to consistently result in cell injury and inflammation (albeit often at high concentrations). A number of new studies have reported that exposure to metals results in detectable health effects (see Attachment B).

These recent studies highlight findings for several metals which may be involved in PM toxicological effects, including Fe, Zn, V, and Ni. Furthermore, the activation of select pro-inflammatory pathways with metal exposure has been linked to particular cell surface receptors. Other research suggests a role for metal-containing PM (including those derived from oil or coal combustion sources) in altering cardiovascular parameters, which is consistent with the epidemiological findings.

Conclusions

Recent analyses continue to indicate that particles related to traffic, residual oil combustion, wood smoke, and regional sulfate pollution and primary coal burning are associated with increased mortality. A number of new studies continue to indicate that traffic-related PM exposures are associated with mortality and morbidity. Recent epidemiologic observations continue to support associations between various fine PM components and both mortality and morbidity effects.

3. SUMMARY AND CONCLUSIONS

The new study results support and expand upon findings in the 2004 PM AQCD and provide interesting new insights into relationships between ambient particles and health effects. The essential conclusions of this provisional assessment are that the science supporting evaluation of the potential health impacts of PM on human health continues to expand and hence provides a larger knowledge base for better characterizing the relationships between fine and thoracic coarse particles and health effects. The new studies provide important insights on the health effects of PM exposure, but the results do not dramatically diverge from previous findings. We find that: (a) the new studies generally strengthen the evidence that acute and chronic exposures to fine particles and acute exposure to thoracic coarse particles are associated with health effects, (b) some of the new epidemiologic studies report effects in areas with lower concentrations of $PM_{2.5}$ or $PM_{10-2.5}$ than earlier reports; (c) new toxicology and epidemiologic studies link various health outcomes with a range of fine particle sources and components, in particular from traffic-related pollution; and (d) new toxicology studies report effects of thoracic coarse particles, but do not provide evidence to support distinguishing effects from exposure to urban and rural particles. This survey and provisional assessment of new studies does not materially change any of the broad scientific conclusions regarding the health effects of PM exposure made in the 2004 PM AQCD.

In brief, this provisional assessment found:

- Recent epidemiologic studies, most of which are follow-ups or extensions of earlier work, continue to find that *long-term exposure to fine particles* is associated with both mortality and morbidity, as was stated in the 2004 PM AQCD. Notably, a follow-up to the Six Cities study shows that an overall reduction in $PM_{2.5}$ levels results in reduced long-term mortality risk. Both this study and an analysis of the ACS cohort data in Los Angeles suggest that previous studies may have underestimated the magnitude of mortality risks. Some studies provide more mixed results, including the suggestion that

higher traffic density may be an important factor. In addition, the California Children's Health study reported measures of $PM_{2.5}$ exposure and PM components and gases were associated with reduction in lung function growth in children, increasing the evidence for increased susceptibility early in life, as was suggested in the 2004 AQCD. In addition, one study reported increased infant mortality from respiratory causes with exposure to $PM_{2.5}$. The results of recent epidemiologic and toxicology studies have also reported new evidence linking long-term exposure to fine particles with a measure of atherosclerosis development and, in a cohort of individuals with cystic fibrosis, respiratory exacerbations.

- Recent epidemiologic studies have also continued to report associations between *acute exposure to fine particles* and mortality and morbidity health endpoints. These include three multi-city analyses, the largest of which (in 204 counties) shows a significant association between acute fine PM exposures and hospitalization for cardiovascular and respiratory diseases, and suggestions of differential effects in eastern U.S. as opposed to western U.S. locations. The new studies support previous conclusions that short-term exposure to fine PM is associated with both mortality and morbidity, including a substantial number of studies reporting associations with cardiovascular and respiratory health outcomes such as changes in heart rhythm or increases in exhaled NO. The fine PM concentrations reported in these studies are in some cases lower than in the previously-published studies.

- New toxicology and epidemiologic studies have continued to link health outcomes with a range of *fine particle sources and components*. Source apportionment epidemiologic analyses were conducted by teams of analysts for two cities, and the results indicate that fine PM from several sources, including regional sulfate and several combustion sources, are associated with mortality. Additionally, a number of new studies indicate that traffic-related PM exposures are associated with mortality and morbidity. A few new toxicology studies have used source apportionment techniques to assess effects related to PM from different emission categories. While limited in number and preliminary in nature, the findings suggest that several PM sources may contribute to toxicity, including combustion-related sources and regional sulfate pollution, as suggested in epidemiologic studies. Several studies have also indicated that particles from resuspended soils, such as road dust, may be associated with health effects. Toxicology studies indicate that various components, including metals, sulfates, and elemental carbon and organic carbon, are linked with health outcomes, albeit at generally high concentrations. Recent epidemiologic studies also report associations between sulfates and mortality and morbidity, and provide new evidence that organic or elemental carbon may be linked with health effects.

- The recent epidemiologic studies greatly expand the evidence on health effects of *acute exposure to thoracic coarse particles*. The 2004 PM AQCD conclusion that $PM_{10-2.5}$ exposure was associated with respiratory morbidity is substantially strengthened with these new studies; several epidemiologic studies, in fact, report stronger evidence of associations for hospital admissions with thoracic coarse particles than for fine particles. Some of the recent morbidity studies were also located in cities with low $PM_{10-2.5}$

concentrations. For example, significant associations have been reported with respiratory hospital admissions in several Canadian studies, where the reported mean and maximum $PM_{10-2.5}$ concentrations ranged from about 6 to 12 $\mu g/m^3$ and 25 to 70 $\mu g/m^3$, respectively. For mortality, many studies do not report statistically significant associations, though one new analysis reports a significant association with cardiovascular mortality in Vancouver, Canada.

- New toxicology studies have demonstrated that exposure to *thoracic coarse particles*, or PM sources generally representative of this size fraction (e.g., road dust), can result in inflammation and other health responses. Clinical exposure of healthy and asthmatic humans to concentrated ambient air particles comprised mostly of $PM_{10-2.5}$ showed changes in heart rate and heart rate variability measures. The results are still too limited to draw conclusions about specific thoracic coarse particle components and health outcomes, but it appears that endotoxin and metals may play a role in the observed responses. Two studies comparing toxicity of dust from soils and road surfaces found variable toxic responses from both rural and urban locations.

- Evidence of associations between *long-term exposure to thoracic coarse particles* and either mortality or morbidity remains limited.

- Significant associations between improvements in health and reductions in PM and other air pollutants have been reported in intervention studies or "found experiments." One new study reported reduced mortality risk with reduced $PM_{2.5}$ concentrations. In addition, several studies, largely outside the U.S., reported reduced respiratory morbidity with lowered air pollutant concentrations, providing further support for the epidemiological evidence that links PM exposure to adverse health effects.

PM PROVISIONAL ASSESSMENT—ABBREVIATIONS AND ACRONYMS

A549	human alveolar basal epithelial cell line
AA	arachidonic acid
ACE	angiotensin converting enzyme
ACS	American Cancer Society
ADMA	asymmetric dimethylarginine
AHSMOG	Adventist Health and Smog
ARIES	Aerosol Research and Inhalation and Epidemiology Study
ALP	alkaline phosphatase
AM	alveolar macrophage
$ApoE^{-/-}$	apolipoprotein deficient (mouse model of atherosclerosis)
AQS	Air Quality System
β-gluc	β-glucuronide
BAD	brachial artery diameter
BALF	bronchoalveolar lavage fluid
BC	black carbon
BEAS-2B	human bronchial epithelial cell line
BN	Brown Norway (rat)
BP	blood pressure
BrdU	bromodeoxyuridine
BS	black smoke
CAPs	concentrated ambient particles
CARB	California Air Resources Board
CB	chronic bronchitis
CBC	complete blood count
CC16	clara-cell 16 protein
CD11b	cell surface receptor
CI	confidence interval
CL	chemiluminescence
CO	carbon monoxide
CO	carbon dioxide
CoH	Coefficient of Haze
CPC	coarse particle concentrator
CRP	C-reactive protein

COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
DD	desert dust
DK	double knockout mouse strain (for ApoE and LDL)
DNA	deoxyribonucleic acid
EC	elemental carbon
ECG	electrocardiogram
eNO	exhaled nitric oxide
eNOS	endothelial nitric oxide synthase
ER	emergency room
ERK	extracellular signal-regulated kinase
ET	endothelein
f	breathing frequency
F344	Fischer 344 (rat)
FA	filtered air
FE_{NO}	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GAM	general additive model
GEE	generalized estimating equations
GGT	γ-glutamyl transferase
GLM	Generalized Linear Model
SD	geometric standard deviation
GSH	reduced glutathione
GSH/GSSG	reduced glutathione/glutathione disulfide (ratio)
GSSG	glutathione disulfide
H&E	hematoxylin and eosin
HAPC	Harvard ambient fine particle concentrator
Hb	hemoglobin
Hct	hematocrit
5-HETE	5-hydroxy-eicosatetraenoic acid
HF	high frequency of heart rate variability
12-HHT	12-hydroxyheptadecatrienoic acid
HO-1	heme oxygenase

HR	heart rate
HRV	heart rate variability
H_2SO_4	sulfuric acid
ICAM	intercellular adhesion molecules
ICD	Implantable cardioverter defibrillator
ICP-MS	inductively coupled plasma mass spectrometry
Ig	immunoglobulin (e.g., IgA, IgE, IgG, IgM)
IHD	ischemic heart disease
IL	interleukin (e.g., IL-5, IL-6, IL-8, IL-13)
IMPROVE	Interagency Monitoring of Protected Visual Environments (network)
iNOS	inducible nitric oxide synthase
IPN	Inhalable Particle Network
IQR	interquartile range
IT	Intratracheal instillation
JNK	Jun kinase
LBW	low birth weight
LDH	lactate dehydrogenase
LF	low frequency component of heart rate variability
$LDL^{-/-}$	low-density lipoprotein receptor deficient
LPS	lipopolysaccharide
LRI	lower respiratory infection
LT	leukotriene (e.g., LTB_4)
L/W	lumen to wall (ratio)
MAP	mean arterial pressure
MCh	methacholine
MCT	monocrotaline
MCV	Mean cell volume
MI	myocardial infarction
MIP	macrophage inflammatory protein (e.g., MIP-1α, MIP-2)
MLRA	multiple linear regression analysis
MMD	mass median diameter
MMEF	maximal mid-expiratory flow
MN	micronuclei
mm Hg	millimeters of mercury
MPO	myeloperoxidase

MV	minute ventilation
n	number of observations
NAC	*N*-acetyl cysteine
NAG	*N*-acetyl-β-D-glucosaminidase
NHAPS	National Human Activity Pattern Survey
NHBE	normal human bronchial epithelial (cells)
NF-κB	nuclear transcription factor-κB
NN	normal-to-normal (R-R) interval of electrocardiogram
NO	nitric oxide
NO_2	nitrogen dioxide
NO_3	nitrate
NOI	nose-only inhalation
NR	not reported
O_3	ozone
OC	organic carbon
OHC	oxygenated hydrocarbons
8-OHdG	8-hydroxy-2'-deoxyguanosine
OR	odds ratio
OVA	ovalbumin
p	probability value
PAF	platelet activating factor
PAH	polycyclic aromatic hydrocarbon
PAU	pause
PE	post-exposure
PEF	peak expiratory flow
PIF	peak inspiratory flow
Penh	enhanced pause
PG	prostaglandin (e.g., PGE_2)
PLA_2	phospholipase-A2
PLN	popliteal lymph node
PM	particulate matter
$PM_{2.5}$	fine particulate matter (mass median aerodynamic diameter ≤2.5 μm)
PM_{10}	combination of coarse and fine particulate matter
$PM_{10\text{-}2.5}$	Thoracic coarse particulate matter (mass median aerodynamic diameter between 10 and 2.5 μm)

PMN	polymorphonuclear leukocyte
PMR	proportionate mortality ratio
PNC	particle number concentration
PNN50	percentage of NN intervals >50 msec (measure of heart rate variability)
ppb	parts per billion
ppm	parts per million
QAI	QA-interval
R4	range 40
RAW 264.7	mouse macrophage cell line
R_{aw}	airway resistance
RBC	red blood cell
RMSSD	root mean square of successive differences of adjacent normal-to-normal intervals
RO	residual oil
ROFA	residual oil fly ash
ROI	reactive oxygen intermediates
ROS	reactive oxygen species
RR	risk ratio
RS	resuspended oil
RTD	road tunnel dust
SaO_2	arterial oxygen saturation
SD	Sprague-Dawley (rat)
SDNN	standard deviation of normal-to-normal intervals
SES	socioeconomic status
SH	spontaneously hypertensive
SIDS	sudden infant death syndrome
SMPS	scanning mobility particle sizer
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SOD	superoxide dismutase
SRM	Standard Reference Material
SpO_2	arterial oxygen saturation
SS	secondary sulfate
TBARS	thiobarbituric acid-reactive species
TEOM	tapered element oscillating microbalance

THP-1	human monocytic leukemia cell line
TLC	total lung capacity
TLR4	toll-like receptor-4
TNF	tumor necrosis factor (e.g., TNF-α)
TRPV1	transient receptor potential vanilloid
TSP	total suspended particulates
TWA	time-weighted average
TX	tromboxane (e.g., TXB_2)
UA	uric acid
UCPC	ultrafine condensation particle counter
UF	ultrafine
URI	upper respiratory infection
USC	University of Southern California
V_T	tidal volume
VACES	versatile aerosol concentration enrichment system
WB	whole blood
WBC	white blood cell
WBI	whole body inhalation
WKY	Wistar-Kyoto (rat)

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APPENDIX A

Summary Information from Recent Studies on the Health Effects of Particulate Matter

Table A1: Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies:				
Harvard Six Cities follow-up Laden et al. (2006)	Initial Harvard impactor data for 1974-1989 (period I). Period II data (1990-1998) based on additional $PM_{2.5}$ data (a) estimated from visibility and PM_{10} measurements and (b) measured at AQS monitors w/in 50 miles; r = 0.93 between estimated and measured $PM_{2.5}$. $PM_{2.5}$ decreases ranged from <1 $\mu g/m^3$/decade in Topeka to 7 $\mu g/m^3$/decade in Steubenville. Recent $PM_{2.5}$ means range from 10.2 to 22 $\mu g/m^3$	8096 white participants, 25+ yr, death records through 1998.	RR (total mortality) for $PM_{2.5}$ (per 10 $\mu g/m^3$): entire study period: 1.16 (1.07-1.26) period I: 1.17 (1.08-1.26) period II: 1.13 (1.01-1.27) RR with $PM_{2.5}$ in year of death: 1.14 (1.06-1.22) RR for reduced mortality risk with reduction in $PM_{2.5}$: 0.73 (0.57-0.95). Similar results presented for cardiovascular and respiratory deaths. Positive, nonsignificant associations reported for lung cancer deaths in different periods, but no significant association for reduced risk.	Lower risk ratios in second period suggests that "$PM_{2.5}$ associated mortality in this 25 year follow-up was at least in part reversible".

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
AHSMOG Chen et al., 2005	1973-1998 CARB data for PM_{10} and gases; $PM_{2.5}$ estimated from visibility; no discussion of $PM_{10-2.5}$ determination. Monthly estimates (1973-1998) of PM for each individual. $PM_{2.5}$ mean = 29.0 μg/m^3 $PM_{10-2.5}$ mean = 25.4 μg/m^3	3239 Adventist adults, fatal coronary heart disease (ICD 410-414) (92 cases)	Significant associations in females, not males; stronger and statistically significant associations in subset of postmenopausal females (80 of 92 cases). Females: $PM_{2.5}$ RR = 1.42 (1.06-1.90) and remains significant in 2-pollutant models (increased size with O_3 and SO_2, no change with NO_2) $PM_{10-2.5}$ RR = 1.38 (0.97-1.95) and increases, becomes significant with O_3 and NO_2 in 2-pollutant models, little change with SO_2. Males: $PM_{2.5}$ RR = 0.90 (0.76-1.05) $PM_{10-2.5}$ RR = 0.92 (0.66-1.29) (both little change with co-pollutants) (all per 10 μg/m^3)	Authors note consistency with results of Kunzli et al. (2005); "suggests that health effects of air pollution are different in males and females." Also observe "we cannot rule out the possibility" that there is differential measurement error since males were more likely to work >5 miles from home. Note: susceptible groups (e.g., CHD, stroke, diabetes) excluded)
ACS, Los Angeles Jerrett et al., 2005	$PM_{2.5}$ from 23 stations in LA basin (and 42 ozone monitors) for year 2000. Kriging and interpolation methods used to assign exposure levels. Also traffic buffers of 500 and 100 m from freeway based on zip code centroids $PM_{2.5}$ mean = NR, range 9-27 μg/m^3	22,905 subjects in 267 zip code areas; death records 1982-2000	Significant associations between $PM_{2.5}$ and deaths from all causes (RR 1.24, 1.11-1.37 per 10 μg/m^3), IHD, cardiopulmonary diseases, lung cancer, endocrine disease, digestive disease. No significant associations with digestive and other cancers, diabetes, accidents and other causes. Associations generally decreased with addition of ecologic covariates. After adjustment for 44 covariates and freeways w/in 500 m, significant associations with death from all causes (RR 1.17, 1.05-1.31) and IHD (RR 1.38, 1.11-1.72).	"Generally, our results agree with recent evidence suggesting that intraurban exposure gradients may be associated with even larger health effects than reported in interurban studies."

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
ACS, cause-specific deaths Pope et al. (2004)	Results reported for average $PM_{2.5}$ exposure levels, using IPN data from 1979-1983 (mean 21.1 $\mu g/m^3$) and AQS data from 1999-2000 (mean 14.0 $\mu g/m^3$). 3-digit zip codes at residence used for exposure estimates. $PM_{2.5}$ mean 17.1 $\mu g/m^3$ (averaged data)	ACS cohort, 16-year follow-up, ~300,000 subjects	Significant associations between average $PM_{2.5}$ and all CV diseases (RR 1.12, 1.08-1.15), IHD (RR 1.18, 1.14-1.23) and dysrhythmias/heart failure/cardiac arrest (RR 1.13, 1.05-1.21). Positive nonsignificant associations with some other CV diseases. Negative association with COPD (RR 0.84, 0.77-0.93) and no associations with diabetes, pneumonia and other respiratory diseases.	When stratified by smoking status, significant associations reported between $PM_{2.5}$ and mortality from all CV diseases and IHD for all three categories (never, former and current smokers). For dysrhythmia and hypertension, significant associations in the current smokers group.

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
Veterans cohort Lipfert et al. (2006)	Traffic density estimated [vehicle-km traveled/county land area] using data from 1985, 1990 and 1997. $PM_{2.5}$ data restricted to 1999-2001, averaged across period. $PM_{2.5}$ mean of 14.6 μg/m^3 for 1997-2001; sulfate mean 10.7 μg/m^3 for 1976-1981; $PM_{10-2.5}$ mean 16.0 μg/m^3 for 1989-1996.	Veterans cohort, deaths through 2001, ~25,000 subjects	For cohort members dying in 1989-1996 who originally lived in counties with AQ data: significant associations with: traffic density (RR 1.176, 1.100-1.258 per 2.6 10^6 vehicles km^2 in 1999 data) $PM_{2.5}$ (RR 1.118, 1.038-1.203 per 8 μg/m^3 1999 data) $PM_{10-2.5}$ (RR 1.072, 1.013-1.124 per 12 μg/m^3 1999 data) nonsulfate $PM_{2.5}$ (RR 1.091, 1.025-1.161) but not sulfates. In 3-poll models, traffic density is little changed, $PM_{2.5}$ effect reduced and nonsignificant (RR 1.032) and $PM_{10-2.5}$ effect negative, nonsignificant. Significant associations between mortality and traffic density in all time periods (RR's range from 1.019-1.036). Also significant associations with peak O_3 (95^{th} percentile of daily max values).	"...modest changes in traffic-related mortality risks over time, from 1976-2001, despite the decline in regulated tailpipe emissions per vehicle since the mid-1970s. This suggests that other environmental effects may be involved, such as particles from brake, tire and road wear, traffic noise, psychological stress, and spatial gradients in socioeconomic status."

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
Veterans cohort Lipfert et al. (in press)	Traffic density and historic air pollution data used as Lipfert et al., 2006, also fine particle speciation data from 2002. Gravimetric $PM_{2.5}$ mean of 13.2 $\mu g/m^3$ for 2002	Veterans cohort, deaths through 2001	In single-pollutant models for 1997-2001 mortality and 1999-2001 AQ data and 2002 speciation data, significant associations reported between mortality and traffic density, EC, nitrate, V and Ni. In two- or three-pollutant models, traffic density associations remain significant. Associations with nitrates, V and Ni also remain significant in some multi-pollutant models. Peak ozone concentration also significantly associated with mortality. $PM_{2.5}$ and sulfates also positively associated with mortality, but not statistically significant.	"Traffic density is also consistently the most important environmental predictor in multiple-pollutant models . . . it is not possible to discern which aspects of traffic (pollution, noise, stress) may be the most relevant to public health or whether an area-based predictor such as traffic density may have an inherent advantage over localized measures of ambient air quality. It is also possible that traffic density could be a marker for unmeasured pollutants or for geographic gradients *per se*."

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
CA cancer prevention study Enstrom et al. (2005)	1979-1983 IPN data for 11 CA counties, average over time and across stations for each county. overall $PM_{2.5}$ mean 23.4 $\mu g/m^3$ (10.6-42.0 range)	35,789 elderly people in 11 CA counties with $PM_{2.5}$ data (28,441 deaths by 2002)	Many results presented. RR's presented for each county relative to Los Angeles ($PM_{2.5}$ mean 28.2 $\mu g/m^3$) and none are significant, many negative. RR's by decade of death-significant associations for 1973-1982, not for 1983-92 or 1993-2002. For 1973-1982 period, RR reduced somewhat but remains significant with addition of individual potential confounders (e.g., age, sex); for 1973-2002 and 1983-2002 more marked reduction in RR size and loss of significance with addition of covariates.	"These epidemiologic results do not support a current relationship between fine particulate pollution and total mortality in elderly Californians, but they do not rule out a small effect, particularly before 1983." Note: use of California county-level average levels as an exposure surrogate likely leads to significant exposure error.
U.S. cystic fibrosis cohort Goss et al. (2004)	AQS data for 2000, annual average, subject assigned data from population-oriented monitor closest to zip code centroid. 713 monitors for $PM_{2.5}$ PM_{10} mean 24.9 (20.3-28.9) $\mu g/m^3$ $PM_{2.5}$ mean 13.7 (11.8-15.9) $\mu g/m^3$	11,484 adults and children >5 yr, enrolled in Cystic Fibrosis Foundation National Patient Registry in 1999-2000.	Main reported results are respiratory symptoms (below). Also evaluated associations with mortality from 22,303 patients in initial cohort (fewer than 200 deaths in cohort). Positive nonsignificant association reported for $PM_{2.5}$ (RR 1.32, 0.91-1.93), no associations with PM_{10}, O_3, NO_2, SO_2 or CO.	

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Mortality Studies (cont'd)**:**				
California Woodruff et al. (2006)	CARB air monitoring data obtained. Birth record data linked to data from monitor w/in 5 miles of mother's residence; data averaged over time period between birth and death. $PM_{2.5}$ means ranged from 17.3 to 19.8 $\mu g/m^3$ for different groups	Birth records for infants born in California 1999-2000 (n = 788 infant deaths)	Median concentrations of $PM_{2.5}$ were somewhat higher for infant deaths from all causes or respiratory causes than concentrations for matched survivors; not for SIDS or external causes. OR for all-cause deaths (adjusted for maternal characteristics) 1.07 (0.93-1.24) , and for respiratory deaths 2.13 (1.12-4.05) per 10 $\mu g/m^3$ $PM_{2.5}$	
Morbidity studies:				
2 atheroschlerosis clinical trials, Los Angeles CA, Kunzli et al. (2005)	Using data from 23 monitoring sites in 2000, modeling used to assign exposure at zip code level. Mean $PM_{2.5}$ exposure level at 20.6 $\mu g/m^3$, range 5.2-26.9 $\mu g/m^3$.	798 adults in 2 studies in LA basin.	Outcome measure = CIMT (carotid intima-media thickness), a measure of atherosclerosis. Significant associations of 5.9% (1-11%) increase in CIMT per 20 $\mu g/m^3$ $PM_{2.5}$ for total study population. Effects significant in women, not in men; strongest association for women >60 yr	
CA Children's Health Study Gauderman et al. (2004)	Means of annual averages (1994-2000) of measurements from stations in 12 communities, included PM_{10} (hourly) and $PM_{2.5}$ (2-week integrated filter), acid vapor, ED and OC. Mean $PM_{2.5}$ ranges from 5 to 28 $\mu g/m^3$ from figure.	Recruited 1759 4^{th} grade children	Significant decreases in FEV_1 growth with $PM_{2.5}$, acid vapor, ED and NO_2. Decreases also for FVC and MMEF growth but less often statistically significant.	"...current levels of air pollution have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in attained FEV_1 as children reach adulthood."

Table A1 (cont'd): Associations Between Long-Term Exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and Mortality and Morbidity

Cohort, Location Study	PM Data, Concentrations	Cohort Description	Quantitative Results	Comments and Author Conclusions
Morbidity studies (cont'd)**:**				
CA Children's Health Study Millstein et al. (2004)	Monthly means of pollutant data (data presented in figures only).	2034 4th grade children, questionnaire in 1995.	Monthly prevalence of asthma medication use associated with monthly average O_3, HNO_3, and acetic acid levels, not with $PM_{2.5}$, PM_{10} or $PM_{10-2.5}$. Prevalence of wheeze associated with $PM_{10-2.5}$ during spring and summer months.	
CA Children's Health Study McConnell et al. (2003)	4-year means of pollutants for 1996-1999 (same sites from Gauderman et al. (2004); $PM_{10-2.5}$ determined by subtraction of $PM_{2.5}$ from PM_{10} (2-wk integrated). Means across communities of 13.8 µg/m^3 $PM_{2.5}$, 17.0 µg/m^3 $PM_{10-2.5}$	475 children with asthma, questionnaire 1996-1999	Bronchitic symptoms associated with yearly variability of $PM_{2.5}$ (per µg/m^3), OR 1.09 (1.01-1.17), with OC, OR 1.41 (1.12-1.78), NO_2 and O_3. No significant associations with $PM_{10-2.5}$. Larger OR's with within-community yearly variability than between-community (per µg/m^3 $PM_{2.5}$ OR = 1.03, 1.01-1.05). OC and NO_2 effects strongest in 2-pollutant models	
U.S. cystic fibrosis cohort Goss et al. (2004)	AQS data for 2000, annual average, subject assigned data from population-oriented monitor closest to zip code centroid. 713 monitors for $PM_{2.5}$ PM_{10} mean 24.9 (20.3-28.9); $PM_{2.5}$ mean 13.7 (11.8-15.9)	11,484 adults and children >5 yr, enrolled in Cystic Fibrosis Foundation National Patient Registry in 1999-2000.	Increased odds of having 2 or more pulmonary exacerbations per 10 µg/m^3 $PM_{2.5}$ (21%, 7-33%) and $PM_{2.5}$ (8%, 2-15%) as well as ozone. No associations with NO_2, SO_2, or CO. Negative associations with lung function in cross-sectional analysis. Decreased FEV_1 with $PM_{2.5}$ and PM_{10}; no clear associations with gaseous pollutants.	"In conclusion, exposure to ambient PM_{10}, $PM_{2.5}$, and ozone may increase the risk for pulmonary exacerbations and increase the rate of change in lung function in the CF population."

Other studies using PM_{10} or other PM indicators:

Mortality:

Evans and Smith (2005) used data from U.S. Health and Retirement Study, a national panel survey of birth cohorts 1931-1941 with follow-up in 1992-2004. Long-term (1990-2000) PM_{10} exposure associated with a new heart condition (reported between 1994 and 1996) (coefficient = 0.004, t = 1.74) and significantly associated with shortness of breath (coefficient = 0.017, t = 2.25) but not with new lung conditions. Recent (1994-6) PM_{10} exposure associated with new heart condition (coeff = 0.0004, t = 1.74); also association with shortness of breath, but not with new lung condition. Long-term O_3 exposure also associated with new lung condition and shortness of breath

Filleul et al. (2005) used data from a respiratory disease survey data of 14,000+ adults in 24 areas in 7 cities. For 24 areas no association was reported between particles (BS) and mortality (RR 0.99, 0.98-1.01). Further analyses excluded data from 6 areas where monitors were in an area "heavily influenced by the local traffic and, so, non-representative of the mean exposure of the population of the entire area" based on NO/NO_2 ratio. For these 18 areas, RR with BS of 1.07 (1.03-1.10) for total mortality; nonsignificant RR's of 1.03 and 1.05 for lung cancer and cardiopulmonary diseases. Significant associations also with TSP for total and cardiopulmonary diseases. Significant associations also with NO, NO_2, but not SO_2. No consistent modifying effect of gender or education level. BS means ranged from 21 to 152 $\mu g/m^3$; "heavy traffic" BS means of 46, 105, 141, 111, and 91 $\mu g/m^3$.

Morbidity:

Tager et al. (2005) used data from UC Berkeley students—255 never-smoking students from LA and San Francisco areas—and reported consistent inverse associations between O_3, PM_{10} and NO_2 and FEF_{75}, FEF_{25-75} in both men and women. O_3 associations were more robust in co-pollutant models than PM_{10} or NO_2. Mean lifetime PM_{10} exposure was 48 $\mu g/m^3$ for men and 45 $\mu g/m^3$ for women.

Salam et al. (2005) used birth certificate information obtained for California-born children participating in the Children's Health Study (n = 3901) to test for associations between air pollution exposure and birth weight. Air pollution estimates assigned using zip code of maternal residence at birth, with spatial interpolation based on data from up to the three nearest stations within 50 km of zip code. Exposure estimates calculated as monthly average of 24 hr measurements, computed for trimesters and full pregnancy. A nonsignificant association was reported between higher PM_{10} exposures during the third trimester and decreased birth weight. Significant associations were reported with first-trimester CO exposure and third-trimester O_3 exposure.

Penard-Morand et al. (2005) uses questionnaire data for 6672 children in six French cities with air pollution data collected at children's schools from 1998-2000. The PM_{10} mean in high and low cities was 23.8 and 18.0 $\mu g/m^3$, respectively; the overall mean was approximately 21 $\mu g/m^3$ (from figure). Significant associations were reported with PM_{10} and asthma, atopic dermatitis, exercise-induced bronchial reactivity and allergic rhinitis.

Pierse et al. (2006) reported an association between PM_{10} and symptoms in children surveyed in 1998 and 2001 in Leicester UK. The OR for prevalence of cough without cold in 1998 and 2001 was 1.21 (1.07-1.38) and 1.56 (1.32-1.84), respectively, PM_{10} was also associated with the incidence of wheeze.

Zhang et al. (2002) used questionnaire data for 7621 children in four Chinese cities and 1995-1996 air pollution data. Grand means were $PM_{2.5}$ = 92 $\mu g/m^3$ (not a typo) and $PM_{10-2.5}$ = 59 $\mu g/m^3$. Significant associations were observed between $PM_{10-2.5}$ and incidence of bronchitis (2.20, 1.14-4.26), persistent cough (1.46, 1.12-1.90) and persistent phlegm (2.83, 1.93-4.16); positive nonsignificant association with incidence of asthma, wheeze, and ever-hospitalization for respiratory disease. For all six endpoints positive but nonsignificant associations were reported with $PM_{2.5}$. No significant associations (some nonsignificant negative) were observed with SO_2 and NO_x.

Bayer-Oglesby et al., (2005) used data from a study of 9591 school-children in nine Swiss communities with a respiratory questionnaire administered in 1992-2001. A decrease in PM_{10} (per 10 $\mu g/m^3$) was associated with a decrease in prevalence of chronic cough (OR 0.65, 0.54-0.79), bronchitis (OR 0.66, 0.55-0.80), common cold (OR 0.78, 0.6800.89), nocturnal dry cough (OR 0.70, 0.60-0.83) and conjunctivitis symptoms. No significant associations were reported with wheeze, asthma, sneezing, or hay fever. PM_{10} decreased 9.8 $\mu g/m^3$ between 1993 and 2000; the decreases in PM_{10} concentration were three times greater in urban than rural communities and ranged from 10-34 $\mu g/m^3$ in 2000.

Table A2. Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$						
Ostro et al. (2006) 9 counties in California Jan 1999-Dec 2002	All nonaccidental, cardiovascular, and respiratory causes, as well as deaths from ischemic heart disease and diabetes; all ages and age >65 yr	24-h avg $PM_{2.5}$: Range of means across counties: 14 (Contra Costa and Sacramento) to 29 (Riverside) Range of daily concentrations across counties 0-160	NO_2, CO, O_3	2-d lag and 0-1 d avg lag	Time-series study. Poisson regression using penalized and natural spline models. Default model used penalized spine regression. County-specific results pooled based on meta-analysis using random-effects model. At least one monitor collected daily $PM_{2.5}$ data in each county. A substantial number of days were missing data, which varied by county and appeared to be generally random.	% excess risk per 10 $\mu g/m^3$: <u>All causes</u>: All ages: Lag 0-1: 0.6% (0.2, 1.0) Age >65 yr: Lag 0-1: 0.7% (0.2, 1.1) <u>Cardiovascular</u>: All ages: Lag 0-1: 0.6% (0.0, 1.1) <u>Respiratory</u>: All ages: Lag 0-1: 2.2% (0.6, 3.9) In multipollutant models, $PM_{2.5}$ effect estimate was attenuated when highly correlated pollutants (NO_2 and CO) were added to the model, but was not affected by the inclusion of O_3. However, in those aged >65 yr, adjusting for gaseous pollutants did not affect the $PM_{2.5}$ coefficient. Analysis of different mortality categories and subpopulations indicated somewhat stronger associations of daily $PM_{2.5}$ with mortality for age >65yr, diabetics, females, white, and non-high school graduates.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Burnett et al. (2004) 12 Canadian cities Jan 1981-Dec 1999	All nonaccidental, cardiovascular, and respiratory causes	24-h avg $PM_{2.5}$: All 12 cities: 12.8 SD not provided. Range of means across cities: 8.1 (St. John) to 16.7 (Windsor)	$PM_{10-2.5}$, PM_{10}, SO_4^{2}, NO_2, SO_2, CO, O_3	0-, 1-, or 2-d lag	Time-series study. Natural spline functions used to model nonlinear associations. $PM_{2.5}$ data collected every 6th day. $PM_{2.5}$ data available on 12% of days with mortality data. In 11 of 12 cities, daily $PM_{2.5}$ data collected from Jan 1998 to Dec 2000.	% excess risk per 12.8 $\mu g/m^3$: <u>All causes</u>: Using all available data: Single-pollutant model: Lag 1: 0.77% (0.04, 1.58) Two-pollutant model with NO_2: Lag 1: -0.13% (-1.10, 0.85) Significant associations observed for NO_2 in two-pollutant model. Similar results observed for $PM_{10-2.5}$. Significant associations observed with PM_{10}, which also became nonsignificant after adjusting for NO_2. Only using data from period when daily $PM_{2.5}$ levels available (1998-2000): Single-pollutant model: Lag 1: 1.13% (95% CI not presented) Two-pollutant model with NO_2: Lag 1: 0.98% (0.16, 2.13) When restricting analysis to only days when daily $PM_{2.5}$ data were available, the NO_2 association was reduced considerably after adjustment for $PM_{2.5}$, whereas $PM_{2.5}$ effect remained fairly robust to NO_2 adjustment.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Dales et al. (2004) 12 Canadian cities Jan 1984-Dec 1999	SIDS; age <1 yr	24-h avg $PM_{2.5}$: All 12 cities: 12.27 IQR 8.98 Range of means across cities: 8.07 (St. John) to 16.67 (Windsor)	$PM_{10-2.5}$, PM_{10}, NO_2, SO_2, CO, O_3	0-, 1-, 2-, 3-, 4-, or 5-d lag; multiday lags of 2 to 6 d	Time-series study. Nonlinear random-effects regression model used. $PM_{2.5}$ data collected every 6th day.	No association observed between incidence of SIDS and $PM_{2.5}$ (no effect estimates presented). Similar results observed for $PM_{10-2.5}$ and PM_{10}. Significant associations observed for NO_2, SO_2, and CO.
Slaughter et al. (2005) Spokane, WA Jan 1995-Jun 2001	All nonaccidental causes	24-h avg $PM_{2.5}$: 10th%-90th% 4.2-20.2	PM_1, $PM_{10-2.5}$, PM_{10}, CO	0-, 1-, 2-, 3-d lag	Time-series study. Poisson GLM with natural splines. Hourly $PM_{2.5}$ data available. Daily averages calculated.	RR per 10 $\mu g/m^3$: Lag 1: 1.01 (0.97, 1.04) No associations observed between nonaccidental mortality and $PM_{2.5}$. Similar results observed for $PM_{10-2.5}$ and PM_{10}.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Mar et al. (in press) Phoenix, AZ Feb 1995-Dec 1997	All nonaccidental and cardiovascular causes; age 65 yr	24-h avg $PM_{2.5}$: Gravimetric sampler: 12.0 SD 6.6 Range 2-39 TEOM sampler: 13.0 SD 7.2 Range 0-42	Various $PM_{2.5}$ sources, including soil, traffic, secondary SO_4^{2}, biomass/wood combustion, sea salt, and copper smelter	0-, 1-, 2-, 3-, 4-d, or 5- lag	Time-series study. Poisson GLM with natural splines. Daily $PM_{2.5}$ data collected using both gravimetric and TEOM samplers. Focus of study was to assess variability of different methods/ investigators in estimating source apportioned $PM_{2.5}$ health effects.	% excess risk per 5th% to 95th% increment (using TEOM sampler): <u>Cardiovascular</u>: Lag 1: 15.0% (1.5, 30.3) Magnitude and lag structure of the association between $PM_{2.5}$ and cardiovascular mortality were similar to those for the combined traffic factor.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Ito et al. (in press) Washington, DC Aug1988-Dec 1997	All nonaccidental, cardiovascular, and cardiorespiratory causes	24-h avg $PM_{2.5}$: 17.8 SD 8.7 5th%-95th% 28.7	Various $PM_{2.5}$ sources, including soil, traffic, secondary SO_4^{2-}, NO_3^-, residual oil, wood smoke, sea salt, incinerator, and primary coal	0-, 1-, 2-, 3-, or 4-d lag	Time-series study. Poisson GLM with natural splines. $PM_{2.5}$ data collected every Wednesday and Saturday. Focus of study was to assess variability of different methods/ investigators in estimating source apportioned $PM_{2.5}$ health effects.	% excess risk per 28.7 $\mu g/m^3$: All causes: Lag 3: 8.3% (3.7, 13.1) Significant association between all cause mortality and $PM_{2.5}$ only observed at lag 3 d.
Klemm et al. (2004) Atlanta, GA Aug 1998-July 2000	All nonaccidental, circulatory, respiratory, cancer, and other causes; age <65 yr and 65 yr	24-h avg $PM_{2.5}$: 19.62 SD 8.32 IQR 11.62 Range 5.29-48.01	$PM_{10-2.5}$, SO_4^{2-}, EC, OC, NO_2, NO_3^-, SO_2, CO, O_3, ultrafines, hydrocarbons, acid	Multiday lag of 0-1 d	Time-series study. Poisson GLM using natural cubic splines with quarterly, monthly, or biweekly knots. Default model used monthly knots. Daily $PM_{2.5}$ data collected.	% excess risk per 19.62 $\mu g/m^3$: All causes: Age 65 yr: Lag 0-1: 11.3% (3.7, 19.4) Results differ across model specifications (i.e., choice of lag and number of knots). Weaker associations observed with $PM_{10-2.5}$. No significant associations observed in those aged <65 yr.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Villeneuve et al. (2003) Vancouver, British Columbia, Canada Jan 1986-Dec 1998	All nonaccidental, cardiovascular, respiratory, and cancer causes; SES status	24-h avg $PM_{2.5}$: Daily data from 1995-1998: 7.9 10th%-90th% 4.0-13.0 Range 2.0-32.0 Every 6th day data from 1986-1998: 11.6 10th%-90th% 4.7-20.4 Range 1.8-43.0	$PM_{10-2.5}$, PM_{10}, TSP, coefficient of haze, SO_4^2, SO_2, NO_2, CO, O_3	0-, 1-, or 2-d lag; multiday lag of 0-2 d	Time-series study. Poisson regression using natural spline functions. Daily $PM_{2.5}$ data collected from 1995 to 1998 using TEOM; $PM_{2.5}$ data collected every 6th day from 1986 to 1998 using a dichotomized sampler.	% excess risk per 9.0 $\mu g/m^3$: Results using daily $PM_{2.5}$ data: <u>All causes</u>: Lag 0:. 0.1% (-4.1, 4.1) <u>Cardiovascular</u>: Lag 0: 4.3% (-1.7, 10.7) <u>Respiratory</u>: Lag 0: 6.7% (-3.7, 18.3) <u>Cancer</u>: Lag 0:. 4.5% (-11.2, 2.8) Collectively, results suggest no association between $PM_{2.5}$ and mortality. There is some suggestive evidence of a modest increase in the risk of cardiovascular mortality among individuals of low SES status. Significant associations with cardiovascular mortality were observed for daily $PM_{10-2.5}$ and PM_{10} data.

Table A2 (cont'd). Associations of Acute $PM_{2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{2.5}$ (cont'd)						
Goldberg et al. (2006) Montreal, Canada 1986-1993	Diabetes, and nonaccidental mortality in subgroups with diabetes diagnosed at least 1 year before death in adults >65 yr. Also considered subgroups with cardiovascular diagnoses.	24-h avg $PM_{2.5}$: 17.4 SD 11.4 24-h avg predicted $PM_{2.5}$: 17.6 SD 8.8	PM_{10}, TSP, coefficient of haze, SO_4^2, predicted SO_4^2, SO_2, NO_2, CO, O_3	0-, 1-, and average of 0- to 2-day lags ("3-day mean")	Time-series study. Poisson regression using natural spline functions. Report results for predicted $PM_{2.5}$; used statistical model to estimate mass when measurements were not available; measured data available on 636 days and predicted data for 3653 days.	% excess risk per 9.5 $\mu g/m^3$: (all 3-day mean lag) mortality from diabetes: 8.37% (1.80, 15.37) nonaccidental mortality in subjects with diabetes: 3.64% (0.07, 7.33) Greater effects seen generally in the warm season. No significant association for nonaccidental mortality in subjects with diabetes, but without cancer, cardiovascular disease or airways disease. Associations reported for nonaccidental mortality in subjects with diabetes who also had any cardiovascular disease, chronic coronary disease and atheroschlerosis.

Table A3. Associations of Acute $PM_{10-2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{10-2.5}$						
Burnett et al. (2004) 12 Canadian cities Jan 1981-Dec 1999	All nonaccidental, cardiovascular, and respiratory causes	24-h avg $PM_{10-2.5}$: All 12 cities: 11.4 SD not provided. Range of means across cities: 5.5 (Vancouver) to 15.9 (Winnipeg)	$PM_{2.5}$, PM_{10}, SO_4^{2}, NO_2, SO_2, CO, O_3	0-, 1-, or 2-d lag	Time-series study. Natural spline functions used to model nonlinear associations. $PM_{10-2.5}$ data collected every 6th day. $PM_{10-2.5}$ data available on 12% of days with mortality data.	% excess risk per 11.3 $\mu g/m^3$: All causes: Single-pollutant model: Lag 1: 0.74% (-0.12, 1.61) Two-pollutant model with NO_2: Lag 1: 0.35% (-0.55, 1.26) No significant associations observed for NO_2 in two-pollutant model.
Dales et al. (2004) 12 Canadian cities Jan 1984-Dec 1999	SIDS; age <1 yr	24-h avg $PM_{10-2.5}$: All 12 cities: 11.28 IQR 8.76 Range of means across cities: 5.46 (St. John) to 15.88 (Winnipeg)	$PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3	0-, 1-, 2-, 3-, 4-, or 5-d lag; multiday lags of 2 to 6 d	Time-series study. Nonlinear random-effects regression model used. $PM_{10-2.5}$ data determined by difference. $PM_{2.5}$ and PM_{10} data collected every 6th day.	No association observed between incidence of SIDS and $PM_{10-2.5}$ (no effect estimates presented). Significant associations observed for NO_2, SO_2, and CO.

Table A3 (cont'd). Associations of Acute $PM_{10-2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{10-2.5}$						
Klemm et al. (2004) Atlanta, GA Aug 1998-July 2000	All nonaccidental, circulatory, respiratory, cancer, and other causes; age <65 yr and ≥65 yr	24-h avg $PM_{10-2.5}$: 9.69 SD 3.94 IQR 5.25 Range 1.71-25.17	$PM_{2.5}$, SO_4^{2-}, EC, OC, NO_2, NO_3^-, SO_2, CO, O_3, ultrafines, hydrocarbons, acid	Multiday lag of 0-1 d	Time-series study. Poisson GLM using natural cubic splines with quarterly, monthly, or biweekly knots. Default model used monthly knots. Daily $PM_{10-2.5}$ data collected.	% excess risk per 9.69 $\mu g/m^3$: <u>All causes</u>: Age ≥65 yr: Lag 0-1: 6.2% (-0.9, 13.7) Results differ across model specifications (i.e., choice of lag and number of knots). No significant associations observed in those aged <65 yr.

Table A3 (cont'd). Associations of Acute $PM_{10-2.5}$ Exposure with Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
$PM_{10-2.5}$ (cont'd)						
Slaughter et al. (2005) Spokane, WA Jan 1995-Jun 2001	All nonaccidental causes	24-h avg $PM_{10-2.5}$: Not reported.	PM_1, $PM_{2.5}$, PM_{10}, CO	0-, 1-, 2-, 3-d lag	Time-series study. Poisson GLM with natural splines. $PM_{10-2.5}$ calculated as difference between PM_{10} and $PM_{2.5}$ measurements. Hourly $PM_{2.5}$ and PM_{10} data available. Daily average values calculated.	No associations observed between nonaccidental mortality and $PM_{10-2.5}$. Quantitative results not provided.
Villeneuve et al. (2003) Vancouver, British Columbia, Canada Jan 1986-Dec 1998	All nonaccidental, cardiovascular, respiratory, and cancer causes; SES status	24-h avg $PM_{10-2.5}$: Daily data from 1995-1998: 6.1 10th%-90th% 2.0-13.0 Range 0.0-72.0 Every 6th day data from 1986-1998: 8.3 10th%-90th% 3.1-15.0 Range 0.7-35.0	$PM_{2.5}$, PM_{10}, TSP, coefficient of haze, SO_4^2, SO_2, NO_2, CO, O_3	0-, 1-, or 2-d lag; multiday lag of 0-2 d	Time-series study. Poisson regression using natural spline functions. Daily $PM_{10-2.5}$ data collected from 1995 to 1998 using TEOM; $PM_{10-2.5}$ data collected every 6th day from 1986 to 1998 using a dichotomized sampler.	% excess risk per 11.0 $\mu g/m^3$: Results using daily $PM_{10-2.5}$ data: All causes: Lag 0: 1.0% (-1.9, 4.0) Cardiovascular: Lag 0: 5.9% (1.1, 10.8) Respiratory: Lag 0: 1.5% (-9.4, 7.1) Cancer: Lag 0: 3.1% (-2.9, 9.4) Significant associations with cardiovascular mortality were observed for daily $PM_{10-2.5}$ and PM_{10} data.

Additional U.S. and Canadian PM-Mortality Studies:

Staniswalis et al. (2005): This study shows that the effects of airborne PM on daily mortality can be underestimated when using daily averages to summarize hourly profiles, because the daily average does not capture information about very acute exposures, that is, large exposures occurring over very short periods of time. A principal component data analysis is shown to be useful for characterizing hourly measurements of air pollution constituents. In addition, it is shown that in El Paso, the risk of PM-induced mortality is higher during still-air inversions (i.e., at low wind speeds) than it is during sandstorms (i.e., at high wind speeds). These results suggest that coarse and fine PM from resuspended fugitive dust is less toxic than fine PM of urban type.

De Leon et al. (2003): The effects of PM_{10} on circulatory and cancer mortality with and without contributing respiratory causes were examined in this study conducted in New York City. Among those aged ≥ 75 yr, effect estimates were greater for circulatory mortality with contributing respiratory causes (6.6% [95% CI: 2.7, 10.6] per 18.16 $\mu g/m^3$ increase in PM_{10}) at a 0- to 1-day lag compared to that without (2.2% [95% CI: 0.8, 3.5]). Unlike in those aged ≥ 75 yr, significantly higher risks were not observed with contributing respiratory causes in individuals aged <75 yr.

Bateson and Schwartz (2004): The association between PM_{10} and all-cause mortality in individuals aged ≥ 65 yr who were previously admitted to the hospital with a primary or secondary diagnosis of heart or lung disease was examined in this case-crossover study in Cook County, IL. A 1.14% (95% CI: 0.44, 1.85) excess risk was observed per 10 $\mu g/m^3$ increase in PM_{10} at a lag of 0 to 1 days. The effect of PM_{10} on the risk of mortality was higher among those with a prior diagnosis of myocardial infarction (1.98%), diabetes (1.49%), and congestive heart failure (1.28%).

Sullivan et al. (2003): In this case-crossover study in King County, WA, the association between PM and out-of-hospital sudden cardiac arrest in individuals with and without preexisting cardiovascular and respiratory disease was examined. $PM_{2.5}$ data was estimated using a nephelometric measure (PM_1). No consistent associations were observed between increased levels of $PM_{2.5}$ or PM_{10} and risk of primary cardiac arrest.

Holloman et al. (2004): To examine the association between cardiovascular mortality and estimated exposure to $PM_{2.5}$ in seven counties in North Carolina, a three-level hierarchical Bayesian model was used: (1) linking monitor readings to ambient levels over the region; (2) linking ambient levels to exposure levels (estimated using NHAPS); and (3) linking exposure levels to mortality. Significant associations were observed between cardiovascular mortality and $PM_{2.5}$ at a lag of 2 days. Results obtained by incorporating a simple exposure simulator into the model indicated that the effect of increased levels of exposure was not equivalent to that of ambient $PM_{2.5}$ on cardiovascular mortality.

Vedal et al. (2003): The associations between PM_{10} and all-cause, cardiovascular, and respiratory mortality were examined in Vancouver, Canada (PM_{10} concentration range 4.1 to 37.2 $\mu g/m^3$). During the summer, statistically significant effects on respiratory mortality were observed for PM_{10}, O_3, and SO_2, and the effects of NO_2 and CO were also nearly significant. Effects on total and cardiovascular mortality were only seen for O_3. During the winter, significant effects on total mortality were observed for PM_{10}, NO_2, and SO_2; NO_2 and SO_2 also

were associated with cardiovascular mortality. No significant associations with respiratory mortality were observed in the winter. The authors report that these findings may support the notion that no threshold pollutant concentrations are present, but they also raise concern that the observed effects may not be due to the measured pollutants themselves, but rather of some other factors present in the air pollution-meteorology mix.

Jerrett et al. (2004): Significant associations between CoH and all-cause mortality were observed in regions of lower SES status at various lags of exposure. Regions of higher SES status displayed no significant associations except at a multiday lag of 0 to 3 days. These findings suggest that the effect of PM on mortality may be modified by SES status. Low educational attainment and high manufacturing employment significantly and positively modified the effects of PM on acute mortality.

Additional Studies Examining Issues Related to Interpreting the PM-Mortality Relationship:

Forastiere et al. (2005): Using a case-crossover design, the associations between daily ambient air pollution levels (particle number concentration [PNC], PM_{10}, CO, NO_2, and O_3) and the occurrence of out-of-hospital fatal coronary events in Rome were examined. The association was statistically significant for PNC, PM_{10}, and CO, with the strongest effect observed on the same day. An IQR increase in PNC (27,790 particles/cm^3) and PM_{10} (29.7 $\mu g/m^3$) was associated with a 7.6% (95% CI: 2.0, 13.6) and 4.8% (95% CI: 0.1, 9.8) excess risk in mortality, respectively. Stronger effects were observed among people aged 65 yr, and possibly in those with hypertension and COPD.

Sunyer et al. (2002): This case-crossover study assessed the acute association between air pollution and all-cause mortality in a population-based cohort of subjects with asthma recruited from emergency room admissions for asthma exacerbation in Barcelona, Spain. No significant associations were observed between PM_{10} or BS and mortality. Slightly larger effect estimates were observed in subjects admitted more than once compared to those admitted only once to the emergency department for asthma, but differences were not significant. Stronger associations were observed for NO_2 and O_3.

Kan et al. (2005): Using time-series Poisson regression, the relationship between daily SARS mortality and ambient air pollution in Beijing was examined. An 10 $\mu g/m^3$ increase in PM_{10} (mean 149.1 $\mu g/m^3$ [SD 8.1]) over a 5-day moving average corresponded to a RR of 1.06 (95% CI: 1.00, 1.12). NO_2, but not SO_2, also was associated with daily SARS mortality (RRs of 1.22 [95% CI: 1.01, 1.48] and 0.74 [95% CI: 0.48, 1.13], respectively).

Goodman et al. (2004): In a Dublin, Ireland study, a constrained (6th order polynomial) distributed lag model used to examine BS effects through 40 days. Results were compared to effects estimated for a 0 to 2 day lag of BS exposure. Stronger associations with BS were consistently observed for all-cause, cardiovascular, and respiratory mortality using the extended follow-up period. Analyses suggest that studies on acute effects of air pollution have underestimated the total effects of PM on mortality.

Table A4. Effects of $PM_{2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$						
Dominici et al. (2006) United States National Database1999-2002	A daily time-series analysis on hospital admission rates (from the Medicare National Claims History Files) for cardiovascular and respiratory outcomes and ambient $PM_{2.5}$ levels, temperature for 204 U.S. urban counties (population >200,000) with 11.5 million Medicare enrollees (aged >65 years) living an average of 5.9 miles from a $PM_{2.5}$ monitor.	$PM_{2.5}$ county annual mean: 13.4 $\mu g/m^3$ IQR (11.3-15.2 $\mu g/m^3$)	O_3	0-2	Nationally, short-term increase in hospital admission rates associated with $PM_{2.5}$ for all health outcomes except injuries. The largest association was for heart failure. Substantial homogeneity of fine particle matter concentration across geographic area. For cardiovascular disease, all estimates in the eastern U.S. were positive and generally statistically significant, while estimates in the western U.S. were close to 0 except for heart failure For respiratory disease, there was greater consistency between regions. The authors noted that they did not find evidence of the effect modification by average concentration of either $PM_{2.5}$ or O_3.	Excess risk per 10 $\mu g/m^3$: Heart failure 1.28% (0.78-1.78%) Annual reduction in admissions attributable to a 10 $\mu g/m^3$ reduction in daily $PM_{2.5}$ level for 204 counties in 2002 Cerebrovascular disease: 1836 (680-2992) Heart failure: 3156 (1923-4389) Respiratory tract infection: 2085 (929-3241)

Table A4 (cont'd). Effects of $PM_{2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)						
Lin et al. (2002) Toronto 1981-1993	Both case-crossover and time-series analyses used to assess the associations between various PM measures and asthma hospitalization among children 6-12 years old.	$PM_{2.5}$ mean: 17.99 µg/m^3 Min 1.22 Max 89.59	$PM_{10-2.5}$, PM_{10}, O_3, NO_2, CO, SO_2	1-7	Significant effects were not found for $PM_{2.5}$, but both analysis methods did find relationships with $PM_{10-2.5}$ for either sex. Individual $PM_{2.5}$ results showed some positive association but not after consideration of both weather conditions and gaseous co-pollutants.	$PM_{2.5}$ (IQR 9.3 µg/m^3) After controlling for gaseous pollutants effect estimates range from -7% to 1% with 95% CI all including 0% for both bidirectional case-crossover and time-series analysis.
Lin et al. (2005) Toronto 1998-2001	Examined the associations between pollutants and hospitalizations for respiratory infections among children younger than 15 years of age. Bi-directional case-crossover design used.	$PM_{2.5}$ Mean: SD 9.59 SD 7.06	$PM_{10-2.5}$, PM_{10}, CO, SO_2, NO_2, O_3		$PM_{2.5}$ showed no significant effects when other pollutants were considered. The effects for $PM_{10-2.5}$ were pronounced.	$PM_{2.5}$ (IQR 7.8 µg/m^3) single-pollutant: 10% (2-22) 4 day lag after adjustment for other pollutants: -6% (-19, 8)

Table A4 (cont'd). Effects of $PM_{2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)						
Yang et al. (2004) Vancouver, British Columbia Jun 1, 1995-Mar 31, 1999	Logistic regression was used to estimate the associations between PM and first hospitalization for children less than 3 years of age, a case-control approach. Also, analysis was conducted using bidirectional-case crossover analysis and time-series analysis.	$PM_{2.5}$ Mean 7.7 µg/m^3 SD 3.7 Range: 2.0-32.0	PM_{10}, $PM_{10-2.5}$, CO, O_3, NO_2, SO_2	0-7	The data indicated possible harmful effects from coarse PM on first hospitalization for respiratory disease. No significant association was found between $PM_{2.5}$ and first hospitalization for respiratory disease. $PM_{2.5}$ concentrations were relatively low. In this study, only the case-control and case-crossover approaches support the notion of effect of daily average $PM_{10-2.5}$ on first hospitalization for respiratory disease in early childhood. It is not clear if these two approaches overestimated or if the time-series analysis underestimated. For $PM_{2.5}$, the authors noted that differences in findings may be explained, in part, by TEOM measurements, which may be lower than those of filter-based samples.	No quantitative results reported.

Table A4 (cont'd). Effects of $PM_{2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)						
Chen et al. (2004) Vancouver, British Columbia Jun 1995-Mar 1999	A time-series analysis assessing the association between low levels of size-fractionated PM and hospitalization for chronic obstructive pulmonary disease (COPD) in the elderly. GAM and GLM models were used.	$PM_{2.5}$ Mean 7.7 µg/m^3 SD (3.7) Range: 2.0-32.0	PM_{10}, $PM_{10-2.5}$, CO, O_3, NO_2, SO_2	1-7	Particle-related measures were significantly associated with COPD hospitalizations in the Vancouver area, but the effects are not independent of other air pollutants.	For a 3-day average $PM_{2.5}$ 9% (3, 16%) This association was not significant when NO_2 included in the model.
Chen et al. (2005) Vancouver, British Columbia Jun 1, 1995-Mar 31, 1999	A time-series analysis was used to evaluate the associations between respiratory admissions and PM, looking at first, second, and overall hospital admission for respiratory disease among the elderly. 8,989 adults, ≥65 yr.	$PM_{2.5}$ Mean 7.7 µg/m^3 SD (3.7) Range: 2.0-32.0	PM_{10}, $PM_{10-2.5}$, CO, O_3, NO_2, SO_2	1-7	$PM_{10-2.5}$ had a larger effect on respiratory admissions than $PM_{2.5}$. For $PM_{10-2.5}$, the second and overall admission rates were higher than the first admission rate.	$PM_{2.5}$ adjusted for copollutants First admission Lag 1: 2% (-1, 6) Second admission: 1% (-3, 6)

Table A5. Effects of $PM_{10-2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$						
Lin et al. (2002) Toronto 1981-1993	Both case-crossover and time-series analyses used to assess the associations between various PM measures and asthma hospitalization among children 6-12 years old.	$PM_{10-2.5}$ Mean 12.17 Range: 0-68	$PM_{2.5}$, PM_{10}, O_3, NO_2, CO, SO_2	1-7	Significant associations with $PM_{10-2.5}$ for either sex; no significant associations with PM2.5.	$PM_{10-2.5}$ (IQR 8.4 µg/m^3) After controlling for gaseous pollutants: 17% (3-3) 6d avg lag, bidirectional case-crossover 15% (6-25) 6d avg lag, time-series analysis.
Lin et al. (2005) Toronto 1998-2001	Examined the associations between pollutants and hospitalizations for respiratory infections among children <15 yr. Bi-directional case-crossover design used.	$PM_{1-10-2.5}$ Mean 10.86 (SD 5.37) Range: 0-45	$PM_{2.5}$, PM_{10}, CO, SO_2, NO_2, O_3		Significant associations with $PM_{10-2.5}$ for either sex; $PM_{2.5}$ showed no significant effects when other pollutants were considered.	$PM_{10-2.5}$ (IQR 6.5 µg/m^3) 6-day avg lag after adjustment for gases boys 15% (2-30) girls 18% (8-34)
Chen et al. (2004) Vancouver, British Columbia Jun 1995-Mar 1999	A time-series analysis assessing the association between low levels of size fractionated PM and hospitalization for chronic obstructive pulmonary disease (COPD) in the elderly. GAM and GLM models were used.	$PM_{10-2.5}$ Mean 5.6 µg/m^3 Range: 0.1-24.6	PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2	1-7	Significant associations for $PM_{10-2.5}$ with COPD hospitalizations in the Vancouver area. Also statistically significant associations with PM_{10}, $PM_{2.5}$, and COH, but the effects are not independent of other air pollutants.	$PM_{10-2.5}$ (IQR 4.2 µg/m^3) 3-day avg lag 8% (2-15) Significance lost with CO, NO_2 and SO_2 but not O_3

Table A5 (cont'd). Effects of $PM_{10-2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$ (cont'd)						
Yang et al. (2004) Vancouver, British Columbia Jun 1, 1995-Mar 31, 1999	Logistic regression was used to estimate the associations between PM and first hospitalization for children <3 yr, a case-control approach. Also, analysis was conducted using bidirectional-case crossover analysis and time-series analysis.	$PM_{10-2.5}$ Mean 5.6 µg/m^3 Range: 0-24.6	PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2	0-7	The data indicated possible harmful effects from coarse PM on first hospitalization for respiratory disease. No significant association was found between $PM_{2.5}$ and first hospitalization for respiratory disease. $PM_{2.5}$ concentrations were relatively low. In this study, only the case-control and case-crossover approaches support the notion of effect of daily average $PM_{10-2.5}$ on first hospitalization for respiratory disease in early childhood. It is not clear if these two approaches overestimated or if the time-series analysis underestimated. For $PM_{2.5}$, the authors noted that differences in findings may be explained, in part, by TEOM measurements, which may be lower than those of filter-based samples.	$PM_{10-2.5}$ (IQR 4.2 µg/m^3) Respiratory hospital admissions, 3-day lag: mean $PM_{10-2.5}$ 12% (-2-25) *22% (2-48) max $PM_{10-2.5}$ 13% (0-27) *14% (-1-32) *after adjustment for gases Associations with asthma and pneumonia hospitalization not statistically significant.

Table A5 (cont'd). Effects of $PM_{10-2.5}$ on Daily Hospital Admissions

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$ (cont'd)						
Chen et al. (2005) Vancouver, British Columbia Jun 1, 1995-Mar 31, 1999	A time-series analysis was used to evaluate the associations between respiratory admissions and PM, looking at first, second, and overall hospital admission for respiratory disease among the elderly. 8,989 adults, ≥65 yr.	$PM_{10-2.5}$ Mean 5.6 µg/m^3 Range: 0.1-24.6	PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2	1-7	$PM_{10-2.5}$ had a larger effect on respiratory admissions than $PM_{2.5}$. For $PM_{10-2.5}$, the second and overall admission rates were higher than the first admission rate. (1) People with a history of respiratory admissions are at a higher risk of respiratory disease in relation to particulate air pollution in urban areas. (2) Analyses based on overall rather than repeated hospital admissions lead to lower estimates of the risk of respiratory disease associated with particulate air pollution.	$PM_{10-2.5}$ (IQR 4.2 µg/m^3) 3 day avg first admission 3% (-2-9) second admission 22% (0-36) overall 6% (2-11) No significant associations with $PM_{2.5}$

Table A6. Effects of $PM_{2.5}$ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$						
Metzger et al. (2004) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific cardiovascular diseases by age groups >19 yr and >65 yr. Time-series study. 4, 407, 535, EDV from 31 Atlanta hospitals.	$PM_{2.5}$ $\mu g/m^3$ Median: 17.8 Range: 8.9 to 32.3	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{10-2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Secondary analyses performed to assess alternative pollutant lag structures, seasonal influences, and age effects. Cardiovascular visits were significantly associated with several pollutants, including NO_2, CO, and $PM_{2.5}$, but not O_3.	$PM_{2.5}$ per 10 $\mu g/m^3$ All ages: Total cardiovascular: 3.3% (1, 5.6) Dysrhythmia: 2.1% (-3, 7.0) Congestive heart failure: 5.5% (0.6, 10.5) Ischemic heart disease: 2.3% (-2, 6.4) Peripheral vascular and cerebrovascular disease: 5 (0.8, 9.3)
Peel et al. (2005) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific respiratory diseases by age groups 0-1, 2-18, >19, and >65 yr. Time-series study.	$PM_{2.5}$ 19.2 ± 8.9 Range: 8.9 to 32.3	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{10-2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GEE and GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Also performed secondary analyses estimating the overall effect of pollution over the previous 2 wk. Seasonal analyses indicated stronger associations with asthma in the warm months, especially for O_3 and $PM_{2.5}$ organic carbon. Quantitative results not presented for multipollutant, age-specific, and seasonal analyses.	$PM_{2.5}$ per 10 $\mu g/m^3$ All ages: All available data: Total respiratory: 1.6% (0, 3.5) Upper respiratory infections: 1.8 (0, 4.3) Asthma: 0.5 (-2, 3.3) Pneumonia: 1.1% (-2, 1.2) COPD: 1.5 (-3, 6.3)

Table A6 (cont'd). Effects of $PM_{2.5}$ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)						
Slaughter et al. (2005) Spokane, WA Jan 1995-Jun 2001	Study of hospital and ED visits for respiratory and cardiac condition in relation to PM_1, $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ using a log-linear generalized linear model for lags 0 to 3 and compared results to a log-linear generalized additive model.	$PM_{2.5}$ 90% of concentration ranged between 4.2 and 20.2 $\mu g/m^3$	CO	1-3	No overall association with respiratory ED visits and any size fraction of PM nor with cardiac hospital admissions.	$PM_{2.5}$ ED visits (10 $\mu g/m^3$ increase) Lag 1: All respiratory: 1% (-2, 4) Acute asthma: 3% (-2, 9) Cardiac admissions: 0% (-4, 3)

Table A7. Effects of $PM_{10-2.5}$ on Daily Emergency Department Visits

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$						
Metzger et al. (2004) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific cardiovascular diseases by age groups >19 yr and >65 yr. Time-series study. 4, 407, 535, EDV from 31 Atlanta hospitals.	$PM_{10-2.5}$ Median: 9.1 $\mu g/m^3$ Range (10%-90%): 4.4-16.2	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Secondary analyses performed to assess alternative pollutant lag structures, seasonal influences, and age effects. Cardiovascular visits were significantly associated with several pollutants, including NO_2, CO, and $PM_{2.5}$, but not with $PM_{10-2.5}$ or O_3.	$PM_{10-2.5}$ per 5 $\mu g/m^3$ 3 day avg lag CVD visits: 1.2% (-1-4.0)
Peel et al. (2005) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific respiratory diseases by age groups 0-1, 2-18, >19, and >65 yr. Time-series study.	$PM_{10-2.5}$ Median: 9.7 $\mu g/m^3$ Range (10%-90%): 4.4-16.2	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons	0-2	Poisson GEE and GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Also performed secondary analyses estimating the overall effect of pollution over the previous 2 wk. No significant associations with $PM_{10-2.5}$. Some significant associations with gaseous pollutants and PM_{10}. Quantitative results not presented for multipollutant, age-specific, and seasonal analyses.	$PM_{10-2.5}$ per 5 $\mu g/m^3$ 3 day avg lag Respiratory visits: 3% (-2-2.5)
Slaughter et al. (2005) Spokane, WA Jan 1995-Jun 2001	Study of hospital and ED visits for respiratory and cardiac condition in relation to PM_1, $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ using a log-linear generalized linear model for lags 0 to 3 and compared results to a log-linear generalized additive model.	$PM_{10-2.5}$ 90% of concentration ranged between 4.2 and 20.2 $\mu g/m^3$	CO, PM_{10}, $PM_{2.5}$	1-3	No overall association with respiratory ED visits and any size fraction of PM nor with cardiac hospital admissions.	$PM_{10-2.5}$ ED visits (10 $\mu g/m^3$ increase) Lag 1: All respiratory: 1% (-2, 4) Acute asthma: 3% (-2, 8) COPD admissions: 1% (-7, 9)

Table A8. Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$					
Pope et al. (2004) Wasatch Front, UT Winter 1999-2000 and summer in Hawthorne and winter 2000-2001 in Bountiful and Lindon	Study of the effects of pollutants on autonomic function measured by changes in HRV and blood markers of inflammation in a panel of 88 elderly subjects using regression analysis.	$PM_{2.5}$ (TEOM) Mean (SD) 18.9±13.4	–	While this study observed statistical associations between $PM_{2.5}$ and HRV and C-reactive protein (CRP), most of the relevant variability in the temporal deviation of these physiological endpoints was not explained by $PM_{2.5}$. These observations therefore suggest that $PM_{2.5}$ may be one of multiple factors that influence HRV and CRP.	$PM_{2.5}$ 100 µg/m^3 increases −35 (SE = 8) in msec decline SDNN −0.81 (SE 0.17) mg/dL increase in CRP
Riedker et al. (2004) North Carolina Autumn 2001	Nine healthy North Carolina Highway Patrol troopers were monitored on 4 successive days for in-vehicle $PM_{2.5}$, roadside $PM_{2.5}$, and ambient $PM_{2.5}$. Ambulatory ECGs performed and various blood indicators measured.	$PM_{2.5}$ (ambient) 32.3 µg/m^3 Range: 9.9-68.9	O_3, CO, NO_2	The troopers showed significant and strong increases of HRV, ectopic beats, blood inflammation and coagulation markers, and MCV in association with the in-vehicle exposure to $PM_{2.5}$ as indication of increase of vagal activity.	$PM_{2.5}$ µg/m^3 In-vehicle 10 µg/m^3 decreased lymphocytes (−11%) increased neutrophils (6%) increased C-reactive protein (32%) ectopic beats (20%)

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Schwartz et al. (2005b) Boston, MA 12 weeks during the summer of 1999	A panel study of 28 elderly subjects (age 61-89 years). Various HRV parameters were measured for 30 min once a week. Analysis using linear mixed models with log-transformed HRV measurements. To examine heterogeneity of effects, hierarchical model was used.	$PM_{2.5}$ during HRV measurement: Median: 10 µg/m^3 BC Median: 1.0 µg/m^3	BC,O_3, CO, SO_2, NO_2	HRV parameters examined included: SDNN, r-MSSD, PNN_{50}, and LF/HF ratio. Strongest association seen for BC, an indicator of traffic particles. The random effects model indicated that the negative effect of BC on HRV was not restricted to a few subjects. Subjects with MI experienced greater BC-related decrements in HRV parameters.	$PM_{2.5}$ 24 h Change in HRV parameters: SDNN: −2.6 (0.8, −6.0) r-MSSD: −10.1 (−2.8, −16.9) BC 24 h SDNN −5.1 (−1.5, −8.6) r-MSSD: −10.1 (−2.4, −17.2)
Park et al. (2005) Greater Boston area, MA Nov 2000-Oct 2003	Cross-sectional study examining the effect of pollutants on HRV in 497 adult males (mean age 72.7 years). Subjects were monitored during a 4-min rest period between 8 a.m. and 1 p.m. Pollutant levels measured at central site 1 km from study site. Exposure averaging times of 4, 24, and 48 h investigated. Modifying effects of hypertension, IHD, diabetes, and use of cardiac/anti-hypertensive medications also examined. Linear regression analyses. This subject group is from the VA Normative Aging Study.	$PM_{2.5}$ Mean (SD): 11.4 (±8.0) Range: 6.45-62.9	O_3, PNC, BC, NO_2, SO_2, CO	Of the pollutants examined, only $PM_{2.5}$ and O_3 showed significant associations with HRV outcomes. The 4-h averaging period was most strongly associated with HRV indices. The PM effect was robust in models including O_3. The associations between PM and HRV indices were stronger in subjects with hypertension (n = 335) and IHD (n = 142). In addition, calcium-channel blockers significantly influenced the effect of PM on low frequency power. Limitations of this study are the use of a short 4-min period to monitor HRV and the lack of repeated measurements for each subject.	$PM_{2.5}$ (8 µg/m^3) 48 h Change in low frequency power: Subjects with hypertension: −10.5% (−25.8, 7.9) Subjects without hypertension: −2.9% (−23.5, 23.2) Subjects with ischemic heart disease: 0.5% (−26.7, 37.7) Subjects without ischemic heart disease: −7.0% (−21.3, 9.9) LF/HF ratio increased 18.6% (95% CI 4.1-35.2%)

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Wheeler et al. (2006) Atlanta, GA Fall 1999 and spring 2000	Examined pollutant effects on HRV in 18 subjects with COPD and 12 subjects with recent MI. Data collected 7 days in fall and spring. Associations examined using linear-mixed effect model. Age range 49-76 yrs.	$PM_{2.5}$ $\mu g/m^2$ Mean: 17.8	O_3, CO, SO_2, NO_2	For COPD patients, $PM_{2.5}$ exposure related to an increase in SDNN. The results for MI subjects were positive, but not significant. Effects were modified by medication use, baseline pulmonary function, and health status. The small numbers studied limit the study.	$PM_{2.5}$ 4-h IQR (11.65 $\mu g/m^3$) COPD 8.3% (1.7, 15.3) MI (IQR: −854 $\mu g/m^3$) 2.9% (−7.8, 2.3)
Rich et al. (2005) Boston, MA Jul 1995-Jul 2002	In 203 patients with implantable cardioverter defibrillators. Case-crossover study design used to examine association between air pollution and ventricular arrhythmias. For each case period, 3-4 control periods were selected. Various moving average concentrations of exposure considered – lags 0-2, 0-6, 0-23, and 0-47 h. Analysis using conditional logistic regression models.	$PM_{2.5}$ ($\mu g/m^3$) 1-h avg Median: 9.2 $PM_{2.5}$ ($\mu g/m^3$) 24-h avg Median: 9.28 IQR: 7.8	O_3, BC, CO, NO_2, SO_2	Associations were observed for $PM_{2.5}$ and O_3 with a 24-h moving average, and for NO_2 and SO_2 with a 48-h moving average. In two-pollutant analyses, only $PM_{2.5}$ and O_3 appeared to act independently.	Odds ratios: 24 h $PM_{2.5}$ per 7.8 $\mu g/m^3$ for ventricular arrhythmia 1.19 (1.02, 1.38) $PM_{2.5}$ with O_3 model: All events: 1.18 (1.01, 1.37)
Rich et al., (2006) Boston, MA Jun 1995-Dec 1999	In 203 patients with implantable cardioverter defibrillators, were 91 episodes of paroxysmal atrial fibrillation (PAF) in 29 subjects. Case-crossover design used to examining association between air pollutants and PAF, with matching control periods on weekday and hour within same calendar month. Conditional logistic regression models used.	$PM_{2.5}$ ($\mu g/m^3$) 1-h avg Median: 9.2 Max: 84.1 $PM_{2.5}$ ($\mu g/m^3$) 24-h avg Median: 9.8 Max: 53.2	O_3, BC, CO, NO_2, SO_2	Positive, but not significant, associations reported with $PM_{2.5}$, BC and NO_2. Significant associations reported with O_3. Authors note reduced statistical power for $PM_{2.5}$ and BC analyses due to missing data. Conclude PAF is associated with exposure to community air pollution.	$PM_{2.5}$ per 9.4 $\mu g/m^3$ IQR, 0-hour lag: OR 1.41 (0.82, 2.42) BC per 0.91 $\mu g/m^3$ IQR, 1-23 hour lag period: OR 1.46 (0.67, 3.17)

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Dockery et al. (2005) Boston, MA Jul 1995-Jul 2002	Effect of air pollution on incidence of ventricular arrhythmias was examined in 203 patients with implantable cardioverter defibrillators using time-series methods. Mean follow-up period was 3.1 yr/subject. All subjects located <40 km of air pollution monitoring site. Two-day mean air pollution level used in analysis. Results analyzed by logistic regression using GEE with random effects. Modifying effects of previous arrhythmia within 3 days also examined.	$PM_{2.5}$ Median: 10.3 $\mu g/m^3$ IQR: 6.9 $\mu g/m^3$	O_3, BC, SO_4^{2-}, particle number, CO, NO_2, SO_2	No associations were observed between air pollutants and ventricular arrhythmias when all events were considered. When only examining ventricular arrhythmias within 3 days of a prior event, positive associations were found for most pollutants except for O_3. The associations suggest a link with motor vehicle pollutants.	$PM_{2.5}$ (6.9 $\mu g/m^3$) Odds ratios: All events: 1.08 (0.96, 1.22) Prior arrhythmia event <3 days: 1.60 (1.30, 1.96) Prior arrhythmia event >3 days: 0.98 (0.86, 1.12)

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Rich et al. (2004) Vancouver, British Columbia, Canada Feb-Dec 2000	Case-crossover study design used to investigate association between air pollution and cardiac arrhythmia in patients aged 15-85 yr (n = 34) with implantable cardioverter defibrillators. Controls periods were selected 7 days before and after each case day. Analysis using conditional logistic regression.	$PM_{2.5}$ Mean: 8.2 µg/m^3 IQR: 5.2	O_3, EC, OC, SO_4^{2-}, CO, NO_2, SO_2	No consistent association between any of the air pollutants and implantable cardioverter defibrillators discharges.	Odds ratios were less than 1.0 at all lags (0, 1, 2, 3) for $PM_{2.5}$.
Gold et al. (2005) Boston, MA Summer of 1999	Study of associations between ambient pollutants and ST-segment levels in repeated measures involving 269 observations in 24 subjects 61-88 yr; each observed 12 times between June-September involving Holter recording. $PM_{2.5}$, BC, and CO were collected at 5 central sites 0.5 km from residences of subjects.	$PM_{2.5}$ 12 h Median: 9.8 µg/m^3 BC Median: 1.14 µg/m^3	CO, O_3, NO_2, SO_2	Elevated BC predicted increased risk of ST-segment depression with the strongest association being for the 5-h lagged value.	BC 12 h mean estimated overall ST-segment change: −0.08 mm p = 0.03

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Dubowsky et al. (2006) St. Louis, MO Mar-June 2002	Investigation of ambient particles and markers of systemic inflammation among repeated measures from 44 subjects (≥60 yr). Trips from senior home in diesel bus into St. Louis. Analyzed using linear mixed model.	$PM_{2.5}$ Mean (SD) $\mu g/m^3$ 16 (6.0) Range 6.5-28	CO, NO_2, SO_2, O_3	Modest positive association found between fine particles and indicators of systemic inflammation with larger association suggested for individuals with diabetes, obesity, and hypertension. Positive associations found for longer moving averages.	$PM_{2.5}$ 4-h IQR (5.4 $\mu g/m^3$) 5-day mean $PM_{2.5}$ (6.1) 14% increased CRP (90% CI: 5.4 to 37%) for all individual and 81% (90% CI: 21, 172) for those with diabetes, obesity, hypertension

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
O'Neill et al. (2005) Boston, MA May 1998-Jan 2000 Baseline period Time trial 2000-2002	270 patients with diabetes or at risk for diabetes were studied in relation to various pollutant levels and evaluated for association with vascular reactivity. Linear regressions were fit to the percent change in brachial artery diameter (flow-mediated and nitroglycerin-mediated) into particulate pollutant index and other factors.	$PM_{2.5}$ (1998-2002) Mean (SD): 11.5 (6.4) µg/m^3 Range: 1.1-40.0	SO_4^{2-}, BC, ultrafine	$PM_{2.5}$ was associated with nitroglycerin-mediated reactivity; an association was also reported with ultrafine particles. Effects were stronger in type II than type I diabetes. BC and SO_4^{2-} increases were associated with decreased flow-mediated reactivity among those with diabetes. Although the strongest associations were with the 6-day moving avg, similar patterns and quantitatively similar results appear in the other lags.	$PM_{2.5}$ 6-day moving average per IQR Nitroglycerin-mediated reactivity: −7.6%; 95% CI: 12.8 to −2.1
Schwartz et al. (2005a) Boston 2000	Examined the associations between $PM_{2.5}$ and HF in 497 subjects in Normative Aging Study (NAS) using linear regression controlling for covariates.	$PM_{2.5}$ Mean: 11.4 µg/m^3 (8.0 SD)	—	In subjects without the allele (for glutathione-*S*-transferase M1) an increase in $PM_{2.5}$ during the 48 h before HF (high-frequency component of HRV) measurement was associated with a decrease in HF. In subjects with the allele, no effect was noted. The effects of $PM_{2.5}$ on HR appear to be mediated by ROS, which may be a lag pathway for effects of combustion particles.	$PM_{2.5}$ µg/m^3 10 µg/m^3 increase HF −34% (−9%, −52%)
Sullivan et al. (2003) Western Washington State 1985-1994	A case-crossover study of 1,206 out-of-hospital cardiac arrest among persons with (n = 774) and without (n = 432) clinically recognized heart disease and daily measures of $PM_{2.5}$.	PM (nephelometry, km^{-1} bsp) Mean: 0.71 Min: 0.05 Max: 5.99	SO_2, CO	There was no consistent association between increased levels of fine particular matter and risk of primary cardiac arrest. This differs from results seen in other airsheds.	For cases with preexisting cardiac disease OR = 0.97 (0.89-1.07)

Table A8 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Mar et al. (2005) Seattle 1999-2001	Study of pollutants in relation to health parameters in 88 subjects (>75 yrs of age). HR, BP, and arterial oxygen saturation was examined using GEE.	$PM_{2.5}$ outdoor $\mu g/m^3$ range from 9.0 (±4.61) for healthy to 12.5 (±7.9) for CVD subjects	PM_{10}	Healthy subjects had decreases in HR associated with $PM_{2.5}$. SaO_2 does not have a consistent response to PM air pollution. Sample size was a limitation in this study.	$PM_{2.5}$ outdoor change in heart rate −0.75 bpm (−1.42, −0.07)
DeMeo et al. (2004) Boston July-August 1999	Investigated the association between $PM_{2.5}$ and oxygen saturation during a 12-wk repeated measures study of 28 older Boston residents using a fixed effects model/GLM.	$PM_{2.5}$ $\mu g/m^3$ IQR (11.45)	—	Demonstrated a statistically significant effect of ambient particle air pollution on decreased oxygen saturation at rest in a population of free-living older individuals with a more-significant interaction in those taking β-blockers. These small changes may be related to a pulmonary vascular and/or inflammatory cascade.	$PM_{2.5}$ Oxygen saturation (6-h rest period) −0.173% (−0.345, −0.001)
Lipsett et al. (2006) Coachella Valley, CA Feb-May 2000	Weekly ambulatory ECG's recorded, using Holter monitor, in 19 nonsmoking adults. Mixed linear regression models used with random effects parameters for inter-individual variation. Subjects' residences w/in 5 miles of one of two PM monitoring sites.	$PM_{2.5}$ $\mu g/m^3$ mean (range): Indio: 23.2 (6.3-90.4) Palm Springs: 14 (4.7-52)	PM_{10}, $PM_{10-2.5}$, O_3	No significant associations reported with $PM_{2.5}$; however were significant associations with $PM_{10-2.5}$.	Coefficient X1000 (p-value): SDNN: 24h $PM_{2.5}$: -1.63 (0.49) 6h $PM_{2.5}$: -1.21 (0.24) 4h $PM_{2.5}$: -0.55 (0.64) 2h $PM_{2.5}$: -0.37 (0.72)
Ebelt et al. (2005) Vancouver, Canada Summer 1998	Outcomes: FEV_1, ectopy, blood pressure, heart rate and variability 16 COPD patients, Vancouver, summer 1998, each subject measured 7 days mixed models	$PM_{2.5}$ Mean: 11.4	$PM_{10-2.5}$, and PM_{10} Ambient concentrations and exposures	$PM_{2.5}$ significantly associated with decreased systolic blood pressure and increased ectopic heart beats Use of ambient exposure instead of ambient concentration yields more meaningful results. Suggest that other Panel studies which depend on ambient concentrations or total personal exposure could fail to observe effects that existed. -day	No quantitative results reported. Results presented in figures only.

Table A9. Effects of Acute $PM_{10-2.5}$ Exposure on Cardiovascular Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$					
Lipsett et al. (2006) Coachella Valley, CA Feb-May 2000	Weekly ambulatory ECG's recorded, using Holter monitor, in 19 nonsmoking adults. Mixed linear regression models used with random effects parameters for inter-individual variation. Subjects' residences w/in 5 miles of one of two PM monitoring sites.	$PM_{10-2.5}$ $\mu g/m^3$ Mean (difference between PM_{10} and $PM_{2.5}$): Indio: 23.2 (6.3-90.4) Palm Springs: 14 (4.7-52)	PM_{10}, $PM_{2.5}$, O_3	Significant associations between $PM_{10-2.5}$ (2h, 4h and 6h avg) and SDNN, SDANN. No significant associations reported with $PM_{2.5}$.	Coefficient X1000 (p-value): SDNN: 24h $PM_{10-2.5}$: 0.23 (0.81) 6h $PM_{10-2.5}$: -1.84 (0.006) 4h $PM_{10-2.5}$: -1.19 (0.024) 2h $PM_{10-2.5}$: -0.72 (0.017)
Ebelt et al. (2005) Vancouver, Canada Summer 1998	Outcomes: FEV_1, ectopy, blood pressure, heart rate and variability 16 COPD patients, Vancouver, summer 1998, each subject measured 7 days mixed models	$PM_{10-2.5}$ Mean: 5.6	$PM_{2.5}$ and PM_{10} Ambient concentrations and exposures	Associations between $PM_{10-2.5}$ and decreased systolic blood pressure and increased ectopic heart beats similar to $PM_{2.5}$ in size, but not statistically significant Use of ambient exposure instead of ambient concentration yields more meaningful results. Suggest that other Panel studies which depend on ambient concentrations or total personal exposure could fail to observe effects that existed.	No quantitative results reported. Results presented in figures only.

Table A10. Effects of Acute $PM_{2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$					
Gent et al. (2003) Southern New England Apr-Sept 2001	Panel study of 271 children (age <12 years) with active, doctor-diagnosed asthma followed over 183 days for respiratory symptoms. For analysis, cohort split into two groups: 130 who used maintenance medication during follow-up and 141 who did not, on assumption that medication users had more severe asthma. Logistic regression analyses performed.	$PM_{2.5}$ Mean: 13.1 (SD 7.9) $\mu g/m^3$	O_3	Correlation between daily $PM_{2.5}$ and 1-h max O_3 was 0.77 during this warm-season study. Significant associations between $PM_{2.5}$ and symptoms in some models, but not significant in two-pollutant models. Significant associations between O_3 and symptoms only in medication users, a group considered to be more sensitive.	$PM_{2.5}$ Shortness of breath OR for levels >19 $\mu g/m^3$ on previous day: 1.26 (1.02, 1.54) with O_3: 1.20 (0.94, 1.52)
Rabinovitch et al. (2006) Denver, CO winters 2001-2002 and 2002-2003	A school-based cohort study of children aged 6-13 years with physician-diagnosed asthma (n = 92), with data on bronchodilator use, urinary leukotriene E_4, and reported respiratory infections. Hourly and 24-h avg $PM_{2.5}$ data available from station 2.7 mi from school, using TEOM and FRM monitors.	$PM_{2.5}$ ($\mu g/m^3$) TEOM: Daily mean (SD) year 1: 6.5 (3.2) year 2: 8.2 (3.7) Morning mean (SD) year 1: 7.4 (4.7) year 2: 9.1 (5.0) Morning max (SD) year 1:15.5 (9.5) year 2: 18.4 (9.6) FRM: Daily mean (SD) year 1: 11.8 (7.2) year 2: 11.2 (5.5)	–	Peak $PM_{2.5}$ associated with bronchodilator use and urinary LTE4. Stronger associations reported with morning mean or max concentrations than daily mean; also stronger associations for severe asthmatics compared with mild/moderate asthmatics.	Morning max $PM_{2.5}$ per 12 $\mu g/m^3$: Increased bronchodilator use in severe asthmatics: 8.1% (2.9, 13.4) In mild/moderate asthmatics: 1.6% (-2.2, 5.4)
Mar et al. (2004) Spokane, WA Mar 1997-Jun 1999	Evaluated the effects of $PM_{2.5}$ on respiratory symptoms in both adults and children with asthma (16 adults, 9 children) using logistic regression.	$PM_{2.5}$ $\mu g/m^3$ Mean range over three years 8.1 to 11.0	PM_{10}, $PM_{10-2.5}$, PM_1	In children a strong association was reported between cough and PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and PM_1. No association for symptoms in adults.	$PM_{2.5}$ (10 $\mu g/m^3$) Cough Lag 1 1.21 (1.00, 1.47)

Table A10 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Jansen et al. (2005) Seattle 2002-2003	Study of 16 older asthma COPD patients' exposure to pollutants in relation to various health outcomes from data collected daily for 12 days analyzed using a linear mixed effect model.	$PM_{2.5}$ Outdoor IQR (SD) 10.47 (8.87) µg/m^3	BC, PM_{10}	FE_{NO} (fractional exhaled nitric oxide) increased in relation to increasing $PM_{2.5}$. No association was found between PM and changes in spirometry, blood pressure, pulse rate, or SaO_2 (oxygen saturation of blood).	$PM_{2.5}$ 10 µg/m^3 increase 4.2 ppb (95% 1.3-7.1) Increase in FE_{NO} for asthma subjects (n = 7)
Koening et al. (2005) Seattle, WA winter 2000 to spring 2001	Examined indoor-generated (E_{ig}) and outdoor generated (E_{ag}) PM pulmonary effects on 19 children with asthma using exhaled nitric oxide (eNO), using a linear model and also by GEE.	$PM_{2.5}$ Outdoor (E_{ag}) Mean: 11.1 µg/m^2 Range: 2.8-40.4	–	Based on a recursive model with a sample size of 8 children. E_{ag} was marginally associated with increases in eNO; no association reported with E_{ig}. Effects were only seen in children not using corticosteroid therapy.	$PM_{2.5}$ (10 µg/m^3) increase in eNO 5.6 ppb (CI: −0.6, 11.9) p = 0.08
Mar et al. (2005) Seattle, WA 1999-2001	Evaluated hourly exposures to $PM_{2.5}$ and FE_{NO} in 19 children with asthma using a polynomial distributed lag model, single and lag model taking into account ambient NO levels and use of inhaled corticosteroids.	$PM_{2.5}$ 1 h avg Ranges from 8.3 µg/m^3 at 3-h lag to 15.2 at 8-h lag	–	FE_{NO} was associated with hourly averages of $PM_{2.5}$ up to 10-12 h after exposure. No effects were seen in subjects on inhaled corticosteroids. Similar results were obtained for both analysis methods.	$PM_{2.5}$ (10 µg/m^3) Single lag 6.9 ppb (3.4 to 10.6)

Table A10 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Adamkiewicz et al. (2004) Steubenville, OH Sept-Dec 2000	Breath samples collected weekly in panel of 29 elderly subjects, and analyzed for FE_{NO}. Indoor NO measured in study room at time of breath sample collection. Ambient measurements from a central monitoring site.	$PM_{2.5}$ ($\mu g/m^3$) Mean (max, IQR): 1h: 19.5 (105.8, 17.9) 24h: 19.7 (57.8, 17.7)	NO, NO_2, O_3, SO_2	Consistent positive, significant associations reported between FE_{NO} and $PM_{2.5}$, also with ambient and indoor NO levels. No associations reported with NO_2, O_3, or SO_2. In 2- and 3-pollutant models, $PM_{2.5}$ remains significant, while ambient and indoor NO associations are reduced and lose significance.	FE_{NO} change per IQR: 1h $PM_{2.5}$: 1.36 ppb change (0.58, 2.14) 24h $PM_{2.5}$: 1.45 ppb change (0.33, 2.57)
Giradot et al. (2006) Great Smoky Mountains NP, NC-TN Fall 2002, summer 2003	Investigated lung function in 354 adult-hikers over 71 days in relation to pollutant exposure using multiple linear regression models by ordinary least squares estimation. Hikers averaged 5.0 h of exercise.	$PM_{2.5}$ Average daily 13.9 ± 8.2 $\mu g/m^3$ Range 1.6-38.4 $\mu g/m^3$	O_3	Findings suggest that low levels of pollutant exposure over several hours may not result in significant declines in lung function in healthy adults engaged in exercise or work.	The coefficient for the percentage change in FEV_1 as a function of $PM_{2.5}$ adjusted for covariates $0.003\%/\mu g/m^3$ $p = 0.937$
Delfino et al. (2004) Alpine, CA Aug-Oct 1999, Apr-Jun 2000	Panel study of 19 asthmatic children (age 9-17 years) followed daily for 2 weeks to determine relationship between air pollutants and FEV_1. Linear mixed model used for analysis. Personal PM measurements made with dataRAM, which approximate $PM_{2.5}$ measurements.	$PM_{2.5}$ (24-h) Outdoor mean (SD) 10.3 (5.6) $\mu g/m^3$ Outdoor home: 11.0 (5.4) $\mu g/m^3$ Indoor home: 12.1 (5.4) $\mu g/m^3$ Personal PM: 37.9 (19.9) $\mu g/m^3$	PM_{10}, O_3	Significant declines in FEV_1 associated with various PM indices but not ambient O_3 levels. Stronger associations with multiday moving averages for both personal and stationary-site PM.	$PM_{2.5}$ Percent predicted FEV_1 with PM from previous 24 h: per 7.5 $\mu g/m^3$ central site: -0.7% (-1.9, 0.4) per 7.1 $\mu g/m^3$ outdoor home: -1.1% (-2.5, 0.1) per 6.7 $\mu g/m^3$ indoor home: -1.6% (-2.8, -0.4) per 30 $\mu g/m^3$ personal: -5.9% (-10.8, -1.0)

Table A10 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Newhouse et al. (2004) Tulsa, OK Sep-Oct 2000	Panel study of 24 subjects aged 9-64 years with physician diagnosis of asthma. Performed PEF twice daily (morning and afternoon), and reported daily respiratory symptoms and medication use. Forward stepwise regression and Pearson correlation analysis.	$PM_{2.5}$ Mean (range): 13.07 (0.50-29.90) $\mu g/m^3$	O_3, CO, SO_2, pollen, fungal spores	Significant associations reported between O_3 and FEV_1 and various respiratory symptoms. In multi-pollutant models, including pollen and mold spores, maximum $PM_{2.5}$ negatively associated with cough, wheeze and shortness of breath; no discussion of these findings.	No quantitative results
Sinclair and Tolsma (2004) Atlanta, GA Aug 1998-Aug 2000	Respiratory medical visit data collected by Kaiser Permanente, including ambulatory care visits for asthma (adult and child), URI and LRI. ARIES air quality data used. Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days (average). Also performed analyses using average lag periods of 3-5 and 6-8 days.	$PM_{2.5}$ mean (SD) 17.62 (9.32) $\mu g/m^3$	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{10-2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons (OHC)	Adult asthma visits associated with ultrafine number count, and negatively associated with $PM_{2.5}$ mass. Child asthma associated with OHC (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC and OC (3-5 day). LRI associated with $PM_{2.5}$ acidity and SO_2 (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC, OC and $PM_{2.5}$ water soluble metals. For URI, significant positive associations with ultrafine PM (0-2) and $PM_{10-2.5}$ (3-5 day) but negative associations with $PM_{2.5}$, SO_2 and sulfate.	$PM_{2.5}$ Quantitative results only for significant associations Adult asthma, per 9.32 $\mu g/m^3$ RR = 0.906 LRI visits: EC, per 1.38 $\mu g/m^3$ RR = 1.079 OC, per 2.2 $\mu g/m^3$ RR = 1.05 $PM_{2.5}$ acidity, per 0.02 $\mu g/m^3$ RR = 1.13 $PM_{2.5}$ water-soluble metals, per 0.03 $\mu g/m^3$ RR = 1.062

Table A10 (cont'd). Effects of Acute $PM_{2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$ (cont'd)					
Lewis et al. (2005) Detroit Winter 2001 thru Spring 2002	A longitudinal cohort study of primary-school age children with asthma, primarily African American and from low-income families, examined the relationship between lung function and PM and O_3 using GEE, considered effects modification by maintenance corticosteroid use and URI as recorded in diaries of 86 children in six 2-wk seasonal assessments for various lags.	$PM_{2.5}$ IQR 12.5 µg/m^3	O_3	Positive associations between $PM_{2.5}$ and O_3 with diurnal variability in FEV_1, and negative associations with lowest daily FEV_1; though many not statistically significant. Authors conclude that ambient air pollution exposure associated with adverse effects on pulmonary function among at-risk children with asthma in Detroit.	$PM_{2.5}$ Lag 1 Children on maintenance CS FEV_1 diurnal variability 1.61 (−0.50, 3.72) single pollutant model
Silkoff et al. (2005) Denver, CO winters 1999-2000 and 2000-2001	Two panels of adults with COPD (n = 16 and 18 for winters 1 and 2, respectively), with diary of twice-daily PEF and FEV_1, symptoms and bronchodilator use. 4-month study period included biweekly visits to collect data.	$PM_{2.5}$ (µg/m^3) Mean (SD): winter 1: 9.0 (5.2) winter 2: 14.3 (9.6)	PM_{10}, CO, NO_2	In winter 1, no evidence of detrimental effects on lung function; some significant associations between PM_{10}, NO_2 and CO with *increased* lung function. In winter 2, significant associations reported between PM_{10}, NO_2 and CO and increased medication use or symptoms. No significant associations reported with $PM_{2.5}$.	No quantitative results reported. Results presented in figures only.
Ebelt et al. (2005) Vancouver, Canada Summer 1998	Outcomes: FEV_1, ectopy, blood pressure, heart rate and variability 16 COPD patients, Vancouver, summer 1998, each subject measured 7 days mixed models	$PM_{2.5}$ Mean: 11.4	$PM_{10-2.5}$, and PM_{10} Ambient concentrations and exposures	Decrease in ΔFEV1 associated with ambient exposure for all PM components Use of ambient exposure instead of ambient concentration yields more meaningful results. Suggest that other Panel studies which depend on ambient concentrations or total personal exposure could fail to observe effects that existed.	No quantitative results reported. Results presented in figures only.

Table A11. Effects of Acute $PM_{10-2.5}$ Exposure on Various Respiratory Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{10-2.5}$					
Sinclair and Tolsma (2004) Atlanta, GA Aug 1998-Aug 2000	Respiratory medical visit data collected by Kaiser Permanente, including ambulatory care visits for asthma (adult and child), URI and LRI. ARIES air quality data used. Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days (average). Also performed analyses using average lag periods of 3-5 and 6-8 days.	$PM_{10-2.5}$ mean (SD) 9.67 (4.74) $\mu g/m^3$	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{2.5}$, ultrafine PM count, SO_4^{2-}, H^+, EC, OC, metals, oxygenated hydrocarbons (OHC)	Adult asthma visits associated with ultrafine number count, and negatively associated with $PM_{2.5}$ mass. Child asthma associated with OHC (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC and OC (3-5 day). LRI associated with $PM_{2.5}$ acidity and SO_2 (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC, OC and $PM_{2.5}$ water soluble metals. For URI, significant positive associations with ultrafine PM (0-2 day) and $PM_{10-2.5}$ (3-5 day) but negative associations with $PM_{2.5}$, SO_2 and sulfate.	$PM_{10-2.5}$ Per 4.74 $\mu g/m^3$ LRI visits: RR = 1.07 Child asthma: RR = 1.053 URI visits: RR = 1.021
Mar et al. (2004) Spokane, WA Mar 1997-Jun 1999	Evaluated the effects of $PM_{2.5}$ on respiratory symptoms in both adults and children with asthma (16 adults, 9 children) using logistic regression.	$PM_{10-2.5}$ Not reported	PM_{10}, $PM_{2.5}$, PM_1	In children a strong association was reported between cough and PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and PM_1. No association for symptoms in adults. These findings also suggest that both larger and smaller particles can aggravate asthma symptoms	$PM_{10-2.5}$ (10 $\mu g/m^3$) Cough Lag 1 OR 1.06 (1.02, 1.10)
Ebelt et al. (2005) Vancouver, Canada Summer 1998	Outcomes: FEV_1, ectopy, blood pressure, heart rate and variability 16 COPD patients, Vancouver, summer 1998, each subject measured 7 days mixed models	$PM_{10-2.5}$ Mean: 5.6	$PM_{2.5}$ and PM_{10} Ambient concentrations and exposures	Decrease in ΔFEV1 associated with ambient exposure for all PM components Use of ambient exposure instead of ambient concentration yields more meaningful results. Suggest that other Panel studies which depend on ambient concentrations or total personal exposure could fail to observe effects that existed.	No quantitative results reported. Results presented in figures only.

Table A12. Effects of Acute $PM_{2.5}$ Exposure on Birth Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
$PM_{2.5}$					
Karr et al. (2006) South Coast Air Basin, CA 1995-2000	Linked hospital discharge for bronchiolitis during first year of life with $PM_{2.5}$ using closest measurements based on zip code. Case-crossover design used, with lag periods of 1-2, 3-5 and 6-8 days.	$PM_{2.5}$ Means range from 23.3 to 24.1 $\mu g/m^3$, for different lag periods	CO, NO_2	No significant associations reported for any of the pollutants.	$PM_{2.5}$ (10 $\mu g/m^3$) 1–2 day lag: OR 0.96 (0.94-0.99) 3-5 day lag: OR 0.98 (0.96, 1.00) 6-8 day lag: OR 0.96, (0.93, 0.98)

Additional Studies Examining Issues Related to Interpreting the PM-Morbidity Relationship:

U.S. and Canadian studies:

Liao et al. (2004): A population-based cross-sectional study of 5,431 members of the Atherosclerosis Risk in Communities cohort study in Minneapolis, MN; Jackson, MS; and Forsyth County, NC. Significant associations were reported between PM_{10} and decreased heart rate variability and increased heart rate. The mean PM_{10} concentration was 24.3 $\mu g/m^3$.

Delfino et al. (2002): Panel study of 22 asthmatic children (9-19 years) with diary of symptoms, medication use and presence of respiratory infection or hay fever for 61 days. Asthma symptoms were significantly associated with 1-h and 8-h PM_{10} (both lag 0 and 3-day average), but association with 24-h PM_{10} was not significant. Also significant associations were observed between asthma symptoms and 1-h ozone (lag 0) and 8-h max NO_2 (lag 0). Associations were stronger in children not using anti-inflammatory medication than in children on medication. Evidence of significant interaction between 1-h PM_{10} and 8-h max NO_2; but in 2-pollutant models, both lose significance.

Dugandzic et al. (2006): Linked 1998-2000 data from Nova Scotia Atlee Perinatal Database with air pollution data, using geocoding to link to monitoring site nearest the home. Significant associations were reported between LBW and exposures during the first trimester for PM_{10} (RR = 1.33, 1.02-1.74 for >75th percentile) and SO_2 (RR = 1.36, 1.04-1.78 for >75th percentile). No associations were reported with pollution exposures during the second and third trimesters. The mean PM_{10} concentration (trimester average) was 17 $\mu g/m^3$.

Letz and Quinn (2005): No correlation observed between Air Quality Index values for $PM_{2.5}$ or ozone with emergency department visits (n = 149) for asthma in military trainees.

Sagiv et al. (2005): Using a time-series analysis, this study investigated the effect of ambient outdoor PM_{10} on risk for preterm delivery counts in three Pennsylvania Counties and the City of Philadelphia from Jan 1, 1997-Dec 31, 2001. Results suggest an increase in preterm birth risk with exposure to PM_{10}, with a RR of 1.07 (0.98, 1.18) per 50 $\mu g/m^3$ PM_{10} (6 weeks preceding birth). The mean PM_{10} concentration was 25.3 $\mu g/m^3$.

International studies:

Romieu et al. (2005): A randomized double-blind trial, evaluating effect of supplementation with omega-3 fatty acids on reduction of $PM_{2.5}$-related HRV reduction. In 50 subjects living in nursing home with 6-month follow-up, HRV high-frequency change associated with 8 $\mu g/m^3$ $PM_{2.5}$ was -0.54% (95% CI -72, -24) with supplementation, and -7% (95% CI -20, +7) without supplementation. The mean $PM_{2.5}$ concentration was 19.6 $\mu g/m^3$.

Sorensen et al. (2003): In Copenhagen, personal exposure to $PM_{2.5}$ was associated with cardiovascular biomarkers (RBC count, hemoglobin) in women, but not men. No significant associations were observed with ambient $PM_{2.5}$ concentrations; however, personal exposure to carbon black was associated with plasma protein oxidation.

Boezen et al. (2005): In a panel of 327 elderly patients, symptom diaries and twice-daily PEF were collected for 3 months. Statically significant associations were reported for PM_{10}, BS and

NO_2 with respiratory symptoms in subjects with airway hyperresponsiveness and high IgE levels (AHR^+/IgE^+). There were no significant associations with the pollutants in the AHR^-/IgE^- subjects.

Chan et al. (2004): In Taipei, Taiwan, continuous measurements of ECG and personal exposure measurements of ultrafine particles ($NC_{0.02-1}$) (time period not indicated) were collected for a panel of nine young adults (19-29 years) and ten elderly patients (42-79 years). Decreases in HRV measures (SDNN, r-MSSD, LF, HF) were reported with personal exposure to $NC_{0.02-1}$ for both age groups.

Chuang et al. (2005): In Taipei, Taiwan, ECG and PM were measured continuously in a panel of 26 subjects (ten with coronary heart disease, 16 with hypertension) from November 2002 through March 2003; HRV measurements were used only for times when the subjects were awake. For all PM indicators, there were associations with decreases in several HRV measurements—SDNN, r-MSSD, LF, and HF—and positive associations with LF/HF. Associations were only significant for $PM_{0.3-1.0}$; the authors concluded that HRV was associated with $PM_{0.3-1.0}$, but not $PM_{1.0-2.5}$ or $PM_{2.5-10}$.

Lanki et al. (2006): In Helsinki, levels of $PM_{2.5}$ were related to ST-segment depression in 45 elderly (mean age 68.2 yrs [6.5]) nonsmoking subjects with stable coronary heart disease. Depression of ST-segment indicates a number of conditions including myocardial ischemia. The mass of fine particles was apportioned between five sources. ST-segment depression was associated with $PM_{2.5}$ originating from local traffic (RR = 1.53 [1.19-1.97] per 1 $\mu g/m^3$, at a 2-day lag) and long-range transport (RR = 1.11 [1.02, 1.20] per 1 $\mu g/m^3$). In multipollutant models where indicator elements were used for sources, only the absorbance (elemental carbon) indicator for local traffic and other combustion was associated with ST-segment depression. The mean $PM_{2.5}$ concentration was 12.8 $\mu g/m^3$

Penttinen et al. (2006): In a panel study of 57 adult asthmatics in Helsinki, subjects were followed for 181 days, and principal component analysis was used to evaluate source apportionment based on $PM_{2.5}$ mass. Decreases in morning PEF was linked to $PM_{2.5}$ from long-range transport and local combustion sources (1- and 2-day lags). There were no associations with $PM_{2.5}$ derived from oil combustion, soil, or sea salt.

Ruckerl et al. (2006): Blood parameters were measured in 57 male patients with coronary heart disease living in Erfurt, Germany, and positive associations were reported between elevated C-reactive protein and all measured pollutants – PM_{10}, $PM_{2.5}$, accumulation mode particles ($PM_{0.1-1}$), ultrafine particles, ED, OC, NO_2 and CO. The authors reported the strongest association with accumulation mode particles (3-day lag); significant associations were also observed with PM_{10}, ultrafine particles, NO_2 and CO (2-day lag strongest). Positive associations were also reported between ICAM-1 (indicator of endothelial dysfunction) and PM_{10}, $PM_{2.5}$, accumulation mode particles, EC and OC. No consistent associations were observed with various clotting factors.

Pekkanen et al. (2002): In three panels of elderly subjects in Amsterdam, Erfurt, and Helsinki (ULTRA study), biweekly submaximal exercise tests were done for six months. ST-segment depression was significantly associated with both $PM_{2.5}$ mass (OR 2.84, 1.42-5.66, 2-day lag) and ultrafine particles (OR 3.14, 1.56-6.32), and also with NO_2 and CO. No consistent associations were reported with thoracic coarse particles.

de Hartog et al. (2003): Three panels of elderly (aged 50+ years) subjects in Amsterdam, Erfurt, and Helsinki (ULTRA study) were followed for six months, with daily diaries and biweekly clinic visits. Prevalence of shortness of breath and phlegm were associated with $PM_{2.5}$, but not with ultrafine particles, CO or NO_2. The authors concluded that $PM_{2.5}$ was more closely correlated with cardiorespiratory symptoms than ultrafine particles.

Timonen et al. (2005): Repeated ECG measurements in panels of elderly subjects in Amsterdam, Erfurt, and Helsinki (ULTRA study) over six months. There were no consistent associations between HRV measurements and $PM_{2.5}$, but a pattern of generally positive associations between ultrafine particles and HF were reported, along with negative associations between ultrafine particles and LF/HF ratio.

Henneberger et al. (2005): Repeated ECG measurements in a panel of 56 patients with ischemic heart disease in Erfurt, Germany. $PM_{2.5}$ (6h average) was significantly associated with decreased T-wave amplitude, increased T-wave complexity and nearly significant with increased variability of the T-wave complex. Associations with 6h $PM_{2.5}$ were stronger than those with 24h $PM_{2.5}$ averages. Similar associations were seen with 6h ultrafine particles, accumulation mode particles, OC and EC, although most were not statistically significant. Significant associations were reported between OC and QT duration.

Table A13. Results of Epidemiologic "Intervention" Studies

Reference, Study Location and Period	Outcome Measure	Change in pollution/emissions	Reported PM Levels ($\mu g/m^3$)	Method/Design	Effect Estimates/Results
U.S. studies					
Lwebuga-Mukasa et al., 2003 Buffalo, NY	Hospital admissions and emergency department visits for respiratory illnesses	50% drop in total traffic at Peace Bridge following 9/11/2001			Statistically significant decreases in number of patients admitted to hospital or seen in emergency departments for respiratory illnesses.
European studies					
Bayer-Oglesby et al., 2005 9 Swiss communities 1991-2001	Respiratory symptoms via questionnaires, collected in 1992-1993 and 1998-2001	General air pollution abatement measures in Switzerland resulting in reduced PM_{10} concentrations	PM_{10} concentration declined an average of 9.8 $\mu g/m^3$ over all communities, ranged from 4.0 to 12.7 $\mu g/m^3$ declines. Mean PM_{10} concentrations in 1997-2000 ranged from 10 to 38 $\mu g/m^3$.	Multivariate logistic regression models used, including adjustment for covariates including indicators for SES, health status, indoor exposure factors, and avoidance behavior.	OR per 10 $\mu g/m^3$ decline in PM_{10}: chronic cough 0.65 (0.54, 0.79) bronchitis 0.66 (0.55, 0.80) common cold 0.78 (0.68, 0.89) nocturnal dry cough 0.70 (0.60, 0.83) conjunctivitis symptoms 0.81 (0.70., 0.95) No significant changes in prevalence of asthma, hay fever, wheeze or sneezing.

Table A13 (cont'd.). Results of Epidemiologic "Intervention" Studies

Reference, Study Location and Period	Outcome Measure	Change in pollution/emissions	Reported PM Levels ($\mu g/m^3$)	Method/Design	Effect Estimates/Results
European studies (cont'd)					
Frye et al., 2003 3 communities in East Germany 1992-1999	Pulmonary function measurements for 2,493 children 11-14 years of age, in 1992-1993, 1995-1996, and 1998-1999.	Reduction in air pollution concentrations following German reunification in 1990.	Mean TSP concentrations fell from 79 to 23 $\mu g/m^3$, while mean SO_2 concentration declined from 113 to 6 $\mu g/m^3$.	Linear regression using MIXED procedure in SAS, with log-transformed lung function measures and covariates including sex, height, season, lung function equipment, parental education, parental atopy, ETS exposure.	Percent change in lung function parameter per 50 $\mu g/m^3$ decrease in TSP: FVC: 4.7% (0.2, 9.5) FEV_1: 2.9% (-1.4, 7.3) Associations larger in magnitude and more often statistically significant for girls than for boys. Similar results reported with decreases in SO_2 concentration.
Heinrich et al., 2002 3 communities in East Germany 1992-1999	Respiratory symptom questionnaires for 4,949 children 11-14 years of age, in 1992-1993, 1995-1996, and 1998-1999.	Reduction in air pollution concentrations following German reunification in 1990.	In 1991, mean TSP concentrations range from 45 to 79 $\mu g/m^3$ in the three communities; in 1998, range from 25 to 33 $\mu g/m^3$. Fine particle concentrations ($NC_{0.01-2.5}$) reported for 1993 (11.7-12.6 $\mu g/m^3$) and 1999 (10.6-16.7 $\mu g/m^3$)	Two-stage analyses, using repeated-measures in generalized estimating equations. GEE logistic regression model used to compute symptom prevalences, adjusting for age, gender, parental education, parental atopy, and four indoor exposure factors (dampness/mold, gas cooking, ETS, cats); in second stage, logits of prevalence regressed against air pollution variables.	OR per 50 $\mu g/m^3$ TSP: Bronchitis: 3.02 (1.72, 5.29) Sinusitis: 2.58 (1.00, 6.65) Frequent colds: 1.90 (1.17, 3.09) Otitis media: 1.45 (0.89, 2.37) Febrile infections: 1.79 (0.92, 3.48) Cough in morning: 1.23 (0.82, 1.84) Shortness of breath: 1.33 (0.83, 2.12)

Table A13 (cont'd.). Results of Epidemiologic "Intervention" Studies

Reference, Study Location and Period	Outcome Measure	Change in pollution/emissions	Reported PM Levels ($\mu g/m^3$)	Method/Design	Effect Estimates/Results
European studies (cont'd)					
Neuberger et al. (2002) Linz, Austria 1985-1990	Lung function measured 2-8 times in 3,451 children in elementary and high schools, repeated measures over study time period.	Uniform decreases across districts of Linz for SO_2 and TSP; some areas report little changes and some dramatic decreases in NO_2 concentrations	NR	NR	Focus on lung function improvements with reduction in NO_2 concentrations; report that TSP and SO_2 do not act as confounders.
Sugiri et al. (2006) East and West Germany 1991-2000	Lung function measurements in 2,574 children aged 5-7 years	Dramatic decline in pollution in East Germany; smaller decline in West Germany	Annual average for TSP in year preceding measurement declined from 74 to 51 $\mu g/m^3$ in East Germany, from 54 to 44 in West Germany, average on the day of investigation decreased from 133 to 30 $\mu g/m^3$.	Linear regression with covariates as for Frye et al. (2003); included test for homogeneity of effects based on proximity to busy streets.	Lung function improved with reduction in air pollution; differences between East and West Germany vanished during study time period. Stronger associations reported for reactive airway measure with short-term TSP exposure measure, and with TLC with chronic TSP exposure measure. Per 40 $\mu g/m^3$ daily mean TSP: Raw: 0.969 (0.936, 1.004) per 40 $\mu g/m^3$ annual mean TSP: TLC: 0.938 (0.884, 0.996) Exposure to traffic also associated with reduced lung function.

Table A13 (cont'd.). Results of Epidemiologic "Intervention" Studies

Reference, Study Location and Period	Outcome Measure	Change in pollution/emissions	Reported PM Levels ($\mu g/m^3$)	Method/Design	Effect Estimates/Results
European studies (cont'd)					
Burr et al., 2003 North Wales, UK 1996-1999	Repeated questionnaires for respiratory symptom prevalence and PEF measures in 448 adults in congested and uncongested neighborhoods, before (1996-7) and after (1998-9) bypass opened and reduced traffic flow in area	Heavy goods vehicle counts and air pollution decreases with bypass opening	$PM_{2.5}$ mean before and after bypass in congested neighborhood : 21.2 $\mu g/m^3$ and 16.2 $\mu g/m^3$ (23.5% reduction) and in uncongested neighborhood: 6.7 $\mu g/m^3$ and 4.9 $\mu g/m^3$ (26.6% reduction) For PM_{10} in congested neighborhood : 35.2 $\mu g/m^3$ and 27.2 $\mu g/m^3$ (22.7% reduction) and in uncongested neighborhood: 11.6 $\mu g/m^3$ and 8.2 $\mu g/m^3$ (28.9% reduction) 46.9% reduction in heavy goods vehicles per hour	Percent subjects reporting improvement calculated for congested and uncongested streets and difference expressed as percent improvement.	% reduction in symptoms:: any wheeze -6.5 (-14.9, 2.0) # attacks -8.5 (-18.2, 1.2) No association with cough, phlegm, consulted doctor, rhinitis. Positive association with "affects activities" 10.3 (3.1, 17.3)

Toxicology studies:

Carvalho-Oliveira et al. (2004): Mutagenesis testing of particles collected during and after a bus strike in Sao Paulo, Brazil. Significant reduction in damage to DNA was observed, without significant changes in overt toxicity to cells, with exposure to PM collected during the strike. $PM_{2.5}$ mass concentrations were high (~40 $\mu g/m^3$) during strike; authors note "intense traffic jam" during this period. Concentrations of sulfur and BETX were lower on strike than non-strike days.

Somers et al. (2004): Study of heritable mutation rates in laboratory mice housed an urban-industrial area (near a major highway and two integrated steel mills) in Ontario, and mice housed in rural area. In both areas, one group of mice exposed to ambient air for 10 weeks and one group housed in a chamber with HEPA filtration system to remove 99.97+% of particles. HEPA filtration reduced heritable mutations in urban-industrial area, with larger effect on paternal mutation rates; no effect in rural area.

Table A14. Associations Between Source-related Fine Particles and Health Outcomes

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
Mar et al. (2006) Phoenix, AZ Feb 1995-Dec 1997	Mortality: All nonaccidental and cardiovascular causes; age 65 yr	$PM_{2.5}$: Estimated mean range across 9 independent analyses (24-h avg): SO_4^2: 1.3 to 3.6 Traffic: 4.0 to 7.7 Cu: 0.2 to 0.8 Sea salt: 0.1 to 0.2 Wood: 0.9 to 2.8 Soil: 0.8 to 2.6 Estimated 5^{th}-95^{th}% range across 9 independent analyses (24-h avg): SO_4^2: 2.5 to 6.9 Traffic: 10.3 to 16.1 Cu: 0.5 to 3.5 Sea salt: 0.2 to 0.6 Wood: 2.3 to 6.2 Soil: 2.0 to 7.9	None	0-, 1-, 2-, 3-, 4-day, or 5- lag	Time-series study. Poisson GLM with natural splines. Eight independent analyses performed. Daily $PM_{2.5}$ data collected using both gravimetric and TEOM samplers. Several teams of investigators used different source apportionment methods with $PM_{2.5}$ data. Traffic and secondary sulfate contributions, as estimated by different analyses, were well correlated.	Results from all investigators combined: Median % excess risk per 5^{th}-95^{th}% increment: (95% CI's not presented) <u>Cardiovascular</u>: Sulfate, lag 0: 16.0% Traffic, lag 1: 13% Cu smelter, lag 0: 12% Sea salt, lag 5: 10% Biomass/wood burning, lag 3: 9% No association reported with soil factor. Among all sources, the largest effect size for cardiovascular mortality observed for secondary SO_4^2, followed by traffic. Associations weaker for all-cause mortality. Variations in results across investigators/methods were small compared to the variations across source categories.

Table A14 (cont'd). Associations between Source-related Fine Particles and Mortality

Reference, Study Location and Period	Outcome Measure	Mean PM Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
Ito et al. (2006) Washington, DC Aug 1988-Dec 1997	Mortality: All nonaccidental, cardiovascular, and cardiorespiratory causes	$PM_{2.5}$: Estimated mean range across 9 independent analyses (24-h avg): SO_4^{2}: 5.1 to 10.7 Traffic: 1.6 to 4.7 NO_3^{-}: 1.6 to 6.7 Residual oil: 0.3 to 0.6 Wood smoke: 0.2 to 1.9 Incinerator: 0.3 to 1.0 Primary coal: 1.2 to 2.1 Sea salt: 0.2 to 0.9 Soil: 0.3 to 3.7 Estimated 5th% to 95th% range across 9 independent analyses (24-h avg): SO_4^{2}: 10.4 to 22.0 Traffic: 3.2 to 9.7 NO_3^{-}: 5.0 to 17.9 Residual oil: 0.9 to 3.3 Wood smoke: 0.6 to 5.7 Incinerator: 0.7 to 1.6 Primary coal: 3.2 to 3.8 Sea salt: 0.7 to 4.3 Soil: 0.9 to 4.8	None	0-, 1-, 2-, 3-, or 4-d lag	Time-series study. Poisson GLM with natural splines. Nine independent analyses performed. $PM_{2.5}$ gravimetric data collected on Thursday and Saturday only (U.S. Park Service, IMPROVE). Traffic contributions, as estimated by different analyses, were not well correlated; however, secondary sulfate contributions were fairly well correlated.	Results from all investigators combined: Median % excess risk per 5^{th}-95^{th}% increment: (95% CI's not presented) All causes: Sulfate, lag 3: 6.7% (1.7, 11.7) Traffic: 2.6% (-1.6, 6.9) Residual oil, lag 2: 2.7% (-1.1, 6.5) Primary coal, lag 3: 5.0% (1.0, 9.1) Soil: 2.1% (-1.8, 4.9) No significant associations were reported with the following factors: NO_3^{-}, wood burning, incinerator and sea salt. Among all sources, largest and most significant association with all-cause mortality observed for secondary SO_4^{2} at lag 3 d. Cardiovascular and cardiorespiratory mortality associations were generally similar to all-cause mortality. Variations in results across investigators/methods were small compared to the variations across source categories.

Table A14 (cont'd). Associations Between Source-related Fine Particles and Health Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean PM Levels	Copollutants Considered	Findings, Interpretation	Quantitative Results
Riediker et al. (2004) Wake County, NC Fall 2001	Cardiovascular outcomes: Nine healthy young non-smoking male troopers studied on 4 consecutive days, working 3PM to midnight shift. HRV measured with ambulatory ECG during shift and subsequent sleep phase. Blood parameters from blood sample drawn 15 min after work shift. Mixed effects regression models used.	In-vehicle $PM_{2.5}$ ($\mu g/m^3$) mean (SD): 23.0 (8.0)	—	Source apportionment of $PM_{2.5}$ mass identified 4 components: crustal material (Al, Si, Ca, Ti, Fe), wear of steel automotive components (Ti, Cr, Fe), gasoline combustion (benzene, CO), and speed-changing traffic (Cu, S, aldehydes). The "speed change" factor was significantly associated with increased heart cycle length, increased HRV, decreased % lymphocytes, decreased protein C and increases in von Willebrand factor, % neutrophils, mean red cell volume, and blood urea nitrogen. The "crustal" factor was significantly associated with increased uric acid. Nearly significant associations were seen between the "gasoline" factor and mean heart cycle length, decreased protein C and increased von Willebrand factor.	No quantitative results reported. Results presented in figures only.

Table A15. Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcome Measure	Mean Component Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
Burnett et al. (2004) 12 Canadian cities Jan 1981-Dec 1999	Mortality: All nonaccidental, cardiovascular, and respiratory causes	24-h avg SO_4^2: All 12 cities: 2.84 SD not provided.	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, NO_2, SO_2, CO, O_3	0-, 1-, or 2-d lag	Time-series study. Natural spline functions used to model nonlinear associations. SO_4^2 data determined from 75% of $PM_{2.5}$ filters. SO_4^2 data available on 9% of days with mortality data.	% excess risk per 2.84 $\mu g/m^3$: All causes: Single-pollutant model: Lag 1: 0.67% (0.00, 1.35) Two-pollutant model with NO_2: Lag 1: 0.46% (0.25, 1.18) NO_2 effect also nonsignificant in two-pollutant model.

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcome Measure	Mean Component Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
Goldberg et al. (2006) Montreal, Canada 1986-1993	Mortality: Diabetes, and nonaccidental mortality in subgroups with diabetes diagnosed at least 1 yr before death in adults >65. Also considered subgroups with cardiovascular diagnoses.	24-h avg measured SO_4^2: mean (SD) 3.3 (3.6) 24-h avg predicted SO_4^2 (from $PM_{2.5}$): mean (SD) 4.1 (3.6)	PM_{10}, TSP, coefficient of haze, $PM_{2.5}$, predicted $PM_{2.5}$, SO_2, NO_2, CO, O_3	0-, 1-, and avg of 0- to 2-day lags ("3-day mean")	Time-series study. Poisson regression using natural spline functions. Report results for SO_4^2 predicted from $PM_{2.5}$; used statistical model to estimate mass when measurements were not available; measured data available on 2680 days and predicted data for 3653 days.	Measured SO_4^2: % excess risk per 2.5 $\mu g/m^3$: mortality from diabetes: 5.1% (0.638, 9.71) nonaccidental mortality in subjects with diabetes: 2.31% (0.11, 4.56) Predicted SO_4^2: % excess risk per 2.9 $\mu g/m^3$: mortality from diabetes: 5.42% (0.44, 10.64) nonaccidental mortality in subjects with diabetes: 2.77% (0.23, 5.38) (all 3-day mean lag) Greater effects seen generally in the warm season. No significant association for nonaccidental mortality in subjects with diabetes, but without cancer, cardiovascular disease or airways disease. Associations reported for nonaccidental mortality in subjects with diabetes who also had any cardiovascular disease, chronic coronary disease, or atherosclerosis.

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcome Measure	Mean Component Levels ($\mu g/m^3$)	Copollutants Considered	Lag Structure Examined	Method/Design	Effect Estimates/Results
Klemm et al. (2004) Atlanta, GA Aug 1998-July 2000	Mortality: All nonaccidental, circulatory, respiratory, cancer, and other causes; age <65 yr and 65 yr	24-h avg mean (SD; range): SO_4^{2-}: 5.46 (0.79-19.34) EC: 2.03 (0.45.-9.76) OC: 4.54 (1.41-14.61) nitrates: 1.17 (0.15-5.40)	$PM_{2.5}$, $PM_{10-2.5}$, EC, OC, NO_2, NO_3^-, SO_2, CO, O_3, ultrafines, hydrocarbons, acid	Multiday lag of 0-1 d	Time-series study. Poisson GLM using natural cubic splines with quarterly, monthly, or biweekly knots. Default model used monthly knots. Analyses done by individual components, as well as three major $PM_{2.5}$ fractions: sulfate, carbon (OC and EC combined) and "balance" (remaining components combined).	% excess risk per 5.46 $\mu g/m^3$ SO_4^{2-}: All causes, age >65: Coefficient (t-statistic) for monthly knot models (lag 0-1): SO_4^{2-}: 0.00843 (1.54) EC: 0.01343 (1.54)) OC: 0.00529 (0.79) NO_3^-: -0.00103 (-0.06) For age >65, significant associations with $PM_{2.5}$ mass (quarterly and monthly knots; not significant for biweekly) but not with any individual $PM_{2.5}$ component. Results differ across model specifications (i.e., choice of lag and number of knots). No significant associations observed in those aged <65 yr.
Villeneuve et al. (2003) Vancouver, British Columbia, Canada Jan 1986-Dec 1998	Mortality: All nonaccidental, cardiovascular, respiratory, and cancer causes; SES status	24-h avg SO_4^{2-}: 2.7 10^{th}-90^{th}% 1.1-4.4 Range 0.4-9.0	$PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, TSP, coefficient of haze, SO_2, NO_2, CO, O_3	0-, 1-, or 2-d lag; multiday lag of 0-2 d	Time-series study. Poisson regression using natural spline functions. SO_4^{2-} data collected every 6th day.	% excess risk (95% CI) per 3.3 $\mu g/m^3$ SO_4^{2-}: All causes: Lag 0: 2.9% (-4.4, 10.8) Cardiovascular: Lag 0:. 3.2% (-14.1, 9.1) Respiratory: Lag 0: 8.3% (-12.3, 33.8) Cancer: Lag 0: 8.0% (-4.5, 22.1)

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean Component Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Metzger et al. (2004) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific cardiovascular diseases by age groups >19 yr and >65 yr. Time-series study. 4, 407, 535, EDV from 31 Atlanta hospitals. Components included acidity (H^+), EC, OC, water-soluble (WS) metals, sulfates	Median ($\mu g/m^3$) (10-90% Range) SO_4^2: 4.5 (1.9-10.7) WS metals: 0.021 (0.006-0.061) OC: 4.1 (2.2-7.1) EC: 1.6 (0.8-3.7)	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafine PM count, oxygenated hydrocarbons	0-2	Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Secondary analyses performed to assess alternative pollutant lag structures, seasonal influences, and age effects. Cardiovascular visits were significantly associated with several pollutants, including NO_2, CO, and $PM_{2.5}$, but not O_3 or sulfates	Relative Risks for: SO_4^2 per 5 $\mu g/m^3$ WS metals per 0.03 $\mu g/m^3$ OC per 2 $\mu g/m^3$ EC per 1 $\mu g/m^3$ All ages: Total cardiovascular: SO_4^2 1.003 (0.968, 1.005) WS metals 1.027 0.998, 1.056) OC 1.026 (1.006, 1.046) EC 1.020 (1.005, 1.036) Congestive heart failure: SO_4^2 1.009 (0.938, 1.162) WS metals 1.040 (0.981, 1.051) OC 1.048 (1.007, 1.091) EC 1.035 (1.003, 1.068) Ischemic heart disease: SO_4^2 0.997 (0.936, 1.090) WS metals 1.000 (0.951, 1.051) OC 1.028 (0.994, 1.064) EC 1.019 (0.992, 1.046) Peripheral vascular and cerebrovascular disease: SO_4^2 1.025(0.964, 1.090) WS metals 1.043 (0.991, 1.036 OC 1.026 (0.990, 1.062) EC 1.021 (0.994, 1.049)

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcomes and Design	Mean Component Levels	Copollutants Considered	Lag Structure Examined	Method, Findings, Interpretation	Effects (Relative Risk and 95% CI)
Peel et al. (2005) Atlanta, GA Aug 1998-Aug 2000	Emergency department visits for total and cause-specific respiratory diseases by age groups 0-1, 2-18, >19, and >65 yr. Time-series study. Components included acidity (H^+), EC, OC, water-soluble (WS) metals, sulfates	Median ($\mu g/m^3$) (10-90% Range) SO_4^2: 5.5 (1.9-10.7) WS metals: 0.028 (0.006-0.061) OC: 4.5 (2.2-7.1) EC: 2.0 (0.8-3.7)	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafine PM count, oxygenated hydrocarbons oxygenated hydrocarbons	0-2	Poisson GEE and GLM regression used for analysis. A priori models specified a lag of 0 to 2 days. Also performed secondary analyses estimating the overall effect of pollution over the previous 2 weeks. Seasonal analyses indicated stronger associations with asthma in the warm months, especially for O_3 and $PM_{2.5}$ organic carbon. Quantitative results not presented for multipollutant, age-specific, and seasonal analyses.	All ages relative risks for: SO_4^2 per 5 $\mu g/m^3$ WS metals per 0.03 $\mu g/m^3$ OC per 2 $\mu g/m^3$ EC per 1 $\mu g/m^3$ All available data: Total respiratory: SO_4^2 0.998 (0.968, 1.028) WS metals 1.005 (0.981, 1.031 OC 1.011 (0.997, 1.025) EC 0.999 (0.987, 1.011) Upper respiratory infections: SO_4^2 1.001 (0.965, 1.039) WS metals 1.010 (0.980, 1.040) OC 1.011 (0.995, 1.028) EC 0.999 (0.985, 1.013) Asthma: SO_4^2 0.991 (0.949, 1.035) WS metals 1.007 (0.973, 1.043) OC 1.000 (0.978, 1.023) EC 0.993 (0.976, 1.011) Pneumonia: SO_4^2 1.013 (0.959, 1.069) WS metals 0.997 (0.958, 1.039) OC 1.028 (1.004, 1.053) EC 1.006 (0.987, 1.026) COPD: SO_4^2 1.004 (0.929, 1.085) WS metals 0.971 (0.913, 1.032 OC 0.996 (0.959, 1.035) EC 0.981 (0.952, 1.012)

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean Component Levels	Copollutants Considered	Findings, Interpretation	Effects
O'Neill et al. (2005) Boston, MA May 1998-Jan 2000 Baseline period Time trial 2000-2002	Cardiovascular Outcomes: 270 patients with diabetes or at risk for diabetes were studied in relation to various pollutant levels and evaluated for association with vascular reactivity. Linear regressions were fit to the percent change in BAD (flow-mediated and nitroglycerin-mediated) into particulate pollutant index and other factors.	SO_4^{2} mean: 3.3 μg/m^3 Range: 0.3 to 12.9	$PM_{2.5}$, BC, ultrafine	$PM_{2.5}$ was associated with nitroglycerin-mediated reactivity; an association was also reported with ultrafine particles. Effects were stronger in type II than type I diabetes. Black carbon and SO_4^{2} increases were associated with decreased flow-mediated reactivity among those with diabetes. Although the strongest associations were with the 6-day morning average, similar patterns and quantitatively similar results appear in the other lags.	Effect estimate per IQR SO_4^{2} 6-day morning average Nitroglycerin-mediated 6.2%; 95% CI, 11.5 to 0.6

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean Component Levels	Copollutants Considered	Findings, Interpretation	Effects
Sinclair and Tolsma (2004) Atlanta, GA Aug 1998-Aug 2000	Respiratory medical visit data collected by Kaiser Permanente, including ambulatory care visits for asthma (adult and child), URI and LRI. ARIES air quality data used. Poisson GLM regression used for analysis. A priori models specified a lag of 0 to 2 days (avg). Also performed analyses using avg lag periods of 3-5 and 6-8 days. Fine particle components included SO_4^2, H^+, EC, OC, water-soluble (WS) metals.	mean (SD) in $\mu g/m^3$: SO_4^2: 5.52 (3.5) H^+: 0.02 (0.02) EC: 2 (1.38) OC: 4.49 (2.2) WS metals: 0.03 (0.03)	NO_2, SO_2, CO, O_3, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, ultrafine PM count, oxygenated hydrocarbons (OHC)	Adult asthma visits associated with ultrafine number count, and negatively associated with $PM_{2.5}$ mass. Child asthma associated with OHC (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC and OC (3-5 day). LRI associated with $PM_{2.5}$ acidity and SO_2 (0-2 day) and with PM_{10}, $PM_{10-2.5}$, EC, OC and $PM_{2.5}$ WS metals. For URI, significant positive associations with ultrafine PM (0-2 day) and $PM_{10-2.5}$ (3-5 day) but negative associations with $PM_{2.5}$, SO_2 and sulfate.	Risk Ratios per SD: Adult asthma visits: SO_4^2 NS H^+ NS EC NS OC NS WS metals NS Child asthma: SO_4^2 NS H^+ NS EC RR = 1.046 OC RR = 1.046 WS metals NS LRI visits: SO_4^2 NS H^+ NS EC RR = 1.079 OC RR = 1.05 WS metals RR = 1.062 URI visits: SO_4^2 RR = 0.976 H^+ NS EC NS OC NS WS metals NS Quantitative results provided only for statistically significant findings.

Table A15 (cont'd). Associations of Acute Exposure to Fine Particle Components with Health Outcomes

Reference, Study Location and Period	Outcomes and Methods	Mean Component Levels	Copollutants Considered	Findings, Interpretation	Effects
Delfino et al. (2003) Los Angeles, CA Nov 1999-Jan 2000	Respiratory outcomes: Panel study of 22 Hispanic children (10-15 yr) with asthma, living in the Huntington Park region of LA. Daily diary with symptoms, inhaler use, and PEF measurements made three times daily. GEE regression methods used.	Mean (range) in $\mu g/m^3$: EC: 5.09 (1.79-9.42) IQR = 2.91 OC: 9.47 (4.29-17.05) IQR = 4.64 (Measured in PM_{10})	NO_2, SO_2, CO, O_3, PM_{10}, numerous air toxics	Significant associations reported between increased asthma symptoms and PM_{10}, EC, OC, NO_2 and SO_2, acetaldehyde, benzene, ethylbenzene and tetrachloroethylene. Associations with PM10, EC, and OC generally decreased in size and lose significance in 2-pollutant models with air toxics. Authors conclude that their findings support the view that air toxics in the pollutant mix from traffic and industrial sources may have adverse effects on asthma in children.	Odds Ratio for asthma symptom per IQR: EC: lag 0: 1.85 (1.11-3.08) lag 1: 1.01 (0.66, 1.53) OC: lag 0: 1.88 (1.12, 3.17) lag 1: 1.08 (0.80, 1.46)

Additional U.S. and Canadian Studies:

Bennett et al. (2006): Assessed relationship between Asian dust event in April 1998 and hospital admissions. No statistically significant difference in hospital admissions rates for either respiratory or cardiovascular diseases between 4-day period in 1998 and corresponding 4-day period in 1997; methods include graphical display and chi-square test for difference.

Clairborn et al. (2002): This report includes discussion of ongoing research in Spokane, WA, that will examine relationships between health outcomes and particle sizes and fine and thoracic coarse particle metal concentrations. In addition, results of previous publications from this research group are discussed, and it is suggested that fine particulate metals, particularly Zn, are significantly associated with asthma hospital admissions.

Henneberger et al. (2005): Repeated ECG measurements in a panel of 56 patients with ischemic heart disease in Erfurt, Germany. $PM_{2.5}$ (6 h avg) was significantly associated with decreased T-wave amplitude, increased T-wave complexity and nearly significant with increased variability of T-wave complex. Associations with 6 h $PM_{2.5}$ were stronger than those with 24 h $PM_{2.5}$. Similar associations were observed with 6 h ultrafine particles, accumulation mode particles, OC and EC, although most were not statistically significant. A significant association was reported between OC and QT duration.

Moshammer and Neuberger (2003): In a panel of 78 children, biweekly lung function tests and daily symptom diaries were collected for 4 weeks. Ambient monitoring was conducted to determine "active surface" of particles by unipolar diffusion charging. The results of this study demonstrated that active surface correlates with PAH levels of particles. Significant associations reported between active surface of particles and evening cough, shortness of breath and wheeze.

Table A16: CAPs Studies with Source Apportionment or Components Analysis

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Factor or Principal Component Analysis					
Huang, Y-C.T et al. (2003)	Human, M (n = 35), F (n = 2) 26.2±0.7 yr	2 h with 15 min alternating rest and exercise ~50 L/min; assessed 18 h PE	Chapel Hill, NC air; HAPC; 72.2 μg/m^3 (range 0–311 μg/m^3) Median soluble components (μg/m^3): sulfate 17.6; V 2.1; Fe 42.6; Zn 66.4; Cu 13.1; As 2.2; Ni 1.2; Se 6.0; Pb 3.4	BALF: Cell counts Cell differential protein Cytokines PGE_2 Protein Fibrinogen NO Fibronectin Venous blood: CBC Ferritin Fibrinogen	Factor 1 (sulfate/Fe/Se) correlated with increases in BALF PMN. Factor 2 (Cu/Zn/V) correlated with elevated blood fibrinogen levels. BALF fibronectin correlated positively with BALF PMN. Factor 1 correlated highly with PM mass.
Batalha et al. (2002)	Rat, M, SD, 200–250 g; CB induced with SO_2	5 h/day for 3 consecutive days in 6 experimental sets; assessed 24 h PE	Boston, MA; HAPC; mean mass conc. 262.21±213 μg/m^3 (range 73.5–733) Elemental composition (μg/m^3); sulfate 66.9; EC 11.45; OC 57.73; Al 1.22; Si 4.62; S 25.61; Cl 0.68; K 1.68; Ca 1.82; Ti 0.20; V 0.05; Cr 0.01; Mn 0.09; Fe 3.47; Ni 0.05; Cu 0.10; Zn 0.26; As 0.01; Se 0.02; Br 0.07; Cd 0.02; Ba 0.73; Pb 0.12	Histopathology Morphometry for L/W ratios (muscular hypertrophy and constriction of vessels)	CAPs caused vasoconstriction of small pulmonary arteries. Exposure to CAPs in normal and CB rats resulted in decreased L/W ratio that was associated with CAPs mass, Si, Pb, sulfate, EC and OC. In normal rats exposed to CAPs, decreased L/W ratio was associated with sulfate and Si. In CB rats, decreases in L/W ratio were associated with Si and OC. No significant associations were observed between the L/W ratio and Day 1 of exposure (reported effects due only to Days 2 and 3).

Table A16 (cont'd): CAPs Studies with Source Apportionment or Components Analysis

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Factor or Principal Component Analysis (cont'd)					
Goldsmith et al. (2002)	Mice, Balb/c; sensitized to OVA on days 7 and 14, pretreated with OVA via inhalation on days 21, 22, and 23	5 h/day for 3 days (21, 22, and 23); exposure to CAPs only, O_3 only (0.3 ppm), or CAPs+O_3; assessed 24 or 48 h PE	Boston, MA; HAPC; mean mass conc. 302±58 μg/m^3; range 63.3–1569 μg/m^3 Elemental composition (μg/m^3): Al nd–17.2, Si 0.9–35.1, S 3.5–187, Cl nd–7.9, K 0.4–5.7, Ca 0.6–12.5, Ti nd–1.9, V nd–0.26, Cr nd–0.05, Mn 0.01–0.43, Fe 1.4–21.9. Ni nd–0.16, Cu 0.02–0.43, Zn 0.06–1.1, Br 0.01–0.24, Ba 0.04–0.83, Pb 0.001–0.34, As nd–0.31, Se nd–0.06, Cd nd	Pulmonary function BALF: Cell viability Cell counts Cell differentials	CAPs alone caused increases in penh (a measure of airway responsiveness) immediately following exposure, although the magnitude of response was small (approximately 0.9% for a 100 μg/m^3 increase in CAPs). CAPs+O_3 exposure resulted in elevated penh when sensitized animals were challenged with methacholine. An Al/Si component for daily and 3-day cumulative concentrations was associated with increased penh for OVA animals exposed to CAPs+O_3. A S component was associated with elevated penh for non-OVA mice exposed to CAPs only.
Wellenius et al. (2003)	Dog, F, retired mongrel; implanted balloon occluder on left anterior descending coronary artery	6 h/day; immediately PE a 5 min preconditioning occlusion followed 20 min later by a 5 min study occlusion	Boston CAPs; HAPC; mean mass conc. 345±194 (range 161–957) Elemental composition (μg/m^3): sulfate 77.90; BC 9.78; EC 21.48; OC 66.71; Al 2.13; As 0.028; Br 0.09; Ca 4.31; Cr 0.03; Cu 0.19; Fe 8.26; K 2.15; Mn 0.18; Ni 0.16; Pb 0.15; S 27.41; Se 0.02; Si 8.17; Ti 0.41; V 0.16; Zn 0.58	ECG: Peak and integrated ST-segment elevation Peak HR Incidence of arrhythmias	CAPs enhanced occlusion-induced peak ST-segment elevation. HR was not affected by CAPs. ST-segment elevation was associated with Si and other crustal elements. CAPs mass or particle number was not associated with any endpoint.

Table A16 (cont'd): CAPs Studies with Source Apportionment or Components Analysis

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Components (Elements, sulfate, nitrate, organic/elemental carbon)					
Gong et al. (2005)	Human, healthy (4F, 2M, 68±11 yr) and COPD (9F,9M, 72±7 yr); exposures were on separate days followed by at least 2 wks	2 h with 15 min alternating rest and exercise; assessed during, at 0h PE, 4 h PE, and day 2 (~22h PE)	Los Angeles, CA; HAPC Exposures to: (a) FA (b) 0.4 ppm NO_2 (c) CAPs - predominantly $PM_{2.5}$ at ~200 µg/m^3 collected with HAPC (d) CAPs + NO_2 <0.1 µm contributed ~6 µg/m^3 in all exp; >2.5 µm contributed ~6 µg/m^3 in FA or NO_2 exp and 12 µg/m^3 in CAPs and CAPs +NO_2 exp; CAPs and CAPs+NO_2 (1–2.5 µm) ~170 µg/m^3 Elemental composition (µg/m^3): Si 4.0; Fe 2.9; EC 10.1; Al 1.6; Ca 2.3; Na 2.0; K 1.1; Cl 2.5; NO_2 42 ppb	ECG SaO_2 Pulmonary function BP HR Sputum: Cell counts Cell differentials	For all exposure groups, there were no changes in symptoms, spirometry, or differential cell counts. In subjects exposed to CAPs and CAPs+NO_2, decrements in MMEF and SaO_2 (greater in healthy than COPD) were observed. Decreased percentages of columnar epithelial cells in sputum were also reported. For subjects exposed to CAPs+NO_2, FEV_1 and FVC decreases were associated with sulfate levels; total mass did not correlate with sulfate. HR increased for both CAPs groups post-exposure; for COPD subjects, the tendency of increased HR was lower with increasing mass. There was a decrease in self-reported symptoms during CAPs+NO_2 that were associated with elevated Fe concentration.
Urch et al. (2004)	Human, healthy (14M, 10F; 35±10 yr)	2 h CAP + O_3 (crossover design); O_3 conc. 120 ppb	Toronto CAPs; HAPC; mean mass conc.148 µg/m^3 (range 102–257) Major constituents (µg/m^3): C 22.7 (OC 19.7, EC 2.5), sulfate 14.2, nitrate 14.0, ammonium 5.4, Ca 0.78	BAD	A decrease in OC or EC concentration was associated with changes in BAD. When multiple linear regression analysis (MLRA) was conducted on the dose metric (a product of mean ventilation, exposure duration, and mass concentration), elevated OC+sulfate was associated with change in BAD (although p-value = 0.06 for sulfate in the MLRA). Sulfate was not associated with changes in BAD alone.

Table A16 (cont'd): CAPs Studies with Source Apportionment or Components Analysis

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Components (Elements, sulfate, nitrate, organic/elemental carbon) (cont'd)					
Urch et al. (2005)	Human, healthy (13M, 10F; 35±10 yr)	1 h CAP + O_3 (crossover design); O_3 conc. 121 ppb	Toronto CAPs; HAPC; mean mass conc.147±27 μg/m^3 (range 102–214); C 28.4 μg/m^3	BP HR	DBP increased an average of 6 mm Hg over the 2 h of exposure. A nonlinear relationship was reported between DBP change and estimated exposure concentration of OC; a similar correlation was observed between MAP and OC.
Dvonch et al. (2004)	Rat, BN, M; 7 rats/group	8 h/day for 3 consecutive days (22–24 July 2004); assessed 24 h PE	Urban Detroit CAPs; HAPC; mean mass conc. 354 μg/m^3 Elemental composition ranges (ng/m^3): sulfur 1393–26839, Mg 173–487; Ca 1137–2125; V 2–15; Fe 1035–2377; Ni 4.3–11.5; Cu 101–152; Cd 0.44–1.75; La 0.3–9.7; Ce 0.6–18.5; Sm 0.03–0.21; Pb 48.6–57.5	Plasma ADMA	Elevated levels of ADMA were observed in CAPs-exposed rats. CAPs mass concentration was the highest on the first day of exposure (4–5 times greater than Days 2 or 3). Increased PM mass was associated with elevated levels of S, V, La, Ce, and Sm. An industrial complex (coal combustion, oil refineries, coke ovens, iron/steel mills, sewage sludge incineration) was located SW of the study location.
Gurgueira et al. (2002)	Rat, SD, 250–300g	1, 3, or 5 h	Boston, MA; HAPC; conc. mass range 100–956 μg/m^3; mean mass conc. 300±60 μg/m^3	Organ CL (for ROS concentration); organ water content; LDH; SOD; catalase	Exposure to CAPs for 5 h resulted in increased oxidative stress in the lung, that was associated with the PM content of Fe, Mn, Cu, and Zn. Oxidative stress observed in the heart following exposure was associated with Fe, Al, Si, and Ti in CAPs. Organ water content and LDH activity also increased. Elevated levels of the antioxidants SOD and catalase were also reported following exposure.
Kodavanti et al. (2005)	Rat, WKY and SH, 10–12 wk old	SH one 4 h exp, assessed 1–3 h PE; SH and WKY 4h/day or 2 days, assessed 1 day PE	Research Triangle Park, NC; HAPC 1-day exp: 1138–1765 μg/m^3, size range 1.07–1.19, mean 1.12 μm 2-day exposure 144-2758 μg/m^3, size range 1.27–1.48, mean 1.39 μm	Pulmonary function BALF: Cell count Cell differentials Total protein, albumin, LDH, NAG, GGT, glutathione, ascorbic acid, cytokines Blood: CBC Plasma fibrinogen ACE activity CRP	In the 1-day exposure, no biologic effects were observed. In the 2-day exposure, WKY rats exposed to CAPs had decreased total cells and AM and increased PMN. Fibrinogen levels were also elevated in these animals. In the 2-day exposure, SH rats exposed to CAPs had increased total protein, GGT activity, ascorbate, UA, and PMN. Decreases in albumin were observed in these rats. For SH rats exposed to CAPs, plasma fibrinogen correlated with Zn and OC when expressed as mg/CAP.

Table A16 (cont'd): CAPs Studies with Source Apportionment or Components Analysis

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Components (Elements, sulfate, nitrate, organic/elemental carbon) (cont'd)					
Morishita et al. (2004)	Rat, BN, M; some sensitized to OVA (days 1-3) and challenged (days 14-16), n = 6/group	4 days after challenge; 10 h/day for either 4 days (July) or 5 days (Sept); assessed 24 h PE	Urban Detroit; HAPC; mean mass conc. 676 µg/m^3 (July), 313 µg/m^3 (Sept) Elemental composition (TWA in ng/m^3 in July): La 1.2; S 77716; V 17; Mn 206 Elemental composition (TWA in ng/m^3 in Sept): La 1.5; S 19272; V 46; Mn 309	BALF (left lung): Cell counts Cell differentials Leukocytes Total protein Right lung: trace elements by ICP-MS	CAPs caused increases in BALF eosinophils and protein in allergenic rats. Increased levels of La, V, Mn, and S in normal rats and greater increases in allergenic rats that were colocalized with eosinophilic infiltrates. For the September allergic CAPs-exposed rats, elevated eosinophils and protein were reported. Increased levels of La were reported in the lungs of rats in both CAPs groups in September. Increased levels of V and S were observed in the lungs of rats in the OVA/CAPs group in September. Heavy industrial source complex located 2 miles downwind of exposure site in September.
Rhoden et al. (2004)	Rat, SD, M, 250-300 g; control and NAC-pretreated	5 h, assessed 24 h PE	Boston, MA; HAPC; 1060300 µg/m^3 (range 150–2520 µg/m^3) Elemental composition (µg/m^3): Na 2.54; Mg 1.93; Al 5.21; Si 14.03; S 141.9; Cl 0.18; K 4.32; Ca 4.59; Ti 0.67; V 0.08; Cr 0.02; Mn 0.69; Fe 10.91; Ni 0.05; Cu 0.18; Zn 1.58; Br 0.20; Cd 0.01; Ba 0.83; Pb 0.10	TBARS Carbonyl BALF: Cell counts Cell differentials Edema	CAPs caused increases in TBARS, oxidized proteins, PMN, and edema. No change in BALF protein, total cells or LDH. NAC pretreatment attenuated increases in TBARS, edema, and PMNs. Component analysis: Al, Si, and Fe correlated with TBARS Cr and NA trended with carbonyl Cr, Zn, and Na trended with PMN

Table A17: Other Acute CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Humans					
Devlin et al. (2003)	Human, M&F (66.9±1.0 yr); healthy elderly subjects (n = 10)	2 h, alternating 15 min exercise and rest; HRV assessed pre-and post-exposure and 24 h PE; cross-over design	Chapel Hill, NC; HPAC; mean mass conc. 40.5 ± 8.6 μg/m^3 (range 21.2–80.3 μg/m^3)	HRV	CAPs caused significant decreases in time and frequency domain HRV parameters (PNN50 and HF) at 0 and 24 h PE. Individual subjects (n = 5) experienced abnormal beats (premature atrial contractions and/or bradycardia). Source apportionment not done.
Ghio et al. (2003)	Human, M (n = 14), F (n = 6), 25.3±0.8 yr; 5 to FA, 15 to CAPs	2 h alternating 15 min rest and exercise ~50L/min; assessed 0 or 24 h PE	Chapel Hill, NC; HAPC; mean mass 121±14.0 μg/m^3, range 15.0 to 358 μg/m^3	Venous blood: CBC Biochemical indices (total protein, albumin, UA, LDH, CRP) Cytokines ET-1 Fibrinogen and other clotting factors	CAPs caused decreases in WBC counts at 24 h PE, but no other changes CRC values. CAPs caused decreases in LDH at 24 h PE, but no other changes in blood chemistries. CAPs caused increases in fibrinogen, but other coagulation factors and inflammatory mediators were unchanged. Source apportionment not done.
Gong et al. (2004a)	Human, M and F; healthy (68±11 yr, n = 6) and COPD (73±8 yr, n = 13)	2 h, alternating 15 min exercise and rest; assessed just PE, at 4h, and at day 2. ECG before, during and after exposure	Los Angeles, CA; HAPC; mean mass conc. 194±26 μg/m^3; range 135–229 μg/m^3 >2.5 μm: 20±7 μg/m^3; range 7 –31 μg/m^3 0.1–2.5 μm: 167±27 μg/m^3; range 104–201 μg/m^3 <0.1 μm: 8±5 μg/m^3; range 3–23 μg/m^3 Mass percentages: 25% nitrate; 10% sulfate; 6% elemental carbon. Element composition (μg/m^3): silicon 4.1; iron 3.1; chlorine 2.7; sodium 2.4; calcium 2.3; aluminum 1.7; potassium 1.2	Pulmonary function SaO_2 BP Exhaled NO HRV Ectopic beat incidence Venous blood: WBC, platelet, and clotting factors Sputum: Cell counts	CAPS had no effect on symptoms, spirometry, or induced sputum. Decreased SaO_2 and increased peripheral basophils in healthy subjects. Modest increase in ectopic beats in COPD subjects. HRV was lower in healthy subjects than COPD subjects. Source apportionment not done.

Table A17 (cont'd): Other Acute CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Animals					
Gong et al. (2004b)	Human, M&F (19-51 yr); healthy (4) and mild asthmatics (12)	2 h, alternating 15 min exercise and rest; assessed immediately PE, at 4h, and at day 2. ECG before, during and after exposure	Los Angeles, CA; CPC; 80% coarse (2.5-10 µm), 20% fine (<2.5 µm); 157 µg/m^3 (range 56–218 µg/m^3) Elemental composition (%): silicon 19; sodium 18; iron 15; chlorine 11; sulfur 9; aluminum 7; potassium 4; magnesium 2; titanium 1; 16 others <1	Pulmonary function BP Exhaled NO HRV Sputum: Cell counts	CAPs caused reduction in overall HRV and increased HR 4-24 h PE. Greater responses in normal subjects. No changes in inflammation, spirometry, respiratory symptoms, or SaO_2. Source apportionment not done.
Campbell et al. (2005)	Mice, M, Balb/c (6 wk); 9 mice/group; pretreated daily with OVA (50 µg) via intranasal instillation prior to CAPs exposure; OVA challenge 1 and 2 wk PE, assessed 1 day after challenge	4 hr/day, 5 day/wk for 2 wk in whole body chambers	Los Angeles, CA; 150 m downwind of heavily trafficked highways; VACES UF (≤180 nm) or F (≤2.5 µm) UF: mass 282.5 µg/m^3; elemental composition (%): EC 5.7, OC 47.8, total metals 15.9, nitrate 8.8, sulfate 8.8 F: mass 441.7 µg/m^3; elemental composition (%): EC 2.8, OC 16.1, total metals 24.6, nitrate 17.0, sulfate 14.7	Brain: IL-1α TNF-α NF-κB	Elevated NF-κB in brain nuclear fraction of mice exposed to UF or F CAPs. Increased amount of IL-1α in cytoplasmic fraction of brain of mice exposed to UF or F CAPs; increased levels of TNF-α in mice exposed to F CAPs only.
Cassee et al. (2005)	Rat, M, SH (8–12 wk) or WKY (7 wk); a subset were preexposed to ozone for 8 h 1 day before CAPs	6 h, assessed 2 h PE	The Netherlands: Bilthoven (suburban), Utrecht (industrial), and freeway; HAPC For Wistar exposures: mean mass conc. 1104 µg/m^3; range 36–2085 µg/m^3 For SH exposures: mean mass conc. 1234 µg/m^3; range 270–3660 µg/m^3	BrdU for cell proliferation BALF: LDH NAG ALP UA Total protein Blood: WBC Fibrinogen CC16	In Wistar rats pretreated with ozone, CAPs induced increased protein, albumin and NAG activity in BALF and elevated Hb, Hct, and RBC in CBC. AM were significantly decreased. No observed effects were reported for antioxidants or cytotoxicity. In SH rats, CAPs caused increased PMN but no other effects were observed in BALF biochemical parameters. CAPs caused no changes in hematological parameters, but did cause increases in fibrinogen and CC16. For both strains, no robust concentration-effect relationship was observed for CAPS as a continuous variable.

Table A17 (cont'd): Other Acute CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Animals (cont'd)					
Chang et al. (2004)	Rat, M, SH, ~200 g, implanted with radiotelemetry transmitters	5 h/day in nose-only exposure chambers in spring (4 days total) and summer (6 days total)	Taipei suburb; VACES; mean mass conc. 202±68.8 μg/m^3 (spring) and 141±54.9 μg/m^3 (summer); particle number 2.30 × 10^5 particles/cm^3 (spring) and 2.78 × 10^5 particles/cm^3 (summer)	HR BP QAI	HR and BP significantly increased during spring CAPs exposure (maximum ↑52 bpm and ↑9 mm Hg, respectively). QAI decreased throughout the CAPs exposure in spring to a maximum of 1.6 msec.
Chang et al. (2005)	Rat, M, SH, ~200 g, implanted with radiotelemetry transmitters	5 h/day in nose-only exposure chambers in spring (4 days total)	Taipei suburb; VACES; mean mass conc. 202±68.8 μg/m^3; particle number 2.30 × 10^5 particles/cm^3	HRV	Statistically significant decreases in SDNN (60–85% of baseline period) were observed during PM exposure. The effects of CAPs on RMSSD were not significant, although there was a trend toward decreased HRV.
Cheng et al. (2003)	Rat, M,. SD, MCT-treated; implanted with telemetry transmitters	6 h/day in nose-only exposure chambers for 3 consecutive days, then rested 4 days; exposed to CAPs on wk 2,3, and 4 and to FA wk 1 and 5	Taipei suburb; VACES; mean mass conc. 240±77 μg/m^3; range 108 to 338 μg/m^3 Elemental composition (μg/m^3): Al 26.5; Mg 6.8; S 2.8; Si 2.7; Fe 1.4; Ga 0.7; P 0.5; Zn 0.2; Ni 0.07; Mn 0.03; Cu 0.02; Co 0.01; V 0.01	HR BP core temperature	An early decrease in HR (↓14.9 bpm) was observed, followed by a gradual increase in HR (↑8.6 bpm) to a maximum observed 11 h after the start of the exposure. BP initially decreased (↓3.3 mm Hg) during the first h of exposure, then returned to normal. No changes in core temperature were observed.
Kleinman et al. (2005)	Mice, Balb/c, M; pretreated with OVA via nasal instillation and challenge one and two weeks after exposure	WBI; 4 h/day for 5 day/wk for 2 wk; assessed 24 h after second OVA challenge; 4 experiments (July and October 2001, June and August 2002)	Los Angeles, CA; 50 or 150 m downwind of heavily trafficked roadway; VACES UF (≤150 nm) or F (≤2.5 μm) UF ranges: mass 283–442 μg/m^3; count 2.9–5.9×10^5 particles/cm^3; elemental composition (μg/m^3): EC 16–18, OC 135–189, total metals 45–51, nitrate 24.7–53.7, sulfate 25.0–35.5 F ranges: mass 313–498 μg/m^3; count 1.6–2.85×10^5 particles/cm^3; elemental composition (μg/m^3): EC 8.5–13, OC 86.0–253.8, total metals 10–109, nitrate 75.0–107, sulfate 25.3–76.9	BALF: Cell counts Cell differentials Cytokines Plasma: Cytokines IgE IgG1	Mice exposed to fine CAPs in 2001 at the 50 m location had elevated eosinophils and cytokines in BALF and elevated IgG1 in blood plasma compared to air controls. Mice exposed to UF CAPs in 2002 at the 50 m location had elevated IL-5 in BALF and increased IgG1 in blood plasma. Significant interactions were observed between treatment and location for IL-5, eosinophils, and IgG1 (i.e., mice exposed to CAPs at 50-m had higher levels of allergic response biomarkers than mice exposed to CAPs at 150-m downwind of the freeway).

Table A17 (cont'd): Other Acute CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Animals (cont'd)					
Lei et al. (2004a)	Rat, SD, M, 60 days old; 318.7±8.3 g; pretreated with single 60 mg/kg ip injection of MCT	6 h/day for 3 days; pulmonary function assessed 5 h PE; blood, lung and BALF 2 days PE	Taipei, Taiwan; VACES; mean mass conc. 371.7 μg/m^3 Elemental composition (μg/m^3): K 33.7;S 25.5; Al 6.1; Fe 4.7; P 2.7; Ca 2.3; Si 2.1; Zn 1.7; Mo 0.5; Ti 0.4; Cu 0.3; Mn 0.2; Pt 0.07; V 0.06; Co 0.04	Pulmonary function BALF: Cell counts Cell differentials Total protein LDH Cytokines	CAPs caused decreased *f* and increased V_T. CAPs caused increased BALF total cells, PMN percentage, protein, IL-6, and LDH. MCh challenge following exposure caused increased penh.
Lei et al. (2004b)	Rat, SD, M, 300–350 g; pretreated with single 60 mg/kg ip injection of MCT; 4 rat/group	Low - 6h; high - 4.5 h; assessed 36 h PE	Taiwan, Asian dust event particles; ACES Low: mean mass conc 315.6 μg/m^3; elemental composition (μg/m^3): Si 53.3; Al 14.0; S 6.25; Ca 6.1; K 3.1; Mg 2.7; Fe 2.1; As 2.1; Ni 0.09; W 0.9; V 0.2 High: mean mass conc 684.5 μg/m^3; elemental composition: Si 41.6; Al 10.7; K 3.6; As 2.9; Mg 1.2; Ca 1.7; W 1.4; V 0.1	BALF: Cell counts Cell differentials Total protein LDH IL-6 Blood: CBC	A dose-dependent increase in WBC was observed following exposure; no other blood parameters were altered. Dose-dependent increases in total cells, percent PMN, total protein, LDH and IL-6 were observed; no increase for AMs or lymphocytes.
Nadziejko et al. (2004)	Rat, M, F344, 18 mo; 6 rats/group, crossover design	4 h/day for 1 day; NOI; repeated twice for CAPs and ultrafine C (500 and 1280 μg/m^3) and 4 times for SO_2 (1.2 ppm)	Tuxedo, NY; centrifugal concentrator; 161 and 200 μg/m^3	HR Body temperature Activity Arrhythmia	Increases were observed in the number of delayed beats following CAPs exposure. No changes in arrhythmia frequency were observed following ultrafine C or SO_2 exposure.
Smith et al. (2003)	Rat, M, SD, 9–10 wk; 6 rats/group	4 h/day for 3 consecutive days in 6 experimental sets (3 weeks in fall, 3 weeks in winter); assessed immediately after exposure on day 3	Fresno, CA; VACES; fall mean mass conc. 260–847 μg/m^3 (number 1.1–1.2×10^5 particles/cm^3), winter mean mass conc. 190–815 μg/m^3 (number 0.9–1.2×10^5 particles/cm^3); largest contributors to PM mass were ammonium nitrate and OC (60–80%) Elemental composition ranges (μg/m^3); sulfate 13–51; nitrate 58–527; OC 61–141; EC 4–59; metals 8–38 (mostly Al, Si, S, Ca, and Fe); unexplained 30–174	BALF: Cell counts Cell differential Cell viability	Elevated PMN were observed following exposure during the first week of fall and the first week of winter. The highest levels of PM mass, nitrate, and OC were observed during these two weeks. The most consistent particle characteristics for all weeks were particle number, OC, Cl, Ti, Fe, Zn, Mn, and Pb. The particle characteristics that varied considerably across the exposure periods were mass, nitrate, sulfate, and trace elements (EC, Al, Si, S, K, Ca, Ba, Ni, Cu, Se, Cd).

Table A17 (cont'd): Other Acute CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Animals (cont'd)					
Zelikoff et al. (2002)	Rat, F-344, M, 7–9 mo, infected with *Streptococcus pneunoniae* (15–20 × 10^6) via IT; 4 rats/group	5 h/day for 1 day; NOI; assessed 4.5, 9, 18, 24, and 120 h PE	NYC; centrifugal concentrator; 65–90 µg/m^3	Lungs (affected rats): Absolute levels of bacteria Bacteria per g lung	Rats exposed to NYC CAPs had increased bacterial burdens at 9 h (10% above control), 18 h (300% greater than control), 24 h (70% above control), and 5 days (30% above control).

Table A18: Subchronic CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Factor Analysis					
Lippman et al. (2005c)	Mice, M, C57, ApoE$^{-/-}$	6 h/day, 5 day/wk for 5 mo.	Tuxedo, NY CAPs; VACES; mean mass conc. 113 µg/m^3 Source categories: 1. Secondary sulfate (SS)—high S, Si, and OC 2. Resuspended soil (RS)—high Ca, Fe, Al, and Si 3. Residual oil (RO)—V, Ni, and Se 4. Motor vehicle (MV) emissions and other	HR HRV (SDNN, RMSSD); data analyzed from 1600–1800 (afternoon) and 130–430 (night)	SS was the largest contributor to PM mass (56%), then RS (12%); MV/other were 30.9% and RO was 1.4%. RS (and PM mass) were associated with decreased HR during CAPs exposure in ApoE$^{-/-}$ mice. SS (but not PM mass) was associated with short-term decreases in HR in the afternoons following exposure in ApoE$^{-/-}$ mice; RS was associated with short-term increases in HR during the same period. MV traffic/other source category was associated with short-term decreases in RMSSD in the afternoons following CAPs exposures in C57. RO was associated with short-term decreases in SDNN and RMSSD in the afternoons following CAPs exposure in ApoE$^{-/-}$ mice. SS was associated with short-term decreases in SDNN and RMSSD (also PM mass) in nighttime following CAPs exposure in ApoE$^{-/-}$ mice. RS was associated with short-term increases in SDNN and RMSSD at night following CAPs exposure in ApoE$^{-/-}$ mice.
Maciejczyk et al. (2005)	BEAS-2B; 0, 100, 300, 500 µg/mL for 24 h 9 10^4 cells/well	Ambient (12.6±9.3 µg/m^3) and CAPs (108.6± 177.5 µg/m^3) filter samples collected 3/4–9/5/2003 M-F (900-1500)	Tuxedo, NY; VACES Source categories: 1. Secondary sulfate (SS)—S, Si, P, EC, and OC 2. Resuspended soil (RS)—K, Ca, Mn, Zn, Fe, Al, and Si 3. Residual oil (RO)—V and Ni 4. Motor vehicle (MV) emissions and other—Zn, Se, Br, Pb, nitrate	NF-κB	The NF-κB response was correlated with the RO source category. SS contributed on average 65% to overall PM mass, RS contributed 20%, and RO contributed 2%; 13% of the CAPs mass was unaccounted for and included high loadings of Pb, Br, Zn, Se, and nitrate. S and OC correlated well with each other.

Table A18 (cont'd): Subchronic CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Other					
Chen and Hwang (2005)	Mice, C57 and ApoE$^{-/-}$; 3–10 rats/group	6 h/day, 5 day/wk for 5 mo (4/11–9/5/2003)	Tuxedo, NY; VACES; mean mass conc. 110 µg/m^3	HR HRV (SDNN, RMSSD); data analyzed from 1600–1800 and 130–430	For ApoE$^{-/-}$ mice, SDNN gradually increased the first 6 wk of CAPs exposure, then slightly decreased for next 12 wk, and progressively increased at the end of study (1600–1800 and 130–430). No changes in evening HR or HRV were observed in C57 mice. Slight increases in SDNN were observed at nighttime after 6 wk of CAPs exposure. No lag effects were observed. There was no clear pattern between CAPs concentration and estimated acute effects (48 h).
Chen and Nadziejko (2005)	Mice, C57, ApoE$^{-/-}$, M&F ApoE$^{-/-}$ + LDL$^{-/-}$ (DK); 4–12 rats/group	6 h/day, 5 day/wk for up to 6 mo (3/10–9/5/2003); C57 6 mo, ApoE$^{-/-}$ 5 mo, DK 4 mo	Tuxedo, NY; VACES ; mean mass conc. 110±79, 120±90, and 131±99 µg/m^3	Heart: histopathology Aorta roots: total atherosclerotic lesion area, lipid contents, cellularity	20 DK mice died (lesions were indicative of myocardial infarction) during air or CAPs exposure. CAPs-exposed DK mice seemed to die earlier than air-exposed DK mice and females were more susceptible. No abnormal lipid deposition in coronary artery in C57 or ApoE$^{-/-}$ mice. More mice in the CAPs group had coronary artery disease (7/10) compared to the air (3/13) group. Similarly, more mice in the CAPs group had complex atherosclerotic lesions in the coronary artery (3/10) compared to the air group (0/13). All DK mice developed extensive lesions in the aortic sinus regions; plaque lesion cellularity was elevated in CAPs-exposed mice (28%). ApoE$^{-/-}$ and DK mice had severe atherosclerosis covering >40% of lumenal surface of aortic tree, which was significantly greater for CAPs-exposed ApoE$^{-/-}$ mice (66%).

Table A18 (cont'd): Subchronic CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Other (cont'd)					
Gunnison and Chen (2005)	Mice, M&F ApoE$^{-/-}$ + LDL$^{-/-}$ (DK); 3 rats/group	6 h/day, 5 day/wk for 4 mo (5/12–9/5/ 2003); sacrifice 3 or 4 days PE	Tuxedo, NY; VACES; median size of 4 exposure days 389±2 nm; mean mass conc. 131±99 μg/m^3 (range 13–441 μg/m^3)	Heart gene expression Lung gene expression	Many genes were up- or down-regulated following exposure to CAPs. The largest functional categories with alterations were heat shock proteins and other stress-response genes. Other genes related to DNA binding and regulation of transcription, defense responses, proteolysis, inflammatory response, and signal transduction and signaling pathways were changed. The Dbp gene associated with circadian rhythm was upregulated.
Hwang et al. (2005a)	Mice, C57 and ApoE$^{-/-}$; 3–10 rats/group	6 h/day, 5 day/wk for 5 mo (4/11–9/5/2003)	Tuxedo, NY; VACES; median size of 4 exposure days 389±2 nm; mean mass conc. 133 μg/m^3 (range 5–627 μg/m^3)	HR Core temperature Activity data analyzed from 130–430 (night) and 1100-1300 (morning)	Chronic CAPs exposure was associated with nighttime decreased HR (~34 bpm), body temperature (~1.0°C), and activity (2.4 count/min) in ApoE$^{-/-}$ mice starting 30 days after exposure began. There were few changes observed in HR, body temperature, or activity at night in C57 mice with CAPs. ApoE$^{-/-}$ mice had increased body temperature and activity during exposure (1100–1300) that was not associated with CAPs (chamber effect). Decreased HR (12.4 bpm) was associated with mean CAPs concentration during exposure. Fluctuation of HR in ApoE$^{-/-}$ mice within longer time intervals (4–7 h) increased 1.35-fold by the end of exposure; fluctuation within short term intervals (15 min) decreased 0.7 fold.
Lippmann et al. (200b)	Mice, C57, ApoE$^{-/-}$, M&F ApoE$^{-/-}$ + LDL$^{-/-}$ (DK)	Whole-body inhalation, 6 h/day, 5 day/wk up to 6 mo.; sacrifice 3 days after last exposure day	Tuxedo, NY; VACES	Same as Lippmann et al. (I)	Summary of results. No inflammation was observed in the lungs as measured by BALF.

Table A18 (cont'd): Subchronic CAPs Studies

Reference	Species	CAPs Exposure	CAPs Characterization	Endpoints	Results
Other (cont'd)					
Veronesi et al. (2005)	Mice, C57 and ApoE$^{-/-}$; 5-9 rats/group	6 h/day, 5 day/wk for 4 mo; sacrifice 3 or 4 days PE	Tuxedo, NY; VACES	Dopamine-containing neurons Astrocytes	In ApoE$^{-/-}$ mice exposed to CAPs, decreased tyrosine hydroxylase-stained neurons (29%) in the substantia nigra region of the brain were observed. Increased glial fibrillary acidic protein-stained astrocytes (8%) in nucleus compacta were observed in CAPs-exposed ApoE$^{-/-}$ mice. There were no effects of CAPs on neurons or astrocytes in C57 mice exposed to CAPs.
Sun et al. (2005)	Mice, M, ApoE$^{-/-}$ fed normal and high fat chow	6 h/day, 5 day/wk for 6 mo	Tuxedo, NY; VACES; mean mass conc. 85 µg/m^3	Composite atherosclerotic plaque in thoracic and abdominal aorta, vasomotor tone changes	The peak constriction due to serotonin or phenylephrine was enhanced in high fat chow mice exposed to CAPs and the half-maximal dose for dilation to acetylcholine was increased in the same group. The mean percentage positive areas of 3-nitrotyrosine and iNOS in aortic sections was observed in normal and high fat chow mice exposed to CAPs compared to the respective air controls; there were no differences in eNOS staining. Mice fed high fat chow and exposed to CAPs had elevated lipid content in the aortic arch. There was increased hydrogen peroxide generation in the aorta of mice exposed to CAPs.

Table A19: Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
Humans					
Schaumann et al. (2004)	Humans, 12 healthy subjects (8 F, 4 M); avg 27 yr	Instillation into lingula, 100 µg/10 mL; BALF collected 24 h PE	Ambient PM from Zerbst, Germany (agricultural sources) or Hettstedt, Germany (industrial and domestic sources); collected in 1999; $PM_{2.5}$	BALF: Cell counts Cell differentials AM surface markers Cytokines Total protein Albumin CL	Exposure to Hettstedt PM resulted in more numerous responses compared to Zerbst PM. Endotoxin levels were very low in both samples.
In Vivo					
Gavett et al. (2003)	Mice, Balb/c, F, 1–21 g; OVA sensitized, 2–12 mice/group	OA, 100 µg total in 50 µL saline (1 or 2 doses); assessed 18 h, 2 and 7 days after challenge 2 exposure protocols: 1) 10 µg OVA on Days 0 and 2 for sensitization 2 h prior to PM exposure on both days and 20 µg OVA on Day 14 for challenge 2) 20 µg OVA on Day 0 and PM exposure on Day 14 with OVA challenge 2 h later	Ambient PM from Zerbst, Germany (agricultural sources) or Hettstedt, Germany (industrial and domestic sources); collected in 1999; $PM_{2.5}$	Pulmonary function after MCh challenge Serum OVA-specific IgE BALF: Cell counts Total protein Albumin LDH NAG Cytokines	Allergic mice exposed to either PM had elevated penh at challenge and a number of BALF markers were increased 2 days post-challenge. Mice exposed to Hettstedt PM also had elevated penh, PMN, eosinophils, and IgE 2 days post-challenge and those exposed to Zerbst PM had increased IL-13. Hettstedt had much greater levels of Zn, Pb, Cu, Cd, Sn, and As. Neither Hettstedt nor Zerbst administered before sensitization enhanced allergic responses (except IgE in Hettstedt-exposed mice).

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vivo (cont'd)					
Corey et al. (2006)	Mice, ApoE$^{-/-}$, 11-12 mo, 2-3 mice/group	Nasal instillation, 1.5 mg/kg; assessed through 4 day PE	Seattle, WA $PM_{2.5}$ collected in close proximity to a freeway and industrial area	HR HRV (SDNN, RMSSD, HF, LF) Activity	Increased HR immediately following exposure; decreased HR on days 2 and 3. Decreased SDNN on days 2, 3, and 4 and decreased RMSSD on days 2 and 3. Lowered LF/HF ratio on days 3 and 4.
Gerlofs-Nijland et al. (2005)	Rats, SH, M, 250–350 g, 4–6 rats/group	IT, 0.3, 1, 3, and 10 mg/kg; assessed 4, 24, or 48 h PE	Road tunnel dust (RTD) collected outside a traffic tunnel in Netherlands; coarse and fine fractions were combined together prior to exposure	BrdU BALF (right lung); Cell counts Cell differentials MPO activity LDH NAG ALP UA Albumin Total protein CC16 GSH, GSSG Cytokines Fibrinogen Hematology ET-1 Histopathology (left lung)	Increased PMN and AM were observed in rats exposed to RTD at 24 h, regardless of dose. Increases in fibrinogen were observed in rats exposed to 10 mg/kg of RTD at 24 and 48 h. A number of BALF biomarkers were increased with exposure to RTD at all time points. There was a dose-dependent increase in the number of inflammatory foci at 24 and 48 h in rats exposed to 3 or 10 mg/kg RTD.
Gilmour et al. (2004)	Mice, F, CD1, 20–25 g, 5 mice/group	IT, 25 and 100 µg/mouse (approx. 1.25 and 5 mg/kg); assessed at 18 h PE	Coal fly ash derived from Montana (low-sulfur subbituminous; 0.83% sulfur, 11.72% ash content) or Western Kentucky (high-sulfur bituminous; 3.11% sulfur, 8.07% ash content); thoracic coarse, fine, and UF fractions	BALF: Cell counts Cell differentials Cell viability Cytokines	There were no differences in effects for either coarse particle types compared to saline. The UF fraction of combusted Montana coal induced greater neutrophilic inflammation and cytokine production than thoracic coarse or fine PM. The fine fraction of the western Kentucky fine PM caused increases in PMN, albumin, and protein.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vivo (cont'd)					
Nygaard et al. (2005)	Mice, BALB/cA, F, 5–9 mice/group	Subcutaneous injection of particles (100 µg) with or without OVA (50 µg) into hind footpads; 20 µL solution; assessed 5 days PE	Ambient PM from Oslo, Rome, Lodz, Amsterdam; spring, summer, and winter 2001/2002; thoracic coarse and fine fractions	Popliteal lymph node (PLN): Cell count Cell surface molecules Cell cytokines Histology	There was no observed difference between most of the coarse and fine fractions in the induction of IL-4 and IL-10. However, the Lodz coarse PM (+OVA) caused effects that were statistically significant compared to the Lodz fine PM (+OVA). Allergic mice exposed to PM had exacerbated effects compared to allergen alone or PM alone. Exposure to Rome or Oslo PM resulted in increased cytokine production. Exposure to Oslo PM caused alterations in PLN cell counts. Exposure to OVA+PM resulted in increased expression of surface molecules on B lymphocytes.
Rhoden et al. (2005)	Rat, SD, M, 300 g; pretreated with 1) atenolol or glycopyrrolate or 2) NAC	CAPs: WBI, 700 µg/m^3, 5 h; assessed immediately PE SRM 1649: IT, 750 µg; assessed 30 min PE	Boston CAPs Urban air particles; SRM 1649	Heart CL SDNN HR TBARS (heart) Wet/dry heart ratios	CAPs caused increases in TBARS, CL, and wet/dry heart ratio. SRM 1649 exposure resulted in elevated TBARS, CL, and SDNN during recovery. Pretreatment with NAC prevented changes in heart rate, SDNN, heart wet/dry ratio, and CL in SRM 1649- and CAPs-exposed rats. Administration of atenolol or glycopyrrolate prior to SRM 1649 or CAPs exposure prevented changes in CL and TBARS.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vivo (cont'd)					
Schins et al. (2004)	Rat, Wistar, F, 350–550 g; 5 rats/group	IT, 0.35 mg/rat (0.6–1 mg/kg); assessed 18 h PE	Ambient PM from Duisburg (D) and Borken (B) Germany collected in weekly intervals Feb–May 2000; thoracic coarse and fine fractions D: heavily-industrialized area; endotoxin 0.3 EU/mg for fine, 5 EU/mg for coarse B: Rural area; endotoxin 0.6 EU/mg for fine, 6.6 EU/mg for coarse	BALF: Cell differentials GSH, GSSG LDH Total protein Cytokines *In vitro* whole blood (WB) assay: Cytokines	Rats exposed to coarse PM (regardless of location) had increased percent PMN in BALF and TNF-α and IL-8 in the whole-blood assay. Only rats exposed to coarse Borken PM had depleted GSH levels and elevated TNF-α in BALF. Rats exposed to coarse Duisburg PM had increased MIP-2 in BALF.
Soares et al. (2003)	Mice, Balb/c, 8–10 weeks; 20 mice/group	WBI, 31–47 μg/m^3 (monthly average) for 120 days; for Sao Paulo SO_2 ranged from 12-20 μg/m^3, CO (8 h) ranged from 2.4–3.2 ppm, and NO_2 ranged from 97-108 μg/m^3	Urban air of Sao Paulo, Brazil (including gases) Urban air of Atibaia (AT) in rural Brazil, 65 km from Sao Paulo	Blood from tail vein: Micronuclei (MN) in peripheral erythrocytes	The greatest MN increase was observed at 90 days. Significant increases in MN frequency were observed for Sao Paulo mice compared to AT mice, with no significant time interaction. A positive association between all air pollution measures (PM_{10}, NO_2, and CO) and MN frequency difference was observed for the previous 8–14 days of exposure.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vivo (cont'd)					
Steerenberg et al. (2005)	Mice, Balb/cByJ.ico, M; 6–8 weeks; OVA sensitization (0.4 mg/ml) at days 0 and 14, challenge +/- PM on days 35, 38, and 41	IN, 0, 3, or 9 mg/mL PM with OVA (150-450 µg PM /mouse); assessed on day 42	Ambient PM collected during spring, winter, and summer from: (1) Oslo (near road), (2) Lodz (near heavy traffic), (3) Rome (rail station), (4) Amsterdam (near busy roadway), or (5) De Zilk (low traffic and natural allergens); thoracic coarse and fine fractions	Serum from abdominal aorta: IgE IgG1 IgG2a BALF: Total cells Cell differentials LDH Cytokines Lung histopathology	Spring and winter PM samples were more potent than summer PM samples. The order of mild response for IgE, IgG1, IgG2a, and eosinophil influx was (Lotz> Rome≥Oslo>Amsterdam). The coarse fraction induced greater adjuvant activity for De Zilk PM compared to the fine fraction. The coarse and fine fractions from Lodz or Rome with OVA exposure induced a number of effects including increased eosinophils, PMN, and monocytes. The adjuvant activity with immunoglobulins was greater with the fine than the coarse fraction. In general, the insoluble portion of the coarse PM was responsible for the observed adjuvant activity.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vivo (cont'd)					
Steerenberg et al. (2006)	Rat, Wistar, M, 8 rats/group (also mice, but data reported in other studies—Nygaard et al. 2005 and Steerenberg et al. 2005)	IT, 1 or 2.5 mg PM/rat; assessed 24-h PE	Ambient PM collected during spring, winter, and summer from: 1) Oslo (near road), 2) Lodz (near heavy traffic), 3) Rome (rail station), 4) Amsterdam (near busy roadway); thoracic coarse and fine fractions combined in the analysis	BALF: Albumin CC16 Cytokines	Correlations between the traffic and industry/combustion/ incinerator source cluster and pathology lesion occurrence and increased IgE were observed in the respiratory allergen model. The combustion of black and brown coal/wood smoke source cluster correlated with albumin in rats and IgE and pathology score in the respiratory allergen model. Crustal material source cluster correlated with CC16 in rats and IL-6, TNF-α, and MIP-2 in macrophage and type 2 cells (*in vitro*). Secondary inorganic/long-range aerosol source cluster correlated with IgE in the systemic allergen model. Sea spray source cluster correlated with CC16 in rats and IL-6 in macrophages (*in vitro*); the CC16 response also correlated with endotoxin.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Becker et al. (2003)	Human AM (3×10^5 cell/mL)	50 µg/mL; 18–20 h	PM downwind of Utrecht (background site; collected March 1999) and west of Utrecht, Netherlands (influenced by light industrial activities and freeway traffic, esp. diesel; collected June 1999); thoracic coarse, fine, and UF fractions	Cytokines Phagocytosis CL Cell surface receptor expression	Increased IL-6, MIP-1α, and phagocytosis and decreased CL and CD11b receptor expression were greater for the thoracic coarse fraction than those observed with the other size fractions. Endotoxin was detected in water extracts of thoracic coarse particles.
Becker et al. (2005)	Human AM ($2–3 \times 10^5$ cells/cm^2) and normal bronchial epithelial (NHBE) cells (1×10^5 cells/cm^2)	AM: 50 µg/mL; NHBE: 11 µg/mL; 18–24 h	Chapel Hill, NC PM; collected Oct 2001, Jan 2002, Apr 2002, Jul 2002; thoracic coarse, fine, and UF fractions	Cytokines ROS CL	Thoracic coarse PM was more potent in inducing IL-6 and IL-8. For IL-6, Oct thoracic coarse PM caused the greatest response. The July thoracic coarse PM exerted the greatest production of ROS as measured in AM. Thoracic coarse Fe and Si were positively associated with IL-6 release in AM.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Becker et al. (2005b)	Human AM ($2–3\times10^5$ cells/cm^2) and normal bronchial epithelial (NHBE) cells (1×10^5 cells/cm^2)	AM: 50 μg/mL; NHBE: 25, 50, 100, 250 μg/mL; 18–24 h	Chapel Hill, NC PM; collected for 72 h; thoracic coarse, fine, and UF fractions	Cytokines Gene expression	Thoracic coarse PM was more potent in inducing IL-8 release in NHBE cells. This response was blocked with an antibody for TLR2 was added. IL-6 release in AM was inhibited by addition of TLR4 agonist or an endotoxin-binding protein for all size fractions. Expression of TLR4 was increased in NHBE cells exposed to thoracic coarse PM only. Expression of TLR2 was increased in AM exposed to all three size fractions, although the largest increase was observed for the thoracic coarse fraction. A decrease in TLR4 expression was observed in AM exposed to thoracic coarse PM. Thoracic coarse PM was the most effective inducer of Hsp70 in NHBE cells. Fine PM also stimulated an increase in Hsp70 expression.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Hetland et al. (2005)	WKY rat AM; 1.5×106 cells/mL	10, 20, 50, or 100 µg/mL; 20 h	Ambient PM collected during spring, winter, and summer 2001/2002 from: 1) Oslo (near road), 2) Lodz (near heavy traffic), 3) Rome (rail station), 4) Amsterdam (near busy roadway); thoracic coarse and fine fractions	Cytokines	Thoracic coarse PM collected during spring and summer from Lodz was the most potent for IL-6 release, followed by Rome and Oslo. Thoracic coarse PM collected from Amsterdam had the greatest IL-6 induction for the winter compared to thoracic coarse PM from other locations. The spring thoracic coarse PM from Rome and Lodz induced TNF-α release. The fine fractions did not induce a marked increase in TNF-α release in any city for any season. The thoracic coarse fractions had higher Fe, Cu, and Al content than fine PM. Endotoxin levels were also greater in the thoracic coarse fractions, but IL-6 release was similar when cells were treated with an endotoxin-binding protein (polymyxin).

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Huang et al. (2003)	Human BEAS-2B and mouse RAW 264.7; 5×10^5 cells/mL	100 µg/mL; 8–16 h	PM from 4 different sites in Taiwan-background (B), urban (U), traffic (T), or industrial (I); thoracic coarse, fine, and UF fractions	BEAS-2B: IL-8 Lipid peroxidation RAW 264.7: TNF-α Cell viability	Increases in TNF-α due to $PM_{1.0}$ exposure correlated with Fe and Cr, although 77% of the response was attributable to the endotoxin content. For thoracic coarse PM, there was significant correlation between IL-8 and lipid peroxidation findings; Mn and Fe were more abundant in the thoracic coarse fraction compared to the other sizes. For the fine PM fraction, increases in IL-8 correlated with Mn and Cr and increases in lipid peroxidation were associated with EC and OC content. Cu and Zn were most abundant in $PM_{1.0 - 2.5}$. There were no differences in Ni, V, and Cr among size fractions.
Li et al. (2002)	RAW 264.7 and THP-1 cells	10–200 µg/mL; 8 h	CAPs from Downey, CA in Los Angeles basin using VACES from Mar 15-Dec 7 2000; thoracic coarse and fine fractions	HO-1 MnSOD JNK B-actin GSH/GSSG Apoptosis	The fine fraction induced a greater effect than thoracic coarse PM on all endpoints. Coarse PM collected in Sept and Dec resulted in increased HO-1 expression and cell cytotoxicity. The highest levels of OC were observed in December. Thoracic coarse PM collected from Jan–Feb 2001 induced HO-1 expression and had higher PAH content than the December thoracic coarse samples.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Li et al. (2003)	Human BEAS-2B and mouse RAW 264.7	8–100 µg/mL (12.3 or 21.1 for coarse, 17.3 or 20.9 for fine, and 1.9 or 3.9 µg/m^3 for ultrafine); 16 h	CAPs from Los Angeles basin (USC as a typical urban site with vehicular traffic and Claremont as a receptor site) using VACES from Nov 2001–March 2002; thoracic coarse, fine, and UF fractions	HO-1 GSH/GSSG ROS	UF PM was the most potent in inducing oxidative stress which was associated with OC and PAH content. Thoracic coarse PM showed little toxic effects. Thoracic coarse PM collected in large cytoplasmic vacuoles in RAW 264.7 cells and UF particles lodged inside mitochondria.
Pozzi et al. (2003)	Mouse RAW 264.7	30 or 120 µg/mL (13.6 or 54.5 µg/cm^2); 5 or 24 h	Ambient PM from Rome, Italy (mainly traffic-derived) collected for 15 days in Sept 1999; thoracic coarse and fine fractions Endotoxin: Thoracic coarse = 7.68 EU/mg Fine = 1.92 EU/mg	LDH AA Cytokines	At 120 µg/mL, thoracic coarse PM induced significant release of LDH and fine PM did not result in any change in LDH release. Thoracic coarse PM fraction was slightly more effective in releasing AA and IL-6 compared to the fine fraction at 5 h. Thoracic coarse PM fraction at 30 µg/mL induced greater amounts of TNF-α production at 5 and 24 h.

Table A19 (cont'd): Size-fractionated and Collected Ambient PM Studies

Reference	Species (*in vivo*)/ Cell Type (*in vitro*)	Exposure	PM Characterization	Endpoints	Results
In Vitro (cont'd)					
Shi et al. (2003)	Human A549; 1.2×10^5 cells/ chamber	50 μg/mL; 2 h	Ambient PM from Dusseldorf, Germany from Jul–Dec 1999; coarse and fine fractions	Hydroxyl radical formation (using electron spin resonance) 8-Hydroxyde-oxyguanosine (8-OHdG) in A549 DNA or calf thymus DNA	Coarse PM had greater ability to generate hydroxyl radicals and 8-OHdG compared to fine PM at equal mass. Cu correlated with hydroxyl radical and 8-OHdG formation in coarse PM. For coarse PM, the autumn/winter samples induced nearly double the hydroxyl radicals generated by the summer samples. Both coarse and fine fractions induced 8-OHdG in A549 cells.
Vernanth et al. (2004)	BEAS-2B; 2.0×10^4 cells/cm^2	10, 20, 40, 80, 160 μg/cm^2; (≈25–400 μg/mL), 24 h	Dust $PM_{2.5}$ (0.3–3 μm): DD: desert dust (unpaved road) WM: west mesa (wind-generated dust area) R4: range 40 (unpaved road) UN: Uinta (wind and recreation activity)	Cell viability Cytokines TRPV1 receptor ROS	The cytotoxicity ranking was as follows: UN>WM>R4>DD. The IL-6 response was as follows at the highest dose: DD>R4>UN>WM. Heating the particles attenuated the IL-6 response. LPS induction of IL-6 and IL-8 release was significantly less than that from DD.
Veranth et al. (2006)	BEAS-2B; 3.5×10^4 cells/cm^2	10, 20, 40 or 80 μg/cm^2 (≈25–200 μg/mL); 24 h	Urban and rural surface soils (32) from the Southwestern U.S.; $PM_{2.5}$	Cell viability Cytokines	Rank order of potency was different at low and high PM concentrations. Coal fly ash samples did not affect IL-6 compared to soil-derived dusts. Strongest correlations for IL-6 and IL-8 were with low volatility EC and OC.

Table A20. Acid Aerosol Studies

Reference	Species	Exposure	Exposure Characterization	Endpoints	Sulfate Effects
Controlled human study					
Tunnicliffe et al. (2003)	Humans, healthy (7F, 5M; avg 34.5 yr) and mild asthmatics (5F, 7M; avg 35.7 yr; all using short-acting β agonists); double blind, random order design; prior to exposure subjects brushed teeth and gargled with mouthwash to reduce oral ammonia levels	1 h; head-only exposure system; measured during, pre- and/or post-exposure, or 5.5–6 h later	Six exposures: 1) FA 2) SO_2 (200 ppb) 3) sulfuric acid (200 µg/m^3; low) 4) sulfuric acid (2000 µg/m^3; high) 5) NH_4HSO_4 (200 µg/m^3; low) 6) NH_4HSO_4 (2000 µg/m^3; high) Particle exposures target MMD 0.3 µm, count mode ≈30 nm.	Self-reported symptoms Ventilation (breaths/min, V_T) Lung function Exhaled NO Nasal lavage (AA and UA)	Asthmatics exposed to SO_2 had increased respiratory rates. Asthmatics exposed to low or high concentrations of NH_4HSO_4 had increased exhaled NO levels. Healthy subjects exposed to low or high concentrations of sulfuric acid or NH_4HSO_4 had elevated UA levels in nasal lavage.
Animal toxicology studies					
Kleinman et al. (2003)	Rat, F344, 22–24 mo; 10–12 rats/group	4 h/day, 3 consecutive day/wk, 4 wk; NOI; 12 h PE	Four exposures: (1) FA (2) O_3 (0.2 ppm) (3) Low conc. particle mixture (50 µg/m^3 EC + 70 µg/m^3 NH_4HSO_4) +O_3 (0.2 ppm)–0.3 µm MMAD, 2.5 GSD (4) High conc. particle mixture (100 µg/m^3 EC + 140 µg/m^3 NH_4HSO_4) + O_3 (0.2 ppm)–0.3 µm MMAD, 2.3 GSD	Lung histology Cell replication in lung epithelial and interstitial cells BALF: Albumin mucus glycoprotein total protein AM Fc receptor binding AM function	Exposure to either concentration of the particle mixture resulted in elevated cell replication (290–340%) and decreased AM Fc receptor binding and respiratory burst activity. Greater cell replication was observed in the interstitial lung compared to the epithelial region. At the end of exposure, AM were activated but by 12 h, function was depressed. Increases in total protein were observed in the low concentration particle mixture group only.

Table A20 (cont'd). Acid Aerosol Studies

Reference	Species	Exposure	Exposure Characterization	Endpoints	Sulfate Effects
In Vitro					
Kleinman et al. (2006)	Rat, SD, M, 200 g; 5–15 rats/group	4 h; NOI; assayed 42 h post-exposure	Nine exposures: (1) FA (2) O_3–0.3 ppm (3) O_3–0.6 ppm (4) H_2SO_4–0.5 mg/m^3 (5) H_2SO_4–1.0 mg/m^3 (6) O_3 + H_2SO_4–0.3 ppm + 0.5 mg/m^3 (7) O_3 + H_2SO_4–0.3 ppm + 1.0 mg/m^3 (8) O_3 + H_2SO_4–0.6 ppm + 0.5 mg/m^3 (9) O_3 + H_2SO_4–0.6 ppm + 1.0 mg/m^3 Aerosol MMD 0.23–0.28 μm (GSD 2.1–2.3).	Lung histology DNA synthesis in nose, trachea, and lung AM Fc receptor binding AM function	Exposure to O_3 resulted in Type 2 lesions in the lung parenchyma at 0.6 ppm; co-exposure with H_2SO_4 attenuated this effect (significant interaction). O_3 and H_2SO_4 do not act synergistically in this study.
Beck-Speier et al. (2003)	Dog, AM (1×10^6/mL) and blood PMN	Sulfite and sulfate at pH 6 or pH 7; 30 min.	1.0 mM	PAF LTB_4 5-HETE 12-HHT TXB_2 PGE_2 PLA_2	Sulfite at pH 7 activates PLA_2 enzymes for release of arachidonic acid and synthesis of PAF. Sulfite activates $cPLA_2$ and $sPLA_2$ through signaling of the ERK1,2 pathway.

APPENDIX B

Bibliographies and Annotated Bibliographies for Recent Studies on the Health Effects of Particulate Matter Exposure

Recent Multicity Epidemiologic Studies
Epidemiologic Studies on Health Effects Associated with Exposure to Traffic
Toxicology Studies of Traffic, Diesel, or Vehicle Exhaust
Toxicology and Epidemiology Studies of Ultrafine Particles
Toxicology and Epidemiology Studies of Metals or Metal-Containing Particles
Toxicology Studies of Traffic, Diesel, or Vehicle Exhaust
Epidemiologic Studies on Health Effects Associated with Exposure to Traffic
Toxicology Studies of Endotoxin/LPS or Endotoxin/LPS-Containing Particles
Toxicology and Epidemiology Studies of Wood Smoke

Recent Multicity Epidemiologic Studies

The following three studies are described in detail in Tables 1 and 2. The remaining studies are grouped by the general issues being evaluated.

> Ostro B, Broadwin R, Green S, Feng W-Y, Lipsett M. 2006. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environ Health Perspect 114: 29-33.
>
> Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, Vincent R, Dann T. 2004. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Health 59:2280236.
>
> Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 295:1127-1134.

Confounding by co-pollutants, weather, influenza epidemics:

Schwartz J. (2004a): Potential confounding of associations between PM_{10} and mortality by weather and season was assessed in 14 U.S. cities. A 0.36% (95% CI: 0.22, 0.50) excess risk in mortality per 10 $\mu g/m^3$ increase in PM_{10} was estimated using symmetrical sampling of control days. Results were little changed when control days were matched on temperature, the time stratified method was applied, or more lags of winter time temperatures were used. These results indicated that associations between PM_{10} and mortality risk are unlikely to be confounded by weather and season, and are robust to the analytical method.

Schwartz J. (2004b): Uses case-crossover design to assess potential confounding of associations between PM10 and mortality by gaseous co-pollutants in 14 U.S. cities. Significant associations reported with case-crossover matching for each of the 4 gaseous co-pollutants; effect estimate sizes range from 0.45% to 0.81% increases per 10 $\mu g/m^3$ PM_{10}.

Welty LJ, and Zeger SL. (2005): Used two flexible versions of distributed lag models to control for weather and season in 100 cities (1987-2000), with a 0-, 1- or 2-day lag for PM_{10}. Results were consistent with previous analyses, with effect estimates of approximately 0.2% increase in mortality per 10 $\mu g/m^3$ PM.

Touloumi G et al. (2005): Used data from 7 APHEA-2 cities and found that adjustment for influenza epidemics increased effect estimate for PM_{10}-mortality associations in most cases.

Concentration-response function and threshold evaluation:

Daniels MK et al. (2004): Applied flexible modeling strategies to daily time-series data for 20 U.S. cities (1987-1994). Spline model showed a linear relation without indicating a threshold for relative risks of death from all causes and for cardiovascular-respiratory cases with short-term PM_{10} exposure.

Evaluation of factors influencing heterogeneity:

Dominici F et al. (2003): City-specific and regional effect estimates provided for the 88-city analysis (1987-1994). The authors report "some modest variation in the relative risks across the nation . . . we were unable to explain the heterogeneity using descriptors of the population, air pollution characteristics, and reliability of the PM_{10} measurement data."

Martins et al. (2004): Significant associations were observed between PM_{10} and respiratory mortality in the elderly ($\geq$60 yr) in the combined analysis for six regions in Sao Paulo, Brazil, with an effect estimate of 5.4% (2.3, 8.6) excess risk per 10 $\mu g/m^3$ increase in PM_{10} at a multiday lag of 0 to 2 days. The greatest effect (14.2% [95% CI: 0.4, 28.0]) was found in the region with the highest % of slums, and the lowest % with college education and high monthly income. The effect of PM_{10} on respiratory mortality was strongly and negatively correlated with two SES indicators: % with college education and family income, and positively correlated with greater % living in slums.

Le Tertre A, et al. (2005): Used data from 21 cities (includes one non-APHEA city), reporting heterogeneity in associations between PM_{10} and mortality and calculates Bayesian estimates. A meta-regression method was then used to adjust for the identified sources of the heterogeneity. The authors state that the heterogeneity present in the data could be better taken into account by deriving an estimated underlying distribution that represents the dispersion observed between cities.

Medina-Ramon M, et al. (2006): Uses case-crossover design to evaluate effects of ozone and PM_{10} on respiratory hospital admissions and evaluate city characteristics that may explain heterogeneity in data from 36 U.S. cities. Significant associations found for both pollutants with pneumonia and COPD hospital admissions (effect estimates per 10 $\mu g/m^3$ PM_{10} of 1.47% and 0.84%, respectively). Effect estimates for PM_{10} reduced with greater air conditioning use in cities; little difference based on percentage of PM_{10} from traffic.

Samoli E, et al. (2005): Using data from 22 cities, found that association between PM_{10} or BS and mortality could be adequately estimated using a linear model. Tested thresholds at 10 and 20 $\mu g/m^3$ PM_{10} and found that linear models had better fit. The authors also report heterogeneity in associations between cities that is partly explained by several factors, with increased effect estimates associated with hotter climates, mean NO_2 concentration as an indicator of traffic emissions, and lower standard mortality rates (more elderly people in population).

Zeka A, et al. (2005): Using case-crossover design, significant associations were reported between PM_{10} and both cardiovascular and respiratory mortality in 20 U.S. cities that were stronger using 3-day cumulative distributed lag model. Associations were increased in size with increasing percent PM_{10} from traffic and with increasing summer temperature variability.

Zeka A, et al. (2006): Using data from 20 U.S. cities with case-crossover design, reported significant associations between PM_{10} and mortality from all causes, respiratory, and heart disease, and positive but not significant associations with MI and stroke deaths. Substantial effect modification was found for some sociodemographic factors (larger with >75 years, little difference for gender or race), location of death (larger for out-of-hospital), season (larger in

spring and fall) and coexisting medical conditions (e.g., secondary diagnoses of pneumonia, diabetes, heart failure).

Lag Structure:

Analitis A, et al. (2006): Used 2-stage hierarchical model with data from 29 APHEA-2 cities, and report significant associations with cardiovascular mortality (0.76% per 10 $\mu g/m^3$ PM_{10}) and respiratory deaths (0.58% per 10 $\mu g/m^3$ PM_{10}) using 0-1 day average lag. With distributed lag model effect sizes increase, particularly for respiratory mortality. The associations are independent of ozone, but reduced in size with adjustment for SO_2 and NO_2.

Roberts, S. (2005): This investigation finds that distributed lag models return particulate air pollution mortality effect estimates that are more robust and less prone to negative bias than single- and multi-day moving average exposure measures. The author concludes that distributed lag models should be preferred in future air pollution mortality time series studies and helps quantify the negative bias that can result from using single or multi-day moving average exposure measures.

Zanobetti A, et al. (2003): Using distributed lag models in 10 cities from the APHEA-2 project, effect estimate size for association with PM_{10} doubles for cardiovascular deaths and is five times higher for respiratory disease deaths compared with 1-day lag models.

Zeka A, et al. (2005): Using case-crossover design, significant associations were reported between PM_{10} and both cardiovascular and respiratory mortality in 20 U.S. cities that were stronger using 3-day cumulative distributed lag model. Associations were increased in size with increasing percent PM_{10} from traffic and with increasing summer temperature variability.

Mortality displacement:

Dominici F, et al. (2003): Used decomposed time series of PM_{10} data for 4 U.S. cities for which daily data were available (1987-1994), and reported larger relative rates of mortality associated with PM_{10} using longer timescale (14 days to 2 months) than shorter timescale (1 to 4 days), indicating that association does not represent advancement of death by just a few days for frail individuals.

Seasonal variation:

Peng RD, et al. (2005): Bayesian semiparametric hierarchical models for estimating time-varying effects of pollution on mortality in multisite time series studies. Effect estimates for winter, spring, summer, and fall were, respectively, 0.15%, 0.14%, 0.36% and 0.14% increases per 10 $\mu g/m^3$ PM_{10} (1-d lag), with an all-year estimate of 0.19% per 10 $\mu g/m^3$ PM_{10}. Effects were stronger in the summer for the Northeast and Industrial Midwest, but little difference across seasons in the southern regions and northwest.

New health outcomes:

Ballester et al. (2006): Significant associations reported between PM_{10} (lag 0-1 day) and emergency admissions for cardiovascular diseases and heart diseases. Significant associations

were also reported with ozone and CO, while associations with SO_2 and NO_2 were more sensitive in two-pollutant models.

Ibald-Mulli A, et al. (2004): Study of 131 adults in Helsinki, Erfurt and Amsterdam with biweekly clinic visits for 6 months. Results suggest decreased blood pressure (diastolic and systolic) and in heart rate.

Timonen KL, et al. (2006): Same cohort as above with analysis of heart rate variability (5-min measurement). Ultrafine particles associated with decreased LF/HF in pooled analysis; $PM_{2.5}$ associated with decreased HF and reduced LF/HF in Helsinki but opposite association in Erfurt, and no clear association in Amsterdam. Suggest that effects may be modified by location and characteristics of individual.

von Klot S, et al. (2005): In cohort of 22,000+ first MI survivors in Augsburg, Barcelona, Helsinki, Rome and Stockholm, significant associations were reported for cardiac hospital readmissions with PM_{10}, ultrafine particle number count, CO, NO_2 and O_3.

Wellenius et al. (2006a): Using case-crossover analysis, a significant association was reported between PM_{10} and hospital admissions for congestive heart failure in the elderly in 7 U.S. cities (7% increase [95% CI 0.35 to 1.10%] per 10 $\mu g/m^3$ PM_{10} [0-day lag]). Effect seemed to be smaller in those with secondary diagnosis of hypertension. No consistent effect modification observed for age, gender, race or other secondary diagnoses.

Wellenius et al. (2006b): Using case-crossover analysis, a significant association was reported between PM_{10} (3-day distributed lag) and hospital admissions for ischemic stroke (1.03% increase [95% CI 0.04 to 2.04%] per 10 $\mu g/m^3$ PM_{10}). No association was found for hemorrhagic stroke admissions.

Zanobetti A, and Schwartz J. (2005): Case-crossover analysis showed significant association between PM_{10} and emergency hospitalization for myocardial infarction in elderly people (0.65% [0.3-1.0] per 10 $\mu g/m^3$ PM_{10}) in 21 U.S. cities. Effect size doubled for subjects with previous admission for COPD or secondary diagnosis of pneumonia (difference in size not statistically significant).

Analytical methods:

Biggeri et al. (2005): A meta-analysis was conducted to examine the associations between PM_{10} and all-cause, cardiovascular, and respiratory mortality in six Italian cities. Daily PM_{10} data were collected in 2 cities; in the other cities, daily TSP collected. Conversion factors, estimated through validation studies, were applied to convert TSP to PM_{10}. Significant associations with PM_{10} were observed for all-cause (0.90% [95% CI: 0.21, 1.66] excess risk per 10 $\mu g/m^3$ increase in PM_{10} at a 0- to 1-day lag) and cardiovascular (1.11% [95% CI: 0.22, 2.19]) mortality. All other pollutants examined (NO_2, SO_2, CO, O_3) also were significantly associated with all-cause mortality. The effect of PM_{10} on mortality was greater during the warm season and for those aged $\geq$ 65 yr.

Daniels MJ, et al. (2004): Investigated impact of variance underestimation in both a simulation study and using NMMAPS data; report that underestimation as large as 40% had little effect on the national average relative risk of mortality.

Roberts S. (2005): Introduces model that uses information available in daily mortality time series to infer otherwise lost information about the effect of PM on mortality, considering that PM measurements may only be available every sixth day while the effect of PM on mortality may be spread over multiple days. Analyses use data from NMMAPS, a simulated data set, and daily PM measurements from Cook County, IL and Allegheny County, PA. New model produces more precise effect estimates compared with standard model.

Roberts S, and Martin, MA. (2006): New model tested use of moving total mortality time series that "allows inference on the information about the effect of PM on mortality that is lost when daily PM data is unavailable." Using the 100-city database (1987-2000), report results that are "consistent with those found in the NMMAPS analysis" with effect estimates of 0.12% increase in total mortality and 0.17% increase in cardiovascular and respiratory mortality per 10 $\mu g/m^3$ PM_{10}.

Simpson et al. (2005): Using three statistical methods—GLM, R, and a two-stage Poisson GAM with stringent convergence criteria—PM-related excess risks of total nonaccidental, cardiovascular, and respiratory mortality in Brisbane, Sydney, Melbourne, and Perth were estimated. Daily $PM_{2.5}$ data were collected using nephelometers in all four cities. Daily $PM_{2.5}$ data were available in all four cities, but Brisbane was excluded from the analysis as more than 40% of data was missing. Daily PM_{10} data were only available in Brisbane, Sydney, and Melbourne. Melbourne, which was included in all analyses, was missing ~30% of $PM_{2.5}$ and PM_{10} data. Significant associations were observed for all cause and cardiovascular mortality using the nephelometric data, but no associations were found with $PM_{2.5}$ or PM_{10}. Results using different statistical methods were similar. Mean $PM_{2.5}$ levels ranged from 9.00 $\mu g/m^3$ (Sydney and Perth) to 9.30 $\mu g/m^3$ (Melbourne) across the 3 cities.

Measurement error:

Zeka A and Schwartz J. (2004): Used 90-city database (1987-1994) and approach developed by Schwartz and Coull (2003) to test associations between pollutants and mortality, correcting for measurement error in the other pollutants. Effect estimates from models adjusting for the gaseous pollutants ranged from 0.14 to 0.35% increases in mortality per 10 $\mu g/m^3$ PM_{10}, with an overall effect of 0.24% per 10 $\mu g/m^3$ PM_{10}.

Review article:

Sandstrom T et al. (2005): Review article, concludes "The PM investigated generally induced significant biological responses, with both coarse (2.5-10 μm) and fine (0.1-2.5 μm) PM being able to induce toxic effects." Three studies briefly described: HEPMEAP (health effects of particles from motor engine exhaust and ambient air pollution) RAIAP (respiratory allergy and inflammation due to ambient particles) PAMCHAR (chemical and biological characterization of ambient air coarse, fine and ultrafine particles for human health risk assessment in Europe).

Epidemiologic Studies on Health Effects Associated with Exposure to Traffic

Mortality

Finkelstein MM, Jerrett M, Sears MR. (2004) Traffic air pollution and mortality rate advancement periods. Am J Epidemiol 160:173-177.

> Firestone Institute pulmonary function cohort (5228 adults), using residence w/in 50 m or major urban road or w/in 100 m of a highway as traffic index. CVD mortality significantly associated with pollution index [RR 1.06 (1.00-1.13)]; stronger association with deprivation index (RR 1.15) and traffic indicator (RR 1.40). In 2- and 3-variable models, pollution index reduced (RR 1.04 and nonsignificant) with little change in traffic indicator and some reduction for deprivation index. Deprivation and pollution indices were highly collinear, so created a combined (sum) index; both traffic and deprivation/pollution index were significantly association with CVD mortality (RR 1.05, 1.01-1.10)

Finkelstein MM, Jerrett M, DeLuca P, Finkelstein N, Verma DK, Chapman K, Sears MR. (2003) Relationship between income, air pollution and mortality: a cohort study. Can Med Assoc J 169(5):397-402.

> Firestone Institute pulmonary function cohort (5228 adults), using residence w/in 50 m or major urban road or w/in 100 m of a highway as traffic index. Significant association between mortality and residence w/in a road/highway buffer: RR 1.18 (1.02-1.38) for all subjects. By interpolation from Ontario life tables, estimated "rate advancement period" associated with traffic pollution of 2.5 years (0.2-4.8).

Finkelstein MM, Jerrett M, Sears MR (2005) Environmental inequality and circulatory disease mortality gradients. J Epidemiol Community Health 59:481-486.

Hart JE, Laden F, Schenker MB, Garshick E. (2006) Chronic obstructive pulmonary disease mortality in diesel exposed railroad workers. Environ Health Perspect 114:(in press)

Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 360(9341):1203-1209.

Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein M, Calle EE, Thun MJ. (2005) Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16:727-736.

American Cancer Society cohort, using traffic buffers of 500 and 100 m from freeway based on zip code centroids (22,905 subjects in 267 zip code areas). Significant association between

$PM_{2.5}$ and deaths from all causes; after adjustment for 44 covariates and freeways w/in 500 m, significant associations were reported with death from all causes (RR 1.17, 1.05-1.31) and IHD (RR 1.38, 1.11-1.72).

Lipfert FW, Wyzga RE, Baty JF, Miller JP. (2006) Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: long-term mortality in a cohort of U.S. veterans. Atmos Environ 40:154-169.

Veterans cohort; traffic volume estimated from [vehicle-km traveled/county land area] using data from 1985, 1990 and 1997. Significant association with traffic (RR 1.176, 1.100-1.258 per 2.6 in 1999 data). In 3-pollutant models, traffic effect was little changed, with the $PM_{2.5}$ effect estimate reduced and not significant (RR 1.032) and $PM_{10-2.5}$ effect negative and nonsignificant.

Lipfert FW, Baty JD, Wyzga RE, Miller JP. (2006) $PM_{2.5}$ constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol (in press).

Veterans cohort; traffic volume estimated from [vehicle-km traveled/county land area], also $PM_{2.5}$ speciation data. Significant associations between mortality and traffic density, EC, nitrates, V and Ni, with the strongest effects for traffic density and EC. Positive, nonsignificant associations with $PM_{2.5}$ mass and sulfates. Negative nonsignificant associations with elements association with crustal particles (Al, Ca, Si).

Maheswaran R, Elliott P. (2003) Stroke mortality associated with living near main roads in England and Wales: a geographical study. Stroke 34(12):2776-2780.

Zeka A, Zanobetti A, Schwartz J. (2005) Short term effects of particulate matter on cause specific mortality: effects of lags and modification by city characteristics. Occup Environ Med 62:718-725.

Multicity study, associations for PM_{10} with cause-specific mortality in 20 U.S. cities. Heterogeneity in effect estimates partially explained by differences in city characteristics, including increased % PM_{10} from traffic.

<u>Respiratory morbidity:</u>

Brauer M, Hoek G, Van Vliet P, Meliefste K, Fishcer PH, Wijga A, Koopman LP, Neijens HJ, Gerritsen J, Kerkhof M, Heinrich J, Bellander T, Brunekreef B. (2002) Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. Am J Respir Crit Care Med 166(8):1092-8.

The Netherlands: respiratory symptoms for 4,135 in birth cohort, 3,730 reassessed at 2 yr; numerous cities. Associations with NO_2, $PM_{2.5}$, soot; long-term average based on 2-wk samples. Positive, borderline significantly associations between all three pollutants and prevalence of wheeze, E, N, T infections, and flu/serious colds

Brunekreef B, Janssen NAH, de Hartog J, Harssema H, Knape M, van Vliet P. (1997) Air pollution from truck traffic and lung function in children living near motorways. Epidemiol 8(3): 298-303.

Buckeridge D, Gozdyra P, Ferguson K, Schrenk M, Skinner J, Tam T, Amrhein C. (1998) A study of the relationship between vehicle emissions and respiratory health in an urban area. Geogr Environ Modeling 2:17-36.

Buckeridge DL, Glazier R, Harvey BJ, Escobar M, Amrhein C, Frank J. (2002) Effect of motor vehicle emissions on respiratory health in an urban area. Environ Health Perspect 110(3):293-300.

> Three year hospitalization rates determined in SE Toronto; $PM_{2.5}$ emissions estimated from traffic data; modeled exposures. Hospitalization rate for subset of respiration diseases (asthma, bronchitis, COPD, pneumonia, URI) significantly increased with $PM_{2.5}$ emission density (RR 1.24, 1.05-1.45)

Burr ML, Karani G, Davies B, Holmes BA, Williams KL. (2004) Effects on respiratory health of a reduction in air pollution from vehicle exhaust emissions. Occupational and Environmental Medicine 61:212-218.

> PM_{10}, $PM_{2.5}$ via dichot, daily for 3-wk and 2-wk periods, before and after bypass; respiratory symptoms in 448 adults living in congested and uncongested neighborhoods. $PM_{2.5}$ means decreased between before/after bypass by 23.5% in congested and 26.6% in uncongested neighborhoods. Reduction in symptoms with decreased traffic for any wheeze -6.5% (-14.9, 2.0) and number of attacks -8.5% (-18.2, 1.2). No association with cough, phlegm, consulted doctor, rhinitis. Positive association with "affects activities" 10.3 (3.1, 17.3).

De Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, Villani S, Ponzio M, Bono R, Carrozzi L, Cavallini R, Cazzoletti L, Dallari R, Ginesu F, Lauriola P, Mandrioli P, Perfetti L, Pignato S, Pirina P, Struzzo P; ISAYA study group. (2002) Italian Study on Asthma in Young Adults. The impact of climate and traffic-related NO2 on the prevalence of asthma and allergic rhinitis in Italy. Clin Exp Allergy 32(10):1405-1412.

Delfino RJ, Gong H, Linn WS, Pellizzari ED, Hu Y. (2003) Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect 111(4):647-656.

> Los Angeles, CA, community with high traffic density. Positive associations with both criteria pollutants and VOCs; two-pollutant models showed stronger association with EC or OC fractions of PM_{10} than PM_{10} mass. Suggest air toxics from traffic and industrial sources may have adverse effects on asthma in children.

Delfino RJ, Gong H, Linn WS, Hu Y, Pellizzari E. (2003) Respiratory symptoms and peak expiratory flow in children with asthma in relation to volatile organic compounds in exhaled breath and ambient air. J Expos Analysis Environ Epidemiol 13:348-363.

> Los Angeles, CA, community with high traffic density. Ambient VOCs, NO_2 and SO_2 associated with decreased peak flow in Hispanic children.

Fritz GJ, Herbarth O. (2004) Asthmatic disease among urban preschoolers: an observational study. Int J Hyg Environ Health 207:23-30.

Garshick E, Laden F, Hart JE, Caron A. (2003) Residence near a major road and respiratory symptoms in U.S. Veterans. Epidemiol 14(6):728-736.

U.S. male veterans in SE Massachusetts: persistent wheeze increased in men living w/in 50 m of major roadway, compared with those living >400 m away.

Gauderman WJ, Avol E, Lurmann, F, Kuenzli N, Gilliland F, Peters J, McConnell R. (2005) Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 16(6):737-743.

Children's Health Study in southern California; NO_2 (from 2000) as indicator of freeway-related pollutants and 3 traffic metrics: proximity to freeway, number of vehicles/day, modeling of traffic-related air pollution. Significant association between asthma history and distance to freeway (OR 1.89, 1.19-3.02) and model-based freeway pollution (OR 2.22, 1.36-3.63); positive nonsignificant association with traffic volume and model-based pollution from other roads.

Gehring U, Cyrys J, Sedlmeir G, Brunedreef B, Belander T, Fischer T, Bauer CP, Reinhardt D, Wichmann HE, Heinrich J. (2002) Traffic-related air pollution and respiratory health during the first 2 yrs of life. Eur Respir J 19(4):690-698.

Gordian ME, Hanuese S, Wakefield J. (2006) An investigation of the association between traffic exposure and the diagnosis of asthma in children. J Expo Sci Environ Epidemiol 16(1):49-55.

Anchorage, AK, survey of parents of children in kindergarten and 1st grade, traffic index based on GIS mapping of traffic density w/in 100 m of home. Increased risk of asthma diagnosis with medium and high exposure; significant for high-exposure group (OR 2.84, 1.23-6.51).

Heinrich J, Topp R, Gehring U, Thefeld W. (2005) Traffic at residential address, respiratory health, and atopy in adults: the National German Health Survey 1998. Environmental Research 98:240-249.

Heinrich, J.; Wichmann, H-E. (2004) Traffic related pollutant in Europe and their effect on allergic disease. Current Opin Clinical Epidemiol 4: 341-348.

Hirsch T, Weiland SK, von Mutius E, Safeca AF, Grafe H, Csaplovics E, Duhme H, Keil U, Leupold W. (1999) Inner city air pollution and respiratory health and atopy in children. Eur Respir J 14(3):669677.

Hirsch T, Neumeister V, Weiland SK, von Mutius E, Hirsch D, Grafe H, Duhme H, Leupold W. (2000) Traffic exposure and allergic sensitization against latex in children. J Allergy Clin Immunol. 106(3):573-8.

Ising H, Lange-Asschenfieldt H, Lieber GF, Weinhold H, Eilts M. (2003) Respiratory and dermatological diseases in children with long-term exposure to road traffic emissions. Noise Health 5:41-50.

Janssen NAH, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, Fishcer P. (2003) The relationship between air pollution from heavy traffic and allergic sensitization, bronchial

hyper responsiveness and respiratory symptoms in Dutch school children. Environ Health Perspect 111(12):1512-1518.

Kim JJ, Smorodinsky S, Ostro B, Lipsett M, Singer BC, Hogdson AT. (2002) Traffic-related air pollution and respiratory health: the East Bay Children's Respiratory Health Study. Epidemiol 13(4):S100.

Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hogdson AT, Ostro B. (2004) Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. American Journal of Respiratory Critical Care Medicine. Am J Respir Crit Care Med 170:520-526.

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