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Table or Figure	Page	Erratum
	iv-v	Table of contents for Chapter 2 updated to correct page numbers.
	xv, xxiii	Page numbers for Chapter 2 figures and tables corrected.
	2-9	Replaced reference to "Table 6-14" in the text with "**Table 6-15**"
	2-10	Replaced reference to "Table 6-14" in the text with "**Table 6-15**"
	2-11	Replaced reference to "Table 6-14" in the text with "**Table 6-15**"
	2-12	Replaced the reference to "Figure 7-8" in the text with "**Figure 7-7**" (cited 3 times)
Figure 2-2	2-15	Mean concentration for Laden et al. (2006, 087605) corrected from 14.8 to **16.4.** Deleted "conducted in locations where the mean annual $PM_{2.5}$ concentrations were <17 $\mu g/m^3$ " in caption.
	2-17	Replaced reference to "Table 6-17" in the text with "**Table 6-18**"
Figure 6-4	6-72	Figure replaced. Lisabeth et al. (2008, 155939) correctly moved to $PM_{2.5}$ study group.
Figure 6-15	6-148	Updated HERO ID numbers.
Figure 7-6	7-85	$PM_{2.5}$ concentrations for Laden et al. (2006, 087605) corrected from 17.6 to **16.4**

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Chapter 6. Integrated Health Effects of Short-Term PM Exposure

6.1. Introduction

This chapter reviews, summarizes, and integrates the evidence of relationships between short-term exposures to PM and a variety of health-related outcomes and endpoints. Cardiovascular and respiratory health effects of short-term exposure to various size fractions and sources of PM have been examined in numerous epidemiologic, controlled human exposure and toxicological studies. In addition, there is a large body of literature evaluating the relationship between mortality and short-term exposure to PM. The association between PM exposure and central nervous system function has also been assessed, although far fewer studies are available. The research approaches used to evaluate health effects of PM exposure are described in Section 1.5 along with advantages and limitations of the various study types. Chapter 5 provides an overview of the potential pathophysiological pathways and modes of action underlying the PM-induced health effects observed in animal and human studies. Evidence from the scientific literature of specific cardiovascular and systemic effects, respiratory effects, and central nervous system (CNS) effects associated with exposure to PM are presented in Sections 6.2, 6.3, and 6.4, respectively. Evidence of associations between short-term exposure to PM and mortality are described in Section 6.5. The chapter concludes with an evaluation of PM-induced health effects attributable to specific constituents or sources (Section 6.6). More detailed descriptions of each study evaluated for this assessment are presented in Annexes C, D, E, and F.

Findings for cardiovascular and respiratory effects are presented by specific endpoint or measure of effect, leading from more subtle health outcome measures (e.g., heart rate variability [HRV]) to the more severe, such as hospitalization and mortality for cardiovascular disease. Conclusions from the 2004 PM AQCD (U.S. EPA, 2004, 056905) are briefly summarized at the beginning of each section, and the evaluation of evidence from recent studies builds upon what was available during the previous review. For each health outcome, results are summarized for studies from the specific scientific discipline, i.e., epidemiologic, controlled human exposure, and toxicological studies. The sections conclude with summaries of the evidence on the various health outcomes and integration of the findings that leads to conclusions regarding causality based upon the framework described in Chapter 1. Determination of causality is made for the overall health effect category, such as cardiovascular effects, with coherence, consistency and biological plausibility being based upon the evidence from across disciplines and also across the suite of related health outcomes ranging from the more subtle health outcomes to cause-specific mortality. In the summary sections for cardiovascular and respiratory effects and all-cause mortality, the evidence is summarized and independent conclusions drawn for relationships with $PM_{2.5}$, $PM_{10-2.5}$, and ultrafine particles (UFPs) (Sections 6.2.12, 6.3.10, and 6.5.3, respectively). Evidence of central nervous system effects is also divided by scientific discipline; however, the lack of data does not allow for informative summaries of effect by PM metric in discussing CNS effects (Section 6.4.4).

▪ Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

6.2. Cardiovascular and Systemic Effects

6.2.1. Heart Rate and Heart Rate Variability

Heart rate (HR), HRV, and BP are all regulated, in part, by the sympathetic and parasympathetic nervous systems. Changes in one or more may increase the risk of cardiovascular events (e.g., arrhythmias, MI, etc.). Decreases in HRV have been associated with cardiovascular mortality/morbidity in older adults and those with significant heart disease (TFESC, 1996, 003061). In addition, decreased HRV may precede some clinically important arrhythmias, such as atrial fibrillation, as well as sudden cardiac death, in high risk populations (Chen and Tan, 2007, 197461; Sandercock and Brodie, 2006, 197465; Thong and Raitt, 2007, 197462).

HRV is measured using electrocardiograms (ECG) and can be analyzed in the time domain (e.g., standard deviation of all NN intervals [SDNN], square root of the mean squared successive NN interval differences [rMSSD]), and/or the frequency domain measured by power spectral analysis (e.g., high frequency [HF], low frequency [LF], ratio of LF to HF [LF/HF]). SDNN generally reflects the overall modulation of HR by the autonomic nervous system (ANS), whereas rMSSD and frequency variations in HR generally reflect parasympathetic activity. Thus, rMSSD is generally well correlated with HF, which also reflects the parasympathetic modulation of HR. LF is predominately determined by both sympathetic parasympathetic tone and increased LF/HF indicates sympathoexcitation, which correlates with decreased overall HRV (SDNN, rMSSD). Thus LF/HF is thought to estimate the ratio of sympathetic influences on HR to parasympathetic influences.

While HRV is commonly described as being a reflection of vagal and adrenergic input to the heart, there is clearly a more complex phenomenon reflected in HRV parameters. Rowan et al. (2007, 191911) provide a review of HRV and its use and interpretation with respect to air pollution studies. To summarize, HRV indices are excellent measures of extrapulmonary effects from inhaled pollutants, but the characterization of the acute, reversible responses to air pollution as being either parasympathetic or sympathetic in origin, much less predictive of some adverse outcomes such as ventricular arrhythmia, is relatively unsupported by the clinical literature. This is consistent with the 2004 PM AQCD (U.S. EPA, 2004, 056905) which stated that there is inherent variability in the minute-to-minute spectral measurements, but long-term HRV measures demonstrate excellent day-to-day reproducibility.

The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented limited evidence of PM-induced changes in HRV. However, findings from epidemiologic, controlled human exposure and toxicological studies demonstrated both decreases and increases in HRV following PM exposure. Recent epidemiologic studies have demonstrated a more consistent decrease in HRV (SDNN and rMSSD), which is supported by several controlled human exposure studies published since 2003. In these studies, decreases in HRV were observed among healthy adults following short-term exposures to $PM_{2.5}$ and $PM_{10-2.5}$ CAPs. It is interesting to note that these effects were not observed in adults with asthma or COPD. The effect of PM on HRV observed in animal toxicological studies continues to vary greatly, which may be due in part to strain differences in baseline HRV.

6.2.1.1. Epidemiologic Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) reviewed several studies of PM exposure and HR or HRV and described mixed findings across studies. Several additional studies have investigated the association between acute changes in multiple HRV parameters and ambient air pollutant concentrations in the U.S., Canada, Europe, Mexico, and Asia. Features and results of these studies are presented in Table 6-1, and are summarized below.

In a multicity study, Liao and colleagues (2004, 056590) used data from the fourth cohort evaluation of the Atherosclerosis Risk in Communities (ARIC) Study (1996-1998). The 6,784 subjects were 45-64 yr of age and lived in Washington County, MD, Forsyth County, NC, or the suburbs of Minneapolis, MN. Linear regression models were used to examine the change in HRV associated with PM_{10}, O_3, SO_2, CO, and NO_2 concentrations in the 1-3 days prior to ECG measurement. Among all subjects, each 11.5 $\mu g/m^3$ increase in mean daily PM_{10} concentration 1 day before the ECG measurement was associated with a 0.06 ms^2 decrease in log-transformed HF (95%

CI: -0.10 to -0.02) and a 1.03 ms decrease in SDNN (95% CI: -1.64 to -0.42). A smaller non-significant decrease was also observed for log transformed LF. This reduction in cardiac autonomic control was larger among hypertensive subjects, suggesting that this group may be susceptible to the effects of PM.

In a study of randomly selected participants in the Women's Health Initiative (WHI), a multicity U.S. study, Whitsel et al. (2009, 191980) found decreases in rMMSD and SDNN in association with PM_{10} concentration. The associations were stronger among participants with diabetes. For example, in subjects with impaired fasting glucose, the reduction in rMSSD was 8.3% (-13.9, -2.4) among those with high levels of insulin and 0.6% (-2.1, 1.6) among those with low levels of insulin. Similar results were observed comparing high and low levels of insulin resistance.

Timonen et al. (2006, 088747) conducted a multicity panel study of elderly subjects with stable coronary heart disease who lived in 3 European cities (Amsterdam, the Netherlands; Erfurt, Germany; or Helsinki, Finland). They collected ECGs biweekly for six months in each subject. This analysis, done as part of the ULTRA Study, examined changes in HRV (resting, paced breathing, supine, and 5-min beat-to-beat NN intervals) associated with changes in fixed monitor particulate concentrations ($PM_{2.5}$, $PM_{10-2.5}$) with an emphasis on counts of UFPs (0.01-0.1 µm particles) and accumulation mode particles (ACP; 0.1-1.0 µm particles). Mixed models were first fit to estimate the change in HRV associated with PM (UFP, ACP, $PM_{2.5}$, and $PM_{10-2.5}$) concentrations on the same and previous 4 days in each city. In pooled analyses, the most consistent results identified were for LF/HF (Table 6-1). Estimates for $PM_{2.5}$, however, differed across cities. $PM_{2.5}$ was associated with decreased HF power and increased LF/HF in Helsinki, increased HF power and decreased LF/HF in Erfurt, and not associated with any HRV metric in Amsterdam. In a subsequent analysis, de Hartog et al. (2009, 191904) investigated whether exposure misclassification, effect modification by medication use, or particle composition differences across the three cities could explain the result observed. These authors found that $PM_{2.5}$ apportioned from traffic, long-range transported $PM_{2.5}$ and outdoor $PM_{2.5}$ were associated with reduced HRV most strongly among those not taking beta-blockers (Table 6-1). Indoor and personal $PM_{2.5}$ were not associated with decreased HRV in this study. Therefore, the authors concluded that effect modification by medication use and particle composition differences across the three cities may, in part, explain the heterogeneous $PM_{2.5}$ findings in the previous analysis.

The association between HRV and short-term increases in $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, other size fractions and components was also examined in single-city studies conducted in the U.S. or Canada (Table 6-1). Among U.S. and Canadian cities, increases in $PM_{2.5}$ were generally associated with decreased SDNN and/or decreased HF power but not in all studies. However, studies also reported increased SDNN associated with $PM_{2.5}$ concentrations (Riediker et al., 2004, 056992; Wheeler et al., 2006, 088453). In addition, Yeatts et al. (2007, 091266) reported increased rMSSD and HF power with increased $PM_{2.5}$ concentrations as well as SDANN5 (standard deviation of the average of normal to normal intervals in all 5-min intervals in a 24-h period), and SDNN24HR (standard deviation of the average of all normal to normal intervals in a 24-h period).

Other size fractions (e.g. coarse PM and UFPs) were also associated with decreases in HRV metrics in several single-city studies conducted in the U.S. or Canada. Lipsett et al. (2006, 088753) reported significantly decreased SDNN associated with increases in 2- and 6-h mean PM_{10} and $PM_{10-2.5}$ concentrations. Yeatts et al. (2007, 091266) reported decreased rMSSD, SDNN24HR, SDANN5, ASDNN5 (mean of the standard deviation in all 5-min segments of a 24-h recording), proportion of NN intervals <50 m apart (pNN50) (7 min and 24 h), and HF power associated with increased $PM_{10-2.5}$ concentration. Of those studies examining HRV associations with particle counts (Adar et al., 2007, 001458; Park et al., 2005, 057331), only Adar et al. (2007, 001458) found clear evidence of such effects (e.g., decreased SDNN, LF, HF). Decreased HRV was also associated with increases in ambient mean SO_4^{2-} concentration (Luttmann-Gibson et al., 2006, 089794), ambient mean BC concentration (Park et al., 2005, 057331; Schwartz et al., 2005, 074317), and traffic generated particles/pollution (Adar et al., 2007, 001458; Riediker et al., 2004, 056992) in these single-city studies.

Studies in Asia, Europe, and Mexico have also reported decreases in one or several HRV metrics (Table 6-1) associated with increases in $PM_{2.5}$ concentration or other size fractions. However, a study conducted in Scotland reported no PM-HRV associations (Barclay et al., 2009, 179935). Riojas-Rodriguez et al. (2006, 156913) reported significantly decreased LF and HF power associated with each 1 ppm increase in CO concentration, but only small non-significant decreases associated with $PM_{2.5}$.

Summary of Epidemiologic Studies of Heart Rate and HRV

HRV studies investigated lagged pollutant concentrations from 2 h-5 days before ECG measurement, reporting effects associated with mean pollutant concentrations lagged as short as 1-2 h, and more consistently with lags of 24-48 h. Taken together, these international and U.S./Canadian studies show decreases in HRV associated with $PM_{2.5}$ in most studies that use SDNN, rMSSD or HF power. The effects of $PM_{10-2.5}$, UFPs, and components were evaluated in fewer studies but associations with decreased HRV (e.g., both time and frequency measures) were observed. PM_{10} studies also found evidence for PM-induced alterations in HRV, however, it is difficult to determine which size fraction of PM_{10} (e.g., $PM_{10-2.5}$, $PM_{2.5}$ or UFPs) imparts the effects observed. As a result, PM_{10} studies provide supportive evidence for the overall effect of PM on HRV, but not for a specific size fraction. The proportion of studies reporting decreases in HRV may be inflated by publication bias (i.e., studies showing little or no effects are not submitted for publication).

HRV Studies Investigating Specific Mechanisms

Panel studies investigating PM-HRV associations have also been useful in investigating potential mechanistic pathways by which PM may elicit a cardiovascular response. A series of analyses using data from the Normative Aging Study, a cohort of older men living in the Boston metropolitan area, has also provided mechanistic insights into the PM-HRV association (Baccarelli et al., 2008, 191959; Chahine et al., 2007, 156327; Park et al., 2005, 057331; Park et al., 2006, 091245; Park et al., 2008, 156845; Schwartz et al., 2005, 086296).

Park et al. (2005, 057331) studied the association between short-term increases in ambient air pollution and changes in HRV using males enrolled in the Normative Aging Study. Using linear regression models, the association between HRV metrics and $PM_{2.5}$, O_3, NO_2, SO_2, CO, BC, and particle number count (PNC) moving averages (ma) in the previous 4, 24, and 48 h were examined. The modifying effects of hypertension, diabetes, ischemic heart disease (IHD), and use of hypertensive medications were also estimated. Of the pollutants examined, only $PM_{2.5}$ and O_3 were associated with reductions in HRV, and each pollutant's effect appeared independent of the other. Each 8 $\mu g/m^3$ increase in mean $PM_{2.5}$ concentration in the previous 48 h was associated with a 20.8% decrease in HF power (95% CI: -34.2 to -4.6), with larger effects among subjects with hypertension, IHD, and diabetes. The authors state that since BC concentrations were also associated with adverse changes in HRV, this suggests that traffic pollution may be partially responsible for the HRV changes.

Schwartz et al. (2005, 086296) examined the hypothesis that adverse changes in HRV due to $PM_{2.5}$ are mediated by an oxidative stress response among participants in the Normative Aging Study. They examined whether the change in HF power associated with each 10 $\mu g/m^3$ increase in 48-h mean $PM_{2.5}$ was modified by the presence or absence of the allele for glutathione S-transferase M1 (GSTM1), use of statins, obesity, high neutrophil counts, higher blood pressure (BP), and/or older age. In subjects without the GSTM1 allele and its protection against oxidative stress, each 10 $\mu g/m^3$ increase in 48-h mean $PM_{2.5}$ concentration was associated with a 34% decrease in HF power (95% CI: -52 to -9). There was no association among those with at least one copy of the allele. Obesity and high neutrophil counts also worsened the effect of PM on HRV regardless of allele.

Park et al. (2006, 091245) investigated whether transition metals may be responsible for cardiorespiratory effects that are observed in association with $PM_{2.5}$. Again using the Normative Aging Study cohort, they investigated whether subjects with two hemochromatosis (HFE) polymorphisms associated with increased iron uptake had a smaller decrease in HF power associated with PM than those subjects without either variant. Each 10 $\mu g/m^3$ increase in 48-h mean $PM_{2.5}$ was associated with a 31.7% decrease in HF (95% CI: -48.1 to -10.3) among subjects without either polymorphism, but not among those with the 2 protective HFE alleles.

Chahine et al. (2007, 156327) reported a 10.5% reduction in SDNN (95% CI: -18.2 to -2.2) associated with each 10 $\mu g/m^3$ increase in the mean 48-h $PM_{2.5}$ concentration among Normative Aging Study participants without the GSTM1 allele, but only a 2.0% SDNN decrease (95% CI: -11.3, 8.3) in those with the allele. This supports the PM-HF power findings of Schwartz et al. (2005, 086296). Further, subjects with the long repeat polymorphism in the HO-1 promoter had a greater decline in SDNN associated with each 10 $\mu g/m^3$ increase in the mean 48-h $PM_{2.5}$

concentration (-8.5% [95% CI: -14.8 to -1.8) than those with the short repeat polymorphism in HO-1 (7.4 % increase [95% CI: -8.7 to 26.2). Again, this suggests that PM-HRV changes are mediated, in part, by oxidative stress.

Baccarelli et al. (2008, 191959) investigated whether the $PM_{2.5}$-HRV association was modified by dietary intakes of methyl nutrients (folate, vitamins B6 and B12, and methionine) and related gene polymorphisms thought to either confer increased or decreased risk of CVD among men enrolled in the Normative Aging Study. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ in the previous 48 h was associated with -8.8% (95% CI: -16.7 to -0.2) and -11.8% (95% CI: -20.8 to -1.8) decreases in SDNN, among those with CC/TT genotypes of the C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism, and the CC genotype of the C1420T cytoplasmic serine hydroxymethyltransferase (cSHMT) polymorphism, respectively. There were no changes among those with CC MTHFR and CC/TT cSHMT. Further, there were similar HRV reductions in those subjects with lower intakes of B6, B12, and/or methionine, but no decreases in those with high intakes. Thus these genetic and nutritional variations in the methionine cycle may modify the PM-HRV association.

Finally, among those Normative Aging Study subjects with high chronic lead exposure as measured using X-ray fluorescence of the tibia, each 7 $\mu g/m^3$ increase in mean $PM_{2.5}$ concentration in the previous 48 h was associated with a 22% decrease in HF power (95% CI: -37.4 to -1.7) (Park et al., 2008, 093027). Decreases in HF HRV were also associated with each 2.5 $\mu g/m^3$ increase in mean SO_4^{2-} concentration in the previous 48 h (22% decrease [95% CI: -40.4 to 1.6). The authors suggest that these findings are consistent with an oxidative stress response. Although this series of studies suggest a role of oxidative stress and perhaps methyl nutrients and related polymorphisms in these short-term associations of $PM_{2.5}$ with HRV, replication by other investigators in other cities and in other populations will aid interpretations of these findings.

Using data from a randomized controlled trial in Mexico City, Romieu et al. (2005, 086297) investigated whether omega-3 fatty acids in fish oil supplements would mitigate the adverse effects of acute PM exposure on HRV. Residents of a Mexico City nursing home were randomized to either 2 g/day of fish oil or 2 g/day of soy oil. They used random-effects regression models to estimate the change in HRV associated with mean $PM_{2.5}$ concentration in the pre-supplementation and supplementation phases. In the group receiving the fish oil supplement, each 8 $\mu g/m^3$ increase in 24-h mean total $PM_{2.5}$ exposure (weighted average of indoor and outdoor $PM_{2.5}$ based on time activity diaries) was associated with a 54% reduction (95% CI: -72 to -24) in log transformed HF power in the pre-supplementation phase. However, in the supplementation phase of the trial, each 8 $\mu g/m^3$ increase in 24-h mean total $PM_{2.5}$ concentration was associated with only a 7% reduction in log transformed HF power (95% CI: -20 to 7). Decreases in other HRV parameters associated with $PM_{2.5}$ were also muted in the supplementation phase. In the group receiving the soy oil supplement, the reduction in HF power was also smaller in magnitude during the supplementation phase. However, among those receiving the soy oil supplement, the differences between the pre-supplementation $PM_{2.5}$-HF change and the supplementation $PM_{2.5}$-HF change were smaller compared to those receiving the fish oil, and were not statistically significant. Romieu et al. (2008, 156922)also report that omega-3 polyunsaturated fatty acids appear to modulate the adverse effect of $PM_{2.5}$ based on measured biomarkers of oxidative response (Section 6.2.9.1).

Summary of HRV Studies Investigating Specific Mechanisms

In summary, several analyses of data from the Normative Aging Study have provided evidence that effect of $PM_{2.5}$ on HRV is modulated by genetic polymorphisms related to oxidative stress (Chahine et al., 2007, 156327; Park et al., 2006, 091245; Schwartz et al., 2005, 086296) or dietary methyl nutrients or related genetic polymorphisms (Baccarelli et al., 2008, 191959). In addition, preexisting conditions such as diabetes, IHD, and hypertension (Park et al., 2005, 057331; Whitsel et al., 2009, 191980), beta-blocker use (Folino et al., 2009, 191902; Park et al., 2005, 057331), chronic lead exposure (Park et al., 2008, 093027) and omega-3 fatty acid (Romieu et al., 2005, 086297) are reported to modulate the effect of $PM_{2.5}$ on HRV.

Table 6-1. Characteristics of epidemiologic studies investigating associations between PM and changes in HRV.

	PM Type, Exposure Lag	Study Subjects	Ambient Concentration ($\mu g/m^3$)*	Recording Length	SDNN	LF	HF, rMSSD	LF/HF
MULTICITY STUDIES								
Liao et al. (2004, 056590)	PM_{10}, 24-h, lag 1-day	N=6784 (mean age = 62 yrs), ARIC study: MD, NC, MN	24.3	5-min	↓	↓	↓	
Whitsel et al. (2009, 191980)	PM_{10}, 24-h, 3-d avg within 5 days preceding exam	N=4295 randomly selected participants in the WHI Trial	28 visit 1 27 visit 2 27 visit 3	10 second	↓		↓	
Timonen et al. (2006, 088747)	UFP, lags 0-2 days	Stable IHD patients (65+ yr) Amsterdam, Netherlands (N=37) Erfurt, Germany (N=47) Helsinki, Finland (N=47)	Amsterdam: 17,300 particles/cm^3 Erfurt: 21,100 particles/cm^3 Helsinki: 17,000 particles/cm^3	5-min (Pooled estimates during paced breathing presented to the right)	↓		↑	↓
	AC, lags 0-2 days		Amsterdam: 2100 particles/cm^3 Erfurt: 1800 particles/cm^3 Helsinki: 1400 particles/cm^3		↓		↑	↓
	$PM_{2.5}$, lags 0-2 days		Amsterdam: 20.0 Erfurt: 23.1 Helsinki: 12.7		↓		↑	↓
	$PM_{10-2.5}$, 2-day lag		Amsterdam: 15.3 Erfurt: 3.7 Helsinki: 6.7		→		→	↓
De Hartog et al. (2009, 191904)	24 h $PM_{2.5}$ outdoor, $PM_{2.5}$ traffic, long-range transported $PM_{2.5}$	Stable IHD patients (65+) Amsterdam, Netherlands (N=37) Erfurt, Germany (N=47) Helsinki, Finland (N=47) (Effects strongest among those NOT taking beta-blockers)	Median Outdoor: Amsterdam: 16.7 Erfurt: 16.3 Helsinki: 10.6	5 min	↓		↓	
U.S. AND CANADIAN STUDIES								
Park et al. (2005, 057331)	$PM_{2.5}$, 48-h avg	N=497 men (mean age = 73 yr), Normative Aging Study Boston, MA	24-h: 11.4 98th: 30.58	4-min	↓	↓	↓	↑
	PNC, 48-h avg		24-h: 28,942 (13,527) particles/cm^3		→	↓	↓	↓
	BC, 48-h avg		24-h: 0.92		↓	↓	↓	↑
Riediker et al. (2004, 056992)	In-vehicle $PM_{2.5}$ (mass) 9-h avg	N=9 healthy state police	9-h in-vehicle: 23	10-min	↑	→	↑	↓
Schwartz et al. (2005, 074317)	BC, 24-h	N=28 older adults (61-89 yr), 12 wk follow-up, Boston, MA	24-h Median: 1.0	23-min	↓		↓	↑
	$PM_{2.5}$, 24-h		24-h Median: 10		↓		↓	↑
	Secondary PM (estimated), 1-h		1-h Median: -1.7		↓		↓	↑
Yeatts et al. (2007, 091266)	$PM_{10-2.5}$, 24-h	N=12 adult asthmatics, Chapel Hill, NC	24-h: 5.3	5-min	↓	↓	↓	
	$PM_{2.5}$,24-h		24-h: 12.5		↑	↓	↑	

	PM Type, Exposure Lag	Study Subjects	Ambient Concentration ($\mu g/m^3$)*	Recording Length	SDNN	LF	HF, rMSSD	LF/HF
Wheeler et al. (2006, 088453)	$PM_{2.5}$, 4-h avg	N=18 COPD, Atlanta, GA	4-h: 17.8	20-min	↑	↑	↑	↑
	$PM_{2.5}$, 4-h avg	N=12 MI, Atlanta, GA			↓	↑	↓	↓
	EC, 4-h avg	N=18 COPD, Atlanta, GA	4-h: 2.3		↑			
	EC, 4-h avg	N=12 MI, Atlanta, GA			↓			
Dales 2004 (2004, 099036)	$PM_{2.5}$, 24-h avg (personal)	N=36 IHD patients, Toronto, Canada	24-h personal: 19.9	Not described	→	→	→	→
Luttmann-Gibson et al. (2006, 089794)	$PM_{2.5}$, lag 1-day	N=32 (65+ yr) Steubenville, OH	24-h: 19.7	~30-min	↓	↓	↓	
	Sulfate, lag 1-day		24-h: 6.9		↓	↓	↓	
	Nonsulfate PM, lag 1-day		24-h: 10.0		↓	↓	↓	
	EC, lag 1-day		24-h: 1.1		↑	↓	→	
Adar et al. (2007, 001458)	$PM_{2.5}$, 24-h avg	N=44 (60+ yr), diesel bus riders St. Louis, MO	24-h: 10.17 98th: 22.43	5-min	↓	↓	↓	↑
	BC, 24-h avg		330 ng/m^3		↓	↓	↓	↑
	PNC fine		42 particles/cm^3		↓	↓	↓	↑
	PNC course		0.02 particles/cm^3		↑	↑	↑	↓
Pope et al. (2004, 055238)	$PM_{2.5}$ (FRM), 24-h, lag 1-day	N=88 (65+ yr; 250 p-days), Utah Valley	23.7	24-h	↓		↓	
Sullivan et al. (2005, 109418)	$PM_{2.5}$, 1, 2, 24-h avg	N=21 (65+ yr) with CVD, Seattle WA	Median:10.7	20-min	→		→	
		N=13 (65+ yr) w/out CVD, Seattle WA			→		→	
Lipsett et al. (2006, 088753)	PM_{10},	N=19 IHD (65+ yr), 12 wk fu, Coachella Valley, CA	31.0 and 46.1	5-min Frequency domain; 2-h, 24-h Time domain	↓	↓	↓	
	$PM_{10-2.5}$		None given		↓	↓	→	
	$PM_{2.5}$		14 and 23.2		↓	↓	↑	
Ebelt et al. (2005, 056907)	PM_{10}, 24 h	N=16 COPD, Vancouver, Canada	17	24-h	↓		↓	
	$PM_{10-2.5}$		5.6		↑		→	
	$PM_{2.5}$, 24-h		11.4 98th: 23		↓		↓	
	$PM_{2.5}$ Sulfate, 24-h outdoor		2.0		↓		→	
Baccarelli et al. (2008, 191959)	$PM_{2.5}$, 48 h	N=549 Normative Aging Study and residents of Boston metropolitan area	Geometric mean (95% confidence interval) 10.5 (10.0, 10.9)	7 min	↓			
Fan et al. (2008, 191979)	$PM_{2.5}$ personal, 1 h	N=11 crossing guards in New Jersey	Only change in 1-h $PM_{2.5}$ reported Morning shift: 35.2 Afternoon shift: 24.1	24 h	↓			
INTERNATIONAL STUDIES								
Chan et al. (2004, 087398)	$NC_{0.02-1}$, 1-4 h	N=9 adults (19-29 yr) with lung function impairment, Taipei, Taiwan	23,407 (19,836) particles/cm^3	5 min	↓	↓	↓	↓
		N=10 adults (42-79 yr) with lung function impairment, Taipei, Taiwan	25,529 (20,783) particles/cm^3		↓	↓	↓	↓
Chuang et al. (2005, 087989)	$PM_{1.0-0.3}$, 1-4 h	N=16, Patients with IHD/ hypertension , Taipei, Taiwan	37.2	5-min	↓	↓	↓	↑
	$PM_{2.5-1.0}$, 1-4 h		12.6		↓	↓	↓	↑
	$PM_{10-2.5}$, 1-4 h		14.0		↓	↓	↓	↑

	PM Type, Exposure Lag	Study Subjects	Ambient Concentration ($\mu g/m^3$)*	Recording Length	SDNN	LF	HF, rMSSD	LF/HF
	$PM_{1.0-0.3}$, 1-4 h	N=10 IHD, Taipei, Taiwan	26.8		↓	↓	↓	→
	$PM_{2.5-1.0}$, 1-4 h		10.9		↓	↓	↓	↓
	$PM_{10-2.5}$, 1-4 h		16.4		↓	↓	↓	↑
Holguin et al. (2003, 057326)	$PM_{2.5}$, 24-h	N=21 without hypertension (60-96 yr), Mexico City	37.2	5-min		↓	↓	↑
		N=13 with hypertension (60-88 yr), Mexico City				↓	↓	↑
Romieu et al. (2005, 086297)	$PM_{2.5}$, 24-h (outdoor and indoor)	N=50 nursing home residents 65+ yr, Mexico City	Outdoor: 19.4 Indoor: 18.3	6-min (Indoor $PM_{2.5}$, pre-supplement phase presented)	↓	↓	↓	
Riojas-Rodriguez et al. (2006, 156913)	Personal $PM_{2.5}$	N=30 IHD patients, Mexico City	Geometric mean: 46.8	5-min		↓	↓	
Barclay et al. (2009, 179935)	PM_{10}, daily PNC, daily Estimated $PM_{2.5}$ and PNC	N=132, stable coronary heart failure Aberdeen, Scotland	Range of daily means: 7.4 to 68	24 h	→			
Cárdenas et al. (2008, 191900)	$PM_{2.5}$-outdoor $PM_{2.5}$-indoor	N=52 (31 women, 21 men; 20-40 yr), southeast of Mexico City	Median $PM_{2.5}$ outdoor: 28.3 $\mu g/m^3$ Median $PM_{2.5}$ indoor: 10.8	15 min		↓	↓	↓
Folino et al. (2009, 191902)	PM_{10}, 24 h $PM_{2.5}$, 24 h $PM_{0.25}$, 24 h	N=39 (36 male, 3 female; mean age = 60 yr) Padua, Italy	PM_{10} Summer: 46.4 Winter:73.0 Spring: 38.3 $PM_{2.5}$ Summer: 33.9 Winter: 62.1 Spring: 30.8 $PM_{0.25}$ Summer: 17.6 Winter: 30.5 Spring: 18.8	24 h	↓			
Min et al. (2008, 191901)	PM_{10}, 12 h	N=1349 (596 males; mean age = 44 yr), Korea	1-h avg: 33.2	5 min	↓	↓	↓	

Notes: Increases (↑), decreases (↓) and no effects (→) in HRV associated with PM concentration are indicated. Statistical significance was not necessary to categorize an effect as an increase or decrease. For time domain measures moving average lags up to 24-h were explored. For frequency domain measures lags of 2-h, 4-h and 24-h were explored.
** All concentrations are means measured in µ/m3, unless otherwise noted.

6.2.1.2. Controlled Human Exposure Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) cited one study in which HRV indicators of parasympathetic activity increased relative to filtered air control following a 2-h exposure with intermittent exercise to $PM_{2.5}$ CAPs (avg concentration 174 $\mu g/m^3$) in both healthy and asthmatic volunteers (Gong et al., 2003, 042106). This effect was observed immediately following exposure and at 1 day post-exposure, but not at 4 h post-exposure. Although not statistically significant, HRV (total power) increased following exposure to filtered air and decreased following exposure to CAPs. More recent controlled human exposure studies are described below.

CAPs

Two new studies have evaluated the effect of $PM_{2.5}$ CAPs (2-h exposures to concentrations of 20-200 $\mu g/m^3$) on HRV in elderly subjects (Devlin et al., 2003, 087348; Gong et al., 2004, 087964). In both studies, subjects experienced significant decreases in HRV following exposure to CAPs relative to filtered air exposures. Interestingly, Gong et al. (2004, 087964) found that decreases in HRV were more pronounced in healthy older adults than in those with COPD. In another study,

healthy and asthmatic adults were exposed to $PM_{10-2.5}$ CAPs (avg concentration 157 μg/m^3) for 2 h with intermittent exercise (Gong et al., 2004, 055628). HRV was not affected immediately following the exposure, but decreased in both groups at 4 and 22 h after the end of the exposure, with greater responses observed in non-asthmatics. In a recent study among healthy adults exposed for 2 h with intermittent exercise to $PM_{10-2.5}$ CAPs (avg concentration 89 μg/m^3, MMAD 3.59 μm, Chapel Hill, NC), Graff et al. (2009, 191981) observed a significant decrease in overall HRV (SDNN) at 20 h post-exposure, although no other measures of HRV were affected. Using a similar study design, the same laboratory also evaluated the effect of ultrafine CAPs (avg concentration 49.8 μg/m^3, <0.16 μm in diameter) on various HRV parameters (Samet et al., 2009, 191913) Relative to filtered air, both HF and LF power increased 18 h following exposure to UF CAPs (36-42% increase per 10^5 particles/cm^3). Exposure to UF CAPs, expressed as mass concentration, was not associated with changes in HF power, and time domain parameters of HRV did not differ between CAPs and filtered air in the 24 h following exposure. Gong et al. (2008, 156483) also recently evaluated changes in HRV following controlled human exposures to UF CAPs and reported a small and transient decrease in LF power ($p < 0.05$) among healthy ($n = 17$) and asthmatic ($n = 14$) adults 4 h after the completion of a 2-h exposure with intermittent exercise in Los Angeles (avg concentration 100 μg/m^3, avg PNC 145,000/cm^3). No other measure of HRV was shown to be significantly affected by exposure to UF CAPs. In one of the largest studies of controlled human exposures to CAPs conducted to date, Fakhri et al. (2009, 191914) evaluated changes in HRV among 50 adult volunteers during 2-h exposures to $PM_{2.5}$ CAPs (127 μg/m^3) and O_3 (114 ppb), alone and in combination. Neither exposure to CAPs nor O_3 resulted in any significant changes in HRV relative to filtered air. However, trends were observed suggesting a negative concentration-response relationship between CAPs concentration and SDNN, rMSSD, HF power and LF power when subjects were concomitantly exposed to O_3.

Diesel Exhaust

In a double-blind, crossover, controlled-exposure study, Peretz et al. (2008, 156855) exposed three healthy adult volunteers and 13 adults with metabolic syndrome while at rest to filtered air and two levels of diluted DE ($PM_{2.5}$ concentrations of 100 and 200 μg/m^3) in 2-h sessions. HRV parameters were assessed prior to exposure, as well as at 1, 3, 6 and 22 h following the start of exposure, and included both time domain (SDNN and rMSSD) and frequency domain parameters (HF power, LF power, and the LF/HF ratio). In an analysis including all 16 subjects, the authors observed an increase in HF power and a decrease in LF/HF 3 h after the start of exposure to 200 μg/m^3 relative to filtered air. Although these changes were statistically significant ($p < 0.05$) the effects were not consistent among the study subjects. No other significant effect of DE on HRV was observed at either concentration or time point. The authors attributed the lack of consistent effects to the small and non-homogeneous population and the timing of measurement. There was no difference in either baseline or diesel-induced changes in HRV parameters between normal individuals and patients with metabolic syndrome, although the number of normal individuals was quite small. It is unclear if patients with metabolic syndrome were taking any medications.

Model Particles

Several additional recent controlled human exposure studies have evaluated the effect of laboratory generated particles on HRV in healthy and health-compromised individuals. In a random order crossover controlled human exposure study, Routledge et al. (2006, 088674) examined the effects of UF elemental carbon (EC) particles (50 μg/m^3) alone and in combination with 200 ppb SO_2 on HRV among 20 healthy older adults (age 56-75 yr), as well as 20 older adults with coronary artery disease (age 52-74 yr). Five minute recordings of HRV data were obtained prior to and immediately following the 1-h exposure, as well as 3 h post-exposure. In healthy subjects, exposure to EC particles resulted in small increases in RR-interval, SDNN, rMSSD, and LF power immediately following exposure compared to filtered air control. At 3 h post-exposure, there were no significant differences in HRV measures between EC particle and filtered air exposures. Conversely, SO_2-induced decreases in HRV were observed at 3 h, but not immediately following exposure. Concomitant exposure to EC particles and SO_2 followed a pattern similar to that observed with SO_2

alone, but did not reach statistical significance. Subjects with coronary artery disease did not experience any significant changes in HRV following exposure to either pollutant. The authors postulated that this lack of effect may be due to differences in medication between the two groups, as 70% of subjects with stable angina reported using β blockers, which are known to increase cardiac vagal control. The lack of any significant effects on HRV following exposure to EC particles is an important finding, as it provides evidence to suggest that the health effects observed following exposure to PM may be due to particle constituents other than carbon, or to reactive species found on the surface of the particle. These findings are in agreement with those of Zareba et al. (2009, 190101) who reported small and variable changes in HRV among a group of healthy adults following exposure to UF EC. While exposure both at rest and during exercise to 10 $\mu g/m^3$ UF EC resulted in an increase in time domain parameters (rMSSD and SNDD), no such effect was observed following exposure to a higher concentration of UF EC (25 $\mu g/m^3$) in the same subjects. A recent pilot study reported no effect of exposure to EC and ammonium nitrate particles (250-300 $\mu g/m^3$) on HRV parameters in five adults with allergic asthma (Power et al., 2008, 191982). However, when the exposure occurred concomitantly with O_3 (0.2 ppm), subjects were observed to experience significant changes in both time and frequency HRV parameters. These observations should be considered very preliminary as the study was limited by a small sample size (n = 5) and did not evaluate the effect of exposure to O_3 without particles. However, these findings are in agreement with the previously described study of CAPs and O_3 conducted by Fakhri et al. (2009, 191914). In addition to the studies of laboratory generated carbon described above, Beckett et al. (2005, 156261) used ZnO as a model particle and exposed twelve resting, healthy adults for 2 h to filtered air and 500 $\mu g/m^3$ in the ultrafine (40.4 ± 2.7 nm) and fine (291.2 ± 20.2 nm) modes. Neither ultrafine nor fine ZnO produced a significant change in any time or frequency domain parameter of HRV.

Summary of Controlled Human Exposure Study Findings for Heart Rate Variability

The results of several new controlled human exposure studies provide limited evidence to suggest that acute exposure to near ambient levels of PM may be associated with small changes in HRV. Changes in HRV parameters, however, are variable with some showing increased parasympathetic activity relative to sympathetic activity and others showing the opposite. Although a direct comparison between younger and older adults has not been made, PM exposure appears to result in a decrease in HRV more consistently in healthy older adults (Devlin et al., 2003, 087348; Gong et al., 2004, 087964).

6.2.1.3. Toxicological Studies

Toxicological studies that examined HR and HRV are presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) and overall demonstrated differing responses, which were collectively characterized as providing limited evidence for PM-related cardiovascular effects. The studies described that reported HR or HRV effects following PM exposure were conducted with a variety of particle types (CAPs, diesel, ROFA, metals), exposure methods (inhalation and IT instillation), and doses (100-3,000 $\mu g/m^3$ for inhalation; up to 8.3 mg/kg for IT instillation).

CAPs

Two groups of SH rats exposed to CAPs in Tuxedo, NY for 4 h (single-day mean $PM_{2.5}$ concentrations 80 and 66 $\mu g/m^3$; February 2001 and May 2001, respectively) demonstrated decreased HR when exposure groups were combined that returned to baseline values when exposure ceased (Nadziejko et al., 2002, 087460). Fine or UF H_2SO_4 exposure (mean concentration 225 and 468 $\mu g/m^3$) did not induce any HR effects. Another study demonstrated a trend toward increased HR in WKY rats following a 1- or 4-day $PM_{2.5}$ CAPs exposure in Yokohama City, Japan (4.5 h/day; May 2004, November 2004, and September 2005), but the correlation between change in HR and cumulative PM mass collected was not significant (Ito et al., 2008, 096823). Increased HR was observed in SH rats exposed to $PM_{2.5}$ CAPs for two 5-h periods during the spring (mean mass concentration 202 $\mu g/m^3$) in a suburb of Taipei, Taiwan (Chang et al., 2004, 055637). The response

was less prominent in the summer (mean mass concentration 141 μg/m^3), despite the number concentrations being similar for the two seasons (2.30×10^5 and 2.78×10^5 particles/cm^3, respectively).

For HRV, decreased SDNN was observed in SH rats exposed to $PM_{2.5}$ CAPs (mean mass concentration 202 μg/m^3; mean number concentration 2.30×10^5 particles/cm^3) for two 5-h periods separated by 24 h (Chang et al., 2005, 088662). Each of the four animals served as their own control and the estimated mean PM effects for the SDNN decreases during exposure were 85-60% of baseline. CAPs effects on rMSSD were less remarkable. In a study of Tuxedo, NY $PM_{2.5}$ CAPs, no acute changes in rMSSD or SDNN were observed in either ApoE$^{-/-}$ or C57 mice when the 48-h time period postexposure was evaluated (6 h/day×5 day/wk; mean mass concentration over 5-mo period 110 μg/m^3) (Chen and Hwang, 2005, 087218).

Diesel Exhaust

Anselme et al. (2007, 097084) used a MI model of congestive heart failure (CHF) where the left anterior descending coronary artery of WKY rats was occluded to induce ischemia. After 3 mo of recovery, rats were exposed to diesel emissions for 3 h (PM concentration 500 μg/m^3; mass mobility diameter 85 nm; NO_2 1.1 ppm; CO 4.3 ppm) and decreases in rMSSD were observed during the first 2 h of the exposure, which returned to baseline values for the last hour of exposure. Healthy rats also demonstrated decreased rMSSD when measured over the entire exposure period.

Model Particles

In WKY rats exposed to UF carbon particles (mass concentration 180 μg/m^3; mean number concentration 1.6×10^7 particles/cm^3) for 24 h, HR increased and SDNN decreased during particle inhalation (Harder et al., 2005, 087371). These measures returned to baseline values during the recovery period. This study provides evidence that ultrafine carbon exerts its effects through changes in ANS mediation, as the HR and HRV responses occurred quickly after exposure started and pulmonary inflammation was only observed at the 24-h time point (and not at 4 h). SH rats exposed to ultrafine carbon particles under the same conditions (mass concentration 172 μg/m^3; mean number concentration 9.0×10^6 particles/cm^3) demonstrated similar responses, albeit not until recovery days 2 and 3 (Upadhyay et al., 2008, 159345).

A model of premature senescence has been developed by Tankersley et al. (2003, 053919), using aged AKR mice whose body weight abruptly declines ~5 wk prior to death and is accompanied by deficiencies in other vital physiological function including HR and temperature regulation. When exposed to carbon black ([CB]; mean concentration 160 μg/m^3; 3 h/day×3 day), terminal senescent mice responded with robust cardiovascular effects, including bradycardia and increased rMSSD and SDNN (Tankersley et al., 2004, 094378). SDNN and LF/HF were also increased in healthy senescent mice exposed to CB. These studies indicate that HR regulatory mechanisms are altered in susceptible mice exposed to PM (sympathetic and parasympathetic changes in healthy senescent mice and increased parasympathetic influence in terminally senescent mice), which may translate into lowered homeostatic competence in these animals. Results from the near-terminal group should be interpreted with caution, as only three mice were in this group.

Subsequent research with a similar exposure protocol (mean CB concentration 159 μg/m^3) used C57BL/6J and C3H/HeJ mice to determine whether an acute PM challenge can modify HR regulation in two mice strains with differing baseline HR (Tankersley et al., 2007, 097910). There were no CB-specific effects on HR or HRV in C3H/HeJ compared to C57BL/6J mice (average HR ~80 bpm lower than C3H/HeJ at baseline). Administration of a sympathetic antagonist (propanolol) to C57BL/6J mice prior to CB exposure resulted in elevated HR and decreased rMSSD compared to air during the last 2 h of exposure, indicating withdrawal of parasympathetic tone. There may be differences in regional particle deposition based on strain-specific breathing patterns that may affect HR and HRV responses. However, this study revealed that inherent autonomic tone, which is genetically varied between these mouse strains, may affect cardiovascular responses following PM exposure. In extrapolating these results to humans, individual variation in genetic factors likely plays some role in PM-induced adjustments in HR control via the ANS.

A recent study in mice (C3H/HeJ, C57BL/6J, and C3H/HeOuJ) examined the effects of a 2-h O_3 (mean concentration 0.584 ppm) pretreatment followed by a 3-h exposure to CB (mean

concentration 536 μg/m^3) on HR and HRV measures (Hamade et al., 2008, 156515) HR decreased to the greatest extent during O_3 pre-exposure for all strains that were then exposed to CB. The percent change in SDNN and rMSSD were increased in C3H mice during O_3 pre-exposure and CB exposure compared to the filtered air group; however, these HRV parameters gradually decreased over the duration of the experiment and appeared to be O_3 dependent. Together, these findings indicate that increases in parasympathetic tone and/or decreases in sympathetic input may explain the observed bradycardia. In a subset of all mice pre-exposed to O_3, rMSSD remained significantly elevated during the CB exposure compared to filtered air. The results from this study confirm what was observed in Tankersley et al. (2007, 097910) in that genetic determinants affect HR regulation in mice with exposure to air pollutants.

Summary of Toxicological Study Findings for Heart Rate and Heart Rate Variability

Both increases and decreases in HR have been observed in rats or mice following PM exposure. Fine or UF H_2SO_4 did not result in HR changes in SH rats. Similarly, decreased SDNN was reported for UF CAPs exposure and lowered rMSSD was observed with diesel exposure. In near-terminal senescent mice, HRV responses were robust following CB exposure and represented increased parasympathetic influence. Strain differences in baseline HR and HRV likely contribute to PM responses. HRV changes with preexposure to O_3 and CB appeared to be O_3 dependent, although rMSSD remained elevated during PM exposure.

Source Apportionment and PM Components

An additional analysis of CAPs data (Chen and Hwang, 2005, 087218; Hwang et al., 2005, 087957) was conducted to link short-term HR and HRV effects to major PM source categories using source apportionment methodology (Lippmann et al., 2005, 087453).

The source categories were: (1) regional secondary SO_4^{2-} comprised of high S, Si, and OC (mean 63.41 μg/m^3); (2) resuspended soil characterized by high concentrations of Ca, Fe, Al, and Si (mean concentration 5.88 μg/m^3); (3) fly ash emissions from power plants burning residual oil in the eastern U.S. and containing high levels of V, Ni, and Se (mean concentration 1.53 μg/m^3); and (4) motor vehicle traffic and other unknown sources (34.92 μg/m^3) (Lippmann et al., 2005, 087453). Exposures occurred from 9:00 a.m. to 3:00 p.m., 5 days/wk for 5 mo. $PM_{2.5}$ mass was associated with a daily interquartile change of -4.1 beat/min HR during exposure in ApoE$^{-/-}$ mice[1] and a similar magnitude of effect was observed with resuspended soil (-4.5 beat/min). Resuspended soil was also associated with a HR increase in the afternoon post-exposure (2.6 beat/min); the secondary SO_4^{2-} factor was linked to lowered HR in the same period (-2.5 beat/min). A 6.2% increase in rMSSD collected in the afternoon post-exposure was associated with the residual oil factor, compared to a 5.6% and 2.4% decrease in rMSSD at night for secondary SO_4^{2-} and $PM_{2.5}$ mass, respectively. Resuspended soil was associated with a 4.3% increase in rMSSD the night following CAPs exposure. The residual oil and secondary SO_4^{2-} categories showed similar statistically significant parameter estimates for SDNN as rMSSD.

Recent studies of ECG alterations in mice have indicated a role for PM-associated Ni in driving the cardiovascular effects. Lippman et al. (2006, 091165) presented a posthoc analysis of daily variations in $PM_{2.5}$ CAPs (mean concentration: 85.6 μg/m^3; 7/21/ 2004–1/12/2005; Tuxedo, NY) and changes in cardiac dynamics in ApoE$^{-/-}$ mice. On the 14 days that the exposed mice had

[1] Atherosclerosis and related pathways have been studied primarily in the Apolipoprotein E (ApoE) knockout mouse. Developed by Nobuyo Maeda's group in 1992 (Piedrahita et al., 1992, 156868; Zhang et al., 1992, 157180), the ApoE-/- mouse and related models have become the workhorse of atherosclerosis research over the past 15 years. The ApoE molecule is involved in the clearance of fats and cholesterol. When ApoE (or the LDL receptor) is deleted from the genome, mice develop severely elevated lipid and cholesterol profiles; ApoE$^{-/-}$ mice on a high-fat ("Western") diet exhibit cholesterol levels exceeding 1000 mgdL (normal is ~150 mgdL) (Huber et al., 1999, 156575; Moore et al., 2005, 156780). As a result, the lipid uptake into the vasculature is increased and the atherosclerotic process is dramatically hastened. Furthermore, the LDLs in ApoE$^{-/-}$ mice are highly susceptible to oxidation (Hayek et al., 1994, 156527), which may be a crucial event in the air pollution-mediated vascular changes. However it should be noted that this model is primarily one of peripheral vascular disease rather than coronary artery disease.

unusually elevated HR, Ni, Cr, and Fe comprised 12.4% of the PM mass, compared to only 1.5% on the other 89 days. Back trajectory analyses indicated high-altitude winds from the northwest that did not traverse population centers and industrial areas except the Sudbury Ni smelter in Ontario, Canada. On the 14 days that high HR was observed, the HR elevation lasted for two days, but only the current day CAPs concentration was statistically significant. SDNN decreases were statistically significant for all three lags (0, 1, 2 days). The GAM regression analysis showed that only Ni produced a statistically significant effect for HR and SDNN.

6.2.2. Arrhythmia

Epidemiologic and toxicological studies presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provided some evidence of arrhythmia following exposure to PM. However, a positive association between PM and ventricular arrhythmias among patients with implantable cardioverter defibrillators was only observed in one study conducted in Boston, MA, while toxicological studies reported arrhythmogenesis in rodents following exposure to ROFA, DE, or metals. Recent epidemiologic studies have confirmed the findings of PM-induced ventricular arrhythmias in Boston, MA, and have also reported increases in ectopic beats in studies conducted in the Midwest and Pacific Northwest regions of the U.S. In addition, two studies from Germany have demonstrated positive associations between traffic and combustion particles and changes in repolarization parameters among patients with IHD. Findings of recent toxicological studies are mixed, with both demonstrated decreases and increases in frequency of arrhythmia following exposure to CAPs.

6.2.2.1. Epidemiologic Studies

Studies of Arrhythmias Using Implantable Cardioverter Defibrillators

One study reviewed in the 2004 PM AQCD assessed the effect of short-term fluctuations in $PM_{2.5}$ on ventricular arrhythmias and several recent studies examining this relationship have been conducted. Ventricular ectopy and arrhythmia include ventricular premature beats (VPBs), ventricular tachycardia (VT), and ventricular fibrillation (VF). VPBs are spontaneous beats originating from either the right or left ventricles. VT refers to three or more VPBs in succession at a rate of 100 beats per minute or greater, while VF is characterized by rapid and disorganized ventricular electrical activation incapable of generating an organized mechanical contraction or cardiac output. AF is the most common type of arrhythmia. In this condition, ectopic electrical impulses arising in the atria or pulmonary veins, i.e., outside their normal anatomic origin (the sinoatrial node), can result in atrioventricular dilatation, dysfunction, and/or thromboembolism. Despite being common, clinical and subclinical forms of AF are associated with reduced functional status and quality of life. Moreover, the arrhythmia accounts for a large proportion of ischemic stroke (Laupacis et al., 1994, 190901; Prystowsky et al., 1996, 156031) and is a strong risk factor for CHF (Roy et al., 2009, 190902), contributing to both cardiovascular disease (CVD) and all-cause mortality (Kannel et al., 1983, 156623).

Ventricular arrhythmia is commonly associated with myocardial infarction, heart failure, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease. Pathophysiologic mechanisms underlying this established cause of sudden cardiac death include activators and facilitators of arrhythmia, such as electrolyte abnormalities, modulation of the ANS, membrane channels, gap junctions, oxidant stress, myocardial stretch and ischemia.

Previously, Peters et al. (2000, 011347) conducted a pilot study in Boston, MA to examine the association between short-term changes in ambient air pollutant concentrations and increased risk of ventricular arrhythmias, among a cohort of patients with implantable cardioverter defibrillators (ICD). ICDs continuously monitor cardiac rhythm and upon detection of an abnormal rhythm (i.e., rapid HR), they can be programmed to deliver pacing and/or shock therapy to restore normal sinus rhythm. Those abnormal rhythms that are most severe or rapid are assumed to be due to VT or VF (i.e., life-threatening arrhythmias), and are thus treated with electric shock. These ICD devices also store information on each abnormal rhythm detected, including the date, time, and therapy given. Thus, using the date and time of those arrhythmias resulting in electric shock, Peters et al. (2000,

011347) reported an increased risk of ICD shock associated with mean NO_2 concentration in the previous two days. Among subjects with frequent events (10 or more during 3 yr of follow-up) an increased risk of ICD shock was also associated with interquartile range increases in CO, NO_2, $PM_{2.5}$, and BC in the previous 2 days. Several studies were conducted to confirm these findings. The study characteristics, as well as the reported effect estimates and 95% CI associated with each PM metric, are shown in Table 6-2.

Dockery et al. (2005, 078995; 2005, 090743) conducted a follow-up study of ICD patients living in eastern Massachusetts and followed subjects for a longer period of time (up to 7 yr). They were the first to review the ECG, classify each ICD-detected arrhythmia (e.g., ventricular arrhythmia, VF, atrial tachycardia, sinus tachycardia, etc.), and include only ventricular arrhythmias (VF or VT; excluding supraventricular arrhythmias). In single-pollutant models using generalized estimating equations, increased risks of confirmed ventricular arrhythmias were associated with IQR increases in every pollutant ($PM_{2.5}$, BC, SO_4^{2-}, NO_2, SO_2, O_3, and PNC). Among those with a prior ventricular arrhythmia in the past three days, interquartile range increases in 2-calendar-day mean $PM_{2.5}$, NO_2, SO_2, CO, O_3, SO_4^{2-}, and BC concentrations were all associated with significant and markedly higher risks of ventricular arrhythmia than among those without a prior arrhythmia. The pollutants associated with increased risk of ventricular arrhythmia implicate traffic pollution.

Rich et al. (2005, 079620) conducted a case-crossover analysis of these same data to investigate moving average pollutant concentrations lagged <48 h. They reported an increased risk of ventricular arrhythmia associated with mean $PM_{2.5}$ and O_3 concentrations in the 24 h before the arrhythmia. Each pollutant effect appeared independent in two pollutant models. In single-pollutant models, NO_2 and SO_2 were associated with increased risk, but when included in two pollutant models with $PM_{2.5}$, only $PM_{2.5}$ remained associated with increased risk. They did not, however, find evidence of a more acute arrhythmic response to pollution (i.e., larger risk estimates associated with moving averages <24 h before arrhythmia detection). In an ancillary case-crossover analysis of data from the Boston ICD study, Rich et al. (2006, 088427) identified 91 confirmed episodes of paroxysmal AF among 29 subjects. In single pollutant models, they reported a significantly increased risk of AF associated with mean O_3 and $PM_{2.5}$ concentrations in the hour before the arrhythmia and BC concentration in the 24 h before the arrhythmia.

Rich et al. (2006, 089814) conducted another case-crossover study in the St. Louis, MO metropolitan area. Using the same methods as in Boston, they reported increased risk of ventricular arrhythmia associated with mean SO_2 concentration in the 24 h before the arrhythmia, but not $PM_{2.5}$ (in single-pollutant models). Again, they found no evidence of an arrhythmic response with moving average pollutant concentrations <24 h before the arrhythmia.

In Vancouver, Canada, Vedal et al. (2004, 055630) did not find increased risk of ICD shocks associated with increases in any pollutant concentration (PM_{10}, O_3, SO_2, NO_2, and CO). Secondary analyses among those subjects with two or more discharges per year, and analyses stratified by season were also null for PM_{10}, although an association with SO_2 (lag 2 days) was observed. A case crossover analysis of these same data examining additional particle pollutant concentrations available for a shorter time frame (e.g., $PM_{2.5}$, SO_4^{2-}, EC, and OC) also found no increased risk of ICD shock associated with any pollutant (Rich et al., 2004, 055631).

The largest ICD study to date examined the risk of ventricular arrhythmias associated with increases in the daily concentration of numerous PM and gaseous pollutants in Atlanta, GA (Metzger et al., 2007, 092856) (see Table 6-2 for specific pollutants evaluated). Similar to Vedal et al. (2004, 055630), they did not find significant or consistently increased risk of a ventricular arrhythmia associated with any IQR increase in mean daily PM or gaseous pollutant concentration at any lag examined.

Ljungman et al. (2008, 180266) conducted a similar study, using case-crossover methods, on ICD patients in Gothenburg and Stockholm, Sweden. They investigated the triggering of confirmed ventricular arrhythmias by ambient PM_{10} and NO_2 concentrations, and reported increased relative odds of ventricular arrhythmia associated with each 10 $\mu g/m^3$ increase in the 2-h ma PM_{10} concentration (OR = 1.22 [95% CI: 1.00-1.51]), with a smaller non-significant risk associated with each 10.3 $\mu g/m^3$ increase in the 24-h ma PM_{10} concentration (OR = 1.23 [95% CI: 0.87-1.73]). The NO_2 and $PM_{2.5}$ effect estimates were much smaller and not statistically significant. Effect estimates were larger for events occurring near the air pollution monitors in Gothenburg (compared to Stockholm).

Albert et al. (2007, 156201), although not investigating associations with ambient pollution, conducted a case-crossover study of the association between ventricular arrhythmia and traffic

exposure in the hours before the arrhythmia. They reported an increased risk of ventricular arrhythmia associated with traffic exposure or driving in the previous hour. They hypothesized that this increased risk was due to either a stress response from being in a car in heavy traffic, or from traffic-generated air pollution, or a combination of both.

Table 6-2. Epidemiologic studies of ventricular arrhythmia and ambient PM concentration, in patients with implantable cardioverter defibrillators.

Reference	Outcome and Sample Size	Study Design and Analytic Method	Copollutants	PM Metric	Ambient Concentration	Lag and its Increment Units	OR	95% Confidence Interval
Dockery et al. (2005, 078995; 2005, 090743) Eastern MA	N=670 days with ≥ 1 confirmed ventricular arrhythmias among n=84 subjects	Generalized estimating equations Lags Evaluated: 2 calendar day means	NO_2, CO, SO_2, O_3	$PM_{2.5}$	Daily Median: 10.3 µg/m^3	2 day 6.9 µg/m^3	1.08	0.96, 1.22
				BC	Daily Median: 0.98 µg/m^3	2 day 0.74 µg/m^3	1.11	0.95, 1.28
				Sulfate	Daily Median: 2.55 µg/m^3	2 day 2.04 µg/m^3	1.05	0.92, 1.20
				PNC	Daily Median: 29,300 particles/cm^3	2 day 19,120 particles/cm^3	1.14	0.87, 1.50
Rich et al. (2005, 079620) Eastern MA	N=798 confirmed ventricular arrhythmias among n=84 subjects	Time-stratified case--crossover study. Conditional logistic regression. Lags evaluated: 3, 6, 24, 48-h ma	NO_2, CO, SO_2, O_3	$PM_{2.5}$	Daily Median: 9.8 µg/m^3	24-h ma 7.8 µg/m^3	1.19	1.02, 1.38
				BC	Daily Median: 0.94 µg/m^3	24-h ma 0.83 µg/m^3	0.93	0.74, 1.18
Rich et al. (2006, 089814) St. Louis metro area	N=139 confirmed ventricular arrhythmias among n=56 subjects	Time-stratified case-crossover study. Conditional logistic regression. Lags Evaluated: 6, 12, 24, 48-h ma	NO_2, CO, SO_2, O_3	$PM_{2.5}$	Daily Median: 16.2 µg/m^3	24-h ma 9.7 µg/m^3	0.95	0.72, 1.27
				EC	Daily Median: 0.6 µg/m^3	24-h ma 0.5 µg/m^3	1.18	0.93, 1.50
				Organic Carbon	Daily Median: 4.0 µg/m^3	24-h ma 2.3 µg/m^3	1.08	0.81, 1.43
Vedal et al. (2004, 055630) Vancouver, BC, Canada	N=257 days with ≥ 1 ICD shock among n=50 subjects	Generalized estimating equations Lags Evaluated: 0, 1, 2, 3 daily ma	NO_2, CO, SO_2, O_3	PM_{10}	Daily Median: 11.6 µg/m^3	Lag Day 0 5.6 µg/m^3	1.00*	0.82, 1.19*
Ljungman et al. (2008, 180266) Gothenburg and Stockholm, Sweden	N=114 ventricular arrhythmias among 73 subjects. 211 total subjects were followed.	Conditional logistic regression Lags evaluated: 2 h, 24 h	NO_2	PM_{10},	Median Gothenburg 2 h: 18.95 µg/m^3 24 h: 19.92 µg/m^3 Stockholm 2 h: 14.62 µg/m^3 24 h: 15.23 µg/m^3	2-h ma: 14.16 µg/m^3 24-h ma: 11:49 µg/m^3	2 h: 1.31 24 h: 1.24	1.00, 1.72 0.87, 1.76
				$PM_{2.5}$	Median Stockholm µg/m^3 2 h: 9.17 24 h: 9.49 µg/m^3	2-h ma: 6.69 µg/m^3 24-h ma: 5.27 µg/m^3	2 h: 1.23 24 h: 1.28	0.84, 1.80 0.90, 1.84
Rich et al. (2004, 055631) Vancouver, BC, Canada	N=77 to 98 days with ≥ 1 ICD shock among n=34 subjects	Ambi-directional case-crossover study. Conditional logistic regression Lags Evaluated: 0, 1, 2, and 3 day ma	NO_2, CO, SO_2, O_3	$PM_{2.5}$	Daily Mean: 8.2 µg/m^3	Lag Day 0 5.2 µg/m^3	1.0†	0.9, 1.1†
				PM_{10}	Daily Mean: 13.3 µg/m^3	Lag Day 0 7.4 µg/m^3	0.9†	0.5, 1.5†
				EC	Daily Mean: 0.8 µg/m^3	Lag Day 0 0.4 µg/m^3	1.1†	0.9, 1.3†
				Organic Carbon	Daily Mean: 4.5 µg/m^3	Lag Day 0 2.2 µg/m^3	1.1†	0.9, 1.3†
				Sulfate	Daily Mean: 1.3 µg/m^3	Lag Day 0 0.9 µg/m^3	0.9†	0.7, 1.2†

Reference	Outcome and Sample Size	Study Design and Analytic Method	Copollutants	PM Metric	Ambient Concentration	Lag and its Increment Units	OR	95% Confidence Interval
Metzger et al. (2007, 092856) Atlanta, GA	N=6287 confirmed ventricular arrhythmias among n=518 subjects	Generalized estimating equations Lags Evaluated: 0, 1, and 2 day ma	NO_2, CO, SO_2, O_3	$PM_{2.5}$	Daily Median: 16.2 μg/m^3	24-h ma 10 μg/m^3	1.00	0.95, 1.0
				PM_{10}	Daily Median: 26.4 μg/m^3	24-h ma 10 μg/m^3	1.00	0.97, 1.03
				$PM_{10-2.5}$	Daily Median: 8.7 μg/m^3	24-h ma 5 μg/m^3	1.03	1.00, 1.07
				$PM_{2.5}$ EC	Daily Median: 1.4 μg/m^3	24-h ma 1 μg/m^3	1.01	0.98, 105
				$PM_{2.5}$ OC	Daily Median: 3.9 μg/m^3	24-h ma 2 μg/m^3	1.01	0.98, 1.03
				$PM_{2.5}$ SO_4^{2-}	Daily Median: 4.1 μg/m^3	24-h ma 5 μg/m^3	0.99	0.93, 1.06
				$PM_{2.5}$ water soluble elements	Daily Median: 0.022 μg/m^3	24-h ma 0.03 μg/m^3	0.95	0.90, 1.00

Estimated from Figure 3 Vedal et al. (2004, 055630).† Estimated from Figure 3 Rich et al. (2004, 055631)

Summary of Epidemiologic Studies of Arrhythmias using ICDs

Since 2004, only two studies (in Boston and Sweden), reported adverse associations of $PM_{2.5}$, other size fractions and components with ICD-detected ventricular arrhythmias (Dockery et al., 2005, 078995; Dockery et al., 2005, 090743; Ljungman et al., 2008, 180266; Rich et al., 2005, 079620). Studies of ICD-detected ventricular arrhythmias conducted elsewhere did not report associations (Dusek et al., 2006, 155756; Metzger et al., 2007, 092856; Rich et al., 2004, 055631; Vedal et al., 2004, 055630) nor was an association observed in a study of PM_{10} and ICD shock in Vancouver, Canada (Vedal et al., 2004, 055630). A range in exposure lags was evaluated in the Boston study (3 h-3 days) (Dockery et al., 2005, 078995; Dockery et al., 2005, 090743; Rich et al., 2005, 079620) and Sweden study (2 h and 24 h) (Ljungman et al., 2008, 180266). Reasons for the inconsistent findings may include differing degrees of exposure misclassification within each study or city due to differences in PM composition and pollutant mixes (e.g., less transition metals and sulfates in the Pacific Northwest than the Northeast U.S.), and differences in the size of study areas (Boston: within 40 km of $PM_{2.5}$ monitoring site; Vancouver: Lower Mainland of British Columbia 90 km east of Vancouver). In addition, Rich et al. (2005, 079620) reported that use of the mean pollutant concentration from the specific 24 h before the arrhythmia rather than just the day of the arrhythmia, resulted in less exposure misclassification and less bias towards the null, possibly explaining the lack of association when using just the day of ICD discharge and daily PM concentrations.

Ectopy Studies Using ECG Measurements

A few panel studies have used ECG recordings to evaluate associations between ectopic beats (ventricular or supraventricular) and mean PM concentrations in the previous hours and/or days (Berger et al., 2006, 098702; Ebelt et al., 2005, 056907; Liao et al., 2009, 199519; Sarnat et al., 2006, 090489).

Ectopic beats are defined as heart beats that originate at a location in the heart outside of the sinus node. They are the most common disturbance in heart rhythm. Ectopic beats are usually benign, and may present with or without symptoms, such as palpitations or dizziness. Such beats can arise in the atria, AV node, conduction system or ventricles. When the origin is in the atria the beat is called an atrial or supraventricular ectopic beat. When such a beat occurs earlier than expected it is referred to as a premature supraventricular or atrial premature beat. Likewise, when the origin is in

the ventricle the beat is defined as a ventricular ectopic beat, or when early a premature ventricular beat. When three or more occur ectopic beats occur in succession, this is called a non-sustained run of either supraventricular (atrial) or ventricular origin. When the rate of the run is greater than 100 beats per minute it is defined as a tachycardia. Sustained VT are the arrhythmias investigated in the ICD studies described above.

Using data from the WHI done in 59 U.S. exam sites in 24 cities, Liao et al. (2009, 199519) estimated mean $PM_{2.5}$ and PM_{10} concentrations at the addresses of 57,422 study subjects undergoing ECG monitoring. They then estimated the risks of ventricular and supraventricular ectopy during that 10-s ECG recording associated with increases in mean PM_{10} and $PM_{2.5}$ concentrations on the same day and previous 2 days, as well as over the previous 30 days. Mean $PM_{2.5}$ and PM_{10} concentrations during the study period were 13.8 and 27.5 $\mu g/m^3$, respectively. Using a 2-stage random effects model, they reported that among smoking subjects, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration on lag day 1 was associated with a significantly increased risk of ventricular ectopy (OR = 2.0 [95% CI: 1.32-3.3]). Similarly, each 10 $\mu g/m^3$ increase in lag 1 PM_{10} concentration was associated with an increased risk of ventricular ectopy (OR = 1.32 [95% CI: 1.07-1.65]). The lag day 2 $PM_{2.5}$ risk estimate was similar in size, but not statistically significant. There were no associations between PM_{10}, $PM_{2.5}$ and supraventricular ectopy among smokers or non-smokers, and no association with any PM metric and ventricular ectopy among non-smokers.

Sarnat et al. (2006, 090489) conducted a panel study among 32 nonsmoking older adults residing in Steubenville, OH. In this study, the median daily $PM_{2.5}$, SO_4^{2-}, and EC concentrations were 17.7, 5.7, and 1.0 $\mu g/m^3$, respectively. They used logistic regression models to examine lagged effects of 1- to 10-day ma concentrations of $PM_{2.5}$, SO_4^{2-}, EC, O_3, NO_2, and SO_2. Supraventricular ectopy and ventricular ectopy were measured using Holter monitors during a 30-minute protocol of alternating rest in the supine position, standing, walking and paced breathing. In single-pollutant models, each 10.0 $\mu g/m^3$ increase in 5-day mean $PM_{2.5}$ concentration was associated with increased risk of supraventricular ectopy (OR = 1.42 [95% CI: 0.99-2.04]), but not ventricular ectopy (OR = 1.02 [95% CI: 0.63-1.65]). Similarly, increased risk of supraventricular ectopy, but not ventricular ectopy, was associated with each interquartile range increase in 5-day mean SO_4^{2-} and O_3 concentration.

Ebelt et al. (2005, 056907) conducted a repeated measures panel study of 16 patients with COPD in Vancouver, British Columbia. Their goal was to evaluate the relative impact of ambient and non-ambient exposures to $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ on several health measures. Subjects wore an ambulatory ECG monitor for 24 h to record heart rhythm data and ascertain supraventricular ectopic beats. The mean $PM_{2.5}$ concentration during this study was 11.4 $\mu g/m^3$. Using mixed models with random subjects effects to investigate only same-day PM concentrations, an increase in supraventricular ectopic beats was associated with same day ambient exposures to each PM size fraction.

Berger and colleagues (2006, 098702) conducted a panel study of 57 men with coronary heart disease living in Erfurt, Germany. Using 24-h ECG measurements made once every 4 wk, they studied associations between runs of supraventricular and ventricular tachycardia and lagged concentrations of $PM_{2.5}$, UFP (0.01-0.1 µm), ACP (0.1-1.0 µm), SO_2, NO_2, CO, and NO. Using GAMs, as well as Poisson and linear regression models, they reported increases in supraventricular tachycardia and the number of runs of ventricular tachycardia associated with 5-day mean $PM_{2.5}$, UFP counts, and ACP counts. They found these associations at all lags evaluated (during ECG recording, 0-23 h before, 24-47 h before, 48-71 h before, 72-95 h before, and 5-day mean), but the largest effect estimates were generally associated with the 24- to 47-h mean and the 5-day mean.

Summary of Ectopy Studies Using ECG Measurements

Four studies of ectopic beats and runs of supraventricular and ventricular tachycardia, captured using ECG measurements, all report at least one positive association. Further, they report findings in regions other than Boston and Sweden (i.e., Midwest U.S., Pacific Northwest, 24 U.S. cities, and Erfurt, Germany). A range of lags and/or moving averages were investigated (0-30 days) with the strongest effects observed for either the 5-day mean, same day, or 1-day lagged PM concentrations. Taken together, these ICD studies and ectopy studies provide evidence of an arrhythmic response to PM, although further study is needed to understand the variable ICD study findings.

ECG Abnormalities Associated with the Modulation of Repolarization

No reported investigations of the relationship of PM concentration and ECG abnormalities indicating arrhythmia were conducted prior to 2002 and thus were not included in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Abnormalities in the myocardial substrate, myocardial vulnerability, and resulting repolarization abnormalities are believed to be key factors contributing to the development of arrhythmogenic conditions such as those discussed above. These abnormalities include ECG measures of repolarization such as QT duration (time for depolarization and repolarization of the ventricles), T-wave complexity (a measure of repolarization morphology), and T-wave amplitude (height of the T-wave). Abnormalities in repolarization may also identify subjects potentially at risk of more serious events such as sudden cardiac death (Atiga et al., 1998, 156231; Berger et al., 1997, 155688; Chevalier et al., 2003, 156338; Okin et al., 2000, 156002; Zabel et al., 1998, 156176). Recent studies of changes in these measures following acute increases in air pollution are described below.

Two studies conducted in Erfurt, Germany, (Henneberger et al., 2005, 087960; Yue et al., 2007, 097968) examined the association between measures of repolarization (QT duration, T-wave complexity, T-wave amplitude, T-wave amplitude variability) and particulate air pollution. Henneberger et al. (2005, 087960) conducted a panel study of 56 males with IHD. Each subject was measured every 2 wk for 6 mo. During the study, the median daily $PM_{2.5}$, EC, and OC concentrations were 14.9, 1.8, and 1.4 $\mu g/m^3$,respectively. The median count of UFP was 11,444 particles/cm^3, while the median count of ACP (0.1-1.0 μm) was 1,238 particles/cm^3. They examined the change in these ECG parameters associated with the mean pollutant (UFP, ACP, $PM_{2.5}$, OC, and EC) concentrations 0-5, 6-11, 12-17, 18-23, and 0-23 h before, and 2-5 days before the ECG measurement. Significant decreases in T-wave amplitude were associated with $PM_{2.5}$ mass, UFP, and ACP. Each 16.4 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentration in the previous 5 h was associated with a 6.46 μV decrease in T-wave amplitude (95% CI: -10.88 to -2.04). Each 0.7 $\mu g/m^3$ increase in the mean OC concentration in the previous 5 h was associated with a 4.15 ms increase in QT interval (95% CI: 0.22-8.09). There was a similar sized effect for 24-h mean OC concentration. Significant increases in the variability of T-wave complexity were also associated with acute increases in EC and OC concentration.

Yue et al. (2007, 097968) then used positive matrix factorization to identify 5 sources of ambient PM (airborne soil, local traffic-related UFP, combustion-generated aerosols, diesel traffic-related particles, and secondary aerosols). Using similar statistical models, they examined the association between these same repolarization changes and incremental increases in the mean concentration of each particle source in the 24 h before the ECG measurement. They also examined associations with CRP and vWF concentrations in the blood. Both UFP from local traffic and diesel particles from traffic had the strongest associations with repolarization parameters.

Summary of Epidemiologic Studies of ECG Abnormalities Associated with the Modulation of Repolarization

These two analyses demonstrate associations between PM pollution and repolarization changes, at lags of 5 h to 2 days. Moreover, the findings from the Yue et al. (2007, 097968) study demonstrate a potential role of traffic particles/pollution.

6.2.2.2. Toxicological Studies

The ECG of animal research models frequently exhibit different characteristics than that of humans. Mice and rats are notable in this regard, as they do not have an isoelectric ST-segment typical of larger species, likely owing to their rapid heart rates (~600 and ~350 bpm, respectively) and repolarizing currents. However, the ultimate function of the pumping heart is conserved and reflected by the ECG in a remarkably consistent manner across species. Thus, atrial depolarization causes an electrical inflection represented by the P-wave, ventricular depolarization elicits the QRS complex, and the T-wave represents repolarization of the ventricles.

The earliest indication that there may be cardiovascular system effects of PM came from ECG studies in susceptible animal models (rats with pulmonary hypertension and dogs with coronary occlusion), which were summarized in the 2004 PM AQCD (U.S. EPA, 2004, 056905). However, a study of dogs exposed to ROFA did not demonstrate ECG changes, perhaps due to differences in disease state, as these were the oldest dogs in the colony with signs of preexisting, naturally occurring heart disease (Muggenburg et al., 2000, 010279). Much of the research conducted since the release of the last PM AQCD has been focused on exploring susceptibility or varying exposure methodologies, with little new evidence into the mechanisms for ECG changes of inhaled PM.

CAPs

Wellenius et al. (2004, 087874) used a susceptible model that was previously shown to produce significant results with exposures to ROFA (Wellenius et al., 2002, 025405) to examine ECG-related $PM_{2.5}$ effects. Using an anesthetized model of post-infarction myocardium sensitivity, Wellenius and colleagues tested the effects of Boston, MA CAPs on the induction of spontaneous arrhythmias in SD rats (1 h; mean mass concentration 523.11 $\mu g/m^3$; range of mass concentration 60.3-2202 $\mu g/m^3$). Decreased (67.1%) VPB frequency was observed during the post-exposure period in rats with a high number of pre-exposure VPB. No interaction was observed with coexposure to CO (35 ppm). CAPs number concentration or the mass concentration of any single element did not predict VPB frequency. In a follow-up publication, a decreased number of supraventricular ectopic beats (SVEB) was reported with CAPs (mean mass concentration 645.7 $\mu g/m^3$) (Wellenius et al., 2006, 156152). Furthermore, an increase in CAPs number concentration of 1,000 particles/cm^3 was associated with a 3.3% decrease in SVEB frequency. The findings of decreased ventricular arrhythmia differ from those observed following ROFA exposure in the same animal model in that an increased frequency of premature ventricular complexes was observed with ROFA, albeit the ROFA exposure concentration was >3,000 $\mu g/m^3$ (Wellenius et al., 2002, 025405). It is difficult to directly compare the results of these studies due to differences in exposure concentrations and particle type, but collectively they may suggest an important role for the soluble components of PM, including transition metals, as only ROFA induced increases in ventricular arrhythmia occurrence.

In older rats (Fisher 344; ~18 months) exposed to $PM_{2.5}$ CAPs in Tuxedo, NY (4 h; mean concentration 180 $\mu g/m^3$; August 2000), the frequency of delayed beats was greater than in rats exposed to air (Nadziejko et al., 2004, 055632). The majority of these beats were characterized as pauses (a delay of 2.5 times the adjacent interbeat intervals) rather than premature beats. When the same animals were exposed to generated UF carbon particles (single-day concentrations 500 and 1280 $\mu g/m^3$) or SO_2 (1.2 ppm), no significant differences were observed in arrhythmia frequency between air controls and exposed animals. The authors also report using the same protocol for young WKY rats (concentration 215 $\mu g/m^3$) and very few arrhythmias were observed, thus precluding statistical analysis. The results of this study indicate (1) involvement of the sino-atrial node, as the observed arrhythmias were mostly of a delayed nature; and (2) particle size and $PM_{2.5}$ constituents may play a role in these effects.

Diesel and Gasoline Exhaust

Anselme and colleagues (2007, 097084) exposed rats with and without induced CHF to DE for 3 h (PM concentration 500 $\mu g/m^3$; mass mobility diameter 85 nm; NO_2 1.1 ppm; CO 4.3 ppm). While no dramatic change was noted in HR, prominent increases in the incidence of VPB were observed in CHF rats, which lasted at least 4-5 h after exposure ceased. The duration of VPB attributable to diesel exposure in CHF rats lasted much longer than the rMSSD change (>5 h post-exposure), indicating that the HRV response was not driving the increased arrhythmia incidence. It is interesting to contrast the work of Anselme with the studies by Wellenius et al. (2002, 025405; 2004, 087874; 2006, 156152), as the arrhythmia incidence in the acute infarction model was greatest with ROFA, while the CHF model demonstrated sensitivity to DE exposure. However, several differences in the research designs preclude strong comparisons.

Using $ApoE^{-/-}$ mice on a high-fat diet as a model of pre-existing coronary insufficiency (Caligiuri et al., 1999, 157365), Campen and colleagues studied the impact of inhaled diesel and gasoline exhaust and road dust (6 h/day×3 day) on ECG morphology (Campen et al., 2005, 083977;

2006, 096879). Moreover, a high efficiency particle filter was used to compare the whole exhaust with an atmosphere containing only the gaseous components. For gasoline exhaust, the PM-containing atmosphere (PM mean concentration 61 μg/m^3; PNMD 15 nm; NO_X mean concentration 18.8 ppm; CO mean concentration 80 ppm) induced T-wave morphological alterations, while the PM-filtered atmosphere did not (Campen et al., 2006, 096879). Resuspended road dust ($PM_{2.5}$), at up to 3500 μg/m^3 had no impact on ECG. For DE (PM mean concentration 512, 770, or 3,634 μg/m^3; MMD 100 nm, CMD 80 nm; NO_X mean concentration 19, 105, 102 ppm for low whole exhaust, high PM filtered, and high whole exhaust, respectively), dramatic bradycardia, decreased T-wave area, and arrhythmia (atrioventricular-node block and VPB) were only observed in mice exposed to high filtered and high whole exhaust (Campen et al., 2005, 083977). These effects remained after filtration of PM, suggesting that the gaseous components of the whole DE drove the cardiovascular findings. The diesel- and gasoline-induced ECG changes contrast, in that the gasoline exhaust required particles to induce T-wave changes, whereas the DE did not require PM to cause an effect on ECG. However, the differing responses could be attributable to higher PM concentrations in the whole DE.

Summary of Toxicological Study Findings for ECG Abnormalities

The above toxicological studies demonstrate mixed results for arrhythmias, which may be somewhat attributable to the different disease models used. Wellenius et al. (2004, 087874; 2006, 156152) showed decreased frequency of VPB and SVEB following $PM_{2.5}$ CAPs exposure in rats with induced MI (>12 h prior to exposure). One study reported increased frequency of premature beats in older rats exposed to CAPs, which were not observed with UF carbon particles (Nadziejko et al., 2004, 055632). Rats with a MI model of CHF (3-mo recovery) had increased incidence of VPB with DE exposure (Anselme et al., 2007, 097084). As for ECG morphology changes, T-wave alterations were reported for gasoline exhaust that were absent when the PM was filtered (Campen et al., 2006, 096879). However, for DE, increased atrioventricular-node block, VPB, and decreased T-wave area were observed with whole exhaust and remained after filtration of PM, indicating that the gases were responsible for the effects (Campen et al., 2005, 083977).

6.2.3. Ischemia

Although no evidence from epidemiologic or controlled human exposure studies of PM-induced myocardial ischemia was included in the 2004 PM AQCD (U.S. EPA, 2004, 056905), one toxicological study was cited that observed ST-segment changes in dogs following a 3-day exposure to CAPs. In epidemiologic studies published since the 2004 PM AQCD (U.S. EPA, 2004, 056905), associations have been demonstrated between PM and ST-segment depression, and one new controlled human exposure study reported significant increases in exercise-induced ST-segment depression among men with prior MI following a controlled exposure to DE. Results from recent toxicological studies confirm the findings presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) and provide coherence and biological plausibility for the effects observed in epidemiologic and controlled human exposure studies.

6.2.3.1. Epidemiologic Studies

ECG Changes Suggestive of Increased Ischemia

The ST-segment duration is typically in the range of 0.08-0.12 s (80-120 ms). The direction of the ST change is influenced by the extent of the acute myocardial injury. If the ischemia or infarction is transmural, i.e., penetrates the entire thickness of the ventricular wall, it usually causes ST-segment elevation, while ischemia confined primarily to the ventricular endocardium often causes ST-segment depression. Clinical ischemia is typically defined to include a downsloping ST segment depression of ≥0.1 mV (ECG voltages are calibrated such that 1 mV equals 10 mm in the vertical direction). The studies described below evaluate a range of ECG changes suggestive of increased

ischemia including subclinical ST segment depressions (e.g. less than 0.1 mV or 1 mm) in relation to ambient PM concentration.

In a large study of the WHI Trial, Zhang et al. (2009, 191970) examined the change and risk of subclinical ST-segment abnormalities, T-wave abnormalities, and T-wave amplitude associated with ambient $PM_{2.5}$ concentrations on the same and previous 6 days. Using logistic regression, each 10 $\mu g/m^3$ increase in the mean $PM_{2.5}$, on lag days 0-2, was associated with a 4% (95% CI: -3 to 10) increase in the relative odds of a ST-segment abnormality, and a 5% (95% CI: 0-9) increase in the relative odds of a T-wave abnormality.

Gold et al. (2005, 087558) studied 24 elderly residents of Boston, MA (aged 61-88 yr) residing at or near an apartment complex that was ~ 0.5 km from an air pollution monitoring station. A protocol of continuous Holter monitoring including 5 min of rest, 5 min of standing, 5 min of outdoor exercise, 5 min of rest, and then 20 cycles of paced breathing was done up to 12 times for each subject (n = 269 ECG measurements for analysis). From these ECG measurements, they identified occurrences of ST-segment depression and examined whether mean BC, CO, and $PM_{2.5}$ concentrations in the previous 5 and 12 h were associated with ST-segment depression. The median 5-h and 12-h mean BC concentrations were 1.28 and 1.14 $\mu g/m^3$, respectively ($PM_{2.5}$ concentrations are in Table 6-3). The mean BC concentrations in the 5 and 12 h before testing predicted ST-segment depression in most portions of the protocol. However, these effects were strongest in the post-exercise periods. For example, during the post-exercise rest period, each 10th-90th percentile increase (1.59 $\mu g/m^3$) in the mean 5-h BC concentration was associated with a -0.11 mm ST-segment depression (95% CI: -0.18 to -0.05). In two pollutant models, CO did not appear to confound this association. $PM_{2.5}$ was not associated with ST-segment depression in this study. These findings suggest traffic-generated particulate pollution may be associated with ST-segment depression.

Previously, Pekkanen et al. (2002, 035050) conducted a panel study of 45 subjects with stable coronary heart disease living in Helsinki, Finland. Each subject had biweekly sub-maximal exercise testing for 6 mo (n = 342 exercise tests with 72 exercise-induced ST-segment depressions). The median daily count of ACP (ACP: 0.1-1.0 µm) was 1,200 particles/cm^3 ($PM_{2.5}$ concentrations are found in Table 6-3). They examined the risk of ST-segment depression associated with mean pollutant concentrations (UFP, ACP, PM_1, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, CO) in the previous 24 h, and the 3 previous lagged 24-h periods. Each 7.9 $\mu g/m^3$ increase in mean $PM_{2.5}$ concentration, lagged 2 days, was associated with significantly increased risk of ST-segment depression >0.1 mV (OR: 2.84 [95% CI: 1.42-5.66]). Each 760 particles/cm^3 increase in the count of ACP, lagged 2 days, was also associated with significantly increased risk of ST-segment depression >0.1 mV (OR: 3.29 [95% CI: 1.57-6.92]). Similarly sized increased risks of ST-segment depression were also found for other particulate pollutants, including $PM_{10-2.5}$, PM_1, and UFP counts.

This same research group, then conducted a principal components analysis to identify five $PM_{2.5}$ sources (crustal, long range transport, oil combustion, salt, and local traffic) (Lanki et al., 2006, 088412). Using similar statistical models, each 1 $\mu g/m^3$ increase in "local traffic" particle concentration, lagged 2 days, was associated with increased risk of ST-segment depression (OR: 1.53 [95% CI: 1.19-1.97]). Similarly, each 1 $\mu g/m^3$ increase in "long-range transport" particle concentration was also associated with increased risk of ST-segment depression (OR: 1.11 [95% CI: 1.02-1.20]). No significant associations for other sources were reported for any lag time.

In Boston, Chuang et al. (2008, 155731) studied 48 patients with a prior percutaneous intervention following MI, acute coronary syndrome (ACS) without MI, or stable coronary artery disease without ACS,. Each patient had a 24-h ECG measurement up to four times during study follow-up. Using logistic regression, they estimated the risk of ST-segment depression of ≥0.1 mm, during 30-min segments, associated with increases in the mean $PM_{2.5}$, BC, CO, NO_2, O_3, and SO_2 concentration in the previous 24 h. Each 6.93 $\mu g/m^3$ increase in mean $PM_{2.5}$ concentration was associated with a significantly increased risk of ST-segment depression (OR = 1.50 [95% CI: 1.19-1.89]). Using linear additive models to estimate the change in ST level associated with the same $PM_{2.5}$ change, they observed a significant -0.031 mm change (95% CI: -0.042 to -0.019). In single pollutant models, risk estimates were of similar magnitude and statistically significant for BC, NO_2, and SO_2. In two pollutant models, however, $PM_{2.5}$ risk estimates were reduced to 1.0 in all models with BC, NO_2, and SO_2. In contrast, the risk estimates for BC, NO_2, and SO_2 remained elevated and statistically significant when modeled with $PM_{2.5}$.

In a panel study of 14 Helsinki resident, non-smoking, elderly subjects with coronary artery disease, Lanki et al. (2008, 191984) used logistic regression to report that each 10 $\mu g/m^3$ increase in personal $PM_{2.5}$ concentration in the previous hour was associated with a significantly increased risk

of ST-segment depression (OR = 3.26 [95% CI: 1.07-9.98]). In addition, each 10 μg/m^3 increase in outdoor mean $PM_{2.5}$ concentration in the previous 4 h was also associated with an increased risk (OR = 2.47 [95% CI: 1.05-5.85]). Last, the risk estimates for all time lags examined (1, 4, 8, 12, and 22 or 24 h) for all PM size fractions were increased, but none other than those described above were statistically significant.

Summary of Epidemiologic Study Findings for Ischemia

These studies demonstrate associations between $PM_{2.5}$ pollution and ST-segment depression at lags of 1 h-2 days. Moreover, these findings demonstrate a potential role for traffic (Chuang et al., 2008, 155731; Gold et al., 2005, 087558) and long-range transported $PM_{2.5}$ (Lanki et al., 2006, 089788). Mean and upper percentile concentrations reported in these studies are found in Table 6-3.

Table 6-3. PM Concentrations reported in epidemiologic studies ECG changes suggestive of ischemia.

Author	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
$PM_{2.5}$			
Zhang et al. (2009, 191970)	Mulitcity, US:WHI Clinical Trial	NR	NR
Pekkanen et al. (2002, 035050)	Helsinki, Finland	24-h avg: 10.6 (median)	75th: 16.0 Max: 39.8
Gold et al. (2005, 087558)	Boston, MA	5-h avg: 9.5 (median) 12-h avg: 9.8 (median)	5-h avg 90th: 25.6 Max: 41.0 12-h avg 90th: 25.9 Max: 35.6
Chuang et al. (2008, 155731)	Boston, MA	12-h avg: 9.91 (median) 24-h avg: 9.20 (median)	12-h avg 75th: 13.18 24-h avg max: 40.38
Lanki et al. (2008, 191984)	Helsinki, Finland	Personal 1-h avg: 11.5 (median) 4-h avg: 10.1 (median) 22-h avg: 9.3 (median) Outdoor 24-h avg: 12.5	Personal 1-h avg 75th: 17.2; Max: 746.3 4-h avg 75th: 15.7; Max 189.6 22-h avg 75th: 13.2; Max 52.9 Outdoor 24-h avg 75th: 17.7; Max: 30.5
$PM_{10-2.5}$			
Pekkanen et al. (2002, 035050)	Helsinki, Finland	24-h avg: 4.8 (median)	75th: 8.5 Max: 37.0

6.2.3.2. Controlled Human Exposure Studies

Diesel Exhaust

Among a group of 20 men with prior MI, Mills et al. (2007, 091206) found that DE (300 μg/m^3 particle concentration, median particle diameter 54 nm) significantly increased exercise-induced ischemic burden during exposure, calculated as the product of exercise duration and change in ST-segment amplitude. The mechanism by which DE induced the exacerbation of ischemic burden remains unclear, and appears to be unrelated to impaired vasodilation. However, the

authors suggest that this discrepancy may be due to the timing of the vascular assessment, as measures of blood-flow were taken 5 h after the observed increase in ischemic burden. Although it is reasonable to assume that the observed increase in ST-segment depression during exercise represents an increased magnitude of ischemia, it is important to note that there are other potential explanations for the ST change. For example, it is possible that the ST-segment depression could be secondary to heterogeneity of electrophysiological responses of particle exposure on the myocardium that is enhanced by the metabolic and ionic conditions associated with ischemia or increased HR. It is also important to note that the effects observed in this study cannot be conclusively attributed to the particles per se, as subjects were also exposed relatively high levels of NO (3.45 ppm), NO_2 (1.01 ppm), CO (2.9 ppm), and total hydrocarbons (2.8 ppm).

6.2.3.3. Toxicological Studies

CAPs

A study that examined ECG changes in dogs (female; retired mongrel breeder dogs) following $PM_{2.5}$ CAPs exposure in Boston, MA (mean mass concentration 345 μg/m^3; 9/2000-3/2001) and left anterior descending coronary artery occlusion as an indicator of myocardial ischemia reported changes in ST-segment (Wellenius et al., 2003, 055691). The experimental protocol was a 6-h exposure to CAPs via tracheostomy, followed by a preconditioning occlusion (5 min), rest interval (20 min), and the experimental occlusion (5 min). Increased ST-segment elevation was observed following $PM_{2.5}$ during the experimental occlusion period compared to filtered air. Furthermore, peak ST-segment elevation attributable to CAPs was reported with the experimental occlusion, which remained elevated 24 h post-exposure. Ventricular arrhythmias were rarely observed during occlusion and when observed, were unrelated to CAPs exposure. The results from this study support those previously observed (Godleski et al., 2000, 000738) and provides greater support that enhanced myocardial ischemia occurs relatively quickly (within hours) following PM exposure.

The Wellenius et al. (2003, 055691) study also attempted to link ST-segment changes with four CAPs elements (Si, Ni, S, and BC) as tracers of $PM_{2.5}$ sources in Boston. In the multivariate regression analyses, peak ST-segment elevation and integrated ST-segment change were significantly associated with only the mass concentration of Si (Si mean concentration 8.17 μg/m^3; Si concentration 2.31-13.93 μg/m^3). In the univariate regression analyses, Pb also demonstrated a significant association for both ST-segment measures, although the p-value was greater than that observed with Si.

A recent study in dogs (female mixed-breed canines) evaluated myocardial blood flow during myocardial ischemia following 5-h $PM_{2.5}$ Boston CAPs exposures (daily mean mass concentration 94.1-1556.8 μg/m^3; particle number concentration 3-69.3×10^3 particles/cm^3; BC concentration 1.3-32.0 μg/m^3) (Bartoli et al., 2009, 179904). Similar methods were used for the coronary occlusion and exposure method as Wellenius et al. (2003, 055691). Immediately following exposure, microspheres were injected (15 μm diameter) into the left atrium after 3 min of ischemia during the second occlusion. Post-mortem analysis of cardiac tissue and blood samples allowed for quantification of microspheres. CAPs-exposed dogs had decreased total myocardial blood flow and increased coronary vascular resistance during occlusion that was greatest in tissue within or near the ischemic zone. The rate-pressure product (product of HR and SBP) during occlusion was unchanged in animals exposed to CAPs, indicating that cardiac metabolic demand was not altered. The multilevel linear mixed models demonstrated that myocardial blood flow and coronary vascular resistance during occlusion were inversely and significantly associated with CAPs mass concentration, particle number concentration, and BC concentration, with the strongest effects observed with particle number concentration. The results of this study provide evidence that exacerbation of myocardial ischemia following PM exposure is due to reduced myocardial blood flow, perhaps via dysfunctional collateral vessels.

Intratracheal Instillation

Cozzi et al. (2006, 091380) exposed ICR mice to UF PM (100 µg IT instillation), followed by ischemia/reperfusion injury to the left anterior coronary artery 24 h later. The area-at-risk (the region of tissue perfused by the left anterior descending coronary artery) and the infarct size were measured 2 h following reperfusion, and while the area-at-risk was not affected by PM exposure, the infarct size was nearly doubled in mice who received UF PM. Increases in infarct size were associated with increased myocardial neutrophil density in the infarct zone and lipid peroxidation in the myocardium.

Summary of Toxicological Study Findings for Ischemia

The studies described above provide evidence that PM can induce greater myocardial responses following ischemic events, as demonstrated by, enhanced ischemia, decreased myocardial blood flow and increased coronary vascular resistance, and increased infarct size.

6.2.4. Vasomotor Function

The most noteworthy new cardiovascular-related revelation in the past six years with regards to PM exposure is that the systemic vasculature may be a target organ. The vasculature of all tissues is lined with endothelial cells that will naturally encounter any systemically absorbed toxin. The endothelium (1) maintains barrier integrity to ensure fluid compartmentalization; (2) communicates dilatory and constrictive stimuli to vascular smooth muscle cells; and (3) recruits inflammatory cells to injured regions. Smooth muscle cells lie within the layer of endothelium and are crucial to the regulation of blood flow and pressure. In states of injury and disease, both cell types can exhibit dysfunction and even pathological responses.

Endothelial dysfunction is a factor in many diseases and may contribute to the origin and/or exacerbation of perfusion-limited diseases, such as MI or IHD, as well as hypertension. Endothelial dysfunction is also a characteristic feature of early and advanced atherosclerosis. A primary outcome of endothelial dysfunction is impaired vasodilatation, frequently due to uncoupling of NOS. It is this uncoupling that appears central to impaired vasodilation and thus endothelial dysfunction.

One controlled human exposure study cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) reported a decrease in bronchial artery diameter (BAD) among healthy adults following exposure to CAPs in combination with O_3. Conclusions based on this finding were limited due to the concomitant exposure to O_3 as well as a lack of published results from epidemiologic and toxicological studies. Recent controlled human exposure studies have provided support to the findings described in the 2004 PM AQCD (U.S. EPA, 2004, 056905), with changes in vasomotor function observed following controlled exposures to DE and EC particles. In addition, epidemiologic studies have observed associations between PM and decreases in BAD and flow mediated dilatation (FMD) in healthy adults and diabetics. These findings are further supported by a large body of new toxicological evidence of impaired vasodilation following exposure to PM.

6.2.4.1. Epidemiologic Studies

O'Neill et al. (2005, 088423) examined the association between 2 measures of vascular reactivity, non-endothelium dependent nitroglycerin mediated reactivity and endothelium-dependent flow-mediated reactivity, and ambient mean particulate pollutant concentration ($PM_{2.5}$, SO_4^{2-}, BC, PNC) on the same and previous few days. They studied a panel of 270 subjects with diabetes or at risk for diabetes, who lived in the greater Boston metropolitan area. Using linear regression models, the change in vascular reactivity associated with moving average pollutant concentrations across the same and previous 5 days was estimated. Interquartile range (values not reported) increases in mean $PM_{2.5}$ concentration, BC concentration, and PNC over the previous 6 days were associated with decreased vascular reactivity among diabetics, but not among subjects at risk for diabetes. For SO_4^{2-}, the mean concentration on lag day 0, lag day 1, and the 3-day, 4-day, and 5-day ma all were associated with similarly sized reductions in both metrics of vascular reactivity. Among diabetics, each interquartile range increase in the mean SO_4^{2-} concentration over the previous 6 days was

associated with a 5.4% decrease in nitroglycerin-mediated reactivity (95% CI: -10.5 to -0.1) and flow-mediated reactivity (-10.7% [95% CI: -17.3 to -3.5]). Also among diabetics, each interquartile range increase in the mean $PM_{2.5}$ concentration over the previous 6 days was associated with a 7.6% decrease in nitroglycerin-mediated reactivity (95% CI: -12.8 to -2.1) and a non-significant 7.6% decrease in flow-mediated reactivity (95% CI: -14.9 to 0.4). Each interquartile range increase in the mean BC concentration over the previous 6 days was associated with a 12.6% decrease in flow mediated reactivity (95% CI: -21.7 to -2.4), but not nitroglycerin-mediated reactivity. PNC was associated with non-significant decreases in both measures. Effect estimates were larger for type 2 diabetics than type 1 diabetics.

Dales et al. (2007, 155743) conducted a panel study of 39 healthy volunteers who sat at 1 of 2 bus stops in Ottawa, Canada for 2 h. FMD of the brachial artery was measured immediately after the bus stop exposure, but not before. They examined the association between FMD and 2-h mean $PM_{2.5}$, PM_1, NO_2, and traffic density at the bus stop (vehicles/h). The authors report that each 30 $\mu g/m^3$ increase in 2-h mean $PM_{2.5}$ concentration was associated with a significant 0.48% reduction in FMD. This represented a 5% relative change in the maximum ability to dilate.

This same research group conducted a panel study of 25 type 1 or 2 diabetic subjects living in Windsor, Ontario (aged 18-65 yr) (Liu et al., 2007, 156705). For each subject, personal PM_{10} concentrations were measured for 24 h before measurements of BAD, FMD, and other biomarkers. Each 10 $\mu g/m^3$ increase in personal 24-h mean PM_{10} concentration was associated with a 0.20% increase in end-diastolic FMD (95% CI: 0.04-0.36) and a 0.38% increase in end-systolic FMD (95% CI: 0.03-0.73), but decreases in end-diastolic basal diameter (-2.52 µm [95% CI: -8.93 to 3.89]) and end-systolic basal diameter (-9.02 µm [95% CI: -16.04 to -2.00]).

Rundell et al. (2007, 156060) examined the change in FMD associated with high and low PM_1 (0.02-1.0 µm) pollution in a panel of 16 young intercollegiate athletes (mean age = 20.5±2.4 yr) in Scranton, PA, who were non-smokers, non-asthmatics, and free of cardiovascular disease (Rundell et al., 2007, 156060). Each subject had FMD of the brachial artery measured 10-20 min before and 20-30 min after each of two 30-min exercise tests (85-90% of maximal HR). The exercise tests were done outside either on an inner campus location free of automobile and truck traffic (low PM_1; mean = 5,309±1,942 particles/cm^3) or on a soccer field adjacent to a major highway (high PM_1; mean = 143,501±58,565 particles/cm^3). The order of the exercise test locations was chosen randomly. Using paired t-tests for analysis, they reported FMD was impaired after high PM_1 exposure (pre-exercise: 6.8±3.58%; post-exercise: 0.30±2.74%), but not low PM_1 exposure (pre-exercise: 6.6±4.04%; post-exercise: 4.89±4.42%). Further, they found basal brachial artery vasoconstriction (4%; pre-exercise BAD: 4.66±0.61 mm; post-exercise BAD: 4.47±0.63 mm) after the 'high PM_1' exposure, but not the 'low PM_1' exposure (-0.3% pre-exercise BAD: 4.66±0.63 mm; post-exercise BAD: 4.68±0.61 mm).

In a prospective panel study of 22 type 2 diabetics (aged 61 ± 8 yr), Schneider et al. (2008, 191985) examined the change in FMD, BAD, small artery elasticity index, larger artery elasticity index, and systemic vascular resistance associated with ambient $PM_{2.5}$ as measured in Chapel Hill, NC (November 2004-December 2005). Using additive mixed models with a random subject effect, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ in the previous 24 h was associated with a decrease in FMD (-17.3% [95% CI: -34.6 to 0.0]). Similarly, each 10 $\mu g/m^3$ increases in $PM_{2.5}$ was associated with a decrease in small artery elasticity index lagged 1 day (-15.1% [95% CI: -29.3 to -0.9]), and lagged 3 days (-25.4% [95% CI: -45.4 to -5.3]). Significant decreases in larger artery elasticity index and increases in systemic vascular resistance lagged 2 and 4 days were also reported. Further, effects were greatest among those with high BMI, high glycosylated hemoglobin A1c, low adiponectin, or the null GSTM1 polymorphism. However, high myeloperoxidase (MPO) levels were associated with greater $PM_{2.5}$ effects on these measures.

In a similar study done in Paris, France, Briet (2007, 093049) similarly reported that each increase in $PM_{2.5}$ was associated with a -0.32% decrease in FMD (95% CI: -1.10 to 0.46). Significant FMD reductions were associated with increased SO_2, NO_2, and CO concentrations. Each 1 standard deviation increase (units not given) in $PM_{2.5}$ in the previous 2 wk was associated with a 15.68% (95% CI: 7.11-23.30) increase in small artery reactive hyperemia. Each 1 standard deviation increase (units not given) in PM_{10} in the previous 2 wk was associated with a 15.91% (95% CI: 7.74-24.0) increase in small artery reactive hyperemia.

Summary of Epidemiologic Study Findings for Vasomotor Function

Vasomotor function has been evaluated using several metrics in the studies described above, including FMD, small artery elasticity index, larger artery index, systemic vascular resistance, BAD, end diastolic basal diameter, and nitroglycerin-mediated reactivity. The most common measures evaluated were BAD, a measure of the relatively static, anatomic/physiological baseline vasomotor function, and FMD, the dynamic measure of post- minus pre-occlusion BAD. Each study demonstrated an acute association between these measures of vascular function and ambient $PM_{2.5}$ concentrations (Briet et al., 2007, 093049; Dales et al., 2007, 155743; Liu et al., 2007, 156705; O'Neill et al., 2005, 088423; Rundell et al., 2007, 156060; Schneider et al., 2008, 191985). An association with PM_{10} was observed in a study conducted in Windsor Ontario (Liu et al., 2007, 156705). Three studies evaluated effects on diabetics (Liu et al., 2007, 156705; O'Neill et al., 2005, 088423; Schneider et al., 2008, 191985), and three evaluated PM-related changes in vasomotor function on young healthy subjects (Briet et al., 2007, 093049; Dales et al., 2007, 155743; Rundell et al., 2007, 156060). Only two studies investigated multiple lags (lag days 0 to 6) (O'Neill et al., 2005, 088423; Schneider et al., 2008, 191985), with one reporting the strongest association with the 6-day mean PM concentration (O'Neill et al., 2005, 088423), and the other with lag day 0. In other studies, responses were observed in as short as 30 min after the exposure (Rundell et al., 2007, 156060). The Rundell et al. (2007, 156060) findings are consistent with other studies showing an adverse response to ambient particulate pollution emitted from vehicular traffic (Adar et al., 2007, 098635; Adar et al., 2007, 001458; Riediker et al., 2004, 056992; Riediker et al., 2004, 091261). Mean and upper percentile concentrations reported in these studies are found in Table 6-4.

Table 6-4. PM concentrations reported in epidemiologic studies of vasomotor function.

Author	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
$PM_{2.5}$			
Briet (2007, 093049)	Paris, France	NR	NR
Dales (2007, 155743)	Ottawa, Canada (bus stops)	Bus stop 1: 40 Bus stop 2: 10	NR
O'Neill (2005, 088423)	Boston, MA	11.5	Range: 1.1 - 20.0
Schneider (2008, 191985)	Chapel Hill, NC	13.6	NR
PM_{10}			
Briet (2007, 093049)	Paris, France	NR	NR
Liu (2007, 156705)	Windsor, Ontario	24h (personal): 25.5	5th to 95th: 9.8 – 133

6.2.4.2. Controlled Human Exposure Studies

Some evidence of a PM-induced increase in brachial artery vasoconstriction is presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Brook et al. (2002, 024987) exposed 24 healthy adults to $PM_{2.5}$ CAPs (150 μg/m^3) along with 120 ppb O_3 for a period of 2 h. A significant decrease in BAD was observed immediately following exposure compared with filtered air control. No significant changes were observed in either endothelial-dependent or endothelial-independent vasomotor function, as determined by FMD and nitroglycerin-mediated dilatation, respectively. As described below, many more recent studies have evaluated the effects of various types of particles on vasomotor function following controlled exposures among healthy and health-compromised individuals.

CAPs

A subsequent analysis of the CAPs constituents from the Brook et al. (2002, 024987) study revealed a significant negative association between the post-exposure change in BAD and both the OC and EC concentrations of CAPs (Urch et al., 2004, 055629). However, the observed vasomotor effects cannot conclusively be attributed to $PM_{2.5}$, as subjects were exposed concurrently to $PM_{2.5}$ and O_3. Mills et al. (2008, 156766) evaluated the effect of fine and UF CAPs on vasomotor function in a group of 12 males with stable coronary heart disease (average age 59 yr), as well as in 12 healthy males (average age 54 yr). Relative to filtered air exposure, exposure to PM (average concentration 190 $\mu g/m^3$) did not significantly affect vascular function in either group. The authors attributed the lack of response in endothelial function to the composition of the CAPs used in the study, which were low in combustion-derived particles and consisted largely of sea salt.

Urban Traffic Particles

The effect of exposure to urban traffic particles on vasomotor function has recently been evaluated among a group of adult volunteers (Bräuner et al., 2008, 191966). In this study, healthy young adults (average age 27 yr) exposed for 24 h to urban traffic particles (average $PM_{2.5}$ concentration 10.5 $\mu g/m^3$) were not observed to experience any change in microvascular function after 6 or 24 h of exposure relative to filtered air.

Diesel Exhaust

Mills et al. (2005, 095757) exposed 30 healthy men (20-38 yr) to both diluted DE (300 $\mu g/m^3$) and filtered air control for 1 h with intermittent exercise. Half of the subjects underwent vascular assessments at 6-8 h following exposure to DE or filtered air, while in the other 15 subjects, vascular assessments were performed at 2-4 h post-exposure. DE attenuated forearm blood flow increase induced by bradykinin, acetylcholine (ACh), and sodium nitroprusside (SNP) infusion measured 2 and 6 h after exposure. The authors postulated that the effect of DE on vasomotor function may be the result of reduced NO bioavailability in the vasculature stemming from oxidative stress induced by the nanoparticulate fraction of DE. A DE-induced decrease in the release of tPA was also observed at 6 h post-exposure, which may provide additional mechanistic evidence supporting the observed association between air pollution and MI. As presented in Tornqvist et al. (2007, 091279), changes in vascular function were also evaluated 24 h following exposure in 15 of the 30 subjects. Compared with filtered air, exposure to DE significantly reduced endothelium-dependent (ACh) vasodilation at 24 h post exposure. Bradykinin-induced vasodilation was marginally attenuated by DE, while no effects of diesel on endothelium-independent vasodilation (SNP) were observed. Although the release of tPA was not affected by DE 24 h following exposure, the authors suggest that the persistent association between diesel exposure and vasomotor function observed in this study provides supporting mechanistic evidence of increases in cardiovascular events occurring 24 h after a peak in PM concentration.

To further investigate the effects of DE on vasomotor function, Mills et al. (2007, 091206) exposed 20 men (avg age 60 yr) with previous MI on two separate occasions to dilute DE (300 $\mu g/m^3$; mean particle size 54 nm) or filtered air for 1 h with intermittent exercise. Contrary to previous findings in younger, healthy adults (Mills et al., 2005, 095757), DE was found not to affect vasomotor function in peripheral resistance vessels at 6 h post-exposure as measured by endothelium-dependent (ACh) and endothelium-independent (SNP) vasodilation (forearm blood flow). However, vascular assessments were not performed at 2 h post-exposure in this study. The same laboratory evaluated the effect of exposure to DE with slightly higher particle concentrations (330 $\mu g/m^3$, particle number $1.26\times10^6/cm^3$) on arterial stiffness among healthy adults (Lundbäck et al., 2009, 191967). Using radial artery pulse wave analysis, significant increases in augmentation pressure and augmentation index, as well as a significant reduction in the time to wave reflection were observed 10 and 20 min following exposure to DE relative to filtered air. This finding of a DE-induced reduction in arterial compliance provides additional evidence to suggest that exposure to particles may adversely affect vasomotor function.

Peretz et al. (2008, 156854) exposed both healthy adults (n = 10) and adults with metabolic syndrome (n = 17) for 2 h to filtered air and two concentrations of diluted DE ($PM_{2.5}$ concentrations of 100 and 200 μg/m^3). Compared with filtered air, DE at 200 μg/m^3 elicited a statistically significant decrease in BAD (0.11 mm [95% CI: 0.02-0.18 mm]) immediately following exposure. A smaller DE-induced decrease in BAD (0.05 mm) was observed following exposure to 100 μg/m^3. Although this latter decrease was not statistically significant, the average decrease was approximately 50% of the decrease at the higher particle concentration, which provides suggestive evidence of a linear concentration response in this range of concentrations. Exposure to DE was not shown to significantly affect endothelium-dependent FMD. Plasma levels of endothelin-1 (ET-1) were observed to increase relative to filtered air exposure approximately 1 h after exposure to 200 μg/m^3 DE ($p = 0.01$). Samples collected following the 100 μg/m^3 exposure session were not assayed for ET-1. The results of this study provide evidence of an acute endothelial response and arterial vasoconstriction resulting from short-term exposure to DE. DE-induced changes in vasoconstriction and ET-1 release were more pronounced in the healthy subjects than in the subjects with metabolic syndrome. The authors postulated that subjects with metabolic syndrome may have stiffer vessels that are not as responsive to vasoconstrictor stimuli. In a study utilizing a similar exposure protocol, Lund et al. (2009, 180257) observed a significant increase in ET-1 in healthy adults following a 2-h exposure to DE with a particle concentration of 100 μg/m^3.

In the previously described studies by Mills et al. (2005, 095757; 2007, 091206), Peretz et al. (2008, 156854), Tornqvist et al. (2007, 091279) and Lund et al. (2009, 180257), subjects were exposed to DE, which, in addition to PM, includes DE gases such as NO_X, CO, and hydrocarbons. Therefore, it is possible that the observed effects may be due in part to exposure to non-particle components of DE. While the majority of these DE exposures have contained relatively high levels of gaseous emissions including NO_2 concentrations >2 ppm, the concentrations of these gases were much lower in the Peretz et al. (2008, 156854) study (NO_2 concentrations ≈ 20 ppb) which used a newer diesel engine (2002 Cummins B-series) operating under load at 75% of rated capacity. In this study, an apparent linear concentration response relationship was observed between increasing DE exposure and decreases in BAD at particle concentrations between 100 and 200 μg/m^3.

Gasoline Emissions

Rundell and Caviston (2008, 191986) exposed 15 college athletes to particles generated using a 2.5 hp gasoline engine, as well as a clean air control during 6-min periods of maximal exercise on a cycle ergometer. Subjects were exposed twice under each condition, with the two clean air exposures occurring first, separated by 3 days. The 2 exposures to gasoline emissions were also separated by 3 days, with the first exposure occurring 7 days after the second clean air exposure. During exposures to gasoline emissions, average PNC of PM <1.0 μm were reported as 336,730 and 396,200 particles/cm^3 during the first and second exposures, respectively, with an average CO concentration of 6.3 ppm. There were no differences observed in total work done (kJ) over the 6-min exercise periods between the two clean air exposures or between the clean air exposures and the first exposure to gasoline exhaust. However, the second gasoline exhaust exposure was demonstrated to significantly decrease work accumulated over the 6-min exercise period compared with either of the other exposure conditions. The results of this study provide limited evidence to suggest that a very short term exposure to gasoline emissions may affect exercise performance in healthy adults. The authors speculated that the observed effect of exposure on work accumulated during maximal exercise could be due to vasoconstriction and decrease in blood flow in the skeletal muscle microcirculation. However, the effect of exposure on vasoreactivity was not explicitly assessed.

Model Particles

The results of a recent study by Shah et al. (2008, 156970) provides evidence that exposure to UF EC particles (50 μg/m^3) without coexposure to organics, metals, or gaseous copollutants may alter vasomotor function in healthy adults. In this study, venous occlusion plethysmography was used to measure reactive hyperemia of the forearm prior to exposure, immediately following exposure, and 3.5 h, 21 h, and 45 h following a 2-h exposure with intermittent exercise. Peak

forearm blood flow was observed to increase after exposure to filtered air, but not following exposure to UF EC at 3.5 h post-exposure ($p = 0.03$).

Summary of Controlled Human Exposure Study Findings for Vasomotor Function

Taken together, the two studies by Mills et al. (2005, 095757; 2007, 091206) along with the studies by Peretz et al. (2008, 156854), Lund et al. (2009, 180257) and Tornqvist et al. (2007, 091279) suggest that, in healthy subjects, DE exposure inhibits endothelium-dependent and endothelium-independent vasodilation acutely (within 2-6 h), and that the suppression of endothelium-dependent vasodilation may remain up to 24 h following exposure. In patients with coronary artery disease, vasodilator function does not appear to be affected 6-8 h following exposure; however, vascular assessments were not performed at earlier time points. In addition, the use of medications in these patients may have blunted the response to PM. The findings of Shah et al. (2008, 156970) suggest that UFP carbon core may be sufficient to produce small changes in systemic vascular function, but the mechanisms remain obscure. The authors demonstrated a decrease in nitrate levels following exposure to UF EC; however, venous nitrite level, which more closely reflects NO production, was unchanged. Exposure to urban traffic particles was not demonstrated to alter vasomotor function among healthy adults.

6.2.4.3. Toxicological Studies

Vascular dysfunction is a function of altered production of vasoconstrictors and vasodilators. In the 2004 PM AQCD (U.S. EPA, 2004, 056905), studies examining ET as an activator of vasoconstriction were limited to those conducted by Bouthiller et al. (1998, 087110) and Vincent et al. (2001, 021184), in which increased plasma ET levels were observed in rats exposed to high concentrations (40 or 5 mg/m^3) of resuspended Ottawa (EHC-93) or diesel PM, respectively. The authors postulated that PM altered vasoconstriction via elevated ET. No studies were cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that looked at direct measures of vasoreactivity.

As this area is newly emerging, some studies are included below that utilize IT exposure or high concentrations; the studies that exposed vessels directly to particles ex vivo are included in Annex D only, as their relevance is questionable. There is clearly a need for more toxicological research examining the relationship between vascular measurements and PM exposures using ambient particles at lower concentrations. Furthermore, no new studies have advanced the knowledge in regards to ET as a biomarker of PM-induced vasoconstriction since the last PM review.

CAPs

SD rats were exposed to $PM_{2.5}$ CAPs (5 h/day×3 days; daily mean mass concentration 73.5-733 $\mu g/m^3$; Boston, MA; 3/1997-6/1998) then the pulmonary arterial vasculature was evaluated (Batalha et al., 2002, 088109). Some animals were repeatedly exposed to SO_2 (5 h/day×5 days/wk×6 wk) to induce chronic bronchitis. Morphometric measurements indicated that the pulmonary artery lumen-to-wall (L/W) ratio (an indicator of arterial narrowing) was decreased for the both CAPs groups compared to the normal/air group. Furthermore, decreased L/W ratio in CAPs-exposed animals (regardless of pre-treatment) was significantly associated with particle mass and composition when the mean concentrations from the second and third exposure days were used in a univariate linear regression. These results indicate a change in vascular tone following acute exposure to PM. Univariate analyses were conducted that regressed log L/W on differential exposure concentrations of tracer elements determined using principal components analysis (Batalha et al., 2002, 088109). For CAPs exposure (regardless of pretreatment), CAPs mass, Si, Pb, SO_4^{2-}, EC, and OC were all negatively correlated with L/W ratio. Si and SO_4^{2-} were negatively correlated with L/W ratio in normal rats and Si and OC were negatively correlated with L/W ratio in bronchitic rats. When a multivariate analysis was conducted using normal and bronchitic animals, only the association with Si remained significant. V was not associated with L/W ratio in any analysis.

Diesel Exhaust

The venous circulation plays a prominent role in heart failure exacerbation (Gehlbach and Geppert, 2004, 155784). In heart failure, patients are often volume overloaded and are subsequently placed on diuretics to alleviate symptoms of pulmonary congestion and chest pain. Knuckles et al. (2008, 191987) hypothesized that if veins constrict in a manner similar to arteries, then patients with severe CHF may have temporary shunting of fluid to the pulmonary circulation, which may elicit signs and symptoms of CHF. Using mesenteric vessels from mice (C57BL/6) exposed to DE (350 μg/m^3×4 h; MMD 100 nm, CMD 80 nm), the authors reported a significant enhancement of ET-1-induced vasoconstriction in veins with much weaker responses in arteries. In an ex vivo experiment, venous constriction was blocked by the arginine analog, L-NAME, which eliminates the feedback NOS activation via endothelial ET_B receptors; this is indicative of impaired or uncoupled eNOS. The authors hypothesized that volatile organic compounds might be responsible these effects, but no significant effects were observed for acetaldehyde, formaldehyde, acetone, hexadecane, or pristane.

Model Particles

A study by Nurkiewicz et al. (2008, 156816) compared the arteriole dilation responses in the spinotrapezius muscle with inhalation exposure to fine or UF TiO_2 (1 μm and 21 nm, respectively; mean mass concentration 3-16 and 1.5-12 mg/m^3, respectively) for durations of 4-12 h in SD rats. Both size fractions of TiO_2 induced impaired dilation with a NO-dependent Ca^{2+} ionophore in a dose-dependent manner. When fine and UF TiO_2 were compared at similar mass doses, the systemic microvascular dysfunction was greater with the UFPs. Furthermore, three exposures of differing durations and concentrations that produced equal calculated pulmonary deposition of UF TiO_2 (30 μg) demonstrated similar dilation responses, indicating that impairment is dependent upon the time×concentration product. No effects on dilation were observed with a dose of 4 μg UF TiO_2 (1.5 mg/m^3 for 4 h) or 8 μg fine TiO_2 (3 mg/m^3 for 4 h).

In a follow-up study, Nurkiewicz et al. (2009, 191961) examined the effect of pulmonary fine and UF TiO_2 exposure on endogenous microvasculature NO production in SD rats. The exposure concentrations and durations were selected to produce ~50% impairment of microvascular reactivity (67 and 10 μg for fine[1] and UF[2] TiO_2, respectively). Similar to the study above (Nurkiewicz et al., 2008, 156816), impaired endothelium-dependent arteriolar dilation was observed 24 h post-exposure with infusion of a Ca^{2+} ionophore. Earlier studies that used residual oil fly ash (ROFA) or TiO_2 via IT instillation reported similar findings, regardless of particle type (Nurkiewicz et al., 2004, 087968; Nurkiewicz et al., 2006, 088611). There was no difference in arteriolar dilation between sham and TiO_2 exposed groups with direct administration of the NO donor SNP to the exterior arteriolar wall and this response was consistent with that observed following ROFA administered intratracheally (Nurkiewicz et al., 2004, 087968). The lack of response to SNP indicates that vascular smooth muscle sensitivity to NO is not altered after particle exposure. The amount of ROS in the microvascular wall was increased following exposure to either TiO_2 size. Local ROS may consume endothelial-derived NO and generate peroxynitrite radicals, as microvascular nitrotyrosine (NT) formation (the end product of peroxynitrite reactions) was demonstrated after TiO_2 exposure. NO production was compromised in a dose-dependent manner following particle exposure (8-90 μg for fine and 4-38 μg for UF TiO_2), and was partially restored with agents for radical scavenging or enzyme inhibition for NADPH oxidase and MPO.

Intratracheal Instillation

Nurkiewicz et al. (2004, 087968; 2006, 088611) have shown impairment of endothelium-dependent dilation in the systemic microvasculature of SD rats following ROFA or TiO_2 exposure (0.1 or 0.25 mg/rat). NO-independent arteriolar dilation was also impaired by ROFA,

[1] Produced by a 300-min exposure to 16 mg/m^3 of fine TiO_2

[2] Produced by a 240-min exposure to 6 mg/m^3 of ultrafine TiO_2

but arteriole adrenergic sensitivity to phenylephrine (PHE) was not affected by 0.25 mg ROFA, indicating that contractile activity was unchanged. In addition, increased venular leukocyte rolling and adhesion in the spinotrapezius muscle was also observed following ROFA exposure (Nurkiewicz et al., 2004, 087968).

Further characterization of the leukocyte adherence and "rolling" effects for both ROFA and TiO_2 were indicative of an activated endothelium (Nurkiewicz et al., 2006, 088611). Vascular deposition of MPO was observed in the spinotrapezius muscle 24 h post-exposure and the authors suggested that the adherent leukocytes may have deposited the MPO to be taken up by endothelial cells (Nurkiewicz et al., 2006, 088611). However, this is in contrast to another study (Cozzi et al., 2006, 091380) that did not find changes in blood neutrophil MPO release in ICR mice exposed to UF PM (100 μg from Chapel Hill, NC; assessed 24 h post-exposure), although this finding may be a reflection of differing protocols. Increased oxidative stress in the arteriolar wall was also reported with exposure to 0.25 mg ROFA. TiO_2 and ROFA induced varying degrees of pulmonary inflammation in these animals, but elicited very similar vascular effects, indicating that the vascular responses may be due to PM presence in the lung rather than its physiochemical properties or intrinsic pulmonary toxicity.

PM_{10}

Tamagawa et al. (2008, 191988) reported reduced ACh-stimulated relaxation in carotid arteries from rabbits (New Zealand White) exposed to PM_{10} (EHC-93) via intrapharyngeal instillation for 5 days or 4 wk (total doses 8 and 16 mg/kg, respectively). Endothelium-dependent NO-mediated vasorelaxation correlated with increased serum IL-6 levels in the acute study and during wk 1 and 2 of the 4-wk exposure, which may indicate a role for systemic inflammation in the response. Maximal SNP-induced dilation was not affected by PM exposure, indicating that the dilatory response was not acting via endothelium-independent NO-mediated mechanisms. This finding is consistent with that by Nurkiewicz et al. (2004, 087968) and suggests that the arteriolar smooth muscle is not involved in the PM-impaired dilatation response.

Vasoreactivity of aortic rings was measured in SH rats following exposure to 10 mg/kg PM_{10} (EHC-93), with an increase in ACh-induced vasorelaxation observed (Bagate et al., 2004, 087945). This endothelium-dependent response was greatest at 4 h and was still present at 24 h. Similarly, vasorelaxation induced by SNP 4-h post-PM exposure was enhanced. The vasorelaxation response was attenuated after denudation of the aortic rings, suggesting that the effect was endothelium dependent. The findings of enhanced dilation with PM exposure contrast with those reported by Nurkiewicz et al. (2004, 087968; 2006, 088611), Tamagawa et al. (2008, 191988), and Cozzi et al. (2006, 091380) and may be attributable to differences in PM type, animal species, or disease models. The authors attribute their findings to the SH rat as a well-documented model of sympathetic hyperactivity (increased affinity of aortic smooth muscle α-adrenergic receptors) that demonstrates upregulation of NO formation and/or release (Safar et al., 2001, 156068). No change in vasoconstriction was observed with PM with PHE or potassium chloride.

Consistent with the impaired vasodilatory responses observed in the microvasculature and aortic rings following PM exposure, Courtois et al. (2008, 156369) demonstrated less relaxation to ACh in intrapulmonary arteries of Wistar rats exposed to a high dose (5 mg) of ambient PM (SRM1648). This response was only observed 12 h after PM exposure and not at shorter (6 h) or longer (24 or 72 h) time points. Fine TiO_2 did not alter ACh-induced relaxation.

Ultrafine PM

Cozzi et al. (2006, 091380) used ICR mice to examine the effects of UF PM exposure (100 μg collected from Chapel Hill, NC) on vascular reactivity following PM exposure and ischemia/reperfusion injury. Aortic rings were evaluated for their contractile and dilatory responses 24 h post-exposure and following the ischemia/reperfusion protocol. Maximum ACh-induced relaxation was impaired in UF PM-exposed vessels, as well as a rightward shift in sensitivity to ACh. There was no difference in constriction to PHE between aortic rings from control and PM-exposed mice. The reduced ACh-induced relaxation may be important for reperfusion of critical vascular beds following occlusion, potentially leading to a greater area of infarction (as in this study). A new study in dogs supports the results observed in the above study and provides evidence of reduced myocardial blood flow following PM exposure (Bartoli et al., 2009, 179904), and is discussed in more detail in Section 6.2.3.3.

Summary of Toxicological Study Findings for Vasoreactivity

The toxicological findings with respect to vascular reactivity are generally in agreement and demonstrate impaired dilation following PM exposure that is likely endothelium dependent. These effects have been demonstrated in varying vessels (right spinotrapezius muscle, carotid arteries, and aortic rings) and in response to different PM types (ROFA, TiO_2, EHC-93, UF ambient PM). The work by Nurkiewicz et al. (2004, 087968; 2006, 088611; 2008, 156816; 2009, 191961) supports a role for increased ROS and RNS production in the microvascular wall that leads to altered NO bioavailability and dysfunction following particle exposure. Only one study showed enhanced dilation with PM exposure, but the authors attributed the conflicting results to the SH rat. No constriction changes in response to PHE were observed following PM exposure. The responses observed in the pulmonary circulation after PM exposure include pulmonary vasoconstriction, decreased L/W ratio, and impaired vasodilation in intrapulmonary arteries. These results are consistent and indicate altered vascular tone. Enhancement of vasoconstriction in mesenteric veins following DE is the first study of its kind to report on venous circulatory effects.

Endothelin

In addition to studies that look at vascular reactivity, three recent studies have examined plasma ET levels following exposure to vehicle emissions and a few studies examined the mRNA expression of ET-1 and ET receptors in the hearts of rodents following PM exposure.

CAPs

The upregulation of mRNA expressions of ET-1 and the ET_A receptor in WKY rats exposed to CAPs (1 or 4 days; 4.5 h/day; mean mass concentration range 1,000-1,900 $\mu g/m^3$; Yokohoma City, Japan) was correlated with increasing PM cumulative mass collected on chamber filters (Ito et al., 2008, 096823). Furthermore, relative cardiac mRNA expressions of ET-1 and ET_A receptor were significantly correlated with CYP1B1 and HO-1 expression, indicating a possible relationship between ET-1 metabolism and oxidative stress.

Another plasma mediator of vasomotor tone is asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of NOS that is associated with impaired vascular function and increased cardiovascular events. Dvonch et al. (2004, 055741) assessed levels of ADMA in Brown Norway rats 24 h following a 3-day $PM_{2.5}$ CAPs exposure in southwest Detroit (8 h/day; July 2002). CAPs (mean mass concentration 354 $\mu g/m^3$) resulted in increased plasma ADMA compared to air controls, although the levels reported were well below the 2 μM range associated with increased CVD risk in humans in chronic studies. Therefore, the preliminary results identified a new potential biomarker of vascular tone that had not previously been used in air pollution toxicological studies.

Traffic-Related Particles

A study of old rats (21 mo; F344) exposed to on-road highway aerosols (number concentration range $0.95\text{-}3.13\times10^5$ particles/cm^3; Interstate 90 between Rochester and Buffalo, NY) for 6 h demonstrated decreased plasma ET-2 (18 h post-exposure) and unchanged levels of ET-1 and ET-3 (Elder et al., 2004, 087354).

Gasoline Exhaust

In contrast to the study above, circulating levels of ET-1 (measured 18 h post-exposure) were elevated in animals exposed to gasoline exhaust and filtration of particles did not reduce this effect (study details in Section 6.2.2.2) (Campen et al., 2006, 096879). The results of Campen et al. (2006, 096879) are consistent with those observed by Bouthillier et al. (1998, 087110) following a very high exposure to EHC-93, but it is difficult to attribute the effects to PM alone, as Campen et al. (2006, 096879) showed that the gaseous components of the gasoline mixture were required for the ET-1 increase.

Aorta ET-1 mRNA expression was increased with a 7-day gasoline exhaust exposure (60 $\mu g/m^3$) in $ApoE^{-/-}$ mice, but was not changed following a single-day exposure (Lund et al., 2009, 180257). The expression and activity of MMP-2 and -9 and oxidative stress in aortas of exposed

mice were also elevated. The ET-1 and MMP-9 mRNA expressions were attenuated with the addition of an ET_A receptor antagonist (but not a radical scavenger), indicating that ET-1 may mediate the expression of MMP-9 through the ET_A receptor.

Model Particles

Another study examined the effects of UF carbon particles (mass concentration 172 $\mu g/m^3$; mean number concentration 9.0×10^6 particles/cm^3) and there was no difference in ET-1, ET_A or ET_B receptor mRNA expression between air- and particle-exposed SH rats 1 or 3 days post-exposure (Upadhyay et al., 2008, 159345). In lung homogenates, ET-1, ET_A and ET_B receptor mRNA expressions were elevated 3 days after exposure to UF carbon particles (Upadhyay et al., 2008, 159345).

Summary of Toxicological Study Findings for Endothelin

The ET responses were mixed, with one study demonstrating ET-1 increases after exposure to gasoline emissions that were particle independent and another reported decreased ET-2, but no change in ET-1 or ET-3 with on-road highway exposure. Elevated levels of ET-1 and ET_A receptor mRNA expression were noted in hearts of rats exposed to CAPs, but not in rats exposed to UF carbon particles. However, ET-1, ET_A and ET_B receptor mRNA expressions were increased in lung homogenates of rats following UF carbon exposure. The ET_A receptor was found to be involved in the ET-1 and MMP-9 responses in the aortas of mice exposed to gasoline exhaust. A relatively novel marker, ADMA, was used to evaluate vasomotor tone in rats and was found to be elevated following exposure to CAPs, although the results are preliminary and have not been confirmed.

6.2.5. Blood Pressure

One of the potential outcomes of air pollution-mediated alterations in vascular tone is its impact on variable BP or hypertension. BP is tightly regulated by autonomic (central and local), cardiac, renal, and regional vascular homeostatic mechanisms with changes in arterial tone being countered by changes in cardiac contractility, HR, or fluid volume. The evidence of PM-induced changes in BP presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) is limited and inconsistent. Recent epidemiologic, controlled human exposure, and toxicological studies have similarly reported conflicting results regarding the effect of PM on BP. However, the majority of these studies have evaluated changes in BP at some point following exposure to PM. Significant increases in DBP have been observed in controlled human exposure studies that evaluated BP during exposure (concomitant exposure to CAPs and O_3). In addition, evidence from toxicological studies suggests that the effect of PM on BP may be modified by health status, as PM-induced increases in BP have been more consistently observed in SH rats.

6.2.5.1. Epidemiologic Studies

Increased BP was associated with PM concentration in two of three studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Increases in left ventricular BP (systolic and diastolic) are well established risk factors for cardiovascular mortality/morbidity (Welin et al., 1993, 156151). Changes in HR and BP both reflect changes in autonomic tone, and have been examined following short-term increases in PM pollution in several recent studies.

Ibald-Mulli et al. (2004, 087415) examined associations between BP and ambient $PM_{2.5}$ concentrations, UFP counts, and ACP counts in a multicity panel study (Amsterdam, the Netherlands; Helsinki, Finland; Erfurt, Germany) of 131 adults with coronary heart disease. Although based on the same ULTRA Study (Timonen et al., 2006, 088747) with study methods as described previously in Section 6.2.1.1, the study period was different. They investigated changes in BP (SBP and DBP) associated with mean $PM_{2.5}$, UFP, and ACP concentration/counts (lag days 0, 1, and 2, as well as the 5-day mean) in each city and then generated a pooled estimate across the cities. The median $PM_{2.5}$ concentration for each city is provided in Table 6-5. Pooled analyses across all 3 cities showed small, but statistically significant decreases in SBP and DBP associated with various single day lagged concentrations/counts of each particulate pollutant. Each 10 $\mu g/m^3$ increase in the

mean $PM_{2.5}$ concentration over the previous 5 days was associated with a 0.36 mmHg decrease in SBP (95% CI: -0.99 to 0.27) and a 0.39 mmHg decrease in DBP (95% CI: -0.75 to -0.03). Each 10,000 particles/cm^3 increase in UFP was associated with a 0.72 mmHg decrease in SBP (95% CI: -1.92 to 0.49), and a 0.70 mmHg decrease in DBP (95% CI: -1.38 to -0.02). Each 1,000 particles/cm^3 increase in 5-day avg ACP was associated with a 1.11 mmHg decrease in SBP (95% CI: -2.12 to -0.09) and a 0.95 mmHg decrease in DBP (95% CI: -1.53 to -0.37). The authors concluded that these findings do not support previous findings of an increase in BP associated with increases in particulate pollutant concentrations.

Single-city studies examining the association between BP and particulate air pollution have been done in several U.S. and Canadian cities. Dales et al. (2007, 155743) conducted a panel study of 39 healthy volunteers who sat outside at two different bus stops for 2-h in Ottawa, Canada. The median $PM_{2.5}$ concentrations measured at the bus stops during each 2-h exposure session were 40 and 10 $\mu g/m^3$. Post-exposure SBP and DBP were not associated with the mean $PM_{2.5}$ concentration measured at the bus stops during the 2-h exposure session. The change in BP from pre- to post-exposure was not evaluated, as health measurements were only made after the 2-h exposure sessions.

Jansen et al. (2005, 082236) studied changes in BP among 16 older subjects (aged 60-86 yr) with asthma or COPD in Seattle, Washington, associated with indoor, outdoor, and personal PM_{10}, $PM_{2.5}$, and BC concentrations on 12 consecutive days. The study authors reported that no associations were observed between BP and daily mean PM_{10}, $PM_{2.5}$, or BC concentrations.

Zanobetti et al. (2004, 087489) examined the association between BP (SBP, DBP, and mean arterial BP) and mean $PM_{2.5}$ concentrations in the previous 24, 48, 72, 96, and 120 h in 62 elderly, cardiac rehabilitation patients in Boston, MA (Zanobetti et al., 2004, 087489). Each 10.4 $\mu g/m^3$ increase in mean $PM_{2.5}$ concentration in the previous 120 h was associated with significant increases in resting DBP (2.82 mmHg [95% CI: 1.26-4.41]), SBP (2.68 mmHg [95% CI: 0.04-5.38]), and mean arterial BP (2.76 mmHg [95% CI: 1.07-4.48]).

Mar et al. (2005, 087566) studied this same $PM_{2.5}$-BP association in 88 subjects aged >57 yr in Seattle, WA. Among healthy subjects taking medications (bronchodilators, inhaled corticosteroids, anti-hypertensives, β-blockers, calcium channel blockers, and/or cardiac glycosides), each 10 $\mu g/m^3$ increase in mean outdoor $PM_{2.5}$ concentration on the same day as the BP measurement was made was associated with small increases in SBP and DBP. However, among all subjects, each 10 $\mu g/m^3$ increase in same day mean $PM_{2.5}$ concentration was associated with non-significant decreases in SBP (-0.81 mmHg [95% CI: -2.34 to 0.73]) and DBP (-0.46 mmHg [95% CI: -1.49 to 0.57]).

As described earlier, Ebelt et al. (2005, 056907) conducted a repeated measures panel study of 16 patients with COPD in the summer of 1998 in Vancouver, British Columbia to evaluate the relative impact of ambient and non-ambient exposures to $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ on multiple health outcomes including ectopy and BP. Using the same analytic methods, pollutant concentrations, and lags, they reported decreased SBP associated with same day ambient exposures to each PM size fraction.

Two similar studies were done in Incheon, South Korea (Choi et al., 2007, 093196) and Taipei, Taiwan (Chuang et al., 2005, 156356). Choi et al. (2007, 093196) reported significantly increased SBP and DBP associated with the mean PM_{10} concentration over the same and previous 2 days in the warm season only (July to September). Chuang et al. (2005, 156356) reported significant increases in SBP and DBP associated with the mean UFP count (0.01-0.1 μm particles) 1-3 h before the BP measurement.

Summary of Epidemiologic Studies of Blood Pressure

These studies (Choi et al., 2007, 093196; Chuang et al., 2005, 156356; Dales et al., 2007, 155743; Ibald-Mulli et al., 2004, 087415; Mar et al., 2005, 087566; Zanobetti et al., 2004, 087489) are not entirely consistent with regard to their BP-PM associations. Most have reported increases in SBP and DBP associated with increases in either $PM_{2.5}$, PM_{10}, or UFP (Choi et al., 2007, 093196; Chuang et al., 2005, 156356; Mar et al., 2005, 087566; Zanobetti et al., 2004, 087489). However, two studies reported small decreases in BP associated with multiple particulate pollutants (Ibald-Mulli et al., 2004, 087415; Mar et al., 2005, 087566), Dales et al. (2007, 155743) reported no change in BP associated with a 2-h exposure to bus stop $PM_{2.5}$ and Jansen at al. (2005, 082236) reported null findings among older adults in Seattle, WA. Exposure lags ranging from 1-3 h (Chuang et al., 2005,

156356), to the same day(Ebelt et al., 2005, 056907; Mar et al., 2005, 087566), to the mean across the previous 5 days (Zanobetti et al., 2004, 087489) were reported as having the strongest associations with BP. Mean and upper percentile concentrations for PM from these studies are presented in Table 6-5.

Table 6-5. Mean PM concentrations reported in epidemiologic studies of blood pressure.

Author	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Dales (2007, 155743)	Ottawa, Canada (bus stops)	Bus stop 1: 40 Bus stop 2: 10	NR
Ebelt (2005, 056907)	Vancouver, Canada	Ambient (measured): 11.4 Personal (estimated): 7.9 Personal (measured): 18.5	Ambient (measured) range: 4.2-28.7 Personal (estimated) range: 0.9-21.3 Personal (measured) range: 2.2-90.9
Ibald-Mulli (2004, 087415)	Amsterdam, Netherlands	20	50th: 16.9 75th: 23.9 Max: 82.2
	Erfurt, Germany	23.1	50th: 16.3 75th: 27.4 Max: 118.1
	Helsinki, Finland	12.7	50th: 10.6 75th: 16 Max: 39.8
Jansen (2005, 082236)	Seattle, WA	10.47	NR
Mar (2005, 087566)	Seattle, WA	Healthy: Personal- 9.3 Indoor- 7.4 Outdoor- 9 CVD: Personal- 10.8 Indoor- 9.5 Outdoor- 12.6 COPD: Personal- 10.5 Indoor- 8.5 Outdoor- 9.2	NR
Zanobetti (2004, 087489)	Boston, MA	Median: 8.8	90th: 17.6
$PM_{10-2.5}$			
Ebelt (2005, 056907)	Vancouver, Canada	Ambient (calculated): 5.6 Personal (estimated): 2.4	Ambient (calculated) range: -1.2 to 11.9 Personal (estimated) range: -0.4 to 7.2
PM_{10}			
Choi (2007, 093196)	Incheon, South Korea	July-Sept: 42.1 Oct.-Dec: 53.5	July-Sept.: 75%: 52.2 Max: 136.7 Oct.-Dec.: 75%: 64.5 Max: 209.6

Author	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
Chuang (2005, 156356)	Taipei, Taiwan	54.1	Range: 10.3-139.8
Ebelt (2005, 056907)	Vancouver, Canada	Ambient (calculated): 17 Personal (estimated): 10.3	Ambient (calculated) range: 7-36 Personal (estimated) range: 1.5-23.8
Jansen (2005, 082236)	Seattle, WA	13.47	NR
Mar (2005, 087566)	Seattle, Washington	Healthy: 14.5 CVD: 18 COPD: 14.3	NR

Right Ventricular Pressure

Several recent studies, summarized in the section on hospital admissions and emergency department (ED) visits for CVD causes, have reported increased risk of hospital admissions for CHF associated with increased PM concentration on the same day (Wellenius et al., 2005, 087483; 2006, 088748). As a possible mechanism for these reported associations, Rich et al. (2008, 156910) hypothesized that these hospital admissions for decompensation of heart failure would be preceded by more subtle increases in pulmonary arterial (PA) and right ventricular (RV) diastolic pressures. They used passively monitored PA and RV pressures on 5,807 person-days, among 11 subjects implanted with the Chronicle Implantable Hemodynamic Monitor [Medtronic, Inc. Medtronic, MN]). Using a two-stage modeling process, they examined the change in daily mean right heart pressures associated with mean $PM_{2.5}$ concentration on the same and previous 6 days. Each 11.62 μg/m^3 increase in same day mean $PM_{2.5}$ concentration was associated with small, but statistically significant increases in estimated PA diastolic pressure (0.19 mmHg [95% CI: 0.05-0.33]) and RV diastolic pressure (0.23 mmHg [95% CI: 0.11-0.34]). These effects were not attenuated when controlling for all lags simultaneously. Thus, PM induced right heart pressure increases may mark another potential pathway between PM exposure and incidence of cardiovascular events, but further studies on this same hypothesis are needed for confirmation.

Wellenius et al. (2007, 092830) conducted a panel study of 28 subjects living in the greater Boston metropolitan area, each with chronic stable heart failure and impaired systolic function. They hypothesized that circulating levels of B-type natriuretic peptide (BNP), measured in whole blood at 0, 6, and 12 wk, were associated with acute changes in ambient air pollution, as a possible mechanistic explanation for the observed association between hospital admissions for CHF and ambient PM concentration (Wellenius et al., 2005, 087483; 2006, 088748). During the study, the mean $PM_{2.5}$ concentration was 10.9 μg/m^3, while the mean BC concentration was 0.73 μg/m^3. Using linear mixed models, they reported no association between any pollutant ($PM_{2.5}$, CO, SO_2, NO_2, O_3, and BC) and BNP at any lag (e.g., each 10 μg/m^3 increase in mean daily $PM_{2.5}$ concentration [0.8% increase in BNP (95% CI: -16.4 to 21.5)]) (Wellenius et al., 2007, 092830). However, BNP the active peptide has a very short half-life and might not be the best biomarker for such a study. Thus the absence of a correlation between PM and BNP may not suggest that PM does not have an impact on RV or LV function in individuals with impaired cardiac mechanics.

6.2.5.2. Controlled Human Exposure Studies

Only one controlled human exposure study cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) reported any PM-induced changes in BP. Gong et al. (2003, 042106) found that exposure to $PM_{2.5}$ (174 μg/m^3) decreased SBP in asthmatics, but increased SBP in healthy subjects. Among healthy adults, BP was not affected following 2-h exposures to 200 μg/m^3 diesel PM (Nightingale et al., 2000, 011659), 150 μg/m^3 $PM_{2.5}$ CAPs with 120 ppb O_3 (Brook et al., 2002, 024987), or 10 μg/m^3 UF carbon particles (Frampton, 2001, 019051). The effect of PM on BP has been further investigated in several recent controlled human exposure studies, which are described below.

CAPs

One recent study demonstrated a significant increase (9.3%) in DBP among healthy adults immediately prior to the end of a 2-h exposure to 150 μg/m^3 $PM_{2.5}$ CAPs in combination with 120 ppb O_3 (Urch et al., 2005, 081080). The authors also found that the magnitude of change in BP was significantly associated with $PM_{2.5}$ carbon content, but not total $PM_{2.5}$ mass. It was postulated that the disparity between these findings and those of a similar study by the same group (Brook et al., 2002, 024987) could be due to differences in experimental methods. The Brook et al. (2002, 024987) study measured post-exposure BP approximately 10 min following exposure, while the study by Urch et al. (2005, 081080) measured BP during exposure. In a follow up study that evaluated changes in BP during a 2-h exposure to $PM_{2.5}$ CAPs, Fakhri et al. (2009, 191914) reported a significant increase in DBP with exposure to CAPs with, but not without, coexposure to O_3.

Diesel Exhaust

Several recent studies have assessed BP changes following a 1-h exposure to DE with a particle concentration of 300 μg/m^3. Mills et al. (2005, 095757) evaluated changes in BP 2 h following exposure to DE and found a 6 mmHg increase in DBP of marginal statistical significance ($p = 0.08$) compared to filtered air control. In this same group of subjects, Tornqvist et al. (2007, 091279) did not observe any such changes in BP 24 h following DE exposure. At lower particle concentrations in diluted DE (100-200 μg/m^3 $PM_{2.5}$), Peretz et al. (2008, 156854) did not observe any changes in systolic or DBP in either healthy adults or adults with metabolic syndrome immediately following a 2-h exposure. Further, although Lundback et al. (2009, 191967) reported an increase in arterial stiffness following exposure to DE with a particle concentration of 330 μg/m^3 among healthy young adults, no changes in systolic or diastolic BP were observed during or following exposure relative to filtered air.

Model Particles

Routledge et al. (2006, 088674) did not observe any changes in BP among healthy older adults and older adults with stable angina following a 1-h exposure to UF EC (50 μg/m^3), with or without coexposure to 200 ppb SO_2. Similarly, neither Shah et al. (2008, 156970), nor Beckett et al. (2005, 156261) reported any changes in BP among healthy adults following exposure to UF EC (50 μg/m^3) or ZnO (500 μg/m^3 fine and ultrafine), respectively.

Summary of Controlled Human Exposure Study Findings for BP

The findings of these new studies do not provide convincing evidence of an association between PM exposure and an increase in BP; however, they do suggest that there is a need for additional investigations of PM-induced changes in BP at various time points following exposure.

6.2.5.3. Toxicological Studies

In healthy animal models, little evidence exists for significant BP changes following inhalation exposure to environmentally-relevant concentrations of PM. Only one animal toxicological study is mentioned in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that examined BP with PM exposure and no effect was observed (Vincent et al., 2001, 021184).

CAPs

In a recent study of dogs, exposure to $PM_{2.5}$ CAPs from Boston (mean mass concentration 358.1 μg/m^3; mass concentration 94.1-1557 μg/m^3) for 5 h resulted in increased SBP (2.7 mmHg), DBP (4.1 mmHg), mean arterial pressure (3.7 mmHg), and lowered pulse pressure (1.7 mmHg) when measured upstream of the femoral artery (Bartoli et al., 2009, 156256). Administration of an

α-adrenergic antagonist (prazosin) prior to CAPs attenuated the BP responses. These findings indicate that CAPs exposure may have activated α-adrenergic receptors and increased peripheral vascular resistance. Baroreflex sensitivity was measured immediately before and after exposure during a transient elevation of arterial pressure that was induced by PHE; increased baroreflex sensitivity was observed in subgroup of dogs exposed to CAPs, which is consistent with an upregulation of vagal reflexes.

Chang et al. (2004, 055637) noted slight increases in SH rat BP (5-10 mmHg) when exposed to $PM_{2.5}$ CAPs (mean mass concentration 202 $\mu g/m^3$) during spring months. However, during summer months, when the CAPs exposure level was less (140 $\mu g/m^3$), this effect was not observed. It was unclear, therefore, whether the effects were seasonal or dose-related. In a preliminary study of SH rats exposed to CAPs during a dust storm event, mean BP was elevated the third and fourth hour of a 6-h exposure, although interpretation of this finding is difficult due to few animals in the exposure group (n = 2) (Chang et al., 2007, 155719). In another study, the increased change in mean BP measured using the tail cuff method following CAPs exposure weakly correlated with PM mass accumulated on chamber filters over the entire exposure duration (Section 6.2.4.3 for details) (Ito et al., 2008, 096823). Furthermore, ET_A receptor mRNA expression in cardiac tissue was positively correlated with the change in mean BP.

Model Particles

In WKY rats, 24-h exposure to UF carbon particles (mass concentration 180 $\mu g/m^3$; mean number concentration 1.6×10^7 particles/cm^3) did not alter mean BP during exposure or the recovery periods (Harder et al., 2005, 087371). SH rats exposed to UF carbon particles for 24 h (mass concentration 172 $\mu g/m^3$; mean number concentration (9.0×10^6 particles/cm^3) resulted in elevated mean BP (by 6 mmHg) on the first and second days of recovery following exposure that was attributable to increases in both SBP and DBP (Upadhyay et al., 2008, 159345). Increased plasma renin concentrations were observed in CB-exposed rats on the first and second days of recovery, although renin activity and angiotensin (Ang) I and II concentrations were not affected by particle exposure.

Summary of Toxicological Study Findings for Blood Pressure

Limited toxicological evidence provides support for elevated BP in dogs or compromised rats with CAPs, UF CAPs, CAPs during a dust storm event, or UF carbon particle exposure. However, most of the CAPs studies were conducted outside of the U.S.

6.2.6. Cardiac Contractility

The 2004 PM AQCD (U.S. EPA, 2004, 056905) did not include any toxicological studies that evaluated cardiac contractility either directly or indirectly following exposure to PM. Two recent animal toxicological studies have demonstrated reductions in cardiac fractional shortening, diminished ejection shortening, or changes in the QA interval following PM exposure. The results of these studies provide some evidence of PM-induced changes in cardiac contractility in animal models.

6.2.6.1. Toxicological Studies

The strength of the contracting heart is reflected by its contractility. In heart failure, contractility wanes significantly and the heart cannot compensate during periods of increased physical activity. Measuring true contractility in a whole animal is difficult, requiring extensive surgical instrumentation and monitoring.

CAPs

Using radiotelemetry to indirectly measure cardiac contractility through the QA interval, SH rats were repeatedly and alternately exposed to UF CAPs in Taiwan on separate days in spring or summer (details provided in Section 6.2.5.3) (Chang et al., 2004, 055637). The QA interval was calculated as the time duration between the Q wave in the ECG and point A (upstroke in aortic pressure) in the pressure trace and is not as reliable as other measures, such as echocardiography. During the spring exposure, QA interval decreased by 1.6 ms (as demonstrated by fixed effects in linear mixed-effects modeling), which indicates an increase in cardiac contractility. There were no changes in QA interval observed for the summer months, which may be attributable to lower UF PM concentrations (mean mass concentration 140 $\mu g/m^3$) or differing PM compositions.

Model Particles

A recent study using old (18-28-mo) mice (C57BL/6, C3H/HeJ, and B6C3F1) demonstrated significant reductions in cardiac fractional shortening (due to increased left ventricular end-diastolic and end-systolic diameters) following a 4-day (3 h/day) exposure to CB ($PM_{2.5}$ mean concentration 401 $\mu g/m^3$; PM_{10} mean concentration 553 $\mu g/m^3$) using echocardiography (Tankersley et al., 2008, 157043). Hemodynamic measurements of diminished ejection fraction and maximum change in pressure over time further supported lowered myocardial contractility. Furthermore, increased right ventricular pressure associated with elevated right atrial and pulmonary vascular pressures and resistance, was indicative of pulmonary vasoconstriction in CB-exposed mice. Heart tissue and isolated cardiomyocytes from exposed animals demonstrated enhanced ROS that was partially attributable to NOS3-uncoupling and elevated MMP-2 and MMP-9 levels, which may implicate myocardial remodeling. The combined results from this study suggest that cellular mechanisms involving NOS-uncoupled ROS generation likely mediate PM-induced cardiac effects. Furthermore, mRNA expression for atrial and brain natriuretic peptides was increased in hearts from exposed mice compared to control, which is consistent with pulmonary congestion. There were no reported strain-related differences in any response.

Intratracheal Instillation

Similar to the responses observed by Tankersley et al. (2008, 157043), decreases in fractional shortening and increases in left ventricular end diastolic diameter measured by echocardiography were also reported for SD rats at 24 h post-IT exposure to DE particles (250 μg) (Yan et al., 2008, 098625). A subset of rats received isoproterenol to induce myocardial injury prior to IT instillation of DE particles and these animals demonstrated lowered fractional shortening at baseline, which was decreased to an even greater extent with DE particle exposure; left ventricular end diastolic diameter was not affected by DE particles in these rats.

Summary of Toxicological Study Findings for Cardiac Contractility

The studies above provide some evidence that cardiac contractility may be altered immediately following PM exposure in animal models. Results from the Tanksersley (2008, 157043) and Yan (2008, 098625) studies provide the strongest support for PM-induced contractility changes with inhalation exposure, as echocardiography and hemodynamic measurements are well-established for examining cardiac function.

6.2.7. Systemic Inflammation

The evidence presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) of increases in markers of systemic inflammation associated with PM was limited and not sufficient to formulate a definitive conclusion. Recent controlled human exposure and toxicological studies continue to provide mixed results for an effect of PM on markers of systemic inflammation including cytokine

levels, C-reactive protein (CRP), and white blood cell (WBC) count. While results from recent epidemiologic studies have also been inconsistent across studies, there is some evidence to suggest that PM levels may have a greater effect on inflammatory markers among populations with preexisting diseases.

6.2.7.1. Epidemiologic Studies

Several studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) investigated the association of short-term fluctuations in PM concentration with markers of inflammation. These studies were found to offer limited support for mechanistic explanations of the associations between PM concentration and heart disease outcomes. Recent studies, published since 2002, are reviewed below. CRP was measured in multiple studies, allowing the consistency of findings across epidemiologic studies to be evaluated. Several other markers were examined in only a few studies, in relation to a wide range PM size fractions and components. These markers included IL-6, TNF-α, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), soluble CD40 ligand (sCD40L), WBCs, and soluble adhesion molecules (sP-selectin and e-selectin).

Diez-Roux et al. (2006, 156400) examined whether CRP increased in response to changes in the mean ambient $PM_{2.5}$ concentrations in the prior day, prior 2 days, prior week, prior 30 days, and prior 60 days among participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Subjects (n = 5,634) lived in either Baltimore City or County, MD, Chicago, IL, Forsyth County, NC, Los Angeles County, CA, Northern Manhattan and the Bronx, NY, or St. Paul, MN. The authors report finding no evidence of a short-term effect of $PM_{2.5}$ on CRP in their population-based sample. Of the five exposure measures examined, only the 30-day and 60-day mean exposures showed positive associations with $PM_{2.5}$ (3% [95% CI: -2 to 10] and 4% [95% CI: -3 to 11] per 10 $\mu g/m^3$, respectively).

Ruckerl et al. (2007, 156931) conducted a multicity longitudinal study to examine whether changes in markers of inflammation were associated with short-term increases in particulate concentrations (PM_{10}, $PM_{2.5}$, PNC) and gaseous pollutant (NO_2, SO_2, CO, O_3). Study subjects were MI survivors (n= 1,003) living in either Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; or Stockholm, Sweden. Repeated measurements of IL-6 and CRP were made during the study. Fibrinogen was also measured in this study and results are discussed in Section 6.2.8.1. The mean city-specific pollutant concentrations during the study are shown below in Table 6-6. In pooled analyses, each interquartile range (not provided) increase in PNC in the 12-17 h before the health measurement was associated with a 2.7% increase in the geometric mean IL-6 levels (95% CI: 1.0-4.6). None of the pollutants, at any lag, were associated with CRP levels in these subjects. There did not appear to be effect modification of these results by smoking, diabetes, or heart failure. Ljungman et al. (2009, 191983) studied the modification of the IL-6 association with several PM size fractions (PM_{10}, $PM_{2.5}$, PNC) by three IL-6 SNPs, one fibrinogen α chain (FGA) single-nucleotide polymorphism (SNP) and one fibrinogen β chain (FGB) SNP. The associations of $PM_{2.5}$ and PM_{10} with plasma level of IL-6 were stronger among those with the homozygous minor allele genotype of FGB rs1800790 and among those homozygous for the major allele genotype of IL-6 rs2069832. Gene-environment interactions were most pronounced for CO. Modification the PNC-IL-6 association by genotype was not apparent in these data, nor was modification of the PM-IL-6 associations by FBA.

Single-city studies of systemic inflammation have also been conducted in the U.S. and Canada. Delfino et al. (2008, 156390) measured CRP, IL-6, TNF-α, sP-selectin, sVCAM-1 and sICAM-1 in blood during a period of 12 wk. Associations of these markers with average PM concentration ($PM_{0.25}$, $PM_{0.25\text{-}2.5}$, $PM_{10\text{-}2.5}$, PNC, EC, OC, BC, primary OC, secondary OC) 24 h to 9 days prior to the blood draw were examined. Subjects included residents of two downtown Los Angeles nursing homes who were >65 yr old with a history of coronary artery disease. Both 24-h avg and multiday average concentrations of $PM_{0.25}$, EC, primary OC, BC, PNC and gaseous pollutants were associated with CRP, IL-6 and sP-selectin.

Pope et al. (2004, 055238) conducted a panel study of 88 non-smoking, elderly subjects residing in the Salt Lake City, Ogden, and Provo metropolitan area of Utah. Each 100 $\mu g/m^3$ increase in same day mean $PM_{2.5}$ concentration was associated with a 0.81 mg/dL increase in CRP (95% CI: 0.48-1.14), but not WBCs. However, when excluding 1 influential subject, each 100 $\mu g/m^3$ increase in same day mean $PM_{2.5}$ concentration was associated with only a 0.19 mg/dL increase in

CRP (95% CI: -0.01 to 0.39). Several markers of coagulation were examined in this study and are discussed in Section 6.2.8.1.

Zeka et al. (2006, 157177) studied 710 elderly members of the VA Normative Aging Study to examine changes in CRP, sediment rate and WBCs with acute changes in PM concentrations in the previous 48 h, 1 wk, and 4 wk. Results for fibrinogen are discussed in Section 6.2.8.1. They did not find consistent or significant associations with any pollutant and CRP or WBC count. Sediment rate was significantly increased with PNC, BC and $PM_{2.5}$ concentration averaged over the previous 4 wk period. Modification of these PM effects by obesity, GSTM1 genotype and statin use was suggested in this study.

O'Neill et al. (2007, 091362) conducted a cross-sectional study of 92 Boston residents with type 2 diabetes, to examine the association between plasma levels of ICAM-1, VCAM-1 and PM concentrations. Results for markers of coagulation measured in this study are discussed in Section 6.2.8.1. $PM_{2.5}$, BC, and SO_4^{2-} concentrations were measured 0.5 km from the patient exam site. For all moving averages examined (1-6 days), increases in mean $PM_{2.5}$ and BC concentration were associated with increased ICAM-1 and VCAM-1 concentrations. Each 7.6 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentration over the previous 6 days was associated with a 11.76 ng/mL increase in VCAM-1 (95% CI: 3.48-20.70), and each 0.6 $\mu g/m^3$ increase in the mean BC concentration over the previous 6 days was associated with a 27.51 ng/mL increase in VCAM-1 (95% CI: 11.96-45.21). There were no consistent associations between mean SO_4^{2-} concentration and any marker at any lag.

Sullivan et al. (2007, 100083) conducted a panel study of 47 subjects (aged >55 yr) either with COPD (n = 23) or without COPD (n = 24) in Seattle, WA. They examined the association between levels of CRP and mean daily $PM_{2.5}$ concentration. Most values for IL-6 and TNF-α were below the limit of detection, so these cytokines were not included in the analyses. Results for fibrinogen and D-dimer are discussed in Section 6.2.8.1. They did not find any associations between 24-h mean $PM_{2.5}$ concentrations and levels of CRP in individuals with or without COPD.

In the study by Liu et al. (2006, 192002; 2007, 156705), conducted in Toronto, Ontario, neither CRP (0.11 μg/mL [95% CI: -0.03 to 0.25]) nor TNF-α (0.03 pg/mL [95% CI: -0.07 to 0.13]) was associated with personal exposure to PM_{10} (24-h averaging time).

Similarly, there was no association with IL-6. However, significant positive associations with markers of oxidative stress, FMD and BP were found and are discussed in Sections 6.2.9.1, 6.2.4.1, and 6.2.5.1, respectively.

In the St. Louis Bus Study, each 5.4 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentration over the previous week was associated with 5.5% increase in WBCs (95% CI: 0.10-11) (Dubowsky et al., 2006, 088750). Each 6.1 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentration over the previous 5 days was associated with a 14% increase in CRP among all subjects (95% CI: -5.4 to 37), but an 81% increase in CRP (95% CI: 21-172) among subjects with diabetes, obesity, and/or hypertension. Associations between $PM_{2.5}$ and IL-6 were only observed among those with diabetes, obesity, and/or or hypertension. In another study of in-vehicle $PM_{2.5}$, each 10 $\mu g/m^3$ increase during a work-shift was associated with decreased lymphocytes, increased mean corpuscular volume, neutrophils, and CRP over the next 10-14 h among 9 healthy North Carolina state troopers (Riediker et al., 2004, 056992). Associations of roadside and ambient $PM_{2.5}$ with systemic inflammatory markers were weaker and non-significant in this population.

International studies of the effect of air pollution on markers of inflammation have been conducted with mixed results. Two studies conducted among 57 male patients with coronary heart disease in Erfurt, Germany, found associations of UFP, ACP and PM_{10} with CRP (Ruckerl et al., 2006, 088754) and UFP and ACP with sCD40L, a marker for platelet activation (Ruckerl et al., 2007, 156931). In a large cross-sectional study of healthy subjects in Tel Aviv, Steinvil et al. (2008, 188893) examined biological markers of inflammation (CRP and WBCs) collected as part of routine health examinations for 3,659 individuals. Associations with air pollutants (including PM_{10}) measured at local monitoring sites for the day of the examination and up to 7 days prior were examined. No significant associations were found between pollutant levels and indications of enhanced inflammation. By contrast, PM_{10}, $PM_{2.5}$, SO_4^{2-} and nitrate (3-day avg concentrations) were associated with increases in hs-CRP in healthy students in Taiwan (Chuang et al., 2007, 091063). PM_{10}, $PM_{2.5}$ and $PM_{0.25}$ were not associated with CRP in a study of MI patients in Italy, although associations with autonomic dysregulation and more severe arrhythmias were observed (Folino et al., 2009, 191902). Kelishadi et al. (2009, 191960) reports that CRP, as well as markers of insulin resistance and oxidative stress (discussed in Section 6.2.9.1), were associated with PM_{10} in a cross-

sectional study of a population-based sample of children 10-18 yr old in Iran (mean PM_{10} concentration 122.08 µg/m^3).

Summary of Epidemiologic Study Findings for Systemic Inflammation

The most commonly measured marker of inflammation in the studies reviewed was CRP. CRP was not consistently associated with short-term PM concentrations ($PM_{2.5}$, PM_{10}, SO_4^{2-}, EC, OC, PNC). A multicity study of MI survivors in Europe (Ruckerl et al., 2007, 156931) failed to provide evidence of an effect of PM (e.g., PM_{10}, $PM_{2.5}$, PNC) on CRP and no effect was observed by Diez-Roux et al. (2006, 156400) in a population-based study when concentrations were averaged over periods less than 30 days. Several other markers of inflammation have been examined in relation to several PM size fractions and components, but the number of studies examining the same marker/PM metric combination is too few to allow results to be compared across epidemiologic studies. Mean and upper percentile concentrations for those epidemiologic studies that evaluated systemic inflammation are included in Table 6-6.

Table 6-6. PM concentrations reported in epidemiologic studies of inflammation, hemostasis, thrombosis, coagulation factors and oxidative stress.

Author	Location	Mean Concentration (µg/m^3)	Upper Percentile Concentrations (µg/m^3)
$PM_{2.5}$			
Chuang (2007, 091063)	Taipei, Taiwan	1-day avg: 31.8 2-day avg: 36.4 3-day avg: 36.5	1-day avg (range): 16.2-50.1 2-day avg (range): 15-53.4 3-day avg (range): 12.7-59.5
Diez-Roux (2006, 156400)	Chicago, IL Baltimore, MD Forsyth County, NC Los Angeles, CA New York City, NY St. Paul, MN	Prior day (median): 14.3 Prior 2 days (median): 14.4 Prior 7 days (median): 15.24 Prior 30 days (median): 15.69 Prior 60 days (median): 15.9	Prior day (75th): 20.9 Prior 2 days (75th): 20.35 Prior 7 days (75th): 19.7 Prior 30 days (75th): 19.22 Prior 60 days (75th): 19.08
Dubowsky (2006, 088750)	St. Louis (bus stops)	16	75th: 22 100th: 28
Folino (2009, 191902)	Padua, Italy	Summer: 33.9 Winter: 62.1 Spring: 30.8	NR
O'Neill (2007, 091362)	Boston, MA	11.4	Range: 0.07-33.7
Park (2008, 156845)	Boston, MA	12	Range: 2-62
Peters (2009, 191992)	Helsinki, Finland Stockholm, Sweden Augsburg, Germany Rome, Italy Barcelona, Spain	Helsinki: 8.2 Stockholm: 8.8 Augsburg: 17.4 Rome: 24.5 Barcelona: 24.2 Total: 16.4	Helsinki (range): 1-28 Stockholm (range): 0-27 Augsburg (range): 6-39 Rome (range): 4-95 Barcelona (range): 3-95 Total (range): 0-95

Author	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
Pope (2004, 055238)	Salt Lake City, Ogden, Provo Utah	FRM-Filled: 23.7 Not filled: 25.8 TEOM: 18.9 RAMS/PC-BOSS: 26.5	FRM-Filled (range): 1.7-74 Not filled (range): 1.7-74 TEOM (range): 2.2-61.5 RAMS/PC-BOSS (range): 5.6-72.4
Riediker (2004, 056992)	North Carolina State Troopers	Light Scatter: 24.1 Mass: 23 Ambient: 32.3 Roadside: 32.1	Light Scatter (range): 4.5-54.4 Mass (range): 7.1-38.7 Ambient (range): 9.9-68.9 Roadside (range): 8.9-62.2
Ruckerl (2007, 156931)	Helsinki, Finland Stockholm, Sweden Augsburg, Germany Rome, Italy Barcelona, Spain Athens, Greece	8.2 (19.4) 8.8 (19.1) 17.4 (29.3) 24.5 (54.1) 24.2 (64.7) 23 (46)	NR NR NR NR NR NR
Sørensen (2003, 157000)	Copenhagen, Denmark	Personal (median): 16.1 Urban background (median): 9.2	Personal (Q25-Q75): 10-24.5 Urban background (Q25-Q75): 5.3-14.8
Sullivan (2007, 100083)	Seattle, WA	Outdoor (median): 7.7 Indoor (median): 7.7	Outdoor: 75th- 11.5 90th- 19.9 Max- 33.9 Indoor: 75th- 12.1 90th- 16 Max- 81.4
Zeka (2006, 157177)	Boston, MA	48h (median): 9.39	75th: 14.57 90th: 21.48
$PM_{10-2.5}$			
Delfino (2008, 156390)	Los Angeles, CA	Outdoor: 10.04 (4.07) Indoor: 4.12 (4.76)	Outdoor (range): 1.76-22.38 Indoor (range): 0.12-37.63
Peters (2009, 191992)	Helsinki, Finland Stockholm, Sweden Augsburg, Germany Rome, Italy Barcelona, Spain	Helsinki: 8.9 Stockholm: 9 Augsburg: 15.8 Rome: 16.8 Barcelona: 16.5 Total: 13.3	Helsinki (range): 1-38 Stockholm (range): 0-40 Augsburg (range): -1 to 35 Rome (range): -33 to 65 Barcelona (range): 1-102 Total (range): -33 to 102
PM_{10}			
Baccarelli (2007, 090733)	Lombardia Region, Italy	Sep-Nov (median): 51.2 Dec-Feb (median): 68.5 Mar-May (median): 64.1 Jun-Aug (median): 44.3	Sep-Nov (max): 148.9 Dec-Feb (max): 238.3 Mar-May (max): 158.5 Jun-Aug (max): 94.7
Baccarelli (2007, 091310)	Lombardia Region, Italy	Median: 34.1	Maximum: 390
Chuang (2007, 091063)	Taipei, Taiwan	1-day avg: 49.2 2-day avg: 55.3 3-day avg: 54.9	1-day avg (range): 29.5-83.4 2-day avg (range): 25.5-85.1 3-day avg (range): 22.2-87.2

Author	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
Folino (2009, 191902)	Padua, Italy	Summer: 46.4 Winter: 73 Spring: 38.3	NR
Kelishadi (2009, 191960)	Isfahan, Iran	122.08	75th: 153 100th: 191
Liao (2005, 088677)	Washington County, MD Forsyth County, NC Minneapolis, MN (suburbs)	29.9	Q4: 47.3
Liu (2007, 156705)	Windsor, Ontario, Canada	Personal (median): 0-24 h before clinical visit: 25.5 0-6 h before clinical visit: 15.3 7-12 h before clinical visit: 17 13-18 h before clinical visit: 28.5 19-24 h before clinical visit: 30.5	Personal (5th to 95th): 0-24 h before clinical visit: 9.8-133 0-6 h before clinical visit: 5.3-83.2 7-12 h before clinical visit: 7.1-186.3 13-18 h before clinical visit: 11.4-167 19-24 h before clinical visit: 10.1-148.2
Peters (2009, 191992)	Helsinki, Finland Stockholm, Sweden Augsburg, Germany Rome, Italy Barcelona, Spain	Helsinki: 17.1 Stockholm: 17.8 Augsburg: 33.1 Rome: 42.1 Barcelona: 40.7 Total: 30.3	Helsinki (range): 4-53 Stockholm (range): 0-57 Augsburg (range): 7-71 Rome (range): 15-91 Barcelona (range): 6-194 Total (range): 0-194
Ruckerl (2007, 156931)	Helsinki, Finland Stockholm, Sweden Augsburg, Germany Rome, Italy Barcelona, Spain Athens, Greece	17.1 17.8 33.1 42.1 40.7 38.5	NR NR NR NR NR NR
Steinvil (2008, 188893)	Tel Aviv, Israel	64.5	75th: 60.7

6.2.7.2. Controlled Human Exposure Studies

Several controlled human exposure studies were included in the 2004 PM AQCD (U.S. EPA, 2004, 056905) which evaluated markers of systemic inflammation following exposure to PM. Salvi et al. (1999, 058637) exposed 15 healthy volunteers (21-28 yr) for 1 h to DE (300 μg/m^3 particle concentration) and observed a significant increase in neutrophils in peripheral blood 6 h post-exposure compared with filtered air control. However, Ghio et al. (2003, 087363) reported no changes in plasma cytokine levels (e.g., IL-6 and TNF-α), WBC count, or CRP 0 or 24 h following a 2-h exposure to $PM_{2.5}$ CAPs (120 μg/m^3). Gong et al. (2003, 042106) did not observe any effect of $PM_{2.5}$ CAPs (174 μg/m^3) on serum amyloid A, while Frampton (2001, 019051) reported no change in leukocyte activation following exposure to a low concentration (10 μg/m^3) of UF carbon. The results of studies published since the completion of the 2004 PM AQCD (U.S. EPA, 2004, 056905) are discussed below.

CAPs

Several controlled human exposure studies have reported no change in plasma CRP levels 0-24 h after exposure to UF (avg concentration 50-100 μg/m^3), $PM_{2.5}$ (avg concentration 190 μg/m^3), or $PM_{10-2.5}$ (avg concentration 89 μg/m^3) CAPs (Gong et al., 2008, 156483; Graff et al., 2009, 191981; Mills et al., 2008, 156766; Samet et al., 2009, 191913). In a study of exposures to $PM_{2.5}$ CAPs (200 μg/m^3), Gong et al. (2004, 087964) observed increased peripheral basophils 4 h following a 2-h exposure in a group of healthy older adults, which provides limited evidence of a CAPs-induced systemic inflammatory response.

Urban Traffic Particles

In a recent investigation of controlled exposures (24 h) to urban traffic particles, Bräuner et al. (2008, 191966) observed no effect of PM concentration (avg $PM_{2.5}$ concentration 10.5 μg/m^3) on markers of inflammation including CRP, IL-6 and TNF- α in peripheral venous blood.

Diesel Exhaust

Recent controlled human exposure studies have observed no effect of DE on plasma CRP concentrations or peripheral blood cell counts (Blomberg et al., 2005, 191991; Carlsten et al., 2007, 155714; Mills et al., 2005, 095757; Mills et al., 2007, 091206; Tornqvist et al., 2007, 091279). Mills et al. (2005, 095757) found no effect of DE (300 μg/m^3) on serum IL-6 or TNF-α among healthy adult volunteers 6 h after exposure. However, as reported by Tornqvist et al. (2007, 091279), a significant increase in these cytokines was observed 24 h after exposure. Although the physiological significance of this finding is unclear, this study does provide evidence of a mild systemic inflammatory response induced by exposure to DE. In an effort to better understand the inflammatory response of exposure to PM, Peretz et al. (2007, 156853) conducted a pilot study in which gene expression in peripheral blood mononuclear cells (PBMCs) of healthy human volunteers was evaluated following a 2-h controlled exposure to DE (200 μg/m^3 $PM_{2.5}$). Adequate RNA samples for microarray analysis from both pre- and 4 h post-exposure to filtered air and DE were available in 4 of the 11 subjects enrolled. The authors found differential expression of 10 genes involved in the inflammatory response when comparing DE exposure (8 upregulated, 2 downregulated) to filtered air. Two participants had paired samples from 20 h post-exposure which were adequate for analysis. At this time point, DE was associated with 4 differentially expressed genes (1 upregulated, 3 downregulated). However, this study is limited by a small sample size with limited statistical power.

Wood Smoke

Barregard et al. (2006, 091381) recently reported an increase in serum amyloid A at 0, 3, and 20 h following a 4-h exposure to wood smoke ($PM_{2.5}$ concentrations of 240-280 μg/m^3) among a group of 13 healthy adults (20-56 yr).

Model Particles

Frampton et al. (2006, 088665) evaluated the effect of varying concentrations (10-50 μg/m^3) of UF EC on blood leukocyte expression of adhesion molecules in healthy and asthmatic adults. Healthy subjects (n = 40) were exposed for 2 h to filtered air and UF EC under three separate protocols: 10 μg/m^3 at rest (n = 12), 10 and 25 μg/m^3 with intermittent exercise (n = 12), and 50 μg/m^3 with intermittent exercise (n = 16). Asthmatics (n = 16) were exposed at a single concentration (10 μg/m^3) for 2 h with intermittent exercise. Leukocyte expression of surface markers were quantified using flow cytometry on peripheral venous blood samples collected prior to and immediately following exposure, as well as at 3.5 and 21 h post-exposure. Among healthy resting adults, UF EC exposure at a concentration of 10 μg/m^3 had no effect on blood leukocytes. The expression of adhesion molecules CD54 and CD18 on monocytes, and CD18 on PMNs was shown

to decrease with UF EC exposure in healthy exercising adults. In exercising asthmatics, expression of CD11b on monocytes and eosinophils, as well as CD54 on PMNs were reduced following exposure to UF EC. In both asthmatics and healthy adults, a UF EC-induced decrease in eosinophils and basophils was observed 0-21 h following exposure. Although the clinical significance of these findings is unclear, the authors concluded that their findings of UF EC-induced changes in leukocyte distribution and expression were consistent with increased retention of leukocytes in the pulmonary vasculature, which may be due to an increase in pulmonary vasoconstriction. Other studies have reported no changes in plasma cytokine levels, peripheral blood counts, or CRP following exposure to ZnO or UF EC (Beckett et al., 2005, 156261; Routledge et al., 2006, 088674).

Summary of Controlled Human Exposure Study Findings for Systemic Inflammation

New studies involving controlled exposures to various particle types have provided limited and inconsistent evidence of a PM-induced increase in markers of systemic inflammation.

6.2.7.3. Toxicological Studies

There has been limited evidence that enhanced hematopoiesis may occur in animals exposed to PM. Two studies in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provided support for this effect, with one study measured stimulated release of PMNs from bone marrow and another examined peripheral blood PMN and blood cell counts; however, one study did not find associations between CAPs and peripheral blood counts. Thus, it was concluded that consistent evidence of PM-induced hematopoiesis remained to be demonstrated. However, in a study of humans exposed to biomass burning during the 1997 Southeast Asian smoke-haze episodes, PM_{10} demonstrated the best relationship with blood PMN band cell counts expressed as a percentage of total PMN at lag 0 and 1, indicating a relatively quick response (Tan et al., 2000, 002304).

CAPs

A 2-day CAPs study employing SH rats did not report increased WBCs 18-20 h post-exposure (Kodavanti et al., 2005, 087946). A study utilizing fine and/or UF CAPs demonstrated decreased WBCs in SH rats 18 h after a 2-day (6 h/day) exposure (Kooter et al., 2006, 097547). The decrease was largely attributable to lowered neutrophils in the fine CAPs-exposed rats and reduced lymphocytes in the fine+UF CAPs-exposed animals.

Model Particles

In a study of fine and UF CB particles (WKY rats; 7 h; mean mass concentration 1,400 and 1,660 $\mu g/m^3$ for fine and UF CB, respectively; mean number concentration 3.8×10^3 and 5.2×10^4 particles/cm^3, respectively), only UF CB induced elevated blood leukocytes at 0 and 48 h post-exposure compared to the control rats and no effect was observed at 16 h (Gilmour et al., 2004, 054175). In another study of SH rats exposed to UF carbon particles for 24 h (mass concentration 172 $\mu g/m^3$; mean number concentration 9.0×10^6 particles/cm^3), the percent neutrophils and lymphocytes were increased on the first recovery day, but not the third day (Upadhyay et al., 2008, 159345); CRP was unchanged. In another study, blood neutrophils were decreased in SH rats exposed to UF CB for 6 h and no effects were observed in old F344 rats (Elder et al., 2004, 055642). Plasma IL-6 levels were unchanged (Elder et al., 2004, 055642).

Coal Fly Ash

Smith et al. (2006, 110864) examined the hematology parameters in SD rats following a 3-day inhalation exposure (4 h/day) to coal fly ash (mean mass concentration 1,400 $\mu g/m^3$) and reported increased blood neutrophils and reduced blood lymphocytes at 36 h but not 18 h post-exposure.

Intratracheal Instillation

Elevated systemic IL-6 and TNF-α levels were observed following PM_{10} instillation in mice (details provided in Section 6.2.8.3) (Mutlu et al., 2007, 121441). IL-6 was decreased with PM exposure in macrophage-depleted mice, indicating that some of the IL-6 release originated from macrophages. For mice (male C57Bl/6J) exposed to $PM_{10-2.5}$ derived from coal fly ash (200 μg), increased plasma IL-6 levels were only observed in animals that also received 100 μg of LPS (Finnerty et al., 2007, 156434) and this response was not observed with LPS alone, indicating a role for $PM_{10-2.5}$.

Summary of Toxicological Study Findings for Systemic Inflammation

Overall, these studies provide evidence of time-dependent responses of systemic inflammation induced by PM exposure. Alterations in WBCs have been reported generally as elevations immediately (0 h) or <36 h post-exposure and no change or reductions are noted from 18-24 h.

6.2.8. Hemostasis, Thrombosis and Coagulation Factors

The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented limited and inconsistent evidence from epidemiologic, controlled human exposure, and toxicological studies of PM-induced changes in blood coagulation markers. The body of scientific literature investigating hemostatic effects of PM has grown significantly since the publication of the 2004 PM AQCD (U.S. EPA, 2004, 056905), with a limited number of epidemiologic studies demonstrating consistent increases in von Willebrand factor (vWf) associated with PM and less consistent associations with fibrinogen. Recent controlled human exposure and toxicological studies have also observed changes in blood coagulation markers (e.g., fibrinogen, vWf, factor VII, t-PA) following exposure to PM. However, the findings of these studies are somewhat inconsistent, which may be due in part to differences in the post-exposure timing of the assessment.

6.2.8.1. Epidemiologic Studies

Several studies investigating the association of short-term fluctuations in PM concentration with markers of coagulation (e.g., blood viscosity and fibrinogen) were included in the 2004 PM AQCD (U.S. EPA, 2004, 056905). These preliminary studies offered limited support for mechanistic explanations of the associations of PM concentration with heart disease outcomes. New studies, published since 2002, are reviewed in this section. Only vWF and fibrinogen were measured in enough comparable studies to allow the consistency of findings to be evaluated across epidemiologic studies. Other markers of coagulation studied included D-dimer, prothombin time, Factor VII/VIII and tPA.

Liao et al. (2005, 088677) used a cross-sectional study to examine the association between short-term increases in air pollutant concentrations (mean PM_{10}, NO_2, CO, SO_2, and O_3 over the previous 3 days) and several plasma hemostatic markers (fibrinogen, factor VIII-C, vWF, albumin). Study subjects were middle aged participants in the ARIC (Atherosclerosis Risk in Communities) study (n = 10,208), and were residents of Washington County, MD, Forsyth County, NC, selected suburbs of Minneapolis, MN, or Jackson, MS. Each 12.8 $\mu g/m^3$ increase in the mean PM_{10} concentration 1 day before the health measurements were made was associated with a 3.93% increase in vWF (95% CI: 0.40-7.46) among diabetics, but not among non-diabetics (-0.54% [95% CI: -1.68 to 0.60]). Each 12.8 $\mu g/m^3$ increase in the mean PM_{10} concentration 1 day before the health measurements were made was also associated with a 0.006 g/dL decrease in serum albumin (95% CI: -0.012 to 0.000) among those with cardiovascular disease (CVD), but not among those without CVD (0.029 g/dL increase [95% CI: -0.004 to 0.062]). The mean CO concentration on the previous day was also associated with a significant decrease in serum albumin. The authors reported significant curvilinear associations between PM_{10} and factor VIII-C, which may indicate a threshold effect. Similar curvilinear associations were observed between O_3 with fibrinogen, and vWF, and SO_2 with factor VIII-C, WBC, and serum albumin (Liao et al., 2005, 088677). No significant associations with fibrinogen and PM10 or gaseous pollutants were observed.

In the European multicity study described in Section 6.2.7.1, Ruckerl et al. (2007, 156931) found that each 13.5 μg/m^3 increase in the mean PM_{10} concentration over the previous 5 days was associated with a 0.6% increase in the arithmetic mean fibrinogen level (95% CI: 0.1-1.1). Further these investigators found that promoter polymorphisms within FGA and FGB modified the association of 5-day avg PM_{10} concentration with plasma fibrinogen levels (Peters et al., 2009, 191992). This association was 8-fold higher among those homozygous for the minor allele genotype of FGB rs1800790 compared with those homozygous for the major allele.

Several smaller studies have been conducted in the U.S. and Canada. Delfino et al. (2008, 156390) measured fibrinogen and D-dimer in blood of subjects who resided at two downtown Los Angeles nursing homes. As described in Section 6.2.7.1, measurements were made over a period of 12 wk and subjects were >65 yr old with a history of coronary artery disease. These markers were not associated with the broad array PM metrics studied (e.g., $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{10-2.5}$, EC, OC, primary OC, BC). In the study of 92 Boston residents with type 2 diabetes described previously, O'Neill et al. (2007, 091362) found that increases in mean $PM_{2.5}$ and BC concentration were associated with vWF concentrations for all moving averages examined (1-6 days). Reidiker et al. (2004, 056992) reported that in-vehicle $PM_{2.5}$ was associated with increased vWF over the next 10-14 h among nine police troopers. Sullivan et al. (2007, 100083) did not observe associations with fibrinogen, or D-dimer in individuals with or without COPD. Red blood cells (RBCs), platelets, nor blood viscosity were associated with $PM_{2.5}$ concentration in a panel study of 88 non-smoking elderly subjects residing in the Salt Lake City, Ogden and Provo metropolitan area of Utah (Pope et al., 2004, 055238). Although Zeka et al. (2006, 157177) did not observe an association with CRP in the analysis of the Normative Aging Study population in Boston (Section 6.3.7.1), increased fibrinogen level was associated with increases in the number of particles/cm^3 over the previous 48 h and 1 wk, and an incremental increase in BC concentration over the previous 4 wk. There were no consistent findings for lagged $PM_{2.5}$ or sulfates (Zeka et al., 2006, 157177).

Several studies of coagulation markers were conducted outside the U.S. and Canada. In a study of healthy individuals in Taiwan, associations were observed for $PM_{2.5}$, PM_{10}, nitrate, and SO_4^{2-} concentrations with fibrinogen and plasminogen activator fibrinogen inhibitor-1 (PAI-1) (Chuang et al., 2007, 091063). In a large cross-sectional study of healthy subjects in Tel-Aviv, Steinvil et al. (2008, 188893) examined fibrinogen collected as part of routine health examinations for 3,659 individuals. No significant associations were found between pollutant levels (lagged 1-7 days) and fibrinogen. Finally, Baccarelli and colleagues reported associations between PM_{10} and prothrombin time among normal subjects (Baccarelli et al., 2007, 090733).

Summary of Epidemiologic Study Findings for Hemostasis, Thrombosis and Coagulation

The most commonly measured markers of coagulation in the studies reviewed were fibrinogen and vWF. Associations of PM_{10} (Liao et al., 2005, 088677) and $PM_{2.5}$ (O'Neill et al., 2007, 091362; Riediker et al., 2004, 056992) with increased vWF were observed across the limited number of studies examining this association among both diabetics and healthy state troopers state troopers (Liao et al., 2005, 088677; Riediker et al., 2004, 056992). Results for fibrinogen were not consistent across epidemiologic studies. Positive associations with fibrinogen were reported in older adults residing in Boston (Zeka et al., 2006, 157177) and in the multicity European study of MI survivors. Liao et al. (2005, 088677) in a population based multicity study and Sullivan et al. (2007, 100083) did not observe associations of PM_{10} or $PM_{2.5}$ with fibrinogen. Several other markers have been examined (e.g., D-dimer, prothrombin time), but not in adequate numbers of studies to allow comparisons across epidemiologic studies. Mean and upper percentile concentrations of the studies discussed in this section are listed in Table 6-6.

6.2.8.2. Controlled Human Exposure Studies

In two separate studies conducted by Ghio and colleagues, controlled exposures (2 h) to fine CAPs (Chapel Hill, NC) at concentrations between 15 and 350 μg/m^3 were shown to increase blood fibrinogen 18-24 h following exposure among healthy adults (Ghio et al., 2000, 012140; Ghio et al., 2003, 087363). Increases in blood fibrinogen or factor VII would suggest an increase in blood coagulability, which could result in an increased risk of coronary thrombosis. However, a similar

study conducted in Los Angeles observed a $PM_{2.5}$ CAPs-induced decrease in factor VII blood levels in healthy subjects and found no association between $PM_{2.5}$ CAPs and blood fibrinogen among healthy and asthmatic volunteers (Gong et al., 2003, 042106). Since the publication of the 2004 PM AQCD (U.S. EPA, 2004, 056905), several new controlled human exposure studies have evaluated the effects of PM on blood coagulation markers.

CAPs

Two studies of controlled human exposures to Los Angeles CAPs among older adults with COPD ($PM_{2.5}$ CAPs) and adults with and without asthma (UF CAPs) reported no significant association between exposure and blood coagulation markers at 0, 4, or 22 h post-exposure (Gong et al., 2004, 087964; 2008, 156483). Graff et al. (2009, 191981) observed a decrease in the concentration of D-dimer of marginal statistical significance in healthy adults (11.3% decrease per 10 $\mu g/m^3$, $p = 0.07$) following exposure to $PM_{10-2.5}$ CAPs (89 $\mu g/m^3$). At 20 h post-exposure, levels of tPA in plasma were shown to decrease by 32.9% from baseline per 10 $\mu g/m^3$ increase in CAPs concentration. No other markers of hemostasis or thrombosis were affected by exposure to $PM_{10-2.5}$ CAPs. However, in a similar study from the same laboratory, Samet et al. (2009, 191913) reported a statistically significant increase in D-dimer immediately following, as well as 18 h, after a 2-h exposure to UF CAPs (49.8 $\mu g/m^3$; 120,662 particles/cm^3) in a group of healthy adults (18-35 yr). Plasma concentrations of PAI-1 were also reported to increase 18 h after exposure to UF CAPs, although this increase was not statistically significant ($p = 0.1$). No changes in fibrinogen, tPA, vWF, plasminogen, or factor VII were observed. The finding of an increase in D-dimer following exposure to UF CAPs provides potentially important information in elucidating the relationship between elevated concentrations of PM and cardiovascular morbidity and mortality observed in epidemiologic studies. Whereas many coagulation markers provide evidence of an increased potential to form clots (e.g., an increase in fibrinogen or a decrease in tPA), D-dimer is a degradation product of a clot that has formed.

Urban Traffic Particles

In a study of controlled 24-h exposures to urban traffic particles (avg $PM_{2.5}$ concentration 10.5 $\mu g/m^3$) among 29 healthy adults, Bräuner et al. (2008, 191966) did not observe any particle-induced change in plasma fibrinogen, factor VII, or platelet count after 6 or 24 h of exposure. Similarly, Larsson et al. (2007, 091375) observed no change in PAI-1 or fibrinogen in peripheral blood of healthy adult volunteers 14 h after a 2-h exposure to road tunnel traffic with a $PM_{2.5}$ concentration of 46-81 $\mu g/m^3$.

Diesel Exhaust

Mills and colleagues have recently demonstrated a significant effect of DE (particle concentration 300 $\mu g/m^3$) on fibrinolytic function both in healthy men ($n = 30$) and in men with coronary heart disease ($n = 20$) (Mills et al., 2005, 095757; 2007, 091206). In both groups of volunteers, bradykinin-induced release of tPA was observed to decrease 6 h following exposure to DE compared to filtered air exposure. The same laboratory did not observe an attenuation of tPA release 24 h after a 1-h exposure to DE (300 $\mu g/m^3$) in a group of health adults (Tornqvist et al., 2007, 091279), or observe any change in markers of hemostasis or thrombosis 6 or 24 h following DE exposure at the same particle concentration among a group of older adults with COPD (Blomberg et al., 2005, 191991). Carlsten et al. (2007, 155714) conducted a similar study involving exposure of healthy adults to DE with a $PM_{2.5}$ concentration of 200 $\mu g/m^3$. Although the authors observed an increase in D-dimer, vWF, and platelet count 6 h following exposure to DE, these increases did not reach statistical significance. In a subsequent study with a similar study design, the same laboratory found no effect of a 2-h exposure to DE (100 and 200 $\mu g/m^3$ $PM_{2.5}$) on prothrombotic markers in a group ($n = 16$) of adults with metabolic syndrome (Carlsten et al., 2008, 156323). The authors postulated that the lack of significant findings could be due to a relatively small sample size. In addition, Carlsten et al. (2007, 155714; 2008, 156323) exposed subjects at rest

while Mills et al. (2005, 095757) exposed subjects to a higher concentration (300 μg/m^3) with intermittent exercise. A more recent study of DE which exposed healthy adults to a slightly higher particle concentration (330 μg/m^3) evaluated the effect of DE on thrombus formation using an ex vivo perfusion chamber (Lucking et al., 2008, 191993). Thrombus formation, as well as in vivo platelet activation, was observed to significantly increase 2 h following exposure to DE relative to filtered air, thus providing some evidence of a potential physiological mechanism which may explain in part the associations between PM and cardiovascular events observed in epidemiologic studies.

Wood Smoke

Barregard et al. (2006, 091381) recently evaluated the effect of wood smoke on markers of coagulation, inflammation, and lipid peroxidation. Subjects (n = 13) were healthy males and females (20-56 yr) and were exposed for 4 h to $PM_{2.5}$ concentrations of 240-280 μg/m^3. The authors reported an increase in the ratio of factor VIII/vWF, which is an indicator of an increased risk of venous thromboembolism, at 0, 3, and 20 h following exposure to wood smoke.

Model Particles

Routledge et al. (2006, 088674) did not observe any changes in fibrinogen or D-dimer following a 1-h exposure to UF carbon among a group of resting healthy older adults and older adults with stable angina. Similarly, Beckett et al. (2005, 156261) found no changes in hemostatic markers (e.g., factor VII, fibrinogen, and vWF) following exposure to UF and fine ZnO (500 μg/m^3).

Summary of Controlled Human Exposure Study Findings for Hemostasis, Thrombosis and Coagulation

Taken together, these new studies have provided some additional evidence that short-term exposure to PM at near ambient levels may have small, yet statistically significant effects on hemostatic markers in healthy subjects or patients with coronary artery disease.

6.2.8.3. Toxicological Studies

In general, the limited toxicological studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) reported positive and negative findings for plasma fibrinogen levels or other factors involved in the coagulation cascade. Rats exposed to New York City CAPs did not have any exposure-related effects on any measured coagulation markers (Nadziejko et al., 2002, 050587), whereas rats exposed to a high concentration of ROFA demonstrated increased plasma fibrinogen (Kodavanti et al., 2002, 025236).

CAPs

A $PM_{2.5}$ CAPs exposure conducted for 2 days (4 h/day; mean mass concentration 144-2,758 μg/m^3; 8-10/2001; RTP, NC) in SH rats induced plasma fibrinogen increases (measured 18-20 h post-exposure) in 5 of 7 separate studies (Kodavanti et al., 2005, 087946). Fibrinogen was not different from the air control group on the two days with the highest CAPs concentrations (1,129 and 2,758 μg/m^3), indicating that the response was likely not attributable to mass alone.

In SH rats exposed to $PM_{2.5}$ CAPs for 6 h in one of three locations in the Netherlands (mean mass concentration range 270-2,400; 335-3,720; and 655-3,660 μg/m^3), plasma fibrinogen was increased 48 h post-exposure when all CAP-exposed animals were combined in the analysis (Cassee et al., 2005, 087962). In WKY rats pre-exposed to O_3 (8 h; 1,600 μg/m^3) and CAPs for 6 h, increases in RBCs, hemoglobin, and hematocrit were observed 2 days after CAPs exposure. For SH rats exposed to CAPs only, decreased mean corpuscular hemoglobin concentration were reported.

A similar study conducted by the same group (Kooter et al., 2006, 097547) reported no changes in plasma fibrinogen measured 18 h after a 2-day exposure (6 h/day) to $PM_{2.5}$ or $PM_{2.5}$+UF CAPs (mean mass concentration range 399.0-1,067.5 and 269.0-555.8 μg/m^3, respectively; 1/2003-4/2004). However, elevated vWF was observed in SH rats exposed to the highest concentration of $PM_{2.5}$ CAPs. Decreases in mean corpuscular volume (MCV), and elevations in mean platelet volume (MPV) and mean platelet component (MPC) were reported in SH rats 18 h following a 2-day exposure to $PM_{2.5}$+UF CAPs in a freeway tunnel.

Traffic-Related Particles

Plasma fibrinogen levels were elevated 18 h following a single 6-h exposure to on-road highway aerosols when groups of rats pretreated with saline or influenza virus were combined (i.e., there was a significant effect of particles) (Elder et al., 2004, 087354).

Model Particles

The coagulation effects of inhaled UF CB at a concentration of 150 μg/m^3 (number count not provided) for 6 h were evaluated 24 h post-exposure in two aged rat models (11-14 mo SH and 23 mo F344), some of which received LPS via intraperitoneal injection prior to particle exposure (Elder et al., 2004, 055642). LPS has been shown to induce the expression of molecules involved in coagulation, inflammation, oxidative stress, and the acute-phase response. In those animals only exposed to CB, SH rats demonstrated increased thrombin-anti-thrombin complexes (TAT) and decreased fibrinogen. For F344 rats, TAT complexes and fibrinogen were elevated only in those that received LPS and CB. Whole-blood viscosity was not altered in either rat strain with particle exposure.

In another study of SH rats exposed to UF carbon particles for 24 h (mass concentration 172 μg/m^3; mean number concentration 9.0×10^6 particles/cm^3), the number of RBCs and platelets and hematocrit percent, were unchanged 1 and 3 days following exposure (Upadhyay et al., 2008, 159345). Fibrinogen levels were similar in both air and UF carbon-exposed groups. However, mRNA expression of PAI-1 and TF in lung homogenates (but not in heart) was increased on recovery day 3 after exposure. A study of similar design that employed SH rats did not report any effect on plasma fibrinogen 4 or 24 h following UF carbon exposure (mass concentration 180 μg/m^3; mean number concentration 1.6×10^7 particles/cm^3) (Harder et al., 2005, 087371). Similarly, clotting factor VIIa and thrombomodulin, PAI-1, and tPA mRNA expression were not affected by UF carbon exposure at 24 h post-exposure.

Coal Fly Ash

One study that employed coal fly ash (mean mass concentration 1,400 μg/m^3; 4 h/day×3 days) demonstrated increases in hematocrit and MCV in SD rats at 36 h but not 16 h post-exposure (Smith et al., 2006, 110864).

Intratracheal Instillation

Mutlu et al. (2007, 121441) used a PM_{10} sample collected from Dusseldorf, Germany, in mice (C57BL/6) with and without the gene coding for IL-6. The authors report using a moderate IT instillation dose (10 μg/mouse; roughly equivalent to 400-500 μg/kg); the PM sample had previously been characterized as having significant Fe, Ni, and V content (Upadhyay et al., 2003, 097370). In C57BL/6 mice, the Dusseldorf PM shortened bleeding (32%), prothrombin (13%), and activated partial thromboplastin (16%) times and increased platelet count, fibrinogen, and Factors II, VIII, and X activities 24 h following exposure. The authors further demonstrated accelerated coagulation by a reduction in the left carotid artery occlusion time (experimentally-derived by direct application of $FeCl_3$). Additional experiments demonstrated that IL-6$^{-/-}$ or macrophage-depleted mice showed dramatically attenuated effects of PM_{10} on hemostatic indices, thrombin generation, and occlusion

time. In IL-$6^{-/-}$ mice, there was no change in total cell counts or differentials in BALF compared to the wild-type mice, despite the lack of IL-6. In contrast, the model of macrophage depletion had reduced levels of macrophages and IL-6 in BALF, following PM exposure. These studies suggest that instillation of Dusseldorf PM_{10} activates clotting through an alveolar macrophage-dependent release of IL-6; however, other factors may also be involved in the prothrombotic response (i.e., activation of neutrophils, other inflammatory cells, or alterations in the levels of other cytokines).

In a study employing $PM_{10-2.5}$ collected from six European locations with contrasting traffic profiles, fibrinogen increases were observed in SH rats exposed to 10 mg/kg via IT instillation at 24 h post-exposure and similar responses were observed with $PM_{2.5}$ (Gerlofs-Nijland et al., 2007, 097840). $PM_{10-2.5}$ and $PM_{2.5}$ samples from Prague or Barcelona administered intratracheally to SH rats (7 mg/kg) resulted in elevated plasma fibrinogen levels 24 h post-exposure compared to rats instilled with water (Gerlofs-Nijland et al., 2009, 190353). No changes were observed in vWF for whole particle suspensions, but Barcelona $PM_{10-2.5}$ organic extract induced greater levels of vWF than Barcelona $PM_{10-2.5}$.

Summary of Toxicological Study Findings for Hemostasis, Thrombosis and Coagulation

Increases in coagulation and thrombotic markers were observed in some studies of rats or mice exposed to PM. Plasma TAT complexes were increased in CB-exposed SH rats and shortened bleeding, prothrombin, and activated partial thromboplastin times were observed in mice exposed via IT instillation to PM_{10}. Furthermore, the latter study also reported increased levels of Factors II, VIII, and X activities in mice. Another study demonstrated increased vWF in response to $PM_{2.5}$ CAPs. As for plasma fibrinogen, these studies provide some evidence that increased levels are observed 18-48 h post-exposure to PM, although one study reported no change and another reported a decrease in this biomarker. Alterations in platelet measurements have also been observed with PM exposure, including increased platelet number, mean platelet volume, and mean platelet component. The toxicological results of RBC-related measurements are limited and inconsistent following PM exposure, which may be attributable to different exposure protocols, time of analysis, or rat strain.

6.2.9. Systemic and Cardiovascular Oxidative Stress

Very little information on systemic oxidative stress associated with PM was available for inclusion in the 2004 PM AQCD (U.S. EPA, 2004, 056905). However, recent epidemiologic studies have provided consistent evidence of PM-induced increases in markers of systemic oxidative stress including plasma thiobarbituric acid reactive substances (TBARS), CuZn-super oxide dismutase (SOD), 8-oxo-7-hydrodeoxyguanosine (8-oxodG), and total homocysteine. This is supported by a limited number of controlled human exposure studies that observed PM-induced increases in free-radical mediated lipid peroxidation, as well as upregulation of the DNA repair gene hOGG1. In addition, recent toxicological studies have demonstrated an increase in cardiovascular oxidative stress following PM exposure in rats.

6.2.9.1. Epidemiologic Studies

No studies of markers of oxidative stress were reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Since 2002, numerous studies have examined whether short-term increases in mean PM concentrations are associated with changes in systemic markers of oxidative stress.

In an analysis of the randomized trial of omega-3 fatty acid supplementation in Mexico City nursing home residents described previously (Section 6.2.1.1), Romieu et al. (2008, 156922) investigated the effect of this intervention on markers of systemic oxidative stress (Cu/Zn SOD activity, LPO in plasma and GSH in plasma). A significant decrease of Cu/Zn SOD was associated with a 10 $\mu g/m^3$ increase of $PM_{2.5}$ in both groups (Fish oil: $\beta = -0.17$ [SE = 0.05], $p = 0.002$; Soy oil: $\beta = -0.06$ [SE = 0.02], $p < 0.001$). A decrease in GSH was associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ in the fish oil group ($\beta = -0.09$ [SE = 0.04], $p = 0.017$).

Two studies evaluated plasma homocysteine levels in relation to PM. Baccarelli et al. (2007, 091310) investigated fasting and post-methionine load total homocysteine (tHcy) among 1,213 normal subjects in Lombardia, Italy. Plasma homocysteine is a risk factor for CVD and a marker for oxidative stress. Among smokers, average PM_{10} level during the 24 h preceding the measurement was associated with 6.3% (95% CI: 1.3-11.6) and 4.9% (95% CI: 0.5-9.6) increases in fasting and post-methionine load tHcy, respectively. No associations were observed among non-smokers. Park et al. (2008, 156845) investigated the association of BC, OC, SO_4^{2-} and $PM_{2.5}$ with tHcy among 960 male participants of the Normative Aging Study. Effect modification by folate and vitamins B6 and B12 was also examined. BC and OC were associated with increases in tHcy and associations were more pronounced in those with lower plasma folate and vitamin B12.

In smaller studies with 25-50 healthy or diseased participants, several markers of oxidative stress have been associated with PM size fractions or components. These associations include TBARS with 24-h PM_{10} (Liu et al., 2006, 192002); Cu/Zn-SOD with several PM metrics (e.g., UF, $PM_{10-2.5}$, EC, OC, BC and PNC) (Delfino et al., 2008, 156390); $PM_{2.5}$, BC, V and Cr with plasma proteins (Sørensen et al., 2003, 157000); DNA damage assessed by 8-oxodG in lymphocytes (Sørensen et al., 2003, 157000), and 8-OHdG with sulfates (Chuang et al., 2007, 091063). In addition, a cross-sectional study of children (10-18 yr) in Iran showed an association of PM_{10} with oxidized LDL (oxLDL), malondialdehyde (MDA) and conjugated diene (CDE) (Kelishadi et al., 2009, 191960).

Summary of Epidemiologic Study Findings for Systemic and Cardiovascular Oxidative Stress

Oxidative stress responses measured by one or more markers (plasma tHcy, CuZn-SOD, TBARS, 8-oxodG, oxLDL and MDA) have been consistently observed (Baccarelli et al., 2007, 091310; Chuang et al., 2007, 091063; Delfino et al., 2008, 156390; Kelishadi et al., 2009, 191960; Liu et al., 2007, 156705; Romieu et al., 2008, 156922; Sørensen et al., 2003, 157000). In addition, a series of analyses examining the modification the PM-HRV association by genetic polymorphisms related to oxidative stress has provided insight into the possible mechanisms of CVD observed in association with PM concentrations (Section 6.2.1.1). Mean and upper percentile concentrations of the epidemiologic studies of systemic oxidative stress are included in Table 6-6.

6.2.9.2. Controlled Human Exposure Studies

Urban Traffic Particles

Bräuner et al. (2007, 091152) recently investigated the effect of urban traffic particles on oxidative stress-induced damage to DNA. Healthy adults (20-40 yr) were exposed to low concentrations of urban traffic particles as well as filtered air for periods of 24 h, with and without two 90-min periods of exercise. Exposures took place in an exposure chamber above a busy road with high traffic density in Copenhagen. Non-filtered air was pumped into the chamber from above the street, with avg $PM_{2.5}$ and $PM_{10-2.5}$ mass concentrations of 9.7 $\mu g/m^3$ and 12.6 $\mu g/m^3$, respectively. The UF/$PM_{2.5}$ (6-700 nm) particle number concentration was continuously monitored throughout the exposure (avg PNC 10,067 particles/cm^3). The $PM_{2.5}$ fraction was rich in sulfur, V, Cr, Fe, and Cu. PBMCs were isolated from blood samples collected at 6 and 24 h. DNA damage, as measured by strand breaks (SB) and formamidopyrimidine-DNA glycosylase (FPG) sites, was evaluated using the Comet assay. The activity and mRNA levels of the DNA repair enzyme 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1) were also measured. The authors observed increased levels of DNA strand breaks and FPG sites following 6 and 24 h of exposure to PM. Using a mixed-effects regression model, the particle concentration at the 57 nm mode was found to be the major contributor of these measures of DNA damage. The results of this study suggest that short-term (6-24 h) exposure to ambient levels of UFPs cause systemic oxidative stress resulting in damage to DNA.

Diesel Exhaust

Tornqvist et al. (2007, 091279) reported an increase in plasma antioxidant capacity in a group of healthy volunteers 24 h after a 1-h exposure to DE with a particle concentration of 300 μg/m^3. The investigators suggested that systemic oxidative stress occurring following exposure may have caused this up-regulation in antioxidant defense. Peretz et al. (2007, 156853) observed some significant differences in expression of genes involved in oxidative stress pathways between exposure to DE (200 μg/m^3 $PM_{2.5}$) and filtered air. However, the conclusions of this investigation are limited by a small number of subjects (n = 4).

Wood Smoke

In a controlled human exposure study of controlled exposure to wood smoke, Barregard et al. (2006, 091381) found an increase in urinary excretion of free 8-iso-prostaglandin2α among healthy adults (n = 9) approximately 20 h following a 4-h exposure to $PM_{2.5}$ (mass concentration of 240-280 μg/m^3). This finding provides evidence of a PM-induced increase in free-radical mediated lipid peroxidation. From the same study, Danielsen et al. (2008, 156382) reported an increase in the mRNA levels of the DNA repair gene hOGG1 in peripheral mononuclear cells 20 h after exposure to wood smoke relative to filtered air.

Summary of Controlled Human Exposure Study Findings for Systemic and Cardiovascular Oxidative Stress

Based on the results of these studies, it appears that exposure to PM at or near ambient levels may increase systemic oxidative stress in human subjects.

6.2.9.3. Toxicological Studies

Very little information was available for inclusion in the 2004 PM AQCD (U.S. EPA, 2004, 056905) on oxidative stress in the cardiovascular system. A few new studies have evaluated ROS in blood or the heart following PM exposure. Some studies have used chemiluminescence (CL), which is measured using the decay of excited states of molecular oxygen, and may also be prone to artifact.

CAPs

Gurgueira et al. (2002, 036535) measured oxidative stress in SD rats immediately following a 5-h CAPs exposure ($PM_{2.5}$ mean mass concentration 99.6-957.5 μg/m^3; Boston, MA; 7/2000-2/2001) and reported increased in situ CL in hearts of CAPs-exposed animals. CL evaluated after 1- and 3-h CAPs exposure did not demonstrate changes from the filtered air group, although a 5-h exposure resulted in increased CL in hearts. When animals were allowed to recover for 24 h, oxidative stress returned to control values. To compare potential particle-induced differences in CL, rats were exposed to ROFA (1.7 mg/m^3 for 30 min) or CB (170 μg/m^3 for 5 h) and only the ROFA-treated animals exhibited increased CL in cardiac tissue. Additionally, levels of antioxidant enzymes in the heart (Cu/Zn-SOD and MnSOD) were increased in CAPs-exposed rats. Individual PM component concentrations were linked to CL levels in rat heart tissue using separate univariate linear regression models, with total PM mass, Al, Si, Ti, and Fe having p-values ≤ 0.007 (Gurgueira et al., 2002, 036535). The highest R^2 value in the regression analyses was for Al (0.67) and its concentration ranged from 0.000 to 8.938 μg/m^3.

Recently, Rhoden et al. (2005, 087878) tested the role of the ANS in driving CAPs-induced cardiac oxidative stress in heart tissues of SD rats. At $PM_{2.5}$ mass concentrations of 700 μg/m^3 (Boston, MA), pretreatment with an antioxidant, a β_1-receptor antagonist, or a muscarinic receptor antagonist attenuated the CL and TBARS effects observed in the heart following a 5-h $PM_{2.5}$ exposure. The wet/dry ratio (edema) of cardiac tissue also returned to control values in animals treated with the antioxidant prior to CAPs. These combined results indicate involvement of both the

sympathetic and parasympathetic pathways in the cardiac oxidative stress response observed following PM exposure.

More recently, a type of irritant receptor, the transient receptor potential vanilloid receptor 1 (TRPV1), was identified as central to the inhaled CAPS-mediated induction of cardiac tissue CL and TBARS in SD rats (Ghelfi et al., 2008, 156468). In these studies ($PM_{2.5}$ mean mass concentration 218 $\mu g/m^3$; Boston, MA), capsazapine (a TRPV1 inhibitor) abrogated cardiac CL, TBARS, edema, and QT-interval shortening when measured at the end of the 5-h exposure. These studies provide some evidence that the ANS may be involved in producing cardiac oxidative stress following exposure to CAPs. Furthermore, this response could be acting, at least in part, via TRPV receptors.

In WKY rats exposed to $PM_{2.5}$ CAPs in Japan, relative mRNA expression of HO-1 was increased in cardiac tissue and was also significantly correlated with the cumulative mass of PM collected on chamber filters throughout the exposure (Ito et al., 2008, 096823).

Road Dust

A composite of $PM_{2.5}$ road dust samples obtained from New York City, Los Angeles, and Atlanta induced cardiac ROS as measured by CL in the low exposure group (306 $\mu g/m^3$) and TBARS in the high exposure group (954 $\mu g/m^3$); thus, the CL and TBARS methods provided different results for the various source types (Seagrave et al., 2008, 191990).

Gasoline and Diesel Exhaust

Gasoline exhaust exposure also resulted in increased ROS (measured by TBARS) in aortas of $ApoE^{-/-}$ mice, as discussed in Section 6.2.4.3 (Lund et al., 2009, 180257). Similarly, a 6-h exposure to gasoline exhaust (PM mass concentration 60 $\mu g/m^3$, CMD 15-20 nm; MMD 150 nm; CO concentration 104 ppm, NO concentration 16.7 ppm, NO_2 concentration 1.1 ppm, SO_2 concentration 1.0 ppm) in SD rats demonstrated increased CL in the heart, but no change in TBARS and the CL response was not duplicated when the particles were filtered (Seagrave et al., 2008, 191990). Increased lipid peroxides in the serum of male SH rats exposed to gasoline exhaust (PM mass concentration 59.1 $\mu g/m^3$; NO concentration 18.4 ppm; NO_2 concentration 0.9 ppm; CO concentration 107.3 ppm; SO_2 concentration 0.62 ppm) was observed following a 1-wk exposure to gasoline exhaust and this effect was attenuated with particle filtration (Reed et al., 2008, 156903). An IT instillation study of diesel particles in mice demonstrated increased myocardial MPO activity 12 and 24 h post-exposure to the residual particle component that remained after extraction with dichloromethane (Yokota et al., 2008, 190109).

Model Particles

Other studies previously presented also demonstrated ROS (via CL) and NT expression (via ELISA) in the left ventricle with CB exposure (Tankersley et al., 2008, 157043) and oxidative stress in the systemic microvasculature following TiO_2 inhalation (Nurkiewicz et al., 2009, 191961) or ROFA IT instillation exposure (Nurkiewicz et al., 2006, 088611). Decreased HO-1 mRNA expression in hearts of SH rats exposed to UF carbon particles was observed 3 days following exposure (Upadhyay et al., 2008, 159345) and there was a trend toward increased HO-1 mRNA expression 1 day post-exposure.

Summary of Toxicological Study Findings for Systemic and Cardiovascular Oxidative Stress

When considered together, the above studies provide evidence that PM exposure results in oxidative stress as measured in cardiac tissue by CL, TBARS, HO-1 mRNA expression, and NT expression. However, the PM concentration/dose and method of ROS measurement could also affect the response. Cardiac oxidative stress may have resulted from PM stimulation of the ANS, although these studies have only been conducted in one laboratory. Multiple studies from two different

laboratories provide support for vascular oxidative stress as demonstrated in aortas following gasoline exhaust exposure and in the microvasculature after TiO_2 inhalation or ROFA IT exposure.

6.2.10. Hospital Admissions and Emergency Department Visits

The 1996 PM AQCD (U.S. EPA, 1996, 079380) considered just two time-series studies regarding the association between daily variations in PM levels and the risk of CVD morbidity as measured by the number of daily hospitalizations with primary discharge diagnoses related to CVD (Burnett et al., 1995, 077226; Schwartz and Morris, 1995, 046186). In contrast, the 2004 PM AQCD (U.S. EPA, 2004, 056905) reviewed more than 25 publications relating PM and risk of CVD hospitalizations. Results from a handful of larger multicity studies were emphasized, with the greatest emphasis placed on findings from the U.S. National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al., 2000, 010269) and a subsequent reanalysis (Zanobetti and Schwartz, 2003, 157174). The NMMAPS study evaluated the effect of daily changes in ambient PM levels on total CVD hospitalizations among elderly Medicare beneficiaries in 14 U.S. cities and found a ~1% excess risk per 10 $\mu g/m^3$ increase in PM_{10}. The 2004 PM AQCD concluded that these results, along with those of the other single- and multicity studies reviewed "generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of [0.6-1.7% per 10 $\mu g/m^3$] PM_{10}, especially among the elderly" (U.S. EPA, 2004, 056905). The 2004 PM AQCD (U.S. EPA, 2004, 056905) also concluded that there was some evidence from single-city studies suggesting an excess risk specifically for hospitalizations related to IHD and heart failure. Furthermore, the 2004 PM AQCD (U.S. EPA, 2004, 056905) found that "insufficient data exist from the time-series CVD admissions studies […] to provide clear guidance as to which ambient PM components, defined on the basis of size or composition, determine ambient PM CVD effect potency" (U.S. EPA, 2004, 056905). The key studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) on this topic included those by Burnett and colleagues (1997, 084194; 1999, 017269), Lippman and colleagues (2000, 011938), Ito (2003, 042856), and Peters et al. (2001, 016546).

Recent large studies conducted in the U.S., Europe, and Australia and New Zealand have confirmed these findings for PM_{10}, and have also observed consistent associations between $PM_{2.5}$ and cardiovascular hospitalizations. However, findings from single-city studies have demonstrated regional heterogeneity in effect estimates. It is apparent from these recent studies that the observed increases in cardiovascular hospitalizations are largely due to admissions for IHD and CHF rather than CBVDs (such as stroke). The new literature on hospitalizations and ED visits for cardiovascular causes published since 2002 is reviewed in the following sections. First, the specific CVD outcomes captured using ICD codes from hospital admissions databases are discussed. Second, the methods used in the large and multicity studies are described. For each outcome considered, evidence from large/multicity studies is emphasized and results from U.S. and Canadian single-city studies are also discussed. Although the single-city studies may lack statistical power needed to evaluate interactions and detect some of the subtle effects of air pollution, they inform the interpretation of the heterogeneous effect estimates that have been observed across North America.

Cardiovascular Disease ICD Codes

When the 2004 PM AQCD (U.S. EPA, 2004, 056905) was written, few studies had evaluated the link between ambient PM and specific CVD outcomes such as CHF, IHD or ischemic stroke. In contrast, the majority of recent studies have focused on specific CVD outcomes. This trend is justified by the fact that the short-term exposure effects of PM may be very different for different cardiovascular outcomes. For example, given the current putative biological pathways involved in the acute response to PM exposure, there is no *a priori* reason why short-term fluctuations in PM levels would have similar effects on the risk of acute MI, chronic atherosclerosis of the coronary arteries, and hemorrhagic stroke.

Almost all of the published time-series studies of cardiovascular hospitalizations and ED visits identified cases based on administrative discharge diagnosis codes as defined by the International Classification of Disease 9th revision (ICD-9) or 10th revision (ICD-10) (NCHS, 2007, 157194). A complicating factor in interpreting the results of these studies is the lack of consistency in both defining specific health outcomes and in the nomenclature used.

Table 6-7. Description of ICD-9 and ICD-10 codes for diseases of the circulatory system.

Description	ICD-9 Codes	ICD-10 Codes
All Cardiovascular Disease	390-459	I00-I99
IHD	410-414	I20-I25
Acute MI	410	I21
Diseases Of Pulmonary Circulation	415-417	I26-I28
CHF	428	I50
Arrhythmia	427	I47, I48, I49
CBVD	430-438	I60-I69
Ischemic Stroke And Transient Ischemic Attack (TIA)	430-432	I63
Hemorrhagic Stroke	433-435	I60-I62
Peripheral Vascular Disease (PVD)	440-448	I70-I79

Table 6-7 shows major groups of diagnostic codes used in air pollution studies for diseases of the circulatory system. The codes ICD-9: 390-459 are frequently used to identify all CVD morbidity. Note that this definition of CVD includes diseases of the heart and coronary circulation, CBVD, and peripheral vascular disease. In contrast, the term cardiac disease specifically excludes diseases not involving the heart or coronary circulation. While this distinction is conceptually straightforward, the implementation of the definition of cardiac disease in terms of ICD-9 or ICD-10 codes varies among authors. Even greater heterogeneity can be found among studies in the implementation of definitions related to CBVD.

Design and Methods of Large and Multicity Hospital Admission and ED Visit Studies

Recently, multiple research groups in the U.S., Europe, and Australia have created large datasets to evaluate specific CVD and respiratory endpoints using more detailed and relevant measures of PM concentration. In the U.S., the MCAPS analyses of Dominici et al. (2006, 088398), Bell et al. (2008, 156266) and Peng et al. (2008, 156850) are large, comprehensive and informative studies based on Medicare hospitalization data. Likewise, the Atlanta-based SOPHIA study (Metzger et al., 2004, 044222; Peel et al., 2005, 056305; Tolbert et al., 2007, 090316) is the largest and most comprehensive study of U.S. cardiovascular and respiratory ED visits. In Europe, the APHEA initiative (Le Tertre et al., 2002, 023746; Le Tertre et al., 2003, 042820) the more recent HEAPSS study (Von Klot et al., 2005, 088070), and the French PSAS program (Host et al., 2008, 155852; Larrieu et al., 2007, 093031) are similarly noteworthy for their large sample size, geographic diversity, and consideration of specific CVD and/or respiratory endpoints. These studies contain adequate data to examine interactions by season and region; the effects of different size fractions, components and sources of PM; or the effect of PM on susceptible populations. The following section provides a detailed review of the study design and methods used by each of the large studies. A discussion of the results of each study can be found later in Section 6.2.10.

MCAPS: Medicare Air Pollution Study

Dominici et al. (2006, 088398) created a database of daily time-series of hospital admission rates (1999-2002) for a range of cardiovascular and respiratory outcomes among Medicare beneficiaries aged ≥65 yr, ambient $PM_{2.5}$ levels, and meteorological variables for 204 U.S. urban counties. The specific CVD outcomes considered were: CBVD (ICD-9: 430-438), peripheral vascular disease (440-448), IHD (410-414, 429), heart rhythm disturbances (426, 427), and CHF

(428). Injuries (800-849) were evaluated as a control outcome. Gaseous and other particulate pollutant size fractions were not considered.

Data on $PM_{2.5}$ were obtained from the AQS database of the U.S. EPA. Within each county, associations between cause-specific hospitalization rates and same-day $PM_{2.5}$ levels were evaluated using Poisson regression models controlling for long-term temporal trends and meteorologic conditions with natural cubic splines. County-specific results were subsequently averaged using Bayesian hierarchical models. In addition to evaluating single-day lags, 3-day distributed lag models (lags 0, 1, and 2 days) were also considered in a subset of 90 U.S. counties with daily $PM_{2.5}$ data available during the study time period.

Subsequently, Peng et al. (2008, 156850) and Bell et al. (2008, 156266) extended the database of daily time-series of hospital admissions, $PM_{2.5}$, and other covariates for 202 U.S. counties through 2005. Importantly, Peng et al. (2008, 156850) added data on $PM_{10-2.5}$ to this database for 108 U.S. counties with one or more co-located $PM_{2.5}$ and PM_{10} monitors. Analyses with $PM_{10-2.5}$ were carried out using similar methods to those of Dominici et al. (2006, 088398). Peng et al. (2008, 156850) evaluated the robustness of $PM_{2.5}$ associations to adjustment for $PM_{10-2.5}$ (Peng et al., 2008, 156850). Gaseous pollutants were not considered in these analyses.

SOPHIA: Study of Particulates and Health in Atlanta

SOPHIA investigators (Metzger et al., 2004, 044222; Peel et al., 2005, 056305; Tolbert et al., 2000, 010320) compiled data on 4,407,535 ED visits between 1993 and 2000 to 31 hospitals in the Atlanta metropolitan statistical area (20 counties). Specific cardiovascular outcomes considered were: IHD (ICD-9: 410-414), acute MI (410), cardiac dysrhythmias (427), cardiac arrest (427.5), CHF (428), peripheral vascular and CBVD (433-437, 440, 443-444, 451-453), atherosclerosis (440), and stroke (436). Finger wounds (883.0) were evaluated as a control outcome.

The air quality data included measurements of criteria pollutants (PM and gaseous pollutants) for the entire study period, as well as detailed measurements of mass concentrations for $PM_{2.5}$ and $PM_{10-2.5}$ and several physical and chemical characteristics of $PM_{2.5}$ for the final 25 mo of the study using data from the ARIES monitoring station. Rates of ED visits for specific causes were assessed in relation to the 3-day ma (lags 0-2 days) of daily measures of air pollutants using Poisson generalized linear models (GLMs) controlling for long-term temporal trends and meteorologic conditions with cubic splines. Tolbert et al. (2007, 090316) published interim results of this study in relation to both cardiovascular and respiratory disease visits, Metzger et al. (2004, 044222) published the main results for CVD visits, and Peel et al. (2005, 056305) published the main results for respiratory conditions. An analysis of co-morbid conditions that may make individuals more susceptible to PM-related cardiovascular risk was carried out by Peel et al. (2007, 090442). Tolbert et al. (2007, 090316) extended the available data through 2002 and compared results from single and multipollutant models, while Sarnat et al. (2008, 097972) evaluated the risk of ED visits for cardiovascular and respiratory diseases in relation to specific sources of ambient PM using the extended dataset.

APHEA and APHEA-2: Air Pollution and Health: a European Approach

APHEA-2 investigators compiled daily data on cardiovascular (Le Tertre et al., 2002, 023746; 2003, 042820) and respiratory (Atkinson et al., 2001, 021959; 2003, 042797) disease hospital admissions in the following 8 European locations: Barcelona, Birmingham, London, Milan, the Netherlands (considered a "city" for this study, due to its small size and dense population), Paris, Rome, and Stockholm. (The publications on respiratory diseases were reviewed in the 2004 PM AQCD). The specific CVD outcomes considered in each city were: cardiac diseases (ICD-9: 390-429), IHD (410-413) and CBVDs (430-438). Routine registers in all cities provided daily data on hospitalizations. Only emergency hospitalizations were considered, except in Milan, Paris, and Rome where only general admissions data were available.

Ambient PM_{10} levels were available in all cities except Paris (PM_{13} used), and Milan and Rome (TSP used). Data on gaseous pollutants (NO_2, SO_2, CO, and O_3) were also available in most cities. Five of the eight cities provided data on black smoke (BS). The length of the available time-series varied by city but generally spanned from the early to mid-1990s.

Within each city, associations between cause-specific hospitalization rates and same-day $PM_{2.5}$ levels were evaluated using Poisson GAMs controlling for long-term temporal trends and meteorologic conditions. City-specific results were subsequently averaged using standard

meta-analytic methods. The original analyses (Atkinson et al., 2001, 021959; Le Tertre et al., 2002, 023746) were carried out using general additive models (GAM) and LOESS smoothers. Following reports of problems associated with using the default convergence criteria in the standard S-plus GAM procedure (Dominici et al., 2002, 030458), study authors reanalyzed the data on cardiac admissions using GAMs and stricter convergence criteria, and GLMs with natural splines and penalized splines (Atkinson et al., 2003, 042797; Le Tertre et al., 2003, 042820). The authors found that the results of the original analyses were insensitive to the choice of convergence criteria and that the use of GLMs with penalized splines yielded very similar results.

HEAPSS: Health Effects of Air Pollution among Susceptible Subpopulations

HEAPSS investigators collected data on patients hospitalized for a first MI in five European cities between 1992 and 2000. Patients were identified from MI registers in Augsburg and Barcelona, and from hospital discharge registers in Helsinki, Rome and Stockholm. Data on daily levels of PM_{10}, were measured at central monitoring sites in each city. Particle number concentration was measured for a year in each city and then modeled retrospectively for the whole study period. Associations of outcomes with gaseous criteria pollutants were also evaluated.

Von Klot et al. (2005, 088070) identified 22,006 survivors of a first MI in the five participating European cities and collected data on subsequent first cardiac re-hospitalizations between 1992 and 2001. Readmissions of interest were those with primary diagnoses of acute MI, angina pectoris, or cardiac disease (which additionally includes dysrhythmias and CHF). Within each city, associations between cause-specific hospitalization rates and same-day levels of PM_{10} were evaluated using Poisson GAMs controlling for long-term temporal trends and meteorologic conditions using penalized splines. City-specific results were combined using standard meta-analytic methods. Subsequently, Lanki et al. (2006, 089788) used HEAPSS data from 26,854 patients to evaluate the association between daily PM_{10} and particle number concentrations and the risk of hospitalization for first MI.

PSAS: The French National Program on Air Pollution Health Effects

Larrieu et al. (2007, 093031) evaluated the association between PM_{10} and the risk of hospitalization in eight French cities between 1998 and 2003. The cities examined were: Bordeaux, Le Havre, Lille, Lyon, Marseille, Paris, Rouen and Toulouse. The specific CVD outcomes considered in each city included: total CVD (ICD-10: I00-I99), cardiac disease (I00-I52), IHD (I20-I25) and stroke (I60-I64, G45-G46). The available data did not differentiate between emergency and non-emergency hospitalizations. Daily mean PM_{10} and NO_2 levels as well as 8-h max O_3 levels were obtained from a network of monitors in each city.

Within each city, associations between cause-specific hospitalization rates and 2-day ma (lag 0-1 days) levels of PM_{10} were evaluated using Poisson GAMs controlling for long-term temporal trends and meteorologic conditions using penalized splines. City-specific results were combined using standard meta-analytic methods. Host et al. (2008, 155852) used a subset of these data (6 cities, 2000-2003) to compare the effects of $PM_{2.5}$ and $PM_{10-2.5}$ on the risk of cardiovascular and respiratory admissions. CVD outcomes assessed in this analysis were all CVD (ICD-10 I00-I99), cardiac disease (I00-I52) and IHD (I20-I25). $PM_{2.5}$ levels were obtained from the same network of background monitors described above. $PM_{10-2.5}$ was calculated by subtracting $PM_{2.5}$ levels from PM_{10} levels. Gaseous pollutants and hospital admissions for stroke were not considered in this analysis.

Multicity Studies in Australia and New Zealand

Barnett et al. (2006, 089770) collected data on daily CVD emergency hospital admissions among older adults and pollution data between 1998 and 2001 in five Australian cities (Brisbane, Canberra, Melbourne, Perth, Sydney) and two cities in New Zealand (Auckland, Christchurch). In 2001, these cities covered 53% of the Australian population and 44% of the New Zealand population. The specific outcomes considered in each city were: all circulatory diseases (ICD-9 390-429, ICD-10 I00-I99 with exclusions); CHF (ICD-9 428, ICD-10 I50); arrhythmia (ICD-9 427 ICD-10 I46-49); cardiac disease (ICD-9 390-429, ICD-10 I00-I52, I97.0, I97.1, I98.1); IHD (ICD-9 410-413, ICD-10 I20-24, I25.2); acute MI (ICD-9 410, ICD-10 I21-22); and stroke (ICD-9 430-438, ICD-10 I60-66, I67, I68, I69, G45-46 with exclusions).

Air pollutants considered were 24-h avg PM_{10}, 24-h avg $PM_{2.5}$, BSP and gaseous pollutants. Within each city, associations between cause-specific hospitalization rates and 2-day ma (lags 0-1 days) of PM_{10} were evaluated using the time-stratified case-crossover approach which controls for long-term and seasonal time trends by design rather than analytically. City-specific results were combined using random effects meta-analytic methods.

EMECAS: Spanish Multicentric Study on the Relation between Air Pollution and Health

Ballester et al. (2006, 088746) collected data on daily cardiovascular emergency hospital admission and air pollution data between approximately 1995 and 1999 in 14 cities in Spain. The specific outcomes considered in each city were: total CVD (ICD-9: 390-459) and heart diseases (410-414, 427, 428). Air pollutants considered were PM_{10}, TSP, BS, SO_2, NO_2 (24-h avg), CO and O_3 (8-h max).

Within each city, associations between cause-specific hospitalization rates and daily levels of each pollutant metric were evaluated using Poisson GAMs with strict convergence criteria. In all models, pollutants were entered as linear continuous variables and included control for confounding by meteorological variables, influenza rates, long-term time trends, and unusual events. The authors considered both distributed lag models (lags 0-3 days) and the 2-day ma of pollution (lags 0-1 days). City-specific results were combined using standard meta-analytic methods.

6.2.10.1. All Cardiovascular Disease

The 2004 PM AQCD (U.S. EPA, 2004, 056905) incorporated the results of a large number of time-series studies in the U.S. and elsewhere relating ambient PM levels and risk of hospitalization for CVD. The 2004 PM AQCD (U.S. EPA, 2004, 056905) noted that the strongest evidence for this association came from the NMMAPS study (Samet et al., 2000, 010269) and the subsequent reanalysis by Zanobetti and Schwartz (2003, 157174).

Since then, the U.S. MCAPS study evaluated the association between $PM_{2.5}$ and risk of CVD hospitalization in 202 U.S. counties between 1999 and 2005 and found a 0.8% (95% posterior interval (PI): 0.6-1.0) increase in risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ on the same day (Bell et al., 2008, 156266; Peng et al., 2008, 156850). In 108 U.S. counties with co-located PM_{10} and $PM_{10-2.5}$ monitors, Peng et al. found a 0.4% (95% PI, 0.1- 0.7, lag 0) increase in risk per 10 $\mu g/m^3$ $PM_{10-2.5}$ and no associations at lags of 1 and 2 days (Peng et al., 2008, 156850). In a two-pollutant model adjusted for $PM_{2.5}$, the association between $PM_{10-2.5}$ and CVD hospitalization lost precision (0.3% [95% PI: −0.1 to 0.6, lag 0]). Bell et al. (2008, 156266) found evidence of substantial and statistically significant variability in the effects of $PM_{2.5}$ on cardiovascular hospitalizations by season and region, with the highest national average estimates occurring in the winter and the highest regional estimates in the northeastern U.S. (1.08% [95% PI: 0.79-1.37, lag 0, per 10 $\mu g/m^3$ increase in $PM_{2.5}$]). Estimates for the nation (1.49% [95% PI: 1.09-1.89, lag 0]) and northeast (2.01% [95% PI: 1.39-2.63, lag 0]) were highest in the winter.

Bell et al. (2009, 191997) and Peng et al. (2009, 191998) used data from the MCAPS study and the EPA's Speciation Trends Network (STN) to identify the components of $PM_{2.5}$ that are most strongly associated with hospitalizations for CVD. Peng et al. (2009, 191998) focused on the components that make up the majority of $PM_{2.5}$ mass (SO_4^{2-}, NO_3^-, Si, EC, OC, Na^+ and NH_4^+) and found that in multipollutant models, only EC and OC were significantly associated with risk of hospitalization for CVD. Bell et al. (2009, 191997) used data from 20 $PM_{2.5}$ components and found that EC, Ni, and V were most positively and significantly associated with the risk of cardiovascular hospitalizations. These results suggest that the observed associations between $PM_{2.5}$ and CVD hospitalizations may be primarily due to particles from oil combustion and traffic.

Additional evidence is provided by several large multicity studies conducted outside of the U.S. The European APHEA2 study (Le Tertre et al., 2002, 023746) looked at admissions for CVD among those aged ≥65 and found a 0.7% (95% CI: 0.4-1.0, lag 0-1 day avg) increase in risk per 10 $\mu g/m^3$ PM_{10}. The Spanish EMECAS study (Ballester et al., 2006, 088746) looked at admissions for CVD and found a 0.9% (95% CI: 0.4-1.5, lag 0-1 day avg) increase in risk per 10 $\mu g/m^3$ PM_{10}. The French PSAS program looked at CVD hospitalizations among the elderly and found a 1.9% (95% CI: 0.9-3.0, lag 0-1 day avg) increase in risk with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and a 1.1% (95% CI: 0.5-1.7) increase in risk with PM_{10} (Host et al., 2008, 155852; Larrieu et al., 2007, 093031). Non-significant increases in CVD hospital admissions association with $PM_{10-2.5}$ were

reported (1.0% [95% CI: -1.0 to 3.0]) (Host et al., 2008, 155852). In multiple cities across New Zealand and Australia, Barnett et al. (2006, 089770) found a 1.3% (95% CI: 0.6-2.0, lag 0-1 day avg) increase in risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$.

The Atlanta-based SOPHIA study found a 3.3% (95% CI: 1.0-5.6, lag 0-2 day avg) and a 0.9% (95% CI: -0.2 to 1.9, lag 0-2 day avg) increase in risk with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10}, respectively (Metzger et al., 2004, 044222). In a more recent analysis from this study with an additional four years of data, ED visits for CVD were not significantly associated with PM_{10} or $PM_{2.5}$, but were significantly associated with total carbon (1.6% [95% CI: 0.5-2.6, per IQR increase]), EC (1.5% [95% CI: 0.5-2.5, per IQR increase]) and OC (1.5% [95% CI: 0.5-2.6, per IQR increase]) components of $PM_{2.5}$ (2007, 090316). A weak non-significant association $PM_{10-2.5}$ was observed in these data (Tolbert et al., 2007, 090316) More recently, Sarnat et al. (2008, 097972) used multiple source-apportionment methods to evaluate the association between all CVD ED visits and specific $PM_{2.5}$ sources and found consistent positive associations with sources related to motor vehicles and biomass combustion. These results were insensitive to the source-apportionment technique used. It is noteworthy that other traffic-related gaseous pollutants were associated with CVD ED visits in the SOPHIA study (Metzger et al., 2004, 044222).

Using meta-regression techniques and the reported association between PM_{10} and CVD hospitalizations from the 14 cities included in the NMMAPS analysis, Janssen et al. (2002, 016743) examined whether the between-city variability in relative risk estimates were related to the local contribution of a number of PM sources. The authors found that in multivariate analyses PM_{10} coefficients increased significantly with increasing percentage of PM_{10} emissions from highway vehicles/diesels and oil combustion.

A small number of additional single-city studies have been published showing positive associations between hospital admissions and ambient PM in Copenhagen, Denmark (Andersen et al., 2007, 093201), weak nonsignificant associations in Spokane, WA (Schreuder et al., 2006, 097959; Slaughter et al., 2005, 073854), and no associations in two small counties in Idaho (Ulirsch et al., 2007, 091332). Schreuder et al. (2006, 097959) performed a source apportionment analysis using seven years of daily speciation data from the same residential monitor in Spokane, WA used by Slaughter et al. (2005, 073854). These authors related daily levels of four sources (wood smoke, an As-rich source, motor vehicle emissions, and airborne soil) to the excess risk of cardiovascular ED visits. During the heating season, the only notable association for CVD-related ED visits was with wood smoke, while in the non-heating season the only notable association was with airborne soil. While neither of these associations reached statistical significance, the study likely lacked the statistical power to find effects of the expected magnitude. In fact, it is doubtful that studies conducted outside of large metropolitan areas have sufficient statistical power to detect associations of the expected magnitude. Delfino et al. (2009, 191994) evaluated the effects of the 2003 California wildfires and observed a slightly larger excess risk of total CVD admissions during the wildfire period compared to the period prior to the wildfire, although excess risk estimates were generally weak and non-significant.

Studies in several cities in Australia have investigated the association of CVD admissions with PM concentration and sources. A study from Sydney, Australia found a 1.8% (95% CI: 0.4-3.2) and 0.3% (95% CI: -0.8 to 1.4) excess risk per 10 $\mu g/m^3$ increase in the 2-day ma (lags 0-1 days) in $PM_{2.5}$ and PM_{10}, respectively (Jalaludin et al., 2006, 189416). Johnston et al. (2007, 155882) and Hanigan et al. (2008, 156518) studied the association between PM_{10} and cardiovascular and respiratory hospitalizations in Darwin, Australia, where the predominant source of PM is from biomass combustion. The authors found little or no evidence of an association between PM_{10} and CVD hospital admissions in the general population.

Crustal material has also been investigated in an effort to explain associations of PM concentration with CVD admissions. Studies of a dust storm in the Gobi desert that transported PM across the Pacific Ocean reaching the western U.S. in the spring of 1998 have been conducted. An analysis of the health impacts of this event on the population of British Columbia's (Canada) Lower Fraser Valley found no excess risk of cardiac or respiratory hospital admissions despite hourly PM_{10} levels >100 $\mu g/m^3$ (Bennett et al., 2006, 088061). On the other hand, a number of studies in Asia and eastern Europe have reported associations between CVD hospital admissions and dust storm events. Middleton et al. (2008, 156760) found that dust storms in Cyprus were associated with a 4.7% (95% CI: 0.7-9.0) and 10.4% (95% CI: -4.7 to 27.9) increase in risk of hospitalization for all causes and CVD, respectively. Chan et al. (2008, 093297) studied the effects of Asian dust storms on cardiovascular hospital admissions in Taipei, Taiwan and also found significant adverse effects

during 39 Asian dust events with high PM_{10} levels (daily PM_{10} >90 µg/m^3). Bell et al. (2008, 091268) analyzed these data independently and concluded that Asian dust storms were positively associated with risk of hospitalization for IHD.

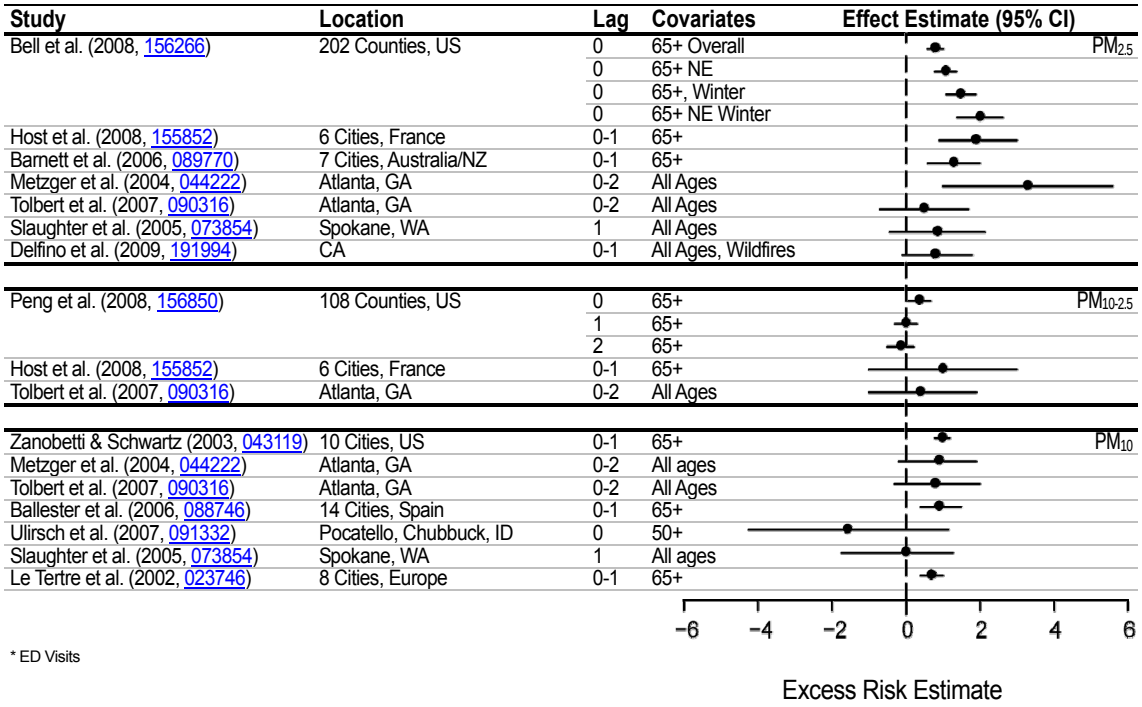


Figure 6-1. Excess risk estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} concentration for CVD ED visits and HAs. Studies represented in the figure include all multicity studies, as well as single-city studies conducted in the U.S. or Canada.

The effect estimates from multicity studies and single-city studies conducted in the U.S. and Canada are included in Figure 6-1. Information on PM concentrations during the relevant study period is presented in Table 6-8. In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide support for an association between short-term increases in ambient levels of $PM_{2.5}$ and PM_{10} and increased risk of hospitalization for total CVD. The evidence for an association of CVD hospitalization with $PM_{10-2.5}$ is relatively limited. Peng et al. (2008, 156850) reported that their $PM_{10-2.5}$ estimate was not robust to adjustment for $PM_{2.5}$ and estimates from the other studies are imprecise. The average excess risk among the U.S. elderly is likely in the range of 0.5-1.0% per 10 µg/m^3 increase in $PM_{2.5}$, although substantial variability by region of the country and season has been demonstrated. An excess risk of ED visits for CVD of a similar magnitude appears likely. The excess risk of CVD hospitalization may be somewhat greater in Europe and Australia/New Zealand than in the U.S. Sources including wood burning, oil burning, traffic and crustal material have been associated with increases in cardiovascular hospitalization or ED visits, but the best evidence suggests that in the U.S., oil combustion, wood burning, and traffic are likely the sources of $PM_{2.5}$ most strongly associated with cardiovascular hospitalizations or ED visits.

Table 6-8. Characterization of ambient PM concentrations in epidemiologic studies of hospital admission and ED visits for cardiovascular diseases.

Pollutant	Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentration ($\mu g/m^3$)
$PM_{2.5}$				
	Barnett et al. (2006, 089770)	7 cities in Australia	8.1-11.0	NR
	Bell et al. (2008, 156266)	202 counties in the U.S.	12.92	34.16
	Burnett et al. (1999, 017269)	Toronto Canada	18	95th: 34.0, Max: 90
	Dominici et al. (2006, 088398)	204 counties in the U.S.	13.4	NR
	Delfino et al. (2009, 191994)	6 counties CA	18.4-32.7	45.3-76.1 (wildfire period)
	Host et al. (2008, 155852)	6 cities in France	13.8-18.8	95th: 25-33
	Ito et al. (2003, 042856); Lippman (2000, 011938)	Detroit, MI	18	98th: 55.2
	Lisabeth et al. (2008, 155939)		7	75th: 10
	Metzger et al. (2004, 044222)	Atlanta, GA	17.8	90th: 32.3 98th: 39.8
	Pope et al. (2006, 091246)	Wasatch Front, Utah	10.1-11.3	Max: 82-144
	Slaughter et al. (2005, 073854)	Spokane, WA	NR	90th: 20.2
	Sullivan et al. (2005, 050854)	King County, WA	12.8	90th 27.3, Max: 147
	Symons et al. (2006, 091258)	Baltimore, MD	16	Max: 69.2
	Tolbert et al. (2007, 090316)	Atlanta, GA	17.1	98th: 38.7
	Villenueve et al. (2006, 090191)	Edmonton, Canada	8.5	75th: 11
	Zanobetti and Schwartz (2005, 088069)	Boston, MA	11.1 (median)	95th: 26.31 98th: 55.2
$PM_{10-2.5}$				
	Burnett et al. (1999, 017269)	Toronto, Canada	12.2	Max: 68
	Host et al. (2008, 155852)	6 cities in France	7-11	95th: 12.5-21.0
	Ito et al. (2003, 042856); Lippman (2000, 011938)	Detroit, MI	13	Max: 50
	Le Tertre et al. (2002, 023746)	8 cities in Europe	NR	NR
	Metzger et al. (2004, 044222)	Atlanta, GA	9.1	90th: 16.2
	Peng et al. (2008, 156850)	204 cities in the U.S.	9.8 (Median)	75th: 15.0
	Peters et al. (2001, 016546)	Boston, MA	7.4	95th: 15.2
	Slaughter et al. (2005, 073854)	Spokane, WA	NR	NR
	Tolbert et al. (2007, 090316)	Atlanta, GA	9	Max: 50.3
PM_{10}				
	Ballester et al. (2006, 088746)	14 cities in Spain	32.8-43.2	90th: 50.3-62.6
	Barnett et al. (2006, 089770)	7 cities in Australia and New Zealand	16.5-20.6	NR
	Burnett et al. (1999, 017269)	Toronto, Canada	30.2	95th: 56.0
	Ito et al. (2003, 042856); Lippman (2000, 011938)	Detroit, MI	31	NR
	Jalaludin et al. (2006, 189416)	Sydney, Australia	16.8	75th: 19.9 Max: 103.9
	Larrieu et al. (2007, 093031)	8 cities in France	21.0-28.9	NR
	Le Tertre et al. (2002, 023746)	8 cities in Europe	Range: 15.5-55.7	Range 75th: 19.9-66

Pollutant	Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentration ($\mu g/m^3$)
	Linn et al. (2000, 002839)	Los Angeles, California	45	78 (summer) -132 (fall)
	Metzger et al. (2004, 044222)	Atlanta, GA	26.3	90th: 44.7
	Morris et al. (1998, 024924)	Chicago, Illinois	41	75th: 51 Max: 117
	Peters et al. (2001, 016546)	Boston, MA	19.4	95th: 37.0
	Schwartz et al. (1995, 046186)	Detroit, MI	48	90th: 82
	Slaughter et al. (2005, 073854)	Spokane, WA	NR	90th: 41.9
	Tolbert et al. (2007, 090316)	Atlanta, GA	26.6	Max: 98.4
	Ulirsch et al. (2007, 091332)*	2 cities in southeast Idaho	24.2/23.2	90th: 40.7/37.4
	Wellenius et al. (2005, 087483)	Pittsburgh, PA	31.1	95th: 70.5
	Wellenius et al. (2005, 088685)	9 cities in the U.S.	28.4 (median)	90th: 57.9
	Wellenius et al. (2006, 088748)	7 cities in the U.S.	28.3 (median)	90th: 57
	Zanobetti and Schwartz (2005, 088069)	Boston, MA	28.4 (median)	90th: 53.6

*Results presented separately for 2 separate time series

6.2.10.2. Cardiac Diseases

Cardiac disease represents a subset of CVD which specifically excludes hospitalizations for CBVD, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. Only a small number of studies published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) have evaluated the association between ambient PM and hospitalizations for cardiac diseases, as most investigators have focused instead on more narrowly defined outcomes.

The French PSAS program found a 2.4% (95% CI: 1.2-3.7, lag 0-1) and 1.5% (95% CI: 0.5-2.2, lag 0-1) excess risk among the elderly per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10}, respectively (Host et al., 2007, 155851; Larrieu et al., 2007, 093031). Host et al. (2008, 155852) also found a positive less precise association with $PM_{10-2.5}$, (excess relative risk per 10 $\mu g/m^3$: 1.6% [95% CI: -0.8 to 4.1]). The European HEAPSS study looked at cardiac readmissions among survivors of a first MI and found a 2.1% (95% CI: 0.4-3.9, lag 0) excess risk per 10 $\mu g/m^3$ increase in PM_{10} (Von Klot et al., 2005, 088070). A 1.9% (95% CI: 1.0-2.7, lag 0-1) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ was observed in several cities in Australia and New Zealand (Barnett et al., 2006, 089770). Single-city studies of hospital admissions from Kaohsiung and Taipei, Taiwan, and an ED visit study from Sydney, Australia also reported statistically significant positive associations(Chang et al., 2005, 080086; Jalaludin et al., 2006, 189416; Yang et al., 2004, 094376). On the other hand, Slaughter et al. (2005, 073854) found no association between either $PM_{2.5}$ or PM_{10} and risk of cardiac hospitalization in Spokane, Washington.

In summary, although relatively few studies have focused on all cardiac diseases, large studies from Europe and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) report positive associations between short-term increases in ambient levels of $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} and increased risk of hospitalization for cardiac disease. The results from small single-city studies are less consistent. The excess risk for cardiac hospitalizations may be somewhat larger than for total CVD hospitalizations.

6.2.10.3. Ischemic Heart Disease

IHD represents a subset of all cardiac disease hospitalizations and typically includes acute MI (ICD 9: 410), other acute and subacute forms of IHD (411), old MI (412), angina pectoris (413), and other forms of chronic IHD (414). Some authors term this category coronary heart disease. Published studies evaluating IHD as a single outcome are considered first, followed by consideration of studies looking at acute MI, a specific form of IHD.

In one of the first studies to evaluate IHD, Schwartz and Morris (1995, 046186) reported a 0.6% (95% CI: 0.2-1.0) excess risk of hospitalization for IHD per 10 $\mu g/m^3$ increase in mean PM_{10}

levels over the previous two days among elderly Medicare beneficiaries living in Detroit between 1986 and 1989. As reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), similar associations were subsequently observed in many single-city studies including: London, England (Atkinson et al., 1999, 007882), Toronto, Canada (Burnett et al., 1999, 017269), and Seoul, Korea (Lee et al., 2003, 095552). Studies in Hong Kong (Wong et al., 1999, 009172; Wong et al., 2002, 023232), Birmingham, England (Anderson et al., 2001, 017033), and London, England (Wong et al., 2002, 023232) yielded positive point estimates of a similar magnitude, but did not reach statistical significance.

The positive associations between short-term changes in PM and IHD hospitalizations observed in the early single-city studies have been confirmed in several large multicity studies. The U.S. MCAPS study (Dominici et al., 2006, 088398) found a 0.4% (95% CI: 0.0-0.8) excess risk of hospitalization for IHD per 10 $\mu g/m^3$ increase in $PM_{2.5}$ two days earlier. The European APHEA-2 study (Le Tertre et al., 2002, 023746) considered PM_{10} and found a 0.8% (95% CI: 0.3-1.2, lag 0-1) excess risk among those aged ≥65 yr. Among the elderly in 5 cities in Australia and New Zealand (Barnett et al., 2006, 089770) there was a 4.3% (95% CI: 1.9-6.4, lag 0-1) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Among the elderly in several French cities there was a 4.5% (95% CI: 2.3-6.8, lag 0-1), 6.4% (95% CI: 1.6-11.4, lag 0-1) and 2.9% (95% CI: 1.5-4.3, lag 0-1) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$, $PM_{10-2.5}$ (Host et al., 2008, 155852), and PM_{10}, respectively (Larrieu et al., 2007, 093031).

With regard to ED visits, the Atlanta-based SOPHIA study (Metzger et al., 2004, 044222) found positive associations with $PM_{2.5}$ and PM_{10} (ranging from 1.1 to 2.3%), but the effect estimates did not reach statistical significance. Similarly, associations of EC and OC with IHD were increased but not significant. In 6 cities across Canada, Szyszkowicz (2009, 191996) observed a 2.4% (95% CI: 1.2-3.6) and 1.4% (95% CI: 0.7-2.0) excess risk of ED visits for angina per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$ and PM_{10}, respectively. Although excess risks were generally weak and non-significant, Delfino et al. (2009, 191994) observed a slightly larger excess risk of IHD during wildfires compared to the pre-wildfire period. In Sydney, Australia, Jalaludin et al. (2006, 189416) found a 2.6% (95% CI: 0.1-5.2) and 0.8% (95% CI: -1.2 to 2.8) excess risk of ED visits for IHD per 10 $\mu g/m^3$ increase in 2-day ma of $PM_{2.5}$ and PM_{10}, respectively. A recent study in Helsinki, Finland, found no evidence of an association of IHD hospital admissions with UFP, ACP, $PM_{2.5}$, $PM_{10-2.5}$, or source-specific $PM_{2.5}$ (Halonen et al., 2009, 180379).

To explore this link further, Pope et al. (2006, 091246) used data from an ongoing registry of patients undergoing coronary angiography at a single referral center in Salt Lake City, UT, between 1994-2004. The authors found a 4.8% (95% CI: 1.0-8.8, lag 0) excess risk of acute MI or unstable angina per 10 $\mu g/m^3$ increase in $PM_{2.5}$ among 4,818 patients. These results were robust to changes in the definition of the outcome. The results of this study are particularly noteworthy given the high specificity of the outcome definition.

In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide support for an association between short-term increases in ambient levels of PM_{10} and $PM_{2.5}$ and increased risk of hospitalization or ED visits for ischemic heart diseases. Although estimates are less precise for $PM_{10-2.5}$, most results from single pollutant models provide evidence of a positive association between $PM_{10-2.5}$ and IHD. Moreover, Host et al. (2008, 155852) found that the effect estimates for the association of $PM_{2.5}$ and $PM_{10-2.5}$ with IHD were very similar when scaled to the IQR of each metric. Estimates of the excess risk vary considerably between studies, but as was the case for total CVD hospitalizations, the excess risk appears to somewhat greater in Europe and Australia/New Zealand. Results from multicity studies and U.S. and Canadian single-city studies are presented in Figure 6-2.

Study	Location	Lag	Age	Effect Estimate (95% CI)
ISCHEMIC HEART DISEASE				
Ito (2003, 042856)	Detroit, MI	1	65+	$PM_{2.5}$
Pope et al. (2006, 091246)	Utah Valley, UT	0	All	
Host et al. (2007, 155851)	6 Cities, France	0-1	All	
Metzger et al. (2004, 044222)*	Atlanta, GA	0-3	All	
Barnett et al. (2006, 089770)	Australia/NZ	0-1	15-64	
Dominici et al. (2006, 088398)	204 Counties, US	0	65+	
		1	65+	
		2	65+	
		0-2 DL	65+	
Barnett et al. (2006, 089770)	Australia/NZ	0-1	65+	
Host et al. (2007, 155851)	6 Cities, France	0-1	65+	
Burnett et al. (1999, 017269)	Toronto, Can	0,1	All	
Delfino et al. (2009, 191994)	6 Counties, CA (Wildfires)	0,1	All	
Ito (2003, 042856)	Detroit, MI	1	65+	$PM_{10-2.5}$
Metzger et al. (2004, 044222)*	Atlanta, GA	0-3	All	
Host et al. (2007, 155851)	6 Cities, France	0-1	All	
		0-1	65+	
Burnett et al. (1999, 017269)	Toronto, Can	0	All	
Ito (2003, 042856)	Detroit, MI	1	65+	PM_{10}
Le Tertre et al. (2002, 023746)	8 Cities, Europe	0-1	<65	
Metzger et al. (2004, 044222)*	Atlanta, GA	0-2	All	
Larrieu et al. (2007, 093031)	8 Cities, France	0-1	All	
Burnett et al. (1999, 017269)	Toronto, Can	0-1	All	
Le Tertre et al. (2002, 023746)	8 Cities, Europe	0-1	65+	
Jalaludin et al. (2006, 189416)*	Sydney, Australia	0-1	65+	
Larrieu et al. (2007, 093031)	8 Cities, France	0-1	65+	
MYOCARDIAL INFARCTION				$PM_{2.5}$
Peters et al. (2001, 016546)	Boston, MA	2 h	61.6 Mean	
		24 h	61.6 Mean	
Sullivan et al. (2005, 050854)	King County, WA	1 h	21-98	
		2 h	21-98	
		4 h	21-98	
		24 h	21-98	
Zanobetti & Schwartz (2006, 090195)	Boston, MA	0	65+	
				$PM_{10-2.5}$
Peters et al. (2001, 016546)	Boston, MA	2 h	61.6 Mean	
		24 h	61.6 Mean	
Linn et al. (2000, 002839)	Los Angeles, CA	0	>30	PM_{10}
Peters et al. (2001, 016546)	Boston, MA	2 h	61.6 Mean	
		24 h	61.6 Mean	
Zanobetti & Schwartz (2005, 088069)	21 Cities, US	0	65+	

* ED Visits
DL Distributed Lag

Excess Risk (%)

Figure 6-2. Excess risk estimates per 10 µg/m^3 increase in 24-h avg (unless otherwise noted) $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} concentration for MI and IHD ED visits and HAs. Studies represented in the figure include all multi-city studies as well as single-city studies conducted in U.S. or Canada.

6.2.10.4. Acute Myocardial Infarction

Because even IHD refers to a heterogeneous collection of diseases and syndromes, several authors have evaluated the association between short-term fluctuations in ambient PM and acute MI, a specific form of IHD.

In 2001, Peters et al. (2001, 016546) published their study evaluating the effects of PM on the risk of MI among 772 Boston-area participants in the Determinants of MI Onset Study. The authors found that a 10 μg/m^3 increase in the 2-h or 24-h avg levels of $PM_{2.5}$ was associated with a 17% (95% CI: 4-32) and 27% (95% CI: 6-53) excess risk of MI, respectively. An imprecise, non-significant association between $PM_{10-2.5}$ and onset of MI was observed in Boston. In contrast, a study among 5793 patients in King County, WA that used similar methods, found no association with $PM_{2.5}$ with lag times of 1, 2, 4, or 24 h (Sullivan et al., 2005, 050854). Among 852 hospitalized patients in Augsburg, Germany, Peters et al. (2005, 087759) also found no association between $PM_{2.5}$ and MI risk within this time frame, although they did find a positive and statistically significant association with time spent in traffic (Peters et al., 2004, 087464).

These three studies are particularly important because in each one: (1) cases were prospectively identified based on clinical criteria rather than retrospectively based on discharge diagnoses; and (2) time of MI symptom onset was used for exposure assessment rather than date of hospital admission. Whether the discrepant results among these studies are due to regional differences in population characteristics and/or air pollution sources remains unclear. The King County study suggests that differences in statistical approaches are unlikely to account for the discrepant results (Sullivan et al., 2005, 050854). Analyses from the U.S. MCAPS study suggest that substantial heterogeneity of effects are to be expected across regions of the country (Bell et al., 2008, 156266)

Several studies have assessed the association between acute exposure to ambient PM and MI using administrative databases. In the U.S., MI was not one of the specific endpoints evaluated in the MCAPS study (Dominici et al., 2006, 088398) or in the Atlanta-based SOPHIA study of ED visits (Metzger et al., 2004, 044222). However, Zanobetti and Schwartz (2005, 088069) found a 0.7% (95% CI: 0.3-1.0) excess risk of MI per 10 μg/m^3 increase in same-day PM_{10} among elderly Medicare beneficiaries in 21 cities. Subsequently, the same authors found that among elderly Medicare beneficiaries living in the Boston metropolitan region, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 4.9% (95% CI: 1.1-8.2) excess risk on the same day (Zanobetti and Schwartz, 2006, 090195).

This body of evidence may implicate traffic-related pollution generally as a risk factor for MI. In the study described above, Peters et al. (2001, 016546) found positive associations between risk of hospitalization for MI and potential markers of traffic-related pollution measured at a central monitor including BC, CO and NO_2. However, none of these associations were statistically significant in models adjusting for season, meteorological variables, and day of week. Zanobetti and Schwartz (2006, 090195) examined the association between traffic-related pollution and risk of hospitalization for MI among Medicare beneficiaries in the Boston area and found that MI risk was positively and significantly associated with measures of $PM_{2.5}$, BC, NO_2, and CO, but not with levels of non-traffic-related $PM_{2.5}$. Peters et al. (2004, 087464) interviewed 691 subjects with MI who survived at least 24-h after the event and found a strong positive association between self-reported exposure to traffic and the onset of MI within 1 h (OR: 2.9 [95% CI: 2.2-3.8]). The association was somewhat stronger among subjects traveling by bicycle or public transportation in the hour prior to the event. Of note, however, this study did not directly measure traffic-related pollution.

Similar studies with administrative databases have been conducted in Europe, Australia, and New Zealand. Barnett et al. (2006, 089770) observed that in five cities in Australia and New Zealand, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 7.3% (95% CI: 3.5-11.4, lag 0-1 day) excess risk. In Rome, D'Ippoliti et al. (2003, 074311) carried out a case-crossover study and found a statistically significant positive association between TSP and the risk of hospitalization for MI. In contrast, the HEAPSS study found no evidence of an association between PM_{10} and risk of hospitalization for a first MI in five European cities (Lanki et al., 2006, 089788), although there is some indication that among survivors of a first MI, risk of re-hospitalization for MI may be related to transient elevations in PM_{10} (Von Klot et al., 2005, 088070).

In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide support for an association between short-term increases in ambient levels of $PM_{2.5}$ and $PM_{10}$and increased risk of hospitalization for MI. Some of the heterogeneity of results is likely explained by regional differences in pollution sources,

components, and measurement error. One study of the effect of 2- and 24-h avg $PM_{10-2.5}$ concentration on admissions for MI produced effect estimates that were positive, but imprecise (Peters et al., 2001, 016546). These results need to be interpreted together with those studies evaluating hospitalization for IHD since MIs make up the majority of hospitalizations for IHD. U.S. studies of MI are included in Figure 6-2.

6.2.10.5. Congestive Heart Failure

Perhaps the first suggestion of an association between ambient PM and hospitalization for CHF was provided by the study of Schwartz and Morris (1995, 046186). These authors reported that among elderly Medicare beneficiaries living in Detroit between 1986-1989, a 10 $\mu g/m^3$ increase in mean PM_{10} levels over the previous two days was associated with a 1.0% (95% CI: 0.4-1.6) increase in risk of hospitalization for CHF. As reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), using similar approaches, statistically significant positive associations with $PM_{2.5}$ or PM_{10} were subsequently reported in single-city studies looking at hospitalizations for CHF in Toronto (Burnett et al., 1999, 017269), Hong Kong (Wong et al., 1999, 009172), and Detroit (Ito, 2003, 042856), but not Los Angeles (Linn et al., 2000, 002839) or Denver (Koken et al., 2003, 049466). Burnett et al. (1999, 017269) reports a significantly increased risk of CHF hospitalization with $PM_{10-2.5}$ while Metzger et al. (2004, 044222) and Ito et al. found (2003, 042856) less precise associations.

Subsequent multicity studies support the presence of a positive association between PM concentration and CHF hospitalization. In the U.S., the MCAPS study found a 1.3% (95%: 0.8-1.8) excess risk per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$ (Dominici et al., 2006, 088398). In addition, Wellenius et al. (2006, 088748) reported a 0.7% (95% CI: 0.4-1.1) excess risk of hospitalization for CHF per 10 $\mu g/m^3$ increase in same-day PM_{10} among elderly Medicare beneficiaries in seven cities. In Australia and New Zealand, Barnett et al. (2006, 089770) found a 9.8% (95% CI: 4.8-14.8, lag 0-1 day) and 4.6% (95% CI: 2.8-6.3, lag 0-1 days) excess risk of hospitalization for CHF associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10}, respectively. Results from more recent single-city studies in Pittsburgh (Wellenius et al., 2005, 087483), Utah's Wasatch Front (Pope et al., 2008, 191969), Kaohsiung, Taiwan (Lee et al., 2007, 196613) and Taipei, Taiwan (Yang, 2008, 157160) have also reported positive associations between PM and CHF hospital admissions. In addition, Yang et al. (2009, 190341) found that hospitalizations for CHF were elevated during or immediately following 54 Asian dust storm events (while single day lags 0-3 were evaluated, maximum excess risk occurred at lag 1: 11.4% [95% CI: -0.7 to 25.0]). Delfino et al. (2009, 191994) observed a slightly larger excess risk of total CHF during wildfires occurring in California compared to the period before the wildfires.

While most studies suggest an association at very short lags (0-1 days), the study by Pope et al. (2008, 191969) failed to find such short term associations and instead suggested that $PM_{2.5}$ levels averaged over the past 2-3 wk may be more important. Pope et al. (2008, 191969) observed a 13.1% (95% CI: 1.3-26.2) increase in CHF hospitalization per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (imputed values used in analysis). Whether findings at longer lags in this population represent true cumulative effects of PM or are due to misclassification of symptom onset times remains to be determined.

Findings from the Atlanta-based SOPHIA study (Metzger et al., 2004, 044222) also support the presence of a positive association between PM and CHF ED visits. Specifically, the SOPHIA study found a 5.5% (95% CI: 0.6-10.5, lag 0-2 days) excess risk of ED visits for CHF per 10 $\mu g/m^3$ increase in the 3-day ma of $PM_{2.5}$. Positive associations were also observed for CHF and EC and OC components of $PM_{2.5}$. No associations were observed with PM_{10} and a weak, imprecise increase was observed in association with $PM_{10-2.5}$.

Only one published study has attempted to evaluate the effects of ambient particles on CHF symptom exacerbation using data which was not derived from administrative databases. Symons et al. (2006, 091258) interviewed 135 patients with prevalent CHF hospitalized for symptom exacerbation in Baltimore, MD. The authors found a 7.4% (95% CI: -7.5 to 24.2) excess risk of hospitalization per 10 $\mu g/m^3$ increase in $PM_{2.5}$ two days prior to symptom onset. This finding did not reach statistical significance and may be attributable to the lack of statistical power needed to find an effect of the expected magnitude.

In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide support for an association between short-term increases in ambient levels of $PM_{2.5}$ and PM_{10} and increased risk of hospitalization and ED visits for CHF. Although the number of studies is fewer (and only Metzger et al., 2004, 044222

is new since the 2005 AQCD), elevated risks of hospitalization or ED visits for CHF in association with $PM_{10-2.5}$ have been observed. The excess risks associated with CHF hospitalizations and ED visits are consistently greater than those observed for other CVD endpoints. The results of multicity studies and U.S. and Canadian single-city studies are summarized in Figure 6-3.

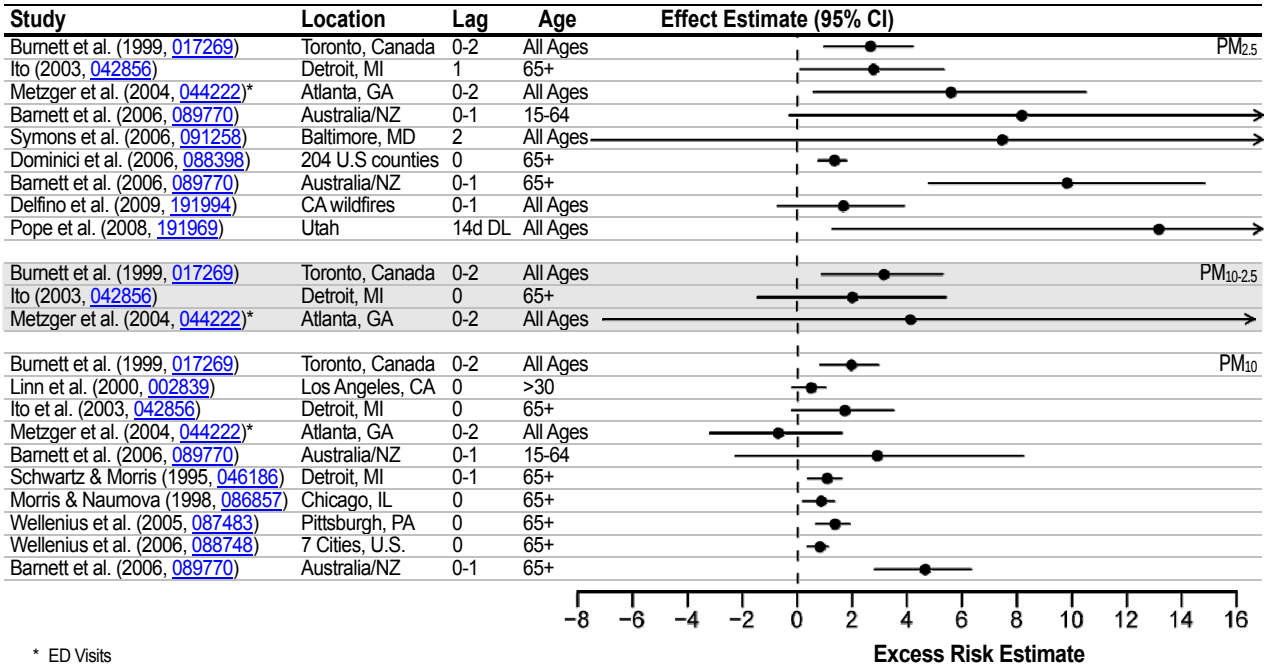


Figure 6-3. Excess risk estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} concentration for CHF ED visits and HAs. Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. and Canada.

6.2.10.6. Cardiac Arrhythmias

A number of studies based on administrative databases have sought to evaluate the association between short-term fluctuations in ambient PM levels and the risk of hospitalization for cardiac arrhythmias (also known as dysrhythmias). Typically in these studies a primary discharge diagnosis of ICD-9 427 has been used to identify hospitalized patients. However, ICD-9 427 includes a heterogeneous group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoarterial node dysfunction. One study in the Netherlands found that the positive predictive value of ICD-9 codes related to ventricular arrhythmias and sudden cardiac death was 82% (De Bruin et al., 2005, 155746). The positive predictive value of other codes related to cardiac arrhythmias is unknown, but likely to be lower.

The results from early studies of arrhythmia-related hospitalizations have been inconsistent, with positive findings in Toronto (Burnett et al., 1999, 017269) and null findings in Detroit (Schwartz and Morris, 1995, 046186), Los Angeles (Linn et al., 2000, 002839), and Denver (Koken et al., 2003, 049466). The U.S. MCAPS study found a statistically significant 0.6% (95% CI: 0.0-1.2) excess risk of hospitalization for the combined outcome of cardiac arrhythmias and conduction disorders (ICD-9: 426, 427) per 10 µg/m^3 increase in same-day $PM_{2.5}$ (Dominici et al., 2006, 088398). A multicity study in Australia and New Zealand found no evidence of an association between arrhythmia hospitalizations and either $PM_{2.5}$ or PM_{10} (Barnett et al., 2006, 089770). A study in Helsinki, Finland, found no evidence of an association between either $PM_{2.5}$ or $PM_{10-2.5}$ and risk of hospitalization for arrhythmias (Halonen et al., 2009, 180379), although there was an association with smaller particles (0.03-0.1 µm).

With regard to ED visits, the Atlanta-based SOPHIA study found no evidence of an association between any measure of ambient PM and the rate of ED visits for cardiac arrhythmias (Metzger et al., 2004, 044222). However, in São Paulo, Brazil, Santos et al. (2008, 192004) found a 3.0% (95% CI: 0.5-5.4) excess risk of ED visits for arrhythmias per 10 $\mu g/m^3$ increase in PM_{10} on the same day.

In summary, the current evidence does not support the presence of a consistent association between short-term increases in ambient levels of $PM_{2.5}$, $PM_{10-2.5}$, or PM_{10} and increased risk of hospitalization for cardiac arrhythmias. However, it should be noted that studies of hospital admissions or ED visits are ill-suited to the study of cardiac arrhythmias since most arrhythmias do not lead to hospitalization. Studies in patients with implanted defibrillators, human panel studies with ambulatory ECG recordings, and animal toxicological studies provide a more appropriate setting for evaluating this endpoint. Results of these studies are described in Section 6.2.2.

6.2.10.7. Cerebrovascular Disease

Time-series studies evaluating the hypothesis that short-term increases in ambient $PM_{2.5}$ or PM_{10} levels are associated with increased risk of hospitalization for CBVD have been inconsistent, with few studies reporting positive associations (Chan et al., 2006, 090193; Dominici et al., 2006, 088398; Metzger et al., 2004, 044222; Wordley et al., 1997, 082745), and several studies reporting null or negative associations (Anderson et al., 2001, 017033; Barnett et al., 2006, 089770; Burnett et al., 1999, 017269; Halonen et al., 2009, 180379; Jalaludin et al., 2006, 189416; Larrieu et al., 2007, 093031; Le Tertre et al., 2002, 023746; Peel et al., 2007, 090442; Villeneuve et al., 2006, 090191; Wong et al., 1999, 009172).

The U.S. MCAPS study found a 0.8% (95% CI: 0.3-1.4) excess risk of hospitalization for CBVD per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$ (Dominici et al., 2006, 088398). The association showed regional variability with the strongest associations observed in the eastern U.S. The Atlanta-based SOPHIA study found a 5.0% (95% CI: 0.8-9.3, lag 0-2 days) excess risk of ED visits for cerebrovascular and peripheral vascular disease combined (excluding hemorrhagic strokes) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and a 2.0% (95% CI: -0.1 to 4.3, lag 0-2 days) excess risk for PM_{10} (Metzger et al., 2004, 044222). Delfino et al. (2009, 191994) observed a weak association between excess risk of CBVD admissions before and during a wildfire occurring in California and slightly higher risks after the wildfire period.

Large multicity studies conducted outside of North America have failed to observe an association between PM and CBVD hospitalizations. The APHEA study found no excess risk (0.0% [95% CI: -0.3 to 0.3]) of hospitalization for CBVD per 10 $\mu g/m^3$ increase in the 2-day ma of PM_{10} in 8 European cities (Le Tertre et al., 2002, 023746). Investigators from the French PSAS program reported a 0.8% (95% CI: -0.9 to 2.5, lag 0-1 days) excess risk per 10 $\mu g/m^3$ increase in PM_{10} among patients aged ≥65 yr and a 0.2% (95% CI: -1.6 to 1.9, lag 0-1 days) excess risk among all patients (Larrieu et al., 2007, 093031). Although neither estimate was statistically significant, the estimated excess risk among the elderly is very similar to that observed in the U.S. MCAPS study. Barnett et al. (2006, 089770) examined this hypothesis in New Zealand and Australia and reported no association.

All of the above studies have identified cases of CBVD based on ICD-9 or ICD-10 codes (most commonly ICD-9 430-438). However, the range of ICD codes commonly used in these studies includes ischemic strokes, hemorrhagic strokes, transient ischemic attacks (TIAs) and several poorly defined forms of acute neurological events (e.g., seizures from a vascular cause) (Table 6-7). It is plausible that ambient PM has different effects on each of these disparate outcomes.

Ischemic Strokes and Transient Ischemic Attacks

An increasing number of studies have specifically evaluated the association between PM_{10} and $PM_{2.5}$ and the risk of ischemic stroke (Chan et al., 2006, 090193; Henrotin et al., 2007, 093270; Linn et al., 2000, 002839; Lisabeth et al., 2008, 155939; Low et al., 2006, 090441; Szyszkowicz, 2008, 192128; Tsai et al., 2003, 080133; Villeneuve et al., 2006, 090191; Wellenius et al., 2005, 087483). Linn et al. (2000, 002839) found a 1.3% (95% CI: 1.0-1.6 per 10 $\mu g/m^3$, PM_{10} lag 0) excess risk of hospitalization for ischemic stroke in the Los Angeles metropolitan area. Wellenius et al. (2005, 087483) reported a statistically significant 0.4% (95% CI: 0.0-0.9) excess risk per 10 $\mu g/m^3$ increase

in same-day PM_{10} among elderly Medicare beneficiaries in nine U.S. cities. Low et al. (2006, 090441) reported an absolute increase of 0.08 (95% CI; 0.002-0.16) ischemic stroke hospitalizations per 10 $\mu g/m^3$ increase in PM_{10} in New York City. In Kaohsiung, Taiwan, Tsai et al. (2003, 080133) found a 5.9% (95% CI: 4.3-7.4, lag 0-2 days) excess risk of hospitalization for ischemic stroke per 10 $\mu g/m^3$ increase in PM_{10} after excluding days with mean daily temperature <20°C. Meanwhile, in Taipei, Taiwan, Chan et al. (2006, 090193) found a 3.0% (95% CI: -0.8 to 6.6, lag 3) and 1.6% (95% CI: -0.8 to 3.9, lag 3) excess risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10}, respectively. Villeneuve et al. (2006, 090191) and Szyszkowicz et al. (2008, 192128) found no association between either $PM_{2.5}$ or PM_{10} and ED visits for acute ischemic stroke in Edmonton, Canada.

Two recent studies are particularly noteworthy given the high specificity of the outcome definition. Henrotin et al. (2007, 093270) used data on 1432 confirmed cases of ischemic stroke from the French Dijon Stroke Register and found 0.9% (95% CI: -7.0 to 9.4) excess risk of ischemic stroke per 10 $\mu g/m^3$ increase in PM_{10} on the same day and a 1.1% (95% CI: -0.2 to 9.4) excess risk on the previous day (lag 1 day). Lisabeth et al. (2008, 155939) used data on 2,350 confirmed cases of ischemic stroke and 1,158 cases of TIA from the Brain Attack Surveillance in Corpus Christi Project (BASIC), a population-based stroke surveillance project designed to capture all strokes in Nueces County, Texas. The authors found a 6.0% (95% CI: -0.8 to 13.2) and 6.0% (95% CI: -1.8 to 14.4) excess risk of ischemic stroke/TIA per 10 $\mu g/m^3$ increase in $PM_{2.5}$ on the previous day and the same day, respectively.

Only the study by Villeneuve et al. (2006, 090191) specifically evaluated the association between ambient PM and the risk of TIAs. This study failed to find any evidence of an association with either $PM_{2.5}$ or PM_{10}.

A limitation of all of these studies is that they have assessed exposure based on the date of hospital admission or ED presentation rather than the date and time of stroke symptom onset. It has been shown that this can bias health effect estimates towards the null by up to 60% (Lokken et al., 2009, 186774). Therefore, if there is a causal link between PM and the risk of stroke, it is likely that the existing studies underestimate the true effects. Moreover, most of these studies have evaluated only very short-term effects (lags of 0-2 days) and none have considered lags longer than 5 days. It is possible that the lag structure of the association between PM and stroke differs from that of other CVDs and it might even differ by stroke type.

Hemorrhagic Strokes

Most of the studies in the preceding section also evaluated the association between ambient PM and the risk of hemorrhagic stroke (Chan et al., 2006, 090193; Henrotin et al., 2007, 093270; Tsai et al., 2003, 080133; Villeneuve et al., 2006, 090191; Wellenius et al., 2005, 087483). In Kaohsiung, Taiwan, Tsai et al. (2003, 080133) noted a 6.7% (95% CI: 4.2-9.4, lag 0-2 days) excess risk of hospitalization for hemorrhagic stroke per 10 $\mu g/m^3$ increase in PM_{10}, after excluding days where the mean temperature was <20°C. However, in the U.S., Wellenius et al. (2005, 088685) failed to find any association between ambient PM_{10} levels and risk of hemorrhagic stroke among Medicare beneficiaries in nine U.S. cities. Similarly, Villeneuve et al. (2006, 090191) found no evidence of an association between ED visits for hemorrhagic stroke and either $PM_{2.5}$ or PM_{10} levels in Edmonton, Canada. Henrotin et al. (2007, 093270) found no evidence of an association between risk of hospitalization and PM_{10} levels in Dijon, France, and Chan et al. (2006, 090193) found no evidence of an association between risk of hospitalization and either $PM_{2.5}$ or PM_{10}levels in Taipei, Taiwan.

In summary, large studies from the U.S., Europe, and Australia/New Zealand published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide inconsistent support for an association between short-term increases in ambient levels of $PM_{2.5}$ and PM_{10} and risk of hospitalization and ED visits for CBVD (Figure 6-4). Studies of $PM_{10-2.5}$ and CBVD or stroke have not been conducted. The heterogeneity in results is likely partly attributed to: (1) differences in the sensitivity and specificity of the various outcome definitions used in the studies; (2) lag structures between PM exposure and stroke onset which may vary by stroke type and patient characteristics; and (3) exposure misclassification due to the use of hospital admission date rather than stroke onset time, which may vary by region, population characteristics, and stroke type. Effect estimates from multicity studies and single-city U.S. and Canadian studies are included in Figure 6-4.

6.2.10.8. Peripheral Vascular Disease

In the U.S., the large MCAPS study Dominici et al. (2006, 088398) evaluated the association between mean daily $PM_{2.5}$ levels and the risk of hospitalization among elderly Medicare beneficiaries in 204 urban counties and found that a 10 μg/m^3 increase in $PM_{2.5}$ was not significantly associated with risk of hospitalization for peripheral vascular disease 0-2 days later. An earlier study in Toronto (Burnett et al., 1999, 017269) found a negative association with $PM_{2.5}$ (point estimate and confidence intervals not reported), a positive statistically significant association with $PM_{10-2.5}$ (2.2% [95% CI: 0.1-4.3]), and a positive non-significant association with PM_{10} (0.5% [95% CI: -0.5 to 1.6]). The Atlanta-based SOPHIA study (Metzger et al., 2004, 044222) of ED visits grouped visits for PVD with those for CBVD, making interpretation of these results challenging.

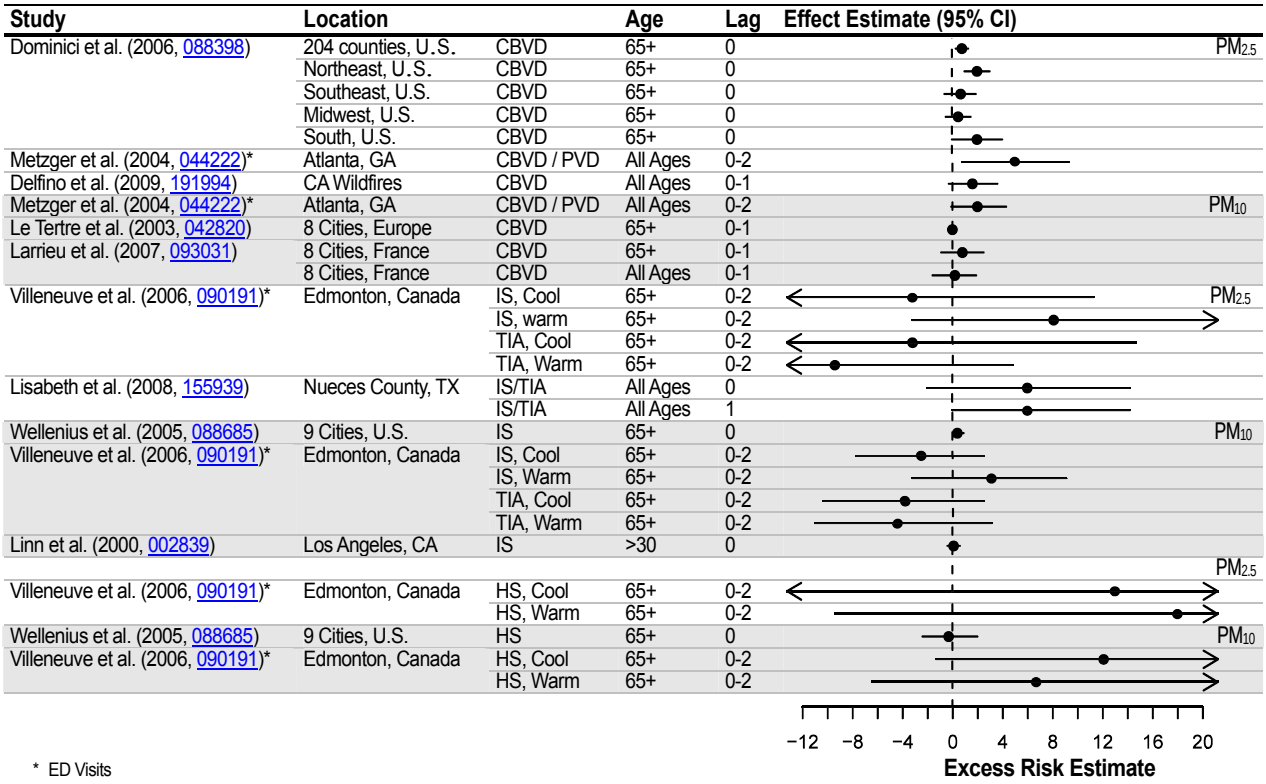


Figure 6-4. Excess risk estimates per 10 μg/m^3 increase in 24-h avg $PM_{2.5}$ and PM_{10} concentration for CBVD ED visits and HAs. Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. and Canada.

In summary, there is insufficient published data to determine whether or not there may be an association between short-term increases in ambient levels of, $PM_{2.5}$, $PM_{10-2.5}$, or PM_{10} and increased risk of hospitalization and ED visits for PVD.

6.2.10.9. Copollutant Models

Relatively few studies have evaluated the effects of $PM_{2.5}$ and $PM_{10-2.5}$ on the risk of hospital admissions and ED visits in the context of two-pollutant models. Generally, results for health effects of both size fractions are similar even after controlling for SO_2 or O_3 levels (Figure 6-5). However, controlling for NO_2 or CO has yielded mixed results. Among the large multicity studies, the Atlanta-based SOPHIA study found that the association between $PM_{2.5}$ (total carbon) and risk of cardiovascular ED visits was somewhat attenuated in two-pollutant models additionally controlling for either CO or NO_2 (Tolbert et al., 2007, 090316). Barnett et al. (2006, 089770) found that the

associations they observed between $PM_{2.5}$ and cardiac hospitalizations in Australia and New Zealand were attenuated after control for 24-h NO_2, but not after control for CO.

Only a few studies have attempted to evaluate the effects of one PM size fraction while controlling for another PM size fraction. The large U.S. MCAPS study evaluating the effects of $PM_{10-2.5}$ on cardiovascular hospital admissions lost precision after controlling for $PM_{2.5}$, but did not consider gaseous pollutants (Peng et al., 2008, 156850). Andersen et al. (2008, 189651) found that associations between both PM_{10} and $PM_{2.5}$ and cardiovascular hospitalizations in Copenhagen were not attenuated by control for particle number concentration.

A number of studies have also evaluated PM_{10} effects in the context of two-pollutant models with inconsistent results. The multicity Spanish EMECAS study (Ballester et al., 2006, 088746) found that the statistically significant positive associations observed between PM_{10} and cardiac hospitalizations were robust to control for other pollutants in two-pollutant models. Jalaludin et al. (2006, 189416) found that the effects of PM_{10} as well as $PM_{2.5}$ on cardiovascular ED visits in Sydney Australia were attenuated by additional control for either NO_2 or CO. Wellenius et al. (2005, 087483) found that the PM_{10}-related risk of hospitalization for CHF in Allegheny County, PA, was attenuated in two-pollutant models controlling for either CO or NO_2. In contrast, Chang et al. (2005, 080086) examined CVD hospitalizations in Taipei and found attenuation of PM_{10} effects by control for NO_2 or CO, but only during warm days. In Kaohsiung, Taiwan, Tsai et al. (2003, 080133) found that the association between PM_{10} and ischemic stroke hospitalizations was not materially attenuated in two-pollutant models controlling for either NO_2 or CO.

The inconsistent findings after controlling for gaseous pollutants or other size fractions are likely due to differences in the correlation structure among pollutants, as well as differing degrees of exposure measurement error.

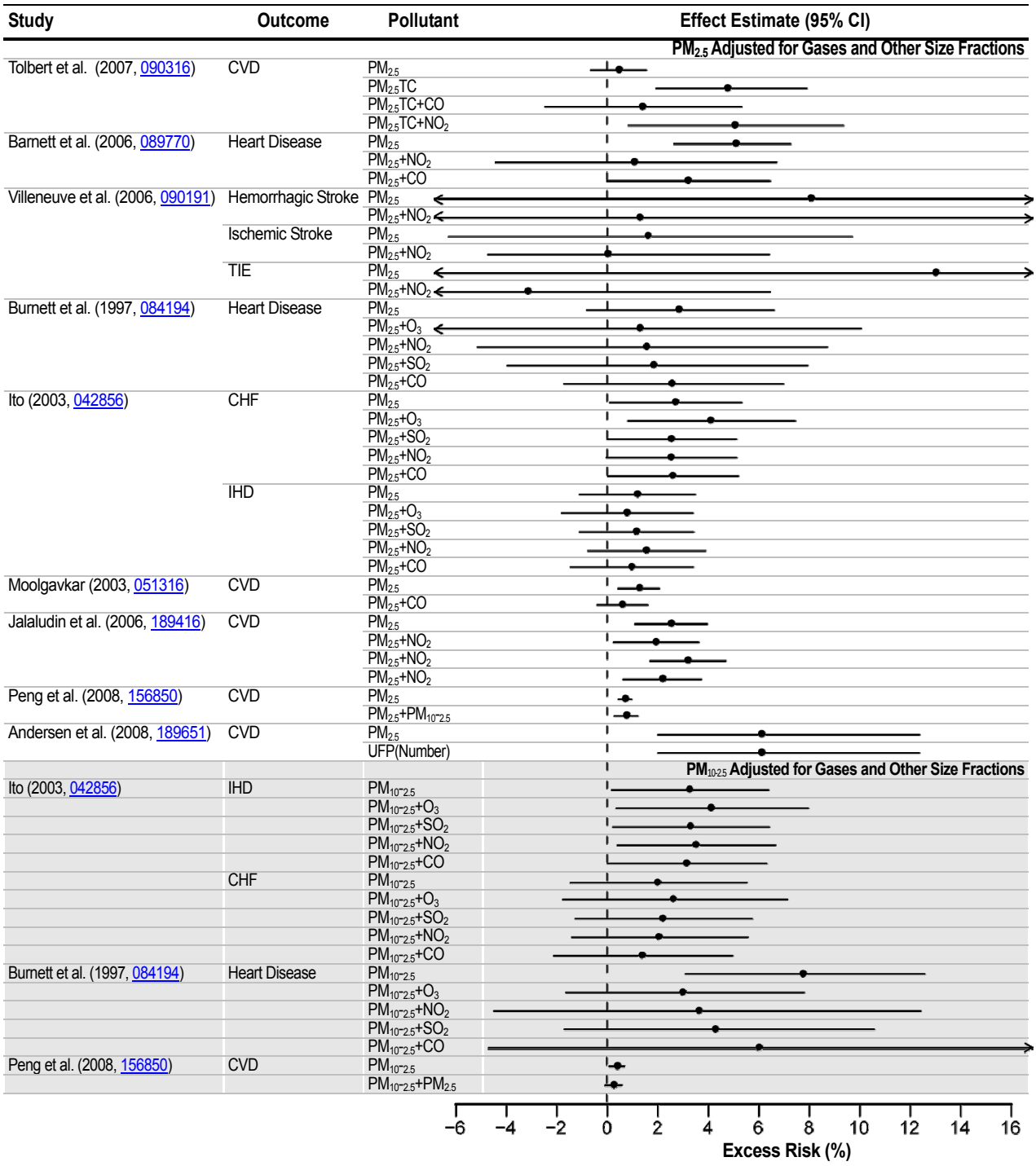


Figure 6-5. Excess risk estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, and $PM_{10-2.5}$ for cardiovascular disease ED visits or HAs, adjusted for co-pollutants.

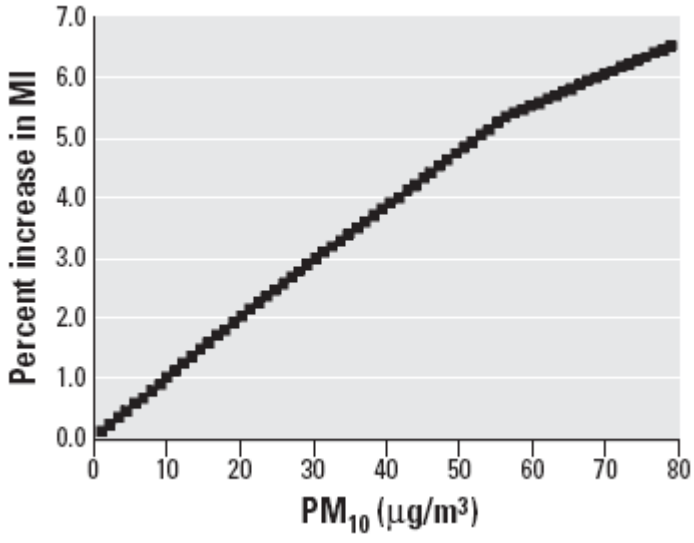
6.2.10.10. Concentration Response

The concentration-response relationship has been extensively analyzed primarily through studies that examined the relationship between PM and mortality. These studies, which have focused on short- and long-term exposures to PM have consistently found no evidence for deviations from linearity or a safe threshold (Daniels et al., 2004, 087343; Samoli et al., 2005, 087436; Schwartz, 2004, 078998; Schwartz et al., 2008, 156963) (Sections 6.5.2.7 and 7.1.4). Although on a more limited basis, studies that have examined PM effects on cardiovascular hospital admissions and ED visits have also analyzed the PM concentration-response relationship, and contributed to the overall body of evidence which suggests a log-linear, no-threshold PM concentration-response relationship.

The evaluation of cardiovascular hospital admission and ED visit studies in 2004 PM AQCD (U.S. EPA, 2004, 056905) found no evidence for a threshold in the dose-response relationship between short-term exposure to PM_{10} and IHD hospital admissions (Schwartz and Morris, 1995, 046186). An evaluation of recent single- and multicity studies of hospital admission and ED visits for CVD further supports this finding.

Ballester et al. (2006, 088746) examined the linearity of the relationship between air pollutants (including PM_{10}) and cardiovascular hospital admissions in 14 Spanish cities within the EMECAM project. In this exploratory analysis, the authors examined the models used when pollutants were added in either a linear or non-linear way (i.e., with a spline smoothing function) to the model. Although the study does not present the results for each of the pollutants evaluated individually, overall Ballester et al. (2006, 088746) found that the shape of the pollutant-cardiovascular hospital admission relationship was most compatible with a linear curve. Wellenius et al. (2005, 087483) conducted a similar analysis when examining the relationship between PM_{10} and CHF hospital admissions among Medicare beneficiaries. The authors examined the assumption of linearity using fractional polynomials and linear splines. The results of both approaches contributed to Wellenius et al. (2005, 087483) concluding that the assumption of linearity between the log relative risk of cardiovascular hospital admissions and PM concentration was reasonable.

Unlike the aforementioned studies that examined the linearity in the concentration-response curve as part of the model selection process (i.e., to determine the most appropriate model to use to examine the relationship between PM and cardiovascular hospital admissions and ED visits), Zanobetti and Schwartz (2005, 088069) conducted an extensive analysis of the shape of the concentration-response curve and the potential presence of a threshold when examining the association between PM_{10} and MI hospital admissions among older adults in 21 U.S. cities. The authors examined the concentration-response curve by fitting a piecewise linear spline with slope changes at 20 and 50 $\mu g/m^3$. This approach resulted in an almost linear concentration-response relationship between PM_{10} and MI hospital admissions with a steeper slope occurring below 50 $\mu g/m^3$ (Figure 6-6). Additionally, Zanobetti and Schwartz (2005, 088069) found no evidence for a threshold.



Source: Zanobetti and Schwartz (2005, 088069).

Figure 6-6. Combined random-effect estimate of the concentration-response relationship between MI emergency hospital admissions and PM_{10}, computed by fitting a piecewise linear spline, with slope changes at 20 µg/m^3 and 50 µg/m^3.

Overall, the limited evidence from the studies that examined the concentration-response relationship between PM and cardiovascular hospital admissions and ED visits supports a no-threshold, log-linear model, which is consistent with the observations made in studies that examined the PM-mortality relationship (Section 6.5.2.7).

6.2.10.11. Out of Hospital Cardiac Arrest

One study of out of hospital cardiac death conducted in Seattle, WA (Checkoway et al., 2000, 015527), which reported no association with PM was included in the 2004 PM AQCD (U.S. EPA, 2004, 056905). In the U.S., the survival rate of sudden cardiac arrest is less than 5%. In addition, as discussed in Section 6.5, Zeka et al. (2006, 088749) found that the estimated mortality risk due to short-term exposure to PM_{10} was much higher for out-of-hospital cardiovascular deaths than for in-hospital cardiovascular deaths. The analysis of studies that examine the association between PM and cardiac arrest could provide evidence for an important link between the morbidity and mortality effects attributed to PM.

Sullivan et al. (2003, 043156) examined the association between the incidence of primary cardiac arrest and daily measures of $PM_{2.5}$ (measured by nephelometry) using a case-crossover analysis of 1,206 Washington State out-of-hospital cardiac arrests (1985-1994) among persons with (n = 774) and without (n = 432) clinically recognized heart disease. The authors examined PM associations at 0- through 2-day lags using the time-stratified referent sampling scheme (i.e., the same day of the week and month of the same year). The estimated relative risk for a 13.8-µg/m^3 increase in 1-day lag $PM_{2.5}$ (nephelometry: IQR = 0.54 10^{-1} km^{-1} bsp) was 0.94 (95% CI: 0.88-1.02), or 0.96 (95% CI: 0.91-1.0) per 10 µg/m^3 increase. Similar estimates were reported for 0- or 2-day lags. The presence or absence of clinically recognized heart disease did not alter the result. This finding is consistent with the previous study of cardiac arrest in Seattle (Levy et al., 2001, 017171) that reported no PM association. It is also consistent with the Sullivan et al. (2005, 050854) analysis of PM and onset of MI, and the Sullivan et al. (2007, 100083) analysis of PM and blood markers of inflammation in the elderly population, both of which were conducted in Seattle. Note also that the analysis of the NMMAPS data for the years 1987-1994 also found no PM_{10} association for all-cause mortality in Seattle. Overall, the results of studies conducted in Seattle consistently found no association between PM and cardiovascular outcomes or all-cause mortality.

Rosenthal et al. (2008, 156925) examined associations between $PM_{2.5}$ and out-of-hospital cardiac arrests in Indianapolis, Indiana for the years 2002-2006 using a case-crossover design with time-stratified referent sampling. Using all the cases (n = 1,374), they found no associations between $PM_{2.5}$ and cardiac arrest in any of the 0- through 3-day lags or multiday averages thereof (e.g., for 0-day lag, OR = 1.02 [CI: 0.94-1.11] per 10 $\mu g/m^3$ increase in $PM_{2.5}$). However, for cardiac arrests witnessed by bystanders (n = 511), they found a significant association with $PM_{2.5}$ exposure (by TEOM, corrected with FRM measurements) during the hour of the arrest (OR = 1.12 [CI: 1.01-1.25] per 10 $\mu g/m^3$ increase in $PM_{2.5}$), and even larger risk estimates for older adults (age 60-75) or those that presented with asystole. There have been very few PM studies that used hourly PM measurements, and further studies are needed to confirm associations at such time scales.

In Rome, Forastiere et al. (2005, 086323) examined associations between air pollution (PNC, PM_{10}, CO, NO_2, and O_3) and out-of-hospital coronary deaths (n = 5,144) for the study period of 1998-2000. A case-crossover design with the time-stratified referent sampling was used to examine the pollution indices at lag 0- through 3 days and the average of 0-1 lags. They found associations between deaths and PNC (lag 0 and 0-1), PM_{10} (lag 0, 1, and 0-1), and CO (lag 0 and 0-1) but not with NO_2 or O_3. The risk estimate for 0-day lag PM_{10} was 1.59% (CI: 0.03-3.18) per 10 $\mu g/m^3$ increase. The older adults (65-74 and ≥75 age groups) showed higher risk estimates than the younger (35-64) age group. Because PNC is considered to be associated with UFPs, and CO was also associated with out-of-hospital cardiac arrests, combustion sources were implicated.

In summary, only a few studies have examined out-of-hospital cardiac arrest or deaths. The two studies from Seattle, WA consistently found no association (also consistent with other cardiac effects and mortality studies conducted in that locale); a study in Indianapolis, IN found an association with hourly $PM_{2.5}$ but not daily $PM_{2.5}$; and a study in Rome found an association with PM_{10}, but also with PNC and CO. Because multicity mortality studies examining this association found heterogeneity in PM risk estimates across regions, future studies of out-of-hospital cardiac arrest will need to consider location and the air pollution mixture during their design. Mean and upper percentile concentrations are found in Table 6-9.

Table 6-9. PM concentrations reported in studies of out-of-hospital cardiac arrest.

Author	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Sullivan et al. (2003, 043156)	Washington State	Nephelometry: 0.71 x 10^{-1} km^{-1} bsp	Maximum: 5.99 x 10^{-1} km^{-1} bsp
Rosenthal et al. (2008, 156925)	Indianapolis, Indiana	NR	NR
PM_{10}			
Sullivan et al. (2003, 043156)	Washington State	28.05	89.83
Zeka et al. (2006, 088749)		Range in Means: 15.9 (Honolulu) - 37.5 (Cleveland)	NR
Forastiere et al. (2005, 086323)	Rome, Italy	52.1	75th: 65.7

6.2.11. Cardiovascular Mortality

An evaluation of studies that examined the association between short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and mortality provides additional evidence for PM-related cardiovascular health effects. Although the primary analysis in the majority of mortality studies evaluated consists of an examination of the relationship between $PM_{2.5}$ or $PM_{10-2.5}$ and all-cause (nonaccidental) mortality, some studies have examined associations with cause-specific mortality including cardiovascular-related mortality.

Multicity mortality studies that examined the $PM_{2.5}$-cardiovascular mortality relationship on a national scale (Franklin et al. (2007, 091257) – 27 U.S. cities; Franklin et al. (2008, 097426) – 25 U.S. cities; and Zanobetti and Schwartz (2009, 188462) – 112 U.S. cities) have found consistent positive associations between short-term exposure to $PM_{2.5}$ and cardiovascular mortality ranging from 0.47 to 0.85% per 10μg/m^3 at lag 0-1 (Section 6.5). The associations observed on a national scale are consistent with those presented by Ostro et al. (2006, 087991) in a study that examined the $PM_{2.5}$-mortality relationship in nine California counties (0.6% [95% CI: 0-1.1] per 10 μg/m^3). Of the multicity studies evaluated, one examined single day lags and found evidence for slightly larger effects at lag 1 compared to the average of lag days 0 and 1 for cardiovascular mortality (94% [95% CI: -0.14 to 2.02] per 10 μg/m^3) (Franklin et al., 2007, 091257). Although the overall effect estimates reported in the multicity studies evaluated are consistently positive, it should be noted that a large degree of variability exists between cities when examining city-specific effect estimates potentially due to differences between cities and regional differences in $PM_{2.5}$ composition (Figure 6-24). Only a limited number of studies that examined the $PM_{2.5}$-mortality relationship have conducted analyses of potential confounders, such as gaseous copollutants, and none examined the effect of copollutants on $PM_{2.5}$ cardiovascular mortality risk estimates. Although the recently evaluated multicity studies did not extensively examine whether $PM_{2.5}$ mortality risk estimates are confounded by gaseous copollutants, evidence from the limited number of single-city studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggests that gaseous copollutants do not confound the $PM_{2.5}$-cardiovascular mortality association. This is further supported by studies that examined the PM_{10}-mortality relationship in both the 2004 PM AQCD (U.S. EPA, 2004, 056905) and this review. The evidence from epidemiologic, controlled human exposure, and toxicological studies that examined the association between short-term exposure to $PM_{2.5}$ and cardiovascular morbidity provide coherence and biological plausibility for the cardiovascular mortality effects observed. Overall, the cardiovascular mortality $PM_{2.5}$ effects were similar to those reported for all-cause (nonaccidental) mortality (Section 6.5), and are consistent with the effect estimates observed in the single- and multicity studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

Zanobetti and Schwartz (2009, 188462) also examined $PM_{10-2.5}$ mortality associations in 47 U.S. cities and found evidence for cardiovascular mortality effects (0.32% [95% CI: 0.00-0.64] per 10 μg/m at lag 0-1) similar to those reported for all-cause (nonaccidental) mortality (0.46% [95% CI: 0.21-0.67] per 10 μg/m). In addition, Zanobetti and Schwartz (2009, 188462) reported seasonal (i.e., larger in spring and summer) and regional differences in $PM_{10-2.5}$ cardiovascular mortality risk estimates. A few single-city studies evaluated also reported associations, albeit somewhat larger than the multicity study, between $PM_{10-2.5}$ and cardiovascular mortality in Phoenix, AZ (Wilson et al., 2007, 157149) (3.4-6.6% at lag 1) and Vancouver, Canada (Villeneuve et al., 2003, 055051) (5.4% at lag 0). The difference in the $PM_{10-2.5}$ risk estimates observed between the multi- and single-city studies could be due to a variety of factors including differences between cities and compositional differences in $PM_{10-2.5}$ across regions (Figure 6-29). Only a small number of studies have examined potential confounding by gaseous copollutants or the influence of model specification on $PM_{10-2.5}$ mortality risk estimates, but the effects are relatively consistent with those studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

6.2.12. Summary and Causal Determinations

6.2.12.1. $PM_{2.5}$

Several studies cited in the 2004 AQCD reported positive associations between short-term $PM_{2.5}$ concentrations and hospital admissions or ED visits for CVD, although few were statistically significant. In addition, U.S. and Canadian-based studies (both multi- and single-city) that examined the $PM_{2.5}$-mortality relationship reported associations for cardiovascular mortality consistent with those observed for all-cause (nonaccidental) mortality and relatively stronger than those for respiratory mortality. Significant associations were also observed between MI and short-term $PM_{2.5}$ concentrations (averaged over 2 or 24 h), as well as decreased HRV in association with $PM_{2.5}$. Several controlled human exposure and animal toxicological studies demonstrated HRV effects from exposure to $PM_{2.5}$ CAPs, as well as changes in blood coagulation markers. However, the effects in these studies were variable. Arrhythmogenesis was reported for toxicological studies and generally

these results were observed in animal models of disease (SH rat, MI, pulmonary hypertension) exposed to combustion-derived $PM_{2.5}$ (i.e., ROFA, DE, metals). One study demonstrated significant vasoconstriction in healthy adults following controlled exposures to CAPs, although this response could not be conclusively attributed to the particles as subjects were concomitantly exposed to relatively high levels of O_3. The results reported for systemic inflammation in toxicological studies were mixed.

A large body of evidence from studies of the effect of $PM_{2.5}$ on hospital admissions and ED visits for CVD has been published since the 2004 PM AQCD. Associations with $PM_{2.5}$ are consistently positive with the majority of studies reporting increases in hospital admissions or ED visits ranging from 0.5 to 3.4% per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Section 6.2.10). The largest U.S.-based multicity study, MCAPs, reported excess risks in the range of approximately 0.7% with the largest excess risks in the Northeast (1.08%) and in the winter (1.49%), providing evidence of regional and seasonal heterogeneity (Bell et al., 2008, 156266; Dominici et al., 2006, 088398). Weak or null findings for $PM_{2.5}$ have been observed in two single-city studies both conducted in Washington state (Slaughter et al., 2005, 073854; Sullivan et al., 2007, 100083) and may be explained by this heterogeneity. Weak associations were also reported in Atlanta for $PM_{2.5}$ and CVD ED visits, with $PM_{2.5}$ traffic components being more strongly associated with CVD ED visits than other components (Tolbert et al., 2007, 090316). Multicity studies conducted outside the U.S. and Canada have shown positive associations with $PM_{2.5}$. Studies of specific CVD outcomes indicate that IHD and CHF may be driving the observed associations (Sections 6.2.10.3 and 6.2.10.5, respectively). Although estimates from studies of cerebrovascular diseases are less precise and consistent, ischemic diseases appear to be more strongly associated with $PM_{2.5}$ compared to hemorrhagic stroke (Section 6.2.10.7). The available evidence suggests that these effects occur at very short lags (0-1 days), although effects at longer lags have rarely been evaluated. Overall, the results of these studies provide support for associations between short-term $PM_{2.5}$ exposure and increased risk of cardiovascular hospital admissions in areas with mean concentrations ranging from 7 to 18 $\mu g/m^3$.

Epidemiologic studies that examined the association between $PM_{2.5}$ and mortality provide additional evidence for $PM_{2.5}$-related cardiovascular effects (Section 6.2.11). The multicity studies evaluated found consistent, precise positive associations between short-term exposure to $PM_{2.5}$ and cardiovascular mortality ranging from 0.47 to 0.85% at mean 24-h avg $PM_{2.5}$ concentrations above 13 $\mu g/m^3$. These associations were reported at short lags (0-1 days), which is consistent with the associations observed in the hospital admission and ED visit studies discussed above. Although only a limited number of studies examined potential confounders of the $PM_{2.5}$-cardiovascular mortality relationship, the studies evaluated in both this review and the 2004 PM AQCD (U.S. EPA, 2004, 056905) support an association between short-term exposure to $PM_{2.5}$ and cardiovascular mortality.

Recent studies that apportion ambient $PM_{2.5}$ into sources and components suggest that cardiovascular hospital admissions associated with $PM_{2.5}$ may be attributable to traffic-related pollution and, in some cases, biomass burning (Section 6.2.10). Further supporting evidence is provided by studies that have used PM_{10} collection filters (median diameter generally <2.5 μm) to identify combustion- or traffic-related sources associated with cardiovascular hospital admissions. Metals have also been implicated in these effects (Bell et al., 2009, 191997). A limited number of older publications have reported that particle acidity of $PM_{2.5}$ is not more strongly associated with CVD hospitalizations or ED visits than other PM metrics.

Changes in various measures of cardiovascular function have been demonstrated by multiple independent laboratories following controlled human exposures to different types of $PM_{2.5}$. The most consistent effect is changes in vasomotor function, which has been demonstrated following exposure to CAPs and DE. The majority of the new evidence of particle-induced changes in vasomotor function comes from studies of exposures to DE (Section 6.2.4.2). None of these studies have evaluated the effects of DE with and without a particle trap. Therefore, the changes in vasomotor function cannot be conclusively attributed to the particles in DE as subjects are also concomitantly exposed to relatively high levels of NO_2, NO, CO, and hydrocarbons. However, it is important to note that a study by Peretz et al. (2008, 156854) used a newer diesel engine with lower gaseous emissions and reported significant DE-induced decreases in BAD. In addition, increasing the particle exposure concentration from 100 to 200 $\mu g/m^3$, without proportional increases in NO, NO_2, or CO, resulted in an approximate 100% increase in response. An additional consideration is that, while fresh DE used in these studies contains relatively high concentrations of $PM_{2.5}$, the MMAD is typically ≤ 100 nm, which makes it difficult to determine whether the observed effects are due to

$PM_{2.5}$ or, more specifically, due to the UF fraction. Further evidence of a particle effect on vasomotor function is provided by significant changes in BAD demonstrated in healthy adults following controlled exposure to CAPs with O_3 (Brook et al., 2002, 024987). These findings are consistent with epidemiologic studies of various measures of vasomotor function (e.g., FMD and BAD were the most common), which have demonstrated an association with short-term $PM_{2.5}$ concentration in healthy and diabetic populations (Section 6.2.4.1). A limited number of epidemiologic studies examined multiple lags and the strongest associations were with either the 6-day mean concentration (O'Neill et al., 2005, 088423) or the concurrent day (Schneider et al., 2008, 191985).

The toxicological findings with respect to vascular reactivity are generally in agreement and demonstrate impaired dilation following $PM_{2.5}$ exposure that is likely endothelium dependent (Section 6.2.4.3). These effects have been demonstrated in varying vessels and in response to different $PM_{2.5}$ types, albeit using IT instillation exposure in most studies. Further support is provided by IT instillation studies of ambient PM_{10} that also demonstrate impaired vasodilation and a $PM_{2.5}$ CAPs study that reported decreased L/W ratio of the pulmonary artery. An inhalation study of Boston $PM_{2.5}$ CAPs reported increases in coronary vascular resistance during ischemia, which indicated a possible role for PM-induced coronary vasoconstriction. The mechanism behind impaired dilation following PM exposure may include increased ROS and RNS production in the microvascular wall that leads to altered NO bioavailability and endothelial dysfunction. Despite the limited number of inhalation studies conducted with concentrations near ambient levels, the toxicological studies collectively provide coherence and biological plausibility for the myocardial ischemia observed in controlled human exposure and epidemiologic studies.

Consistent with the observed effects on vasomotor function, one recent controlled human exposure study reported an increase in exercise-induced ST-segment depression (a potential indicator of ischemia) during exposure to DE in a group of subjects with prior MI (Mills et al., 2007, 091206). In addition, toxicological studies from Boston that employed CAPs provide further evidence for $PM_{2.5}$ effects on ischemia, with changes in ST-segment and decreases in total myocardial blood flow reported (Section 6.2.3.3). These findings from toxicological and controlled human exposure studies provide coherence and biological plausibility for the associations observed in epidemiologic studies, particularly those of increases in hospital admissions and ED visits for IHD. Several epidemiology studies have reported associations between short-term $PM_{2.5}$ concentration (including traffic sources or components such as BC) and ST-segment depression or abnormality (Section 6.2.3.1).

Toxicological studies provide biological plausibility for the $PM_{2.5}$ associations with CHF hospital admissions by demonstrating increased right ventricular pressure and diminished cardiac contractility in rodents exposed to CB and DE (Section 6.2.6.1). Similarly, increased coronary vascular resistance was observed following $PM_{2.5}$ CAPs exposure in dogs with experimentally-induced ischemia. Further, a recent epidemiology study reported small but statistically significant decreases in passively monitored diastolic pressure and right ventricular diastolic pressure (Rich et al., 2008, 156910).

In addition to the effects of PM on vasomotor response, there is a growing body of evidence that demonstrates changes in markers of systemic oxidative stress following controlled human exposures to DE, wood smoke, and urban traffic particles. However, these effects may be driven in part by the UF fraction of $PM_{2.5}$. Toxicological studies provide evidence of increased cardiovascular ROS following $PM_{2.5}$ exposure to CAPs, road dust, CB, and TiO_2, as well as increased systemic ROS in rats exposed to gasoline exhaust (Section 6.2.9.3). Epidemiologic studies of markers of oxidative stress (e.g., tHcy, CuZn-SOD, TBARS, 8-oxodG, oxLDL and MDA) are consistent with these toxicological findings (Section 6.2.9.1).

A few epidemiologic studies of ventricular arrhythmias recorded on ICDs that were conducted in Boston and Sweden (Table 6-2) found associations with short-term $PM_{2.5}$ concentration (also BC and sulfate). While Canadian and U.S. studies conducted outside of Boston did not find positive associations between $PM_{2.5}$ and ICD recorded ventricular arrhythmias, several such studies observed associations with ectopic beats and runs of supraventricular or ventricular tachycardias (Section 6.2.2.1). Toxicological studies also provide limited evidence of arrhythmia, mainly in susceptible animal models (i.e., older rats, rats with CHF) (Section 6.2.2.2).

Most epidemiologic studies of HRV have reported decreases in SDNN, LF, HF, and rMSSD (Section 6.2.1.1). While there are also a significant number of controlled human exposure studies reporting PM-induced changes in HRV, these changes are often variable and difficult to interpret (Section 6.2.1.2). Similarly, HRV increases and decreases have been observed in animal toxicological studies that employed CAPs or CB (Section 6.2.1.3). In a study in mice, resuspended

soil, secondary sulfate, residual oil, and motor vehicle/other sources, as well as Ni were implicated in HRV effects (Lippmann et al., 2006, 091165). Further, cardiac oxidative stress has been implicated as a consequence of ANS stimulation in response to CAPs. Modification of the PM-HRV association by genetic polymorphisms related to oxidative stress has been observed in a series of analyses of the population enrolled in the Normative Aging Study. Changes in HRV measures (whether increased or decreased) are likely to be more useful as indicators of PM exposure rather than predictive of some adverse outcome. Furthermore, the HRV result may be reflecting a fundamental response of an individual that is determined in part by a number of factors including age and pre-existing conditions.

Although not consistently observed across studies, some investigators have reported $PM_{2.5}$-induced changes in BP, blood coagulation markers, and markers of systemic inflammation in controlled human exposure studies (Sections 6.2.5.2, 6.2.8.2, and 6.2.9.2, respectively). Findings from epidemiologic studies, which are largely cross-sectional and measure a wide array markers of inflammation and coagulation, are not consistent; however, a limited number of recent studies of gene-environment interactions offer insight into potential individual susceptibility to these effects (Ljungman et al., 2009, 191983; Peters et al., 2009, 191992). Similarly, toxicological studies demonstrate mixed results for systemic inflammatory markers and generally indicate relatively little change at 16-20 h post-exposure (Section 6.2.7.3). Increases in BP have been observed in toxicological studies (Section 6.2.5.3), with the strongest evidence coming from dogs exposed to $PM_{2.5}$ CAPs. For blood coagulation parameters, the most commonly reported change in animal toxicological studies is elevated plasma fibrinogen levels following $PM_{2.5}$ exposure, but this response is not consistently observed (Section 6.2.8.3).

In summary, associations of hospital admissions or ED visits with $PM_{2.5}$ for CVD (predominantly IHD and CHF) are consistently positive with the majority of studies reporting increases ranging from 0.5 to 3.4% per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Seasonal and regional variation observed in the large multicity study of Medicare recipients is consistent with null findings reported in several single city studies conducted in the Western U.S. The results from the hospital admission and ED visit studies are supported by the associations observed between $PM_{2.5}$ and cardiovascular mortality, which also provide additional evidence for regional and seasonal variability in $PM_{2.5}$ risk estimates. Changes in various measures of cardiovascular function that may explain these epidemiologic findings have been demonstrated by multiple independent laboratories following controlled human exposures to different types of $PM_{2.5}$. The most consistent $PM_{2.5}$ effect is for vasomotor function, which has been demonstrated following exposure to CAPs and DE. Toxicological studies finding reduced myocardial blood flow during ischemia and altered vascular reactivity provide coherence and biological plausibility for the myocardial ischemia that has been observed in both controlled human exposure and epidemiologic studies. Further, $PM_{2.5}$ effects on ST-segment depression have been observed across disciplines. In addition to ischemia, $PM_{2.5}$ may act through several other pathways. Plausible biological mechanisms (e.g., increased right ventricular pressure and diminished cardiac contractility) for the associations of $PM_{2.5}$ with CHF have also been proposed based on toxicological findings. There is a growing body of evidence from controlled human exposure, toxicological and epidemiologic studies demonstrating changes in markers of systemic oxidative stress with $PM_{2.5}$ exposure. Inconsistent effects of PM on BP, blood coagulation markers and markers of systemic inflammation have been reported across the disciplines. Together, the collective **evidence is sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposures and cardiovascular effects**.

6.2.12.2. $PM_{10-2.5}$

There was little evidence in the 2004 AQCD regarding $PM_{10-2.5}$ cardiovascular health effects. Two single-city epidemiologic studies found positive associations of $PM_{10-2.5}$ with cardiovascular hospital admissions in Toronto (Burnett et al., 1999, 017269) and Detroit, MI (Ito, 2003, 042856; Lippmann, 2000, 024579) and the effect estimates were of the same general magnitude as for PM_{10} and $PM_{2.5}$. Both studies reported positive associations and estimates appeared robust to adjustment for gaseous copollutants in two-pollutant models. An imprecise, non-significant association between $PM_{10-2.5}$ and onset of MI was observed in Boston (Peters et al., 2001, 016546). No controlled human exposure or toxicological studies of $PM_{10-2.5}$ were presented in the 2004 AQCD.

Several recent epidemiologic studies of the effect of ambient $PM_{10-2.5}$ concentration on hospital admissions or ED visits for CVD were conducted (Section 6.2.10). In a study of Medicare patients in

108 U.S. counties, Peng et al. (2008, 156850) reported a significant association between $PM_{10-2.5}$ and CVD hospitalizations in their single pollutant model. In a study of six French cities, Host et al. (2008, 155852) reported a significant increase in IHD hospital admissions in association with $PM_{10-2.5}$. In contrast, associations of cardiovascular outcomes with $PM_{10-2.5}$ were weak for CHF and null for IHD in the Atlanta-based SOPHIA study (Metzger et al., 2004, 044222). Results from single-city studies are generally positive, but effect sizes are heterogeneous and estimates are imprecise (Section 6.2.10). Crustal material from a dust storm in the Gobi desert that was largely coarse PM (generally indicated using PM_{10}) was associated with hospitalizations for CVD, including IHD and CHF in most studies (Section 6.2.10). Mean $PM_{10-2.5}$ concentrations in the hospital admission and ED visit studies ranged from 7.4-13 $\mu g/m^3$. A few epidemiologic studies that examined the association between short-term exposure to $PM_{10-2.5}$ and cardiovascular mortality (Section 6.2.11) provide supporting evidence for the hospital admission and ED visit studies at similar 24-h avg $PM_{10-2.5}$ concentrations (i.e., 6.1-16.4 $\mu g/m^3$). A multicity study reported risk estimates for cardiovascular mortality of similar magnitude to those for all-cause (nonaccidental) mortality (Zanobetti and Schwartz, 2009, 188462). However, the single-city studies evaluated (Villeneuve et al., 2003, 055051; Wilson et al., 2007, 157149) reported substantially larger effect estimates, but this could be due to differences between cities and compositional differences in $PM_{10-2.5}$ across regions. Of note is the lack of analyses within the studies evaluated that examined potential confounders of the $PM_{10-2.5}$-cardiovascular mortality relationship.

The U.S. study of Medicare patients (Peng et al., 2008, 156850) and the multicity study that examined the association between $PM_{10-2.5}$ and mortality (Zanobetti and Schwartz, 2009, 188462) were the only studies to adjust $PM_{10-2.5}$ for $PM_{2.5}$. Peng, et al. (2008, 156850) found that the $PM_{10-2.5}$ association with CVD hospitalizations remained, but diminished slightly after adjustment for $PM_{2.5}$. These results are consistent with those reported by Zanobetti and Schwartz (2009, 188462), which found $PM_{10-2.5}$-cardiovascular mortality risk estimates remained relatively robust to the inclusion of $PM_{2.5}$ in the model. Because of the greater spatial heterogeneity of $PM_{10-2.5}$, exposure measurement error is more likely to bias health effect estimates towards the null for epidemiologic studies of $PM_{10-2.5}$ versus PM_{10} or $PM_{2.5}$, making it more difficult to detect an effect of the coarse size fraction. In addition, models that include both $PM_{10-2.5}$ and $PM_{2.5}$ may suffer from instability due to collinearity. Further, the lag structure of $PM_{10-2.5}$ effects on risk of cardiovascular hospital admissions and ED visits, as well as mortality, has not been examined in detail.

Several epidemiologic studies of cardiovascular endpoints including HRV, BP, ventricular arrhythmia, and ECG changes indicating ectopy or ischemia were conducted since publication of the 2004 PM AQCD. Supraventricular ectopy and ST-segment depression were associated with $PM_{10-2.5}$ (Section 6.2.3.1), and the only study to examine the effect of $PM_{10-2.5}$ on BP reported a decrease in SBP (Ebelt et al., 2005, 056907) (Section 6.2.5.1). HRV findings were mixed across the epidemiologic studies (Section 6.2.1.1). A limited number of studies have evaluated the effect of controlled exposures to $PM_{10-2.5}$ CAPs on cardiovascular endpoints in human subjects. These studies have provided some evidence of decreases in HRV (SDNN) and tPA concentration among healthy adults approximately 20 hours following exposure (Section 6.2.1.2). However, it is important to note that no other measures of HRV (e.g., LF, HF, or LF/HF), nor other hemostatic or thrombotic markers (e.g., fibrinogen) were significantly affected by particle exposure in these studies.

There are very few toxicological studies that examined the effect of exposure to $PM_{10-2.5}$ on cardiovascular endpoints or biomarkers in animals. The few studies that evaluated cardiovascular responses were comparative studies of various size fractions, and only blood or plasma parameters were measured (Sections 6.2.7.3 and 6.2.8.3). These studies used IT instillation methodologies, as there are challenges to exposing rodents via inhalation to $PM_{10-2,5}$, due to near 100% deposition in the ET region for particles >5 μm (Raabe et al., 1988, 001439) and only 44% nasal inhalability of a 10 μm particle in the rat (Ménache et al., 1995, 006533). These studies also employed relatively high doses of $PM_{10-2.5}$. Despite these shortcomings, increased plasma fibrinogen was observed and the response was similar to that observed with $PM_{2.5}$. At this time, evidence of biological plausibility for cardiovascular morbidity effects following $PM_{10-2.5}$ exposure is sparse, due to the small number of studies, few endpoints examined, and the limitations related to the interpretation of IT instillation exposures.

In summary, several epidemiologic studies report associations with cardiovascular endpoints including IHD hospitalizations, supraventricular ectopy, and changes in HRV. Further, dust storm events resulting in high concentrations of crustal material are linked to increases in cardiovascular disease hospital admissions or ED visits for cardiovascular diseases. A large proportion of inhaled

coarse particles in the 3-6 μm (d_{ae}) range can reach and deposit in the lower respiratory tract, particularly the TB airways (Figures 4-3 and 4-4). The few toxicological and controlled human exposure studies examining the effects of $PM_{10-2.5}$ provide limited evidence of cardiovascular effects and biological plausibility to support the epidemiologic findings. Therefore the available evidence is **suggestive of a causal relationship between $PM_{10-2.5}$ exposures and cardiovascular effects**.

6.2.12.3. UFPs

There was very little evidence available in the 2004 PM AQCD (U.S. EPA, 2004, 056905) on the cardiovascular effects of UFPs. Findings from one study presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) of controlled exposures to UF EC suggested no particle-related effects on various cardiovascular endpoints including blood coagulation, HRV, and systemic inflammation. No epidemiologic studies of short-term UFP concentration and cardiovascular endpoints were included in the 2004 AQCD and there were no relevant toxicological studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that exposed animals to UFPs. A small number of new epidemiologic studies, as well as several controlled human exposure and toxicological studies have been conducted in recent years, but substantial uncertainties remain as to the cardiovascular effects of UFPs. For a given mass, the enormous number and large surface area of UFPs highlight the importance of considering the size of the particle in assessing response. For example, UFPs with a diameter of 20 nm, when inhaled at the same mass concentration, have a number concentration that is approximately six orders of magnitude higher than for a 2.5-μm diameter particle. Particle surface area is also greatly increased with UFPs. Many studies suggest that the surface of particles or substances released from the surface (e.g., transition metals, organics) interact with biological substrates, and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity, resulting in greater toxicity of UFPs per particle surface area than larger particles. Additionally, smaller particles may have greater potential to cross cell membranes and epithelial barriers.

Controlled human exposure studies are increasingly being utilized to evaluate the effect of UFPs on cardiovascular function. While the number of studies of exposure to UFPs is still limited, there is a relatively large body of evidence from exposure to fresh DE, which is typically dominated by UFPs. As described under the summary for $PM_{2.5}$, studies of controlled exposures to DE (100-300 $\mu g/m^3$) have consistently demonstrated effects on vasomotor function among adult volunteers (Section 6.2.4.2). In addition, exposure to UF EC (50 $\mu g/m^3$, 10.8×10^6 particles/cm^3) was recently shown to attenuate FMD (Shah et al., 2008, 156970). Changes in vasomotor function have been observed in animal toxicological studies of UFPs, although very few studies have been conducted (Section 6.2.4.3). Inhaled UF TiO_2 impaired arteriolar dilation when compared to fine TiO_2 at similar mass doses (Nurkiewicz et al., 2008, 156816). This response may have been due to ROS in the microvascular wall, which may have led to consumption of endothelial-derived NO and generation of peroxynitrite radicals. Support for an UFP effect on altered vascular reactivity is also provided by studies of DE and IT instillation exposure to ambient PM. The response to DE did not appear to be due to VOCs. One epidemiologic study showed that PNC was associated with a nonsignificant decrease in flow- and nitroglycerine-mediated reactivity as measures of vasomotor function in diabetics living in Boston (O'Neill et al., 2005, 088423).

New studies have reported increases in markers of systemic oxidative stress in humans following controlled exposures to different types of PM consisting of relatively high concentrations of UFPs from sources including wood smoke, urban traffic particles, and DE (Section 6.2.9.2). Increased cardiac oxidative stress has been observed in mice and rats following gasoline exhaust exposure and it appeared the effect was particle-dependent (Section 6.2.9.3).

The associations between UFPs and HRV measures in epidemiologic studies include increases and decreases (Section 6.2.1.1), providing some evidence for an effect. Exposure to UF CAPs has been observed to alter parameters of HRV in controlled human exposure studies, although this effect has been variable between studies (Section 6.2.1.2). Alterations in HR, HRV, and BP were reported in rats exposed to <200 $\mu g/m^3$ UF CB (<1.6×10^7 particles/cm^3) (Sections 6.2.1.3 and 6.2.5.3). The effects of UFPs on BP have been mixed in epidemiologic studies (Section 6.2.5.1).

There is some evidence of changes in markers of blood coagulation in humans following controlled exposure to UF CAPs, as well as wood smoke and DE; however, these effects have not

been consistently observed across studies (Section 6.2.8.2). Toxicological studies demonstrate mixed results for systemic inflammation and blood coagulation as well (Sections 6.2.7.3 and 6.2.8.3).

Few time-series studies of CVD hospital admissions have evaluated UFPs. The SOPHIA study found no association between any outcome studied (all CVD, dysrhythmia, CHF, IHD, peripheral vascular and cerebrovascular disease) and 24-h mean levels of UFP (Metzger et al. 2004). The median UF particle count in Atlanta during the study period was 25,900 particles/cm^3. UFP were not associated with CVD hospitalizations in the elderly in Copenhagen, Denmark, but were associated with cardiac readmission or fatal MI in the European HEAPSS study (Section 6.2.10). In the Copenhagen study, the mean count of particles with a 100 nm mean diameter was 0.68×10^4 particles/cm^3, whereas the PNC range was approximately $1.2\text{-}7.6\times10^4$ particles/cm^3 in HEAPSS study. Spatial variation in UFP concentration, which diminishes within a short distance from the roadway, may introduce exposure measurement error, making it more difficult to observe an association if one exists.

A limited number of epidemiologic studies have evaluated subclinical cardiovascular measures and a number of these were conducted in Boston. UFPs have been linked to ICD-recorded arrhythmias in Boston and supraventricular ectopic beats in Erfurt, Germany (Section 6.2.2.1). One study reported no UFP association with ectopy (Barclay et al., 2009, 179935). ST-segment depression in subjects with stable coronary heart disease was associated with UFPs in Helsinki (Section 6.2.3.1). The limited number of studies that examine this size fraction makes it difficult to draw conclusions about these cardiovascular measures.

In summary, there is a relatively large body of evidence from controlled human exposure studies of fresh DE, which is typically dominated by UFPs, demonstrating effects of UFP on the cardiovascular system. In addition, cardiovascular effects have been demonstrated by a limited number of laboratories in response to UF CB, urban traffic particles and CAPs. Responses include altered vasomotor function, increased systemic oxidative stress and altered HRV parameters. Studies using UF CAPs, as well as wood smoke and DE, provide some evidence of changes in markers of blood coagulation, but findings are not consistent. Toxicological studies conducted with UF TiO_2, CB, and DE demonstrate changes in vasomotor function as well as in HRV. Effects on systemic inflammation and blood coagulation are less consistent. PM-dependent cardiac oxidative stress was noted following exposure to gasoline exhaust. The few epidemiologic studies of UFPs conducted do not provide strong support for an association of UFPs with effects on the cardiovascular system. Based on the above findings, the evidence is **suggestive of a causal relationship between ultrafine PM exposure and cardiovascular effects.**

6.3. Respiratory Effects

6.3.1. Respiratory Symptoms and Medication Use

The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented evidence from epidemiologic studies of increases in respiratory symptoms associated with PM, although this was not supported by the findings of a limited number of controlled human exposure studies. Recent epidemiologic studies have provided evidence of an increase in respiratory symptoms and medication use associated with PM among asthmatic children, with less evidence of an effect in asthmatic adults. The lack of an observed effect of PM exposure on respiratory symptoms in controlled human exposure studies does not necessarily contradict these findings, as very few studies of controlled exposures to PM have been conducted among groups of asthmatic or healthy children.

6.3.1.1. Epidemiologic Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) concluded that the effects of PM_{10} on respiratory symptoms in asthmatics tended to be positive, although they were somewhat less consistent than PM_{10} effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant for PM_{10}. The results from one study of respiratory symptoms and $PM_{10\text{-}2.5}$ (Schwartz and

Neas, 2000, 007625) found a statistically significant association with cough with $PM_{10-2.5}$. The results of two studies examining respiratory symptoms and $PM_{2.5}$ revealed slightly larger effects for $PM_{2.5}$ than for PM_{10}.

Asthmatic Children

Two large, longitudinal studies in urban areas of the U.S. investigated the effects of ambient PM on respiratory symptoms and/or asthma medication use with similar analytic techniques (i.e., multistaged modeling and generalized estimating equations [GEE]): the Childhood Asthma Management Program (CAMP) (Schildcrout et al., 2006, 089812) and the National Cooperative Inner-City Asthma Study (NCICAS) (Mortimer et al., 2002, 030281). A number of smaller panel studies conducted in the U.S. evaluated the effects of ambient PM concentrations on respiratory symptoms and medication use among asthmatic children (Delfino et al., 2002, 093740; 2003, 090941; 2003, 050460; Gent et al., 2003, 052885; 2009, 180399; 2006, 088031; Slaughter et al., 2003, 086294).

In the CAMP study, the association between ambient air pollution and asthma exacerbations in children (n = 990) from eight North American cities was investigated (Schildcrout et al., 2006, 089812). In contrast to several past studies (Delfino et al., 1996, 080788; 1998, 051406), no associations were observed between PM_{10} and asthma exacerbations or medication use. PM_{10} concentrations were measured on less than 50% of study days in all cities except Seattle and Albuquerque. While PM_{10} effects were not observed for the entire panel of children, they were observed in recent reports on the children participating at the Seattle center (Slaughter et al., 2003, 086294; Yu et al., 2000, 013254). In a smaller panel study of asthmatic children (n = 133) enrolled in the CAMP study, daily particle concentrations averaged over three central sites in Seattle was used as the exposure metric (Slaughter et al., 2003, 086294). Children were followed for 2 months, on average. Daily health outcomes included both a 3-category measure of asthma severity based on symptom duration and frequency, and inhaled albuterol use. In single-pollutant models, an increased risk of asthma severity was associated with a 10 $\mu g/m^3$ increase in lag 1 $PM_{2.5}$ (OR 1.20 [95% CI: 1.05-1.37]) and with a 10 $\mu g/m^3$ increase in lag 0 PM_{10} (OR 1.12 [95% CI: 1.05-1.22]). In copollutant models with CO, the associations remained (OR for $PM_{2.5}$ 1.16 [95% CI: 1.03-1.30]; OR for PM_{10} 1.11 [95% CI: 1.03-1.19]). Associations between inhaler use and PM were positive in single-pollutant models (RR lag 1 $PM_{2.5}$ 1.08 [95% CI: 1.01-1.15]; RR lag 0 PM_{10} 1.05 [95% CI: 1.00-1.09]), but attenuated and no longer statistically significant in copollutant models.

The eight cities included in the NCICAS (Mortimer et al., 2002, 030281) were all in the East or Midwest: New York City (Bronx, E. Harlem), Baltimore, Washington DC, Cleveland, Detroit, St. Louis, and Chicago. In this study, 864 asthmatic children, aged 4-9 yr, were followed daily for four 2-wk periods over the course of nine months. Morning and evening asthma symptoms (analyzed as none vs. any) and peak flow were recorded. For the three urban areas with air quality data, each 10 $\mu g/m^3$ increase in the mean of the previous 2 days (lag 1-2) PM_{10}, increased the risk for morning asthma symptoms (OR 1.12 [95% CI: 1.00-1.26]). This effect was robust to the inclusion of O_3 (OR 1.12 [95% CI: 0.98-1.27]). In a related study, O'Connor et al. (2008, 156818) examined the relationship between short-term fluctuations in outdoor air pollutant concentrations and changes in pulmonary function and respiratory symptoms among children with asthma in seven U.S. inner-city communities. $PM_{2.5}$ concentration was not statistically associated with respiratory symptoms in this study.

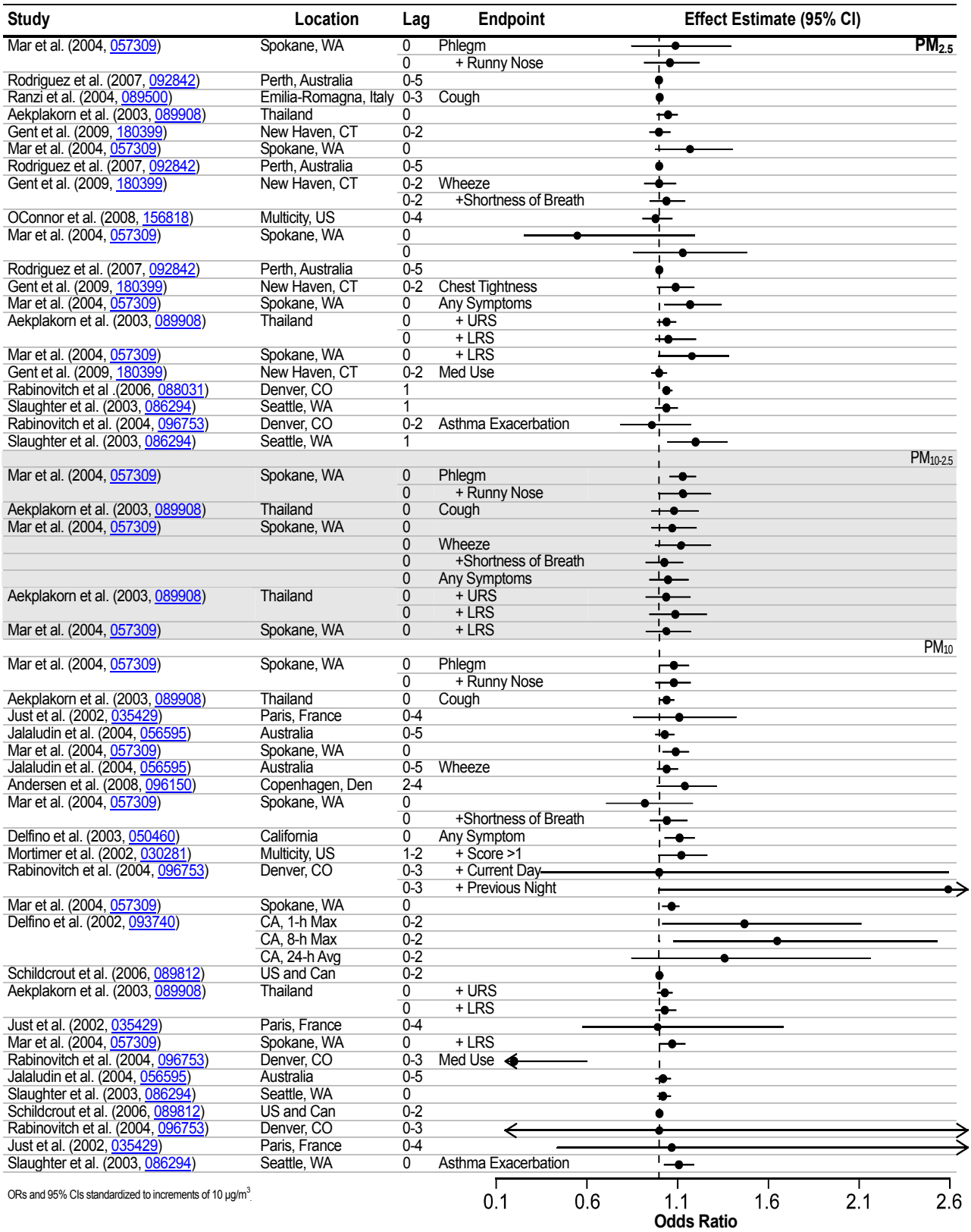


Figure 6-7. Respiratory symptoms and/or medication use among asthmatic children following acute exposure to PM.

Table 6-10. Characterization of ambient PM concentrations from epidemiologic studies of respiratory morbidity and short-term exposures in asthmatic children and adults. All concentrations are for the 24-h avg unless otherwise noted.

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Adamkiewicz et al. (2004, 087925)	Steubenville, OH	20.43	75th: 23 98th: 51.79 Max: 51.79
Adar et al. (2007, 001458)	St. Louis, MO	10.13	98th: 22.43 Max: 23.24
Aekplakorn et al. (2003, 089908)	North Thailand		Max: 24.8-26.3
Allen et al. (2008, 156208)	Seattle, WA	11.2	Max: 40.38
Barraza-Villarreal et al. (2008, 156254)	Mexico City	8-h max: 28.9	Max: 102.8
Bourotte et al. (2007, 150040)	Sao Paulo, Brazil	11.9	Max: 26.6
de Hartog et al. (2003, 001061)	Multicity, Europe	12.8-23.4	Max: 39.8-118.1
Delfino et al. (2006, 090745)	Southern CA	3.9-6.9	Max: 8.8-11.6
DeMeo et al. (2004, 087346)	Boston, MA	10.8	NR
Ebelt et al. (2005, 056907)	Vancouver, Canada	11.4	98th: 23 Max: 28.7
Ferdinands et al. (2008, 156433)	Atlanta, GA	27.2	Max: 34.7
Fischer et al. (2007, 156435)	The Netherlands	56	75th: 187
Gent et al. (2003, 052885)	CT & MA	13.1	60th: 12.1 80th: 19.0
Gent et al. (2009, 180399)	New Haven, CT	17.0	NR
Girardot et al. (2006, 088271)	Smoky Mountains	13.9	Max: 38.4
Hogervorst et al. (2006, 156559)	The Netherlands	19.0	NR
Hong et al. (2007, 091347)	Incheon City, Korea	20.27	Max: 36.28
Jansen et al. (2005, 082236)	Seattle, WA	14.0	Max: 44
Johnston et al. (2006, 091386)	Darwin, Australia	11.1	Max: 36.5
Koenig et al. (2003, 156653)	Seattle, WA	13.3	Max: 40.4
Lagorio et al. (2006, 089800)	Rome, Italy	27.2	Max: 100
Lee et al. (2007, 093042)	Seoul, South Korea	51.15	75th: 87.54 Max: 92.71
Lewis et al. (2004, 097498)	Detroit, MI	15.7-17.5	Max: 56.1
Liu et al. (2009, 192003)	Windsor, Ontario	7.1	95th: 19.0 98th: 19.0.
Mar et al. (2004, 057309)	Spokane, WA	8.1-11.0	NR
Mar et al. (2005, 088759)	Seattle, WA	5-26	NR
McCreanor et al. (2007, 092841)	London, England	1-h avg: 11.9-28.3	1-h max: 55.9-76.1
Moshammer et al. (2006, 090771)	Linz, Austria	8-h avg: 15.70	Max 24-h avg: 76.39
Murata et al. (2007, 189159)	Tokyo, Japan	39.0	Max 1-h avg: 120
O'Connor et al. (2008, 156818)	Multicity, U.S.	14	Max: 35

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Peled et al. (2005, 156015)	Multicity, Israel	23.9-29.2	NR
Penttinen et al. (2006, 087988)	Helsinki, Finland	8.37	75th: 11.15 Max: 33.53
Rabinovitch et al. (2004, 096753)	Denver, CO	10.8	98th: 29.3 Max: 53.5
Rabinovitch et al. (2006, 088031)	Denver, CO	10.8	98th: 23.4
Ranzi et al. (2004, 089500)	Emilia-Romagna, Italy	Urban: 53.07 Rural: 29.11	NR
Rodriguez et al. (2007, 092842)	Perth, Australia	1-h avg: 20.8 24-h avg: 8.5	Max 1-h avg: 93.4 Max 24-h avg: 39.4
Slaughter et al. (2003, 086294)	Seattle, WA	7.3[a]	75th: 11.3
Strand et al. (2006, 089203)	Denver, CO	12.7	Max: 32.3
Timonen et al. (2004, 087915)	Multicity, Europe	12.7-23.1	Max: 39.8-118.1
Trenga et al. (2006, 155209)	Seattle, WA	8.6-9.6[a]	75th: 13.1-14.8 Max: 40.4-41.5
von Klot et al. (2002, 034706)	Erfurt, Germany	30.3[b]	75th: 41.3[b] Max: 133.8[b]
Ward et al. (2002, 025839)	Birmingham and Sandwell, U.K.	12.3-12.7	Max: 28-37
$PM_{10-2.5}$			
Aekplakorn et al. (2003, 089908)	North Thailand	NR	NR
Bourotte et al. (2007, 150040)	Sao Paulo, Brazil	21.7	Max: 62.0
Ebelt et al. (2005, 056907)	Vancouver, Canada	5.6	Max: 11.9
Lagorio et al. (2006, 089800)	Rome, Italy	15.6	Max: 39.6
Mar et al. (2004, 057309)	Spokane, WA	8.7-13.5	NR
von Klot et al. (2002, 034706)	Erfurt, Germany	10.3	75th: 14.6 Max: 64.3
PM_{10}			
Aekplakorn et al. (2003, 089908)	North Thailand	31.9-37.5	Max: 113.3-153.3
Andersen et al. (2008, 096150)	Copenhagen, Denmark	25.1	75th: 30.2
Boezen et al. (2005, 087396)	The Netherlands	26.6-44.1	Max: 89.9-242.2
de Hartog et al. (2003, 001061)	Multicity, Europe	19.6-36.5	Max: 67.4-112.0
Delfino et al. (2002, 093740)	Alpine, CA	20	90th: 32 Max: 42
Delfino et al. (2003, 050460)	Los Angeles, CA	59.9	90th: 86/0/Max: 126
Delfino et al. (2004, 056897)	Alpine, CA	29.7	90th: 40.9 Max: 50.7
Delfino et al. (2006, 090745)	Southern CA	35.7-70.8	Max: 105.5-154.1
Desqueyroux et al. (2002, 026052)	Paris, France	23-28	Max: 63-84
Ebelt et al. (2005, 056907)	Vancouver, Canada	17	Max: 36
Hong et al. (2007, 091347)	Incheon City, Korea	35.3	Max: 124.87
Jalaludin et al. (2004, 056595)	Sydney, Australia	22.8	75th: 122.8
Jansen et al. (2005, 082236)	Seattle, WA	18.0	Max: 51

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Johnston et al. (2006, 091386)	Darwin, Australia	20	Max: 43.3
Just et al. (2002, 035429)	Paris, France	23.5	Max: 44.0
Lagorio et al. (2006, 089800)	Rome, Italy	42.8	Max: 123
Laurent et al. (2008, 156672)	Strasbourg, France	20.8	Max: 106.3
Lee et al. (2007, 093042)	Seoul, South Korea	71.40	75th: 87.54 Max: 148.34
Mar et al. (2004, 057309)	Spokane, WA	16.8-24.5	NR
Mortimer et al. (2002, 030281)	Multicity, U.S.	53	NR
Moshammer et al. (2006, 090771)	Linz, Austria	8-h avg: 24.85	Max 24-h: 76.39
Odajima et al. (2008, 192005)	Fukuoka, Japan	3-h avg: 32.6-41.5	Max 3-h avg: 126.0-191.3
Peacock et al. (2003, 042026)	Southern England	21.2	Max: 87.9
Peled et al. (2005, 156015)	Multicity, Israel	31.0-67.1	NR
Preutthipan et al. (2004, 055598)	Bangkok, Thailand	111.0	Max: 201
Rabinovitch et al. (2004, 096753)	Denver, CO	28.1	Max: 102.0
Ségala et al. (2004, 090449)	Paris, France	24.2	Max: 97.4
Schildcrout et al. (2006, 089812)	Multicity, U.S.	17.7-32.4[a]	75th: 26.2-42.7 90th: 32.5-53.9
Slaughter et al.(2003, 086294)	Seattle, WA	21.0[a]	75th: 29.3
Steinvil et al. (2008, 188893)	Tel Aviv, Israel	64.5	75th: 60.7
von Klot et al. (2002, 034706)	Erfurt, Germany	45.4	75th: 59.7 Max: 172.4

[a]Median
[b]Includes UFP, for complete information on number concentration from this study, please see corresponding table in Annex E.

Mar et al. (2004, 057309) studied asthmatic children (n = 9) in Spokane, WA. Increases in 0-, 1- or 2-day lags of each of the PM size classes studied were associated with cough. When all lower respiratory tract symptoms (wheeze, cough, shortness of breath, sputum production) were grouped together, positive associations were reported for each 10 $\mu g/m^3$ increase in same-day PM_{10} (OR 1.07 [95% CI: 1.00-1.14]), or lag 0 or lag 1 $PM_{2.5}$ (OR 1.18 [95% CI: 1.00-1.38]; OR 1.21 [95% CI: 1.00-1.46], respectively), and 10 $\mu g/m^3$ increase in lag 0 and lag 1 $PM_{1.0}$ (OR 1.21 [95% CI: 1.01-1.44]; OR 1.25 [95% CI: 1.01-1.55], respectively). No associations were reported for $PM_{10-2.5}$ and grouped lower respiratory tract symptoms (Mar et al., 2004, 057309).

Gent et al. (2003, 052885) reported on daily symptom and medication use during one summer for 271 asthmatic children living in southern New England. In single-pollutant models for users of maintenance medication (n = 130), $PM_{2.5}$ $\geq$19 $\mu g/m^3$ lagged by 1 day was associated with a 10-25% increase in risk of symptoms compared to $PM_{2.5}$ <6.9 $\mu g/m^3$: OR for persistent cough 1.12 (95% CI: 1.02-1.24); OR for chest tightness 1.21 (95% CI: 1.00-1.46); OR for shortness of breath 1.26 (95% CI: 1.02-1.54). Effects were attenuated in models including O_3 (OR for persistent cough 1.00 [95% CI: 0.88-1.15]; OR for chest tightness 0.91 [95% CI: 0.71-1.17]; OR for shortness of breath 1.20 [95% CI: 0.94-1.52]). No statistical associations between ambient particle exposure and respiratory health were found for asthmatic children not on maintenance medication.

Annual $PM_{2.5}$ levels at monitoring sites in New Haven, CT exceed the annual standard of 15 $\mu g/m^3$. Gent et al. (2009, 180399) conducted a study here to examine the associations between daily exposure to $PM_{2.5}$ components and sources identified through source apportionment, and daily symptoms and medication use in asthmatic children. Asthmatic children (n = 149) aged 4-12 yr were enrolled in the study between 2000 and 2003. Factor analysis was used to identify six sources of $PM_{2.5}$ (motor vehicle, road dust, sulfur, biomass burning, oil, and sea salt). Total $PM_{2.5}$ was not associated with any symptoms or medication use; however trace elements originating from motor vehicle, road dust, biomass burning and oil sources were associated with symptoms and/or

medication use. For example, an increased risk of wheeze, shortness of breath, chest tightness or short-acting inhaler use was associated with increasing EC mass concentration. Risks remain in models that include all six $PM_{2.5}$ sources as well as NO_2, which may be considered a marker for traffic. NO_2 was found to be an independent risk factor for increased wheeze.

Two panel studies were conducted over the course of three winters at a school in Denver (Rabinovitch et al., 2004, 096753; 2006, 088031). In the first report, approximately 86 different children contributed data on asthma symptoms and medication use over three consecutive winters (Rabinovitch et al., 2004, 096753). The exposure metric was the 3-day average concentration of $PM_{2.5}$ measured at a site located next to the school for the first two winters and from a central site located 4.8 km (3 miles) away for the third. A strong correlation was observed during the first two winters between $PM_{2.5}$ values measured locally and at a downtown monitoring station (Pearson product-moment correlation = 0.93) and between PM_{10} values measured locally and at a downtown monitoring station (correlation = 0.84). Therefore, in year 3, all ambient data were collected from nearby community monitoring stations. No statistical associations were found between asthma symptoms or medication use and PM. Rabinovitch et al. (2006, 088031) enrolled a panel of 73 children and evaluated associations with morning maximum $PM_{2.5}$ measured at the central site. PM measurements were available hourly from two co-located monitors, an FRM and a TEOM monitor. Each 10 $\mu g/m^3$ increase in morning maximum 1-h $PM_{2.5}$ concentration was associated with an increased likelihood of rescue medication use (OR for FRM 1.02 [95% CI: 1.01-1.03]; OR for TEOM 1.03 [95% CI: 1.00-1.6]). Interestingly, the association between inhaler use and particle exposure was not evident when the 24-h avg $PM_{2.5}$ was used in the model.

Two smaller panel studies enrolling asthmatic children conducted by Delfino et al. (2002, 093740; 2003, 050460) in southern California examined the health effects of different averaging times for PM_{10} (1-h, 8-h, 24-h) (Delfino et al., 2002, 093740), and 24-h avg of two PM_{10} components (EC and OC) (Delfino et al., 2003, 050460). In the first study, 22 children living in a "lower" pollution area were followed daily for two months in spring. In contrast with Gent et al. (2003, 052885), positive statistical associations with asthma symptoms (measured on a 6-point severity scale) were found only for the children not taking anti-inflammatory medication. For these 12 children, in single-pollutant models each 10 $\mu g/m^3$ increase in lag 0 1-h max PM_{10} nearly doubled the risk of clinically meaningful symptoms (i.e., an asthma symptom score $\geq$3) (OR 1.14 [95% CI: 1.04-1.24]) and each 10 $\mu g/m^3$ increase in 3-day avg 24-h PM_{10} increased the risk by 1.25 (95% CI: 1.06-1.48). No statistical associations were found between exposure to ambient particles and symptoms in the ten children who were taking anti-inflammatory medication. No multipollutant models were reported. The second study enrolled 22 asthmatic children living in an area of higher pollution. For children living in this community, each 10 $\mu g/m^3$ increase in lag 0, 24-h PM_{10} was associated with an increased risk of asthma symptom score >1: OR 1.10, (95% CI: 1.03-1.19) (Delfino et al., 2003, 050460). The correlation among PM_{10}, EC and OC was substantial: 0.80 between PM_{10} and either EC or OC, and 0.94 between EC and OC. Associations between EC or OC and asthma symptoms were very similar to those for PM_{10}: each 3 $\mu g/m^3$ increase in lag 0, 24-h EC or 5 $\mu g/m^3$ increase in lag 0, 24-h OC was associated with an increased risk of asthma symptoms (OR 1.85 [95% CI: 1.11-3.08] or OR 1.88 [95% CI: 1.12-3.17], respectively) (Delfino et al., 2003, 050460).

The association between incident wheezing symptoms and air pollution was assessed in the Copenhagen Prospective Study of Asthma in Children among a birth cohort of 205 children in Copenhagen, Denmark. In addition to PM_{10} and other gaseous air pollutants, the study examined UFP concentrations collected from a central background monitoring station. This is the only study identified that examined the association between UFPs and respiratory symptoms in children. There were strong adverse effects for PM_{10} and UFPs, as well as for NO_2, NO_X, and CO for wheezing symptoms in infants which attenuated after the age of 1 yr (lag 2-4 PM_{10} OR 1.21 (95% CI 0.99-1.48); lag 2-4 UFP OR 1.92 (95% CI: 0.98-3.76)). These associations remained in copollutant models including NO_2, NO_X and CO.

Studies from Australia (Rodriguez et al., 2007, 092842), Europe (Andersen et al., 2008, 096150; Laurent et al., 2008, 156672; Laurent et al., 2009, 192129; Ranzi et al., 2004, 089500), and Asia (Aekplakorn et al., 2003, 089908) provide additional evidence of an association between ambient PM and respiratory symptoms and/or medication use among asthmatic children. Two studies (Jalaludin et al., 2004, 056595; Just et al., 2002, 035429) found no association between ambient PM levels and these health endpoints.

Asthmatic Adults

Since the 2004 PM AQCD (U.S. EPA, 2004, 056905), one U.S. and several European studies have investigated the effects of ambient PM levels on respiratory symptoms and medication use among asthmatic adults. The respiratory symptom and medication use results from these studies are summarized by particle size and displayed in Table 6-10 and Figure 6-8. Relatively few studies examined these effects in healthy adults, and they did not identify a relationship between ambient PM levels and respiratory symptoms or medication use. These studies of healthy adults are summarized in Annex E, but will not be described in detail in this section.

Mar et al. (2004, 057309) studied asthmatic adults (n = 16) in Spokane, WA over a 3-yr time period. No associations were found between PM and respiratory symptoms among the adults.

Several panel studies conducted in Europe have examined effects of daily exposures to air pollution on adults with asthma, including studies in the Pollution Effects on Asthmatic Children in Europe (PEACE) study (Boezen et al., 2005, 087396), Exposure and Risk Assessment for Fine and UFPs in Ambient Air (ULTRA) study (De Hartog et al., 2003, 001061), in Germany (Von et al., 2002, 034706), and in Paris (Desqueyroux et al., 2002, 026052; 2004, 090449). Boezen et al. (2005, 087396) enrolled 327 elderly adults in the Netherlands to examine the role of airway hyperresponsiveness (AHR) and IgE levels in susceptibility to air pollution. For subjects with both AHR (defined as $\geq$ 20% FEV_1 decline at $\leq$ 2 mg cumulative methacholine [Mch]) and high total IgE (>20 kU/L), each 10 $\mu g/m^3$ increase in lag 2 PM_{10} concentration was associated with an increased risk of upper respiratory symptoms (URS) among males (OR 1.06 [95% CI: 1.02-1.10]), and at lag 0 with increased cough among females (OR 1.04 [95% CI: 1.00-1.08]). Each 10 $\mu g/m^3$ increase in BS at lag 0, lag 1, and the 5-day mean was associated with URS and cough among males. The strongest association in both cases was for the 5-day mean (OR for URS 1.43 [95% CI: 1.20-1.69]; OR for cough 1.16 [95% CI: 1.05-1.29]). The authors suggest that the sex differences observed may be explained by differential daily exposure to traffic exhaust experienced by men compared to women (Boezen et al., 2005, 087396).

As part of the multicenter ULTRA study, de Hartog et al. (2003, 001061) enrolled 131 older adults with coronary artery disease in three cities (Amsterdam, Erfurt [Germany], and Helsinki). Pooling data from all 3 cities, associations were observed between $PM_{2.5}$ and shortness of breath and phlegm: each 10 $\mu g/m^3$ increase in the 5-day avg $PM_{2.5}$ was associated with an increased risk of symptoms (OR for shortness of breath 1.12 [95% CI: 1.02-1.24]; OR for phlegm 1.16 [95% CI: 1.03-1.32]). Unlike fine particles, UFPs were not consistently associated with symptoms.

In a study that took place in Erfurt, Germany, von Klot et al. (2002, 034706) examined daily, winter time exposure to ambient $PM_{10-2.5}$, $PM_{2.5-0.01}$ and $PM_{0.1-0.01}$ and respiratory health effects in 53 adult asthmatics. The authors examined associations between wheeze, use of inhaled, short-acting β_2-agonists or inhaled corticosteroids and exposure to particles in single and multipollutant models. Particle exposure metrics examined included same-day, 5-day and 14-day average concentrations. No effects were observed for wheeze and exposure to $PM_{10-2.5}$ for any averaging time. The strongest association between wheeze and exposure to UFPs was for a 14-day avg: each 7,700 increase in the $NC_{0.01-0.1}$ increased the risk of wheeze by 27% (OR 1.27 [95% CI: 1.13-1.43]). The effect was attenuated in copollutant models that also included $PM_{2.5-0.01}$ (OR 1.12 [95% CI: 1.01-1.24]), NO_2 (OR 1.12 [95% CI: 0.99-1.26]), CO (OR 1.05 [95% CI: 0.92-1.19]) or SO_2 (OR 1.14 [95% CI: 1.04-1.26]). The correlations between UFPs and two gaseous pollutants, NO_2 and CO, were high: 0.66 for each.

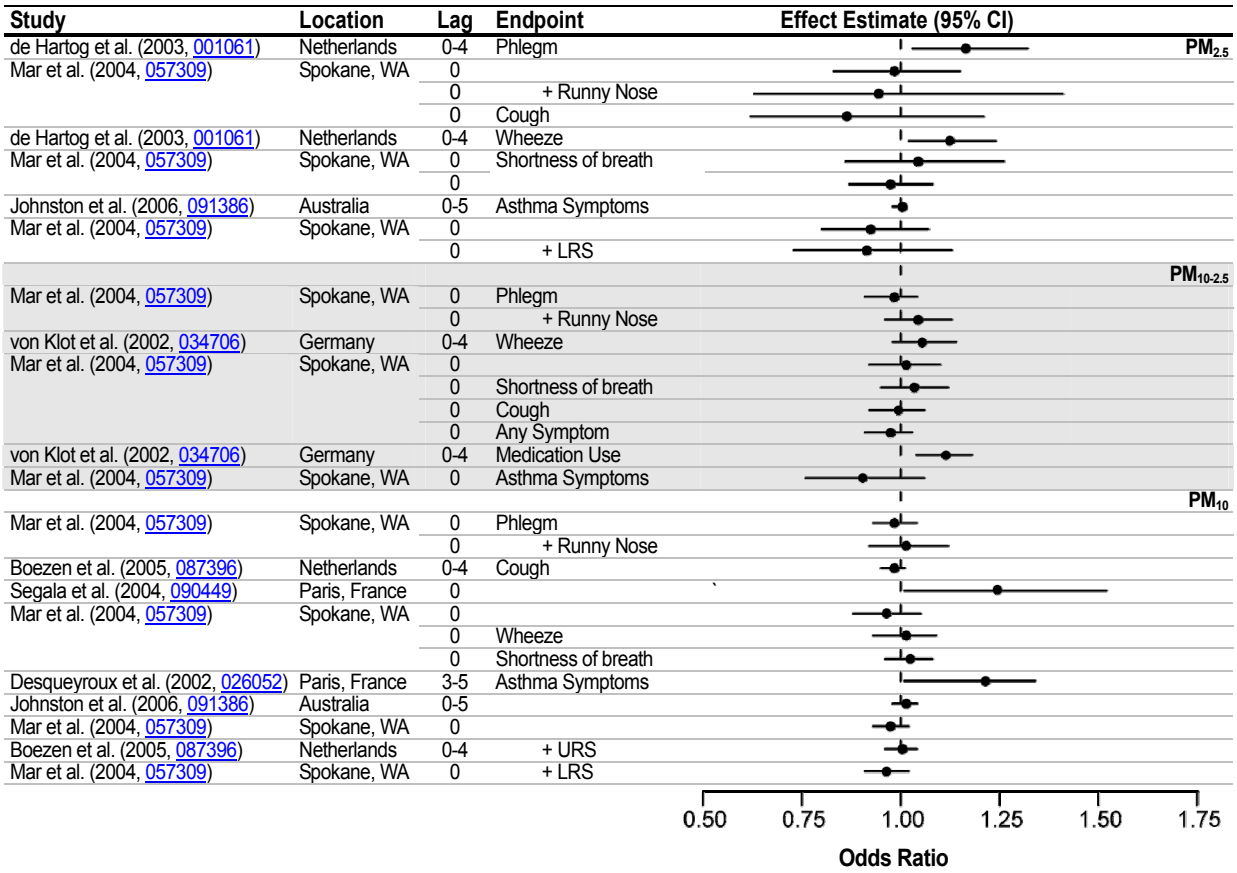


Figure 6-8. Respiratory symptoms and/or medication use among asthmatic adults following acute exposure to particles. Summary of studies using 24-h avg of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$. ORs and 95% CIs were standardized to increments of 10 µg/m^3.

In the same study, no association was found between exposure to $PM_{10-2.5}$,, $PM_{2.5}$, or UFPs and use of short-acting inhalers, though there was an association with maintenance medication. Increased likelihood of maintenance medication was significantly associated with PM of all sizes and all averaging times (same-day, 5- and 14-day avg) and gaseous copollutants in single or copollutant models. The strongest effects were seen for 14-day avg of $PM_{10-2.5}$ (for each 10 µg/m^3 increase OR 1.43 [95% CI: 1.28-1.60]), $PM_{2.5-0.01}$ (for each 20 µg/m^3 increase OR 1.54 [95% CI: 1.43-1.66]), $NC_{0.01-0.1}$ (for each 7,700 increase OR 1.45 [95% CI: 1.29-1.63]). For $PM_{2.5-0.01}$, effects were unchanged in copollutant models, including a model with UFPs. The authors conclude that this is evidence for independent effects of $PM_{2.5}$ and UFPs (Von et al., 2002, 034706).

In Paris, Segala et al. (2004, 090449) recruited 78 adults from an otolaryngology clinic and followed them for three months. Both PM_{10} and BS (which were highly correlated [r =.88]) were associated with cough: OR 1.24 (95% CI: 1.01-1.52) for a 10 µg/m^3 increase in mean 0-4 day PM_{10} and OR 1.18 (95% CI: 1.02-1.39) for a 10 µg/m^3 increase in BS.

Also in Paris, 60 severe asthmatics were followed for 13 months and the relationship between daily air quality (including 24-h PM_{10} as measured at the site nearest to the subject's home) and asthma attack (defined as the need to increase rescue medication use and one or more positive signs on clinical exam of wheezing, expiratory brake, thoracic distention, hypertension with tachycardia, polypnea) were examined with GEE models (Desqueyroux et al., 2002, 026052). Each 10 µg/m^3 increase in PM_{10} increased the risk of asthma attack, but only after lags of 3-5 days. The strongest effect was seen for the mean lag of days 3-5 (OR 1.21 [95% CI: 1.04-1.40]). Effect sizes were larger among patients not on regular oral steroid therapy: for PM_{10} lag 3-5 (OR 1.41 [95% CI: 1.15-1.73]). This effect persisted in copollutant models for winter time levels of PM_{10} and SO_2 (OR 1.51 [95%

CI: 1.20-1.90]) or NO_2 (OR 1.43 [95% CI: 1.16-1.76]), but not in summer time models with O_3 (OR 1.09 [95% CI: 0.71-1.67]).

Copollutant Models

A limited number of respiratory symptoms studies reported results of copollutant models. Generally, the associations between respiratory symptoms and PM were robust to the inclusion of copollutants (Figure 6-9), though Desqueyroux et al. (2002, 026052) indicate the effects of PM may be potentiated by NO_2 and SO_2 during the winter months. Gent et al. (2003, 052885) also reported the results of copollutant models, though the categorical exposure groups used in the analysis did not allow these results to be included in Figure 6-9. As reported above, the investigators found that effects were attenuated in models including O_3.

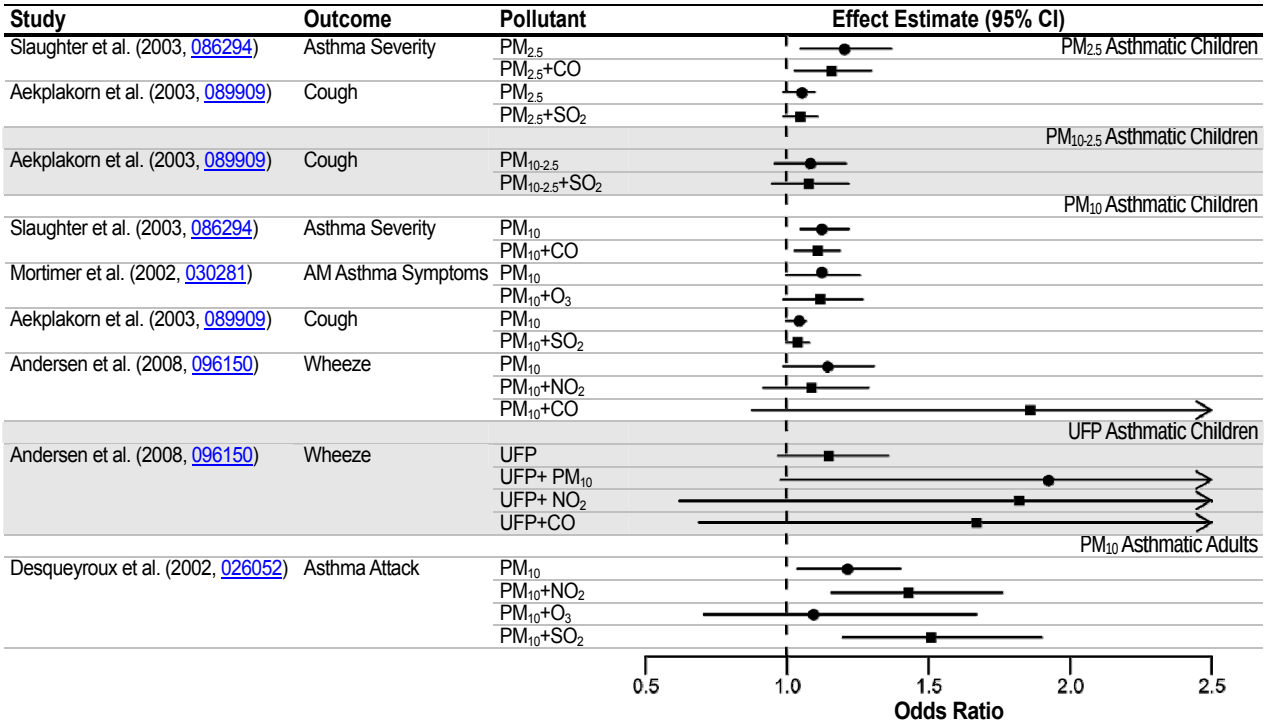


Figure 6-9. Respiratory symptoms following acute exposure to particles and additional criteria pollutants. Circles represent single pollutant effect estimates and squares represent copollutant effect estimates.

6.3.1.2. Controlled Human Exposure Studies

CAPs

Neither new controlled human exposure studies nor studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) have found significant effects of CAPs on respiratory symptoms among healthy or asthmatic adults, or among older adults with COPD (Gong et al., 2000, 155799; 2003, 042106; 2004, 087964; 2004, 055628; 2005, 087921; 2008, 156483; Petrovic et al., 2000, 004638).

Urban Traffic Particles

One new study reported an increase in respiratory symptoms (upper and lower airways) among healthy volunteers (19-59 yr) during a 2-h exposure to road tunnel traffic ($PM_{2.5}$ concentration 46-81 $\mu g/m^3$) (Larsson et al., 2007, 091375). However, information on specific respiratory symptoms (e.g., throat irritation, wheeze or chest tightness) was not provided. In addition, this study only evaluated respiratory symptoms pre- versus post-exposure, and did not compare response with a filtered air control exposure.

Diesel Exhaust

Respiratory symptoms including mild nose and throat irritation have been reported following controlled exposure to DE; however, other symptoms such as cough, wheeze and chest tightness have not been observed (Mudway et al., 2004, 180208).

Model Particles

Pietropaoli et al. (2004, 156025) found no association between exposure to UF carbon particles and respiratory symptoms in healthy adults at concentrations between 10 and 50 $\mu g/m^3$, or asthmatics at a concentration of 10 $\mu g/m^3$. Beckett et al. (2005, 156261) exposed healthy subjects to UF and fine ZnO (500 $\mu g/m^3$) and observed no difference in respiratory symptoms compared to filtered air control 24 h following exposure. In a study evaluating respiratory effects of exposure to ammonium bisulfate or aerosolized H_2SO_4 (200 and 2,000 $\mu g/m^3$) among healthy and asthmatic adults, Tunnicliffe et al. (2003, 088744) observed no change in respiratory symptoms with either particle type or concentration relative to filtered air. This finding is in agreement with many similar older studies which have generally reported no increase in respiratory symptoms following exposure to acid aerosols at concentrations <1,000 $\mu g/m^3$ (U.S. EPA, 1996, 079380; 2004, 056905).

Summary of Controlled Human Exposure Study Findings for Respiratory Symptoms

These new studies confirm previous reports that have found no association between PM exposure and respiratory symptoms.

6.3.2. Pulmonary Function

Epidemiologic studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) observed small decrements in pulmonary function associated with both $PM_{2.5}$ and PM_{10} (U.S. EPA, 2004, 056905). The majority of controlled human exposure studies reported no effect of PM on pulmonary function, while the results from toxicological studies were mixed, with some evidence of changes in tidal volume and respiratory rate following exposure to CAPs. Epidemiologic studies published since the 2004 PM AQCD (U.S. EPA, 2004, 056905) have reported an association between $PM_{2.5}$ concentration and decrements in forced expiratory volume in one second (FEV_1), particularly among asthmatic children. These findings are coherent with recent toxicological evidence of AHR following CAPs exposure. Results from recent controlled human exposure studies have been inconsistent, with some studies demonstrating small decreases in arterial oxygen saturation, FEV_1 or maximal mid-expiratory flow following exposure to CAPs or EC. It is interesting to note that these effects appear to be more pronounced among healthy adults than adults with asthma or COPD. A number of recent animal toxicological studies demonstrated alterations in respiratory frequency following short-term exposure to CAPs.

6.3.2.1. Epidemiologic Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) concluded that both $PM_{2.5}$ and PM_{10} appeared to affect lung function in asthmatics. A limited number of studies evaluated UFPs and found them to be associated with a decrease in peak expiratory flow (PEF). Few analyses were able to clearly distinguish the effects of $PM_{2.5}$ and PM_{10} from other pollutants. Results for PM_{10} PEF analyses in non-asthmatic studies were inconsistent, with fewer studies reporting strong associations.

Asthmatic Children

Several recent panel studies have been conducted in the U.S. examining the association of exposure to ambient PM and lung function in asthmatic children (Allen et al., 2008, 156208 in Seattle; Lewis et al., 2003, 088413 in Southern California; 2004, 097498; Lewis et al., 2005, 081079 in Detroit; O'Connor et al., 2008, 156818; Rabinovitch et al., 2004, 096753 in Denver). Mean concentration data from these studies are summarized in Table 6-10. In the Inner-City Asthma Study (ICAS), FEV_1 and PEF tidal were statistically related to the 5-day avg of $PM_{2.5}$ but not to the 1-day avg concentration (O'Connor et al., 2008, 156818). The risk of experiencing a percent-predicted FEV_1 more than 10% below personal best was related to the 5-day avg concentration of $PM_{2.5}$ (1.14 [95% CI: 1.01-1.29]). The risk of experiencing a percent-predicted PEF rate more than 10% below personal best was related to $PM_{2.5}$ (1.18 [95% CI: 1.03-1.35]). This effect remained robust in copollutant models with O_3 and NO_2 for the FEV_1 effect, but not the PEF rate effect.

The Denver study (Rabinovitch et al., 2004, 096753), described in Section 6.3.1.1, also examined daily FEV_1 and PEF in 86 asthmatic children over the course of three winters (some subjects participated in more than one winter). Lung function measurements were performed under supervision daily at the elementary school where all subjects attended, and without supervision every evening and on nonschool days. As described above, the authors chose to use a 3-day moving average of 24-h $PM_{2.5}$ or PM_{10} as the exposure metric. No statistical associations were observed between morning or afternoon FEV_1 or PEF and particle exposure. The same group of researchers (Strand et al., 2006, 089203) used regression calibration to estimate personal exposures to ambient $PM_{2.5}$ and found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 2.2% (95% CI: 0.0-4.3) decrease in FEV_1 at a 1-day lag as compared with the estimate of a 1.0% decrease in FEV_1 using ambient $PM_{2.5}$ concentrations from fixed monitors. These results underscore the effects of exposure error on epidemiologic study results; the effect estimate using an estimate of personal exposure to ambient $PM_{2.5}$ was twice that for central site $PM_{2.5}$.

From winter 2001 to the spring of 2002, the same number (n = 86) of primary school-age asthmatic children participated in six 2-wk seasonal assessments of lung function in Detroit (Lewis et al., 2005, 081079). Using a protocol similar to that used in Rabinovitch et al. (2004, 096753), morning lung function measurements (FEV_1, PEF) were self-administered at school under supervision by research staff. Evening and weekend measurements were recorded by subjects at home, without supervision from research staff. Community-level exposure was assessed using monitors placed on a school roof top of both of the communities. Most of the subjects (82 of 86) lived within 5 km of their respective community monitors. In single-pollutant models using GEE and only among children reporting the use of maintenance medication (corticosteroids), each 10 $\mu g/m^3$ increase in lag 2 PM_{10} was associated with a decrease in the lowest daily percent predicted FEV_1 (a reduction of 1.15%, [95% CI: -2.1 to -0.25]). Among children reporting presence of URI on the day of lung function measurement, increases in the average of lag 3-5 of either $PM_{2.5}$ or PM_{10} resulted in a decrease in the lowest daily FEV_1 (for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ the reduction was 2.24% [95% CI: -4.4 to -0.25]; and for a 10 $\mu g/m^3$ increase in PM_{10} the reduction was 2.4% [95% CI: -4.5 to -0.3]). In copollutant models that included one particle pollutant and O_3, and among children using maintenance medication, lag 3-5 $PM_{2.5}$ continued to be associated with lowest daily FEV_1 as well as diurnal FEV_1 variability: each 10 $\mu g/m^3$ increase was associated with a 2.23% decrease in FEV_1 (95% CI: -3.92 to -0.57) and a 2.22% increase in FEV_1 variability (95% CI: 1.0 to 3.50). Increases in lag 1 or lag 2 of PM_{10} were associated with FEV_1 and FEV_1 diurnal variability in copollutant models. The strongest association was with lag 2 for diurnal variability (for each 10 $\mu g/m^3$ increase variability increased by 7.0% [95% CI: 4.2-9.6). It is unclear what role the lack of supervision during the evening and weekend measures may have had on these diurnal results.

Two panel studies in southern California examined the association of PM exposure on lung function in asthmatic children (Delfino et al., 2003, 050460; 2004, 056897). In Delfino et al. (2003,

050460), described above, no association between exposure to particles and PEF was found for 22 Hispanic, asthmatic children living in an area of relatively high pollution. In Delfino et al. (2004, 056897) 19 asthmatic children, aged 9-17 yr, were followed for 2 weeks and daily, self-administered FEV_1 measurements were taken. Particle exposures studied included central-site PM_{10} in addition to personal PM (in the range of 0.1-10 μm range, with the highest response in the fine PM range), and home stationary measurements of both $PM_{2.5}$ and PM_{10}. The authors report inverse associations between percent expected FEV_1 and PM indicators. The strongest association for exposure to personal PM was for a 5-day moving average of 12-h daytime PM: for each 10 $\mu g/m^3$ increase, FEV_1 decreased by 7.1% (95% CI: -9.9 to -2.9). Effects for all stationary sites (inside and outside of residence, central site) for $PM_{2.5}$ were on the order of 1-2% reductions in FEV_1, with the strongest associations for the 5-day moving average (presented in figures only). Likewise for PM_{10} measured at stationary sites, the strongest effects were for the 5-day moving average and ranged from approximately 3.8% reduction associated with indoor monitors to about 1.5% for both the outdoor and central site monitors (presented in figures only). A helpful comparison among all 24-h measures is given for 10 $\mu g/m^3$ increases in personal PM and $PM_{2.5}$ associated with decreases in percent predicted FEV_1: an increase of 10 $\mu g/m^3$ personal PM is associated with a decrease in FEV_1 of 3.0% (95% CI: -5.6 to -0.5); 10 $\mu g/m^3$ increase in indoor PM with 2.4% decrease (95% CI: -4.2 to -0.6); 10 $\mu g/m^3$ increase in outdoor PM with 1.5% decrease (95% CI: -3.4 to 0.1); 10 $\mu g/m^3$ increase in central site PM with 0.9% decrease (95% CI: -2.6 to 0.5).

Trenga et al. (2006, 155209) reported associations among personal, residential, and central site $PM_{2.5}$ and lung function in 17 asthmatic children in Seattle. The only statistical association with decline in FEV_1 was with indoor measurements of $PM_{2.5}$: each 10 $\mu g/m^3$ increase in lag 1 indoor $PM_{2.5}$ was associated with a decline in FEV_1 of 64.8 mL (95% CI: -111.3 to 18.3) (a 3.4% decline from the mean of 1.9 L). Indoor $PM_{2.5}$ (lag 1) was also associated with declines in PEF (by 9.2 L/min [95% CI: -17.5 to -0.9], a 3.6% decline from the 254 L/min avg) and in maximal mid-expiratory flow (MMEF) for the six subjects not taking anti-inflammatory medication (by 12.6 L/min [95% CI: -20.7 to -4.6], a 13.7% decline from the 92 L/min avg). Personal $PM_{2.5}$ (lag 1) was only statistically associated with PEF for the six subjects not on anti-inflammatory medication: each 10 $\mu g/m^3$ increase resulted in a 10.5 L/min ([95% CI: -18.7 to -2.3], a 4.5% decline from the 233 L/min avg) reduction in PEF. Anti-inflammatory medication use attenuated associations with $PM_{2.5}$.

Also in Seattle, Allen et al. (2008, 156208) evaluated the effect of different $PM_{2.5}$ exposure metrics in relation to lung function among children in wood smoke-impacted areas. The authors found that the ambient-generated component of $PM_{2.5}$ exposure was associated with decrements in lung function only among children not using inhaled corticosteroids, whereas no association was reported with the nonambient exposure component. All of the ambient concentrations were associated with decrements in both PEF and maximal expiratory flow (MEF). There were no associations between any exposure metrics and forced vital capacity (FVC). The authors suggest that lung function may be especially sensitive to the combustion-generated component of ambient $PM_{2.5}$, whereas airway inflammation may be more closely related to some other source.

In a longitudinal study, Liu et al. (2009, 192003) examined the association between acute increases in ambient air pollutants and pulmonary function among children (ages 9-14 yr) with asthma. FEV_1 and $FEF_{25-75\%}$ exhibited a consistent trend of negative associations with $PM_{2.5}$ across lag days 0, 1, 0-1, and 0-2, with the strongest effects for $FEF_{25-75\%}$ on lag day 0 (-1.12% [95% CI: -2.06 to -0.18]) and lag days 0-1 (-1.18% [95% CI: -2.24 to -0.12]). Copollutant models including O_3, SO_2 or NO_2 did not result in marked changes in the $PM_{2.5}$ risk estimates for FEV_1 or $FEF_{25-75\%}$.

Moshammer and Neuberger (2003, 041956) used a novel technique for assessing exposure to PM in a study they conducted in Austria. They employed a diffusion charging particle sensor (model LQ 1-DC, Matter Engineering AG, Wohlen, Switzerland) and a photoelectric aerosol sensor (model PAS 2000 CE, EcoChem Analytics, League City, TX) to relate the spirometry scores of Upper Austrian children, aged 7-10 yr, to particle surface area and particle-bound PAH concentration, respectively. Details on these methods for measuring surface area and PAH can be found in Shi et al. (2001, 078292) and Burtscher (2005, 155710), respectively. By measuring the surface area distribution, it was possible to understand potential for contact area with respiratory tract cells. The authors found that acute decrements of pulmonary function (FVC, FEV_1, MEF_{50}) were related to the active surface of particles after adjustment for PM_{10}. For short-term lung impairments, this indicates that active particle surface is a better index of exposure than PM mass.

A number of additional panel studies conducted outside of the U.S. and Canada also examined lung function using more traditional exposure metrics. Several European and Asian studies reported

associations with PM measurements and decrements in pulmonary function (FEV_1, FVC, FEF, MEF, PEF rate) (Hogervorst et al., 2006, 156559; Hong et al., 2007, 091347; Moshammer et al., 2006, 090771; Odajima et al., 2008, 192005; Peacock et al., 2003, 042026; Peled et al., 2005, 156015). Others found little evidence for a relationship between PM and daily changes in PEF after correction for the confounding effects of weather, trends in the data, and autocorrelation (Fischer et al., 2002, 025731; Holguin et al., 2007, 099000; Just et al., 2002, 035429; Preutthipan et al., 2004, 055598; Ranzi et al., 2004, 089500; Ward, 2003, 157111).

Adults

Trenga et al. (2006, 155209) examined personal, residential, and central site monitoring of particles and the relationship with lung function in Seattle. In models controlling for gaseous copollutants (CO, NO_2), adults, regardless of COPD status, experienced a decline in FEV_1 associated only with measurements of $PM_{2.5}$ at the central site: each 10 $\mu g/m^3$ increase in lag 0 $PM_{2.5}$ was associated with a 35.3 mL (95% CI: -70 to -1.0) decrease in FEV_1. This represents a 2.2% decline in mean FEV_1 (mean 1.6 L during the study). Results for personal, indoor and outdoor measures of $PM_{2.5}$ were inconsistent. No statistical associations were reported with outdoor $PM_{10-2.5}$.

Girardot et al. (2006, 088271) assessed the effects of $PM_{2.5}$ on the pulmonary function of adult day hikers in the Great Smoky Mountains National Park. Hikers performed spirometry both before their hike and when they returned from their hike. The authors reported no statistically significant responses in pulmonary function with an average of five hours of outdoor exercise at ambient $PM_{2.5}$ levels that were below the current NAAQS. Specifically, post-hike percentage changes in FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, and PEF were not associated with $PM_{2.5}$ exposure.

Ebelt et al. (2005, 056907) developed an approach to separately estimate exposures to PM of ambient and non-ambient origin based on a mass balance model. These exposures were linked with respiratory and cardiovascular health endpoints for 16 patients with COPD in Vancouver, Canada (mean age 74 yr). Effect estimates for estimated ambient exposure were generally equal to or larger than those for the respective ambient concentration levels for post-FEV and ΔFEV_1, and were statistically significant for all ΔFEV_1 comparisons (estimated from figure).

Several studies outside of the U.S. and Canada examined the relationship between PM concentrations and lung function and all reported a decrease in lung function in adults (FEV_1, FVC, PEFR) associated with PM exposure (Boezen et al., 2005, 087396; Bourotte et al., 2007, 150040; Lagorio et al., 2006, 089800; Lee et al., 2007, 093042; McCreanor et al., 2007, 092841; Penttinen et al., 2006, 087988).

Measures of Oxygen Saturation

Oxygen saturation measures the percentage of hemoglobin binding sites in the bloodstream occupied by oxygen. DeMeo et al. (2004, 087346) estimated the change in oxygen saturation and mean $PM_{2.5}$ concentration in the previous 24 h in a panel of elderly subjects. They used the same panel of elderly Boston residents (n = 28) and study protocol and analytic methods (12 wk of repeated oxygen saturation measurements) as Gold et al. (2005, 087558) and Schwartz et al. (2005, 074317) in studies of ST-segment depression and HRV, respectively. At each clinic visit, subjects had 5 min each of rest, standing, post-exercise rest, and 20 cycles of paced breathing. The median $PM_{2.5}$ concentration during the study period was 10.0 $\mu g/m^3$ (Schwartz et al., 2005, 074317). Each 10 $\mu g/m^3$ increase in the mean $PM_{2.5}$ concentration in the previous 6 h was associated with a 0.15% decrease in oxygen saturation (95% CI: -0.22 to 0.0) during the baseline rest period. Each 10 $\mu g/m^3$ increase in mean 6-h $PM_{2.5}$ concentration was also associated with a decline in oxygen saturation during the post-exercise period (-0.15% [95% CI: -0.22 to 0.0]), and post-exercise paced breathing period (-0.07% [95% CI: -0.22 to 0.0]), but not during the exercise period. The authors suggest that these oxygen saturation reductions may result from pulmonary vascular and inflammatory changes.

In a similar study, Goldberg et al. (2008, 180380) examined the association between oxygen saturation, pulse rate, and ambient $PM_{2.5}$, NO_2, and SO_2 concentrations in a panel of 31 subjects in Montreal, with NYHA Class II or III heart failure who were aged 50-85 yr. Although each 10 $\mu g/m^3$ increase in $PM_{2.5}$ on lag day 0 was associated with a -0.119 (95% CI = -0.196 to -0.042) change in oxygen saturation in unadjusted models, once adjusted for temperature and barometric pressure, the estimated change was smaller and no longer significant (-0.077 [95% CI = -0.160 to 0.007). Only

SO_2 was significantly associated with reduced oxygen saturation in copollutant models. None of the pollutants examined, including $PM_{2.5}$, were associated with a change in pulse rate.

6.3.2.2. Controlled Human Exposure Studies

As with respiratory symptoms, there is little evidence from controlled human exposure studies of PM-induced changes in pulmonary function. One study cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) noted a significant decrement in thoracic gas volume in healthy adults following a 2-h exposure to $PM_{2.5}$ CAPs (92 μg/m^3); however, no significant changes were observed in spirometric measurements, diffusing capacity (DLCO), total lung capacity, or airways resistance (Petrovic et al., 2000, 004638). Other studies found no significant changes in pulmonary function in healthy adults following exposure to inhaled iron oxide particles (Lay et al., 2001, 020613) or UF EC (Frampton, 2001, 019051), or in healthy and asthmatic adults following exposure to CAPs (Ghio et al., 2000, 012140; Gong et al., 2000, 155799; 2003, 087365). Rudell et al. (1996, 056577) reported a significant increase in specific airways resistance following exposure to DE, an effect that was not attenuated by reducing the particle number by 46% (2.6×10^6 particles/cm^3 compared with 1.4×10^6 particles/cm^3) using a particle trap. The particle trap did not affect the concentrations of other measured diesel emissions including NO_2, NO, CO, or total hydrocarbons. As described below, more recent controlled human exposure studies provide limited and inconsistent evidence of changes in lung function following exposure to particles from various sources.

CAPs

Among a group of healthy and asthmatic adults exposed to UFPs (Los Angeles, mean concentration 100 μg/m^3), Gong et al. (2008, 156483) observed small, yet statistically significant decrements in arterial oxygen saturation immediately following exposure, 4 h post-exposure, and 22 h post-exposure (0.5% mean decrease relative to filtered air across all time points, $p < 0.05$). A statistically significant decrease in FEV_1 was also observed, but only at 22 h post-exposure (2% decrease relative to filtered air, $p < 0.05$). The responses demonstrated in this study were not affected by health status. No such effects were observed in a similar study conducted in Chapel Hill, NC which exposed healthy adults to a lower concentration of UF CAPs (49.8 μg/m^3) (Samet et al., 2009, 191913). In addition, two studies evaluating effects of exposure to $PM_{10-2.5}$ CAPs (average concentration 89-157 μg/m^3) on lung function observed no changes in spirometric measurements, DLCO or arterial oxygen saturation 0-22 h post-exposure in asthmatic or healthy adults (Gong et al., 2004, 055628; Graff et al., 2009, 191981). While Gong et al. (2004, 087964) did not observe a significant association between exposure to $PM_{2.5}$ CAPs and spirometry in older subjects (60-80 yr), the investigators did report a decrease in oxygen saturation immediately following CAPs exposure. This effect was observed more consistently in healthy older adults than in older adults with COPD. These findings were confirmed by a subsequent study conducted by the same laboratory (Gong et al., 2005, 087921). The authors also observed a small decrease in MMEF following a 2-h exposure to $PM_{2.5}$ CAPs (200 μg/m^3) which was more pronounced in healthy subjects.

Urban Traffic Particles

Neither short-term exposure to relatively high levels of urban traffic particles nor longer exposures to lower concentrations of urban particles have been observed to alter pulmonary function in controlled exposures among healthy adults. Larsson et al. (2007, 091375) exposed 16 adults for 2 h to $PM_{2.5}$ concentrations of 46-81 μg/m^3 in a room adjacent to a busy road tunnel, with concomitant exposure to NO_2 (0.12 ppm), NO (0.71 ppm), and CO (5 ppm). Although respiratory effects in this study were not compared to filtered air control, no difference in lung function was observed 14 h after exposure to traffic particles relative to lung function measured on a day following typical activities that did not include transit though a road tunnel. In a study of 24-h exposures to urban traffic particles ($PM_{2.5}$ 9.7 μg/m^3), no change in lung function was reported at 2.5 h after the start of exposure relative to filtered air (Brauner et al., 2009, 190244).

Diesel Exhaust

Mudway et al. (2004, 180208) exposed 25 healthy adults to DE with an average particle concentration of 100 μg/m^3 and observed mild bronchoconstriction (airways resistance) immediately following exposure relative to filtered air. No changes were observed in FEV_1 or FVC following DE exposure in these subjects, or in a group of 15 asthmatics exposed using the same protocol (Mudway et al., 2004, 180208; Stenfors et al., 2004, 157009).

Model Particles

Pietropaoli et al. (2004, 156025) observed a reduction in MMEF and DLCO in healthy adults 21 h after a 2-h exposure to UF carbon particles (50 μg/m^3). This reduction in DLCO may reflect a PM-induced vasoconstrictive effect on the pulmonary vasculature. Tunnicliffe et al. (2003, 088744) did not observe any significant change in lung function following exposure to ammonium bisulfate or aerosolized H_2SO_4 (200 and 2,000 μg/m^3) in healthy or asthmatic adults, which is consistent with findings of the majority of studies of controlled exposures to acid aerosols presented in the last two PM AQCDs (U.S. EPA, 1996, 079380; 2004, 056905).

Summary of Controlled Human Exposure Study Findings for Pulmonary Function

Taken together, the majority of controlled human exposure studies do not provide evidence of PM-induced changes in pulmonary function; however, some investigators have observed slight decreases in DLCO, MMEF, FEV_1, oxygen saturation, or increases in airways resistance following exposure to CAPs, DE, or UF EC.

6.3.2.3. Toxicological Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) included three animal toxicological studies which measured pulmonary function following multiday short-term inhalation exposure to CAPs. A decreased respiratory rate was noted in the one study involving dogs. Increased tidal volume was observed in one study involving rats while no changes were observed in the other rat study. AHR was found in four studies of mice, healthy rats or SH rats exposed to ROFA by IT instillation or inhalation. Studies conducted since the last review are discussed below.

CAPs

SH rats exposed to Tuxedo, NY CAPs via nose-only inhalation for 4 h (mean concentration 73 μg/m^3; single-day concentrations 80 and 66 μg/m^3; 2/2001 and 5/2001, respectively) had a statistically significant decreased respiratory rate compared with air-exposed controls (Nadziejko et al., 2002, 087460). This measure was obtained from BP fluctuations using radiotelemetry. The decrease in respiratory rate of 25-30 breaths/min was an immediate response to CAPs, beginning shortly after the exposure began and ceasing with the end of exposure. It was accompanied by a decrease in HR (Section 6.2.1.3). Rats were also exposed to fine (MMAD 160 nm; 49-299 μg/m^3) and UF H_2SO_4 (MMAD 50-75 nm; 140-750 μg/m^3) (Nadziejko et al., 2002, 087460) because H_2SO_4 aerosols have the potential to activate irritant receptors. Irritant receptors, found at all levels of the respiratory tract, include rapidly-adapting receptors and sensory C-fiber receptors (Alarie, 1973, 070967; Bernardi et al., 2001, 019040; Coleridge and Coleridge, 1994, 156362; Widdicombe, 2003, 157145; Widdicombe, 2006, 155519). Activation of trigeminal afferents in the nose causes CNS reflexes resulting in decreases in respiratory rate through a lengthened expiratory phase, closure of the glottis, closure of the nares with increased nasal airflow resistance and effects on the cardiovascular system such as bradycardia, peripheral vasoconstriction and a rise in systolic arterial blood pressure. Sneezing, rhinorrhea and vasodilation with subsequent nasal vascular congestion are also nasal reflex responses involving the trigeminal nerve (Sarin et al., 2006, 191166). Activation of vagal afferents in the tracheobronchial and alveolar regions of the respiratory tract causes CNS reflexes resulting in bronchoconstriction, mucus secretion, mucosal vasodilation, cough, and apnea

followed by rapid shallow breathing. Besides effects on the respiratory system, effects on the cardiovascular system can also occur including bradycardia and hypotension or hypertension. Fine H_2SO_4 induced an overall decrease in respiratory rate, with UF H_2SO_4 resulting in elevated respiratory rate compared to control (Nadziejko et al., 2002, 087460). The authors suggested that both CAPs and fine H_2SO_4 aerosols activated sensory irritant receptors in the upper airways, resulting in a decreased respiratory rate. The response to UF H_2SO_4 aerosols differed from the other responses and was thought to be due to deposition of UFPs deeper into the lung with the subsequent activation of pulmonary irritant receptors which trigger an increase in respiratory rate. Since irritant receptors in nasal, tracheobronchial and alveolar regions act via trigeminal- and vagal-mediated pathways, this study indicates a role for neural reflexes in respiratory responses to CAPs.

Kodavanti et al. (2005, 087946) measured respiratory frequency 1 day after a 2-day exposure of SH and WKY rats to CAPs from RTP, NC (mean mass concentration range 144-2,758 $\mu g/m^3$; <2.5 µm in size; 8/27-10/24/2001) for 4 h/day. Increases in inspiratory and expiratory times were seen in SH, but not WKY rats, exposed to CAPs compared with filtered air controls.

Effects of CAPs on pulmonary function were also investigated in a rat model of pulmonary hypertension using SD rats pre-treated with monocrotaline (Lei et al., 2004, 087999). In this study, rats were exposed to CAPs from an urban high traffic area in Taiwan (mean mass concentration 371 $\mu g/m^3$) for 6 h/day on three consecutive days and pulmonary function was evaluated 5 h post-exposure using whole-body plethysmography. A statistically significant decrease in respiratory frequency and an increase in tidal volume were observed following CAPs exposure, along with an increase in airway responsiveness (measured as Penh) following Mch challenge.

In many animal studies changes in ventilatory patterns are assessed using whole body plethysmography, for which measurements are reported as enhanced pause (Penh). Some investigators report increased Penh as an indicator of AHR, but these are inconsistently correlated and many investigators consider Penh solely an indicator of altered ventilatory timing in the absence of other measurements to confirm AHR. Therefore use of the terms AHR or airway responsiveness has been limited to instances in which the terminology has been similarly applied by the study investigators.

Diesel Exhaust

Li et al. (2007, 155929) exposed BALB/c and C57BL/6 mice to clean air or to low dose DE (containing 100 $\mu g/m^3$ particles) for 7 h/day and 5 days/wk for 1, 4 and 8 wk. Average gas concentrations were reported to be 3.5 ppm CO, 2.2 ppm NO_2, and <0.01 ppm SO_2. AHR was evaluated by whole-body plethysmography at day 0 and after 1, 4 and 8 wk of exposure. Exposure to DE for 1 wk resulted in an increased sensitivity of airways to Mch, measured as Penh, in C57BL/6 but not BALB/c, mice. Other short-term responses of this study are discussed in Sections 6.3.3.3 and 6.3.4.2.

McQueen et al. (2007, 096266) investigated the role of vagally-mediated pathways in respiratory responses to PM. Respiratory minute volume (RMV) was increased in anesthetized Wistar rats 6 h after treatment with 500 µg DE particles (SRM2975) by IT instillation. This response was blocked by severing the vagus nerve or pretreatment with atropine. The absence of a respiratory response with vagotomy or atropine indicated that the increase in RMV following DE particle exposure involved a neural reflex acting via vagal afferents. No statistically significant changes in mean BP, HR or HRV were observed in response to DE particles in this study. Vagally-mediated inflammatory responses to DEP were also observed in this study and are discussed in Section 6.3.3.3.

Model Particles

In a study by Last et al. (2004, 097334), BALB/c mice were exposed to 250 $\mu g/m^3$ laboratory-generated iron-soot (size range 80-110 nm; about 200 $\mu g/m^3$ as soot) for 4 h/day and 3 days/wk for 2 wk. Pulmonary function was measured by whole-body plethysmography after challenge with Mch. No AHR, as measured by Penh, was observed following 2-wk exposure to iron-soot. Other findings of this study are reported in Sections 6.3.3.3 and 6.3.5.3.

Summary of Toxicological Study Findings for Pulmonary Function

Several recent studies demonstrated alterations in respiratory frequency and in airway responsiveness following short-term exposure to CAPs and DE. Two studies provide evidence for the involvement of irritant receptors and vagally-mediated neural reflexes in mediating changes in respiratory functions.

6.3.3. Pulmonary Inflammation

The discussion of the effects of PM on pulmonary inflammation in the 2004 PM AQCD (U.S. EPA, 2004, 056905) was limited by a relative lack of information from controlled human exposure and toxicological studies. Although no epidemiologic studies of pulmonary inflammation were described in the 2004 PM AQCD (U.S. EPA, 2004, 056905), several recent studies have observed a positive association between PM concentration and exhaled NO (eNO). New controlled human exposure and toxicological studies have also generally observed an increase in markers of inflammation in the pulmonary compartment following exposure to PM.

6.3.3.1. Epidemiologic Studies

No epidemiologic studies of pulmonary inflammation were described in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

Exhaled Nitric Oxide – Asthmatic Children

Exhaled NO, a biomarker for airway inflammation, was the outcome studied in panels of asthmatic children in southern California (Wu et al., 2006, 157156) and Seattle (Allen et al., 2008, 156208; Koenig et al., 2003, 156653; 2005, 087384; Mar et al., 2005, 088759). Mean concentration data from these studies are summarized in Table 6-10. Delfino et al. (2006, 157156) followed 45 asthmatic children for ten days with offline fractional eNO and examined the associations with exposures to personal $PM_{2.5}$ and 24-h $PM_{2.5}$, EC and OC as well as ambient $PM_{2.5}$, EC and OC. The strongest associations were between eNO and 2-day avg pollutant concentrations: for a 10 $\mu g/m^3$ increase in personal $PM_{2.5}$, eNO increased by 0.46 ppb (95% CI: 0.04-0.79); for 0.6 $\mu g/m^3$ personal EC, eNO increased by 0.7 ppb (95% CI: 0.3-1.1). An association with exposure to ambient $PM_{2.5}$ was only statistically significant in 19 subjects taking inhaled corticosteroids: for each 10 $\mu g/m^3$ increase in $PM_{2.5}$, eNO increased by 0.77 ppb (95% CI: 0.07-1.47).

In a panel of 19 asthmatic children in Seattle, effects were observed only among the ten non-users of inhaled corticosteroids. For each 10 $\mu g/m^3$ increase in personal, outdoor, indoor, or central site $PM_{2.5}$, eNO increased from 3.82 ppb (associated with central site, 95% CI: 1.22-6.43) to 4.48 ppb (with personal $PM_{2.5}$, 95% CI: 1.02-7.93) (Koenig et al., 2003, 156653). Further analysis examining the association between eNO and outdoor and indoor-generated particles suggested that eNO was associated more strongly with ambient particles, but only for non-users of medication: each 10 $\mu g/m^3$ increase in estimated ambient $PM_{2.5}$ results in an increase in eNO of 4.98 ppb (95% CI: 0.28-9.69) (Koenig et al., 2005, 087384).

Also in Seattle, WA, Mar et al. (2005, 088759) examined the association between eNO and ambient $PM_{2.5}$ concentration among children (aged 6-13 yr) recruited from an asthma/allergy clinic. Fractional exhaled nitric oxide (FeNO) was associated with hourly averages of $PM_{2.5}$ up to 10-12 h after exposure. Each 10 $\mu g/m^3$ increase in 1-h mean $PM_{2.5}$ concentration was associated with a 6.99 ppb increase in eNO (95% CI: 3.43-10.55) among children not taking inhaled corticosteroids, but associated with only a 0.77 ppb decrease in eNO (95% CI: -4.58 to 3.04) among those taking inhaled corticosteroids.

Allen et al. (2008, 156208), in a reanalysis of data from Koenig et al. (2005, 087384), evaluated the effect of different $PM_{2.5}$ exposure metrics in relation to airway inflammation among children in wood smoke-impacted areas of Seattle. The authors found that for the nine non-users of inhaled corticosteroids, the ambient-generated component of $PM_{2.5}$ exposure was associated with respiratory responses, both airway inflammation and decrements in lung function, whereas the non-ambient $PM_{2.5}$ exposure component was not. They did note, however, different relationships for

airway inflammation and decrements in lung function, with the former significantly associated with total personal $PM_{2.5}$, personal light-absorbing carbon (LAC), and ambient generated personal $PM_{2.5}$ and the latter related to ambient $PM_{2.5}$ and its combustion markers. The different results between FeNO and lung function were not unexpected; epidemiologic data show that airway inflammation indicated by FeNO does not correlate strongly with either respiratory symptoms or lung function (Smith and Taylor, 2005, 192176). The authors conclude that lung function decrements may be associated with the combustion-generated component of ambient $PM_{2.5}$, whereas airway inflammation may be related to some other component of the ambient $PM_{2.5}$ mixture.

In a longitudinal study, Liu et al. (2009, 192003) examined the association between acute increases in ambient air pollutants and FeNO among children (ages 9-14 yr) with asthma. FeNO had a trend of positive associations with $PM_{2.5}$, with the strongest association on lag day 0 (3.12% [95% CI: -2.12 to 8.82]). Copollutant models including O_3, SO_2 or NO_2 did not result in marked changes in the $PM_{2.5}$ risk estimates for FeNO.

A few studies outside of the U.S. examined eNO in relation to PM exposure among children. Fischer et al. (2002, 025731) and Murata et al. (2007, 189159) found a statistical association between increases in PM and increases in the percent of eNO. Holguin et al. (2007, 099000) found no association between exposure to PM and eNO. However, they did see statistical associations between increases in eNO for the 95 asthmatic subjects and measures of road density of roads 50- and 75-m from the home.

Exhaled Nitric Oxide – Adults

Three recent panel studies examined the effects of particle exposure on eNO measured in older adults (Adamkiewicz et al., 2004, 087925 in Steubenville, OH; Adar et al., 2007, 001458; Jansen et al., 2005, 082236 in Seattle). Mean concentration data from these studies are characterized in Table 6-10. Breath samples were collected weekly for 12 weeks from a group of 29 elderly adults in Steubenville, OH (Adamkiewicz et al., 2004, 087925). In single-pollutant models, each 10 $\mu g/m^3$ increase in 24-h ambient $PM_{2.5}$ increased eNO by 0.82 ppb (95% CI: 0.19-1.45), a change of 15% compared to mean eNO (9.9 ppb). Effects were essentially unchanged in copollutant models that included ambient and/or indoor NO. The effect estimates for the seven COPD subjects were higher than for normal subjects (2.20 vs. 0.45 ppb, $p = 0.03$) (Adamkiewicz et al., 2004, 087925).

In the Seattle panel of older adults (aged 60-86 yr), seven subjects were asthmatic and nine had a diagnosis of COPD (five with asthma and four without) (Jansen et al., 2005, 082236). Exhaled NO was measured daily for 12 days, along with personal, indoor, outdoor and central site PM_{10}, $PM_{2.5}$ and BC. The strongest associations between 24-h avg PM and eNO were found for the asthmatic subjects: 10 $\mu g/m^3$ increases in outdoor levels (measured outside the subjects' homes) of $PM_{2.5}$ or PM_{10} were associated with increases in eNO of 4.23 ppb (95% CI: 1.33-7.13), an increase of 22% above the group mean of 19.2 ppb, and 5.87 ppb (95% CI: 2.87-8.88), an increase of 31%, respectively. BC measured indoors, outdoors or personally was also associated with increases in eNO (of 3.97, 2.32, and 1.20 ppb, respectively) (Jansen et al., 2005, 082236).

Adar et al. (2007, 001458) conducted a panel study of 44 non-smoking senior citizens residing in St. Louis, MO. As part of the study, subjects were taken on group trips to a theater performance, Omni movie, outdoor band concert, and a Mississippi River boat cruise. Subjects were driven to and from each event aboard a diesel bus. Before and after each bus trip, eNO was measured on each subject. Two carts containing continuous air pollution monitors were used to measure group-level micro-environmental exposures to $PM_{2.5}$, BC, and size-specific particle counts (0.3-2.5 µm and 2.5-10 µm) on the day of each trip. Each 10 $\mu g/m^3$ increase in 24-h mean $PM_{2.5}$ concentration was associated with a 36% increase in eNO pre-trip (95% CI: 5-71). Each 10 $\mu g/m^3$ increase in micro-environmental $PM_{2.5}$ concentration (i.e., during the bus ride) was associated with a 27% increase in eNO post-trip (95% CI: 17-38).

These studies all demonstrated an association between increased levels of eNO and increases in PM in the previous 4-24 h. Further, three studies demonstrated effects in elderly populations (Adamkiewicz et al., 2004, 087925; Adar et al., 2007, 001458; Jansen et al., 2005, 082236) while four others reported a similar acute increase in eNO among children (Delfino et al., 2006, 090745; Koenig et al., 2003, 156653; 2005, 087384; 2005, 088999).

Outside of the U.S., one study examined eNO in a panel of 60 adult asthmatic subjects in London. McCreanor et al. (2007, 092841) reported that 1 $\mu g/m^3$ increase in personal exposure to EC

was associated with increases of approximately 1.75-2.25% in eNO (results were presented graphically only) for up to 22 h post-exposure.

Other Biomarkers of Pulmonary Inflammation and Oxidative Stress

Other biomarkers of respiratory distress that have been examined in recent panel studies include urinary leukotriene E4 (LTE_4) in asthmatic children (Rabinovitch et al., 2006, 088031); two oxidative stress markers: TBARS and 8-isoprostane in asthmatic children (Liu et al., 2009, 192003) and breath acidification in adolescent athletes (Ferdinands et al., 2008, 156433). Mean concentration data from these studies are characterized in Table 6-10.

In Rabinovitch et al. (2006, 088031), LTE_4, an asthma-related biological mediator, was used to study the response to short-term particle exposure. In the second winter of their 2-yr study of asthmatic children (described above in Section 6.3.1.1), urine samples were collected at approximately the same time of day from 57 subjects for eight consecutive days. Controlling for days with URI symptoms, each 10 $\mu g/m^3$ increase in morning maximum $PM_{2.5}$ (measured by TEOM), was associated with an increase in LTE_4 levels by 5.1% (95% CI: 1.6-8.7). No statistically significant effects were observed on the same day or up to 3 days later based on 24-h averaged concentrations from the TEOM monitor or from the FRM central site monitor.

In a longitudinal study conducted in Windsor, Ontario, Liu et al. (2009, 192003) examined the association between acute increases in ambient air pollutants and TBARS and 8-isoprostane among children (ages 9-14 yr) with asthma. TBARS, but not 8-isoprostane, was positively associated with $PM_{2.5}$ (percent change in TBARS 40.6% [95% CI: 11.8-81.3], lag 0-2 days). The association with TBARS persisted for at least three days. Adverse changes in pulmonary function (Section 6.3.2.1) were consistent with those of TBARS in response to $PM_{2.5}$ with a similar lag structure, suggesting a coherent outcome for small airway function and oxidative stress.

The effects of vigorous outdoor exercise during peak smog season in Atlanta, GA on breath pH, a biomarker of airway inflammation, in adolescent athletes (n = 16, mean age = 14.9 yr) were examined by Ferdinands et al. (2008, 156433). Median pre-exercise breath pH was 7.58 (range 4.39-8.09) and median post-exercise breath pH was 7.68 (range 3.78-8.17). The authors observed no significant association between ambient PM and post-exercise breath pH. However both pre- and post-exercise breath pH were strikingly low in these athletes when compared to 14 relatively sedentary healthy adults and to published values of breath pH in healthy subjects. The authors speculate that repetitive vigorous exercise may induce airway acidification.

Effect of Measurement Location on Studies of Pulmonary Function and Inflammation

A number of studies examining exposure to $PM_{2.5}$ and pulmonary function and inflammation have compared the results of exposure assessment based on concentrations recorded from personal, indoor, outdoor, and/or ambient monitors (Allen et al., 2008, 156208; Delfino et al., 2004, 056897; Delfino et al., 2006, 090745; Koenig et al., 2005, 087384; Trenga et al., 2006, 155209). Two investigations evaluated $PM_{2.5}$ concentrations from indoor, outdoor, personal and central site monitors and the relationship with FEV_1. Delfino et al. (2004, 056897) reported that personal exposure estimates showed a stronger association with FEV_1 than any of the stationary exposures, and that indoor exposure estimates were associated with a stronger effect than either outdoor or central site exposure estimates. However, Trenga et al. (2006, 155209) reported the largest declines in FEV_1 associated with central site exposure estimates, though the most consistent association with declines in FEV_1 came from the exposure estimates measured by indoor monitors. Delfino et al. (2006, 090745) used personal and ambient exposure estimates in a study of FeNO among asthmatic children and found that the personal exposure estimates were more robust than the ambient exposure estimates. Two studies conducted in Seattle, WA partitioned personal exposure to $PM_{2.5}$ into its ambient-generated and indoor-generated components. Koenig et al. (2005, 087384) reported that ambient-generated $PM_{2.5}$ was consistently associated with an increase in FeNO, while the indoor-generated component of $PM_{2.5}$ was less strongly associated with FeNO. This could reflect the difference in composition of indoor-generated $PM_{2.5}$ as compared to ambient-generated $PM_{2.5}$. Similarly, Allen et al. (2008, 156208) found that FeNO was associated with the ambient-generated

component of personal $PM_{2.5}$ exposure, but not with ambient $PM_{2.5}$ concentrations measured by central site monitors. Overall, these studies provide a unique perspective on how measurement location influences the findings of epidemiologic studies. This small group of studies indicates that effects are associated with all types of PM measurement, suggesting health effects of both ambient-generated and indoor-generated particles. It is likely that variability in season, meteorology, topography, geography, behavior and exposure patterns contribute to the observed differences.

6.3.3.2. Controlled Human Exposure Studies

Studies of controlled human exposures presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provided evidence of pulmonary inflammation induced by exposure to PM. Lay et al. (1998, 007683) found that instillation of iron oxide particles (2.6 μm) produced an increase in alveolar macrophages and neutrophils in bronchoalveolar lavage fluid (BALF) collected 24 h post-instillation. Ghio and Devlin (2001, 017122) evaluated the inflammatory response following bronchial instillation of particles extracted from filters collected in the Utah Valley both prior to and after the closure of an area steel mill. Subjects who underwent pulmonary instillation of particles (500 μg) collected while the steel mill was operating (n = 16) had significantly higher levels of neutrophils 24 h post-instillation compared with either saline instillation or with subjects (n = 8) who were instilled with the same mass of PM collected during the mill's closure. This finding indicates that metals may be an important PM component for this health outcome. In an inhalation study of exposure to $PM_{2.5}$ CAPs (23-311 $\mu g/m^3$) from Chapel Hill, NC, Ghio et al. (2000, 012140) observed an increase in airway and alveolar neutrophils 18 h after the 2-h exposure. A similar finding was reported by Rudell et al. (1999, 001964) following exposure to DE among healthy adults. In this study, reducing the particle number from 2.6×10^6 particles/cm^3 to 1.3×10^6 particles/cm^3 while maintaining the concentration of gaseous diesel emissions was not observed to attenuate the response. One study of controlled exposures to UF EC among healthy adults did not report particle-related effects on eNO (Frampton, 2001, 019051). As summarized below, several recent studies of controlled exposures have provided some additional evidence of pulmonary inflammation associated with PM.

CAPS

A series of exposures to UF, $PM_{2.5}$, and $PM_{10-2.5}$ CAPs from Los Angeles with average particle concentrations between 100 and 200 $\mu g/m^3$ have not been shown to have a significant effect on markers of airway inflammation in healthy or health-compromised adults (Gong et al., 2004, 087964; 2004, 055628; 2005, 087921; 2008, 156483). However, two recent studies conducted in Chapel Hill, NC reported significant increases in percent PMNs and concentration of IL-8 in BALF among healthy adults 18-20 h following controlled exposures to $PM_{10-2.5}$ (89 $\mu g/m^3$) and UF (49.8 $\mu g/m^3$) CAPs, respectively (Graff et al., 2009, 191981; Samet et al., 2009, 191913). As discussed above, the same laboratory previously reported a mild inflammatory response in the lower respiratory tract following exposure to $PM_{2.5}$ CAPs (Ghio et al., 2000, 012140). In a follow-up analysis, Huang et al. (2003, 087377) found the increase in BALF neutrophils demonstrated by Ghio et al. (2000, 012140) to be positively associated with the Fe, Se, and SO_4^{2-} content of the particles.

Alexis et al. (2006, 154323) recently evaluated the effect of $PM_{10-2.5}$ on markers of airway inflammation, specifically focusing on the impact of biological components of $PM_{10-2.5}$. Healthy men and women (n = 9) between the ages of 18 and 35 inhaled nebulized saline (0.9%) as well as aerosolized $PM_{10-2.5}$ collected from ambient air. Subjects were exposed to $PM_{10-2.5}$ on two separate occasions, once using $PM_{10-2.5}$ that had been heated to inactivate biological material and once using non-heated $PM_{10-2.5}$. Approximately 0.65 mg $PM_{10-2.5}$ was deposited in the respiratory tract of subjects during the exposures. Markers of inflammation and immune function were analyzed in induced sputum collected 2-3 h after inhalation of saline or $PM_{10-2.5}$. Both heated and non-heated $PM_{10-2.5}$ were observed to increase the neutrophil response compared with saline. Exposure to non-heated $PM_{10-2.5}$ was found to increase levels of monocytes, eotaxin, macrophage TNF-α mRNA, and was also associated with an upregulation of macrophage cell surface markers. No such effects were observed following exposure to biologically inactive $PM_{10-2.5}$. These results suggest that while $PM_{10-2.5}$-induction of neutrophil response is not dependent on biological components, heat sensitive

components of $PM_{10-2.5}$ (e.g., endotoxin) may be responsible for PM-induced alveolar macrophage activation.

Traffic Particles

Larsson et al. (2007, 091375) exposed 16 healthy adults to air pollution in a road tunnel for 2 h during the afternoon rush hour in Stockholm, Sweden. The median $PM_{2.5}$ and PM_{10} concentrations during the road tunnel exposures were 64 μg/m^3 and 176 μg/m^3, respectively. Bronchial biopsies were obtained and bronchoscopy and BAL were performed 14 h after the exposure. The results were compared with a control exposure which consisted of exposure to urban air during normal activity. The authors reported significant BALF increases in percentage of lymphocytes, total cell number, and alveolar macrophages following exposure to road tunnel exposure versus control. These results provide evidence of a significant association between exposure to road tunnel air pollution and airway inflammation. However, unlike other controlled exposure studies, the control exposure was not a true clean air control, but only a lower exposure group with no characterization of personal exposure. In addition, it is not possible to separate out the contributions of each air pollutant, including PM, on the observed inflammatory response.

Diesel Exhaust

In a recent study evaluating the effect of DE exposure on markers of airway inflammation, Behndig et al. (2006, 088286) exposed healthy adults (n = 15) for 2 h with intermittent exercise to filtered air or DE with a reported PM_{10} concentration of 100 μg/m^3. Eighteen hours after exposure to DE, the authors found significant increases in neutrophil and mast cell numbers in bronchial tissue, as well as significant increases in neutrophil numbers and IL-8 in BALF compared with filtered air control. Similarly, Stenfors et al. (2004, 157009) observed an increase in pulmonary inflammation (e.g., airways neutrophilia and an increase in IL-8 in BALF) among healthy adults 6 h following exposure to DE (PM_{10} average concentration 108 μg/m^3). It is interesting to note, however, that no such inflammatory effects were observed in a group of mild asthmatic subjects in the same study. The DE-induced neutrophil response in the airways of healthy subjects observed in these two studies (Behndig et al., 2006, 088286; Stenfors et al., 2004, 157009) is qualitatively consistent with the findings of Ghio et al. (2000, 012140) who exposed healthy subjects to Chapel Hill $PM_{2.5}$ CAPs. In a group of healthy volunteers, Bosson et al. (2007, 156286) demonstrated that exposure to O_3 (2 h at 0.2 ppm) may enhance the airway inflammatory response of DE relative to clean air (1-h exposure to 300 μg/m^3). Exposure to O_3 was conducted 5 h after exposure to DE, and resulted in an increase in the percentage of neutrophils in induced sputum collected 18 h after exposure to O_3. In a subsequent study using a similar protocol at the same concentrations, prior exposure to DE was shown to increase the inflammatory effects of O_3 exposure, demonstrated as an increase in neutrophil and macrophage numbers in bronchial wash (Bosson et al., 2008, 196659).

Wood Smoke

Barregard et al. (2008, 155675) examined the effect of a short-term exposure (4 h) to wood smoke (240-280 μg/m^3) on markers of pulmonary inflammation in a group of healthy adults. Exposure to wood smoke increased alveolar NO compared to filtered air (2.0 ppb versus 1.3 ppb) 3 h after exposure. Although these results provide some evidence of a PM-induced increase in pulmonary inflammation, the physiological significance of the relatively small increase in alveolar NO is unclear.

Model Particles

Pietropaoli et al. (2004, 156025) observed a lack of airway inflammatory response 21 h after exposure to UF EC particles (10-50 μg/m^3) among healthy and asthmatic adults. The same laboratory reported no effect of exposure to UF or fine ZnO (500 μg/m^3) on total or differential sputum cell

counts 24 h after exposure in a group of healthy adults (Beckett et al., 2005, 156261). Tunnicliffe et al. (2003, 088744) measured levels of eNO as a marker of airway inflammation following 1-h controlled exposures to ammonium bisulfate or aerosolized H_2SO_4 (200 and 2,000 μg/m^3) in a group of healthy and asthmatic adults. While exposure to ammonium bisulfate increased the concentration of eNO immediately following exposure in asthmatics, no such effect was observed in healthy adults, or in either healthy or asthmatic adults following exposure to aerosolized H_2SO_4.

Instillation

Schaumann et al. (2004, 087966) investigated the inflammatory response of human subjects instilled with $PM_{2.5}$ (100 μg) collected from two different cities in Germany, Hettstedt and Zerbst. Although endobronchial instillation of PM from both cities were shown to induce airway inflammation, instillation of PM from the more industrial area (Hettstedt) resulted in greater influxes of BALF monocytes compared to PM collected from Zerbst. The authors postulated that the difference in response between PM from the two cities may be due to the higher concentration of transition metals observed in the samples collected from Hettstedt. Another study reported no change in inflammatory markers in nasal lavage fluid 4 and 96 h following intranasal instillation of DEP (300 μg/nostril) in asthmatics and healthy adults (Kongerud et al., 2006, 156656). Pre-exposure of DEP to O_3 was not shown to have any effect on the response. Although not a cross-over design, these findings suggest that exposure to DEP without the gaseous component of DE may have little effect on inflammatory responses in human subjects.

Summary of Controlled Human Exposure Study Findings for Pulmonary Inflammation

These new studies strengthen the evidence of PM-induced pulmonary inflammation; however, the response appears to vary significantly depending on the source and composition of the particles.

6.3.3.3. Toxicological Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) discussed numerous studies investigating pulmonary inflammation in response to CAPs, ROFA, DEPs, metals and acid aerosols. A wide variety of responses was reported depending on the type of PM and route of administration. In general, IT instillation exposure to fly ash and metal PM resulted in notable pulmonary inflammation. In contrast, inhalation of sulfates and acid aerosols had minimal, if any, effect on pulmonary inflammation. More recent animal toxicological studies using CAPs, DE and other relevant PM types are summarized below.

CAPs

The 2004 PM AQCD (U.S. EPA, 2004, 056905) found that exposure to $PM_{2.5}$ CAPs at concentrations of 100-1,000 μg/m^3 for 1-6 h/day and 1-3 days generally resulted in minimal to mild inflammation in rats and dogs. Somewhat enhanced inflammation was observed in a model of chronic bronchitis. Since the last review, numerous studies have investigated inflammatory responses to $PM_{2.5}$ and UF CAPs in both healthy and compromised animal models.

In one study of healthy animals, SD rats were exposed to CAPs for 4 h/day on 3 consecutive days in Fresno, CA, in fall 2000 and winter 2001 ($PM_{2.5}$ mean mass concentration 190-847 μg/m^3) (Smith et al., 2003, 042107). The particle concentrator used in these studies was capable of enhancing the concentration of UF as well as fine particles. Immediately after exposure on the third day, BALF was collected and analyzed for total cells and neutrophils. Statistically significant increases were observed in numbers of neutrophils during the first week of the fall exposure period and in numbers of total cells, neutrophils and macrophages during the first week of the winter exposure period. CAPs concentrations were >800 μg/m^3 during both of those weeks.

Two studies were conducted using CAPs in Boston. In a study by Godleski et al. (2002, 156478), healthy SD rats were exposed for 5 h/day for 3 consecutive days to CAPs ranging in

concentration from 73.5-733.0 μg/m^3. BALF and lung tissue were collected for analysis 1 day later. Neutrophilic inflammation was indicated by a statistically significant increase in percent neutrophils in BALF. Microarray analysis of RNA from lung tissue and BALF cells demonstrated increased gene expression of pro-inflammatory mediators, markers of vascular activation and enzymes involved in organic chemical detoxification. This study overlapped in part with previously described studies by Saldiva et al. (2002, 025988) and Batalha et al. (2002, 088109) (Section 6.2.4.3). In another study (Rhoden et al., 2004, 087969), healthy SD rats were exposed for 5 h to CAPs (mean mass concentration 1228 μg/m^3; June 20-August 16, 2002). A statistically significant increase in BALF neutrophils was observed 24 h following CAPs exposure. Histological analysis confirmed the influx of inflammatory cells (Section 6.3.5.3). Inflammation was accompanied by injury which is discussed in Section 6.3.5.3.

Kodavanti et al. (2005, 087946) reported two sets of studies involving $PM_{2.5}$ CAPs exposure during fall months in RTP, NC. In the first study, SH rats were exposed to filtered air or CAPs (mean mass concentration range 1,138-1,765 μg/m^3; <2.5 μm) for 4 h and analyzed 1-3 h later. No increase in BALF inflammatory cells or other measured parameter was observed. In the second study, SH and WKY rats were exposed to filtered air or CAPs (mean mass concentration range 144-2,758 μg/m^3; <2.5 μm) for 4 h/day on 2 consecutive days and analyzed 1 day afterward. Differences in baseline parameters were noted for the two rat strains since SH rats had greater numbers of BALF neutrophils than WKY rats. Following the 2-day CAPs exposure, increased BALF neutrophils were observed in the WKY rats but not in the SH rats compared with filtered air controls. Inflammation was not accompanied by increases in BALF markers of injury (Section 6.3.5.3).

Two CAPs studies involving SH rats were conducted in the Netherlands. In the first, SH rats were exposed by nose-only inhalation to CAPs (ranging in concentration from 270-3,660 μg/m^3 and in size from 0.15-2.5 μm) from three different sites in the Netherlands (suburban, industrial and near-freeway) for 6 h (Cassee et al., 2005, 087962). Increased numbers of neutrophils were observed in BALF 2 days post-exposure compared to air controls. When CAPs exposure was used as a binary term, the relationship between CAPs concentration and number of PMN in BALF was statistically significant. In contrast, Kooter et al. (2006, 097547) reported no changes in markers of pulmonary inflammation measured 18 h after a 2-day exposure (6 h/day) of SH rats to $PM_{2.5}$ or $PM_{2.5}$+UFP CAPs from sites in the Netherlands (mean mass concentration range 399-3613 and 269-556 μg/m^3, respectively; $PM_{2.5}$ CAPs site in Bilthoven and $PM_{2.5}$+UF CAPs site in freeway tunnel in Hendrik-Ido-Ambacht).

Pulmonary inflammation was investigated in two studies using a rat model of pulmonary hypertension (i.e., SD rats pre-treated with monocrotaline). In the first study, rats were exposed to $PM_{2.5}$ CAPs from an urban high traffic area in Taiwan (mean mass concentration of 371 μg/m^3) (Lei et al., 2004, 087999) for 6 h/day on 3 consecutive days and BALF was collected 2 days later. A statistically significant increase in total cells and neutrophils was observed in BALF. Levels of TNF-α and IL-6 in the BALF were not altered by CAPs exposure. In the second study, rats were exposed to $PM_{2.5}$ CAPs (mean mass concentration 315.6 and 684.5 μg/m^3 for 6 and 4.5 h, respectively; Chung-Li area, Taiwan) during a dust storm event occurring March 18-19, 2002 (Lei et al., 2004, 087884). Only one animal served as control during the 6-h exposure (from 2100-300 on the first exposure day) so results from that one animal were combined with that of three control animals from the 4.5-h exposure (from 300-730) on the second exposure day. A statistically significant increase in total cells and neutrophils in BALF occurred in both CAPs-exposed groups. In addition, increases in BALF IL-6 and markers of injury (Section 6.3.5.3) were observed as a function of CAPs exposure.

In summary, pulmonary inflammation was noted in all three studies involving multiday exposure of healthy rats to CAPs from different locations. No pulmonary inflammation was seen in one study of SH rats exposed to CAPs for 4 h and analyzed 1-3 h later. In studies involving multiday exposure of SH rats, one demonstrated pulmonary inflammation while two did not. In the rat monocrotaline model of pulmonary hypertension, both single-day and multiday exposures to CAPs resulted in mild pulmonary inflammation.

On-Road Exposures

In a study by Elder et al. (2004, 087354) old rats (21 mo) were exposed to on-road highway aerosols (particle concentration range 0.95-3.13×10^5 particles/cm^3; mass concentration estimated to be 37-106 μg/m^3; Interstate 90 between Rochester and Buffalo, NY) for 6 h on one or three

consecutive days. No increase in BALF inflammatory cells was observed 18 h post-exposure in any of the treatment groups.

Urban Air

To evaluate inflammatory responses to ambient particles from vehicles, Wistar rats were exposed to ambient urban air from a high traffic site (concentration range 22-225 μg/m^3 PM_{10}; Porto Alegre, Brazil) or to the same air which was filtered to remove the PM (Pereira et al., 2007, 156019). Concentrations of gases were not reported. Compared with controls exposed to filtered urban air, a significant increase in total number of BALF cells was observed 24 h following the 20 h continuous exposure, but not following the 6 h of exposure to unfiltered urban air.

Diesel Exhaust

The 2004 PM AQCD (U.S. EPA, 2004, 056905) summarized findings of the 2002 EPA Diesel Document regarding the health effects of DE. Short-term inhalation exposure to low levels of DE results in the accumulation of diesel PM in lung tissue, pulmonary inflammation and alveolar macrophage aggregation and accumulation near the terminal bronchioles. More recent studies are summarized below.

Pulmonary inflammatory responses were investigated in C57BL/6 mice exposed to DE 7 h/day for 6 consecutive days (Harrod et al., 2003, 097046). Compared with controls, inflammatory cell counts in BALF were increased in mice exposed to the higher concentration of DE (1,000 μg/m^3 PM) but not in mice exposed to the lower concentration of DE (30 μg/m^3 PM). Concentrations of gases present in the higher dose DE were reported to be 43 ppm NO_X, 20 ppm CO and 364 ppb SO_2.

In a second study evaluating DE effects on BALF inflammatory cells, no increases in numbers of neutrophils, lymphocytes or eosinophils were observed in BALB/c mice exposed by inhalation to 500 or 2,000 μg/m^3 DE particles for 4 h/day on 5 consecutive days (Stevens et al., 2008, 157010). Concentrations of gases reported in this study were 4.2 ppm CO, 9.2 ppm NO, 1.1 ppm NO_2, and 0.2 ppm SO_2 for the higher concentration of DE. Transcriptional microarray analysis demonstrated upregulation of chemokine and inflammatory cytokine genes, as well as genes involved in growth and differentiation pathways, in response to the higher concentration of DE. No gene expression results were reported for the lower concentration of DE. Sensitization and challenge with ovalbumin (OVA) significantly altered these findings (Section 6.3.6.2). These results demonstrate that changes in gene expression can occur in the absence of measurable pulmonary inflammation or injury markers (Section 6.3.5.3).

Li et al. (2007, 155929) exposed mice to clean air or to low dose DE (100 μg/m^3 PM) for 7 h/day and 5 days/wk for 1, 4 and 8 wk as described in Section 6.3.2.3. Analysis of BALF and histology of lung tissues was carried out at day 0 and after 1, 4 and 8 wk of exposure. Total numbers of cells and macrophages in BALF were significantly increased in C57BL/6 mice, but not in BALB/c mice, after 1-wk exposure to DE compared with 0 day controls. Neutrophils and lymphocytes were increased after 1-wk exposure to DE in both strains compared with 0 day controls. Differences in BALF cytokines were also noted between the two strains after 1-wk exposure to DE. No changes were observed by histological analysis. Pulmonary function and oxidative responses were also evaluated (Sections 6.3.2.3 and 6.3.4.2). Long-term exposure responses are discussed in Sections 7.3.2.2, 7.3.3.2 and 7.3.4.1.

Healthy F344 rats and A/J mice were exposed to DE containing 30, 100, 300 and 1,000 μg/m^3 PM by whole body inhalation for 6 h/day, 7 days/wk for either 1 wk or 6 months in a study by Reed et al. (2004, 055625). Concentrations of gases were reported to be from 2.0-45.3 ppm NO, 0.2-4.0 ppm NO_2, 1.5-29.8 ppm CO and 8-365 ppb for SO_2 in these exposures. One week of exposure resulted in no measurable effects on pulmonary inflammation. Long-term exposure responses are discussed in Section 7.3.3.2.

In a study by Wong et al. (2003, 097707), also reported by Witten et al. (2005, 087485), F344/NH rats were exposed nose-only to filtered room air or to DE at concentrations of 35.3 μg/m^3 and 669.3 μg/m^3 PM (particle size range 7.2-294.3 nm) for 4 h/day and 5 days/wk for 3 wk. Gases associated with the high dose exposure were reported to be 3.59 ppm NO, 3.69 ppm NO_X, 0.1 ppm NO_2, 2.95 ppm CO, 518.96 ppm CO_2 and 0.031 ppm total hydrocarbon. The focus of this study was

on the possible role of neurogenic inflammation in mediating responses to DE. Neurogenic inflammation is characterized by both the influx of inflammatory cells and plasma extravasation into the lungs following the release of neuropeptides from bronchopulmonary C-fibers. Pulmonary inflammation was evaluated by histological analysis of lung tissue at the end of the 3-wk exposure period. Following high, but not low, concentration exposure to DE, a large number of alveolar macrophages was found in the lungs. Small black particles, presumably DE particles, were found in the cytoplasm of these alveolar macrophages. Perivascular cuffing consisting of mononuclear cells was also observed in high dose-exposed animals. Influx of neutrophils or eosinophils was not seen, although mast cell number was increased in high-dose exposed animals. Pulmonary plasma extravasation was measured by the ^{99m}Technecium-albumin technique and found to be dose-dependently increased in the bronchi and lung parenchyma. Alveolar edema was also observed by histology in high concentration-exposed animals. A significant decrease in substance P content in lung tissue was reported in DE-exposed rats. These responses initially suggested that DE resulted in stimulation of C-fibers and activation of a local axon reflex resulting in the repeated release of the stored neuropeptide substance P. Subsequent experiments were conducted using capsaicin pretreatment, which inhibits neurogenic inflammation by activating C-fibers and causing the depletion of neuropeptide stores. Pretreatment with capsaicin was found to reduce the influx of inflammatory cells, but not plasma extravasation, in response to DE. Hence, DE is unlikely to act through bronchopulmonary C-fibers to cause neurogenic edema in this model, although there may be a different role for bronchopulmonary C-fibers in mediating the inflammatory cell influx.

Stimulation of bronchopulmonary C-fibers can result in activation of both local and CNS reflexes through vagal parasympathetic pathways. McQueen et al. (2007, 096266) investigated the role of vagally-mediated pathways in acute inflammatory responses to DE particles. A statistically significant increase in BALF neutrophils was observed 6 h after IT instillation treatment of anesthetized Wistar rats with 500 µg DE particles (SRM2975). This response was blocked by severing the vagus nerve or pretreatment with atropine (McQueen et al., 2007, 096266). Similarly, atropine treatment blocked the increase in BALF neutrophils seen 6 h after DE particle exposure in conscious Wistar rats. These results provide evidence for the involvement of a pulmonary vagal reflex in the inflammatory response to DE particles.

In summary, several studies demonstrate that short-term inhalation exposure to DE (100-1,000 µg/m^3 PM) causes pulmonary inflammation in rodents. No attempt was made in these studies to determine whether the responses were due to PM components or to gaseous components. However, PM from DE was found to be capable of inducing an inflammatory response, as demonstrated by the one IT instillation study described above. Evidence was presented suggesting that DEP may act through bronchopulmonary C-fibers to stimulate pulmonary inflammation.

Gasoline Emissions and Road Dust

Healthy male Swiss mice were exposed to gasoline exhaust (635 µg/m^3 PM and associated gases) or filtered air for 15 min/day for 7, 14, and 21 days (Sureshkumar et al., 2005, 088306). BALF was collected for analysis 1 h after the last exposure. Histological analysis was also carried out at 7, 14, and 21 days. The number of leukocytes in BALF was increased after exposure to gasoline exhaust, but this increase did not achieve statistical significance. However, levels of the pro-inflammatory cytokines TNF-α and IL-6 were significantly increased in BALF following 14 and 21 days of exposure. Furthermore, inflammatory cell infiltrate in the peribronchiolar and alveolar regions were observed by histology. Evidence of lung injury was also found (Section 6.3.5.3). In this study, BALF analysis of inflammatory cells was a less sensitive indicator of pulmonary inflammation than BALF analysis of cytokines and histological analysis of lung tissue. Results of this study cannot entirely be attributed to the presence of PM in the gasoline exhaust since 0.11 mg/m^3 SO_X, 0.49 mg/m^3 of NO_X and 18.7 ppm of CO were also present during exposure.

Using ApoE$^{-/-}$ mice on a high-fat diet, Campen et al. (2006, 096879) studied the impact of inhaled gasoline emissions and road dust (6 h/day×3 day) on pulmonary inflammation. For gasoline emissions, the PM-containing atmosphere (PM mean concentration 61 µg/m^3; NO_X mean concentration 18.8 ppm; CO mean concentration 80 ppm) failed to increase numbers of inflammatory cells in BALF collected 18 h after the last exposure. However, a statistically significant increase in total cells and macrophages was observed in response to resuspended road dust ($PM_{2.5}$) at 3,500 µg/m^3, but not at 500 µg/m^3.

Model Particles

In a study by Elder et al. (2004, 055642), pulmonary inflammation was investigated in two compromised, aged animal models (11-14 mo old SH and 23 mo old F344) exposed by inhalation to UF CB (count median diameter = 36 nm) at a relevant concentration (150 $\mu g/m^3$). No changes in BALF cells were seen 24 h post-exposure in either model.

An increase in BALF neutrophils was observed at 24 h, but not at 4 h, in WKY rats exposed to UF carbon particles (median particle size 38 nm; mass concentration 180 $\mu g/m^3$; mean number concentration 1.6×10^7 particles/cm^3) for up to 24 h (Harder et al., 2005, 087371). Changes in HR and HRV demonstrated in this study (Section 6.2.1.3) occurred much more rapidly than the inflammatory response.

No evidence of pulmonary inflammation was found by analysis of BALF or histology one or three days following 24-h exposure of SH rats to UF carbon particles under similar conditions (median particle size 31 nm; mass concentration 172 $\mu g/m^3$; mean number concentration 9.0×10^6 particles/cm^3) (Upadhyay et al., 2008, 159345). However increased expression of HO-1, ET-1, ET_A and ET_B, tPA and, plasminogen activator-1 was found in lung tissue three days following exposure.

In a study by Gilmour et al. (2004, 054175), adult Wistar rats were exposed for 7 h to fine and UF CB particles (mean mass concentration 1,400 and 1,660 $\mu g/m^3$ for fine and UF CB, respectively; mean number concentration 3.8×10^3 and 5.2×10^4 particles/cm^3, respectively; count median aerodynamic diameter 114 nm and 268 nm, respectively). Both treatments resulted in increased BALF neutrophils 16 h post-exposure, with the UFPs having the greater response. UFPs also increased total BALF leukocytes and macrophage inflammatory protein-2 (MIP-2) mRNA in BALF cells. Although these exposures may not be relevant to ambient exposures, this study demonstrated the greater propensity of UF CB particles to cause a pro-inflammatory response compared with fine CB particles.

In a study by Last et al. (2004, 097334), mice were exposed to 250 $\mu g/m^3$ laboratory-generated iron-soot over a 2-wk period as described in Section 6.3.2.3. BALF was collected 1-h after the last exposure and analyzed for total cells. No increase in total cell number was observed following iron-soot exposure. Other findings of this study are described in Sections 6.3.2.3 and 6.3.5.3.

Pinkerton et al. (2008, 190471) exposed young adult male SD rats to filtered air, iron, soot or iron-soot for 6 h/day for 3 days. The iron particles were mainly less than 100 nm aerodynamic diameter, while the soot particles were initially 20-40 nm in diameter but formed clusters of 100-200 nm in diameter. The size-distribution of iron-soot particles was bimodal over 10-250 nm and averaged 70-80 nm in diameter. Rats were exposed to 45, 57 and 90 $\mu g/m^3$ iron or to 250 $\mu g/m^3$ soot alone or in combination with 45 $\mu g/m^3$ iron. Increased levels of the pro-inflammatory cytokine IL-1β were observed in lung tissue of rats exposed for 6 h/day for 3 days to 90 $\mu g/m^3$, but not 57 $\mu g/m^3$, iron. No change in BALF inflammatory cells was observed after exposure to 57 $\mu g/m^3$ or 90 $\mu g/m^3$ iron. Exposures to 250 $\mu g/m^3$ soot in combination with 45 $\mu g/m^3$ iron also resulted in increased levels of lung IL-1β and activation of the transcription factor NF-κB. Levels of lung IL-1β were increased in neonatal rats exposed to 250 $\mu g/m^3$ soot in combination with 100, but not 30, $\mu g/m^3$ iron. Other endpoints of this study are described in Section 6.3.4.2.

Summary of Toxicological Study Findings for Pulmonary Inflammation

New studies involving short-term exposures to CAPs and urban air strengthen the evidence of PM-induced pulmonary inflammation. In addition, several studies demonstrated pulmonary inflammation in response to diesel and gasoline exhaust; however it is not known whether PM or gaseous components of the exhaust were responsible for these effects. Mixed results were obtained in studies using model particles such as CB and iron-soot.

6.3.4. Pulmonary Oxidative Responses

The results of a small number of controlled human exposure and toxicological studies presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provided some initial evidence of an association between exposure to PM and pulmonary oxidative stress. Recent controlled human

exposure studies have provided support for previous findings of an increase in markers of pulmonary oxidative stress following exposure to DE, and one new study has observed a similar effect following controlled exposure to wood smoke. New findings from toxicological studies provide further evidence that oxidative species are involved in PM-mediated effects. No epidemiologic studies have evaluated the association between PM concentration and pulmonary oxidative response.

6.3.4.1. Controlled Human Exposure Studies

Two studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) observed effects on markers of airway oxidative response in healthy adults following controlled exposures to fresh DE or resuspended DE particles (Blomberg et al., 1998, 051246; Nightingale et al., 2000, 011659). Several recent studies are described below which have further evaluated the oxidative response following exposure to particles in human volunteers.

Diesel Exhaust

Pourazar et al. (2005, 088305) exposed 15 adults (11 males and four females) for 1 h to air or DE (PM_{10} concentration 300 μg/m^3) in a controlled cross-over study. Bronchoscopy with airway biopsy was performed 6 h after exposure. The expression of NF-κB, AP-1 (c-jun and c-fos), p38, and JNK in bronchial epithelium was quantified using immunohistochemical staining. DE was observed to significantly increase nuclear translocation of NF-κB, AP-1, phosphorylated p38, and phosphorylated JNK; however, the findings of this study require confirmation with more quantitative methods such as Western blot analysis. The observed activation of redox-sensitive transcription factors by DE may result in the induction of pro-inflammatory cytokines. There is some evidence to suggest that this bronchial response to DE is mediated through the epidermal growth factor receptor signaling pathway (Pourazar et al., 2008, 156884). Behndig et al. (2006, 088286) evaluated the upregulation of endogenous antioxidant defenses following exposure to DE (100 μg/m^3 PM_{10}) in a group of 15 healthy adults. Increases in urate and reduced GSH were observed in alveolar lavage, but not bronchial wash, 18 h after exposure. In a study utilizing the same exposure protocol, Mudway et al. (2004, 180208) observed an increase in GSH and ascorbate in nasal lavage fluid 6 h following exposure to DE in a group of 25 healthy adults.

Wood Smoke

Barregard et al. (2008, 155675) observed a significant increase in malondialdehyde levels in breath condensate of healthy volunteers (n = 13) immediately following and 20 h after a 4-h exposure to wood smoke (240-280 μg/m^3 PM).

Endobronchial Instillation

Schaumann et al. (2004, 087966) demonstrated an increased oxidant radical generation of BALF cells following endobronchial instillation of urban particles compared with instillation of particles collected in a rural area. The authors suggested that this difference was likely due to the greater concentration of transition metals found in the urban particles.

Summary of Controlled Human Exposure Study Findings for Pulmonary Oxidative Responses

Taken together, these studies suggest that short-term exposure to PM at near ambient levels may produce mild oxidative stress in the lung. Limited data suggest that proximal and distal lung regions may be subject to different degrees of oxidative stress during exposures to different pollutant particles.

6.3.4.2. Toxicological Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) reported one study which provided evidence that ROS were involved in PM-mediated responses. This particular study used pre-treatment with the antioxidant DMTU to block the neutrophilic response to ROFA. More recently, several studies evaluated the effects of PM exposure on pulmonary oxidative stress. Oxidative stress can be directly determined by measuring ROS or oxidation products of lipids and proteins. An indirect assay involves measurement of the enzyme HO-1 or of the antioxidant enzymes SOD or catalase, all of which can be induced by oxidative stress. Antioxidant interventions which inhibit or prevent responses are a further indirect measure of oxidative stress playing a role in the pathway of interest.

CAPs

Gurgueira et al. (2002, 036535) measured oxidative stress as in situ CL. Immediately following a 5-h $PM_{2.5}$ CAPs exposure (mean mass concentration range 99.6-957.5 $\mu g/m^3$; Boston, MA) increased CL was observed in lungs of CAPs-exposed SD rats. CL evaluated after CAPs exposure durations of 3 h was also increased but did not achieve statistical significance compared to the filtered air group. When animals were allowed to recover for 24 h following the 5-h CAPs exposure, CL levels returned to control values. Interestingly, a decrease in lung CL was observed in rats breathing filtered air for three days compared with rats breathing room air for the same duration. To compare potential particle-induced differences in in situ CL, rats were exposed to ROFA (1.7 mg/m^3 for 30 min) or CB (170 $\mu g/m^3$ for 5 h). Only the ROFA-treated animals exhibited increased CL in lung tissue. Additionally, levels of antioxidant enzymes in the lung (MnSOD and catalase) were increased in CAPs-exposed rats. A CAPs-associated increase in CL was also seen in the heart (Section 6.2.9.3), but not the liver.

In a similar study, Rhoden et al. (2004, 087969) exposed SD rats for 5 h to $PM_{2.5}$ CAPs from Boston (mean mass concentration 1,228 $\mu g/m^3$) or to filtered air. Significant increases in TBARS and protein carbonyl content (a measure of protein oxidation) were observed 24 h post-exposure to CAPs. Pretreatment with the thiol antioxidant NAC (50 mg/kg i.p.) 1-h prior to exposure prevented not only the lipid and protein oxidation observed in response to CAPs, but also the increase in BALF neutrophils and pulmonary edema in this model (Sections 6.3.3.3 and 6.3.5.3). Results of this study demonstrate the key role played by oxidative stress in these CAPs-mediated effects.

A later study by Rhoden et al. (2008, 190475) investigated the role of superoxide in mediating pulmonary inflammation following exposure to ambient air particles. In this study, adult SD rats were exposed by IT instillation to 1 mg of SRM1649. Two hours prior to exposure, half of the rats were pretreated with the membrane-permeable SOD mimetic MnTBAP (10 mg/kg, i.p.). MnTBAP abrogated the inflammatory response, measured by increased BALF inflammatory cells, and the increase in lung superoxide, measured by CL, observed 4 h following exposure to urban air particles.

Kooter et al. (2006, 097547) reported an increase in HO-1 in BALF and lung tissue measured 18 h after a 2-day exposure (6 h/day) of SH rats to $PM_{2.5}$ or $PM_{2.5}$+UF CAPs (mean mass concentration range 399-3613 and 269-556 $\mu g/m^3$, respectively; $PM_{2.5}$ CAPs site in Bilthoven and $PM_{2.5}$+UF site in freeway tunnel in Hendrik-Ido-Ambacht, the Netherlands). This occurred in the absence of any measurable pulmonary inflammation (Section 6.3.3.3).

Urban Air

To evaluate oxidative stress responses to ambient particles from vehicles, Wistar rats were exposed to ambient urban air from a high traffic site (concentration range 22-225 $\mu g/m^3$ PM_{10}; Porto Alegre, Brazil) or to the same air which was filtered to remove the PM (Pereira et al., 2007, 156019). Several exposure regimens were carried out: 6- and 20-h continuous exposures or to intermittent exposures of 5 h/day for four consecutive days. A significant increase in lipid peroxidation (measured as malondialdehyde) was seen in lung tissue immediately following the 20-h continuous exposure, but not following the 6-h exposure or the intermittent exposures. Inflammation-related endpoints are described in Section 6.3.3.3.

Diesel Exhaust

Li et al. (2007, 155929) exposed mice to clean air or to low dose DE (100 μg/m^3 PM) for 7 h/day and 5 days/wk for 1, 4 and 8 wk as described in Section 6.3.2.3. HO-1 mRNA and protein were increased in lung tissues of both mouse strains after 1 wk of DE exposure. In addition, AHR and changes in BALF cells and cytokines were observed (Sections 6.3.2.3 and 6.3.3.3). Pretreatment with the thiol antioxidant NAC (320 mg/kg, i.p.) on days 1-5 of DE exposure greatly attenuated the AHR and inflammatory response seen after 1 wk of DE exposure. Long-term responses are discussed in Sections 7.3.2.2, 7.3.3.2 and 7.3.4.1.

A study by Whitekus et al. (2002, 157142) investigated the adjuvant effects of DE particles in an allergic animal model and is discussed in detail below (Section 6.3.6.3). Intervention with the thiol antioxidants bucillamine and NAC inhibited the increases in allergen-specific IgE and IgG_1 as well as the increases in protein carbonyl and lipid hydroperoxides in the lung following DE particle exposure.

Gasoline Exhaust

Pulmonary oxidative stress was evaluated by measurement of CL and TBARS following exposure of SD rats to gasoline engine exhaust (Seagrave et al., 2008, 191990). Animals were exposed for 6 h in a nose-only inhalation exposure system. PM mass concentration was reported to be 60 μg/m^3; count median diameter 20 nm; mass median diameter 150 nm; while the concentrations of gaseous copollutants were 104 ppm CO, 16.7 ppm NO, 1.1 ppm NO_2 and 1.0 ppm SO_2. A statistically significant increase in lung CL was observed without a concomitant increase in lung TBARS. Discordant results were also observed for road dust exposures in the heart (Section 6.2.9.3). The discrepancy between oxidative stress indicators suggests that the responses may follow different time courses. Furthermore, no CL was seen when the gasoline exhaust was filtered to remove the particulate fraction.

Model Particles

Increased expression of HO-1 was observed in lung tissue three days following 24-h exposure of SH rats to UF carbon particles (median particle size 31 nm; mass concentration 172 μg/m^3; mean number concentration 9.0×10^6 particles/cm^3) despite no evidence of pulmonary inflammation (Section 6.3.3.3) (Upadhyay et al., 2008, 159345)

In a study conducted by Pinkerton et al. (2008, 190471), young adult male SD rats were exposed to filtered air, soot, iron or iron-soot for 6 h/day for three days as described in Section 6.3.3.3. A statistically significant decrease in total antioxidant power and a statistically significant increase in glutathione-S-transferase activity were observed in lung tissue from rats exposed to 90 μg/m^3 iron. This high concentration iron exposure also resulted in increased levels of ferritin protein in lung tissue, indicating the presence of free iron which has the potential to redox cycle and cause oxidative stress. Lung tissue total antioxidant power was decreased and glutathione redox ratio was increased by the combined exposure to 250 μg/m^3 soot and 45 μg/m^3 iron. The iron-soot exposure also increased oxidized glutathione in BALF and lung tissue. These results demonstrate that co-exposure to soot enhanced iron-mediated oxidative stress. Furthermore, co-exposure to soot and iron resulted in increased expression of cytochrome P450 isozymes CYP1A1 and CYP2E1 in lung tissue, an effect not observed in response to either agent alone. Inflammation-related endpoints observed in this study are described in Section 6.3.3.3.

In a parallel study, Pinkerton et al. (2008, 190471) exposed neonatal male SD rats to iron-soot or filtered air 6 h/day for three days during the second and fourth week of life. Both 30 μg/m^3 and 100 μg/m^3 iron in combination with 250 μg/m^3 soot resulted in increased BALF oxidized glutathione, glutathione redox ratio and glutathione-S-transferase activity and decreased total antioxidant power. The higher concentration exposure resulted in increased ferritin expression in lung tissue. Effects on cellular proliferation in specific regions of the lung were also noted as described in Section 6.3.5.3.

Nurkiewicz et al. (2009, 191961) exposed SD rats to fine (count median diameter 710 nm) and UF (count median diameter 100 nm) TiO_2 particles via aerosol inhalation at concentrations of 1.5-16

mg/m^3 for 240-720 min. These exposures were chosen in order to produce deposition of 4-90 μg/rat, which was demonstrated in a previous study to result in different degrees of impaired microvascular function (Nurkiewicz et al., 2008, 156816). Histological analysis of lung tissue did not find any significant inflammation, although particle accumulation in alveolar macrophages and a frequent association of alveolar macrophage with the alveolar wall was observed 24 h following exposure (Nurkiewicz et al., 2008, 156816). Although the main focus of the more recent study was on effects of TiO_2 on NO production and microvascular reactivity in the spinotrapezius muscle (Section 6.2.4.3), the presence of nitrotyrosine was determined in both lung tissue and spinotrapezius muscle as a measure of peroxynitrite formation. Peroxynitrite formation occurs mainly as a result of the rapid reaction of NO with superoxide and suggests an increase in local superoxide production. The area of lung tissue containing nitrotyrosine immunoreactivity increased three-fold 24 h following exposure to 10 μg UF TiO_2. Nitrotyrosine immunoreactivity was localized in inflammatory cells found in the alveolar region of the lung.

Summary of Toxicological Study Findings for Pulmonary Oxidative Responses

New studies involving short-term exposure to CAPs, urban air, diesel and gasoline exhaust, and model particles such as CB, iron-soot and TIO_2 consistently demonstrate pulmonary oxidative responses. Furthermore, antioxidant treatment ameliorated effects observed in response to CAPs, DE and DE particles.

6.3.5. Pulmonary Injury

The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented evidence from several toxicological studies of small PM-induced increases in markers of pulmonary injury including thickening of alveolar walls and increases in BALF protein. These findings are consistent with the results of recent toxicological and controlled human exposure studies demonstrating mild pulmonary injury accompanying inflammatory responses to CAPs and wood smoke. One recent epidemiologic study has also observed a positive association between PM and urinary concentrations of lung Clara cell protein.

6.3.5.1. Epidemiologic Studies

One epidemiologic study examined biomarkers of pulmonary injury. The mean concentration data from this study are characterized in Table 6-10. Timonen et al. (2004, 087915) enrolled subjects with coronary heart disease in Amsterdam (n = 37), Erfurt, Germany (n = 47) and Helsinki (n = 47) to study daily variation in PM and urinary concentrations of lung Clara cell protein (CC16). No associations were seen between the PNC of the smallest particles ($NC_{0.01-0.1}$) and CC16. Significant associations with $NC_{0.1-1}$ and $PM_{2.5}$ (which were strongly correlated with each other [r = 0.8]) were seen only for Helsinki subjects: same day, lag 3 and 5-day mean $NC_{0.1-1}$ increases of 1000 particles/cm^3 were associated with increases in ln (CC16/creatinine) of 15.5% (95% CI: 0.001-30.9), 17.4% (95% CI: 3.4-31.4), and 43.2% (95% CI: 17.4-69.0), respectively. Similar associations were seen for 10 μg/m^3 increases in $PM_{2.5}$: lag 0 and 5-day mean $PM_{2.5}$ were associated with increases in ln (CC16/creatinine) of 23.3% (95% CI: 6.3-40.3) and 38.8% (95% CI: 15.8-61.8), respectively.

6.3.5.2. Controlled Human Exposure Studies

No studies of controlled human exposures presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) specifically examined the effect of PM on pulmonary injury. However, several recent studies have evaluated changes in markers of injury and increased alveolar permeability following exposures to various types of particles.

Urban Traffic Particles

Bräuner et al.(2009, 190244) evaluated the effect of exposure to urban traffic particles (24-h exposure, $PM_{2.5}$ 9.7 μg/m^3) on the integrity of the alveolar epithelial membrane in a group of 29 healthy adults, with and without exercise. Following 2.5 h of exposure, alveolar epithelial permeability was assessed by measuring the pulmonary clearance of ^{99m}Tc-DTPA, which was administered as an aerosol during 3 min of tidal breathing. While pulmonary clearance of ^{99m}Tc-DTPA was observed to increase following exercise, there was no significant difference in clearance between exposure to urban traffic particles and filtered air. In addition, PM exposure was not observed to affect the level of CC16 in plasma or urine at 6 or 24 h after the start of exposure.

Diesel Exhaust

Relative to filtered air, exposure for 1 h to DE (300 μg/m^3 PM) was not observed to affect the plasma CC16 concentration at 6 or 24 h post exposure in a group of 15 former smokers with COPD (Blomberg et al., 2005, 191991).

Wood Smoke

In a study examining the respiratory effects of wood smoke, Barregard et al. (2008, 155675) exposed two groups of healthy adults in separate 4-h sessions to wood smoke with median particle concentrations of 243 and 279 μg/m^3. At 20 h post-exposure, the mean serum CC16 concentration was significantly higher after exposure to wood smoke when compared with filtered air. However, when the analysis was stratified by exposure session, a statistically significant effect of wood smoke on serum CC16 was observed in the subjects in session 1 but not those in session 2. It is interesting to note that while the mean particle concentration was only slightly higher in session 1, the mean particle number in session 1 was almost 90% higher than the particle number in session 2, with geometric mean particle diameters of 42 and 112 nm, respectively.

Summary of Controlled Human Exposure Study Findings for Pulmonary Injury

The findings from these studies provide limited evidence to suggest that exposures to particles may increase markers of pulmonary injury in healthy adults.

6.3.5.3. Toxicological Studies

The 2004 PM AQCD (U.S. EPA, 2004, 056905) reported mild increases in BALF protein, a marker of pulmonary injury, in several studies involving inhalation exposure to CAPs. In addition, histological analysis demonstrated that the bronchoalveolar junction was the site of the greatest inflammation following CAPs exposure. Low level exposure to DE was associated with Type 2 cell proliferation and thickening of alveolar walls near alveolar macrophages according to the 2002 EPA Diesel Document (U.S. EPA, 2002, 042866). In addition, IT instillation of fly ash and metal-containing PM generally caused pulmonary injury as measured by increases in BALF protein, LDH and albumin. Proliferation of bronchiolar epithelium was also noted. More recent studies of BALF markers of pulmonary injury and histological analysis of lung tissue are summarized below.

BALF Markers of Pulmonary Injury and Increased Permeability

CAPs

Kodavanti et al. (2005, 087946) exposed SH and WKY rats to filtered air or $PM_{2.5}$ CAPs from RTP, NC as described in Section 6.3.3.3. Differences in baseline parameters were noted for the two rat strains since SH rats had greater levels of protein and lower levels of LDH, NAG, ascorbate and

uric acid in the BALF compared with WKY rats. One day after the 2-day CAPs exposure, increased levels of GGT were observed in BALF (a marker of epithelial injury) of SH rats, but not WKY rats, compared with filtered air controls. Injury was not accompanied by inflammation (Section 6.3.3.3).

In a study by Cassee et al. (2005, 087962), SH rats were exposed for 6 h by nose-only inhalation to CAPs from three different sites in the Netherlands as described in Section 6.3.3.3. The pulmonary injury marker CC16 was increased in BALF two days following CAPs exposure. Inflammation was also observed (Section 6.3.3.3).

Gurgueira et al. (2002, 036535) exposed SD rats to Boston, MA CAPs as described in Section 6.3.4.2 and reported a small but statistically significant increase in lung wet/dry ratios after 3 and 5 h of exposure, indicating the presence of mild edema. This response was accompanied by increased oxidative stress as measured by in situ CL (Section 6.3.4.2). In a similar study, Rhoden et al. (2004, 087969) reported an increase in lung wet/dry ratio in rats 24 h following a 5-h exposure to Boston CAPs which was diminished by pre-treatment of the antioxidant NAC (Section 6.3.4.2).

Pulmonary injury was investigated in two studies using a rat model of pulmonary hypertension (SD rats pre-treated with monocrotaline) which is described in greater detail in Section 6.3.3.3 (Lei et al., 2004, 087999). Significant increases in BALF LDH and protein were observed in response to CAPs. Pulmonary inflammation was observed in both of these studies (Section 6.3.3.3).

Diesel Exhaust

In a study evaluating the effects of DE, no changes were observed in BALF protein and LDH in mice exposed by inhalation to concentrations of 50 and 2000 μg/m^3 DE particles for 4 h/day on 5 consecutive days as described in Section 6.3.3.3 (Stevens et al., 2008, 157010). Changes in gene expression were observed in the higher exposure group. This study demonstrates that changes in gene expression can occur in the absence of measurable markers of injury or pulmonary inflammation.

In a study by Wong et al. (2003, 097707), also reported by Witten et al. (2005, 087485), rats were exposed nose-only to filtered room air or to DE over a 3-wk period. This study, focusing on neurogenic inflammation, is described in greater detail in Section 6.3.3.3. Pulmonary plasma extravasation was measured by the ^{99m}Technecium-albumin technique and found to be dose-dependently increased in the bronchi and lung. Pretreatment with capsaicin, which inhibits neurogenic inflammation by activating C-fibers and causing the depletion of neuropeptide stores, did not reduce plasma extravasation following DE exposure. Hence, DE is unlikely to act through bronchopulmonary C-fibers to cause neurogenic edema in this model. Inflammatory responses measured in this study are discussed in Section 6.3.3.3.

Gasoline Exhaust

Healthy male Swiss mice were exposed to gasoline exhaust (635 μg/m^3 PM and associated gases) or filtered air for 15 min/day for 7, 14, and 21 days as described in Section 6.3.3.3 (Sureshkumar et al., 2005, 088306). BALF was collected for analysis 1-h after the last exposure. Statistically significant increases in BALF markers of lung injury, alkaline phosphatase, gamma-glutamyl transferase and LDH, were observed at all time points studied. Alveolar edema was noted following 14 and 21 days of exposure. Other findings of this study, including inflammation and histopathological changes, are discussed in Section 6.3.3.3 and below.

Histopathology

CAPs

Histopathological changes were demonstrated in rats exposed for 5 h to Boston CAPs as described in Section 6.3.3.3 (Rhoden et al., 2004, 087969). Slight bronchiolar inflammation and thickened vessels at the bronchiole were observed 24 h post-exposure, consistent with the influx of polymorphonuclear leukocytes observed in BALF (Section 6.3.3.3).

Diesel Exhaust

In a study by Wong et al. (2003, 097707), also reported by Witten et al. (2005, 087485), rats were exposed nose-only to filtered room air or to DE over a 3-wk period. This study, focusing on neurogenic inflammation, is described in greater detail in Section 6.3.3.3. Pulmonary inflammation was evaluated by histological analysis of lung tissue. Following high, but not low, concentration-exposure to DE, a large number of alveolar macrophages was found in the lungs. Small black particles, presumably DE particles, were found in the cytoplasm of these alveolar macrophages. Perivascular cuffing consisting of mononuclear cells was also observed in the high exposure animals. Influx of neutrophils or eosinophils was not seen although mast cell number was increased. Other indices of injury demonstrated in this study are described above.

Gasoline Exhaust

Another study, which is described in greater detail in Section 6.3.3.3, demonstrated histopathological responses to gasoline exhaust in mice exposed to gasoline exhaust or filtered air for 15 min/day for 7, 14, and 21 days (Sureshkumar et al., 2005, 088306). Histological observations showed inflammatory cell infiltrate in the peribronchiolar and alveolar region, alveolar edema and thickened alveolar septa at 14 and 21 days post-exposure. Levels of pro-inflammatory cytokines and marker enzymes of lung damage were also increased in BALF. The numbers of inflammatory cells in BALF was increased but not significantly, demonstrating that BALF analysis of inflammatory cells was a less sensitive indicator of pulmonary inflammation in this study than histological analysis. Other indices of injury found in this study are described above.

Model Particles

In a study investigating the effects of iron-soot, mice were exposed to 250 $\mu g/m^3$ laboratory-generated iron-soot as described in Sections 6.3.2.3 and 6.3.3.3 (Last et al., 2004, 097334). Analysis of airway collagen content was conducted by histology and by biochemical analysis of microdissected airways. No increases in airway collagen content were found by either method in mice exposed to iron-soot for two weeks. Furthermore, no goblet cells were observed in airways of air or iron-soot exposed animals. Other findings of this study are described in Sections 6.3.2.3 and 6.3.3.3.

One study demonstrating histopathological responses to PM in neonatal rats was reported by Pinkerton et al. (2004, 087465). Rat pups (10 days old) were exposed to soot and iron particles (mean mass concentration of 243 $\mu g/m^3$; iron concentration 96 $\mu g/m^3$; size range 10-50 nm) for 6 h/day on 3 consecutive days. Cell proliferation in different lung regions was evaluated following bromodeoxyuridine injection 2 h prior to necropsy. The rate of cell proliferation in the proximal alveolar region (immediately beyond the terminal bronchioles) was significantly reduced in iron-soot exposed animals compared to controls. This was a region-specific response since the rate of cell proliferation was not altered in the terminal bronchioles or the general lung parenchyma. However alveolar septation, the process by which alveoli are formed during development, and alveolar growth were not altered by iron-soot exposure. Decreased cell viability and increased LDH was also noted in BALF of neonatal rats (Pinkerton et al., 2008, 190471). The authors suggest the possibility of greater susceptibility to air pollution during the critical postnatal lung development period which occurs in animals and humans and that neonatal exposure to PM may contribute to impaired lung growth seen in children.

Summary of Toxicological Study Findings for Pulmonary Injury

New studies involving short-term exposure to CAPs and diesel and gasoline exhaust demonstrate mild pulmonary injury, including enhanced BALF markers of injury, pulmonary edema and histopathology. In general, injury responses were accompanied by inflammatory responses. In addition, altered cellular proliferation in the proximal alveolar region was observed in neonatal rats exposed to iron-soot, suggesting the possibility of greater susceptibility to PM during postnatal lung development.

Relative Toxicity of PM Size Fractions

Ambient PM Studies

A recently undertaken multinational project entitled "Chemical and biological characterization of ambient thoracic coarse ($PM_{10-2.5}$), fine ($PM_{2.5-0.2}$), and UFPs ($PM_{0.2}$) for human health risk assessment in Europe" (PAMCHAR) takes a systematic approach to expanding the present knowledge about the physiochemical and toxicological effects of these three PM size fractions. Six European cities were selected that represented contrasting ambient PM profiles: Helsinki, Duisburg, Prague, Amsterdam, Barcelona, and Athens. For PM collected at all sites, $PM_{10-2.5}$ induced the greatest pulmonary effects in C57BL/6J mice IT instilled with 1, 3, or 10 mg/kg of particles (Happo et al., 2007, 096630). Dose-response relationships in BALF parameters measured 24 h post-IT instillation exposure, including cell number and protein, were observed for all sites following $PM_{10-2.5}$, and neutrophils were the predominant cell type present in the BALF (Happo et al., 2007, 096630). Prague $PM_{10-2.5}$ exposure resulted in decreased macrophages in BALF at 12 h, and Amsterdam, Barcelona, and Athens $PM_{10-2.5}$ induced lymphoplasmacytic cells in BALF (Happo et al., 2007, 096630). No inflammatory responses were observed for UFPs measured 12-h after exposure. Protein was elevated for $PM_{10-2.5}$ for all locations with the 10 mg/kg dose; Athens UFPs induced protein release only at the two lowest doses 12 h post-exposure. For TNF-α and IL-6, the greatest response was observed with $PM_{10-2.5}$ 4 h following exposure (Happo et al., 2007, 096630). Exposure to UFPs from Duisburg resulted in elevated TNF-α for the 1 and 3 mg/kg doses. Only the Helsinki sample appeared to induce the same level of IL-6 release for $PM_{10-2.5}$ and $PM_{0.2}$ at 10 mg/kg, albeit the collection times differed. In vitro TNF-α and IL-6 responses did not always reflect in vivo effects (Table 6-11), as the Duisburg $PM_{10-2.5}$ sample was the most potent in vivo compared to the other sites and elicited much lower cytokine release compared to other cities (except Helsinki) in vitro (Happo et al., 2007, 096630; Jalava et al., 2006, 155872; Jalava et al., 2008, 098968). Helsinki PM was collected in the spring and generally had the lowest in vivo and in vitro activity for $PM_{10-2.5}$ compared to the other cities (Happo et al., 2007, 096630; Jalava et al., 2006, 155872; Jalava et al., 2008, 098968). Spring-time samples were collected because episodes of resuspended road dust occur frequently during this season (Pennanen et al., 2007, 155357). There was a high correlation between EC content in $PM_{2.5}$ and $PM_{10-2.5}$, indicating that traffic impacted both size fractions (Sillanpaa et al., 2005, 156980). Duisburg PM collected in fall had the greatest amounts of Mn and Zn compared to PM samples from other locations (Pennanen et al., 2007, 155357). Metals industries in Duisburg are likely contributors to the observed PM metals concentrations. For the Prague winter PM samples, the As content was higher than at any other location (Pennanen et al., 2007, 155357). Prague also had the highest PAH levels in all three size fractions, possibly attributable to stable atmosphere conditions and incomplete combustion of coal and biomass in residential heating (Pennanen et al., 2007, 155357). High levels of ammonium and nitrate in PM samples from Amsterdam suggest traffic as a large source of air pollution (Pennanen et al., 2007, 155357). Approximately one-third of $PM_{10-2.5}$ mass from Amsterdam was comprised of sea salt (Sillanpaa et al., 2005, 156980), double that of any other city. In Barcelona and Athens, high calcium or Ca^{2+} contents in spring and summer $PM_{2.5}$ and $PM_{10-2.5}$ are indicative of resuspended soil-derived particles (Pennanen et al., 2007, 155357).

Table 6-11. PAMCHAR $PM_{10-2.5}$ inflammation results with ambient PM.

City and Season	In Vivo[a] (mg/kg)						In Vitro[b] (µg/mL)		
	BALF protein	BALF TNF-α	BALF IL-6	BALF KC	BALF PMN	BALF AM	TNF-α	IL-6	MIP-2
Helsinki spring	+10	+10	+10	[+3 10]	+10	--	+150,300	+150,300	+150,300
Duisburg fall	+10	+10	+10	+10	+10	--	+150,300	+150,300	+300
Prague winter	+10	[+3 10]	+10	[+3 10]	+10	+10	+150,300	+150,300	+150,300
Amsterdam winter	+10	+10	+10	+10	+10	--	+150	+150,300	+150,300
Barcelona spring	+10	+10	[+3 10]	+10	+10	--	+150,300	+150,300	+150,300
Athens summer	+10	[+3 10]	[+3 10]	[+3 10]	+10	--	+150,300	+150,300	+150,300

[a]Source: Happo et al. (2007, 096630); 2 cell lines used for in vitro study were RAW264.7
[b]Source: Jalava et al. (2006, 155872); + indicates increased response and numbers that follow indicate at which dose the response was observed

Schins et al. (2004, 054173) employed PM from two cities in Germany, Duisburg and Borken, in another study. In contrast to the PAMCHAR study where animals were administered PM suspended in pathogen-free water (Happo et al., 2007, 096630), animals received PM via IT instillation suspended in saline at a dose of 320 µg (Schins et al., 2004, 054173). In female Wistar rats, neutrophils in BALF were significantly elevated for $PM_{10-2.5}$ from Duisburg and Borken (Table 6-12), albeit the percent of neutrophils with the $PM_{10-2.5}$ from Borken was nearly double that of Duisburg. The responses with $PM_{2.5}$ were much smaller. When these $PM_{10-2.5}$ particles were introduced into whole blood to determine overall inflammogenic capacity, IL-8 and TNF-α were released in greater quantities than in response to $PM_{2.5}$. Furthermore, $PM_{10-2.5}$ from Borken induced higher cytokine responses than Duisburg $PM_{10-2.5}$.

An in vivo study involving SH rats was conducted using $PM_{10-2.5}$ and $PM_{2.5}$ from six different European locations with varying traffic densities (3 or 10 mg/kg IT instillation; UFPs were not collected) (Gerlofs-Nijland et al., 2007, 097840). It was reported that $PM_{10-2.5}$ generally induced greater responses than $PM_{2.5}$. IT instillation of $PM_{10-2.5}$ from a location with high traffic influence in Munich, Germany, demonstrated the greatest response in terms of LDH activity, protein, total cells, neutrophils, and lymphocytes in BALF 24 h post-exposure. $PM_{10-2.5}$ collected from a low traffic site in Munich induced the greatest cytokine response for TNF-α and MIP-2. Some correlations were observed between $PM_{10-2.5}$ components (Ba and Cu) and BALF parameters, but were largely driven by one location (Gerlofs-Nijland et al., 2007, 097840).

Table 6-12. Other ambient PM – in vivo $PM_{10-2.5}$ studies – BALF results, 18-24 h post-IT exposure.

Location	Endotoxin (~ Values)	Dose (mg/kg)	Cell Differentials	Cytokines	Injury Biomarkers	Reference
Germany, Borken; rural Feb-May 2000	6.6 EU/mg	0.58-0.91	↑* % PMN	↑ TNF-α		Schins et al. (2004, 054173)
Germany, Duisburg; heavy industry Feb-May 2000	5.0 EU/mg	0.58-0.91	↑ % PMN	↑ MIP-2		Schins et al. (2004, 054173)
USA, Seattle, WA Feb-March 2004	6.0 EU/mg	1.25, 5.0				Gilmour, et al. (2007, 096433)
USA, Salt Lake City, UT Apr-May 2004	6.3 EU/mg	1.25, 5.0			↑ protein	Gilmour, et al. (2007, 096433)
USA, South Bronx, NY Dec 2003-Jan 2004	2.8 EU/mg	1.25, 5.0	↑ PMN	↑ MIP-2		Gilmour, et al. (2007, 096433)
USA, Sterling Forest, NY Dec 2003-Jan 2004	2.9 EU/mg	1.25, 5.0				Gilmour, et al. (2007, 096433)

Location	Endotoxin (~ Values)	Dose (mg/kg)	Cell Differentials	Cytokines	Injury Biomarkers	Reference
USA, RTP, NC Oct-Nov 1996	0.96 EU/mg	0.5, 2.5, 5.0	↑↑ PMN	↑ IL-6		Dick (2003, 088776)
Germany, Munich Ost Bahnhof; high traffic A Aug 2002	2.9 EU/mg	3, 10	↑↑* total cells ↑↑ AM ↑↑*PMN ↑↑* Lymph	↑↑ MIP-2 ↑↑ TNF-α	↑↑* LDH ↑* protein	Gerlofs-Nijland, et al. (2007, 097840)
Netherlands, Hendrik-Ido-Ambacht; high traffic Sept 2002	6.5 EU/mg	3, 10	↑↑ total cells ↑↑*AM ↑↑ PMN ↑↑ Lymph	↑ MIP-2 ↑↑ TNF-α	↑↑ LDH ↑ protein	Gerlofs-Nijland, et al. (2007, 097840)
Italy, Rome; high traffic Apr 2002	1.5 EU/mg	3, 10	↑ total cells ↑↑ AM ↑↑ PMN ↑↑ Lymph	↑↑ MIP-2 ↑↑ TNF-α	↑↑ LDH	Gerlofs-Nijland, et al. (2007, 097840)
Netherlands, Dordrecht; moderate traffic Apr 2002	0.6 EU/mg	3, 10	↑↑ total cells ↑ AM ↑↑ PMN ↑ Lymph		↑↑ LDH ↑ protein	Gerlofs-Nijland, et al. (2007, 097840)
Germany, Munich Grosshadern Hospital; low traffic Jun-Jul 2002	2.9 EU/mg	3, 10	↑ total cells ↑↑ AM ↑↑ PMN ↑↑ Lymph	↑↑* MIP-2 ↑↑* TNF-α	↑↑* LDH ↑ protein	Gerlofs-Nijland, et al. (2007, 097840)
Sweden, Lycksele; low traffic Feb-March 2002	0.9 EU/mg	3, 10	↑↑ total cells ↑ AM ↑↑ PMN ↑ Lymph		↑↑ LDH ↑ protein	Gerlofs-Nijland, et al. (2007, 097840)

For Gerlofs-Nijland study, composition data were averaged across seasons. ↑ significant only at highest dose.
↑↑ Significant at lowest and highest dose.
* Greatest potency for that endpoint and study. Gilmour et al. (2007, 096433)exposure was via aspiration.

A more recent study by these investigators (Gerlofs-Nijland et al., 2009, 190353) compared responses to PM from three different European cities based on size fraction and content of metals and PAH. SH rats were IT instilled with 7 mg/kg PM, and markers of toxicity and inflammation were measured in BALF 24 h later. Blood markers of coagulation were also measured and are described in Section 6.2.8.3. In the first part of the study, both $PM_{2.5}$ and $PM_{10-2.5}$ from Duisburg were found to have dramatic effects on inflammatory cell influx and activation as well as on the injury markers LDH, protein and albumin in the BALF. The antioxidant species uric acid was increased in BALF from rats exposed to both size fractions and was interpreted as an adaptive response to oxidative stress. Statistical analysis demonstrated that $PM_{10-2.5}$ was more potent in eliciting these responses than $PM_{2.5}$. In the second part of the study, responses to metal-rich PM from Duisburg and metal-poor PM from Prague were determined. A statistically significant greater enhancement of BALF markers of inflammation and injury was observed for the Duisburg PM compared with the Prague PM. Furthermore, responses to PAH-rich $PM_{10-2.5}$ from Prague and PAH-poor $PM_{10-2.5}$ from Barcelona were determined. $PM_{10-2.5}$ from Prague was found to have statistically significant greater effects compared with $PM_{10-2.5}$ from Barcelona. However, organic extracts of these $PM_{10-2.5}$ fractions had very little capacity to produce inflammation or toxicity in this model. These findings suggest an important role for specific components associated with $PM_{10-2.5}$ in mediating the pro-inflammatory effects.

In another study investigating specific components of $PM_{10-2.5}$, BALB/c mice were IT instilled with 25 and 50 µg $PM_{10-2.5}$ from a rural area of the San Joaquin Valley, California (Wegesser and Last, 2008, 190506). Inflammatory cell influx into BALF began at 6 h and peaked at 24 h following IT instillation with 50 µg PM, with the increase in neutrophils preceding the increase in macrophages. Pro-inflammatory effects were found to be mainly due to insoluble components of PM. Furthermore, heat-treatment, which was capable of inactivating endotoxin, had no effect on inflammation. Numbers of neutrophils in the BALF were found to correlate with the content of MIP-2, a known neutrophil chemoattractant released from macrophages and epithelial cells. Taken together, these results demonstrate that the pro-inflammatory effect of this $PM_{10-2.5}$ was associated with insoluble components and not with endotoxin.

In an in vivo study that employed ambient PM collected in fall 1996 from RTP, NC, neutrophilic influx was observed in BALF of female CD1 mice 18 h post-IT instillation (10, 50 or 100 µg) of coarse PM (3.5-20 µm), although a dose-response relationship was not evident (Dick et al., 2003, 088776). Mice were also exposed to fine (1.7-3.5 µm) and fine/ultrafine (<1.7 µm) PM fractions. Only the two highest doses of PM for the smaller size fractions induced elevated neutrophils. Significant responses in albumin and TNF-α were only observed for the fine PM (1.7-3.5 µm) exposure group. Total protein, LDH and NAG responses were unchanged from control levels for all PM size fractions. Levels of IL-6 were elevated in mice exposed to 100 µg for coarse, fine, and fine/ultrafine (<1.7 µm) PM. When dimethylthiourea (DMTU) was administered intravenously prior to exposure, the neutrophil response was attenuated in all groups to levels below control.

Another study compared $PM_{10-2.5}$, $PM_{2.5}$, and UFPs collected in Seattle, WA, Salt Lake City, UT, South Bronx, NY, and Sterling Forest, NY (Gilmour et al., 2007, 096433). In female BALB/c mice, the 100 µg dose of $PM_{10-2.5}$ (approximately 5 mg/kg) from Salt Lake City induced a significant increase in protein in BALF, and the level released was almost as high as that observed after LPS exposure. $PM_{10-2.5}$ from the South Bronx resulted in dose-related increases in neutrophil number and MIP-2 levels in BALF. In contrast, no effects were observed with $PM_{10-2.5}$ from Sterling Forest. The greatest amount of LPS was observed in the Salt Lake City and Seattle $PM_{10-2.5}$ samples. There was a less discernable pattern of response with fine and UFPs.

Coal Fly Ash

Coal fly ash of differing size fractions and composition was administered to female CD1 mice via oropharyngeal aspiration (25 or 100 µg) to assess lung inflammation and injury 18 h following exposure (Gilmour et al., 2004, 057420). Montana (low-sulfur subbituminous; 0.83% sulfur, 11.72% ash content) or western Kentucky (high-sulfur bituminous; 3.11% sulfur, 8.07% ash content) coal was combusted using a laboratory-scale down-fired furnace. Interestingly, no significant effects on BALF neutrophils, TNF-α, MIP-2, albumin, total protein, LDH activity, or NAG activity were observed 18 h post-exposure to $PM_{10-2.5}$ from either coal fly ash. However, the UF fraction ($PM_{0.2}$) of combusted Montana coal induced greater numbers of neutrophils than $PM_{10-2.5}$ or $PM_{2.5}$ at both doses. TNF-α was only elevated in animals exposed to 100 µg of the Montana UFPs; MIP-2 was also increased at both doses. The $PM_{2.5}$ western Kentucky coal fly ash caused increased BALF neutrophils, MIP-2, albumin, and protein (Gilmour et al., 2004, 057420).

In a similar study employing Montana subbituminous coal fly ash particles >2.5 µm, C57BL/6J mice were IT instilled with PM alone or PM+LPS and BALF was obtained 18 h post-exposure (Finnerty et al., 2007, 156434). TNF-α and IL-6 in lung homogenates were only elevated in the animals exposed to PM+100 µg LPS, although it appeared that there was a greater-than additive effect. Total cells and cell differentials were not measured.

Summary of Toxicological Study Findings for Relative Toxicity of PM Size Fractions

Biomarkers of injury and inflammation were measured in in vivo and in vitro studies comparing the toxicity of different size fractions of ambient PM from various locations. Responses were measured in BALF from rodents following IT instillation or aspiration of PM. In general, the $PM_{10-2.5}$ size fraction was more potent than $PM_{2.5}$ or UFPs and endotoxin levels did not appear responsible. In one study, rural $PM_{10-2.5}$ from Germany induced a greater inflammatory and cytokine response than $PM_{10-2.5}$ from an industrial location. In contrast, $PM_{10-2.5}$ from Sterling Forest, NY did not lead to any change in BALF inflammation or injury markers. A study that employed coal fly ash

indicated that the UF fraction was the most inflammogenic. All of these studies were conducted using high doses of PM (0.58-10 mg/kg) and it is unclear if similar effects would be observed at lower doses.

6.3.6. Allergic Responses

A large number of toxicological and controlled human exposure studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) reported an exacerbation of existing allergic airway disease following exposure to laboratory-generated and ambient particles. In addition, numerous studies have demonstrated that PM can alter the immune response to challenge with specific antigens and suggest that PM may act as an adjuvant to promote allergic sensitization. Recent toxicological studies have provided evidence of enhanced allergic responses and allergic sensitization following exposure to CAPs and DE that is consistent with the findings presented in the 2004 PM AQCD. PM can enhance allergic responses by facilitating delivery of allergenic material and promoting subsequent immune reactivity. The initiation or exacerbation of allergic responses has important implications for allergic asthma, the most common form of asthma. Additionally, PM has been shown to alter ventilatory measures in non-allergic animal models, suggesting a possible role in other forms of asthma.

6.3.6.1. Epidemiologic Studies

Allergy contributes to a number of respiratory morbidity outcomes, including asthma. However, relatively few epidemiologic studies of PM have specifically examined indicators of allergy. The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented one study (Hajat et al., 2001, 016693) showing an association between doctor visits for allergic rhinitis and PM_{10} among children in London. This association was strongest at a lag of 3 or 4 days. Similar results were obtained in a new study by Tecer et al. (2008, 180030), which found significant associations between $PM_{2.5}$, $PM_{10\text{-}2.5}$, and PM_{10} with hospital admissions for allergic rhinitis in Turkish children, particularly at lag day 4. While exacerbation of allergic symptoms may occur relatively rapidly, repeated or longer exposures may be required for allergic sensitization to develop; a number of studies associating long-term exposure to PM with specific indicators of allergic sensitization are described in Chapter 7.

6.3.6.2. Controlled Human Exposure Studies

Exacerbation of Allergic Responses

Diesel Exhaust and Diesel Exhaust Particles

Exposure to DE particles was shown to increase the allergic response among atopic individuals in several controlled human exposure studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Nordenhall et al. (2001, 025185) found that exposure to DE significantly decreased the concentration of Mch required to induce a 20% decrease in FEV_1 in a group of atopic asthmatics 24 h post-exposure. In addition, Diaz-Sanchez et al. (1997, 051247) demonstrated an increase in allergen-specific IgE following exposure via intranasal spray to ragweed plus DE particles (0.3 mg) relative to ragweed allergen alone. Decreases in IFN-γ and IL-2, as well as increases in IL-4, IL-5, IL-6, IL-10, and IL-13 were also observed when ragweed allergen was administered with DE particles. It should be noted that the DE particles used in this study were collected during a cold start of a light-duty Isuzu diesel engine, and thus contained relatively high levels of incomplete combustion materials and semi-volatiles organics (e.g., PAHs). One new study using the same source of DE particles (Bastain et al., 2003, 098690) also observed an increase in IL-4 and allergen specific IgE, as well as a decrease in IFN-γ following intranasal administration of ragweed allergen with DE particles (0.3 mg) in atopic adults. The protocol was repeated in this study for all subjects, and the enhancement of allergic response by coexposure to DE particles was observed to be highly reproducible within individuals. In addition, Gilliland et al. (2004, 156471) demonstrated that GST

polymorphisms may alter the adjuvant effects of DE particles on allergic response, with individuals with GSTM1 null or GSTP1 I105 wild type genotypes showing the largest effects.

Allergic Sensitization

Diesel Exhaust Particles

One controlled human exposure study has demonstrated that de novo sensitization to a neoantigen can be induced by exposure to DE particles. In this study, Diaz-Sanchez et al. (1999, 011346) dosed 25 atopic adults intranasally with 1 mg keyhole limpet hemocyanin (KLH), followed by two biweekly challenges with 100 μg KLH. In 15 of the 25 subjects, cold-start DE particles (0.3 mg) were administered intranasally 24 h prior to each KLH exposure, while in the other ten subjects, no DE particles were administered. No KLH-specific IgE was observed in the nasal lavage fluid of any of the subjects exposed to KLH without exposure to DE particles. However, KLH-specific IgE was present in the nasal lavage fluid of 9 out of 15 subjects 28-32 days after the initial KLH immunization when exposures were preceded by administration of DE particles.

CAPs

Increased levels of eotaxin, a marker of allergic activation, were observed in healthy adult volunteers after inhalation of nebulized ambient Chapel Hill $PM_{10-2.5}$ (Alexis et al., 2006, 154323). This particular effect was found to be due to endotoxin, based on its elimination by heat-inactivation; study details are provided in Section 6.3.3.2.

6.3.6.3. Toxicological Studies

Exacerbation of Allergic Responses

Increased use of actual ambient air particle mixes in toxicological studies since the 2004 CD has greatly expanded evidence relevant to assessing these and other immunotoxic effects. A number of studies have also included ambient-level concentrations, although many still include relatively high doses of questionable relevance compared to the doses inhaled by humans. Recent dosimetric models reveal that a small fraction of epithelial cells located at the carinal ridges of airway bifurcations can receive massive doses that may be even a few hundred times higher than the average dose for the whole airway (Chapter 4). These areas, coincidentally, are locations of bronchus associated lymphoid tissues (BALT) which are sites at which interaction of T and B lymphocytes with antigen presenting cells (APC) occurs. Hence the deposited particles are in near-ideal proximity to immunologically active tissues. Doses used for assessing PM immunotoxicity should be viewed with this perspective. In many animal studies, changes in ventilatory patterns are assessed using whole body plethysmography, for which measurements are reported as enhanced pause (Penh). Some investigators report increased Penh as an indicator of AHR, but these are inconsistently correlated and many investigators consider Penh solely an indicator of altered ventilatory timing in the absence of other measurements to confirm AHR. Therefore use of the terms AHR or airway responsiveness has been limited to instances in which the terminology has been similarly applied by the study investigators.

CAPs

Existing allergic sensitization confers susceptibility to the effects of PM in rodent models. For example, studies in allergic rats (Harkema et al., 2004, 056842; Morishita et al., 2004, 087979) suggest that allergic sensitization enhances the retention of PM in the airways. Recovery of anthropogenic trace elements (La, V, Mn, S) from lung tissue was greater for Detroit $PM_{2.5}$ CAPs exposed OVA sensitized/challenged BN rats than for air exposed or non-allergic CAPs exposed controls (24 h post-exposure for 4 or 5 consecutive 10-h days during July or September; time weighted avg mass concentration of 676 ± 288 or 313 ± 119 $\mu g/m^3$, respectively) (Harkema et al.,

2004, 056842). Interestingly, despite lower avg mass concentration, increases in these elements were observed in September, when the avg number concentration of UFPs was nearly double that of July (10,879 ± 5,126 vs. 5,753 ± 2,566 particles/cm^3). September CAPs was associated with eosinophil influx and BALF protein content, as well as significantly increased airway mucosubstances, and the authors speculated that the high concentration of UFPs facilitated particle penetration into the alveolar region of the lungs. IT instillation of fractionated insoluble $PM_{2.5}$ collected from this period resulted in a mild pulmonary neutrophilic inflammation in healthy BN rats, but no differential effects were obtained after IT instillation of total, soluble, or insoluble $PM_{2.5}$ in allergic rats.

Research has also been conducted to determine the effect of proximity to the roadway on exacerbation of existing allergic disease. OVA-allergic BALB/c mice were exposed to $PM_{2.5}$ or UF (≤0.15 μm) CAPs, (avg total concentration 400 μg/m^3) for five 4-h days a week over 2 wk at 50 or 150 m downwind of a heavily trafficked road (Kleinman et al., 2005, 087880). Markers of allergy (serum OVA-specific IgE and IgG1, lung IL-5 and eosinophils) were significantly higher in mice exposed to CAPs ($PM_{2.5}$ or UF) than in air-exposed mice after OVA challenge. IL-5, IgG1, and eosinophils were higher in mice closer to the roadway (50 m) than in mice 150 m downwind. The authors suggest that the enhanced responses closer to the roadway may reflect a greater proportion of UFPs in this vicinity, given that the concentrations of sub-25-nm particles decrease rapidly with distance from the roadway and the $PM_{2.5}$ CAPs closer to the roadway contained a greater number of particles for a similar mass, a portion of which were UF. Animal-to-animal variability among the biomarkers tested made it necessary to combine values from two exposures spanning two years for statistical power (determined prior to the start of the experiment). A subsequent publication (Kleinman et al., 2007, 097082) included a third exposure regimen as well as compositional analysis. $PM_{2.5}$ CAPs mass concentration was intentionally adjusted to an avg concentration of approximately 400 μg/m^3, ranging from 163 to 500 μg/m^3, with an estimated particle number of 2.1×10^5 particles/cm^3 at 50 m and 1.6×10^5 particles/cm^3 at 150 m. UFPs ranged from 146 to 430 μg/m^3, with particle counts of $4.9 \pm 1.4\times10^5$ particles/cm^3 at 50 m, and $4.4 \pm 2.1\times10^5$ particles/cm^3 at 150 m. Analysis of results from the three exposures indicated that OVA-sensitized mice exposed 50 m downwind of the roadway exhibited increased levels of IL-5 and IgG_1 compared to mice exposed 150 m downwind or exposed to air. No markers of allergy-related responses were observed in the 150 m exposure groups, and very little difference was seen between $PM_{2.5}$ and UF CAPs responses, perhaps because $PM_{2.5}$ contained 20-32% UF components. The strongest associations between component concentrations and biological markers of allergy (IL-5 and IgG1) were with EC and OC. These studies demonstrate that CAPs can enhance allergic responses, and that proximity to a source may be an important factor.

In a BN rat model for allergic asthma (Heidenfelder et al., 2009, 190026), thirteen 8-h days of exposure to Grand Rapids, MI $PM_{2.5}$ CAPs alone did not result in differential gene expression or indicators of asthmatic pathology in the lung, but the combination of CAPs and OVA resulted in differential expression of genes predominantly related to inflammation and airway remodeling, along with significant increases in IgE, mucin, and total protein in BALF. Consistent with these changes in gene expression and BALF markers, OVA with CAPs also induced a more severe allergic bronchopneumonia (distribution and severity of bronchiolitis and alveolitis) and increased mucus cell metaplasia/hyperplasia and mucosubstances, indicating exacerbation of allergic or asthmatic disease. CAPs was collected in July and characterized as having an average mass of 493±391, OC 244±144, EC 10±4, SO_4^{2-} 79±131 (13 day avg was only about 10% of the CAPs, but a spike occurred during the first week), nitrate 39±67, ammonium 39±59, and urban dust (estimated from Fe, Al, Ca, and Si) 18±6 (mean ± SD in μg/m^3).

Diesel Exhaust Particles

Resuspended DE particles influences airway responses in mice with existing allergic sensitization. A single 5-h nose-only exposure to 870 μg/m^3 aerosolized filter-collected DE particles ($PM_{2.5}$) increased Mch-induced increases in ventilatory timing (Penh) in OVA sensitized/challenged C57BL/6J mice (Farraj et al., 2006, 088469). Intranasal pretreatment with an antibody against the pan neurotrophin receptor p75 attenuated the DE particle-induced increase in airflow obstruction, indicating a role for neurotrophins. Neurotrophins are expressed by various structural, nerve and immune cells within the respiratory tract and are linked to the etiology of asthma in both humans and animal models. DE particles alone in unsensitized mice caused a significant increase in lung macrophages; this response was also inhibited by anti-p75, which may suggest mediation of macrophage influx by neurotrophin or alternatively may reflect anti-p75 dependent depletion of

macrophages due to expression of the p75 receptor. Aside from increased macrophages, the single exposure to DE particles had little effect on other markers of airway inflammation. In a similar subsequent study, these authors demonstrate neurotrophin-mediated DE particle-induced airflow obstruction in OVA sensitized and challenged BALB/c mice (Farraj et al., 2006, 141730), in this case using a higher 2000 μg/m^3 single 5-h exposure to aerosolized filter-collected $PM_{2.5}$. Differences between whole body plethysmography and tracheal ventilation measurements indicated that airflow obstruction may have originated in the nasal passages. Again, very few indices of inflammation were increased; however, similar neurotrophin-dependent increases in lung macrophages were observed after DE particle exposure alone, and BALF IL-4 protein levels were increased 5-fold in sensitized, challenged, DE particle-exposed mice. This neurotrophin-dependent IL-4 response was not evident in the first study, and may be related to the higher dose used in the second study or the characteristic allergic/Th2 bias of the BALB/c strain. Airflow obstruction in the absence of airway inflammation in OVA-sensitized animals seen in both studies by Farraj et al. (2006, 088469; 2006, 141730) may reflect DE particle-induced acute enhancement of neurogenic as opposed to immunologic inflammation.

Diesel Exhaust

Exposure to relatively low doses of DE has been shown to exacerbate asthmatic responses in OVA sensitized/challenged BALB/c mice (Matsumoto et al., 2006, 098017). Mice were intranasally challenged one day prior to chamber exposure to DE (100 μg/m^3 PM; CO, 3.5 ppm; NO_2, 2.2 ppm; SO_2 <0.01 ppm) for 1 day or 1, 4, or 8 wk (7h/day, 5 days/wk, endpoints 12-h post-DE exposure). Results from the 8 wk study are described in Section 7.3.6.2. It should be noted that control mice were left in a clean room as opposed to undergoing chamber exposure to filtered air. Significant AHR upon Mch challenge was observed after 1 and 4 wk of exposure, and airway sensitivity (provocative concentration of Mch causing a 200% increase in Penh) was significantly increased after 1 wk of exposure but not 4 wk. DE had no effect on total cells in BALF, but transiently increased expression of IL-4, IL-5, and IL-13 after 1 day of exposure, MDC after 1 wk, and RANTES after 2 and 3 wk. Eotaxin, TARC, and MCP-1 were elevated without statistical significance after short-term (1 day or wk) exposure. Statistical power may have been lacking due to few animals in the exposure group (n=3). Protein levels of IL-4 and RANTES were significantly elevated after one day of DE exposure. DE had no effect on OVA challenge-induced peribronchial inflammatory or mucin positive cells. Therefore DE-induced AHR was observed in the absence of neutrophilic inflammation, similar to the responses described for aerosolized or nebulized DE particles by Farraj et al. (2006, 088469; 2006, 141730) and Hao et al. (2003, 096565).

Gasoline Exhaust

Acute exposure to fresh gasoline engine exhaust PM does not appear to exacerbate allergic responses (Day et al., 2008, 190204). BALB/c mice were exposed to whole exhaust diluted 1:10 (H), 1:15 (M), or 1:90 (L), filtered exhaust at the 1:10 (HF), or clean air for 6 h/day over three days. Analytes for the high (H) and high filtered (HF) concentrations were: PM mass (μg/m^3) 59.1±28.3 (H) and 2.3±2.6 (HF); PM number (particles/cm^3) 5.0×10^5 and 1.1×10^4; CO (mg/m^3) 102.8±33.0 and 99.5±1.6; NO (mg/m^3) 18.4±2.8 and 17.2±1.9; NO_2 (mg/m^3) 1.4±0.3 and 1.7±0.2; SO_2 (μg/m^3) 1366.8±56.0 and 1051.1±43.0; NH_3 (μg/m^3) 1957.7±8.1 and 1241.5±6.1; NMHC (mg/m^3) 15.9 and 25.9. Particles represented only 0.04% of the total exposure mass and particle size in the H exposure ranged from 5.5 to 150 nm with the majority between 5-20 nm (MMD 150 nm) (McDonald et al., 2008, 191978). Although particles were filtered out, it should be noted that NMHC (non-methane volatile organics) increased by 62%. Mice were exposed with or without prior sensitization to OVA, after one aerosol challenge and with or without secondary challenge. Acute gasoline engine exhaust exposure had variable effects on inflammatory and allergic markers depending on the exposure protocol, but there were no statistically significant differences between the H and HF exposure results, suggesting that the PM fraction of gasoline engine exhaust does not appear to contribute significantly to observed health effects.

Hardwood Smoke

One study indicated that hardwood smoke exposure only minimally exacerbated indices of allergic airway inflammation in an OVA-sensitized BALB/c mouse model and did not alter Th1/Th2

cytokine levels (Barrett et al., 2006, 155677). Trend analysis indicated increasing BALF eosinophils with increasing dose of hardwood smoke, becoming significantly elevated at 300 μg/m^3 (CO, 1.6±0.3 ppm; total vapor hydrocarbon, 0.6±0.2 ppm; NO_X, below limit of quantitation, PM MMAD 0.35±2.0 μm), and increasing, but not significantly, OVA-specific IgE levels with hardwood smoke up to 1,000 μg/m^3.

Model Particles

Exposures to an aerosol of soot and iron oxide generated from ethylene (0.235 mg/m^3 $PM_{2.5}$) were conducted to test whether the sequence of exposure to OVA aerosol challenge and PM affected the observed response of OVA sensitized BALB/c mice (Last et al., 2004, 097334). Though called $PM_{2.5}$, the authors characterized the PM material as UF, 80-110 nm, with the iron oxide crystals often spatially segregated from the soot (200 μg/m^3 soot, remainder iron oxide, CO <0.8 ppm, NO_X <0.4 ppm, PAH below detection). Mice were exposed to PM via chamber inhalation for 2 wk (4h/day, 3 days/wk) before or after 4 wk of OVA inhalation, or simultaneously to PM and OVA for 6 wk. Among endpoints (BALF cells, Penh, airway collagen, and goblet cells) only goblet cell counts were significantly increased with PM exposure in any combination with OVA. There was a trend toward increased Penh responses with exposure to PM alone or with OVA, particularly when PM exposure immediately preceded Mch challenge (after or during OVA challenge). Results from this study are difficult to interpret due to the varied elapsed times between cessation of PM or OVA treatment and endpoint determination. The mild responses to PM may be related to the intraperitoneal sensitization protocol used, reputed to generate a highly allergic mouse in which any additive effects of PM may be obscured by maximal responses to antigen challenge (Deurloo et al., 2001, 156396; Hao et al., 2003, 096565).

Residual Oil Fly Ash

Arantes-Costa and colleagues (2008, 187137) estimated that 60 μg of ROFA would be inhaled by a mouse during one day of exposure to Sao Paulo air. This dose, given intranasally every other day for 4 days, increased AHR in both nonsensitized and OVA sensitized/challenged BALB/c mice upon Mch challenge 2 days after the last exposure. ROFA had no significant impact on eosinophil or macrophage numbers in the lung, nor did it increase the chronic lung inflammation or thickening induced by OVA. In many studies, particular effects such as airway obstruction are only evident when allergic sensitization precedes exposure, but this study and a few others demonstrate allergen-independent AHR after exposure to PM including CAPs (Lei et al., 2004, 087999) and DE or DE particles (Hao et al., 2003, 096565; Li et al., 2007, 155929).

Allergy in Pregnancy or Early Life

Pregnancy or in utero exposure may confer susceptibility to PM-induced asthmatic responses. Exposure of pregnant BALB/c mice to aerosolized ROFA leachate by inhalation or to DE particles intranasally increased asthma susceptibility in their offspring (Fedulov et al., 2008, 097482; Hamada et al., 2007, 091235). The offspring from dams exposed for 30 min to 50 mg/mL ROFA 1, 3, or 5 days prior to delivery responded to OVA immunization and aerosol challenge with AHR and increased antigen-specific IgE and IgG1 antibodies. AHR was also observed in the offspring of dams intranasally instilled with 50 μg of DE particles or TiO_2, or 250 μg CB, indicating that the same effect could be demonstrated using relatively "inert" particles. Pregnant mice were particularly sensitive to exposure to DE particles or TiO_2 particles, and genetic analysis indicated differential expression of 80 genes in response to TiO_2 on the pregnant background. Thus pregnancy may enhance responses to PM, and exposure to even relatively inert particles may result in offspring predisposed to asthma.

Allergic Sensitization

A large number of in vivo animal studies and in vitro studies have demonstrated that particles can alter the immune response to challenge with specific antigens and suggest that PM acts as an adjuvant to promote allergic sensitization. This phenomenon was introduced in the 2002 Diesel

Document, and has been noted in multiple animal and human studies by the 2004 PM AQCD (U.S. EPA, 2004, 056905). Adjuvants enhance the immune response to antigens through various means, including chemoattraction, cytokines, or enhanced antigen presentation and costimulation, and may act on a number of cell types. Importantly, adjuvants may be major contributors to the development of inappropriate immune responses. These immune responses, mediated by T helper cells, fall along a continuum from T helper type 1 (Th1) to T helper type 2 (Th2). Th1 responses, characterized by IFN-γ, are inflammatory and in excess can lead to tissue damage. Alternatively, Th2 responses are characterized by IL-4, IL-5, IL-13, eosinophils, and IgE, and are associated with allergy and asthma. Autoimmune diseases may be driven by Th1, Th2, or mixed responses, but allergic diseases are predominantly Th2 mediated, and many of the immunologic effects observed for PM fall into the Th2 category.

It has been suggested that the capacity of particles to enhance allergic sensitization is associated more strongly with particle number and surface area than particle mass, and several studies comparing size fractions of the same material show greater adjuvant activity for an equivalent mass dose of smaller particles (de Haar et al., 2006, 144746; Inoue et al., 2005, 088625; Nygaard et al., 2004, 058558). This is particularly true of inert or homogeneous materials, such as carbon, polystyrene, and TiO_2, which vary little in composition with size fraction. Studies using CAPs have also observed that adjuvancy and allergic exacerbation are more strongly associated with the UF fraction, possibly due to greater oxidative potential (Kleinman et al., 2005, 087880; Kleinman et al., 2007, 097082; Li et al., 2009, 190457). In some studies of ambient PM, however, $PM_{10-2.5}$ or PM_{10} have demonstrated equal or greater adjuvancy compared to $PM_{2.5}$ (Nygaard et al., 2004, 058558; Steerenberg et al., 2004, 096024; Steerenberg et al., 2005, 088649). More inhalation studies to compare size fractions are needed in order to elucidate the role of particle size in mediating adjuvancy, but this may prove difficult given the influence of composition, e.g., combustion related materials (Steerenberg et al., 2006, 088249) and metal content (Gavett et al., 2003, 053153), which differs among various size fractions and sources.

CAPs

As little as 0.1 µg of UF Los Angeles CAPs administered intranasally with OVA was able to significantly boost allergic antibody responses in BALB/c mice (Li et al., 2009, 190457). A comparison of UFPs (aerodynamic diameter <0.15 µm) with a mix of sub-2.5 µm particles ($PM_{2.5}$/UFP) collected 200 m from a major freeway delivered intranasally five times over the course of nine days showed that UFP but not $PM_{2.5}$/UFP were associated with significant adjuvant effects. 0.5 µg of UFP with OVA (but not alone) led to an increase in BALF eosinophils, allergic cytokines, inflammatory mediators, and serum OVA-specific IgE/IgG1, as well as allergic tissue inflammation in the upper and lower airways. Adjuvant effects of UFP were observed with two independently collected samples (1/2007 and 9/2006) and could not be replicated by administering the same amount of endotoxin measured in the particles, indicating that the effects were not unique to the sampling period nor mediated by contaminating endotoxin. UFP had a greater OC and PAH content than $PM_{2.5}$/UFP, and induced greater oxidative stress in vitro. Partial blocking of the adjuvant effects by antioxidant administration implicates redox potential as a key factor in mediating these effects. The authors suggest that the lack of adjuvancy for UF carbon particles (being mostly EC) is due to a lack of redox cycling compounds, but this was not tested. In contrast, UF (30-50 nm) CB particles have demonstrated intranasal adjuvant activity in other studies (de Haar et al., 2005, 097872) when administered with OVA over three consecutive days. A 200-µg dose increased serum OVA-specific IgE, local lymph node dendritic cells and OVA-specific Th2 lymphocytes in the lung draining lymph nodes and lung, as well as post-challenge airway eosinophilia. Doses as low as 20 µg were able to activate adoptively transferred OVA-specific T cells.

Diesel Exhaust Particles

Resuspended DE particles have been shown to enhance OVA-specific IgG1 and IgE in BALB/c mice exposed via inhalation to doses as low as 200 and 600 $\mu g/m^3$, respectively (Whitekus et al., 2002, 157142). Mice were exposed to DE particles (200, 600 and 2,000 $\mu g/m^3$) for 1 h daily for 10 days prior to aerosol OVA challenge. Compared with responses to OVA alone, antibody levels were increased by all OVA+DE particle exposures. Statistical significance was reached for IgG1 at all DE particle exposure levels, whereas OVA specific IgE was significantly increased at the 600 and 2,000 $\mu g/m^3$ doses and total IgE was significantly elevated at 2,000 $\mu g/m^3$. Although strong adjuvant

effects were observed, no general markers of inflammation such as eosinophils, IL-5, GM-CSF, mucin, morphological changes, or eosinophilic major basic protein (MBP) deposition in the airways were observed in exposed mice. In vitro experiments using the RAW 264.7 macrophage-like cell line indicated a DE particle-induced lipid peroxidation and protein oxidation, which could be inhibited by a variety of antioxidants. Also observed was a decrease in the GSH:GSSG ratio and an increase in HO-1 expression, both of which were inhibited only by the thiol antioxidants NAC and BUC. These same thiol antioxidants were able to completely block DE particle-related increases in IgE and IgG1, as well as lipid peroxides and oxidized proteins recovered from BALF at the 2,000 $\mu g/m^3$ dose. Thus solid correlations between in vivo and in vitro antioxidant activities were found, and the reversal of adjuvant effects by antioxidants in vivo clearly indicates a link between oxidative stress and DE particle adjuvancy. However, the intranasal adjuvant activity of Ottawa, Canada, dust (EHC-93) in the same strain of mice was not inhibited by NAC pretreatment (Steerenberg et al., 2004, 087981), suggesting that disparate pathways may be utilized by different materials to exert immune stimulation.

Diesel Exhaust

DE inhalation during allergen exposure has been shown to augment IgE production and alter methylation of T helper genes in BALB/c mice (Liu et al., 2008, 156709) Animals were exposed to DE (1280 $\mu g/m^3$ PM) over a 3-wk period, 5 h per day, concurrent with periodic intranasal sensitization to the common fungus *Aspergillus fumigatus*. Gas concentrations were not reported. Total IgE and BALF eosinophils were elevated with *A. fumigatus* sensitization and further increased by concomitant DE exposure. Greater methylation of the IFN-γ promoter was observed following DE and *A. fumigatus* exposure (but not DE alone) compared to *A. fumigatus* alone, indicating that combined DE and allergen exposure might induce methylation and thus suppress expression of Th1 genes. Furthermore, hypomethylation of the IL-4 promoter was detected after exposure to *A. fumigatus* and DE compared with exposure to *A. fumigatus* or DE alone, suggesting pro-allergic Th2 gene activation upon combined exposure to allergen and DE. The changes in methylation status of these genes were associated with alterations in IgE levels in individual animals, indicating that modifications at the genetic level could result in predicted downstream effects. This study shows for the first time that DE exposure can exert pro-allergic in vivo effects on the mouse immune system at the epigenetic level.

A toxicogenomic approach to investigate early response mechanisms of DE adjuvancy was taken by Stevens et al. (2008, 157010). BALB/c mice were chamber exposed to filtered air, 500 or 2,000 $\mu g/m^3$ PM in DE for 4 h/day over 5 consecutive days and intranasally exposed to OVA on each of the first 3 days. In the low (500 $\mu g/m^3$) vs. high (2,000 $\mu g/m^3$) DE exposures, CO, NO, NO_2, and SO_2 were <0.1 versus 4.3, <2.5 vs. 9.2, <0.25 vs. 1.1 and <0.06 vs. 0.2 ppm; particle number median diameters were 80 and 86 nm, and volume median diameters were 184 and 195 nm, respectively. Lung tissues were assessed for alterations in global gene expression (n = 4) 4 h after the last DE exposure on day 4. Mice were intranasally challenged with OVA or saline on day 18 and then with OVA on day 28. Post-challenge results demonstrated mild adjuvancy with antigen and DE exposure as evidenced by significant increases in eosinophils, neutrophils, lymphocytes, and IL-6 in the BALF. Antibody responses were not significantly affected by DE exposure, although a slight increase in IgE after high concentration exposure was observed. DE alone only increased neutrophils, indicating the need for combined exposure to DE and antigen in the development of allergic outcomes. Comparison of low DE /OVA vs. air/OVA resulted in no significant changes in gene sets associated with this treatment. Comparison of the high DE/OVA versus air/OVA, however, showed significant changes in 23 gene sets, including neutrophil homing and other chemokines, inflammatory cytokines, numerous interleukins and TNF subtypes, and growth/differentiation pathways.

Summary of Toxicological Study Findings for Allergic Responses

Studies conducted since the last review confirm and extend the 2004 PM AQCD's (U.S. EPA, 2004, 056905) finding that PM can modulate immune reactivity in both humans and animals to promote allergic sensitization and exacerbate allergic responses. Numerous forms of PM, including inert materials, have been shown to function as adjuvants, and although toxicological studies of relatively homogeneous materials demonstrate greater adjuvancy for smaller particles, some analyses

of ambient PM do not. Recent toxicological studies comparing size fractions of well-characterized ambient PM for adjuvant activity in a direct, controlled fashion via inhalation exposure suggest a role for oxidative potential, but thus far the relative contributions of size and composition are not entirely clear. Although epidemiologic studies examining specific allergic outcomes and short-term exposure PM are relatively rare, the available studies, conducted primarily in Europe, positively associate various PM size fractions with allergic rhinitis. Similar findings from a number of long term studies are described in Chapter 7.

6.3.7. Host Defense

The normal and very important role of respiratory immune defense is the detection and/or destruction of pathogens that enter the lung via inhalation and removal of damaged, transformed (cancerous), or infected cells. Innate immune defenses of the respiratory tract include mucociliary clearance, release of toxic antimicrobial proteins into airway surface liquid, and activation of alveolar macrophages. The innate immune system is the earliest responder to irritation or infection, initiating the normal inflammatory response including the majority of detrimental inflammatory processes discussed. Activated macrophages and epithelial cells release cytokines and chemokines that can bring into play the adaptive immune system, which in turn can produce long-lasting pathogen-specific immune responses critical for resolving and preventing infections.

6.3.7.1. Epidemiologic Studies

Collectively, results from multicity studies of hospital admissions and ED visits for respiratory infection as well as single-city studies conducted in the U.S. and Canada (summarized in Figure 6-14) show a positive association between PM and respiratory infections. Lag structure was not investigated in most studies and effects have been observed in association with current day concentration (Zanobetti and Schwartz, 2006, 090195) as well as with concentrations modeled using a 14-day distributed lag function (Peel et al., 2005, 056305). Of studies examining multiple lag times, associations with increasing lag times were observed (Dominici et al., 2006, 088398; Peel et al., 2005, 056305; Peng et al., 2008, 156850). Although no significant positive associations were reported, Slaughter et al. (2005, 073854) observed a trend of increasing association with increasing lag for acute respiratory infection ED visits with PM_1, $PM_{2.5}$, PM_{10} and $PM_{10-2.5}$. This delay in the onset of disease may reflect the time necessary for an infection to become established and symptomatic. The majority of toxicological evidence, described below and in the 2004 PM AQCD (U.S. EPA, 2004, 056905), suggests that PM impairs innate immunity, the first line of defense in preventing infection.

6.3.7.2. Toxicological Studies

Several toxicological studies were cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that demonstrated increased susceptibility to infectious agents following exposure to PM. A limited number of new studies have evaluated the effect of PM on host defense in rodents. Two recent studies have observed an increase in susceptibility to influenza infection and respiratory syncytial virus in mice. However, one new study found that wood smoke had no effect on bacterial clearance in rodents.

Bacterial Infection

Several studies included in the 2004 PM AQCD (U.S. EPA, 2004, 056905) demonstrated increased susceptibility to infectious agents following exposure to various forms of PM. CAPs exposed aged rats demonstrated increased *S. pneumoniae* burdens when a 24-h exposure (65 $\mu g/m^3$) followed infection (Zelikoff et al., 2003, 039009). In another study, IT instillation exposure to ROFA was found to affect bacterial clearance (Antonini et al., 2002, 035342). Examinations of mechanisms related to PM interference with host defenses have demonstrated impaired mucociliary clearance and modified macrophage phagocytosis and chemotaxis. Prolonged exposure to inhaled particles at sufficiently high concentrations can lead to diminished clearance of PM from the alveolar region of

the lung, resulting in the accumulation of retained particles and an accompanying chronic alveolar inflammation. Diminished clearance of PM may also increase susceptibility to pulmonary infection by impeding clearance of pathogens. Impaired phagocytosis by alveolar macrophages may contribute to a decrease in the lung's capacity to deal with increased particle loads (as occurs during high-pollution episodes) or infections and affect the local and systemic responses through the release of biologically active compounds (cytokines, ROS, NO, isoprostanes).

Diesel Exhaust

Since the last review, several additional studies have reported impairment of pathogen clearance following exposure to various sources of PM. All levels of DE (30, 100, 300 or 1,000 $\mu g/m^3$) decreased lung bacterial clearance in C57BL/6 mice exposed for 1 wk (7 days/wk, 6 h/day) prior to infection with *Pseudomonas aeruginosa* (Harrod et al., 2005, 088144). This effect appeared concentration dependent up to 100 $\mu g/m^3$ and was not enhanced at higher concentrations. Lung inflammation was not induced by DE in the absence of infection, but infection-induced inflammation was exacerbated by DE at all concentrations without apparent concentration dependency. Measures of histopathology in infected animals were increased by DE exposure in a concentration-dependent manner, peaking at 100 $\mu g/m^3$ and leveling off or decreasing with higher concentrations. Particle deposition was readily apparent in the lungs after exposure to the lowest concentration of 30 $\mu g/m^3$. A loss of ciliated cells was observed at 30 $\mu g/m^3$ and 100 $\mu g/m^3$ in large airways and in small airways at the higher concentration. Alterations in Clara cell morphology and function were observed at both concentrations as well. Concentrations of gases were reported to be 2.0-45.3 ppm NO, 0.2-4.0 ppm NO_2, 1.5-29.8 ppm CO and 8-365 ppb for SO_2 (McDonald et al., 2004, 055644). PM mass median diameter was ~100-150 nm at all exposure levels (>90% below 1 µm in aerodynamic diameter), with lower exposure concentrations having a slightly smaller size distribution (Reed et al., 2004, 055625).

Gasoline Exhaust

In a study by Reed et al. (2008, 156903), short or long-term exposure to fresh gasoline exhaust (6h/day, 7day/wk for 1 wk or 6 mo) did not affect clearance of *P. aeruginosa* from the lungs of C57BL/6 mice. Atmospheric characterizations are described above for the Day et al. (2008, 190204) and McDonald et al. (2008, 191978) studies in Section 6.3.6.3.

Hardwood Smoke

Similar to gasoline exhaust, hardwood smoke does not appear to have significant impact on pathogen clearance. C57BL/6 mice were exposed to 30-1,000 $\mu g/m^3$ hardwood smoke by whole-body inhalation for 1 wk and 6 months (Reed et al., 2006, 156043). Long-term responses are discussed in Sections 7.3.3.2 and 7.3.7.2. Concentrations of gases ranged from 229.0-14,887.6 mg/m^3 for CO, 54.9-139.3 $\mu g/m^3$ for ammonia, and 177.6-3,455.0 $\mu g/m^3$ for nonmethane volatile organic carbon in these exposures. Bacterial clearance of instilled *P. aeruginosa* was unaffected by hardwood smoke.

Intratracheal Instillation

Studies demonstrate that ROFA impairs host defenses and that soluble metals are important contributors. Antonini et al. (2004, 097199) compared sources of ROFA in SD rats. Precipitator ROFA induced an inflammatory response and diminished pulmonary clearance of *L. monocytogenes* while air heater ROFA had no effect on lung bacterial clearance at the same IT dose of 1 mg/100g body weight. Precipitator ROFA generated a metal-dependent hydroxyl radical suggesting that differences in metal composition were a determinant of the immunotoxicity of ROFA. Subsequent studies using soluble extracts of ROFA with or without a chelating agent confirmed that soluble metals were responsible for weakening defenses against bacterial infection and impairing both innate and adaptive lung immune responses (Roberts et al., 2004, 196994; Roberts et al., 2007, 097623) ROFA has also been shown to result in ciliated cell loss in BALB/c mice after intranasal administration of 60 µg every other day for 4 days (Arantes-Costa et al., 2008, 187137).

Viral Infection

Diesel Exhaust

Viral respiratory infections in early life are associated with increased incidence of childhood asthma and other pulmonary diseases. DE exposure can enhance the progression of influenza infection. BALB/c mice that were chamber exposed to DE 4 h/day for 5 days and subsequently IT instilled with influenza A/Bangkok/1/79 virus had increased susceptibility to influenza infection (Ciencewicki et al., 2007, 096557). Exposures to two concentrations of DE were conducted: 500 μg/m^3 (0.9 ppm CO, <0.25 ppm NO_2, <2.5 ppm NO, and 0.06 ppm SO_2) and 2,000 μg/m^3 (5.4 ppm CO, 1.13 ppm NO_2, 10.8 ppm NO, and 0.32 ppm SO_2). Responses were greater for animals exposed to 500 μg/m^3 DE than to 2,000 μg/m^3, and were associated with a significant increase in IL-6 protein and mRNA expression and IFN-β expression. The authors present the possibility that damage to the epithelium at the higher exposure prevented viral infection and replication. After exposure to 500 μg/m^3 DE alone or prior to infection, decreased expression of surfactant proteins (SP) A and D was observed. These proteins are part of the IFN-independent defense against influenza.

Similarly, Harrod et al. (2003, 097046) demonstrated decreased SP-A expression in the lungs following DE exposure and linked it to increased susceptibility to respiratory syncytial virus (RSV), the most common cause of respiratory infection in young children. C57BL/6 mice, a relatively RSV-resistant strain, were exposed via inhalation to DE at a concentration of 30 or 1,000 μg/m^3 PM 6h/day for 7 consecutive days prior to intratracheal viral inoculation. Gaseous copollutants ranged from 2.0-43.3 ppm for NO_X (~ 90% NO), 0.94-29.0 ppm CO, and 8.3-364.9 ppb SO_2. Exposure to 30 μg/m^3 DE did not induce a statistically significant increase in BALF cell numbers compared to air-treated, infected animals. However, distinct consolidated inflammatory infiltrates were observed in the peribronchial regions of RSV-infected animals exposed to this concentration, along with alterations in Clara cell morphology, decreased CCSP production by these cells, and occasional regional myofibril layer thickening. These changes were more pronounced in RSV-infected animals exposed to 1000 μg/m^3, and the higher concentration also resulted in significant increases in inflammatory cells, predominantly macrophages, in both uninfected and infected mice compared to air-exposed controls. Both doses elicited significant levels of TNF-α and IFN-γ in the lungs of infected animals, but decreased levels of SP-A. Consistent with this study's finding of decreased SP-A and increased viral gene and inflammatory cytokine expression after DE exposure, SP-A$^{-/-}$ mice demonstrate decreased clearance of RSV concordant with increased lung inflammation (Levine et al., 1999, 156687). Thus, DE may enhance susceptibility to respiratory viral infections by reducing the expression and production of SP (Ciencewicki et al., 2007, 096557; Harrod et al., 2003, 097046), although the contribution of gaseous copollutants, in some instances concentrated 1,000 times, should be considered for both studies. SP are also essential for clearance of other pathogens, including group *B Streptococcus* (GBS), *Haemophilus influenzae*, and *P. aeruginosa* (LeVine and Whitsett, 2001, 155928).

A reduction in host defense molecules and an increase in viral entry sites was observed by Gowdy et al. (2008, 097226) after BALB/c mice were exposed to HEPA filtered room air or DE at 0.5 or 2.0 mg/m^3 for 4hr/day for one or five consecutive days [O_2 (%) 21.0±0.10 or 20.7±0.09, CO (ppm) 1.7±0.15 or 5.4±0.07, NO_X (ppm) 2.0±0.36 or 7.4±0.61, SO_2 (ppm) 0.0±0.0 or 0.4±0.3, number median (nm) 96.2±2 or 97±2, volume median (nm) 238±2 or 249±2, OC/EC (wt ratio) 0.4±0.04 or 0.4±0.07 for the 0.5 or 2.0 mg/m^3 exposures, respectively]. One of the more notable features of this study was the observation that effects of extended exposure to the lower concentration (0.5 mg/m^3 for 5 days) tended to persist beyond 18 h post-exposure. Exposure to DE significantly increased BALF neutrophils in the higher exposure group, and this response persisted beyond 18 h only after the five day exposure. An increase in ICAM-1 expression (a viral entry site) was observed in both exposure groups, and was persistent in the lower concentration group after a 5-day exposure. Persistently elevated expression of pro-inflammatory cytokines IL-6 and TNF-α and pro-allergic cytokine IL-13 was observed after five days of low concentration exposure. Non-statistically significant effects of either concentration or exposure regimen included increased IFN-γ and MIP-2. Host defense molecules CCSP, SP-A and SP-D were decreased after either exposure regimen, persisting beyond 18 h in the low concentration group.

Taken together, these data suggest that exposure to DE can weaken host defenses, in some cases persistently. A role for PM in these responses is supported by studies demonstrating changes in host defense molecules and viral entry sites in vitro consistent with those observed in vivo. In lung epithelial cells, DE particles increased the mRNA expression of ICAM-1, LDL and platelet-activating factor (PAF) receptors, which can act as receptors for viruses or bacteria (Ito et al., 2006, 096648). DE particles may therefore enhance the susceptibility to infection by the upregulation of bacterial and viral invasion sites in the lungs. Expression of the β-defensin-2 gene, which is one antimicrobial mechanism of host defense in the airway, was significantly inhibited by V and not Ni or Fe in airway epithelial cells incubated with aqueous leachate of ROFA (Klein-Patel et al., 2006, 097092).

Immunosuppressive Effects of PM

Diesel Exhaust

DE may affect systemic immunity. Decreased thymus weight was observed in female F344 rats exposed to 300 μg/m^3 DE for 1 wk by Reed et al. (2004, 055625). Concentrations of gases for this PM concentration were reported to be approximately 16.1 ppm for NO, 0.8 ppm for NO_2, 9.8 ppm for CO, and 115 ppb for SO_2. Long-term responses are discussed in Section 7.3.8.

Summary of Toxicological Study Findings for Host Defense

Toxicological studies demonstrate that short-term inhalation exposures to CAPs and DE, but not gasoline exhaust or wood smoke, can increase susceptibility to infection by bacterial and viral pathogens. While gaseous copollutants may be contributing factors, a role for particles is demonstrated by studies utilizing IT instillation exposure and in vitro studies of PM where biomarkers parallel those observed in vivo. Although ethical considerations limit controlled exposure studies in humans, epidemiologic evidence reflects an association between most PM size fractions and hospital admissions for respiratory infections. Importantly, toxicological studies demonstrate impaired host defense against the etiological agents of influenza, pneumonia (*S. pneumoniae*), and bronchiolitis (RSV), which are commonly reported respiratory morbidities associated with PM.

6.3.8. Respiratory ED Visits, Hospital Admissions and Physician Visits

The epidemiologic evidence presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) linking short-term increases in PM concentration with respiratory hospitalizations and ED visits was consistent across studies. Recent investigations provide further support for this relationship, with larger effect estimates observed among children and older adults. However, effect estimates are clearly heterogeneous, with evidence of both regional and seasonal differences at play.

Excess risk estimates for hospitalizations or ED visits for all respiratory diseases combined, reported in studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) fell within the range of approximately 1-4% per 10 μg/m^3 increase in PM_{10}. On average, excess risks for asthma were higher than excess risks for COPD and pneumonia. Associations with $PM_{2.5}$ (including PM_1) and $PM_{10-2.5}$ were also reported in the limited body of evidence reviewed in the 2004 AQCD. Excess risk estimates fell within the range of approximately 2.0-6.0% per 10 μg/m^3 increases in $PM_{2.5}$ or $PM_{10-2.5}$ for all respiratory diseases combined as well as COPD admissions. Larger estimates were reported for asthma admissions. Many of the associations of respiratory admissions and ED visits with short-term $PM_{2.5}$ concentration were statistically significant. The associations with $PM_{10-2.5}$ were less precise with fewer reaching statistical significance (U.S. EPA, 2004, 056905). Finally, several studies reviewed in the 2004 AQCD reported associations of PM with outpatient physician visits, suggesting that the population impacted by short-term increases in PM is not restricted to those admitted to the hospital or seeking medical attention through an ED.

Table 6-13. Description of ICD-9 and ICD-10 codes for diseases of the respiratory system.

Description	ICD 9 Codes	ICD 10 Codes
Diseases of the Respiratory System	460-519	J00-J99
Asthma	493	J45
COPD and allied conditions	490-496 (asthma, chronic bronchitis, emphysema, bronchiectasis, extrinsic allergic alveolitis)	
Chronic lower respiratory diseases		J40-J47 (bronchitis, emphysema, other COPD, asthma, status asthmaticus, bronchiectasis)
Acute Respiratory Infections	460-466 (common cold, sinusitis, pharyngitis, tonsillitis, laryngitis & tracheitis, bronchitis & bronchiolitis)	
Acute Upper Respiratory Infections		J00-J06 (common cold, sinusitis, pharyngitis, tonsillitis, laryngitis & tracheitis, croup & epiglottitis)
Acute bronchitis and bronchiolitis	466	J20-J22
Allergic Rhinitis	477	J30.1
Pneumonia	480-486	J13-J18
Wheezing	786.09	

Hospital admissions or ED visits for respiratory diseases and ambient concentrations of PM have been the subject of more than 90 peer-reviewed research publications since 2002 (Annex E). Included among these new publications are several large single-city and multicity studies. These new studies complement those reviewed in the 2004 AQCD by examining the effect of several PM size fractions and components on increasingly specific disease endpoints, as well as evaluating the presence of effect modification by factors such as season and region.

Specific design and methodological considerations of the large and multicity studies included in this review were discussed previously (Section 6.2.10). Like the CVD endpoints discussed, the respiratory endpoints examined in these studies were heterogeneous and approaches to selecting cases for inclusion in the studies were varied. ICD codes commonly used in hospital admission and ED visits studies for diseases of the respiratory system are found in Table 6-13.

6.3.8.1. All Respiratory Diseases

Findings from new studies of PM and respiratory hospitalization and ED visits among children are summarized in Figure 6-10. Results from new studies of adults are summarized in Figure 6-11. Information on the PM concentrations during the relevant study periods is found in Table 6-14.

Children

Barnett et al. (2005, 087394) used a case-crossover design to study respiratory hospital admissions (ICD-9 460-519) of children (age groups 0, 1-4, and 5-14 yr) in seven cities in Australia and New Zealand from 1998 to 2001. All respiratory diseases (ICD10 J00-J99) except Mendelson's Syndrome, post-procedural disorders, asphyxia and certain other symptoms (ICD10 codes J95.4-J95.9, R09.1, R09.8) were included in the study. In addition, scheduled admissions and transfers from other hospitals were excluded. Using an a priori lag (0- to 1-day avg), increases in respiratory hospital admissions of 2.0% (95% CI: -0.13 to 4.3) among infants <1 yr old, 2.3% (95% CI: 1.9-7.3) among children 1-4 yr old and 2.5% (95% CI: 0.1-5.1) among children 5-14 yr old per 10 $\mu g/m^3$ increase in 24-h avg PM_{10} were observed. Increases of 6.4% (95% CI: 2.7-10.3) among infants <1 yr and 4.5% (95% CI: 1.9-7.3) among children 1-4 yr per 10 $\mu g/m^3$ increase in $PM_{2.5}$ were observed.

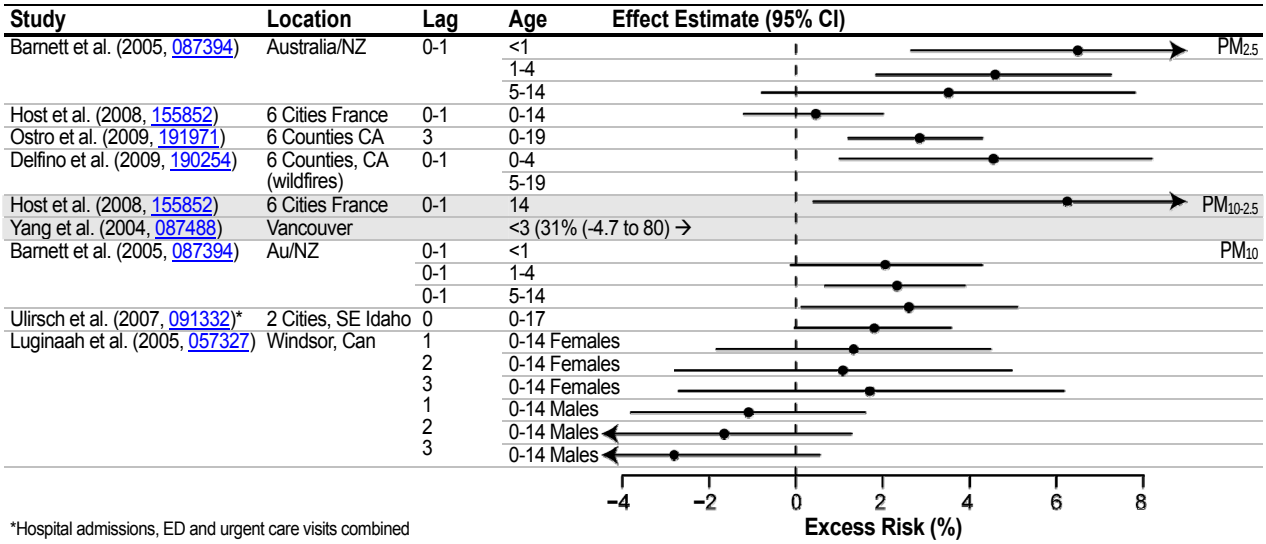
Ostro et al. (2009, 191971) studied the effect of $PM_{2.5}$ and components on respiratory disease (ICD9 460-519) hospitalizations among children <19 yr from 2000 to 2003 in six counties in California. The nine components examined (EC, OC, nitrates, sulfates, Cu, Fe, K, Si and Zn), were chosen because they made up relatively large proportion of $PM_{2.5}$, had a signal to noise ratio >2, or

the majority of their values were greater than the level of detection. Single day lags of 0-3 days were evaluated. The largest risks were observed at lag 3 days for $PM_{2.5}$ (2.8% [95%CI: 1.2-4.3] per 10 $\mu g/m^3$), EC (5.4% [95% CI: 0.8-10.3] per IQR) and Fe (4.7% [95% CI: 2.2-7.2] per IQR increase). Although not as great, positive associations were also observed for OC, SO_4^{2-}, nitrate, Cu and Zn.

In a study of $PM_{2.5}$ from wildfires in California during 2003, Delfino et al. (2009, 191994) evaluated conducted stratified analyses comparing $PM_{2.5}$ associations pre-, post- and during the wildfires. Four age groups (0-4, 5-19, 20-64 and ≥65 yr) were considered in these analyses. Authors found increased respiratory disease admissions in the periods before (2.6% [95%CI: -5.4 to 11.3]) and during (2.7% [95%CI: -1.6 to 7.6]) the wildfires among children 5-19 yr old, but not after the wildfire period. Among younger children (0-4 yr), hospital admissions were increased during fire periods (4.5% [95% CI: 1-8.2]), but not before or after the wildfire period. Estimated zip code level $PM_{2.5}$ concentrations were 90 $\mu g/m^3$ and 75 $\mu g/m^3$ during heavy and light smoke conditions, respectively, compared to 20 $\mu g/m^3$ during non-fire periods.

In the study of six cities in France described previously (PSAS), investigators report a change of 0.4% (95%CI: -1.2 to 2) per 10 $\mu g/m^3$ increases in $PM_{2.5}$ for all respiratory diseases combined (ICD-10: J00-J99) among children from 0-14 yr old (Host et al., 2008, 155852). The same study reported a larger increase associated with $PM_{10-2.5}$ of 6.2% (95% CI: 0.4-12.3, 0-1 day avg) per 10 $\mu g/m^3$ increase among children. A relatively large effect for $PM_{10-2.5}$ (31% [95% CI: -4.7 to 80]) was also observed in a single-city study of children <3 yr in Vancouver (Yang et al., 2004, 087488). The non-significant $PM_{2.5}$ effect estimates were not presented in the publication. Luginaah et al. (2005, 057327) did not observe significant increases in respiratory hospitalizations with increasing PM_{10} concentrations among male or female children in Ontario Canada, while Ulirsch et al. (2007, 091332) reported increased admissions for respiratory hospitalizations, ED and urgent care visits combined among children <17 yr in association with PM_{10}.

As shown in Figure 6-10, studies of respiratory hospitalizations or ED visits reported increased risks to children in association with all size fractions. However, increased risk among boys was not observed in Ontario (Luginaah et al., 2005, 057327). Estimates are imprecise and it is not clear if associations with $PM_{2.5}$, $PM_{10-2.5}$, or both are driving associations observed with PM_{10}.



*Hospital admissions, ED and urgent care visits combined

Figure 6-10. Excess risk estimates per 10 $\mu g/m^3$ 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} concentration for ED visits and HAs for respiratory diseases in children. Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. or Canada.

Adults and All Ages Combined

In the study of four million ED visits from 31 hospitals in Atlanta described previously, SOPHIA investigators reported an excess risk of 1.3% (95% CI: 0.4-2.1, lag 0-2) per 10 $\mu g/m^3$ increase in 24-h avg PM_{10} for ED visits for respiratory causes combined (ICD-9: 460-466, 477, 480-486, 491-493, 496, 786.09) among all ages during January 1993-August 2000 (Peel et al., 2005, 056305). $PM_{2.5}$, $PM_{10-2.5}$, UF number count and $PM_{2.5}$ components (SO_4^{2-}, acidity, EC, OC, and an index of water-soluble transition metals) were available for inclusion in analyses beginning August 1, 1998. Excess risks of 1.6% (95% CI: -0.003 to 3.5) per 10 $\mu g/m^3$ increase in 24-h avg $PM_{2.5}$ and 0.6% (95% CI: -3.6 to 5.1) per 10 $\mu g/m^3$ increase in $PM_{10-2.5}$ were reported. Weaker, less precise associations with components were reported and no increase with UF PNC was observed.

Analyses with four additional years of data were conducted and more recently reported by SOPHIA investigators (Tolbert et al., 2007, 090316). Single-pollutant results are included in Figure 6-11. The effect of PM_{10} remained with the additional years of data, while the effect of $PM_{2.5}$ was diminished and a decrease in ED visits with $PM_{10-2.5}$ was observed. The association of PM_{10} with respiratory disease ED visits was robust to adjustment for O_3, CO and NO_2. In another recent analysis using SOPHIA data from 1998 through 2002 to compare source apportionment methods, Sarnat et al. (2008, 097972) reported that $PM_{2.5}$ from mobile sources, $PM_{2.5}$ from biomass burning and SO_4^{2-}-rich secondary $PM_{2.5}$ were associated with respiratory ED visits and associations were robust to the choice of the method. Excess risks were statistically significant, ranging from approximately 2-4%, depending on the method.

In a French multicity study, larger increases were observed in association with 24-h avg $PM_{10-2.5}$ concentration compared to $PM_{2.5}$ concentration among adults as well as children. Among adults 15-64 yr, investigators reported increases in respiratory hospitalizations of 0.8% (95%CI: -0.7 to 2.3) and 2.6% (95%CI: -0.5 to 5.8) per 10 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$, respectively (lag 0-1 days) (Host et al., 2008, 155852).

In a study of respiratory hospital admission and ED visits (ICD-9 Codes 460-519) among all ages conducted in Spokane, Washington, no associations were observed with any size fraction of PM considered (e.g., PM_1, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}) (Slaughter et al., 2005, 073854). Furthermore, several of the same investigators conducted a source apportionment analysis using daily $PM_{2.5}$ filter samples from the same residential monitor in Spokane (Schreuder et al., 2006, 097959). In this investigation, $PM_{2.5}$ from vegetative burning in the previous day (lag 1) was associated with respiratory hospital admissions (2.3% [95% CI: 0.9-3.8] per interquartile range increase in the source marker). In a study of $PM_{2.5}$ from wildfires in California during 2003, associations with respiratory hospitalizations were generally stronger relative to associations in the periods before and after the fires (Delfino et al., 2009, 191994). Among adults 20-64 yr, an increase of 2.4% (95% CI: 0.5-4.4 per 10 $\mu g/m^3$) was reported during the wildfire period compared to 0.9% (95%CI: -0.1 to 1.8 per 10 $\mu g/m^3$) for all periods combined (pre-, post- and during wildfires).

Luginaah et al. (2005, 057327) examined respiratory hospital admissions in relation to PM_{10} concentration across strata for age and gender and compared time series to case-crossover approaches. The results for all ages combined, which were relatively precise, stratified by gender and all lags are presented in Figure 6-11; the largest estimates for PM_{10} were for adult males (15-64 yr old). Fung et al. (2005, 093262) did not report evidence of an association between respiratory admissions and 24-h PM_{10} concentration among adults <65 yr, in a study in Ontario, Canada, while Ulirsch et al. (2007, 091332) reported a significant positive association among all ages and adults (18-64 yr) in two Southeast Idaho cities for hospitalizations, ED and urgent care visits combined. This estimate was robust to adjustment for gaseous pollutants.

Older Adults

Among older adults, MCAPS investigators observed largely null findings for $PM_{2.5}$ and respiratory hospitalizations (ICD-9: 490-492, 464-466, 480-487) for the U.S. as a whole, but reported heterogeneity in effect estimates across the country that were explained by regional and seasonal factors (Bell et al., 2008, 156266). The nationwide excess risk of respiratory admissions with $PM_{2.5}$ was 0.22% (95% PI: -0.12 to 0.56, lag 0) (Bell et al., 2008, 156266). The largest increase was observed during the winter in the Northeast (1.76% [95% PI: 0.60-2.93], lag 0). Significant increases in respiratory admissions were also observed at lag 2. In an analysis of $PM_{10-2.5}$, MCAPS

investigators observed small imprecise increases in respiratory admissions with 24-h $PM_{10-2.5}$ concentration (0.33% [95% PI: -0.21 to 0.86, per 10 μg/m^3, lag 0]) (Peng et al., 2008, 156850), which decreased after adjustment for $PM_{2.5}$ (0.26% [95% PI: -0.32 to 0.84 per 10 μg/m^3 lag 0]). Associations with $PM_{2.5}$ increased (0.7% [95% PI: 0-1.5, lag 0]) or persisted (0.6% [95% PI: -0.2 to 1.25, lag 2]), after adjustment for $PM_{10-2.5}$.

Two recent MCAPS analyses evaluate the effect of $PM_{2.5}$ components on respiratory hospital admissions. Bell et al. (2009, 191997) analyzed a subset of MCAPS data restricted to 106 counties with data available for both long-term average concentrations of $PM_{2.5}$ components (Bell et al., 2007, 155683) and $PM_{2.5}$ total mass (1999-2005). The components evaluated included 20 chemicals with demonstrated toxicity or that contribute a large proportion of $PM_{2.5}$ mass (Al, NH_4^+, As, Ca, Cl, Cu, EC, OCM, Fe, Pb, Mg, Ni, NO_3^-, K, Si, Na^+, Ti, V, Zn). Increases in effect estimates of 511% (95% PI: 80.7-941) for EC, 223% (95% PI: 36.9-410) for Ni and 392% (95% CI: 46.3-738) for V per IQR increases in county-specific component fraction were observed. Associations were somewhat reduced and non-significant in two-pollutant models. When Queens or New York County were excluded, the association of V with hospital admissions lost significance. Associations were also diminished when alternative lag structures were considered.

Peng et al. (2009, 191998) linked data on hospital admissions for respiratory causes among older adults from 2000-2006 to daily air levels from the STN in 119 counties in which both sets of data were available. Chemical constituents evaluated were SO_4^{2-}, nitrate, Si, EC, OCM, sodium and ammonium ions. Single-day lags of 0-2 days were considered. These investigators found a 0.82% increase (95% PI: 0.22-1.44) per IQR increase in same day OCM. After adjustment for the other components, a 1.01% (95% PI: 0.04-1.98, lag 0) increase in respiratory admissions per IQR increase OCM was observed.

French PSAS investigators reported a non-significant increase in hospitalizations for respiratory diseases (ICD-10 J00-J99) with 24-h avg $PM_{10-2.5}$ among older adults. $PM_{2.5}$ estimates were also not significant (Host et al., 2008, 155852). Adjusted estimates from two-pollutant models were not presented. Positive associations of first hospitalization, overall hospitalizations and readmission for respiratory diseases and $PM_{10-2.5}$ were also reported among older adults in Vancouver (Chen et al., 2005, 087555). $PM_{10-2.5}$ was associated with an increase of 15% (95% CI: 4.8-22.8) in overall admissions per 10 μg/m^3. Increases associated with $PM_{10-2.5}$ were larger for readmissions compared to overall admissions. The association for $PM_{2.5}$ with overall admissions was 5.1% (95% CI: -4.9 to 13) and the association with readmissions was not larger. In this study, effect estimates for $PM_{10-2.5}$ and PM_{10} lost precision, but were robust to adjustment for gaseous pollutants, while the estimate for $PM_{2.5}$ was null after adjustment for gaseous pollutants. In Vancouver, Fung et al. (2006, 089789) report increased admissions of 1.8% (95% CI: -2.5 to 5.8) per 10 μg/m^3 increase in $PM_{2.5}$ and 3.8% (95% CI: 0-7.6) per 10 μg/m^3 increase in $PM_{10-2.5}$ (lag 0-1 day avg) among adults ≥65 yr.

In a multicity Australian study, Simpson et al. (2005, 087438) examined the association between $PM_{2.5}$ measured by nephelometry and respiratory hospital admissions (ICD-9 460-519) among older adults (≥65 yr) and reported significant associations (1.055 [95% CI: 1.008-1.1045], lag 0-1 day avg) from a meta-analysis combining effect estimates from all cities. Results from three statistical models were considered, including standard GAM, which produced similar results.

Delfino et al. (2009, 191994) reported that $PM_{2.5}$ from wildfire in California was associated with respiratory hospital admissions among older adults (3% 95% CI: 1.1-4.9 per 10 μg/m^3). In two analyses of data collected in Copenhagen, Denmark between 1999 and 2004, several size fractions including UF and accumulation mode (Andersen et al., 2008, 189651) and PM_{10} sources (Andersen et al., 2007, 093201) were investigated in relation to respiratory hospitalizations (J41-42, J43, J44-46) among adults >65 yr of age. Of the size fractions examined (NC total, NC median diameter of 12 nm [NC_{a12}], NC_{a23}, NC_{a57}, NC_{a100}, NC_{a212}, PM_{10}, $PM_{2.5}$) NC_{a212}, typically aged secondary long-range transported, NC_{a57} and PM_{10} were significantly associated with respiratory hospitalizations (Andersen et al., 2008, 189651). PM_{10} sources including biomass combustion, secondary inorganic compounds, oil combustion, and crustal were associated with respiratory hospitalizations (excess risks ranged from 3.5% to 5.4% per interquartile range, respectively) (Andersen et al., 2007, 093201). PM_{10} associations were diminished somewhat in two-pollutant models (Andersen et al., 2007, 093201; 2008, 189651); the authors note that it was difficult to separate the effects of PM_{10} and NC_{a212}, which were highly correlated in these data. $PM_{2.5}$ was not associated with respiratory hospitalizations in these data.

Results from other single-city studies offer somewhat consistent evidence for the effect of PM_{10} on respiratory admissions among older age groups. Ulirsch et al. (2007, 091332) found

increases in hospitalizations, ED and urgent care visits combined among this age group in two cities of Southeast Idaho. Two studies in Vancouver report increased admissions for respiratory causes with the largest effects observed for a 3-day ma (0-2 days) (Chen et al., 2005, 087555; Fung et al., 2006, 089789). Fung et al. (2005, 093262) observed non-significant increases in admissions with PM_{10} among older adults in Ontario, Canada, while another study conducted in Ontario (Luginaah et al., 2005, 057327) did not provide compelling evidence for an effect that was robust to method selection, although some increases among males were observed. Finally, a study of hospital admissions for cardiopulmonary conditions combined among older adults (≥ 65 yr) in Allegheny County, PA found a positive association with PM_{10} at lag 0 (Arena et al., 2006, 088631).

Effect estimates for adults (and combined age groups) as well as older adults are found in Figure 6-11. Effects observed in single-city studies are generally imprecise but most studies report positive associations. Regional and seasonal variation was observed with the largest effect estimate reported by Bell et al. (2008, 156266) in the Northeast during the winter. Although the number of studies examining components or sources was limited, EC, OC, Ni, V, and $PM_{2.5}$ from mobile sources were associated with increased respiratory admissions. Several additional studies conducted outside the U.S. and Canada reported positive associations of respiratory hospitalizations with PM_{10} for different age groups and lags (Bedeschi et al., 2007, 090712; Chen et al., 2005, 087555; Chen et al., 2006, 087947; Hanigan et al., 2008, 156518; Lai and Cheng, 2008, 180301; Larrieu et al., 2009, 180294; Middleton et al., 2008, 156760; Oftedal et al., 2003, 055623), $PM_{2.5}$ (Hinwood et al., 2006, 088976; Neuberger et al., 2004, 093249; Vigotti et al., 2007, 090711), BS (Bartzokas et al., 2004, 093252; Tecer et al., 2008, 180030) and with $PM_{10-2.5}$ (Tecer et al., 2008, 180030). Other studies reported no associations with PM_{10} (Vegni and Ros, 2004, 087448) or TSP (Llorca et al., 2005, 087825).

6.3.8.2. Asthma

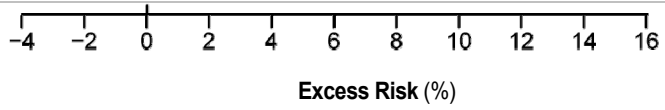
Results from multicity studies of hospital admissions and ED visits for asthma as well as single-city studies conducted in the U.S. and Canada are summarized in Figure 6-12. Studies reviewed in the 2004 AQCD are included for continuity. Concentrations of PM for the relevant study period are found in Table 6-14.

Children

SOPHIA investigators (Peel et al., 2005, 056305) reported that, of the PM mass indicators examined, the largest effect estimate observed using the a priori lag (0- to 2-day avg) was the association of PM_{10} with pediatric (2-18 yr) asthma ED visits (1.6% [95% CI: -0.2 to 3.4]). ED visits for both asthma (ICD-9: 493) and wheezing (ICD-9: 786.09) were included in their study. New York State DOH (2006, 090132) conducted a study comparing effect estimates for ED visits for asthma and 24-h $PM_{2.5}$ and 1-h $PM_{2.5}$ across two communities in New York City (the Bronx and Manhattan). No associations with 24-h $PM_{2.5}$ were reported for either borough for age categories 0-4 or 5-18 yr. Non-significant increases with 1-h maximum $PM_{2.5}$ were reported for the Bronx. Asthma hospital admissions (ICD-10 J45, J46, J44.8) in children <14 yr were examined in the Australia/New Zealand multicity study (Barnett et al., 2005, 087394). In this study, associations for asthma hospital admissions with $PM_{2.5}$ and PM_{10} were increased but imprecise.

Lin et al. (2002, 026067) used both time series and case-crossover approaches to investigate the influence of PM on asthma hospitalization in children, 6-12 yr old, in Toronto from 1981 to 1993. These authors report relatively small differences in results obtained through bi-directional case crossover and time series approaches, but indicate that unidirectional case-crossover methods may overestimate the relative risks. Single- to 7-day avg lags were investigated and estimates appeared to increase and then level off at the longer lags (0- to 2-day and 0- to 5-day lags are shown in Figure 6-12). Effect estimates for $PM_{2.5}$ are not easily distinguished from the null, but $PM_{10-2.5}$ is significantly associated with asthma admissions among boys and among girls. These associations were imprecise, but robust to adjustment for gaseous pollutants, among all children combined.

Study	Location	Lag	Age	Gender	Effect Estimate (95% CI)	
ADULTS OR ALL AGES COMBINED						
Peel et al. (2005, 056305)*	Atlanta, GA	0-2	All			$PM_{2.5}$
Tolbert et al. (2007, 090316)*	Atlanta, GA	0-2	All			
Slaughter et al. (2005, 073854)*	Spokane, WA	1	All			
Host et al. (2008, 155852)	6 Cities, France	0-1	15-64			
Delfino et al. (2009, 191994)	California Wildfires	0-1	20-64			
Peel et al. (2005, 056305)*	Atlanta, GA	0-2	All			$PM_{10-2.5}$
Tolbert et al. (2007, 090316)*	Atlanta, GA	0-2	All			
Slaughter et al. (2005, 073854)*	Spokane, WA	1	All			
Host et al. (2008, 155852)	6 Cities, France	0-1	15-64			
Peel et al. (2005, 056305)*	Atlanta, GA	0-2	All			PM_{10}
Tolbert et al. (2007, 090316)*	Atlanta, GA	0-2	All			
Luginaah et al. (2005, 057327)	Windsor, Can	1	All	Female		
		2	All	Female		
		3	All	Female		
		1	All	Male		
		2	All	Male		
		3	All	Male		
Slaughter et al. (2005, 073854)*	Spokane, WA	1	All			
		2	All			
		3	All			
Ulirsch et al. (2007, 091332)**	Idaho	0	All			
		0	18-64			
Fung et al. (2005, 093262)	Ontario, Can	0	<65			
		0-1	<65			
		0-2	<65			
OLDER ADULTS (65+ YR)						
Bell et al. (2008, 156266)	202 Counties, US	0				$PM_{2.5}$
		1				
		2				
	Winter, US	0				
	Winter, Northeast	0				
Host et al. (2008, 155852)	6 Cities, France	0-1				
Fung et al. (2006, 089789)	Vancouver, Can	0				
		0-2				
		0-4				
		0-6				
Chen et al. (2005, 087555)	Vancouver, Can	1				
		0-1				
		0-2				
Delfino et al. (2009, 191994)	California Wildfires	0-1				
Host et al. (2008, 155852)	6 Cities, France	0-1				$PM_{10-2.5}$
Peng et al. (2008, 156850)	108 Counties, US	0				
		1				
		2				
Fung et al. (2006, 089789)	Vancouver, Can	0				
		0-2				
		0-4				
		0-6				
Chen et al. (2005, 087555)	Vancouver, Can	1				
		0-1				
		0-2				
Fung et al. (2006, 089789)	Vancouver, Can	0				PM_{10}
		0-2				
		0-4				
		0-6				
Ulirsch et al. (2007, 091332)**	2 Cities in ID	0				
Chen et al. (2005, 087555)	Vancouver, Can	0				
		0-1				
		0-2				
Fung et al. (2005, 093262)	Ontario, Can	0				
		0-1				
		0-2				



Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. or Canada

* ED Visits

** Hospitalization, ED, and Urgent Care Visits Combined

Figure 6-11. Excess risks estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} for ED visits and HAs for respiratory diseases among adults.

Although Ostro et al. (2009, 191971) presented estimates for all respiratory diseases combined, these authors note that $PM_{2.5}$ and its components were associated with asthma hospitalizations among the children in six counties of Los Angeles studied. Delfino et al. (2009, 191994) examined the association of $PM_{2.5}$ before, during, and after wildfires in California with asthma hospitalizations among age and gender subgroups. Associations were observed for children 0-4 yr among children during the wildfire period (8.3% [95% CI: 2.1-14.9] per 10 $\mu g/m^3$), but not before or after the wildfire period. For older children, 5-19 yr, non-significant increases in asthma hospitalizations were found before the wildfire period, but not during or after the fires.

Hirshon et al. (2008, 180375) studied hospital admissions and ED visits by children 0-17 yr old in Baltimore, MD from June 2002-November 2002, in relation to Zn as a component in $PM_{2.5}$. Single day lags from 0-2 days were tested with the highest estimates observed for the previous day. A 23% (95% CI: 7-41) increase in admissions was observed comparing medium (8.63-20.76 ng/m^3) concentrations on the previous day to low concentrations (<8.63 ng/m^3) on the previous day. Previous day high concentration (>20.76 ng/m^3) was associated with an increase in admissions of 16% (95% CI: -3 to 39) compared to previous day low concentration. Zinc associations were robust to adjustment for EC, CO, NO_2, Ni, and Cr. However, evidence of effect modification by EC and NO_2 at lags 1 and 2 was observed.

Mohr et al. (2008, 180215) used measurements of EC, O_3, SO_2, and total NO_X from the EPA supersite in St. Louis for June 2001-May 2003, to examine the association of EC, temperature and season with asthma ED visits among children 2-17 yr old. The association of EC with asthma ED visits varied by age, season and weekday versus weekend. The largest associations were observed for 2-5 yr olds during the fall weekends (3% [95% CI: 1-5] per 0.1 $\mu g/m^3$) and 11-17 yr olds during winter weekdays (3% [95% CI: 0-5] per 0.1 $\mu g/m^3$) and summer weekends (9% [95% CI: 2-17] per 0.1 $\mu g/m^3$). Investigators also report that temperature modified the effect of EC after adjusting for gaseous copollutants, such that the association of ED visits with EC increased with increasing temperature during the summer and increased with decreasing temperature during the winter. Authors attribute the temperature modification to time-activity patterns among this age group.

Sinclair and Tolsma (2004, 088696) investigated respiratory ambulatory care visits using ARIES data in Atlanta, GA (also used by SOPHIA investigators) and health insurance records. These authors evaluated three 3-day ma lags (0-2, 2-5 and 6-8 days) and reported relative risks, with no confidence intervals, for significant results only (not included in Figure 6-12). For childhood asthma outpatient visits, OHC, $PM_{10-2.5}$, PM_{10}, EC and OC were significantly associated with ambulatory care visits at lags 0-2 or 2-5 days.

A study in Anchorage used medical records to examine effects of particle exposure on pediatric asthma outpatient visits, inpatient visits and prescriptions for short-acting inhalers (Chimonas and Gessner, 2007, 093261). Authors examined Medicaid claims for asthma-related and lower respiratory infection visits among children less than 20 yr of age for 5 yr (approximately 25,000 children were enrolled in Medicaid each year between 1999 and 2003). Citing work done in the mid-1980's, the authors describe their city's particles as arising primarily from natural, geologic sources (PM_{10}), and to a lesser extent from local automotive emissions ($PM_{2.5}$) (Pritchett and Cooper, 1985, 156886). Using GEE in a time-series analysis of daily and weekly effects of particle exposure on health outcomes, the authors found that each 10 $\mu g/m^3$ increase in 24-h avg PM_{10} was associated with a 0.6% increase (95% CI: 0.1-1.3) in outpatient visits for asthma. The same increase in weekly PM_{10} concentration resulted in a 2.1% increase (95% CI: 0.4-3.8) in asthma visits, after adjustment for gaseous pollutants. No meaningful associations were observed for $PM_{2.5}$.

In Copenhagen, Denmark, Anderson et al. (2007, 093201) found an association between PM_{10} attributed to vehicle emissions and asthma hospitalizations among children 5-18 yr (5.4% 95% CI: 0.57-22.9 per 10 $\mu g/m^3$, 0- to 5-day avg). In an analysis of size distribution and number concentration, accumulation mode particles were most strongly associated with asthma admissions (8% [95% CI: 0-17] per 495 particles/cm^3, lag 0-5). (Andersen et al., 2008, 189651). In Helsinki, Halonen et al. (2008, 189507) examined the association of various size fractions of PM (e.g., Aitken, accumulation mode, $PM_{2.5}$, $PM_{10-2.5}$) with ED visits for asthma among children <15 yr. These authors evaluated lags 0-5 and noted a different lag structure depending on age with children experiencing greater effects at lags 3-5 days compared to adults at lag 0. Aitken, accumulation mode particles and traffic-related PM were significantly and most strongly associated with asthma visits among children, while no association with $PM_{10-2.5}$ was observed in this age group.

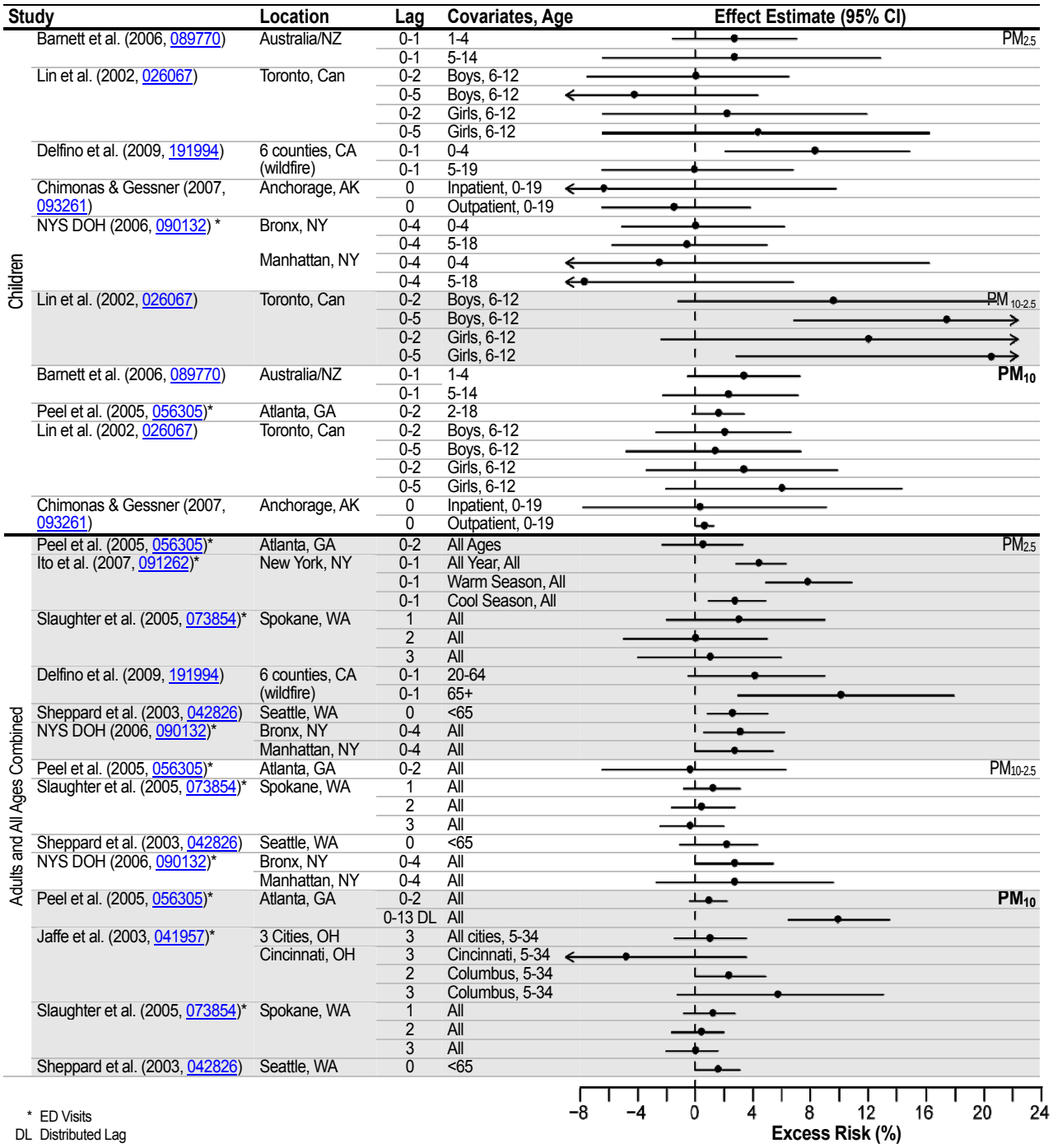


Figure 6-12. Excess risk estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} for asthma ED visits and HAs. Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. or Canada.

Adults and All Ages Combined

Results from the Atlanta SOPHIA study based on the a priori models examining a 3-day ma (lag 0-2 days) revealed no statistically significant associations with asthma (ICD-9 493, 786.09)

among all ages for any of the PM metrics studied (e.g., $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, UF PNC, PM components) (Peel et al., 2005, 056305). However, the 14-day unconstrained distributed lag model produced an excess risk of 9.9% (95% CI: 6.5-13.5 per 10 μg/m^3 PM_{10}). The authors note that associations of $PM_{2.5}$ and OC with asthma tended to be stronger during the warmer months. Sinclair and Tolsma (2004, 088696) report a significant association between adult outpatient visits for asthma and UFPs, but not other PM size fractions (not included in Figure 6-12 because only significant results were presented).

Jaffe et al. (2003, 041957) examined the effects of ambient pollutants (PM_{10}, O_3, NO_2 and SO_2) during the summer months (June through August) on the daily number of ED visits for asthma among Medicaid recipients aged 5-34 yr from 1991 to 1996 in Cincinnati, Columbus, and Cleveland. Lags 1 to 3 were tested and only statistically significant lags were presented. For all cities combined, the overall effect estimate for 24-h avg PM_{10} was 1.0% (95% CI: -1.44 to 3.54 per 10 μg/m^3 increase). The effect estimate for Cleveland was the only significantly elevated estimate (2.3% [95% CI: 0.0-4.9] per 10 μg/m^3 increase) when the cities were examined independently. The authors reported results from analyses indicating a possible concentration response for O_3, but no consistent effects for PM_{10}.

In New York City, Ito et al. (2007, 156594) examined numbers of ED visits for asthma among all ages (ICD-9 493) in relation to pollution levels from 1999 to 2002; several weather models were evaluated. Although the association with NO_2 was the strongest, $PM_{2.5}$ was significantly associated with asthma ED visits in each weather model (strongest during the warm months) and remained significant after adjustment for O_3, NO_2, CO and SO_2. Slaughter et al. (2005, 073854) reported no associations with ED visits or hospitalizations for asthma, among all ages, in Spokane, Washington for the PM size fractions studied (PM_1, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$). An association with CO, which the authors attribute to combustion related pollution in general, was observed. The effect of 24-h avg and 1-h max $PM_{2.5}$, $PM_{10-2.5}$, EC and OC on ED visits for asthma among all ages combined, comparing two communities in New York City was investigated (ATSDR, 2006, 090132). In the Bronx, an increase in visits of 3.1% (95% CI: 0.6-6.2 per 10 μg/m^3) was observed in relation to 24-h avg $PM_{2.5}$. For $PM_{10-2.5}$, an increase of 2.7% (95% CI: 0.0-5.4) was observed in the Bronx. Smaller, less precise estimates were observed for Manhattan. Increased asthma visits were observed with OC, EC and total metals. In the Bronx, the association of 1-h max $PM_{2.5}$ with ED visits was larger than the association with 24-h $PM_{2.5}$ when standardized to the mean concentration for both communities and was generally robust to adjustment for copollutants.

Delfino et al. (2009, 191994) examined the association of $PM_{2.5}$ before, during and after wildfires in California with asthma hospitalizations among age and gender subgroups. The increase among older adults >65 yr of 10% (95% CI: 3-17.8 per 10 μg/m^3) was larger than the increase among adults 20-64 yr of 4.1% (95% CI: -0.5 to 9 per 10 μg/m^3). For older adults, the association was stronger during the wildfire period compared to the pre-wildfire period and did not diminish during the post-wildfire period.

Effect estimates from studies of hospital admissions and ED visits for asthma are summarized in Figure 6-12. Associations with $PM_{2.5}$ concentration among children are imprecise and not consistently positive across different age groups and lags. Findings from two studies of $PM_{10-2.5}$ (Sinclair and Tolsma, 2004, 088696), as well as PM_{10} studies both show positive associations, although estimates lack precision. Among adults and adults and children combined, associations of asthma hospital admissions and ED visits with $PM_{2.5}$ concentration were observed in most studies. Positive, non-significant associations of $PM_{10-2.5}$ concentration with asthma admissions and ED visits were observed in some studies of adults. Again, PM_{10} estimates are more consistently positive and precise compared to other size fractions. Associations were observed with several $PM_{2.5}$ components (e.g., EC, OC and Zn) and sources (e.g., traffic, wildfires). Many factors (e.g., the underlying distribution of individual sensitivity and severity, medication use and other personal behaviors) can influence the lag time observed in observational studies (Forastiere et al., 2008, 186937). Excess risk estimates for asthma were generally sensitive to choice of lag and increase with longer or cumulative lags times. Most additional single-city studies conducted in Europe, South America and Asia, have investigated the associations of asthma hospitalizations, ED visits or doctor visits and most have reported evidence of an association with TSP (Arbex et al., 2007, 091637; Migliaretti and Cavallo, 2004, 087425; 2005, 088689), PM_{10} (Bell et al., 2008, 156266; Bell et al., 2008, 091268; Chardon et al., 2007, 091308; Chen et al., 2006, 087947; Erbas et al., 2005, 073849; Galan et al., 2003, 087408; Jalaludin et al., 2004, 056595; Kim et al., 2007, 092837; Ko et al., 2007, 091639; Kuo et al., 2002, 036310; Lee et al., 2002, 034826; Lee et al., 2006, 090176) and $PM_{2.5}$ (Chardon et al., 2007, 091308;

Ko et al., 2007, 091639; Ko et al., 2007, 092844) while a few have not shown an association with PM_{10} (Larrieu et al., 2009, 180294; Masjedi et al., 2003, 052100; Tsai et al., 2006, 089768; Yang and Chen, 2007, 092847; Yang et al., 2007, 092848).

6.3.8.3. Chronic Obstructive Pulmonary Disease

Results from multicity studies of hospital admissions and ED visits for COPD as well as single-city studies conducted in the U.S. and Canada are summarized in Figure 6-13. Studies reviewed in the AQCD are included in the figure for continuity. Concentrations of PM for the relevant study period are found in Table 6-14.

In a study of Medicare recipients in 204 U.S. counties, Dominici et al. (2006, 088398) reported an overall increase of about 1% in COPD hospitalizations (ICD-9 490-492) associated with 24-h avg $PM_{2.5}$, with the largest effects at lags 0 and 1. In this study effect estimates were heterogeneous across the U.S. with a significant increase of about 4% observed in the Southeast at lag 0. In another study using Medicare data in 36 U.S. cities (1986-1999) short-term exposure to PM_{10} was associated with an increase in COPD hospital admissions (ICD-9 490-496, excluding 493) of 1.47% (95% CI: 0.93-2.01, lag 1) during the warm season (Medina-Ramon et al., 2006, 087721). A smaller effect was observed during the cold season.

In Atlanta, SOPHIA investigators reported a comparably sized effect estimate for COPD (ICD-9 491, 492, 496) and 24-h avg $PM_{2.5}$ (1.5% [95% CI: -3.1 to 6.3], 0- to 2-day avg]). The association of PM_{10} with COPD reported by Peel et al. (2005, 056305) was 1.8% (95% CI: -0.6 to 4.3). No associations were observed for $PM_{10-2.5}$, UF or $PM_{2.5}$ components. Slaughter et al. (2005, 073854) reported no associations between any size fraction of PM in Spokane, Washington ($PM_{2.5}$, $PM_{10-2.5}$, PM_{10}) and COPD (ICD-9 491, 492, 494, 496). In contrast, Chen et al. (2004, 087262) reported increases in COPD admissions (ICD-9 490-492, 494, 496) for $PM_{2.5}$ (17.1% [95% CI: 4.6-31.0], 0- to 2-day avg), $PM_{10-2.5}$ (10.0% [95% CI: -1.2 to 22.8, 0- to 2-day avg]), and PM_{10} (16.5% [95% CI: 6.88-27.02], 0- to 2-day avg]). However, the estimates for PM metrics were diminished after adjustment for NO_2.

Delfino et al. (2009, 191994) examined the association of $PM_{2.5}$ from the wildfires of 2003 in California with COPD hospitalizations among age and gender subgroups. Among older adults (≥65 years), associations were similar across pre-, post- and wildfire periods with none reaching significance. The increase for all periods combined in this age group was 1.9% (95% CI: -0.6 to 4.4, per 10 $\mu g/m^3$). Michaud et al. (2004, 188530) reported an association for asthma and COPD ED visits combined with PM_1 (lag 1) in Hilo, Hawaii in a study designed to investigate the effect of volcanic fog.

Halonen et al. (2008, 189507) conducted a study of ED visits for COPD and asthma combined (J41, J44-J46) among adults 15-64 yr and older adults >65 yr. These authors examined the effects of Aitken mode particles, accumulation mode particles, $PM_{2.5}$ and $PM_{10-2.5}$ as well as several sources of $PM_{2.5}$ (traffic, long range transported particles, road dust and coal/oil combustion). Concentrations, lagged from 0-5 days, were examined and the largest effects among older adults were observed in association with concurrent day $PM_{2.5}$, $PM_{10-2.5}$, accumulation mode particles, NO_2, and CO concentrations. The $PM_{2.5}$ association was diminished with adjustment for UFPs, NO_2 and CO. A similar diminishment was observed when $PM_{10-2.5}$ was adjusted for $PM_{2.5}$, NO_2 and CO. However, traffic related particles and long range transported particles (e.g., accumulation mode particles such as carbon compounds, sulfates and nitrates from central Europe and Russia) were associated with COPD and asthma among older adults. This same research group conducted additional analyses of hospital admissions using the same PM metrics focusing on older adults (≥65 yr) (Halonen et al., 2009, 180379). The $PM_{2.5}$ results and lag structure were similar to the earlier ED visit study. The strongest effect was for accumulation mode particles with COPD/asthma admissions. Traffic related $PM_{2.5}$ was associated with COPD/asthma admissions at lag 1 while no effect was observed with concurrent day concentration. Long range transported particles and road dust were also associated with admissions for asthma and COPD.

With the exception of one study conducted in Spokane Washington (Slaughter et al., 2005, 073854), associations have been consistently observed for $PM_{2.5}$ and PM_{10} with COPD in multicity and single-city studies conducted in the U.S. and Canada. Associations with $PM_{10-2.5}$ are fewer and less consistent. A study that examined seven single-day lags in association with pooled COPD and asthma ED visits in Finland reported that $PM_{2.5}$, $PM_{10-2.5}$, traffic sources as well as gaseous pollutants

had a more immediate effect in older adults (lags 0 and 1) compared to children experiencing asthma (3- to 5-day lags) (Halonen et al., 2008, 189507). Larger estimates at shorter lags were not observed consistently across other studies. Most single-city studies conducted outside of the U.S. or Canada focused on PM_{10} (Chiu et al., 2008, 191989; Hapcioglu et al., 2006, 093263; Ko et al., 2007, 091639; Ko et al., 2007, 092844; Martins et al., 2002, 035059; Masjedi et al., 2003, 052100; Sauerzapf et al., 2009, 180082; Yang and Chen, 2007, 092847).

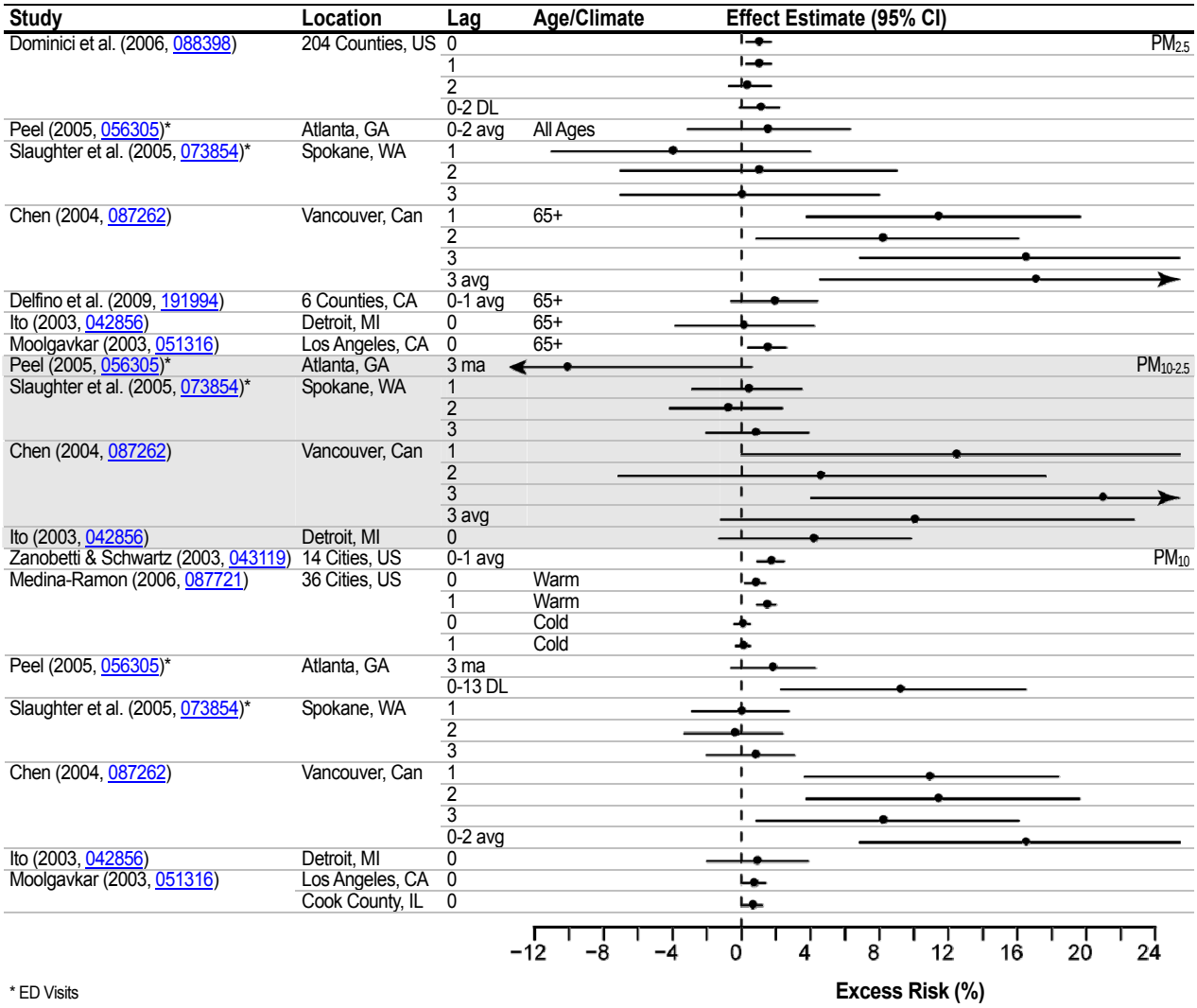


Figure 6-13. Excess risks estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} for COPD ED visits and HAs among older adults (65+ yr, unless other age group is noted). Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S. or Canada.

6.3.8.4. Pneumonia and Respiratory Infections

Results from multicity studies of hospital admissions and ED visits for respiratory infection as well as single-city studies conducted in the U.S. and Canada are summarized in Figure 6-14. The figure includes studies of respiratory infection reviewed in the 2004 AQCD. Concentrations of PM for the relevant study period are found in Table 6-14.

Children

In the study of seven cities in Australia and New Zealand, associations of $PM_{2.5}$ with pneumonia and acute bronchitis (ICD-10 J12-J17, J18.0, J18.1, J18.8, J18.9, J20, J21) were observed among infants <1 yr old (4.54% [95% CI: 0.00-9.20]) and children 1-4 yr old (6.44% [95% CI: 0.26-12.85]) (Barnett et al., 2005, 087394). Although quantitative results were only presented for all respiratory diseases combined, Ostro et al. (2009, 191971) examined several specific respiratory diseases including acute bronchitis and pneumonia. They reported that $PM_{2.5}$ and its components were more strongly associated with these endpoints compared to other respiratory diseases. Delfino et al. (2009, 191994) reports imprecise increases in admissions among children during wildfire periods for acute bronchitis and bronchiolitis, as well as pneumonia.

Inpatient and outpatient visits for lower respiratory tract infections among children in Anchorage, Alaska, were not associated with $PM_{2.5}$ or PM_{10} (Chimonas and Gessner, 2007, 093261). Lin et al. (2005, 087828) observed associations of respiratory infections (ICD-9 464, 466, 480-487) with $PM_{10-2.5}$ and PM_{10} that persisted after adjustment for gaseous pollutants among subjects <15 yr old living in Toronto. Analyses were stratified by gender and both single and multiple day lags were examined (4- and 6-day avg were presented). The largest significant effect estimates were for $PM_{10-2.5}$. The size of the $PM_{2.5}$ estimate varied by gender and was sensitive to the choice of lag. $PM_{2.5}$ results were not generally robust to adjustment for gases.

All Ages and Older Adults

SOPHIA investigators examined ED visits for upper respiratory tract infections (URI) (ICD-9 460-466, 477) and pneumonia (ICD-9 480-486) among all ages. An excess risk of 1.4% (95% CI: 0.4-2.5 per 10 $\mu g/m^3$, lag 0- to 2-day avg) for PM_{10} was associated with URI visits. With the exception of a small increase in risk for OC of 2.8% (95% CI: 0.4-5.3 per 2 $\mu g/m^3$, 0- to 2-day avg) with pneumonia visits, Peel et al. (2005, 056305) reported no association with other PM size fractions or components evaluated. However, Sinclair and Tolsma (2004, 088696), who also used ARIES data in their analysis, reported significant associations with outpatient visits for LRI. These associations were generally observed for 3- to 5-day ma lags, in association with $PM_{10-2.5}$, PM_{10}, EC, OC, and $PM_{2.5}$ water soluble metals (not pictured in figure because only significant lags were reported). No associations with pneumonia for any size fractions were observed among all ages in a study conducted in Spokane, Washington (effect estimates were not reported) (Slaughter et al., 2005, 073854).

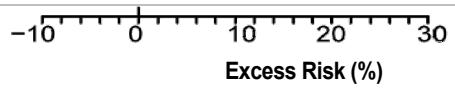
French PSAS investigators examined the effect of $PM_{2.5}$ and $PM_{10-2.5}$ on hospital admissions for respiratory infection (ICD-10: J10-22) among all ages. Increases of 2.5% (95% CI: 0.1-4.8) and 4.4% (95%CI: 0.9-8.0) per 10 $\mu g/m^3$ were observed in association with $PM_{2.5}$ and $PM_{10-2.5}$, respectively (Host et al., 2008, 155852). In a multicity study of older adults (≥65 yr) Medina-Ramon et al. (2006, 087721) examined hospital admissions for pneumonia (ICD-9 480-487) in 36 U.S. cities in relation to 24-h avg PM_{10} concentration. An increase in pneumonia admissions of 0.84% (95% CI: 0.50-1.19 per 10 $\mu g/m^3$, lag 0) was reported by these investigators during the warm season. Cold season associations were weaker (0.30% [95% CI: 0.07-0.53] per 10 $\mu g/m^3$, lag 0) as were lag 1 associations. Dominici et al. (2006, 088398) investigated hospital admissions for all respiratory infections including pneumonia (ICD-9 464-466, 480-487) among older adults in 204 urban U.S. counties in relation to $PM_{2.5}$ and reported a significant increased risk only at lag 2. Heterogeneity in effect estimates was observed across the U.S. with the largest associations reported for the South and Southeast.

In Boston, excess risks of pneumonia hospitalization in association with $PM_{2.5}$, BC, and CO were observed among older adults (Zanobetti and Schwartz, 2006, 090195). A measure of non-traffic PM, e.g., the residuals from the regression of $PM_{2.5}$ on BC, was not associated with pneumonia hospitalization in these data. In a California study (Delfino et al., 2009, 190254), effect estimates were of similar magnitude for pneumonia admissions associated with $PM_{2.5}$ from wildfires among all ages combined and older adults (2.8% [95% CI: 0.7-5.0] per 10 $\mu g/m^3$, all ages combined). The $PM_{2.5}$ association with acute bronchitis and bronchiolitis admissions during the wildfire period for all age groups showed an approximately 10% increase (9.6% 95% CI: 1.8-17.9, per 10 $\mu g/m^3$). The increase was not larger during the wildfire period compared to the pre-fire period for either outcome.

In a study of four cities in Australia, statistically significant associations of pneumonia and acute bronchitis with particles measured by nephelometry (but not $PM_{2.5}$ mass) and NO_2 were observed among older adults (Simpson et al., 2005, 087438). Halonen et al. (2009, 180379) examined pneumonia among older adults (ICD10 J12-J15) in their most recent analysis. Associations of $PM_{2.5}$ (5.0% [95% CI: 1.0-9.3] per 10 µg/m^3, lag 5-day mean), as well as accumulation mode particles, with pneumonia admissions were observed.

Although the body of literature is small, several studies of children reported associations of $PM_{2.5}$, $PM_{10-2.5}$ and PM_{10} with respiratory infections but the outcomes studied are heterogeneous and effect estimates are imprecise. Studies of adults show a similar pattern of increased risk for each of these size fractions. Several other single-city studies conducted outside the U.S. and Canada reported associations for PM_{10} (Cheng et al., 2007, 093034; Hwang and Chan, 2002, 023222; Nascimento et al., 2006, 093247) and $PM_{2.5}$ (Hinwood et al., 2006, 088976) with hospitalization or ED visits for respiratory infections.

Study	Location	Lag	Age	Outcome	Effect Estimate (95% CI)	
CHILDREN						
Barnett et al. (2006, 089770)	7 Cities, Australia/NZ	0-1	<1	Pneumonia		$PM_{2.5}$
		0-1	1-4	Pneumonia		
Chimonas & Gessner (2007, 093261)	Anchorage, AK	0	0-19	LRI	Outpatient	
		0	0-19	LRI	Inpatient	
Delfino et al. (2009, 191994)	6 Counties, S. CA	0-1	0-4	Bronchitis, Bronchiolitis	Wildfire	
		0-1	0-4	Pneumonia	Wildfire	
		0-1	5-19	Pneumonia	Wildfire	
Lin et al. (2005, 087828)	Ontario, Can	0-3	<15	RTI		
Lin et al. (2005, 087828)	Ontario, Can	0-3	<15	RTI		$PM_{10-2.5}$
Barnett et al. (2006, 089770)	7 Cities, Australia/NZ	0-1	<1	Pneumonia, Acute Bronchitis		PM_{10}
		0-1	1-4	Pneumonia, Acute Bronchitis		
Chimonas & Gessner (2007, 093261)	Anchorage, AK	0	0-19	LRI	Outpatient	
		0-1	0-19	LRI	Inpatient	
Lin et al. (2005, 087828)	Ontario, Can	0-3	<15	RTI		
ALL AGES COMBINED OR OLDER ADULTS						
Dominici et al. (2006, 088398)	204 Counties, US	0	65+	RTI		$PM_{2.5}$
		1	65+	RTI		
		2	65+	RTI		
Dominici et al. (2006, 088398)	90 Counties, US	0-2 DL	65+	RTI		
Zanobetti & Schwartz (2006, 090195)	Boston, MA	0	65+	Pneumonia		
		0-1	65+	Pneumonia		
Peel et al. (2005, 056305)*	Atlanta, GA	0-3	All	URI		
		0-3	All	Pneumonia		
Host et al. (2008, 155852)	6 Cities, France	0-1	All	RTI		
Delfino et al. (2009, 191994)	6 Counties, S.CA	0-1	All	Pneumonia	Wildfire	
		0-1	All	Bronchiolitis	Wildfire	
Ito (2003, 042856)	Detroit, MI	0	65+	Pneumonia		
Peel et al. (2005, 056305)*	Atlanta, GA	0-3	All	Pneumonia		$PM_{10-2.5}$
		0-3	All	URI		
Host et al. (2008, 155852)	6 Cities, France	0-1	All	RTI		
Ito (2003, 042856)	Detroit, MI	0	65+	Pneumonia		
Medina-Ramon et al. (2006, 087721)	36 Cities, US	0	65+	Pneumonia	Warm	PM_{10}
		1	65+	Pneumonia	Warm	
		0	65+	Pneumonia	Cold	
		1	65+	Pneumonia	Cold	
Peel et al. (2005, 056305)*	Atlanta, GA	0-3	All	URI		
		0-13 DL	All	URI		
		0-3	All	Pneumonia		
		0-13 DL	All	Pneumonia		
Zanobetti (2003, 043119)	14 Cities, US	0-1	65+	Pneumonia		
Ito (2003, 042856)	Detroit, MI	0	65+	Pneumonia		



*ED Visits
DL = Distributed Lag

Figure 6-14. Excess risks estimates per 10 µg/m^3 increase in 24-h avg $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} for respiratory infection ED visits* and HAs. Studies represented in the figure include all multicity studies as well as single-city studies conducted in the U.S.

Table 6-14. PM concentrations in epidemiologic studies of respiratory diseases.

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Andersen et al. (2007, 093201)	Copenhagen, Denmark	10	99th: 28
Barnett et al. (2005, 087394)	7 Cities Australia, NZ	8.1-11	Max: 29.3-122.8
Bell et al. (2008, 156266)	202 U.S. counties	12.92	98th: 34.16
Chardon et al. (2007, 091308)	Paris, France	14.7	75th: 18.2
Chen et al. (2004, 087262; 2005, 087555)	Vancouver, Canada	7.7	Max: 32
Chimonas and Gessner (2007, 093261)	Anchorage, AK	6.1	Max: 69.8
Delfino et al. (2009, 191994)	6 counties, CA	18.4-32.7	45.3-76.1 (mean during wildfire period)
Dominici et al. (2006, 088398)	204 U.S. counties	13.4	75th: 15.2
Fung et al. (2006, 089789)	Vancouver, Canada	7.72	Max: 32
Halonen et al. (2008, 189507)	Helsinki, Finland	NR; Median = 9.5	Max: 69.5
Host et al. (2008, 155852)	6 Cities France	13.8-18.8	95th: 25.0-33.0
Ito et al. (2007, 091262)	New York, NY	All yr: 15.1	All yr: 95th: 32
Lin et al. (2002, 026067)	Toronto Canada	17.99	Max: 89.59
Lin et al. (2005, 087828)	Ontario, Canada	9.59	Max: 73
Moolgavkar (2003, 051316)	Los Angeles, CA	22 (median)	Max: 86
New York State DOH (2006, 090132)	Bronx/Manhattan	15.0/16.7	NR
Peel et al. (2005, 056305)	Atlanta, GA	19.2	90th: 32.3; 98th: 39.8
Sinclair and Tolsma (2004, 088696)	Atlanta, GA	17.62	NR
Sheppard et al. (2003, 042826)	Seattle, WA	16.7	98th: 46.6
Slaughter et al. (2005, 073854)	Spokane, WA	NR	Max: 20.2 (using 90% of concentrations)
Tolbert et al. (2007, 090316)	Atlanta, GA	17.1	90th: 28.8; 98th: 38.7
Yang et al. (2004, 087488)	Vancouver, Canada	7.7	Max: 32.0
Zanobetti and Schwartz (2006, 090195)	112 U.S. cities	11.1 (Median)	95th: 26.31
$PM_{10-2.5}$			
Chen et al. (2004, 087262; 2005, 087555)	Vancouver, Canada	5.6	Max: 24.6
Fung et al. (2006, 089789)	Vancouver, Canada	5.6	Max: 27.07
Halonen et al. (2008, 189507)	Helsinki, Finland	NR; Median: 9.9	Max: 101.4
Host et al. (2008, 155852)	6 Cities France	7.0-11.0	95th: 12.5-21.0
Lin et al. (2002, 026067)	Toronto, Canada	12.17	Max: 68.00
Lin et al. (2005, 087828)	Ontario, Canada	10.86	Max: 45
New York State DOH	Bronx/Manhattan	7.69/7.10	NR
Peel et al. (2005, 056305)	Atlanta, GA	9.7	90th: 16.2
Peng et al. (2008, 156850)	108 U.S. counties	NR; Median: 9.8	75th: 15.0
Sinclair and Tolsma (2004, 088696)	Atlanta, GA	9.67	NR
Sheppard et al. (2003, 042826)	Seattle, WA	16.2	Max: 88
Slaughter et al. (2005, 073854)	Spokane, WA	NR	NR
Tolbert et al. (2007, 090316)	Atlanta, GA	9	90th: 15.1; Max: 50.3
Yang et al. (2004, 087488)	Vancouver, Canada	7.7	Max: 24.6
PM_{10}			
Andersen et al. (2007, 093201)	Copenhagen, Denmark	25/24	75th: 30 / 99th: 72
Barnett et al. (2005, 087394)	7 Cities, Australia, NZ	16.5-20.6	Max: 50.2-156.3
Chardon et al. (2007, 091308)	Paris, France	23	Max: 97.3
Chen et al. (2004, 087262; 2005, 087555)	Vancouver, Canada	13.3	Max: 52.2
Chimonas and Gessner (2007, 093261)	Anchorage, AK	27.6	Max: 421
Fung et al. (2005, 093262)	Ontario, Canada	38	Max: 248
Fung et al. (2006, 089789)	Vancouver, Canada	13.3	Max: 52.17
Gordian and Choudhury (2003, 054842)	Anchorage, AK	36.11	Max: 210.0
Jaffe et al. (2003, 041957)	Cincinnati, OH	43	Max: 90

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile concentrations ($\mu g/m^3$)
Jalaludin et al. (2004, 056595)	Sydney, Australia	22.8	Max: 44.9
Lin et al. (2002, 026067)	Toronto, Canada	30.16	Max: 116.20
Lin et al. (2005, 087828)	Ontario, Canada	20.41	Max: 73
Luginaah et al. (2005, 057327)	Ontario, Canada	50.6	Max: 349
Medina-Ramon et al. (2006, 087721)	36 U.S. Cities	15.9-44.0	NR
Moolgavkar (2003, 051316)	Los Angeles, CA	22 (median)	Max: 86
Moolgavkar (2003, 051316)	Cook County, IL	35 (median)	Max: 365
Peel et al. (2005, 056305)	Atlanta, GA	27.9	Max: 44.7
Sinclair and Tolsma (2004, 088696)	Atlanta, GA	29.03	NR
Slaughter et al. (2005, 073854)	Spokane, WA	NR	Max: 41.9 (using 90% of concentrations)
Tolbert et al. (2007, 090316)	Atlanta, GA	26.6	90th: 42.8
Ulirsch et al. (2007, 091332)	Idaho	23.2	Max: 183.0
Yang et al. (2004, 087488)	Vancouver, Canada	13.3	Max: 52.2
Zanobetti (2003, 043119);Samet et al. (2000, 010269)	14 U.S. Cities	24.4-45.3	Max 94.8-605.8
UFP			
Andersen et al. (2008, 189651)	Copenhagen, Denmark	Mean particles/cm^3: 6847	99th: 19,895 particles/cm^3
Halonen et al. (2008, 189507)		NR: Median particles/cm^3: 8,203	Max: 50,990 particles/cm^3

6.3.8.5. Copollutant Models

Some studies have investigated potential confounding by copollutants through the application of multipollutant models (Figure 6-15). Several Canadian studies of respiratory hospital admissions reported larger effects for $PM_{10-2.5}$ compared to $PM_{2.5}$ that were robust to adjustment for gaseous pollutants (Chen et al., 2005, 087555; Lin et al., 2002, 026067; Yang et al., 2004, 087488). The COPD associations between $PM_{2.5}$ and $PM_{10-2.5}$ reported by Chen et al. (2004, 087262) remained positive but were diminished slightly after adjustment for NO_2. The associations reported by Ito et al. (2003, 042856) of $PM_{2.5}$ and $PM_{10-2.5}$ with pneumonia hospital admissions remained after adjustment for gases, while the association of $PM_{10-2.5}$ with COPD admissions was not robust to adjustment for O_3. Associations reported by Burnett et al. (1997, 084194), Moolgavkar et al. (2003, 042864) and Delfino et al. (1998, 093624) were not consistently robust to adjustment for gaseous copollutants. In the MCAPS study, the effect of $PM_{2.5}$ was robust to adjustment for $PM_{10-2.5}$, while the $PM_{10-2.5}$ effect on respiratory admissions was diminished after adjustment for $PM_{2.5}$ (Peng et al., 2008, 156850). Effect estimates for PM_{10} were robust to adjustment for gases in several recent studies (Andersen et al., 2007, 093201; Tolbert et al., 2007, 090316; Ulirsch et al., 2007, 091332).

Multiple pollutant analyses for other size fractions and components have been conducted in a some additional studies. PM_{10} associations with respiratory disease did not change in models also containing total PNC, nor did the association of ACP diminish after adjustment for UFP concentration(Andersen et al., 2008, 189651). Peng et al. (2009, 191998) reports an OCM effect that was robust to adjustment for other components while the associations with Ni, V, and EC were somewhat diminished in models containing multiple components.

Inconsistency across these study findings is likely due to differences in the correlation structure among pollutants as well as differing degrees of exposure measurement error.

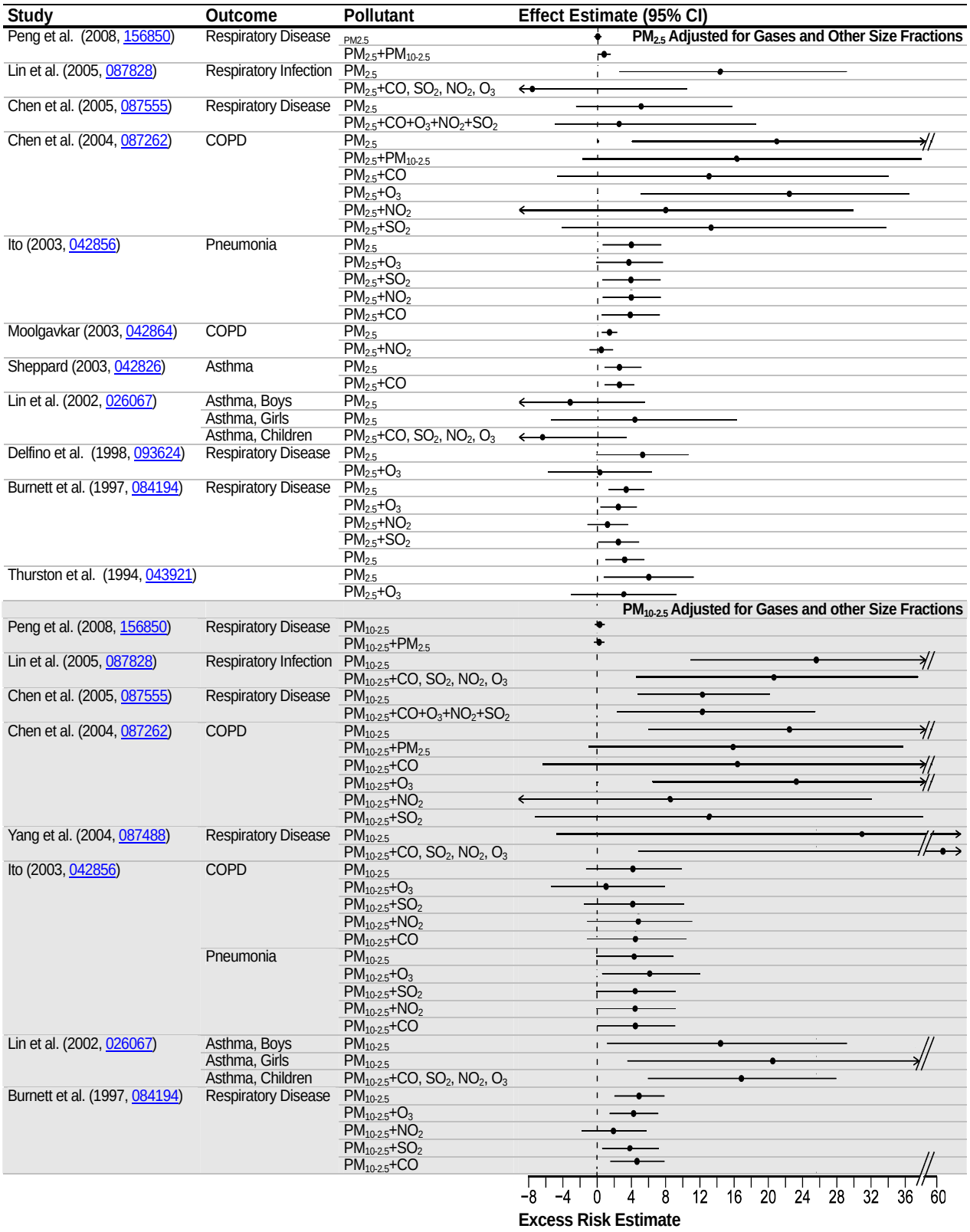


Figure 6-15. Excess risk estimates per 10 μg/m^3 increase in 24-h avg $PM_{2.5}$, and $PM_{10-2.5}$ for respiratory disease ED visits or HAs, adjusted for co-pollutants.

6.3.9. Respiratory Mortality

An evaluation of studies that examined the association between short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$ and mortality provides additional evidence for PM-related respiratory health effects. Although the primary analysis in the majority of mortality studies evaluated consists of an examination of the relationship between $PM_{2.5}$ or $PM_{10-2.5}$ and all-cause (nonaccidental) mortality, some studies have examined associations with cause-specific mortality including respiratory-related mortality.

Multicity mortality studies that examine the PM-respiratory mortality relationship on a national scale – Franklin et al. (2007, 091257): 27 U.S. cities and Zanobetti and Schwartz (2009, 188462): 112 U.S. cities – have found consistent positive associations between short-term exposure to $PM_{2.5}$ and respiratory mortality of approximately 1.68% per 10 $\mu g/m^3$ at lag 0-1 (Section 6.5). The associations observed on a national scale are consistent with those presented by Ostro et al. (2006, 087991) in a study that examined the $PM_{2.5}$-mortality relationship in nine California counties (2.2% [95% CI: 0.6-3.9] per 10 $\mu g/m^3$). An evaluation of studies that examined additional lag structures of associations found smaller respiratory mortality effect estimates when using the average of lag days 1 and 2 (1.01% [95% CI: -0.03 to 2.05] per 10 $\mu g/m^3$) (Franklin et al., 2008, 097426), and associations consistent with those observed at lag 0-1 when examining single-day lags, specifically lag 1 (1.78% [95% CI: 0.2-3.36]). Although the overall effect estimates reported in the multicity studies evaluated are consistently positive, it should be noted that a large degree of variability exists between cities when examining city-specific effect estimates potentially due to differences between cities and regional differences in $PM_{2.5}$ composition (Figure 6-25). Only a limited number of studies that examined the $PM_{2.5}$-mortality relationship have conducted analyses of potential confounders, such as gaseous copollutants, and none examined the effect of copollutants on $PM_{2.5}$ respiratory mortality risk estimates. Although the recently evaluated multicity studies did not extensively examine whether $PM_{2.5}$ mortality risk estimates are confounded by gaseous pollutants, evidence from the limited number of single-city studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggest that gaseous copollutants do not confound the $PM_{2.5}$-respiratory mortality association. This is further supported by studies that examined the PM_{10}-mortality relationship in both the 2004 PM AQCD (U.S. EPA, 2004, 056905) and this review. Overall, the respiratory $PM_{2.5}$ effects observed in the new studies evaluated were larger, but less precise than those reported for all-cause (nonaccidental) mortality (Section 6.5), and are consistent with the effect estimates observed in the single- and multicity studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

Zanobetti and Schwartz (2009, 188462) also examined $PM_{10-2.5}$ mortality associations in 47 U.S. cities and found evidence for respiratory mortality effects (1.16% [95% CI: 0.43-1.89] per 10 $\mu g/m^3$ at lag 0-1), which are somewhat larger than those reported for all-cause (nonaccidental) mortality (0.46% [95% CI: 0.21-0.671] per 10 $\mu g/m^3$). In addition, Zanobetti and Schwartz (2009, 188462) reported seasonal (i.e., larger in spring) and regional differences in $PM_{10-2.5}$ respiratory mortality risk estimates. However, single-city studies conducted in Atlanta, GA (Klemm et al., 2004, 056585) and Vancouver, Canada ((Villeneuve et al., 2003, 055051) reported no associations between short-term exposure to $PM_{10-2.5}$ and respiratory mortality. The difference in the results observed between the multi- and single-city studies could be due to a variety of factors including differences between cities and compositional differences in $PM_{10-2.5}$ across regions (Figure 6-30). Only a small number of studies have examined potential confounding by gaseous copollutants or the influence of model specification on $PM_{10-2.5}$ mortality risk estimates, but the effects are relatively consistent with those studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

6.3.10. Summary and Causal Determinations

6.3.10.1. $PM_{2.5}$

Several studies of the effect of $PM_{2.5}$ on hospital admissions for respiratory diseases reviewed in the 2004 AQCD (U.S. EPA, 2004, 056905) reported positive associations for several diseases. The 2004 AQCD (U.S. EPA, 2004, 056905) presented limited epidemiologic evidence of $PM_{2.5}$ being associated with respiratory symptoms (including cough, phlegm, difficulty breathing, and bronchodilator use); observations for $PM_{2.5}$ were positive, with slightly larger effects for $PM_{2.5}$ than

for PM_{10}. In addition, mortality studies reported relatively higher $PM_{2.5}$ risk estimates for respiratory-related mortality compared to all-cause (nonaccidental) mortality. Controlled human exposure studies did not provide support for effects of CAPs on respiratory symptoms. Small decrements in peak flow for both $PM_{2.5}$ and PM_{10} in asthmatics and nonasthmatics were reported in epidemiologic studies included in the 2004 PM AQCD (U.S. EPA, 2004, 056905), whereas controlled human exposure and animal toxicological studies reported few or no effects on pulmonary function with inhalation of CAPs. In addition, the 2004 PM AQCD (U.S. EPA, 2004, 056905) presented a number of controlled human exposure and toxicological studies that reported mild pulmonary inflammation following exposure to $PM_{2.5}$ CAPs and DE or DE particles, as well as ROFA or other metal-containing PM in animals. The 2004 PM AQCD (U.S. EPA, 2004, 056905) described controlled human exposure studies showing increases in allergic responses among previously sensitized atopic subjects after short-term exposure to DE particles. These observations were supported by many toxicological studies that added to existing evidence demonstrating that various types of PM could promote allergic disease and exacerbate allergic asthma in animal models. Toxicological studies also indicated that $PM_{2.5}$ increased susceptibility to respiratory infection.

Overall, in recent studies $PM_{2.5}$ effects on respiratory hospitalizations and ED visits have been consistently observed. Most effect estimates were in the range of ~1-4% and were observed in areas with mean 24-h $PM_{2.5}$ concentrations between 6.1 and 22 $\mu g/m^3$. Further, recent studies have focused on increasingly specific disease endpoints such as asthma, COPD, and respiratory infection. The strongest recent evidence of an association comes from large multicity studies of COPD, respiratory tract infection, and all respiratory diseases among Medicare recipients (≥65 yr) (Bell et al., 2008, 156266; Dominici et al., 2006, 088398). Studies of children have also found evidence of an effect of $PM_{2.5}$ on hospitalization for all respiratory diseases, including asthma and respiratory infection. However, many of these effect estimates are imprecise, their magnitude and statistical significance are sensitive to choice of lag, and some null associations were observed. Although the association of $PM_{2.5}$ with pediatric asthma was not examined specifically, it is noteworthy that one of the strongest associations observed in the Atlanta-based SOPHIA study was between PM_{10} and pediatric asthma visits; $PM_{2.5}$ makes up a large proportion of PM_{10} in Atlanta (Peel et al., 2005, 056305). Positive associations between $PM_{2.5}$ (or PM_{10}) and hospital admissions for respiratory infection (Figure 6-14) are supported by animal toxicological studies which add to previous findings of increased susceptibility to infection following exposure to $PM_{2.5}$. These include studies demonstrating reduced clearance of bacteria (*Pseudomonas, Listeria*) or enhanced pathogenesis of viruses (influenza, RSV) after exposure to DE or ROFA.

Epidemiologic studies that examined the association between $PM_{2.5}$ and mortality provide additional evidence for $PM_{2.5}$-related respiratory effects (Section 6.3.9). The multicity studies evaluated found consistent, precise positive associations between short-term exposure to $PM_{2.5}$ and respiratory mortality ranging from 1.67 to 2.20% increases at mean 24-h $PM_{2.5}$ avg concentrations above 13 $\mu g/m^3$. Although only a limited number of studies examined potential confounders of the $PM_{2.5}$-respiratory mortality relationship, the studies evaluated in both this review and the 2004 PM AQCD (U.S. EPA, 2004, 056905) support an association between short-term exposure to $PM_{2.5}$ and respiratory mortality.

Epidemiologic studies of asthmatic children have observed increases in respiratory symptoms and asthma medication use associated with higher $PM_{2.5}$ or PM_{10} concentrations. Associations with respiratory symptoms and medication use are less consistent among asthmatic adults, and there is no evidence to suggest an association between respiratory symptoms with $PM_{2.5}$ among healthy individuals. In addition, respiratory symptoms have not been reported following controlled exposures to $PM_{2.5}$ among healthy or health-compromised adults (Section 6.3.1.2).

Although more recent epidemiologic studies of pulmonary function and $PM_{2.5}$ have yielded somewhat inconsistent results, the majority of studies have found an association between $PM_{2.5}$ concentration and FEV_1, PEF, and/or MMEF. In asthmatic children, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ is associated with a decrease in FEV_1 ranging from 1-3.4% (Section 6.3.2.1). A limited number of controlled human exposure studies have reported small decreases in arterial oxygen saturation and MMEF following exposure to $PM_{2.5}$ CAPs with more pronounced effects observed in healthy adults than in asthmatics or older adults with COPD (Section 6.3.2.2). In toxicological studies, changes in pulmonary function have been observed in healthy and compromised rodents after inhalation exposures to CAPs from a variety of locations or DE. A role for the PM fraction of DE is supported by altered pulmonary function in healthy rats after IT instillation of DE particles (Section 6.3.2.3).

Several lines of evidence suggest that $PM_{2.5}$ promotes and exacerbates allergic disease, which often underlies asthma (Section 6.3.6). Although epidemiologic studies examining specific allergic outcomes and short-term exposure to PM are relatively rare, the available studies, conducted primarily in Europe, positively associate $PM_{2.5}$ and PM_{10} with allergic rhinitis or hay fever and skin prick reactivity to allergens. Short-term exposure to DE particles in controlled human exposure studies has been shown to increase the allergic response among previously sensitized atopic subjects, as well as induce de novo sensitization to an antigen. Toxicological studies continue to provide evidence that $PM_{2.5}$, in the form of CAPs, resuspended DE particles, or DE, but not wood smoke, spurs and intensifies allergic responses in rodents. Proposed mechanisms for these effects include mediation by neurotrophins and oxidative stress, and one study demonstrated that effects were mediated at the epigenetic level (Liu et al., 2008, 156709).

A large body of evidence, primarily from toxicological studies, indicates that various forms of PM induce oxidative stress, pulmonary injury, and inflammation. Notably, CAPs from a variety of locations induce inflammatory responses in rodent models, although this generally requires multiday exposures. The toxicology findings are consistent with several recent epidemiologic studies of $PM_{2.5}$ and the inflammatory marker eNO, which reported statistically significant, positive effect estimates with some inconsistency in the lag times and use of medication. In asthmatic children, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ is associated with an increase in eNO ranging from 0.46 to 6.99 ppb. Several new controlled human exposure studies report traffic or DE-induced increases in markers of inflammation (e.g., neutrophils and IL-8) in BALF from healthy adults. Recent studies have provided additional evidence in support of a pulmonary oxidative response to DE in humans, including induction of redox-sensitive transcription factors and increased urate and GSH concentrations in nasal lavage. In addition, exposure to wood smoke has recently been demonstrated to increase the levels of eNO and malondialdehyde in breath condensate of healthy adults (Barregard et al., 2008, 155675). Preliminary findings indicate little to no pulmonary injury in humans following controlled exposures to $PM_{2.5}$ urban traffic particles or DE, in contrast to a number of toxicological studies demonstrating injury with CAPs or DE (Sections 6.3.5.2 and 6.3.5.3, respectively).

Recent studies have reported associations of hospital admissions, ED or urgent care visits for several respiratory diseases with $PM_{2.5}$ components and sources including Ni, V, OC and EC, wood smoke and traffic emissions, in studies of both children and adults. Delfino et al. (2003, 090941; 2006, 090745) found positive associations between EC and OC components of PM and asthma symptoms and between EC and eNO. Particle composition and/or source also appears to heavily influence the increase in markers of pulmonary inflammation demonstrated in studies of controlled human exposures to $PM_{2.5}$. For example, whereas exposures to $PM_{2.5}$ CAPs from Chapel Hill, NC have been shown to increase BALF neutrophils in healthy adults, no such effects have been observed in similar studies conducted in Los Angeles. In addition, differential inflammatory responses have been observed following bronchial instillation of particles collected at different times or from different areas (Section 6.3.3.2). One new study found that the increased airway neutrophils previously observed by Ghio et al. (2000, 012140) in human volunteers after Chapel Hill CAPs exposure could be largely attributed to the content of sulfate, Fe, and Se in the soluble fraction (Huang et al., 2003, 087377).

In summary, new evidence of ED visits and hospital admissions builds upon the positive and statistically significant evidence presented in the 2004 PM AQCD to support a consistent association with ambient concentrations of $PM_{2.5}$. Most effect estimates with respiratory hospitalizations and ED visits were in the range of ~1-4% and were observed in areas with mean 24-h $PM_{2.5}$ concentrations between 6.1 and 22 $\mu g/m^3$. The evidence for $PM_{2.5}$-induced respiratory effects is strengthened by similar hospital admissions and ED visit associations for PM_{10}, along with the consistent positive associations observed between $PM_{2.5}$ and respiratory mortality in multicity studies. Panel studies also indicate associations with $PM_{2.5}$ and respiratory symptoms, pulmonary function, and pulmonary inflammation among asthmatic children. Further support for these observations is provided by recent controlled human exposure studies in adults demonstrating increased markers of pulmonary inflammation following DE and other traffic-related exposures, oxidative responses to DE and wood smoke, and exacerbations of allergic responses and allergic sensitization following exposure to DE particles. Although not consistent across studies, some controlled human exposure studies have reported small decrements in various measures of pulmonary function following exposures to $PM_{2.5}$. Numerous toxicological studies demonstrating a wide range of responses provide biological plausibility for the associations between $PM_{2.5}$ and respiratory morbidity observed in epidemiologic studies. Altered pulmonary function, mild pulmonary inflammation and injury, oxidative responses,

AHR in allergic and non-allergic animals, exacerbations of allergic responses and increased susceptibility to infections were observed in a large number of studies involving exposure to CAPs, DE, other traffic-related PM, and wood smoke. The evidence for an effect of $PM_{2.5}$ on respiratory outcomes is somewhat restricted by limited coherence between some of the findings from epidemiologic and controlled human exposure studies for the specific health outcomes reported and the sub-populations in which those health outcomes occur. For instance, although there is evidence for respiratory symptoms among asthmatic children in epidemiologic panel studies, the studies of hospital admissions and ED visits provide more evidence for effects from COPD and respiratory infections than for asthma. Additionally, controlled human exposure studies report greater effects in healthy adults when compared to asthmatics or those suffering from COPD. Finally, there is limited information which could explain the relationship between the clinical and subclinical respiratory outcomes observed and the magnitude of the $PM_{2.5}$-respiratory mortality associations reported. Therefore, the evidence is sufficient to conclude that a **causal relationship is likely to exist between short-term $PM_{2.5}$ exposures and respiratory effects.**

6.3.10.2. $PM_{10-2.5}$

The 2004 PM AQCD (U.S. EPA, 2004, 056905) presented the results from several epidemiologic studies of respiratory symptoms and $PM_{10-2.5}$, which provided limited evidence for cough and effects on morning PEF. Toxicology data for $PM_{10-2.5}$ were extremely limited, and there were no controlled human exposure studies presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that evaluated the effect of $PM_{10-2.5}$ on respiratory symptoms, pulmonary function, or inflammation. Epidemiologic studies of the effect of $PM_{10-2.5}$ on hospitalizations or ED visits for respiratory diseases (i.e., pneumonia, COPD and respiratory diseases combined) reviewed in the 2004 AQCD (U.S. EPA, 2004, 056905) reported positive associations. Additionally, the few mortality studies that examined cause-specific mortality suggested somewhat larger risk estimates for respiratory mortality compared to all-cause (nonaccidental) mortality.

Several new studies report associations between $PM_{10-2.5}$ and respiratory hospitalizations with the most consistent evidence among children (Figure 6-10 through Figure 6-14), however, effect estimates are imprecise. Although a number of studies provide evidence of respiratory effects in older adults, a recent analysis of MCAPS data reports that weak associations of $PM_{10-2.5}$ with respiratory hospitalizations are further diminished after adjustment for $PM_{2.5}$. It is not clear that $PM_{10-2.5}$ estimates across all populations and regions are confounded by $PM_{2.5}$. An examination of $PM_{10-2.5}$ mortality associations on a national scale found a strong association between $PM_{10-2.5}$ and respiratory mortality, but this association varied when examining city-specific risk estimates (Zanobetti and Schwartz, 2009, 188462). The regional variability in $PM_{10-2.5}$ mortality risk estimates is further confirmed by the negative associations reported in the single-city studies evaluated. However, there is greater spatial heterogeneity in $PM_{10-2.5}$ compared to $PM_{2.5}$ and consequently greater potential for exposure measurement error in epidemiologic studies relying on central site monitors. This exposure measurement error may bias effect estimates toward the null and could explain some of the regional variability in the observed associations between $PM_{10-2.5}$ and respiratory morbidity and mortality.

Mar et al. (2004, 057309) provide evidence for an association with increased respiratory symptoms in asthmatic children, but not asthmatic adults. Consistent with this, controlled human exposures to $PM_{10-2.5}$ have not been observed to affect lung function or respiratory symptoms in healthy or asthmatic adults. However, increases in markers of pulmonary inflammation have been demonstrated in healthy volunteers. In these studies, an increase in neutrophils in BALF or induced sputum was observed, with additional evidence of alveolar macrophage activation associated with biological components of $PM_{10-2.5}$ (i.e., endotoxin). Toxicological studies using inhalation exposures are still lacking, but pulmonary injury and inflammation have been observed in animals after IT instillation exposure and both rural and urban $PM_{10-2.5}$ have induced these responses. In some cases, $PM_{10-2.5}$ from urban air was more potent than $PM_{2.5}$ (Section 6.3.3.3). $PM_{10-2.5}$ respiratory effects may be due to components other than endotoxin (Wegesser and Last, 2008, 190506).

Overall, the most compelling new evidence comes from a number of recent epidemiology studies conducted in Canada and France showing significant associations between respiratory ED visits or hospitalization and short-term exposure to $PM_{10-2.5}$. Effects have been observed in areas where the mean 24-h avg $PM_{10-2.5}$ concentrations ranged from 7.4 to 13.0 $\mu g/m^3$. The strongest relationships were observed among children, whereas studies of adults and older adults show less

consistent evidence of an association. While controlled human exposure studies have not observed an effect on lung function or respiratory symptoms in healthy or asthmatic adults in response to exposure to $PM_{10-2.5}$, healthy volunteers have exhibited increases in markers of pulmonary inflammation. Toxicological studies using inhalation exposures are still lacking, but pulmonary injury has been observed in animals after IT instillation exposure to both rural and urban $PM_{10-2.5}$, which may not be entirely attributed to endotoxin. Overall, epidemiologic studies, along with the limited number of controlled human exposure and toxicological studies that examined $PM_{10-2.5}$ and respiratory outcomes, provide evidence that is **suggestive of a causal relationship between short-term $PM_{10-2.5}$ exposures and respiratory effects.**

6.3.10.3. UFPs

The 2004 PM AQCD (U.S. EPA, 2004, 056905) included a few epidemiologic and controlled human exposure studies that examined the effect of UFPs on respiratory morbidity. Collectively these studies provided limited evidence of an association between UFPs and respiratory symptoms, medication use, inflammation, and decreased pulmonary function. Evidence from toxicological studies presented in the 2004 AQCD, although limited, suggested that exposure via inhalation to high concentrations of UF TiO_2 may increase pulmonary inflammation in healthy rodents. Since the publication of the 2004 AQCD there has been an increased focus among the scientific community on gaining a better understanding of the potential health effects associated with exposure to UFPs (U.S. EPA, 2004, 056905). A number of recent controlled human exposure and toxicological studies have evaluated respiratory responses following exposures to UF CAPs, model particles, and fresh diesel or gasoline exhaust. While DE contains both $PM_{2.5}$ and UFPs, the MMAD is typically $\leq$ 100 nm, and therefore the results of these studies may be used to support findings from studies utilizing other sources of UFP.

UFPs were associated with incident wheezing symptoms among infants (<1 yr) in a study conducted in Copenhagen, Denmark, where the mean UFP number concentration was 8,092 particles/cm^3, though this association did not persist for children between ages 1-3 yr (Andersen et al., 2008, 096150). Recent epidemiologic studies conducted in Copenhagen, Denmark and Helsinki, Finland, reported associations between UFPs and hospital admissions or ED visits for respiratory diseases, including childhood asthma and pneumonia in adults (Andersen et al., 2008, 189651; Halonen et al., 2008, 189507). The median UFP number concentrations in Copenhagen and Helsinki were 6,243 particles/cm^3 and 8,203 particles/cm^3, respectively. Associations between UFP and ED visits for respiratory diseases were not observed in the Atlanta-based SOPHIA study, where the mean UFP number concentration was 38,000 particles/cm^3.

A single recent epidemiologic study has examined associations between UFP and pulmonary function, and observed that asthmatic adults exhibited decreased lung function after exposure to diesel traffic pollution in London (McCreanor et al., 2007, 092841). Two new controlled human exposure studies have reported small decreases in pulmonary function among healthy adults approximately following exposure to Los Angeles UF CAPs or UF EC (Gong et al., 2008, 156483; Pietropaoli et al., 2004, 156025). Exposures to lower concentrations of UF CAPs from Chapel Hill, NC did not result in any changes in pulmonary function (Samet et al., 2009, 191913). However, while Gong et al. (2008, 156483) did not observe any effect of exposure to UF CAPs on markers of pulmonary inflammation, Samet et al. (2009, 191913) reported an UF CAPs-induced increase in IL-8 in BALF at 18 hours post-exposure. A limited number of controlled human exposure studies have also demonstrated increases in the pulmonary inflammatory response following exposure to UF and $PM_{2.5}$ from DE, which may be enhanced by exposure to O_3 (Section 6.3.3.2).

Altered pulmonary function and inflammation have also been observed in toxicological studies of DE and UF model particles (Sections 6.3.2.3 and 6.3.3.3). In one rat model, pulmonary inflammation was observed after exposure to UF CB at concentrations as low as 180 $\mu g/m^3$ (Harder et al., 2005, 087371). However, inflammatory responses vary considerably depending on the animal model, dose, test material, and exposure duration. In cases where pulmonary inflammation was not observed, oxidative stress was often evident (Section 6.3.4.2). Oxidative stress is a major mechanism by which PM may exert effects (Chapter 5), and some toxicological studies suggest that UFPs are more potent than $PM_{2.5}$, possibly due to a higher proportion of pro-oxidative OC and PAH content and greater surface area with which to deliver these components.

The relationship between exposure to UFP and pulmonary injury has not been widely examined. No association with pulmonary injury biomarkers was found for UFP in a European

multicity epidemiologic study (Timonen et al., 2004, 087915). In controlled human exposure studies, UFP from wood smoke resulted in significantly increased markers of injury in healthy adults, but this effect was not evident in COPD sufferers exposed to DE (Section 6.3.5.2). Exposure of neonatal rats to UF iron-soot particles resulted in a significantly reduced rate of cell proliferation in the proximal alveolar region, which suggests that postnatal lung development may be susceptible to air pollution, consistent with impaired lung function growth observed in children (Pinkerton et al., 2004, 087465). In contrast, no histopathological responses were evident in adult mice exposed to UF iron-soot particles (Last et al., 2004, 097334). Some toxicological studies have reported pulmonary injury after inhalation of DE or gasoline exhaust (Section 6.3.5.3). In studies that evaluated ambient PM size fractions from a variety of European and U.S. cities for relative toxicity in rodents following IT instillation exposure, UFPs were generally less injurious than the larger size fractions. However, the UF fraction of Montana coal fly ash induced greater injury and inflammation than the $PM_{10-2.5}$ fraction (Gilmour et al., 2004, 057420).

In rodent studies, UF CAPs appeared to be more potent than $PM_{2.5}$ CAPs in inducing and exacerbating allergic responses (Section 6.3.6.3). In addition to CAPs, UF CB or iron-soot particles, but not particles from fresh gasoline exhaust, have been shown to induce or exacerbate allergic responses in mice. Bacterial clearance appears unaffected by hardwood smoke or gasoline engine exhaust. However, host defenses are impaired by DE, which has been shown to reduce bacterial clearance, impair defenses against viral infection, and reduce thymus weight, indicating systemic immunosuppression.

Several toxicological studies demonstrated oxidative, inflammatory, and allergic responses following exposure to a number of different UFP types, including model particles (i.e., CB, iron-soot particles), CAPs, and DE. Although the respiratory effects of controlled exposures to UFPs have not been extensively examined in humans, two controlled human exposure studies have observed small UFP-induced decreases in pulmonary function; however, no increases in respiratory symptoms have been reported. In a limited number of studies, markers of pulmonary inflammation were increased following controlled human exposures to UFP, which has been most consistently observed in studies using fresh DE. In both controlled human exposure and animal toxicological studies using fresh DE, the relative contributions of gaseous copollutants to the observed effects remain unresolved. However, similar effects are reported using resuspended DE particles, and although not UFPs, these particles can be assumed to have similar composition. A limited number of epidemiologic studies have provided some evidence of an association between short-term exposure to UFPs and respiratory symptoms, as well as asthma hospitalizations. However, the interpretation of these findings is difficult due to the spatial variability of UFPs. Thus, the current collective evidence is **suggestive of a causal relationship between short-term UFP exposure and respiratory effects.**

6.4. Central Nervous System Effects

While evidence of an effect of PM on the CNS was not presented in the 2004 PM AQCD (U.S. EPA, 2004, 056905), a limited number of recent epidemiologic, controlled human exposure and toxicological studies provide some evidence that exposure to PM may be associated with changes in neurological function. The majority of studies included in this section are of short-term exposure, however, there are also a few studies of long-term exposure. As CNS effects of PM are a newly emerging area, and since there are so few studies, all studies that evaluate CNS responses are included in this section.

6.4.1. Epidemiologic Studies

Chen and Schwartz (2009, 179945) used extant data on CNS function from the Third National Health and Nutrition Examination Survey (NHANES III) to characterize the association between cognitive function in adults (ages 20-59 yr) and exposure to ambient air pollution. Three computerized neurobehavioral tests were used: a simple reaction time test (SRTT), a basic measure of visuomotor speed; a symbol digit substitution test (SDST) on coding ability; and a serial digit learning test (SDLT) on attention and short-term memory. The authors used annual PM_{10} concentrations to approximate the long-term exposure to ambient air pollution prior to the

NHANES-III examination. Increased PM_{10} levels were associated with reduced performance in all three neurobehavioral tests, and were particularly strong for SDST and SDLT scores in models adjusted for age and sex. However, after additional adjustment for race/ethnicity or SES, the magnitudes of these associations were greatly diminished and largely null. It is possible that the observed associations disappeared after adjustment for race/ethnicity and SES due to the potential confounding by residential segregation of ethnic minorities and poorer people in areas with high levels of ambient PM_{10} concentrations.

Two additional epidemiologic studies evaluated the effect of ambient PM on the CNS (Calderón-Garcidueñas et al., 2008, 156317; Suglia et al., 2008, 157027). These studies examined long-term exposure to non-specific PM indicators and are detailed in Annex E.

6.4.2. Controlled Human Exposure Studies

In a recent controlled human exposure study, Cruts et al. (2008, 156374) exposed 10 healthy males (18-39 yr) to filtered air and dilute DE (300 μg/m^3 PM) for 1 h using a randomized crossover study design. Changes in brain activity were measured during and following exposure using quantitative electroencephalography (QEEG). Exposure to DE was observed to significantly increase the median power frequency (MPF) in the frontal cortex during exposure, as well as in the hour following the completion of the exposure. While this study does provide some evidence of an acute cortical stress response to DE, it is important to note that the QEEG findings are very nonspecific, and could have been caused by factors other than diesel PM such as DE gases (e.g., CO, NO and NO_2) or the odor of the DE.

6.4.3. Toxicological Studies

Evidence is mounting that the CNS may be a critical target of PM and that adverse health effects may result from PM exposure. Whether these health effects are a direct or indirect effect of PM has not yet been established. One hypothesis suggests that UFPs which deposit onto nasal olfactory epithelium enter the CNS by axonal olfactory transport to the olfactory bulb and lead to a cascade of effects involving inflammatory cytokines and ROS. An increased potential for neurodegenerative processes may ensue. Evidence for translocation of UFPs to the olfactory bulb via olfactory neurons is discussed in Chapter 4, but its relevance to CNS health effects is unknown. Another hypothesis suggests that brain inflammation occurs secondarily to PM-mediated systemic inflammation. Finally, it has been suggested that PM-stimulation of the ANS via respiratory tract receptors results in inflammatory or other effects in the CNS. This is an emerging field with many unknowns.

6.4.3.1. Urban Air

Calderon-Garciduenas et al. (2003, 156316) conducted a long-term observational study in mongrel dogs from Mexico City and Tlaxcala. DNA damage and inflammation in the brain and respiratory tract were evaluated in dogs living in Mexico City (exposed group) and dogs living in Tlaxcala (control group). These cities are similar in altitude but differ in air pollutant levels. Measurements of air pollutant levels were presented only for Mexico City, the more polluted city. Statistically significant greater levels of apurinic/apyrimidinic sites (an indicator of DNA damage) were observed in the olfactory bulbs and hippocampus of Mexico City dogs compared with controls. These differences were not seen in other brain regions examined or in nasal respiratory epithelium. In addition, Mexico City dogs demonstrated greater histopathological changes in the respiratory and olfactory epithelium of the nasal cavity compared with controls. Immunohistochemical staining of brain tissue from the Mexico City dogs demonstrated greater immunoreactivity for NF-κB, iNOS, cyclooxygenase-2, glial fibrillatory acidic protein (GFAP), ApoE, amyloid precursor product and β-amyloid compared with controls. These results are indicative of inflammation and stress protein responses. This study has several limitations given that the dogs were of mixed breeds and of variable ages and that there was no standardization of exposures or diets. However results suggest a possible relationship between air pollution and brain inflammation.

6.4.3.2. CAPs

Several new inhalation studies have provided evidence of CNS effects due to ambient PM exposures. In one study, Campbell et al. (2005, 087217) exposed OVA-sensitized BALB/c mice to filtered air or near-highway Los Angeles CAPs (a 20-fold concentration of $PM_{2.5}$+UFPs or UFPs only; mean exposure concentration UFPs 282.5 μg/m^3 and $PM_{2.5}$ 441.7 μg/m^3) for 4 h/day and 5 days/wk over a 2-wk period. The animals were subsequently challenged with OVA to elicit an allergic response in the lungs; brain tissue was obtained one day later. Exposure to CAPs, but not filtered air, resulted in activation of the immune-related transcription factor NF-κB and upregulation of the cytokines TNF-α, and IL-1α in the brain, demonstrating pro-inflammatory responses that could contribute to neurodegenerative disease. While this study demonstrates CAPs effects in an allergic animal model, it is not known whether these responses also occur in non-allergic animals.

In a second study, control or OVA-sensitized and challenged Brown Norway rats were exposed for 8 h to filtered air or $PM_{2.5}$ CAPs (500 μg/m^3) in Grand Rapids, MI (Sirivelu et al., 2006, 111151). Brain tissue was obtained 1 day later. CAPs exposure resulted in brain region-specific modulation of neurotransmitters. In animals which were not pretreated with OVA, statistically significant increases in norepinephrine were observed in the paraventricular nucleus and olfactory bulb of CAPs-exposed rats compared with filtered air controls. In animals which were pretreated with OVA, a statistically significant increase in dopamine was observed in the medial preoptic area in CAPs-exposed rats compared with controls. Furthermore, exposure to CAPs resulted in a statistically significant increase in serum corticosterone. These data suggest that the hypothalamo-pituitary-adrenal axis (i.e., stress axis) may be activated by PM exposure, causing aggravation of allergic airway disease. The authors discuss the possible role of the olfactory bulb in mediating neuroendocrine control of autonomic activities involved in respiratory and cardiovascular functions; however these relationships require clarification.

Pro-inflammatory responses were examined in a subchronic CAPs study involving normal (C57BL/6J) and ApoE$^{-/-}$ mice (Kleinman et al., 2008, 190074). Mice were exposed to filtered air or to two concentrations of UF CAPs from a near-highway area of central Los Angeles (average of 30.4 and 114.2 μg/m^3) for 5 h/day and 3 days/wk over a 6-wk period. Brain tissue was harvested one day after the last exposure and cortical samples prepared. CAPs exposure resulted in activation of transcription factors, with a dose-dependent increase observed for AP-1 and an increase in NF-κB observed at the higher concentration. Increased levels of GFAP (representing activation of astrocytes) and phosphorylated JNK (representing MAP kinase activation) were observed at the lower but not higher concentration of CAPs. No changes were observed in levels of or activation of the other MAP kinases p38 and ERK or of IκB. These findings provide evidence that inhalation of CAPs can lead to activation of cell signaling pathways involved in upregulation of pro-inflammatory cytokine genes in the cortical region of the mouse brain.

In another study utilizing normal (C57BL/6) and ApoE$^{-/-}$ mice, brain histopathology was examined following a 4-month chronic exposure to $PM_{2.5}$ CAPs from Tuxedo, NY (March, April or May through September 2003) (Veronesi et al., 2005, 087481). The average $PM_{2.5}$ exposure concentration was 110 μg/m^3. CAPs exposure resulted in a statistically significant decrease in dopaminergic neurons, measured by tyrosine hydroxylase immunoreactivity, in the substantia nigra of ApoE$^{-/-}$ mice but not in control mice. This population of neurons is targeted in neurodegenerative diseases such as Parkinson's. Furthermore, a statistically significant increase in GFAP immunoreactivity, a marker for astrocytes, was observed in the nucleus compacta of CAPs-exposed ApoE$^{-/-}$ mice compared to air-exposed ApoE$^{-/-}$ mice. These results suggest that the ApoE$^{-/-}$ mice, a genetic model involving increased oxidative stress, are susceptible to PM-induced neurodegeneration. Evidence for brain oxidative stress has also been found in normal animals following IT instillation of high concentrations of $PM_{2.5}$ from Taiyuan, China (Liu and Meng, 2005, 088650) and of gasoline exhaust (Che et al., 2007, 096460) and following chronic exposure to ROFA by intranasal instillation (Zanchi et al., 2008, 157173).

6.4.3.3. Diesel Exhaust

A recent study tested the effects of DE inhalation on spatial learning and memory function-related gene expression in the hippocampus (Win-Shwe et al., 2008, 190146). Male BALB/c mice were exposed to DE (148.86 μg/m^3 PM) for 5 h/day and 5 day/wk over a 4-wk period. Particle size was 26.21±1.50 nm and PNC was $1.92\times10^6 \pm 6.18\times10^4$ particles/m^3. Concentrations of gases were

3.27 ppm CO, 0.01 ppm SO_2, 0.53 ppm NO_2, 0.98 ppm NO and 0.07 ppm CO_2. Half of the animals were injected i.p. once per week with lipoteichoic acid (LTA), a bacterial cell wall component used to induce systemic inflammation. The ability of the mice to perform spatial learning tasks was examined the day after the final exposure to DE and on two subsequent days. Impaired acquisition of spatial learning was observed in DE-exposed mice on the first day and on all three days in DE-exposed mice that had also been treated with LTA. LTA by itself had no effect. Since the NMDA (a type of neurotransmitter) receptors in the hippocampus play an important role in spatial learning ability, mice were sacrificed and total RNA from hippocampus was extracted and analyzed for expression of NMDA receptor subunits. DE exposure resulted in a statistically significant increase in the expression of one subunit while the combined exposure to DE and LTA resulted in statistically significant increases in the expression of three subunits compared with controls. The expression of pro-inflammatory cytokines was also examined in the hippocampus. DE exposure resulted in a statistically significant increase in TNF-α mRNA, while LTA exposure resulted in a statistically significant increase IL-1β mRNA compared with controls. Neither exposure altered the expression of HO-1. These results demonstrated that subchronic exposure to UF-rich DE resulted in impaired spatial learning and altered expression of hippocampal genes involved in memory function and inflammation. These responses were modulated by systemic inflammation.

6.4.3.4. Summary of Toxicological Study Findings of CNS Effects

In summary, PM may produce adverse effects in the CNS by direct or indirect mechanisms which are at present incompletely understood. Two recent short-term $PM_{2.5}$ CAPs inhalation studies demonstrated pro-inflammatory responses in the brain and brain region-specific modulation of neurotransmitters and suggest the involvement of neuroimmunological pathways. One recent chronic $PM_{2.5}$ CAPs inhalation study demonstrated loss of dopaminergic neurons in the substantia nigra and suggested that oxidative stress contributes to neurodegeneration. Veronesi et al. (2005, 087481) have noted that the brain is very vulnerable to the oxidative stress induced by PM due to the brain's high energy demands, low levels of endogenous free radical scavengers, and high content of lipids and proteins. PM-mediated upregulation of inflammatory cytokines and mediators may also contribute to neurodegeneration. In fact, a recent subchronic study involving UF CAPs demonstrated the activation of cell signaling pathways associated with upregulation of pro-inflammatory cytokines in brain cortical regions. Furthermore, a subchronic study involving UF-rich DE demonstrated impaired spatial learning and altered expression of pro-inflammatory and neurotransmitter receptor genes in the hippocampus. Further investigations are required to delineate mechanisms involved in these responses.

6.4.4. Summary and Causal Determination

Recent animal toxicological studies involving acute or chronic CAPs exposure have demonstrated pro-inflammatory responses in the brain, brain region-specific modulation of neurotransmitters and loss of dopaminergic neurons in the substantia nigra (Campbell et al., 2005, 087217; Kleinman et al., 2008, 190074; Sirivelu et al., 2006, 111151; Veronesi et al., 2005, 087481). However, the mechanisms underlying these effects need to be delineated. A single controlled human exposure study provides some evidence of an acute cortical stress response to DE, though these findings are nonspecific and could have been caused by DE gases rather than DE particles (Cruts et al., 2008, 156374). Similar consideration is warranted for the single animal toxicological study involving DE which demonstrated impaired spatial learning and altered expression of pro-inflammatory and neurotransmitter genes in the hippocampus following subchronic exposure (Win-Shwe et al., 2008, 190146). The single epidemiology study that examined CNS outcomes did not find associations between long-term exposure to PM_{10} and cognitive function in adults after adjustment for race/ethnicity or SES (Chen and Schwartz, 2009, 179945). Though the effect of ambient air pollution on CNS outcomes has recently begun to draw more attention, the evidence for a PM-induced CNS effect is limited. While most available studies have evaluated the effects of fine particle exposures, there is insufficient evidence to draw conclusions regarding effects of specific PM size fractions. Overall, the **evidence is inadequate to determine if a causal relationship exists between short-term exposures to $PM_{2.5}$, $PM_{10-2.5}$, or UFPs and CNS effects.**

6.5. Mortality

The relationship between short-term exposure to PM and mortality has been extensively addressed in previous PM assessments (U.S. EPA, 1982, 017610; 1996, 079380; 2004, 056905). A positive association between PM concentration and mortality was consistently demonstrated across studies cited in the 2004 PM AQCD (U.S. EPA, 2004, 056905); these results are summarized below in Section 6.5.1. Numerous studies have been published since the previous review, including a number of multicity analyses and many single-city studies. The current body of evidence examines the association between short-term exposure to PM of various size fractions (i.e., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and UFPs) and mortality through the use of time-series and/or case-crossover studies. Both study designs aim to disentangle the PM-mortality effect through either complex modeling (i.e., time-series) or matching strategies (i.e., case-crossover). Overall, the results of the more recent studies build upon the conclusions from the previous review, showing consistent positive associations between mortality and short-term exposure to $PM_{2.5}$ and $PM_{10-2.5}$.

Section 6.5.2 reviews and summarizes the results of recent studies that examined mortality associations with the four PM size classes listed above. Each section integrates the results of recent studies with those available in previous PM reviews. This assessment first focuses on multicity studies that examined mortality associations with PM_{10} because this is an important body of literature that provides information on potential effect modifiers, potential confounding by copollutants, evaluation of concentration-response relationships, and the influence of different modeling approaches on the PM-mortality relationship (Section 6.5.2.1). The PM_{10} studies have provided the most data among the PM indices thus far; therefore this evaluation begins with the consideration of those findings as they relate to the general association between PM and mortality. It is difficult to interpret the extent to which these studies inform an evaluation of the effects of $PM_{2.5}$ or $PM_{10-2.5}$, since data are combined from multiple cities with different PM composition. Interpretations of the PM size fraction that contributes the most to the PM_{10} effects observed are provided when appropriate in the following review. The multicity studies that examine the association between PM_{10} and mortality also offer new evidence on regional and seasonal differences in effect estimates, building upon observations made in the 2004 PM AQCD (U.S. EPA, 2004, 056905).

Recent study findings on associations with $PM_{2.5}$, $PM_{10-2.5}$, and UFPs are evaluated in Sections 6.5.2.2, 6.5.2.3, and 6.5.2.4, respectively. For $PM_{2.5}$, the focus of the assessment remains on multicity study findings; however, for $PM_{10-2.5}$ and UFPs, some additional emphasis is placed on single-city studies, due to the relative sparseness of peer-reviewed literature on these size fractions. Some studies have also evaluated relationships between mortality and specific components and sources of PM, and the results are summarized in Sections 6.5.2.4 and 6.5.2.5. Finally, Section 6.5.2.6 assesses evidence on the concentration-response relationship between short-term PM exposure and mortality.

6.5.1. Summary of Findings from 2004 PM AQCD

The 2004 PM AQCD (U.S. EPA, 2004, 056905) found strong evidence that PM_{10} and $PM_{2.5}$, or one or more $PM_{2.5}$ components, acting alone and/or in combination with gaseous copollutants, are associated with total (nonaccidental) mortality and various cause-specific mortality outcomes. For PM_{10}, several multicity studies in the U.S., Canada, and Europe provided strong support for this conclusion, reporting associations with total mortality highlighted by effect estimates ranging from ~0.2 to 0.7% (per 10 $\mu g/m^3$ increase in PM_{10}) (U.S. EPA, 2004, 056905). Numerous studies also reported PM_{10} associations with cause-specific mortality, specifically cardiovascular- and respiratory-related mortality. For $PM_{2.5}$, the strength of the evidence varied across categories of cause-specific mortality, with relatively stronger evidence for associations with cardiovascular compared to respiratory mortality. The resulting effect estimates reported from the U.S.- and Canadian-based studies (both multi- and single-city) analyzed for these two categories ranged from 1.2 to 2.7% for cardiovascular-related mortality and 0.8 to 2.7% for respiratory-related mortality, per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (U.S. EPA, 2004, 056905). In regards to $PM_{10-2.5}$, the PM AQCD found a limited body of evidence that was suggestive of associations between short-term exposure to ambient $PM_{10-2.5}$ and various mortality outcomes (e.g., 0.08-2.4% increase in total [nonaccidental] mortality per 10 $\mu g/m^3$ increase in $PM_{10-2.5}$). The positive effect estimates obtained from studies that analyzed the association between $PM_{10-2.5}$ and mortality resulted in the conclusion that $PM_{10-2.5}$, or some

constituent component(s) (including those on the surface) of $PM_{10-2.5}$, may contribute, in certain circumstances, to increased human health risks.

Some additional studies examined the association between specific $PM_{2.5}$ chemical components and mortality. These studies observed associations for SO_4^{2-}, NO_3^-, and CoH, but not crustal particles. The strength of the association for each component varied from city to city (U.S. EPA, 2004, 056905). Source-oriented analyses were also conducted to identify specific source-types associated with mortality. These studies implicate $PM_{2.5}$ from anthropogenic origin, such as motor vehicle emissions, coal combustion, oil burning, and vegetative burning, as being important in contributing to increased mortality (U.S. EPA, 2004, 056905).

6.5.2. Associations of Mortality and Short-Term Exposure to PM

The recent literature examines the association between short-term exposure to various PM size fractions (i.e., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, UFPs, or species [e.g., OC, EC, transition metals, etc.]) and mortality. This ISA, similar to previous AQCDs, focuses more heavily on multicity studies, and especially those conducted in the U.S. and Canada (Table 6-15). By using this approach it is possible to: (1) obtain a more representative sample of or insight into the PM-mortality relationship observed across the U.S.; (2) analyze the association between mortality and short-term exposure to PM at or near ambient conditions observed in the U.S.; (3) examine the potential heterogeneity in effect estimates between cities and regions; and (4) analyze the confounders and/or effect modifiers that may explain the PM-mortality relationship in the U.S. Although this section focuses on mortality outcomes in response to short-term exposure to PM, it does not evaluate studies that examine the association between PM and infant mortality. These studies are evaluated in Section 7.5,,although it is possible that short- and long-term in utero exposures may contribute to infant mortality. In addition, the exposure windows of interest for this unique health outcome can be difficult to characterize and may span both short- and long-term exposure periods.

Table 6-15. Overview of U.S. and Canadian multicity PM studies of mortality analyzed in the 2004 PM AQCD and the PM ISA[b].

Study	Location	Mean Concentration ($\mu g/m^3$)	98th; 99th Percentiles ($\mu g/m^3$)	Upper Percentile: Concentrations ($\mu g/m^3$)
PM_{10}				
Dominici et al. (2003, 156407)[a]	90 U.S. cities	15.3-53.2	---	NR
Burnett and Goldberg (2003, 042798)[a]	8 Canadian cities	25.9	---	95th: 54; Maximum: 121
Peng et al. (2005, 087463)	100 U.S. cities	13-49	---	50th: 27.1; 75th: 32.0 Maximum: 48.7
Dominici et al. (2007, 097361)[f]	100 U.S. cities	13-49	---	50th: 27.1; 75th: 32.0 Maximum: 48.7
Welty and Zeger (2005, 087484)[f]	100 U.S. cities	13-49	---	50th: 27.1; 75th: 32.0 Maximum: 48.7
Bell et al. (2009, 191007)	84 U.S. urban communities	NR	---	NR
Burnett et al. (2004, 086247)	12 Canadian cities	NR	---	NR
Samoli et al. (2008, 188455)	12 Canadian cities 90 U.S. cities[e] 22 European cities	NR	---	NR
Schwartz (2004, 078998)	14 U.S. cities	23-36[d]	---	75th: 31-57
Schwartz (2004, 053506)	14 U.S. cities	23-36[d]	---	75th: 31-57
Zeka et al. (2005, 088068)	20 U.S. cities	15-37.5	---	NR
Zeka et al. (2006, 088749)	20 U.S. cities	15.9-37.5	---	NR

Study	Location	Mean Concentration ($\mu g/m^3$)	98th; 99th Percentiles ($\mu g/m^3$)	Upper Percentile: Concentrations ($\mu g/m^3$)
$PM_{2.5}$				
Burnett and Goldberg (2003, 042798)[a]	8 Canadian cities	13.3	38.9; 45.4	95th: 32; Maximum: 86
Dominici et al. (2007, 097361)	96 U.S. cities	NR	---	NR
Zanobetti and Schwartz (2009, 188462)	112 U.S. cities	13.2	34.3; 38.6	Maximum: 57.4
Franklin et al. (2007, 091257)	27 U.S. cities	15.6	45.8; 54.7	Maximum: 239
Franklin et al. (2008, 097426)[g]	25 U.S. cities	14.8	43.0; 50.9	Maximum: 239.2
Ostro et al. (2006, 087991)	9 California counties	19.9	68.2; 82.0	95th: 61.3; Maximum: 160.0
Ostro et al. (2007, 091354)	6 California counties	18.4	61.2; 70.1	Maximum: 116.1
Burnett et al. (2004, 086247)	12 Canadian cities	12.8	38.0; 45.0	Maximum: 86.0
$PM_{10-2.5}$				
Burnett and Goldberg (2003, 042798)[a]	8 Canadian cities	12.6	---	95th: 30; Maximum: 99
Zanobetti and Schwartz (2009, 188462)	47 U.S. cities	11.8	40.2; 47.2	Maximum: 88.3
Burnett et al. (2004, 086247)	12 Canadian cities	11.4	---	Maximum: 151
Villeneuve et al. (2003, 055051)	Vancouver, Canada	6.1	---	90th: 13.0; Maximum: 72.0
Klemm et al. (2004, 056585)	Atlanta, Georgia	9.7	20.7	50th: 9.34; 75th: 11.94 Maximum: 25.17
Slaughter et al. (2005, 073854)	Spokane, Washington	NR	---	NR
Wilson et al. (2007, 157149)	Phoenix, Arizona	NR	---	NR
Kettunen et al. (2007, 091242)	Helsinki, Finland	Cold season: 6.7[d] Warm season: 8.4[d]	---	Cold season: 50th: 6.7 75th: 12.5; Maximum: 101.4 Warm season: 50th: 8.4 75th: 11.8; Maximum: 42.0
Perez et al. (2008, 156020)	Barcelona, Spain	Saharan Dust Days: 16.4 Non-Saharan Dust Days: 14.9	---	Saharan Dust Days 50th: 14.8; 75th: 21.8 Maximum: 36.7 Non-Saharan Dust Days 50th: 12.6; 75th: 18.9 Maximum: 93.1

[a] Multicity studies examined in the 2004 PM AQCD (U.S. EPA, 2004, 056905)
[b] Because only two multicity study was identified that examined $PM_{10-2.5}$, single-city and international studies that examined $PM_{10-2.5}$ were analyzed in this ISA and are included in this table.
[c] The majority of multicity studies examined in the PM ISA provide the mean PM concentration of each individual city, not an overall PM concentration across all cities. As a result, the range of PM concentrations for a particular study are presented, which represents the lowest and highest mean PM concentrations reported across cities, if an overall mean is not provided within the study.
[d] Median PM concentration.
[e] The study included 90 U.S. cities in the 1-day lag analysis, but only 15 U.S. cities in the analysis of the average of lag days 0-1.
[f] The concentrations reported for these studies were estimated from Peng et al. (2005, 087463) because they used the same number of cities and years of data from NMMAPS.
[g] This study did not present an overall mean 24-h avg $PM_{2.5}$ concentration across all cities for each season. The range of mean 24-h avg concentrations reported in this table for each season represents the lowest mean 24-h avg $PM_{2.5}$ concentration and the highest 24-h avg $PM_{2.5}$ concentration reported across all cities included in the study.

6.5.2.1. PM_{10}

The majority of studies that examined the association between short-term exposure to PM and mortality focused on effects attributed to PM_{10}. Although these studies do not characterize the compositional differences in PM_{10} across the cities examined in each of the studies evaluated, they can provide an underlying basis for the overall pattern of associations observed when examining the relationship between $PM_{10-2.5}$ and $PM_{2.5}$ and mortality. The studies evaluated in this review analyzed the PM_{10}-mortality relationship through either a time-series or case-crossover design.[1]

[1] Schwartz (1981, 078988) used a case-crossover study design, but also conducted a time-series analysis to validate the results obtained using the case-crossover approach.

Time-Series Analyses

Mortality associations with short-term exposure to PM_{10} in the U.S. have been examined in several updated time-series analyses of the NMMAPS. In the previous NMMAPS analysis (Dominici et al., 2003, 156407; Samet et al., 2000, 005809; Samet et al., 2000, 010269) of the 1987-1994 data, which was reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), the strongest association was found for nonaccidental mortality for 1-day lag, with a combined estimate across 90 cities of 0.21% (95% PI: 0.09-0.33) per 10 $\mu g/m^3$ increase in PM_{10}. The association was found to be robust to the inclusion of other gaseous copollutants in the regression models, but the investigators found heterogeneity across regions, with the strongest associations in northeastern cities. In the new updated analyses, the investigators examined additional issues surrounding the association between PM and mortality including: seasonal effect modification; change in risk estimates over time; sensitivity of results to alternative weather models; and effect modification by air conditioning use. The NMMAPS data has also been used to examine the PM concentration-response relationship using PM_{10} data from 20 cities (Section 6.5.2.7). A few multicity studies conducted in Canada and Europe provide additional information, which further clarifies and supports the association between PM and mortality presented in the NMMAPS analyses.

Seasonal Analyses of PM_{10}-Mortality Associations

Using the updated NMMAPS data, which consisted of 100 U.S. cities for the period 1987-2000, Peng et al. (2005, 087463) examined the effect of season on PM_{10}-mortality associations. In their first stage regression model, for each city, the PM_{10} effect was modeled to have a sinusoidal shape that completes a cycle in a year, but was constrained to be periodic across years using sine/cosine terms. The authors also considered a model that consisted of PM_{10}-season interactions using season indicators. Both of these models also included covariates that were used in their earlier NMMAPS analyses. In the second stage model, the seasonal patterns of PM_{10} mortality coefficients were estimated for seven geographic regions and on average for the entire U.S. Peng et al. (2005, 087463) found for 1-day lag, at the national level, season specific increases in nonaccidental mortality per 10 $\mu g/m^3$ increase in PM_{10} of: 0.15% (95% PI: -0.08 to 0.39), 0.14% (95% PI: -0.14 to 0.42), 0.36% (95% PI: 0.11-0.61), and 0.14% (95% PI: -0.06 to 0.34) for winter, spring, summer, and fall, respectively. The corresponding all-season estimate was 0.19% (95% PI: 0.10-0.28). After the inclusion of SO_2, O_3, or NO_2 in the model with PM_{10} in a subset of cities (i.e., 45 cities) for which data existed, PM_{10} risk estimates remained fairly robust. An analysis by geographic region found a strong seasonal pattern in the Northeast. Figure 6-16 presents the estimated seasonal pattern of PM_{10} risk estimates by region from Peng et al. (2005, 087463), which includes a sensitivity analysis aimed to determine the appropriate number of degrees of freedom for temporal adjustment. It is clear from Figure 6-16 that the Northeast has the strongest association with PM_{10} and mortality, which peaks in the summer and is robust to the extent of temporal adjustment. The industrial Midwest also shows the summer peak, but with smaller risk estimates. Other regions have either no seasonal pattern (Southeast) or a suggestion of a spring peak that appears to be sensitive to the extent of temporal adjustment. On a nationwide basis, the PM_{10} risk estimates appear to peak between spring and summer. Overall, this study identified an effect modifier that may be useful in identifying the specific chemical component(s) of PM that are related to specific regions and times of the year.

Change in PM_{10}-Mortality Associations over Time

Dominici et al. (2007, 097361) conducted an analysis of the extended NMMAPS data set (i.e., 1987-2000) to examine if short-term PM_{10}-mortality risk estimates changed during the course of the study period. The investigators estimated the average PM_{10} mortality risk coefficient for 1-day lag, using essentially the same model specification as in their 2003 analysis, separately for three time periods (i.e., 1987-1994, 1995-2000, and 1987-2000) the ‘‘eastern U.S.’’ (62 counties), the ‘‘western U.S.’’ (38 counties), and all 100 U.S. counties. To produce national and regional estimates, two-stage hierarchical models were used as in the previous NMMAPS studies. As shown in Table 6-16, the authors found a continuation of the PM_{10}-mortality association in the nationwide data for the entire study period. A comparison of the relative risk estimates for 1987-1994 vs. 1995-2000 suggests weak evidence (not a statistically significant difference) that short-term effects declined. Most of the decline in the national estimate appears to be attributable to the eastern U.S. counties. However, the decline in the risk estimate for all-cause mortality in the eastern U.S. appears to be

disproportionately influenced by the reduction in the risk estimate for the "other" mortality category (i.e., all-cause minus cardio-respiratory category, which may be 40-50% of all-cause deaths in U.S. cities). Likewise, the apparent increase in the risk estimate for all-cause mortality in the western U.S. appears to be affected by the increase in the risk estimate for the "other" mortality category. Because the study does not clearly identify the specific cause(s) in the "other" mortality category that are affected by PM, interpreting the reduction in risk estimates for all-cause mortality requires caution. In contrast, the apparent reductions (~23%) in PM_{10} risk estimates for cardio-respiratory deaths were more comparable between the two regions.

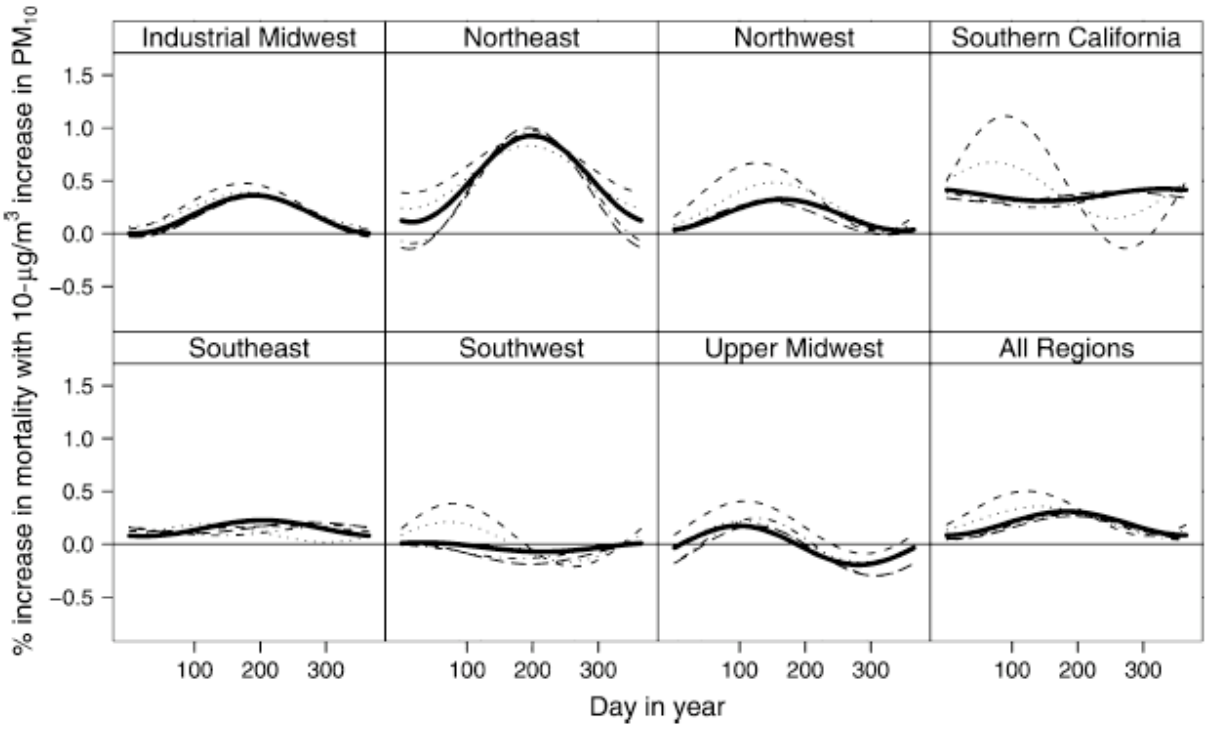


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Figure 6-16. National and regional estimates of smooth seasonal effects for PM_{10} at a 1-day lag and their sensitivity to the degrees of freedom assigned to the smooth function of time in the updated NMMAPS data 1987-2000. Note: The degrees of freedom chosen were 3 df (short-dashed line), 5 df (dotted line), 7 df (solid line), 9 df (dotted-and-dashed line), and 11 df (long-dashed line) per year of data.

In addition, the investigators estimated time-varying PM_{10} mortality risk as a linear function of calendar time for the period 1987-2000, producing the percentage rate change in the PM_{10} risk estimate with a change in time of 1 yr. The estimated rate of decline in slope for all-cause mortality and the combination of cardiovascular and respiratory mortality were -0.012 (95% PI: -0.037 to 0.014) and -0.016 (95% PI: -0.058 to 0.027), respectively. The authors also estimated a $PM_{2.5}$ mortality risk for the period 1999-2000 (discussed in Section 6.5.2.2.).

Table 6-16. NMMAPS national and regional percentage increase in all-cause, cardio-respiratory, and other-cause mortality associated with a 10 μg/m^3 increase in PM_{10} at lag 1 day for the periods 1987-1994, 1995-2000, and 1987-2000.

	1987-1994	95% PI	1996-2000	95% PI	1987-2000	95% PI
ALL CAUSE						
East	0.29	0.12, 0.46	0.13	-0.19, 0.44	0.25	0.11, 0.39
West	0.12	-0.07, 0.30	0.18	-0.07, 0.44	0.12	-0.02, 026
National	0.21	0.10, 0.32	0.18	0.00, 0.35	0.19	0.10, 0.28
CARDIORESPIRATORY						
East	0.39	0.16, 0.63	0.30	-0.13, 0.73	0.34	0.15, 0.54
West	0.17	-0.07, 0.40	0.13	-0.23, 0.50	0.14	-0.05, 0.33
National	0.28	0.14, 0.43	0.21	-0.03, 0.44	0.24	0.13, 0.36
OTHER						
East	0.21	-0.03, 0.44	0.00	-0.49, 0.50	0.15	-0.09, 0.39
West	0.09	-0.21, 0.38	0.23	-0.15, 0.62	0.11	-0.10, 0.33
National	0.15	-0.02, 0.32	0.17	-0.07, 0.41	0.15	0.00, 0.29

Source: Reprinted with Permission of HEI from Dominici et al. (2007, 097361)

The objective of the Dominici et al. (2007, 097361) study described above was motivated by accountability research, the idea of measuring the impact of policy interventions. However, unlike the intervention studies conducted in Hong Kong (Hedley et al., 2002, 040284) and Dublin, Ireland (Clancy et al., 2002, 035270) that were reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), this study was not designed to estimate a reduction in mortality in response to a sudden change in air pollution. In fact, the figure of observed trend in PM_{10} levels presented in the Dominici et al. (2007, 097361) study indicates that the decline in PM_{10} levels during the study period was very gradual, with much of the decline appearing in the first few years (median values of ~33 μg/m^3 in 1987 to ~25 μg/m^3 in 1992, then down to ~23 μg/m^3 in 2000). A flaw in the use of the time-series study design for this type of analysis is that it adjusts for long-term trends, and, therefore, does not estimate the change in mortality in response to the gradual change in PM_{10}. The apparent change, though weak, in the PM_{10} risk estimates may also reflect a potential change in the composition of PM_{10} (i.e., $PM_{10-2.5}$ or $PM_{2.5}$). The study listed a number of PM_{10}-related air pollution control programs that were implemented between 1987 and 2000. Some of these programs, such as the Acid Rain Control Program, did result in major reductions in emissions, and, therefore, could have contributed to the results observed, but the analytic approach used in the study does not allow for a systematic analysis of the effect of air pollution policies on the risk of mortality.

Sensitivity of PM-Mortality Associations to Alternative Weather Models

To examine the sensitivity of PM_{10}-mortality risk estimates to alternative weather models that consider longer lags, Welty and Zeger (2005, 087484) analyzed the updated NMMAPS 100 U.S. cities data. All of the previous NMMAPS analyses only considered temperature and dew point up to 3-day lags. In this analysis, the authors considered various forms of a constrained distributed lag model: (1) containing a step function of temperature with steps at lag 0, 2, 7 and extended to 14 days; (2) similar to (1) but with time-varying coefficients to change over season and study period; and, (3) containing a smooth function to account for non-linearity in the temperature-mortality relationship. With the combination of degrees of freedom for temporal trends and the number of distributed lags, more than 20 models were applied to each of the 3 lag days (0, 1, and 2) of PM_{10}. These city-specific risk estimates were then combined across the 100 cities in the second stage Bayesian model. The combined PM_{10} risk estimates were generally consistent within the lag. In particular, the risk estimates for nonaccidental mortality for lag 1 day ranged between 0.15% and

0.25% per 10 μg/m^3 increase in PM_{10}, and were always statistically significant regardless of the model used. In addition, the range of these point estimates across the models was found to be much narrower than the regression posterior intervals. Thus, the PM_{10} risk estimates at lag 1 day were robust to alternative temperature models that considered temperature effects lasting up to a 2-week period.

In summary, the above three analyses of the updated NMMAPS data provided useful information on PM-mortality risks, resulting in the following conclusions: (1) estimated PM_{10} mortality risk is particularly high in the northeast and in the summer; (2) there remains an overall PM_{10}-mortality association in the 1987-2000 time period as well as the 1995-2000 time period; (3) there is a weak indication that PM_{10}-mortality risk estimates are declining; and (4) PM_{10}-mortality risk estimates were not sensitive to alternative temperature models.

Effect Modification of PM_{10}-Mortality Associations by Air Conditioning Use

It has been hypothesized that air conditioning (AC) use reduces an individual's exposure to PM and subsequently modifies the PM-mortality association. Bell et al. (2009, 191007) investigated the role of AC use on the relationship between PM_{10} and all-cause mortality using the NMMAPS PM_{10} risk estimates from 84 U.S. urban communities from 1987-2000.[1] Bayesian hierarchical modeling was used to examine if AC prevalence (i.e., fraction of households with central or any AC) explained city-to-city variation in PM_{10} risk estimates. The authors calculated yearly, summer-only, and winter-only effect estimates stratified by housing stock that had either central AC or any AC, which includes window units. Risk estimates for lag 1 (previous day) were used in the analysis because this lag showed the strongest association with mortality in the original NMMAPS analyses. Community-specific AC prevalence was calculated from national survey U.S. Census American Housing Survey (AHS) data, which is available every two years. The investigators computed percent change in PM_{10} effect estimates per an additional 20% of the population acquiring AC.

The AC variables were not strongly correlated with socio-economic variables (poverty rate, unemployment, and education) from the U.S. Census (correlation ranged from -0.27 to 0.29). Bell et al. (2009, 191007) found that communities with higher AC prevalence had lower PM_{10} mortality risk estimates for all-cause mortality (-30.4% [95% PI: -80.4 to 19.6] per an additional 20% of the population acquiring any AC; -39.0% [95% PI: -81.4 to 3.3] for central AC), but results were not statistically significant. When restricting the analysis to the summer months and focusing on the 45 cities with summer-peaking PM_{10} concentrations, the authors reported positive, non-significant risk estimates (29.9% [95% PI: -84.0 to 144] per an additional 20% of the population acquiring any AC; -2.0% [95% PI: -60.3 to 64.3] for central AC). A similar analysis was conducted for winter months using data from six cities with winter peaking PM_{10} concentrations, but the confidence bands were too wide (due to the small sample size) for meaningful interpretation.

Although the estimated reductions in PM_{10} all-cause mortality risks from AC use reported in the Bell et al. (2009, 191007) study were not statistically significant, their large magnitude suggests that AC use may reduce an individual's exposure to PM. Given the expected additional increase in AC use in the future, and the results from recent multicity studies, which have reported stronger PM-mortality associations during the warm season, AC use may play a larger role in determining an individuals exposure to PM. Studies that have examined the effect of AC use on the $PM_{2.5}$-mortality association have reported similar results. For example, Franklin et al. (2007, 091257) (discussed in detail in Section 6.5.2.2) found that AC use non-significantly modified $PM_{2.5}$ mortality risk estimates, but the result was suggestive of higher $PM_{2.5}$ effects in cities with lower AC use, especially in cities with summer-peaking $PM_{2.5}$ concentrations. Overall, further investigation is needed to fully understand the relationship between AC use and mortality attributed to short-term exposure to PM.

PM_{10}-Mortality Associations in Canada and Europe

Burnett et al. (2004, 086247) examined the association between mortality and various air pollutants in 12 Canadian cities, and reported that the most consistent association was found for NO_2. For this analysis, PM was measured every 6th day for the majority of the study period, and the PM_{10} concentrations used in the study represent the sum of the $PM_{2.5}$ and $PM_{10\text{-}2.5}$, which were directly measured by dichotomous samplers. The authors found that the simultaneous inclusion of

[1] This study also examined risk estimates for cardiovascular and respiratory hospital admissions in older adults (≥ 65).

NO_2 and PM_{10} in a model, on those days with PM data, greatly reduced the PM_{10} association with nonaccidental mortality, from 0.47% (95% CI: 0.04-0.89) to 0.07% (95% CI: -0.44 to 0.58) per 10 μg/m^3 increase. The previous Canadian multicity analysis (Burnett and Goldberg, 2003, 042798), a re-analysis of Burnett et al. (2000, 010273) reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), did not consider gaseous pollutants. Thus, PM_{10} risk estimates in the Canadian data appear to be more sensitive to NO_2 than those estimates reported in U.S. studies.

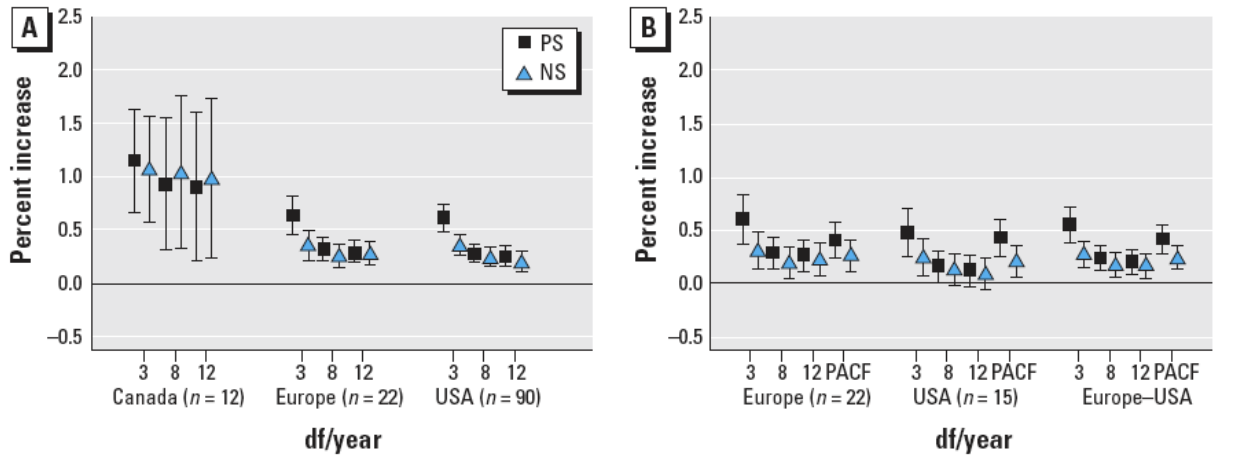
The association between PM_{10} and mortality in Europe was also reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) through Katsouyanni et al. (2003, 042807), which presented results from the APHEA-2 study, a multicity study that examined PM_{10} effects on total mortality in 29 European cities. Analitis et al. (2006, 088177) published a brief report on effect estimates for cardiovascular and respiratory deaths also based on the 29 European cities, within the APHEA2 study. They reported for the average of 0- and 1-day lags, PM_{10} risk estimates per 10 μg/m^3 of 0.76% (95% CI: 0.47-1.05) for cardiovascular deaths and 0.71% (95% CI: 0.22-1.20) for respiratory deaths in random effects models.

Comparison of PM-Mortality Associations in Europe, Canada, and the U.S.

The APHENA study (Samoli et al., 2008, 188455) was a collaborative effort by the APHEA, NMMAPS, and the Canadian multicity study investigators to evaluate the coherence of PM_{10} mortality risk estimates across locations and possible effect modifiers of the PM-mortality relationship using a common protocol. To adjust for temporal trends, Samoli et al. (2008, 188455) used 3, 8, and 12 degrees of freedom (df) with natural splines and penalized splines, as well as the minimization of the sum of the absolute values of the partial auto-correlation function (PACF). The investigators also included a smooth function of temperature on the same day of death and the day before death. The study reported risk estimates for a 1-day lag (from all three data sets), the average of lag day 0 and 1 (all but for the Canadian data because PM data was collected every 6th day), and an unconstrained distributed lag model using lags of 0, 1, and 2 days (all but for the Canadian data). The second-stage regression included: (a) the average pollution level and mix in each city; (b) air pollution exposure characterization (e.g., number of monitors, density of monitors); (c) the health status of the population (e.g., cardio-respiratory deaths as a percentage of total mortality, crude mortality rate, etc.); and (d) climatic conditions (e.g., mean and variance of temperature). In addition, unemployment rate was examined for 14 European cities and all U.S. cities. Effect modification patterns were examined only for cities with complete time-series data and using the average of lags 0 and 1 day, resulting in the exclusion of the Canadian data.

Generally, the risk estimates from Europe and the U.S. were similar, but those from Canada were substantially higher.[1] For example, the percent excess risks per 10 μg/m^3 increase in PM_{10} for all ages using 8 df/yr and penalized splines were 0.84% (95% CI: 0.30-1.40), 0.33% (95% CI: 0.22-0.44), and 0.29% (95% CI: 0.18-0.40) for the Canadian, European, and U.S. data, respectively. Note that the risk estimate for the 90 U.S. cities is slightly larger than that reported in the original NMMAPS study (0.21%, using natural splines, and more temperature variables). In the all ages model, the average of lag days 0 and 1, and the distributed lag model with lags 0, 1, and 2 did not result in larger risk estimates compared to those for a 1 day lag. In copollutant models, PM_{10} risk estimates did not change when controlling for O_3. Figure 6-17 shows the risk estimates from the three data sets for alternative extent of temporal smoothing and smoothing methods. The Canadian data appear less sensitive to the extent of temporal smoothing or smoothing methods (Panel A of Figure 6-17). When stratifying by age the risk estimates for the older age group (≥ 75 yr) were consistently larger than those for the younger age group (<75 yr) (e.g., 0.47% vs. 0.12% for the U.S. data) for all the three data sets. Although the study did not quantitatively present the results from the effect modification analyses, some evidence of effect modification across the study regions was observed. The investigators reported that, in the European data, higher levels of NO_2 and a larger NO_2/PM_{10} ratio were associated with greater PM_{10} risk estimates, and that while this pattern was also present in the U.S. data, it was less pronounced. Additionally, in the U.S. data, smaller PM_{10} risk estimates were observed among older adults in cities with higher O_3 levels. Effect modification by temperature was also observed, but only in the European data.

[1] The risk estimate reported for the 12 Canadian cities examined in the APHENA study is higher than that reported by Burnett et al. (2004, 086247). This is because the APHENA study did not use the 12 cities data from Burnett et al. (2004, 086247), but instead used a composite of the data from three previous studies conducted by the same group by the same group (Burnett and Goldberg, 2003, 042798; 1998, 029505; Burnett et al., 2000, 010273).



Source: Samoli et al. (2008, 188455)

Figure 6-17. Percent increase in the daily number of deaths, for all ages, associated with a 10-μg/m^3 increase in PM_{10}: lag 1 (A) and lags 0 and 1 (B) for all three centers. PACF indicates df based on minimization of PACF.

In this study, the underlying basis for the larger PM_{10} risk estimates (by twofold) in the Canadian data compared to the European and U.S. data could not be identified, even when consistent statistical methods were applied across each of the data sets. Because the effect modification of PM_{10} risk estimates were not examined in the Canadian data, the potential influence of air pollution type or mixture could not be ruled out as a potential source of heterogeneity across the three data sets. It should be noted that both the original U.S. and European studies reported regional heterogeneity in PM risk estimates, and the U.S. data also demonstrated seasonal heterogeneity. In both of these cases the specific characteristics associated with the regions that contributed to the heterogeneity observed were not identified. Thus, further investigation is needed to identify factors that influence the heterogeneity in PM risk estimates observed between different countries and across regions.

Case-Crossover Analyses

Since the 2004 PM AQCD (U.S. EPA, 2004, 056905) investigators have used the case-crossover study design more frequently as an alternative to time-series analyses to examine the association between short-term exposure to PM and mortality. This study design allows for the control of seasonal variation, time trends, and slow time varying confounders without the use of complex models. However, similar to any study design, biases can be introduced into the study depending on the control (i.e., referent) period selected (Janes et al., 2005, 087535). The multicity case-crossover analyses discussed below match cases (i.e., days in which a death occurred) to controls (i.e., days in which a death did not occur), to control for (1) seasonal patterns and gaseous pollutants; or (2) temperature. In addition, the studies attempted to examine the heterogeneity of effect estimates through the analysis of individual-level and city-specific effect modification.

Controlling for Temperature

Schwartz (2004, 078998) investigated the PM_{10}-mortality association in 14 U.S. cities for the years 1986-1993 (some cities started in later years because of PM_{10} data availability) using a case-crossover study design. Note that in this analysis, four more cities (Boulder, CO; Cincinnati, OH; Columbus, OH; and Provo-Orem, UT) were added to the cities Schwartz (2003, 042800) previously analyzed using a time-series study design. These cities were chosen for this analysis because they collected daily PM_{10} data, unlike most U.S. cities, which only monitor PM_{10} every six days. Lag 1-day PM_{10} risk estimates were computed using several methods. Model 1 (i.e., the main model) and Model 2 were constructed from a case-crossover analysis with bidirectional control days

(7-15 days before and after the case). Model 1 obtained city-specific estimates in the first stage analysis, followed by a second stage random-effects model to obtain a combined estimate. Model 2 is the same as Model 1, but consisted of a single stage model, which included data from all 14 cities. Models 3 and 4 were also constructed from a case-crossover analysis, but used time-stratified control days (i.e., matched on season and temperature within the same degree in Celsius). Model 3 obtained single-city estimates in the first stage analysis, followed by a second stage random-effects model to obtain combined estimates. Model 4 used the same approach as Model 3, but consisted of a single stage model including data from all 14 cities. The final model, Model 5 consisted of a two-stage Poisson time-series model, which produced city-specific estimates in the first stage, and combined estimates across cities in the second stage. In the main model the estimated excess risk for nonaccidental mortality was 0.36% (95% CI: 0.22-0.50) per 10 $\mu g/m^3$ increase in PM_{10}. The other models yielded a similar magnitude of effect estimates, ranging from 0.32% (Model 2) to 0.53% (Model 4). Thus, the methods used to select control days and adjust for weather in the case-crossover design did not result in major differences in effect estimates, and in addition, were comparable to the estimates obtained from the time-series analysis, 0.40% (Model 5).

Controlling for Gaseous Pollutants

In a subsequent analysis, Schwartz (2004, 053506) analyzed the same 14 cities data described above, using a case-crossover design, to investigate the potential confounding effects of gaseous pollutants. For each case day, control days were selected from all other days of the same month of the same year. In addition, control days were selected if they had gaseous pollutant concentrations within: 1 ppb, 1 ppb, 2 ppb, or 0.03 ppm for SO_2, NO_2, 1-h max O_3, and CO, respectively, of the case day. Unlike the study described above (Schwartz, 2004, 078998) in this analysis, the excess risk was estimated for the average of 0- and 1-day lag PM_{10} (rather than 1-day lag). In addition, apparent temperature (a composite index of temperature and humidity) was used rather than temperature and humidity individually. The case-crossover analysis was conducted in each city, and a combined estimate was computed in a second-stage random effects model. The number of cities analyzed varied across pollutants depending on the availability of monitors. The study reported PM_{10} risk estimates for nonaccidental mortality of 0.81% (95% CI: 0.47-1.15), 0.78% (95% CI: 0.42-1.15), 0.45% (95% CI: 0.12-0.78), and 0.53% (95% CI: 0.04-1.02) per 10 $\mu g/m^3$ increase, for the analysis matched by SO_2 (10 cities), NO_2 (8 cities), O_3 (13 cities), and CO (13 cities), respectively.

Schwartz (2004, 053506) only presented PM_{10} risk estimates matched by gaseous pollutants, therefore, it is unclear in this analysis how matching by gaseous pollutants affected (i.e., reduced or increased) unmatched PM_{10} risk estimates. The estimates reported were computed using the average of 0- and 1-day lagged PM_{10} and, therefore, cannot be directly compared to the 1-day lag PM_{10} risk estimates obtained in the Schwartz (2004, 078998) 14-city study described above. The estimates reported in the case-crossover analysis that controlled for gaseous pollutants (Schwartz, 2004, 053506) are generally larger than those obtained in the analysis that controlled for temperature (Schwartz, 2004, 078998), which was expected since the Schwartz (2004, 053506) analysis used 2-day avg PM_{10}. However, the estimates reported in Schwartz (2004, 053506) are comparable to the average of 0- and 1-day lagged PM_{10} risk estimate for nonaccidental mortality (0.55% [95% CI: 0.39-0.70]) per 10 $\mu g/m^3$ increase from the 10-city study (Schwartz, 2003, 042800), which was reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Overall, Schwartz (2004, 053506) provided an alternative method to assess the influence of gaseous copollutants. The results suggest that PM_{10} is significantly associated with all-cause mortality after controlling for each of the gaseous copollutants.

City-Level Effect Modification

Zeka et al. (2005, 088068) expanded the 14 cities analyses conducted by Schwartz (2004, 078998; 2004, 053506) to 20 cities, added more years of data (1989-2000), and investigated PM_{10} effects on total and cause-specific mortality using a case-crossover design. Individual 0-, 1-, and 2-day lags as well as an unconstrained distributed lag model with 0, 1, and 2 lag days were examined. For each case day, control days were defined as every third day in the same month of the same year, to eliminate serial correlation. The authors also investigated potential effect modifiers in the second stage regression using city-specific variables including percent using AC, population density, standardized mortality rates, the proportion of elderly in each city, daily minimum apparent

temperature in summer, daily maximum apparent temperature in winter, and the estimated percentage of primary PM_{10} from traffic sources.

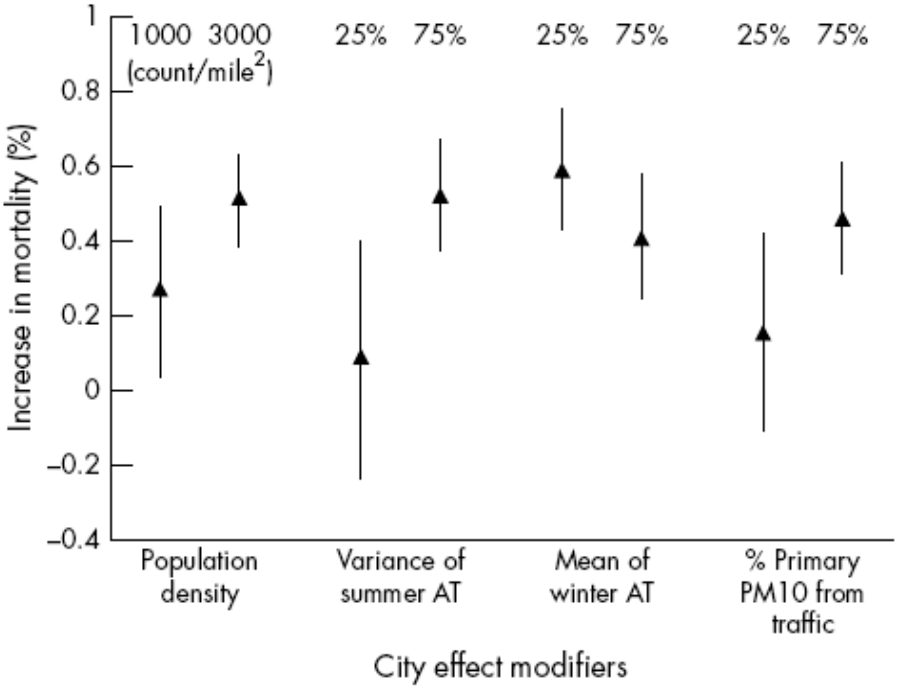


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Figure 6-18. Effect modification by city characteristics in 20 U.S. cities. Note: The two estimates and their CI for each of the modifying factors represent the percentage increase in mortality for a 10 μg/m³ increase in PM_{10}, for the 25th percentile, and 75th percentile of the modifier distribution across the 20 cities.

The investigators found that, for all-cause (nonaccidental) mortality, lag 1 day showed the largest risk estimate (0.35% [95% CI: 0.21-0.49] per 10 μg/m³) among the individual lags. Respiratory mortality exhibited associations at lag 0, 1, and 2 days (0.34%, 0.52%, and 0.51%, respectively), whereas cardiovascular mortality was most strongly associated with PM_{10} at lag day 2 (0.37%). The sum of the distributed lag risk estimates (e.g., 0.45% [95% CI: 0.25-0.65] for all-cause mortality) was generally larger than those for single-day lag estimates. The excess risk estimates for single-day lags for specific respiratory and cardiovascular causes had generally wider confidence intervals due to their smaller daily mortality counts, but some of the categories showed markedly larger estimates when included in the combined distributed lag model (e.g., pneumonia 1.24% [95% CI: 0.46-2.02]). As shown in Figure 6-18, Zeka et al. (2005, 088068) also found evidence indicative of several PM_{10} effect modifiers including higher population density and the estimated percentage of primary PM_{10} from traffic. When 25th versus 75th percentiles of these city-specific variables were evaluated, the estimated percent increase in mortality attributed to PM_{10} appears to contrast substantially (e.g., 0.09% vs. 0.52% for variance of summer time apparent temperature).

The effect modifiers investigated by Zeka et al. (2005, 088068) consisted of city-specific variables. Some of these variables are ecological in nature, and therefore, interpreting the meaning of "effect modification" requires some caution. As the investigators pointed out, the population density and the estimated percentage of primary PM_{10} from traffic were correlated in this data set ($r = 0.65$)[1]. These variables may also be a surrogate for another or composite aspects of "urban" characteristics.

[1] The correlation coefficient was calculated based on the numbers provided in Table 1 of Zeka et al. (2005, 088068).

Thus, the apparent effect modification by traffic-related PM_{10} needs further investigation. Interestingly, the percent of homes with central AC was not a significant effect modifier of PM_{10} risk estimates, which questions the impact of reduced building ventilation rates on PM exposure. Overall, this study presented PM_{10} risk estimates that are consistent with those found in other analyses, but also provided new information on the risk estimated for broad and specific respiratory and cardiovascular mortality designations, along with possible effect modifying city-specific characteristics.

Individual-level Effect Modification

In an additional analysis, Zeka et al. (2006, 088749) examined individual-level, instead of city-specific, effect modification of PM_{10}-mortality associations in the 20 U.S. cities described above using the same case-crossover design. City-specific estimates were obtained in the first stage model, followed by a second stage model which estimated the overall effects across all cities. Figure 6-19 shows PM_{10} excess risks by four of the individual characteristics examined in the study (i.e., gender, race, age group, and education). It should be noted that the lag and averaging of days for the associations reported varied across the outcomes: all-cause and heart disease deaths used the average of lag 1 and 2 days; respiratory deaths used the average of lag 0 through 2 days; MI deaths used lag 0 day; and stroke deaths used lag 1 day. PM_{10} risk estimates do not appear to differ by gender or by race. However, significant differences were found for the youngest vs. oldest age groups for all-cause and heart disease mortality. For all-cause mortality, the level of education appeared to be inversely related to the PM_{10} risk estimates (i.e., greater risk for lower education level), but this observation was not statistically significant. The study also examined effect modification by location of death ("out-of-hospital" versus "in-hospital") and season (Figure 6-20). The "out-of-hospital" deaths showed larger PM_{10} risk estimates than were found for "in-hospital deaths" with a significant difference per 10 $\mu g/m^3$ for all-cause (0.71% versus 0.22%) and heart disease (0.93% versus 0.15%) deaths. Stroke deaths also showed a significant difference (0.87% vs. 0.06%, not shown in Figure 6-20).

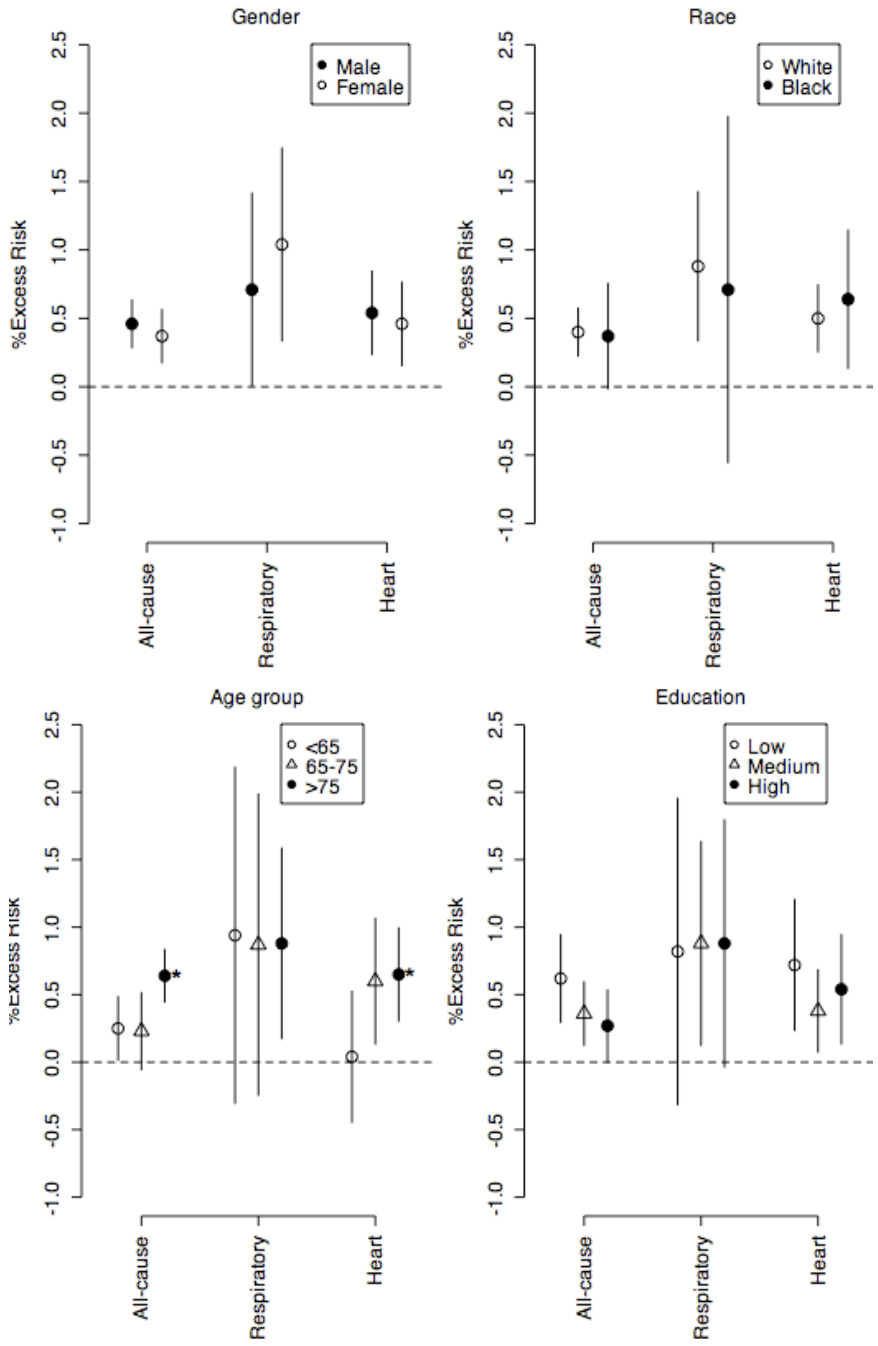


Figure 6-19. Percent excess risk in mortality (all-cause [nonaccidental] and cause-specific) per 10 µg/m^3 increase in PM_{10} by individual-level characteristics. The risk estimates and 95% confidence intervals were plotted using numerical results from tables in Zeka et al. (2006, 088749). The estimates with * next to them are significantly higher than the lowest estimate in the group.

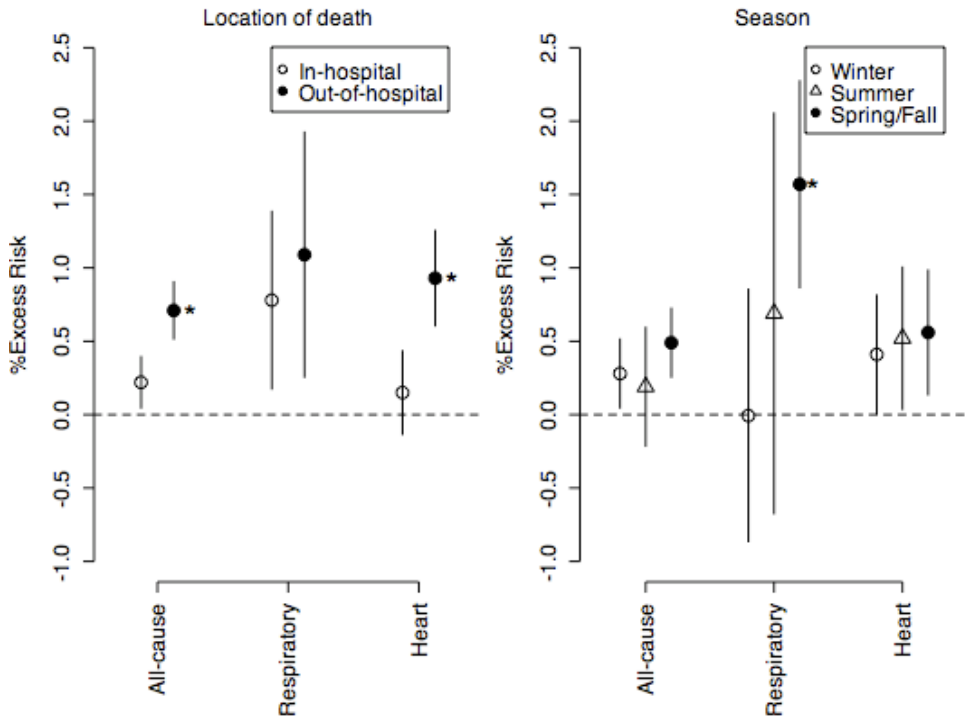
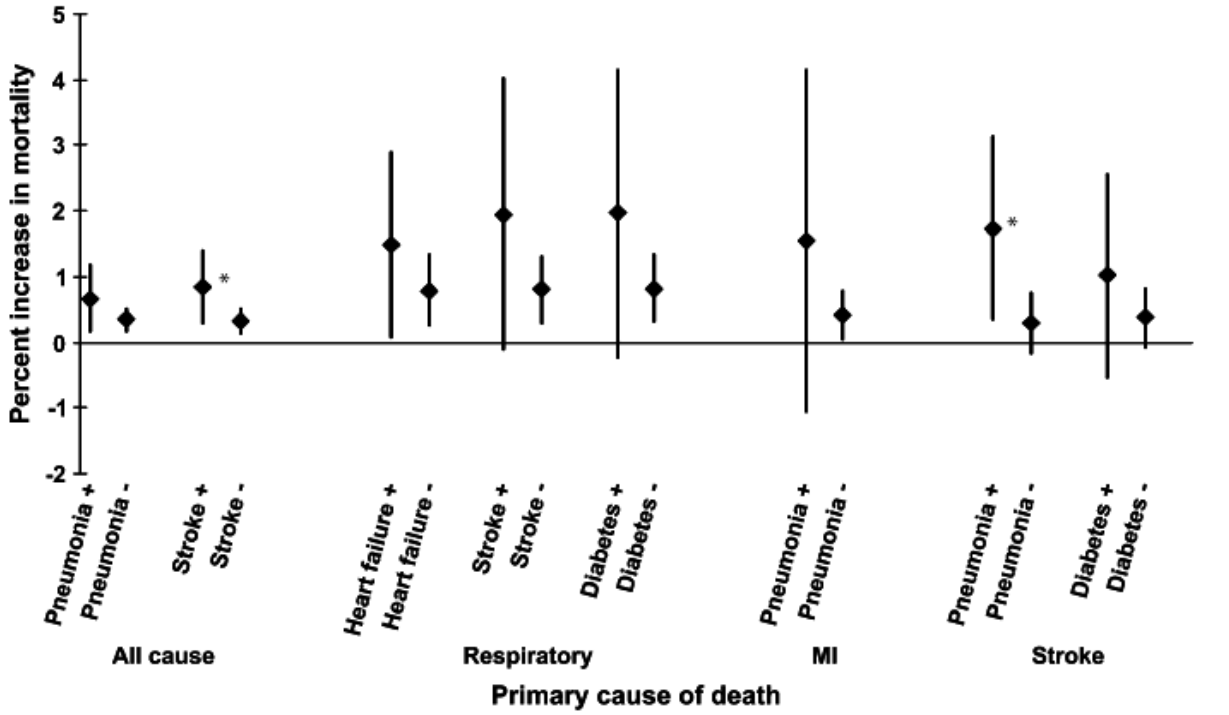


Figure 6-20. Percent excess risk in mortality (all-cause [nonaccidental] and cause-specific) per 10 µg/m^{3}increase in PM_{10} by location of death and by season. The risk estimates and 95% confidence intervals were plotted using numerical results from tables in Zeka et al. (2006, 088749). The estimates with * next to them are significantly higher than the lowest estimate in the group.

Overall, Zeka et al. (2006, 088749) showed a consistent pattern of effect modification by contributing causes of death (i.e., pneumonia, stroke, heart failure, and diabetes) on PM_{10} risk estimates for primary causes of death (Figure 6-21; not all results for contributing cause are shown). However, because the contributing causes of death counts were relatively small, as reflected by the wide confidence intervals in Figure 6-21, most of the differences observed did not achieve statistical significance.



Source: Adatped with Permission of Oxford University Press from Zeka et al. (2006, 088749)

Figure 6-21. Percent increase in mortality (all-cause [nonaccidental] and cause-specific) per 10 µg/m^3 increase in PM_{10} by contributing causes of death. The estimates with * (added to the original figure) indicates a significant difference.

In addition, when examining the other effect modifiers, the results that show no difference in PM_{10} risk estimates between gender or race for all-cause and cardiovascular deaths are important, given the relatively narrow confidence bands of these estimates. The effect modification by the location of death has been reported previously in smaller studies, but the large contrast found for all-cause and cardiovascular mortality in this large multicity analysis is noteworthy. The elevated PM_{10} risks reported by Zeka et al. (2006, 088749) for all-cause, heart disease (and stroke) "out-of-hospital" deaths are also consistent with the hypothesis of acute PM_{10} effects on "sudden deaths" brought on by systemic inflammation or dysregulation of the ANS. The finding regarding the seasonal effect modification, though significant only for respiratory deaths, is somewhat in contrast with the Peng et al. (2005, 087463) analysis of the extended NMMAPS data, which observed the greatest effects during the summer season. The apparent inconsistency may be due to the difference in geographic coverage (i.e., 20 versus 100 cities) or methodology (i.e., case-crossover with referent days in the same month of the same year vs. time-series analysis with adjustment for temporal trend in the regression model).

Summary of PM_{10} Risk Estimates

Overall, the recent studies continue to show an association between short-term exposure to PM and mortality. Although these studies do not examine mortality effects attributed to PM size fractions that compose PM_{10}, the regional, seasonal, and effect modification analyses conducted contribute to the evidence for the $PM_{2.5}$ and $PM_{10-2.5}$ associations presented in Sections 6.5.2.2and 6.5.2.3, respectively. Of the PM_{10} studies evaluated, depending on the lag/averaging time and the number of cities included, the estimates for all-cause (nonaccidental) mortality for all ages ranged from 0.12% (Dominici et al., 2007, 097361) to 0.84% (Samoli et al., 2008, 188455) per 10 µg/m^3 increase in PM_{10}, regardless of the study design used (i.e., time-series vs. case crossover). Although this range of PM mortality risk estimates is smaller than those reported for $PM_{10-2.5}$ and $PM_{2.5}$ they do support the

association between PM and mortality. The majority of studies examined present estimates for either a lag of 1 day or a 2-day avg (lag 0-1), both of which have been found to be strongly associated with the risk of death (Schwartz, 2004, 078998; 2004, 053506). The use of a distributed lag model (using lag 0, 1, and 2 days) was found to result in slightly larger (by ~30%) estimates compared to those for single-day lags in the 20 cities study (Zeka et al., 2005, 088068), but when using the 15 cities data from NMMAPS analyzed in the APHENA study (Samoli et al., 2008, 188455), the 1-day lag combined risk estimate was larger than the distributed lag (lag, 0, 1, and 2 days) estimate. Overall, an examination of the PM_{10} risk estimates stratified by cause-specific mortality and age, for all U.S.- and Canadian-based studies, further supports the findings of the multicity studies discussed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) (i.e., consistent positive associations between short-term exposure to PM_{10} and mortality) and this ISA, however, it must be noted that a large degree of variability exists between cities when examining city-specific risk estimates.

The variability in PM_{10} mortality risk estimates reported within and between multicity studies may be due to the difference in the cities analyzed and the potential regional differences in PM composition. The NMMAPS studies have found that geographic regions and seasons are the two most important factors that determine the variability in risk estimates, with estimates being larger in the eastern U.S. and during the summer. These findings were fairly consistent across studies, but Zeka et al. (2006, 088749) observed the strongest association during the transition period (spring and fall); however, this may be due to the difference in geographic coverage or the difference in the model specification used compared to Peng et al. (2005, 087463).

Finally, examination of potential confounders showed that the size of PM_{10} risk estimates are fairly robust to the inclusion of gaseous copollutants in models (Peng et al., 2005, 087463) or by matching days with similar gaseous pollutant concentrations (Schwartz, 2004, 053506). These findings further confirmed that PM_{10} risk estimates are not, at least in a straightforward manner, confounded by gaseous copollutants.

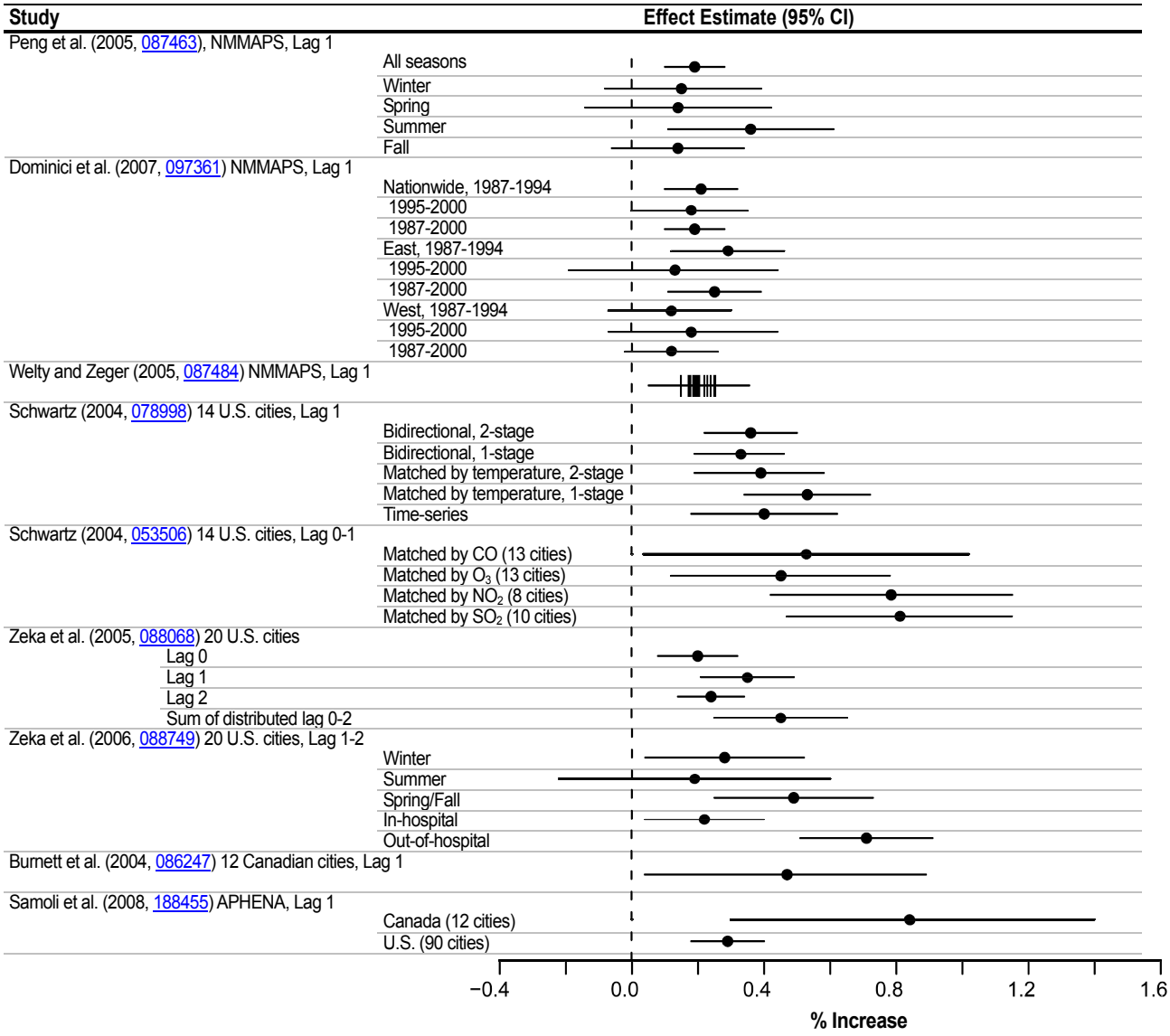


Figure 6-22. Summary of percent increase in all-cause (nonaccidental) mortality from recent multicity studies per 10 μg/m^3 increase in PM_{10}. The number after the study location indicates lag/average used for PM_{10} (e.g., "01" indicates the average of lag 0 and 1 days). For Welty and Zeger (2005, 087484), the vertical lines represent point estimates for 23 different weather models, and the horizontal band spans the 95% posterior intervals of these point estimates.

6.5.2.2. $PM_{2.5}$

A nationwide monitoring system for $PM_{2.5}$ was not established until 1999. This in conjunction with the unavailability of nationwide mortality data from the National Center of Health Statistics (NCHS) starting in 2001[1], has contributed to the relatively small literature base that has examined

[1] In 2008 the EPA facilitated the availability of the mortality data for EPA-funded researchers, which should eventually increase the literature base of studies that examine the association between short-term exposure to $PM_{2.5}$ and mortality.

the association between short-term exposure to $PM_{2.5}$ and mortality. To date, the studies that have been conducted examined national (i.e., in multiple cities across the country) or regional (i.e., in one location of the country) $PM_{2.5}$ associations with mortality.

$PM_{2.5}$ – Mortality Associations on a National Scale

The NMMAPS study conducted by Dominici et al. (2007, 097361) (described in Section 6.5.2.1), also conducted a national analysis of $PM_{2.5}$-mortality associations using the same methodology and data for 1999-2000. The $PM_{2.5}$ risk estimates at lag 1 day were 0.29% (95%PI: 0.01-0.57) and 0.38% (95%PI: -0.07 to 0.82) per 10 $\mu g/m^3$ increase for all-cause and cardio-respiratory mortality, respectively. The authors also conducted a sensitivity analysis of the risk estimates based on the extent of adjustment for temporal trends in the model, changing the degrees of freedom (df) of temporal adjustment from 1 to 20/yr (the main result used 7 df/yr). In comparison to the PM_{10} results, the $PM_{2.5}$ risk estimates appeared more sensitive to the extent of temporal adjustment between 5 and 10 df/yr, but this may be in part due to the much smaller sample size used for the $PM_{2.5}$ analysis (i.e., mortality counts from 1999-2000) compared to the PM_{10} analysis (i.e., mortality counts from 1987-2000).

Franklin et al. (2007, 091257) analyzed 27 cities across the U.S. that had $PM_{2.5}$ monitoring and daily mortality data for at least two years of a 6-yr period, 1997-2002. The mortality data up to year 2000 were obtained from the NCHS, while the 2001-2002 data were obtained from six states (CA, MI, MN, PA, TX, and WA), resulting in 12 out of the 27 cities having data up to 2002. The start year for each city included in the study was set at 1999, except for Milwaukee, WI (1997) and Boston, MA (1998), which is due to $PM_{2.5}$ data availability in these two cities. In the case-crossover analysis in each city, control days for each death were chosen to be every 3rd-day within the same month and year that death occurred in order to reduce autocorrelation. The first stage regression examined the interaction of effects with age and gender, while the second stage random effects model combined city-specific $PM_{2.5}$ risk estimates and examined possible effect modifiers using city-specific characteristics (e.g., prevalence of central AC and geographic region). For all of the mortality categories, the estimates for lag 1 day showed the largest estimates. The combined estimates at lag 1 day were: 1.2% (95%CI: 0.29-2.1), 0.94% (95%CI: -0.14 to 2.0), 1.8% (95%CI: 0.20-3.4), and 1.0% (95%CI: 0.02-2.0) for all-cause, cardiovascular, respiratory, and stroke deaths, respectively, per 10 $\mu g/m^3$. When examining the city-specific risk estimates most of the cities with negative estimates were also those with a high prevalence of central AC (Dallas, 89%; Houston, 84%; Las Vegas, 93%; Birmingham, 77%). It is unclear why these cities exhibit negative (and significant) risk estimates rather than null effects.

In the analysis of effect modifiers, Franklin et al. (2007, 091257) found that individuals $\geq$ 75 yr showed significantly higher $PM_{2.5}$ risk estimates than those individuals < 75 yr. The estimated effects were also found to vary by geographic location with larger estimates in the East than in the West, which are consistent with the regional pattern found in the NMMAPS PM_{10} risk estimates. In addition, a higher prevalence of central AC was associated with decreased $PM_{2.5}$ risk estimates when comparing the lower (25th percentile) versus the higher (75th percentile) AC use rates, especially in the cities where $PM_{2.5}$ concentrations peak in the summer. Finally, the risk estimates were not found to be different between communities with $PM_{2.5}$ concentrations $\leq$ 15 vs. >15 $\mu g/m^3$. The risk estimates for each effect modifier are presented in Figure 6-25. Note the wide confidence intervals associated with each of the risk estimates, specifically for Franklin et al. (2007, 091257) and Ostro et al. (2006, 087991), which suggests low statistical power for testing the differences between effect modifiers.

Franklin et al. (2008, 097426) analyzed 25 cities that had $PM_{2.5}$ monitoring and daily mortality data between the years 2000-2005 (with the study period varying from city to city). The choice of the 25 communities was based on the availability of $PM_{2.5}$ mass concentrations and daily mortality records for at least four years, along with $PM_{2.5}$ speciation data for at least 2 years between 2000 and 2005. Similar to Franklin et al. (2007, 091257), all-cause, cardiovascular, respiratory, and stroke deaths were examined; however, of the 25 cities included in the study, only 15 overlap with the 27 cities analyzed in Franklin et al. (2007, 091257). The authors obtained mortality data from the NCHS and various state health departments (CA, MA, MI, MN, MO, OH, PA, TX, and WA). Although the main objective of the study was to examine the role of $PM_{2.5}$ chemical species in the second stage analysis (Section 6.5.2.5), the first stage analysis conducted a time-series regression of

mortality on $PM_{2.5}$. In addition, the first stage regression performed a seasonal analysis in order to take advantage of seasonal variation in $PM_{2.5}$ chemical species across cities and to possibly explain the city-to-city variation in $PM_{2.5}$ mortality risk estimates. From this analysis a strong seasonal pattern was observed with the greatest effects occurring in the spring and summer seasons (Figure 6-25).

Overall, the risk estimates for all-cause, cardiovascular, and respiratory deaths reported by Franklin et al. (2008, 097426) are comparable to those presented in the 27 cities study (2007, 091257), as shown in Figure 6-26. When comparing the 2007 and 2008 studies conducted by Franklin et al. (2007, 091257; 2008, 097426), although only 15 cities overlap between the two studies and each study was designed differently (i.e., time-series vs. case-crossover), the magnitude of the $PM_{2.5}$ risk estimates reported were similar for the same averaging time, and both studies reported a regional pattern (East > West) similar to that found in the NMMAPS studies previously discussed.

Zanobetti and Schwartz (2009, 188462) conducted a multicity time-series study to examine associations between $PM_{2.5}$ and mortality in 112 U.S. cities. The cities included in this analysis encompass the majority of cities included in the Franklin et al. (2007, 091257; 2008, 097426) analyses. In this analysis a city represents a single county; however, 14 of the cities represent a composite of multiple counties. In addition to examining $PM_{2.5}$, the investigators also analyzed $PM_{10-2.5}$; these results are discussed in Section 6.5.2.3. Zanobetti and Schwartz (2009, 188462) analyzed $PM_{2.5}$ associations with all-cause, cardiovascular disease (CVD), MI, stroke, and respiratory mortality for the years 1999-2005. To be included in the analysis, each of the cities selected had to have at least 265 days of $PM_{2.5}$ data per year and at least 300 days of mortality data per year. The authors conducted a city- and season-specific Poisson regression to estimate excess risk for $PM_{2.5}$ lagged 0- and 1-days, adjusting for smooth functions (natural cubic splines) of days (1.5 df per season), the same-day and previous day temperature (3 df each), and day-of-week. The city specific estimates were then combined using a random effects model. Based on the assumption that climate affects PM exposures (e.g., ventilation and particle characteristics), the investigators combined city-specific estimates into six regions based on the Köppen climate classification scheme (e.g., "Mediterranean climates" for CA, OR, WA, etc.).

The overall combined excess risk estimates were: 0.98 % (95% CI: 0.75, 1.22) for all-cause; 0.85 % (95% CI: 0.46-1.24) for CVD, 1.18 % (95% CI: 0.48-1.89) for MI; 1.78 % (95% CI: 0.96-2.62) for stroke, and 1.68 % (95% CI: 1.04-2.33) for respiratory mortality for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ at lag 0-1. When the risk estimates were combined by season, the spring estimates were the largest for all-cause and for all of the cause-specific mortality outcomes examined. For example, the risk estimate for all-cause mortality for the spring was 2.57% (95% CI: 1.96-3.19) with the estimates for the other seasons ranging from 0.25% to 0.95%. When examining cities that had both $PM_{2.5}$ and $PM_{10-2.5}$ data (i.e., 47 cities), the addition of $PM_{10-2.5}$ in the model did not alter the $PM_{2.5}$ estimates substantially, only decreasing slightly from 0.94% in a single pollutant model to 0.77% in a copollutant model with $PM_{10-2.5}$. When the risk estimates were combined by climatic regions, the estimated $PM_{2.5}$ risk for all-cause mortality were similar (all above 1% per 10 $\mu g/m^3$ increase) for all the regions except for the "Mediterranean" region (0.5%) which includes cities in CA, OR and WA, though the estimates in that region were significantly heterogeneous (Figure 6-24).

Source: Data from Zanobetti and Schwartz (2009, 188462).

Figure 6-23. Percent increase in all-cause (nonaccidental) and cause-specific mortality per 10 μg/m^3 increase in the average of 0- and 1-day lagged $PM_{2.5}$, combined by climatic regions.

The $PM_{2.5}$ risk estimate for all-cause mortality reported by Zanobetti and Schwartz (2009, 188462) for 112 cities (0.98% per 10 µg/m^3 increase in the average of 0- and 1-day lags) is generally consistent with that reported by Franklin et al. (2007, 091257) for 27 cities (0.82% [0.02-1.63]) and Franklin et al. (2008, 097426) for 25 cities (0.74% [95% CI: 0.41-1.07]) using the same 0- and 1-day avg exposure time. The seasonal pattern (i.e., higher risk estimates in the spring) found in this study is also consistent with the result from Franklin et al. (2008, 097426). Figure 6-23 highlights the risk estimates for all-cause, CVD, and respiratory morality combined by region. The regional division based on climatic types used in this study makes it difficult to directly compare the regional pattern of results from previous studies. However, an examination of empirical Bayes-adjusted effect estimates for each of the cities included in the analysis further confirms the heterogeneity observed between some cities and regions of the country (Figure 6-24). It is noteworthy that, unlike NMMAPS, which focused on PM_{10} and indicated larger risk estimates in the northeast, Zanobetti and Schwartz (2009, 188462) found that the all-cause mortality risk estimates were fairly uniform across the climatic regions, except for the "Mediterranean" region.

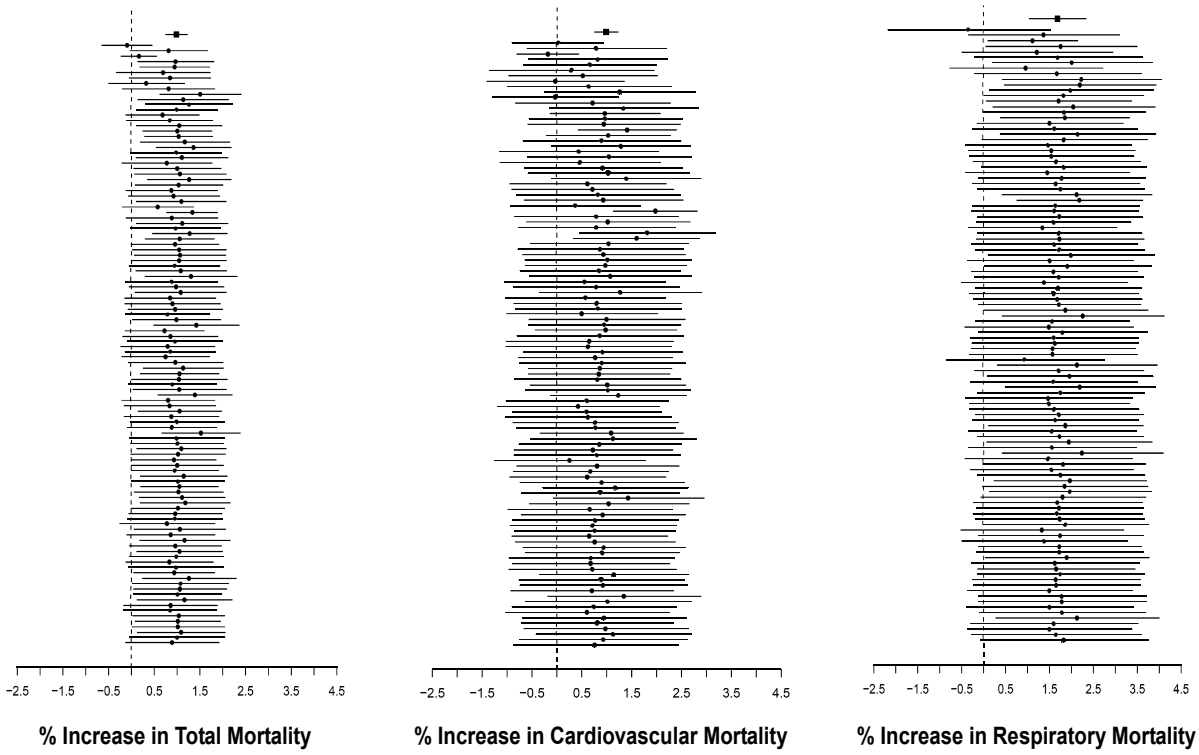


Figure 6-24. Empirical Bayes-adjusted city-specific percent increase in total (nonaccidental), cardiovascular, and respiratory mortality per 10 µg/m^3 increase in the average of 0- and 1-day lagged $PM_{2.5}$ by decreasing mean 24-h avg $PM_{2.5}$ concentrations. Based on estimates calculated from Zanobetti and Schwartz (2009, 188462) using the approach specified in Le Tertre et al. (2005, 087560).

Key to Figure 6-24

City	Mean	98th	City	Mean	98th	City	Mean	98th	City	Mean	98th
Rubidoux, CA	24.7	68.0	Taylors, SC	15.0	32.2	Waukesha, WI	13.4	35.3	Phoenix, AZ	11.4	30.7
Bakersfield, CA	21.7	80.3	Toledo, OH	14.9	36.6	Baton Rouge, LA	13.4	30.1	Tacoma, WA	11.4	38.1
Los Angeles, CA	19.7	51.1	Anaheim, CA	14.9	44.1	Memphis, TN	13.3	32.4	Port Arthur, TX	11.1	25.7
Fresno, CA	18.7	64.9	New York, NY	14.7	38.1	Erie, PA	12.9	36.1	Cedar Rapids, IA	11.0	31.0
Atlanta, GA	17.6	38.2	Washington, PA	14.7	37.0	Dallas, TX	12.8	28.7	Dodge, WI	10.9	32.9
Steubenville, OH	17.1	41.4	Winston, NC	14.7	34.1	Houston, TX	12.8	27.5	Oklahoma, OK	10.8	26.1
Cincinnati, OH	17.1	39.9	Elizabeth, NJ	14.6	38.2	Chesapeake, VA	12.8	29.8	Des Moines, IA	10.5	27.9
Birmingham, AL	16.5	38.8	Philadelphia, PA	14.6	36.6	Wilkes-Barre, PA	12.8	32.5	Jacksonville, FL	10.5	25.3
Middletown, OH	16.5	38.4	St. Louis, MO	14.5	33.7	Norfolk, VA	12.7	29.6	Omaha, NE	10.5	28.0
Indianapolis, IN	16.4	38.2	Allentown, PA	14.4	38.9	Sacramento, CA	12.6	45.0	Denver, CO	10.5	26.4
Cleveland, OH	16.3	40.5	Richmond, VA	14.3	33.0	Springfield, MA	12.5	35.1	Pinellas, FL	10.4	23.1
Dayton, OH	16.3	38.3	Spartanburg, SC	14.2	31.4	New Orleans, LA	12.5	29.0	Austin, TX	10.4	24.5
Columbus, OH	16.2	38.3	Durham, NC	14.2	32.9	Ft. Worth, TX	12.4	27.7	Orlando, FL	10.3	24.3
Detroit, MI	16.2	41.0	Little Rock, AR	14.2	31.8	Pensacola, FL	12.3	31.2	Klamath, OR	10.2	40.7
Akron, OH	16.0	39.0	Easton, PA	14.2	39.7	Davenport, IA	12.3	32.1	Seattle, WA	10.1	27.9
Louisville, KY	15.9	38.0	Raleigh, NC	14.1	31.8	Avondale, LA	12.3	28.6	Medford, OR	10.0	37.3
Chicago, IL	15.8	39.1	Greensboro, NC	14.1	31.0	Boston, MA	12.3	30.2	Bath, NY	9.6	29.3
Pittsburgh, PA	15.7	43.1	Mercer, PA	14.1	36.4	Holland, MI	12.1	35.0	Provo, UT	9.5	38.5
Harrisburg, PA	15.6	40.2	Annandale, VA	14.0	34.6	Charleston, SC	12.1	27.9	Miami, FL	9.4	20.5
Baltimore, MD	15.6	38.8	Nashville, TN	13.9	31.0	Tampa, FL	12.1	25.8	El Paso, TX	9.0	24.4
Youngstown, OH	15.6	38.1	Dumbarton, VA	13.8	31.9	Tulsa, OK	12.1	32.3	Spokane, WA	8.9	30.6
Knoxville, TN	15.5	32.9	Columbia, SC	13.7	30.7	Kansas, MO	12.0	28.6	San Antonio, TX	8.9	21.9
Gary, IN	15.5	37.5	Milwaukee, WI	13.7	36.3	Scranton, PA	11.9	33.0	Portland, OR	8.9	25.4
Charlotte, NC	15.3	32.7	New Haven, CT	13.6	36.8	Hartford, CT	11.8	33.5	Davie, FL	8.4	19.1
Warren, OH	15.2	37.4	Grand Rapids, MI	13.6	36.4	Minneapolis, MN	11.6	31.6	Eugene, OR	8.1	29.9
Washington, DC	15.2	37.2	El Cajon, CA	13.5	34.9	Worcester, MA	11.5	30.2	Palm Beach, FL	7.8	18.4
Wilmington, DE	15.1	37.6	Gettysburg, PA	13.4	36.5	Salt Lake, UT	11.5	52.4	Bend, OR	7.7	23.5
Carlisle, PA	15.1	40.0	State College, PA	13.4	38.5	Providence, RI	11.5	30.5	Albuquerque, NM	6.6	17.9

Note: The top effect estimate in the figures represents the overall effect estimate for that mortality outcome across all cities. The remaining effect estimates are ordered by the highest (i.e., Rubidoux, CA) to lowest (i.e., Albuquerque, NM) mean 24-h $PM_{2.5}$ concentrations across the cities examined. In the key the cities are reported in this order, which represents the policy relevant concentrations for the annual standard, but the policy relevant $PM_{2.5}$ concentrations for the daily standard (i.e., 98th percentile of the 24-h average) are also listed for each city (from Zanobetti and Schwartz (2009, 188462))

$PM_{2.5}$-Mortality Associations on a Regional Scale: California

Ostro et al. (2006, 087991) examined associations between $PM_{2.5}$ and daily mortality in nine heavily populated California counties (Contra Costa, Fresno, Kern, Los Angeles, Orange, Riverside, Sacramento, San Diego, and Santa Clara) using data from 1999 through 2002. The authors used a two-stage model to examine all-cause, respiratory, cardiovascular, ischemic heart disease, and diabetes mortality individually and by potential effect modifier (i.e., age, gender, race, ethnicity, and education level). The a priori exposure periods examined included the average of 0- and 1-day lags (lag 0-1) and the 2-day lag (lag 2). The authors selected these non-overlapping lags (i.e., rather than selecting lag 1 as the single-day lag) because previous studies have reported stronger associations at lags of 1 or 2 days or with cumulative exposure over three days. It is unclear why the investigators chose these non-overlapping lags (i.e., single-day lag of 2 instead of 1) even though they state they based the selection of their lag days on results presented in previous studies, which found the strongest association for PM lagged 1 or 2 days. Using the average of 0- and 1-day lags Ostro et al.

(2006, 087991) reported combined estimates of: 0.6% (95% CI: 0.2-1.0), 0.6% (95% CI: 0.0-1.1), 0.3% (95% CI: -0.5 to 1.0), 2.2% (95% CI: 0.6-3.9), and 2.4% (95% CI: 0.6-4.2) for all-cause, cardiovascular, ischemic heart disease, respiratory, and diabetes deaths, respectively, per 10 $\mu g/m^3$. The authors also conducted a sensitivity analysis of risk estimates based on the extent of temporal adjustment, which showed monotonic reductions for all of the death categories examined when 4, 8, and 12 degrees of freedom per year were used.

Five of the nine counties examined in the Ostro et al. (2006, 087991) analysis contain cities that are among the 27 cities examined in the Franklin et al. (2007, 091257) analysis for the same period, 1999-2002. While the lags used were different between these two studies, both presented $PM_{2.5}$ risk estimates in individual cities or counties (graphically in the Franklin et al. study (2007, 091257); in a table in the Ostro et al. study (2006, 087991)), which allowed for a cursory evaluation of consistency between the two analyses. In Franklin et al. (2007, 091257), $PM_{2.5}$ risk estimates at lag 1 day for the cities Los Angeles and Riverside were slightly negative, whereas Fresno, Sacramento, and San Diego showed positive values above 1% per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The 2-day lag result presented in Ostro et al. (2006, 087991) is qualitatively consistent, with Los Angeles and Riverside, both of which show slightly negative estimates, while the other 3 locations all show positive, but somewhat smaller estimates, than those reported by Franklin et al. (2007, 091257). The estimates for the average of 0- and 1-day lags for these five counties in Ostro et al. (2006, 087991), which contain cities examined in Franklin et al. (2007, 091257), were all positive. Thus, these two $PM_{2.5}$ studies showed some consistencies in risk estimates even though they used different lag periods and a different definition for the study areas of interest (i.e., counties vs. cities). The risk estimates for Franklin et al. (2007, 091257) and Ostro et al. (2006, 087991), stratified by various effect modifiers (e.g., gender, race, etc.), are summarized in Figure 6-25. Of note is the contrast in the results presented for the effect modification analysis for "in-hospital" versus "out-of-hospital" deaths for Ostro et al. (2006, 087991), which differs from the results presented in the PM_{10} study conducted by Zeka et al. (2006, 088749). Ostro et al. (2006, 087991) observed comparable risk estimates for "in-hospital" vs. "out-of-hospital" deaths, whereas Zeka et al. (2006, 088749) observed a large difference between the two in the 20 cities study discussed earlier. This difference in effects observed between the two studies is more than likely due to the compositional differences in PM_{10} in the cities examined in Zeka et al. (2006, 088749) (i.e., PM_{10} more or less dominated by $PM_{2.5}$ and the subsequent composition of $PM_{2.5}$).

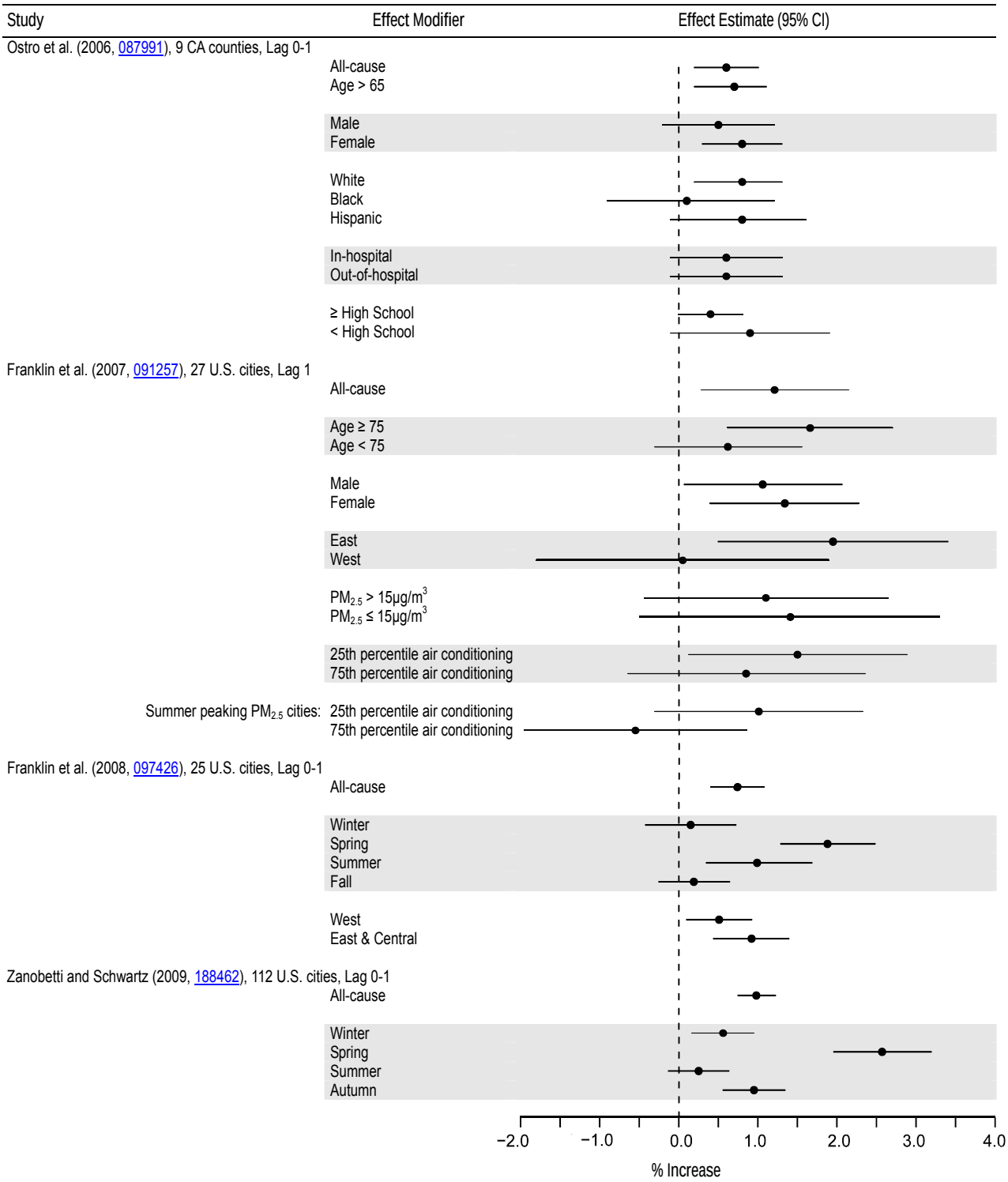


Figure 6-25. Summary of percent increase in all-cause (nonaccidental) mortality per 10 µg/m^3 increase in $PM_{2.5}$ by various effect modifiers.

$PM_{2.5}$-Mortality Associations in Canada

An analysis of multiple pollutants, including $PM_{2.5}$, in 12 Canadian cities found the most consistent associations for NO_2 (Burnett et al., 2004, 086247). In this analysis, $PM_{2.5}$ was only measured every 6th day in much of the study period, and the simultaneous inclusion of NO_2 and $PM_{2.5}$ in a model on the days when $PM_{2.5}$ data were available eliminated the $PM_{2.5}$ association (from 0.60% to -0.10% per 10 $\mu g/m^3$ increase in $PM_{2.5}$). However, the investigators noted that during the later study period of 1998-2000 when daily TEOM $PM_{2.5}$ data were available for 11 of the 12 cities, a simultaneous inclusion of NO_2 and $PM_{2.5}$ resulted in considerable reduction of the NO_2 risk estimate, while the $PM_{2.5}$ risk estimate was only slightly reduced from 1.1% to 0.98% (95% CI: -0.16 to 2.14). Thus, the relative importance of NO_2 and $PM_{2.5}$ on mortality effect estimates has not been resolved when using the Canadian data sets.

Summary of $PM_{2.5}$ Risk Estimates

The risk estimates for all-cause mortality for all ages ranged from 0.29% Dominici et al. (2007, 097361) to 1.21% Franklin et al. (2007, 091257) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Figure 6-26). An examination of cause-specific risk estimates found that $PM_{2.5}$ risk estimates for cardiovascular deaths are similar to those for all-cause deaths (0.30-1.03%), while the effect estimates for respiratory deaths were consistently larger (1.01-2.2%), albeit with larger confidence intervals, than those for all-cause or cardiovascular deaths using the same lag/averaging indices. Figure 6-27 summarizes the $PM_{2.5}$ risk estimates for all U.S.- and Canadian-based studies by cause-specific mortality.

An examination of lag structure observed results similar to those reported for PM_{10} with most studies reporting either single day lags or two-day avg lags with the strongest effects observed on lag 1 or lag 0-1. In addition, seasonal patterns of $PM_{2.5}$ risk estimates were found to be similar to those reported for PM_{10}, with the warmer season showing the strongest association. An evaluation of regional associations found that in most cases the eastern U.S. had the highest $PM_{2.5}$ mortality risk estimates, but this was dependent on the geographic designations made in the study. When grouping cities by climatic regions, similar $PM_{2.5}$ mortality risk estimates were observed across the country except in the Mediterranean region, which included CA, OR, and WA.

Of the studies evaluated, only Burnett et al. (2004, 086247), a Canadian multicity study, analyzed gaseous pollutants and found mixed results, with possible confounding of $PM_{2.5}$ risk estimates by NO_2. Although the recently evaluated U.S.-based multicity studies did not analyze potential confounding of $PM_{2.5}$ risk estimates by gaseous pollutants, evidence from single-city studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggest that gaseous copollutants do not confound the $PM_{2.5}$-mortality association, which is further supported by studies that examined the PM_{10}-mortality relationship.

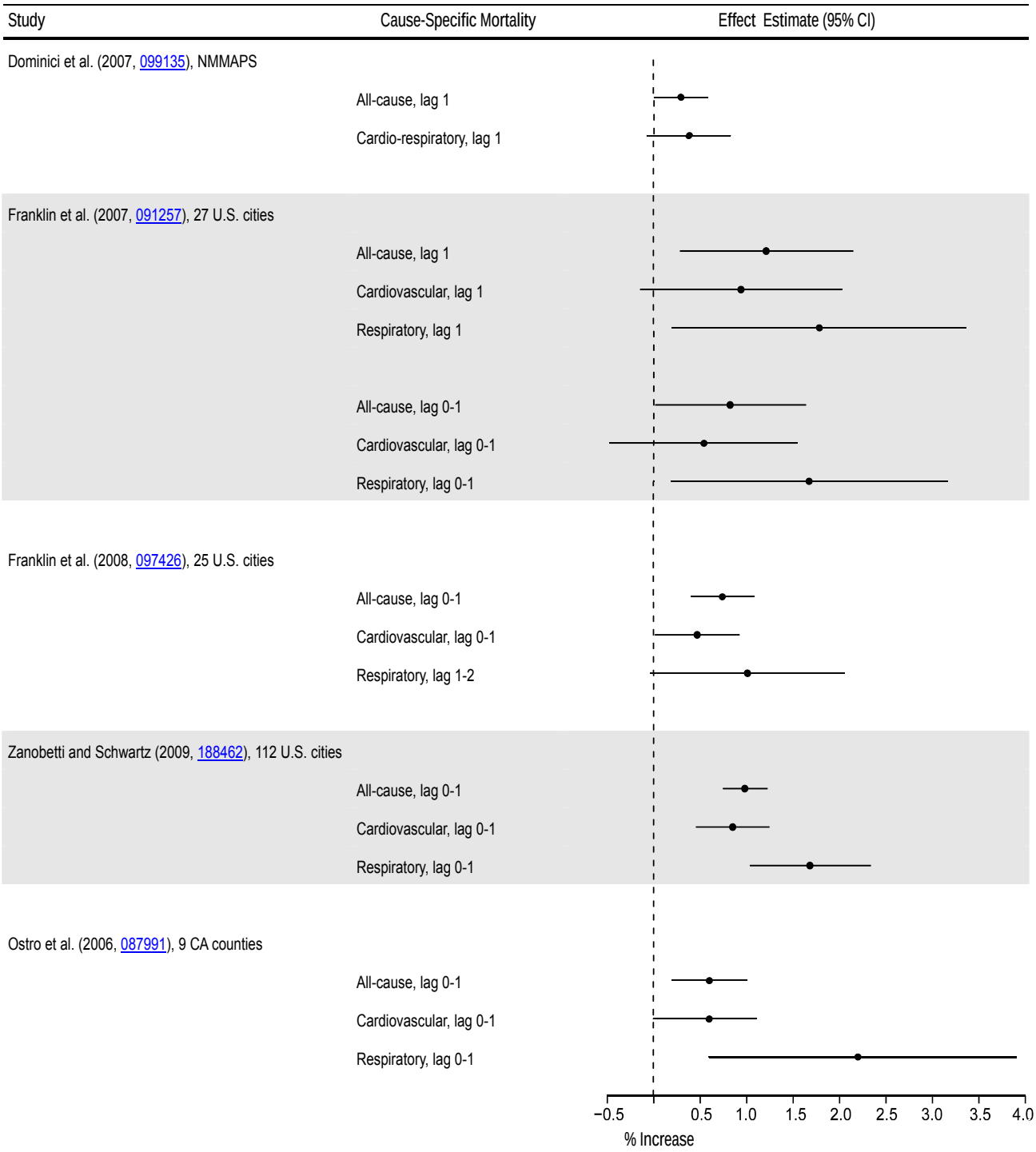


Figure 6-26. Summary of percent increase in all-cause (nonaccidental) and cause-specific mortality per 10 μg/m^3 increase in $PM_{2.5}$ from recent multicity studies.

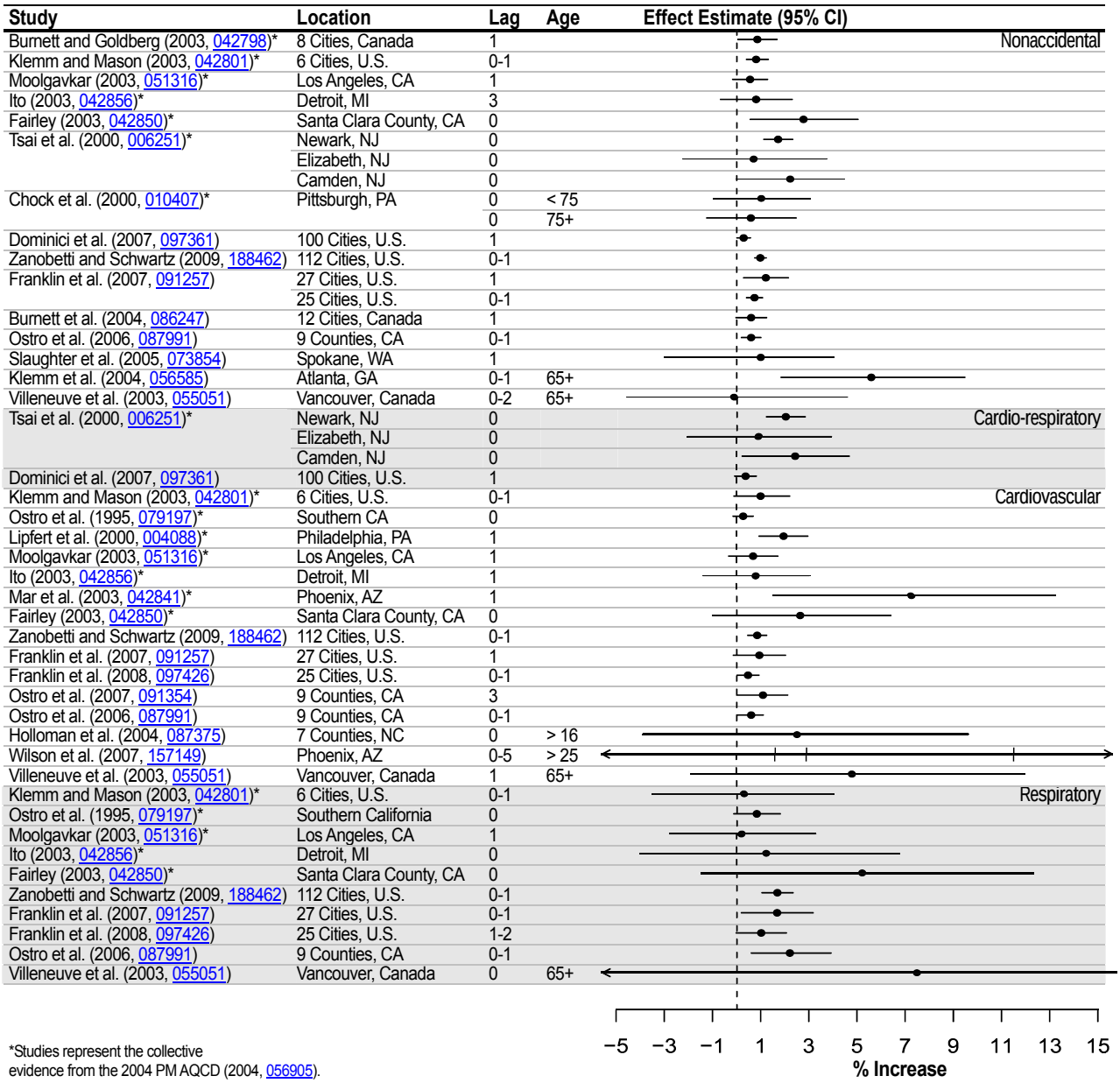


Figure 6-27. Summary of percent increase in all-cause (nonaccidental) and cause-specific mortality per 10 μg/m^3 increase in $PM_{2.5}$ for all U.S.- and Canadian-based studies. The three vertical lines for the Wilson et al. (2007, 157149) estimate represent the central, middle, and outer Phoenix estimates.

6.5.2.3. Thoracic Coarse Particles ($PM_{10-2.5}$)

In the 2004 PM AQCD (U.S. EPA, 2004, 056905), a limited number of studies, mostly single-city analyses, were evaluated that examined thoracic coarse ($PM_{10-2.5}$) PM for its association with mortality. Of these studies a small number examined both $PM_{2.5}$ and $PM_{10-2.5}$ effects, and found some evidence for $PM_{10-2.5}$ effects of the same magnitude as $PM_{2.5}$. However, multiple limitations in these studies were identified including measurement and exposure issues for $PM_{10-2.5}$ and the correlation between $PM_{2.5}$ and $PM_{10-2.5}$. These limitations increased the uncertainty surrounding the concentrations at which $PM_{10-2.5}$-mortality associations are observed.

A thorough analysis of $PM_{10-2.5}$ mortality associations requires information on the speciation of $PM_{10-2.5}$. This is because, while a large percent of the composition of coarse particles may consist of crustal materials by mass, depending on available sources, the surface chemical characteristics of $PM_{10-2.5}$ may also vary from city to city. Thus, without information on the chemical speciation of $PM_{10-2.5}$, the apparent variability in observed associations between $PM_{10-2.5}$ and mortality across cities is difficult to characterize. Although this type of information is not available in the current literature, the relative importance of the associations observed between $PM_{10-2.5}$ and mortality in the following studies is of interest.

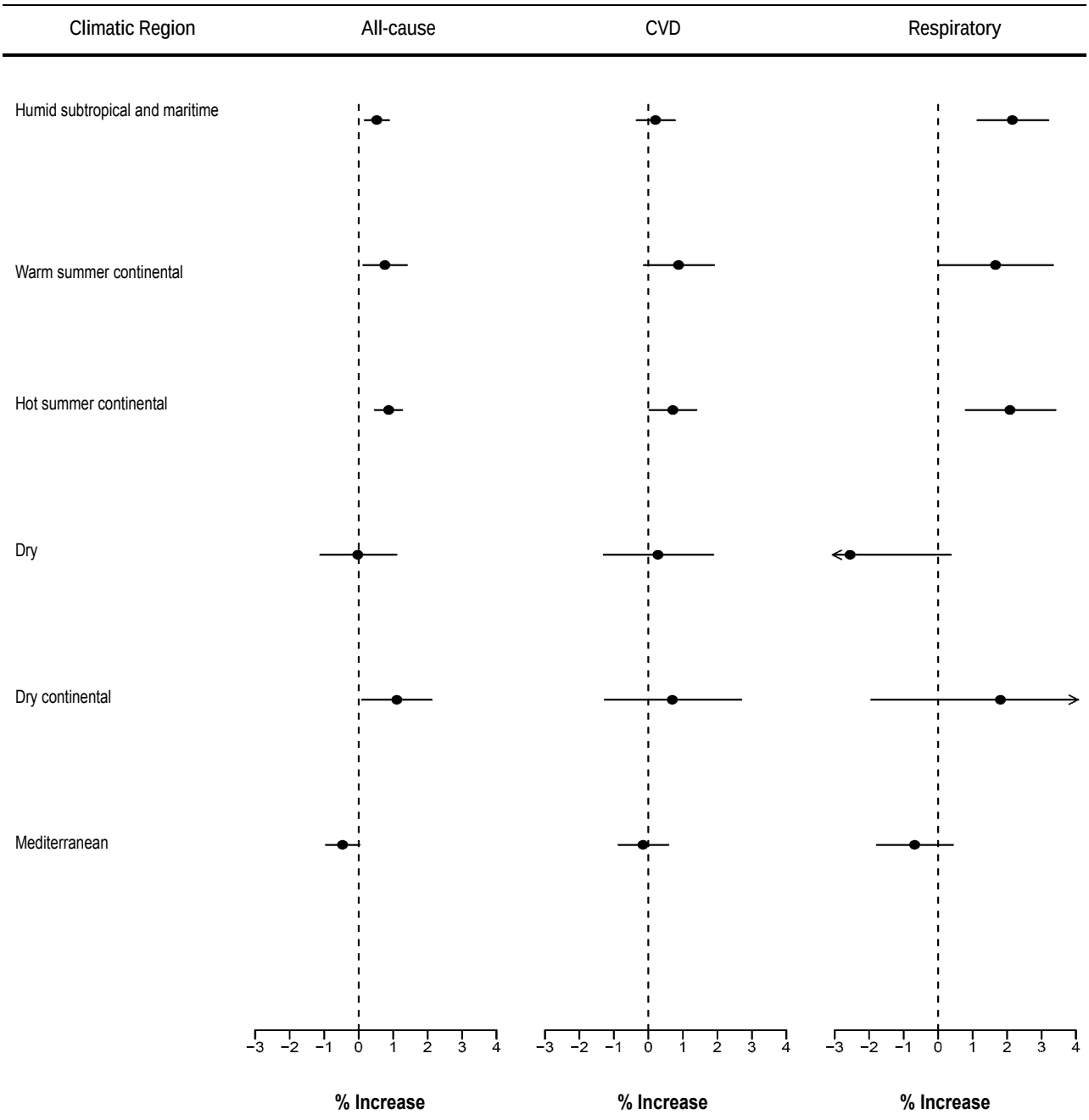
$PM_{10-2.5}$ Concentrations Estimated Using the Difference Method

The Zanobetti and Schwartz (2009, 188462) multicity analysis, described for $PM_{2.5}$ section (Section 6.5.2.2), also examined the association between computed $PM_{10-2.5}$ and all-causes, cardiovascular disease (CVD), MI, stroke, and respiratory mortality for the years 1999-2005. Of the 112 cities included in the $PM_{2.5}$ analysis only 47 cities had both $PM_{2.5}$ and PM_{10} data available. $PM_{10-2.5}$ was estimated in these cities by differencing the countywide averages of PM_{10} and $PM_{2.5}$. In addition to examining the association between $PM_{10-2.5}$ and mortality for the average of lags 0 and 1 day, the investigators also considered a distributed lag of 0-3 days. The risk estimates for $PM_{10-2.5}$ were presented for both a single pollutant model and a copollutant model with $PM_{2.5}$, and were also combined by season and climatic regions as was done in the $PM_{2.5}$ analysis.

The study found a significant association between the computed $PM_{10-2.5}$ and all-cause, CVD, stroke, and respiratory mortality. The combined estimate for the 47 cities using the average of 0- and 1-day lag $PM_{10-2.5}$ for all-cause mortality was 0.46% (95% CI: 0.21-0.71) per 10 $\mu g/m^3$ increase. The estimate obtained using the distributed lag model was smaller (0.31% [95% CI: 0.00-0.63]). The seasonal analysis showed larger risk estimates in the spring for all-cause (1.01%) and respiratory mortality (2.56%) (i.e., the same pattern observed in the $PM_{2.5}$ analysis); however, for CVD mortality, the estimates for spring (0.95%) and summer (1.00%) were comparable. When the risk estimates were combined by climatic region (Figure 6-28), for all-cause mortality, the "dry, continental" region (which included Salt Lake City, Provo, and Denver, all of which had relatively high estimated $PM_{10-2.5}$ concentrations) showed the largest risk estimate (1.11% [95% CI: 0.11-2.11]), but the "dry" region (which included Phoenix and Albuquerque, the two cities with high $PM_{10-2.5}$ concentrations) and the "Mediterranean" region (which included cities in CA, OR, and WA) did not show positive associations. The other three regions (i.e., "hot summer, continental," "warm summer, continental," and "humid, subtropical and maritime"), which included cities that correspond to the mid-west, southeast, and northeast geographic regions as defined in previous NMMAPS analyses, all showed significantly positive associations. Similar regional patterns of associations were found for CVD and respiratory mortality, which are further confirmed when examining the empirical Bayes-adjusted city-specific estimates in Figure 6-29. The regional pattern of associations for MI and stroke are less clear, because of the wider confidence intervals due to the smaller number of deaths in these specific categories. The lack of a $PM_{10-2.5}$-mortality association in the "dry" region reported in this study is in contrast to the results from three studies that analyzed Phoenix data and found associations, as reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), and Wilson et al. (2007, 157149) (discussed below).

Although the results from this analysis are informative because it is the first multicity U.S.-based study that examined the association between short-term exposure to $PM_{10-2.5}$ and mortality on a large scale, some limitations do exist. Specifically, it is not clear how the computed $PM_{10-2.5}$ measurements used by Zanobetti and Schwartz (2009, 188462) compare with the $PM_{10-2.5}$ concentrations obtained by directly measuring $PM_{10-2.5}$ using a dichotomous sampler, or the $PM_{10-2.5}$ concentrations computed using the difference of PM_{10} and $PM_{2.5}$ measured at co-located samplers.

Additional studies evaluated the association between short-term exposure to $PM_{10-2.5}$ and mortality using $PM_{10-2.5}$ concentrations estimated by subtracting PM_{10} from $PM_{2.5}$ concentrations at co-located monitors. Although $PM_{10-2.5}$ concentrations estimated using this approach are not ideal, the results from these studies are informative in evaluating the $PM_{10-2.5}$ mortality association.



Source: Data from Zanobetti and Schwartz (2009, 188462).

Figure 6-28. Percent increase in all-cause (nonaccidental) and cause-specific mortality per 10 μg/m^3 increase in the average of 0- and 1-day lagged $PM_{10-2.5}$, combined by climatic regions.

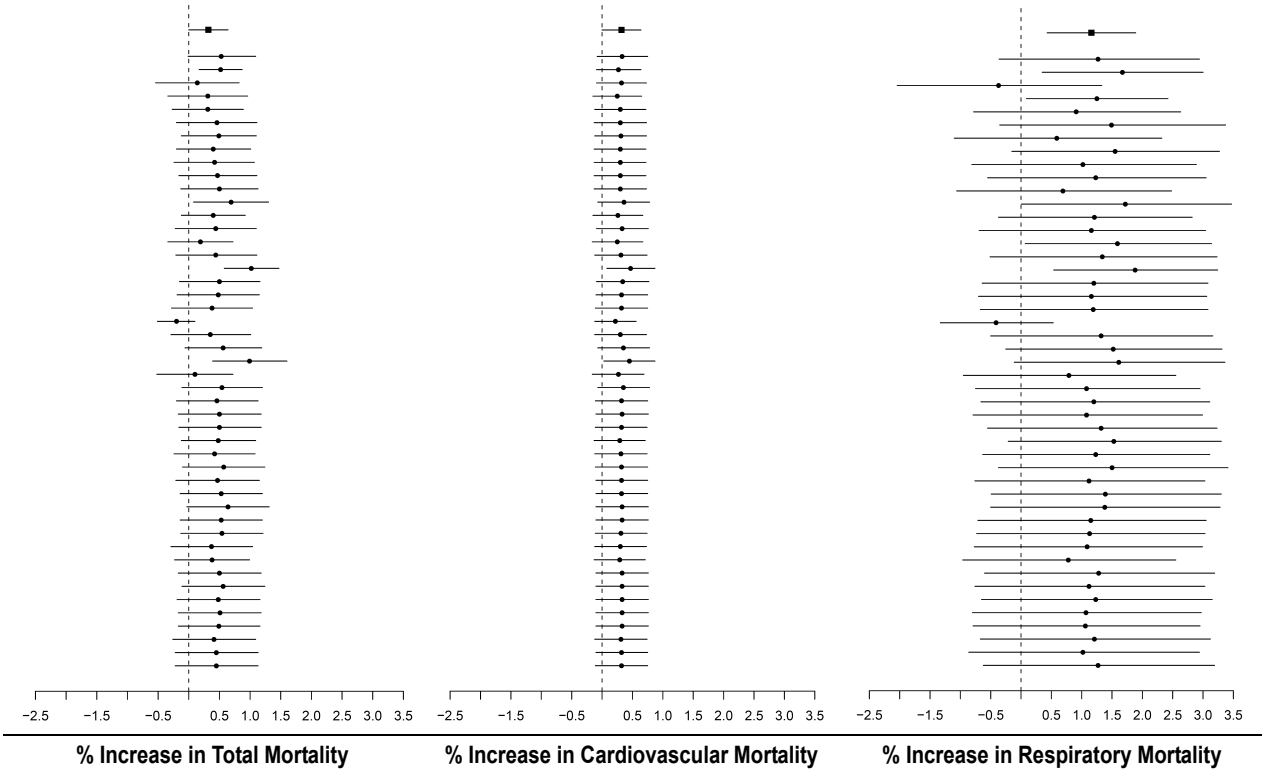


Figure 6-29. Empirical Bayes-adjusted city-specific percent increase in total (nonaccidental), cardiovascular, and respiratory mortality per 10 μg/m^3 increase in the average of 0- and 1-day lagged $PM_{10-2.5}$ by decreasing 98th percentile of mean 24-h avg $PM_{10-2.5}$ concentrations. Based on estimates calculated from Zanobetti and Schwartz (2009, 188462) using the approach specified in Le Tertre et al. (2005, 087560).

Key for Figure 6-29

City	98th	Mean	City	98th	Mean	City	98th	Mean	City	98th	Mean
El Paso, TX	105.1	25.4	Cleveland, OH	51.2	15.2	Sacramento, CA	31.5	10.2	Louisville, KY	23.3	8.3
St. Louis, MO	81.9	15.2	Davenport, IA	49.9	15.3	Tampa, FL	29.1	12.9	Wilkes-Barre, PA	22.2	6.2
Phoenix, AZ	80.1	33.3	Birmingham, AL	49.6	14.2	Toledo, OH	28.8	7.6	New York, NY	22.0	6.4
Detroit, MI	77.5	17.3	Provo, UT	49.3	18.2	Washington, PA	27.8	6.5	Wilmington, DE	21.8	7.0
Gary, IN	71.3	6.9	Chicago, IL	46.1	12.4	Allentown, PA	27.8	4.5	Raleigh, NC	20.9	6.9
Omaha, NE	65.6	24.7	Easton, PA	43.9	12.0	Atlanta, GA	27.4	8.6	Scranton, PA	19.2	6.1
Albuquerque, NM	64.3	22.9	Steubenville, OH	43.5	12.1	Davie, FL	25.5	9.4	Harrisburg, PA	18.6	5.4
New Haven, CT	58.4	11.9	Columbia, SC	42.9	8.4	Taylors, SC	25.4	8.0	Akron, OH	17.7	5.3
Bakersfield, CA	55.9	16.1	Los Angeles, CA	42.5	13.5	Memphis, TN	24.3	9.3	Charleston, SC	17.6	6.6
Des Moines, IA	55.0	16.2	Spokane, WA	41.8	13.8	Seattle, WA	23.7	9.0	Winston, NC	16.5	7.4
Denver, CO	53.8	18.1	Columbus, OH	40.0	11.2	Baltimore, MD	23.5	8.9	Erie, PA	14.9	3.1
Salt Lake, UT	52.6	19.2	Pittsburgh, PA	32.0	9.4	Cincinnati, OH	23.3	7.8			

Note: The top effect estimate in the figures represents the overall effect estimate for that mortality outcome across all cities. The remaining effect estimates are ordered by the highest (i.e., El Paso, TX) to lowest (i.e., Erie, PA) 98th percentile of the mean 24-h $PM_{10-2.5}$ concentrations across the cities examined, which is the policy relevant concentration for the daily standard [from Zanobetti and Schwartz (2009, 188462)].

Slaughter et al. (2005, 073854) examined the association of various PM size fractions (PM_1, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$) and CO with ED visits, HAs, and mortality in Spokane, WA for the period 1995-2001. Although the authors did not report mortality risk estimates for $PM_{10-2.5}$, they did not find an association between any PM size fraction (or CO) and mortality or cardiac HAs at lags of 0-3 days.

Wilson et al. (2007, 157149) examined the association between size-fractionated PM ($PM_{2.5}$ and $PM_{10-2.5}$) and cardiovascular mortality in Phoenix for the study period 1995-1997, using mortality data aggregated for three geographic regions: "Central Phoenix," "Middle Ring," and "Outer Phoenix," which were constructed as a composite of zip codes of residence in order to compare population size among the three areas. The authors reported apparently different patterns of associations between $PM_{2.5}$ and $PM_{10-2.5}$ in terms of the size of the risk estimate across the three areas and temporal patterns of associations. In the "Middle Ring" where $PM_{10-2.5}$ showed the strongest association, the estimated risk per 10 $\mu g/m^3$ increase for a 1 day lag was 3.4% (95% CI: 1.0-5.8). The estimated risk for $PM_{2.5}$ found for "Central Phoenix" was 6.6% (95% CI: 1.1-12.5) for lag 1. The authors speculated that the apparent difference in estimated risks across the areas might be due to the lower SES in "Central Phoenix" or the lower exposure error, but the relatively wide confidence bands of these estimates make it difficult to establish such relationships (Section 8.1.7 for a detailed discussion on SES and susceptibility to PM exposure).

Kettunen et al. (2007, 091242) analyzed UFPs, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, and gaseous pollutants for their associations with stroke mortality in Helsinki during the study period of 1998-2004. The authors did not observe an association between air pollution and mortality for the whole year or cold season, but they did find associations for $PM_{2.5}$ (13.3% [95% CI: 2.3-25.5] per 10 $\mu g/m^3$), PM_{10}, and CO during the warm season, most strongly at lag 1 day. An association was also observed for $PM_{10-2.5}$ during the warm season (7.8% [95% CI: -7.4 to 25.5] per 10 $\mu g/m^3$ at lag 1 day); however, it was weaker than $PM_{2.5}$.

The Perez et al. (2008, 156020) analysis tested the hypothesis that outbreaks of Saharan dust exacerbate the effects of $PM_{2.5}$ and $PM_{10-2.5}$ on daily mortality. Changes of effects between Saharan and non-Saharan dust days were assessed using a time-stratified case-crossover design involving 24,850 deaths between March 2003 and December 2004 in Barcelona, Spain. Saharan dust days were identified from back-trajectory and satellite images. Chemical speciation, but not an analysis for microbes or fungi, was conducted approximately once a week during the study period. On Saharan dust days, mean concentrations were 1.2 times higher for $PM_{2.5}$ (29.9 $\mu g/m^3$) and 1.1 times higher for $PM_{10-2.5}$ (16.4 $\mu g/m^3$) than on non-Saharan dust days. During Saharan dust days (90 days out of 602), the $PM_{10-2.5}$ risk estimate was 8.4% (95% CI: 1.5-15.8) per 10 $\mu g/m^3$ increase at lag 1 day, compared with 1.4% (95% CI: -0.8 to 3.4) during non-Saharan dust days. In contrast, there was not an additional increased risk of daily mortality for $PM_{2.5}$ during Saharan dust days (5.0%

[95% CI: 0.5-9.7]) compared with non-Saharan dust days (3.5% [95% CI: 1.6-5.5]). However, differences in chemical composition (i.e., $PM_{2.5}$ was primarily composed of nonmineral carbon and secondary aerosols; whereas $PM_{10-2.5}$ was dominated by crustal elements) did not explain these observations. Note also when examining all days combined, both size fractions were associated with mortality, but the $PM_{2.5}$ association was found to be stronger.

$PM_{10-2.5}$ Concentrations Directly Measured

In Burnett et al. (2004, 086247), which analyzed the association of multiple pollutants with mortality in 12 Canadian cities, described previously; the authors also examined $PM_{10-2.5}$. In this study the authors collected $PM_{10-2.5}$ using dichotomous samplers with an every-6th-day schedule. When both NO_2 and $PM_{10-2.5}$ were included in the regression model, the $PM_{10-2.5}$ effect estimate was reduced from 0.65% (95% CI: -0.10 to 1.4) to 0.31% (95% CI: -0.49 to 1.1) per 10 $\mu g/m^3$ increase in 1-day lag $PM_{10-2.5}$. These risk estimates are similar to those reported for $PM_{2.5}$, which were also reduced upon the inclusion of NO_2 in the two-pollutant model, but to a greater extent, from 0.60% (95% CI: -0.03 to 1.2) to -0.1% (95% CI: -0.86 to 0.67).

Villeneuve et al. (2003, 055051) analyzed the association between $PM_{2.5}$, $PM_{10-2.5}$, TSP, PM_{10}, SO_4^{2-}, and gaseous copollutants in Vancouver, Canada, using a cohort of approximately 550,000 whose vital status was ascertained between 1986 and 1999. In this study $PM_{2.5}$ and $PM_{10-2.5}$ were directly measured using dichotomous samplers. The authors examined the association of each air pollutant with all-cause, cardiovascular, and respiratory mortality, but only observed significant results for cardiovascular mortality at lag 0 for both $PM_{10-2.5}$ and $PM_{2.5}$. They found that $PM_{10-2.5}$ (5.4% [95% CI: 1.1-9.8] per 10 $\mu g/m^{3)}$, was more strongly associated with cardiovascular mortality than $PM_{2.5}$ (4.8% [95% CI: -1.9 to 12.0] per 10 $\mu g/m^{3)}$.

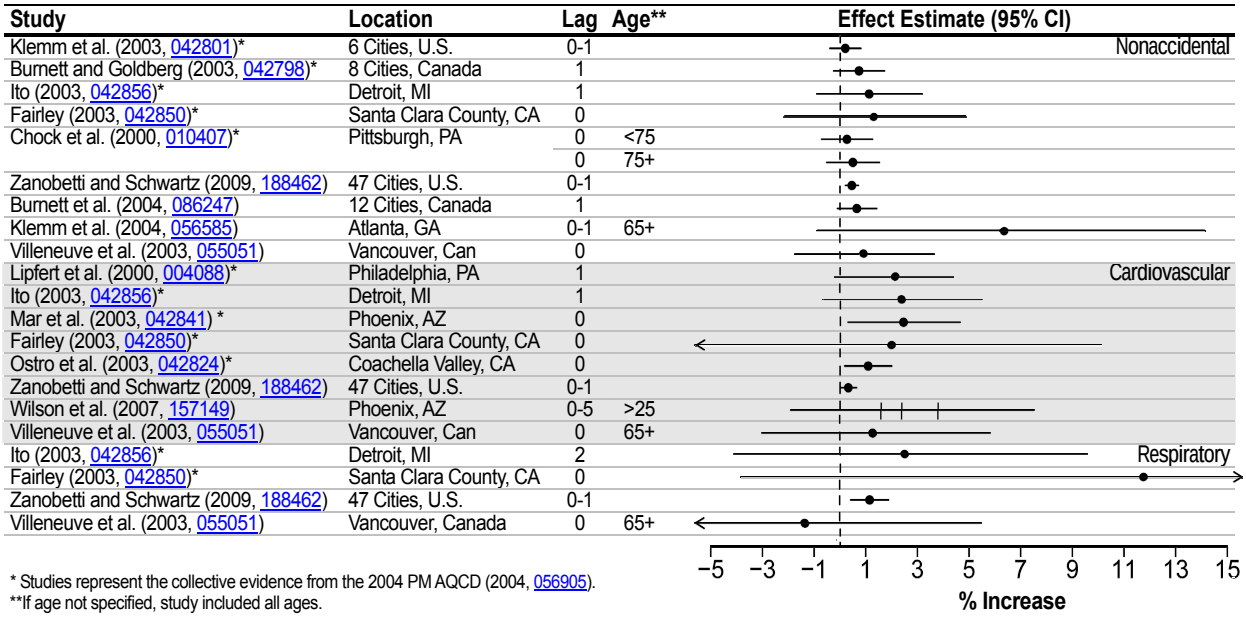
Klemm et al. (2004, 056585) analyzed various components of PM and gaseous pollutants for their associations with mortality in Fulton and DeKalb Counties, Georgia for the 2-yr period, 1998-2000. $PM_{10-2.5}$ concentrations were obtained from the ARIES database, which directly measured $PM_{10-2.5}$ using dichotomous samplers. In this analysis the authors adjusted for temporal trend using quarterly, monthly, and biweekly knots, and reported estimates for all-cause, circulatory, respiratory, cancer, and other causes mortality for each scenario. Overall, $PM_{2.5}$ was, more strongly associated with mortality than $PM_{10-2.5}$. For example, using the average of 0- and 1-day lags, the risk estimates for $PM_{2.5}$ and $PM_{10-2.5}$ in the monthly knots model for all-cause mortality, ages $\geq$ 65 yr were 5.6% (95% CI: 1.9-9.5) and 6.4% (95% CI: -0.5 to 14.1) per 10 $\mu g/m^3$ increase, respectively.[1]

Summary of $PM_{10-2.5}$ Risk Estimates

The results from newly available studies that examined the association between short-term exposure to $PM_{10-2.5}$ primarily consisted of single-city studies. Collectively these studies found consistent, positive associations, with the precision of each association varying by study location. The evidence from those single-city studies conducted in the U.S. and Canada in combination with the multicity studies evaluated (i.e., in the U.S. and Canada), provide evidence for $PM_{10-2.5}$ effects. However, the various methods used to estimate exposure to $PM_{10-2.5}$ (e.g., direct measurement of $PM_{10-2.5}$ using dichotomous samplers, calculating the difference between PM_{10} and $PM_{2.5}$ concentrations) in the studies evaluated add uncertainty to the associations observed. Specifically, a new U.S. multicity study (Zanobetti and Schwartz, 2009, 188462) estimated $PM_{10-2.5}$ by calculating the difference between the county-average PM_{10} and $PM_{2.5}$ concentrations. Although there are limitations in the method used by Zanobetti and Schwartz (2009, 188462) associations between $PM_{10-2.5}$ and mortality were observed throughout multiple regions of the country. However, some of the findings of this new multicity study (e.g., no associations in "dry" region where $PM_{10-2.5}$ levels are high) are not consistent with the findings of the $PM_{10-2.5}$ studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905), and suggest that the coarse fraction is associated with mortality in areas of the U.S. where $PM_{10-2.5}$ levels are not high. Limitations also exist in the $PM_{10-2.5}$ associations reported due to the small number of $PM_{10-2.5}$ studies that have investigated confounding by gaseous

[1] The monthly knot model was selected for comparison because, overall, $PM_{2.5}$ showed the strongest association with all-cause mortality among the 15 air pollution indices examined when using this model.

copollutants or the influence of model specification on $PM_{10-2.5}$ risk estimates. Additionally, more data is needed to characterize the chemical and biological components that may modify the potential toxicity of $PM_{10-2.5}$. Figure 6-30 summarizes the $PM_{10-2.5}$ risk estimates for all U.S.-, Canadian-, and international-based studies by cause-specific mortality.



* Studies represent the collective evidence from the 2004 PM AQCD (2004, 056905).
**If age not specified, study included all ages.

Figure 6-30. Summary of percent increase in total (nonaccidental) and cause-specific mortality per 10 µg/m^3 increase in $PM_{10-2.5}$ for all U.S.-, Canadian-, and international-based studies. The three vertical lines for the Wilson et al. (2007, 157149) estimate represent the central, middle, and outer Phoenix estimates.

6.5.2.4. Ultrafine Particles

The 2004 PM AQCD (U.S. EPA, 2004, 056905) reviewed Wichmann et al.'s (reanalyzed by Stolzel et al., 2003, 042842; 2000, 013912) study of fine and ultrafine particles (UFPs) (diameter: 0.01-0.1 µm) in Erfurt, Germany, for the study period 1995-1998. Stölzel et al. (2007, 091374) extended the study period to include the years 1995-2001 and updated the analysis. Number concentrations (NC) for four size ranges of UFPs (0.01-0.1, 0.01-0.03, 0.03-0.05, and 0.05-0.1 µm) as well as mass concentration (MC) for three size ranges (0.01-2.5, 0.1-0.5, and 10 µm) were analyzed. The authors found associations with UFP NC and all-cause as well as cardio-respiratory mortality, each for a 4 day lag. The risk estimates associated with a 9,748/cm^3 increase in UFP NC was 2.9% (95% CI: 0.3-5.5) for all-cause mortality and 3.1% (95% CI: 0.3-6.0) for cardio-respiratory mortality. The UFP-mortality association, and the lag structure of association, is consistent with the results from their earlier analysis, but the $PM_{2.5}$ association found in the previous study was not observed in the updated analysis. Both UFP and $PM_{2.5}$ concentrations were higher during the cold season in this locale.

Breitner et al. (2009, 188439) analyzed UFP data from Erfurt, Germany, over a 10.5-yr period (October 1991-March 2002) after the German unification, when air quality improved. In this analysis associations between all-cause mortality and UFPs and $PM_{2.5}$ were analyzed from September 1995 to March 2002, while PM_{10}, NO_2 and CO was analyzed for the whole study duration. The exposure time window / averages used in this study were different from those used by Stölzel (2003, 042842) and Stölzel et al. (2007, 091374). Breitner et al. (2009, 188439) investigated the cumulative effect of air pollution on mortality at lags 0-5 and 0-14, using (a) a semiparametric Poisson regression model; and (b) a third degree polynomial distributed lag (PDL) model. The authors estimated the mortality risk for the entire study period as well as specific time periods to examine the effect of declining air pollution levels on the air pollution-mortality association. Of the air pollutants examined, UFPs were

found to be most consistently associated with mortality. NO_2 and CO were also found to be significantly associated with mortality using the 15-day PDL and 15-day avg models, respectively. $PM_{2.5}$ and PM_{10} also showed positive, but much weaker associations with mortality. In this data set, UFPs were only moderately correlated with $PM_{2.5}$ (r = 0.48) and PM_{10} (r = 0.57). Of the pollutants examined, NO_2 showed the strongest (but overall a moderate) correlation with UFPs (r = 0.62). When the risk estimates were compared between the two latter time periods of the study (September 1995-February 1998; and March 1998-March 2002), the estimates obtained using the 6-day avg for these pollutants generally declined. For example, the all-cause mortality risk estimates associated with a 8,439/cm^3 increase in UFP NC was 5.5% (95% CI: 1.1-10.5) for the earlier period and -1.1% (95% CI: -6.8 to 4.9) for the later period. However, such patterns were less clear when using 15-day avg pollutant concentrations. In summary, UFPs appear to be the pollutant most consistently associated with mortality in Erfurt, Germany, but combined with the results for NO_2 and CO, these associations may implicate the role of local combustion sources on the mortality association observed.

Kettunen et al.'s (2007, 091242) study in Helsinki also examined the relationship between UFPs and stroke mortality. As described earlier, $PM_{2.5}$, PM_{10}, and CO was associated with stroke mortality only during the warm season. The association with UFPs was borderline non-significant (8.5% [95% CI: -1.2 to19.1] per 4,979/cm^3 increase in UFPs at lag 1 day), but its lag structure of association and the magnitude of the effect estimate per interquartile-range are similar to those for $PM_{2.5}$. Note that the UFP NC levels in Helsinki (median equals 8,986/cm^3 during the cold season and 7,587/cm^3 during the warm season) are lower than those in Erfurt (mean = 13,549/cm^3), but clearly higher in the cold season.

Summary of UFP Risk Estimates

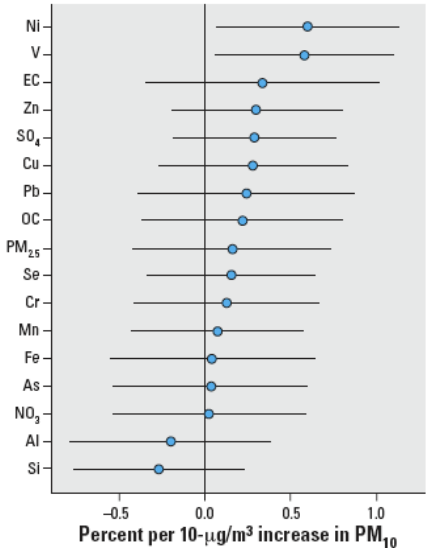
Only a few new studies, all of them conducted in Europe, examined and reported associations between UFPs and mortality. In Erfurt, UFPs showed the strongest associations with mortality among all of the PM indices, but its lag structure of association is either unique with the strongest association at lag 4 days in Stölzel et al. (2007, 091374), not consistent with the lag structure of associations found in other mortality studies, or the time-windows examined are longer (0-5 and 0-14 days) ((Breitner et al., 2009, 188439), making it difficult to compare whether the associations observed are consistent with those reported in other studies. In Helsinki, the association between UFPs and stroke mortality was weaker than that for $PM_{2.5}$, but its lag structure of association was similar to that for $PM_{2.5}$ (strongest at lag 1 day). However, Kettunen et al. (2007, 091242) only examined lags 0-3 days. Overall, the results of these studies should be viewed with caution because UFPs were consistently found to be correlated with gaseous pollutants derived from local combustion sources, and one or more of the gaseous pollutants were also found to be associated with mortality. Clearly, more research is needed to further investigate the role of UFPs on PM-mortality associations.

6.5.2.5. Chemical Components of PM

A few recent studies have examined the association between mortality and components of $PM_{2.5}$. This endeavor has been undertaken by some investigators through the use of the newly available $PM_{2.5}$ chemical speciation network data. The $PM_{2.5}$ chemical speciation network consists of more than 250 monitors that have been collecting over 40 chemical species since 2000; however, most sites started collecting data in 2001. One caveat to the new network is that because the sampling frequencies of the monitors are either every third day or every sixth day, there have not been, generally, a sufficient number of days to examine associations with mortality in single cities. To circumvent this issue, some investigators (Bell et al., 2009, 191997; Dominici et al., 2007, 099135; Franklin et al., 2008, 097426; Lippmann et al., 2006, 091165) have used the $PM_{2.5}$ chemical species data in a second stage regression to explain the heterogeneity in PM_{10} or $PM_{2.5}$ mortality risk estimates across cities. However, it should be noted these studies assume that the relative contributions of $PM_{2.5}$ have remained the same over time. There have also been some studies that directly analyzed speciated $PM_{2.5}$ data (e.g., Klemm et al., 2004, 056585; Ostro et al., 2007, 091354).

Explaining the Heterogeneity of PM_{10} Risk Estimates Using $PM_{2.5}$ Chemical Speciation Data

Lippmann et al. (2006, 091165), in addition to their primary analysis[1], investigated the consistency of the associations between specific elements and health outcomes by examining the heterogeneity of published 1-day lagged NMMAPS PM_{10} mortality risk estimates for 1987-1994 across cities as a function of the average $PM_{2.5}$ chemical components across cities. They matched $PM_{2.5}$ chemical species in 60 out of 90 cities. Lippmann et al. (2006, 091165) noted that the concentrations of the 16 chemical species examined averaged over the years 2000-2003 were highly skewed across cities. They therefore regressed PM_{10} risk estimates on each of the $PM_{2.5}$ components, raw and log-transformed, with weights based on the standard error of the PM_{10} risk estimates. The log-transformed values yielded better predictive power, and the authors subsequently presented the results with log-transformed values. As shown in Figure 6-31, the 16 $PM_{2.5}$ species showed varying extent of predictive power in explaining the PM_{10} risk estimates across 60 cities, with Ni and V being the best predictors.



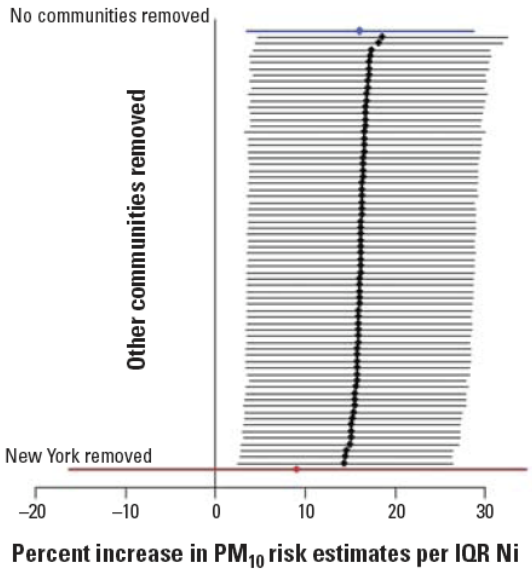
Source: Lippmann et al. (2006, 091165)

Figure 6-31. Percent increase in PM_{10} risk estimates (point estimates and 95% CIs) associated with a 5th-95th percentile increase in $PM_{2.5}$ and $PM_{2.5}$ chemical components. The $PM_{2.5}$ chemical components were log-transformed in the regression. The PM_{10} risk estimates were for 60 NMMAP cities for 1987-1994.

Dominici et al. (2007, 099135) examined the influence of Ni and V on the updated NMMAPS PM_{10} mortality risk estimates for 1987-2000, using 72 counties in which Ni and V data were collected. A Bayesian hierarchical model was used to estimate the role of Ni and V on the heterogeneity of PM_{10} risk estimates. While they found both Ni and V to be significant predictors of variation in PM_{10} mortality risk estimates across cities, they also noted that this result was sensitive to the inclusion of the New York City data. Lippmann et al. (2006, 091165) and Dominici et al. (2007, 099135) both reported that the Ni levels in New York City are particularly high (~10 times the national average). Figure 6-32 shows the result of the sensitivity analysis for Ni. Note that the Ni in this result was not log-transformed, as clearly reflected in the change in the width of confidence bands when the New York data were removed (i.e., a skewed distribution produces narrow bands).

[1] The main focus of the study was to examine the role of $PM_{2.5}$ chemical components in a mouse model of atherosclerosis ($ApoE^{-/-}$) exposed to concentrated fine PM (CAPs) in Tuxedo, NY.

Dominici et al. (2007, 099135) further noted that they reached "the same conclusion" when log-transformed data were used in the analysis, but the results were not presented.



Source: Reprinted with Permission of Oxford University Press from Dominici et al. (2007, 099135)

Figure 6-32. Sensitivity of the percent increase in PM_{10} risk estimates (point estimates and 95% CIs) associated with an interquartile increase in Ni. The Ni concentration was not log-transformed in this regression model. The PM_{10} risk estimates were for 72 NMMAP cities for 1987-2000. The top estimate is achieved by including data for all the 69 communities. The other estimates are calculated by excluding one of the 69 communities at a time.

Bell et al. (2009, 191997) presented a supplemental analysis similar to both Lippmann et al. (2006, 091165) and Dominici et al. (2007, 099135) in their examination of whether the variation in $PM_{2.5}$ risks for cardiovascular and respiratory hospital admissions is due to differences in $PM_{2.5}$ chemical composition. The authors used the 100 U.S. cities included in the Peng et al. (2005, 087463) analysis and PM_{10} data for the years 1987-2000 along with $PM_{2.5}$ chemical component data for 2000-2005. Using a Bayesian hierarchical model, Bell et al. (2009, 191997) found that PM_{10} relative risks for total mortality were greater in counties and during seasons with higher $PM_{2.5}$ Ni concentrations. However, in a sensitivity analysis when selectively removing cities from the overall estimate, the significant association between the PM_{10} mortality risk estimate and the $PM_{2.5}$ Ni fraction was diminished upon removing New York city from the analysis, which is consistent with the results presented by Dominici et al. (2007, 099135).

Explaining the Heterogeneity of $PM_{2.5}$ Risk Estimates Using $PM_{2.5}$ Chemical Speciation Data

The first stage of the Franklin et al. (2008, 097426) 25 cities study, described previously, focused on a time-series regression of mortality on $PM_{2.5}$ by season. In the second stage random effects meta regression, the $PM_{2.5}$ mortality risk estimates (25 cities×4 seasons = 100 estimates) were regressed on the ratio of mean seasonal $PM_{2.5}$ species to the total $PM_{2.5}$ mass. The authors included those species that had at least 25% of the reported concentrations above the minimum detection limit, which resulted in 18 species being included in the analysis. Their rationale for using species proportions as effect modifiers, according to the investigators, was that "in the first stage of the analysis the mortality risk was estimated per unit of the total $PM_{2.5}$ mass, which encompassed all

measured species, and therefore it would not be meaningful to use the species concentrations directly as the effect modifier" (Franklin et al., 2008, 097426). In the second stage regression model, Franklin et al. (2008, 097426) also included a quadratic function of seasonally averaged temperature to capture the inverted U-shape relationship between $PM_{2.5}$ penetration and temperature. They found that the fitted relationship between $PM_{2.5}$ risk estimates across cities and seasonally averaged temperature substantiates the use of temperature as a surrogate for ventilation (Franklin et al., 2008, 097426). Table 6-17 shows the resulting effect modification by $PM_{2.5}$ species. Al, As, Ni, Si, and SO_4^{2-} were found to be significant effect modifiers of $PM_{2.5}$ risk estimates, and simultaneously including Al, Ni, and SO_4^{2-} together, or Al, Ni, and As together further increased explanatory power. Of all the species examined, Al and Ni explained the most residual heterogeneity. Franklin et al. (2008, 097426) also examined the effect of demographic variables on $PM_{2.5}$ risk estimates and found that only median household income was significantly associated with mortality.

Table 6-17. Effect modification of composition on the estimated percent increase in mortality with a 10 μg/m^3 increase in $PM_{2.5}$.

Cause	Species	p-value for effect modification by species to $PM_{2.5}$ mass proportion	% increase in nonaccidental mortality per 10 μg/m^3 increase in $PM_{2.5}$ for an interquartile increase in species to $PM_{2.5}$ mass proportion*	Heterogeneity explained (%)†
Nonaccidental Univariate	Al	<0.001	0.58	45
	As	0.02	0.55	35
	Br	0.11	0.38	5
	Cr	0.12	0.33	16
	EC	0.79	0.06	0
	Fe	0.43	0.12	3
	K	0.10	0.41	28
	Mn	0.42	0.14	10
	Na+	0.22	0.20	14
	Ni	0.01	0.37	41
	NO_3	0.07	-0.49	28
	NH_4^+	0.84	0.04	3
	OC	0.59	-0.02	4
	Pb	0.31	0.17	11
	Si	0.03	0.41	25
	SO_4^{2-}	0.01	0.51	33
	V	0.28	0.30	3
	Zn	0.19	0.23	15
Nonaccidental Multivariate (1)	Al	<0.001	0.79	100
	Ni	0.01	0.34	
	SO_4^{2-}	<0.001	0.75	
Nonaccidental Multivariate (2)	Al	<0.001	0.61	100
	Ni	0.01	0.35	
	As	<0.001	0.58	

*Adjusted for temperature
†Includes heterogeneity explained by temperature

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Although Lippmann et al. (2006, 091165) used NMMAPS PM_{10} risk estimates and Franklin et al. (2008, 097426) used $PM_{2.5}$ risk estimates to examine effect modification due to various PM

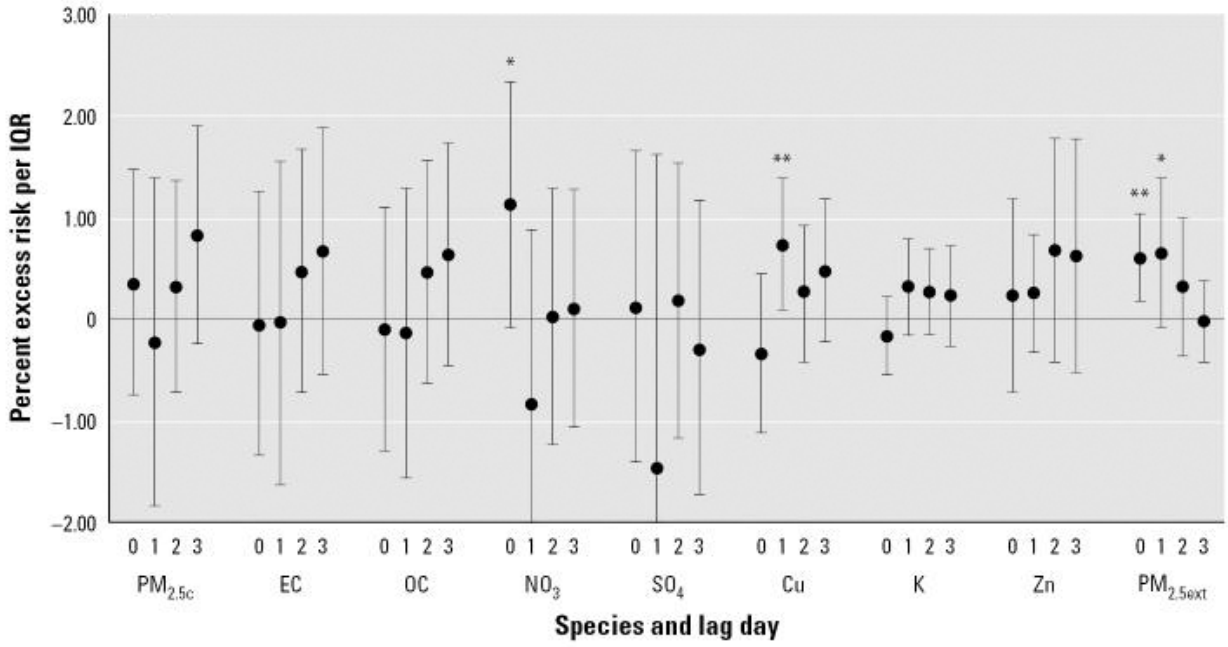
species, 14 out of the 18 species analyzed in these two studies overlap (Figure 6-31 and Table 6-17). Both studies found that Ni explained the heterogeneity in PM risk estimates. Note that New York City was not included in the 25 cities examined in Franklin et al. (2008, 097426) and, thus, could not influence the result. Sulfate positively, but not significantly, explained the PM_{10} risk estimates in the Lippmann et al. (2006, 091165) analysis. However, SO_4^{2-} was a significant predictor of $PM_{2.5}$ risk estimates in the Franklin et al. (2008, 097426) analysis. Al and Si were negative (i.e., less than the average PM_{10} risk estimates across cities), though not significant predictors in the Lippmann et al. (2006, 091165) analysis. Unlike the Franklin et al. (2008, 097426) analysis, arsenic (As) showed no association with mortality in the Lippmann et al. (2006, 091165) analysis. The source of these differences may be due to the difference in geographic coverage, PM size ($PM_{2.5}$ may represent more secondary aerosols than PM_{10}), or the difference in the analytical methods used in each study. Specifically, the analytical approach used by Franklin et al. (2008, 097426) does have an advantage of delineating seasonal variations in PM components and the associated potential seasonal mortality effects.

In light of the results presented in speciation studies it must be noted that second stage analyses that use PM chemical species as effect modifiers have some limitations. Unlike analyses that directly examine the associations between chemical species and mortality, if an effect modification is observed it may be confounded if the variations of the mean levels of the chemical species examined are correlated with other demographic factors that vary across cities. Thus, more concrete conclusions could be formulated if direct associations are found between mortality and PM chemical components in time-series analyses.

Association between $PM_{2.5}$ Chemical Components and Mortality

Ostro et al. (2007, 091354) examined associations between $PM_{2.5}$ chemical components and mortality in six California counties (Fresno, Kern, Riverside, Sacramento, San Diego, and Santa Clara), which had at least 180 days of speciation data for the years 2000-2003. The study examined all-cause, cardiovascular, and respiratory mortality for individual lags of 19 specific $PM_{2.5}$ chemical components. The second stage random-effects model combined risk estimates at each lag across cities. The number of available days for chemical species data ranged from 243 (San Diego County) to 395 (Sacramento County). The authors found an association between mortality, especially cardiovascular mortality, and several chemical components. For example, cardiovascular mortality was associated with EC, OC, nitrate, Fe, K, and Ti at various lags.

Even though this was a multicity study, the relatively small number of available days and the every-third-day (or every-sixth-day) sampling frequency for $PM_{2.5}$ chemical species made it difficult to interpret the results of the lag structure of associations observed for the chemical species. To evaluate the impact of non-daily sampling frequency, Ostro et al. (2007, 091354) examined both the $PM_{2.5}$ series that coincides with the speciation sampling days (for the initial six counties [i.e., $PM_{2.5c}$]) and $PM_{2.5}$ data that was available on all days for an extended set of counties (the initial six counties plus Contra Costa, Los Angeles, and Orange Counties [i.e., $PM_{2.5ext}$]). Figure 6-33 shows the association between all-cause mortality and selected $PM_{2.5}$ chemical species as well as for $PM_{2.5c}$ and $PM_{2.5ext}$. Note the wide confidence bands for the risk estimates for each $PM_{2.5}$ chemical species and $PM_{2.5c}$, apparently reflecting the low statistical power of the data. The lag structure of associations is more clearly defined for $PM_{2.5ext}$, and appears to be different from that for $PM_{2.5}$.



Source: Ostro et al. (2007, 091354)

Figure 6-33. Percent excess risk (CI) of total (nonaccidental) mortality per IQR of concentrations. Note: $PM_{2.5}$ has the same sampling days as chemical species. $PM_{2.5}$ has all available $PM_{2.5ext}$ data for nine counties. * p < 0.10; ** p < 0.05

Ostro et al. (2008, 097971) used the speciation data from the six counties analyzed in their 2007 analysis, described above, in an additional analysis to examine effect modification of cardiovascular mortality effects, which showed the strongest association in the 2007 analysis, attributed to $PM_{2.5}$ and 13 chemical components by socio-economic and demographic factors. The results of the analysis were combined using random effects meta-analysis. The investigators tested statistical differences in risk estimates between strata using a t-test, and reported that, for many of the $PM_{2.5}$ chemical species; there were significantly higher effect estimates among those with lower educational attainment and Hispanics. While these patterns were apparent in their results table, interpretation of the results is not straightforward because the table only presented the most significant (and positive) lags, and they were often different between the strata (e.g., the most frequent significant lag for the Hispanic group was 1 day, while it was 2 or 3 days for the White group). As the investigators pointed out, the every-third-day sampling frequency of the speciation data also complicates the interpretation of the results for different lags.

Overall, the two studies by Ostro et al. (2007, 091354) were the first attempt to directly analyze associations between the newly available chemical speciation data and mortality. While suggestive associations between several chemical species and mortality were reported, a longer length of observations is needed to more clearly determine the associations.

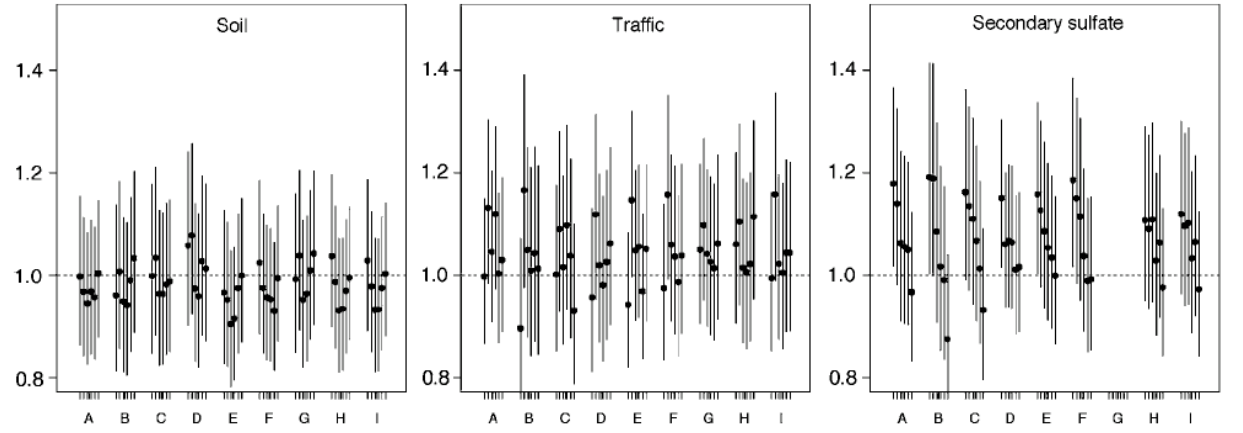
6.5.2.6. Source-Apportioned PM Analyses

Chemically speciated PM data allow for the source apportionment of PM. The idea of using source-apportioned PM for health effects analyses is appealing because, if such source-apportionment could be reliably conducted, it would allow for an evaluation of $PM_{2.5}$ mass concentrations by source types. However, the uncertainties associated with source-apportionment methods have not been well characterized.

To address this issue, in 2003, several groups of EPA-funded researchers organized a workshop and independently conducted source apportionment on two sets of data: Phoenix, AZ, and Washington, DC, compared the results (Hopke et al., 2006, 088390), and then conducted time-series

mortality regression analyses using each group's source-apportioned data (Ito et al., 2006, 088391; Mar et al., 2006, 086143; Thurston et al., 2005, 097949). The various research groups generally identified the same major source types, each with similar elemental compositions. Inter-group correlation analyses indicated that soil-, SO_4^{2-}-, residual oil-, and salt-associated mass concentrations were most unambiguously identified by various methods, whereas vegetative burning and traffic were less consistent. Aggregate source-specific mortality relative risk (RR) estimate confidence intervals overlapped each other, but the SO_4^{2-}-related $PM_{2.5}$ component was most consistently significant across analyses in these cities.

The results from the source-apportionment workshop quantitatively characterized the uncertainties associated with the factor analysis-based methods, but they also raised new issues. The mortality analyses conducted in Phoenix, AZ, and Washington, DC, both found that different source-types showed varying lag structure of associations with mortality. For example, Figure 6-34 shows cardiovascular mortality risk estimates for three of the $PM_{2.5}$ sources from the Phoenix, AZ, analysis (Mar et al., 2006, 086143). The strongest associations for "traffic" $PM_{2.5}$ was found for lag 1-day, while for "secondary SO_4^{2-}" $PM_{2.5}$, it was lag 0, with a monotonic decline towards longer lags. These results are consistent with those in the 2004 PM AQCD (U.S. EPA, 2004, 056905), in which associations were reported with combustion-related $PM_{2.5}$, but not crustal source $PM_{2.5}$. It is conceivable that PM from different source types produces different lagged effects, but it is also likely that different PM species have varying lagged correlations with the covariates in the health effects regression models (e.g., temperature, day-of-week) resulting in apparent differences in lagged associations with mortality. Thus, interpretation of these source-apportioned PM health effect estimates remains challenging.



Source: Reprinted with Permission of Nature Publishing Group from Mar et al. (2006, 086143)

Figure 6-34. Relative risk and CI of cardiovascular mortality associated with estimated $PM_{2.5}$ source contributions. Y-axis: relative risk per 5th-to-95th percentile increment of estimated $PM_{2.5}$ source contribution. X-axis: the alphabet denotes investigator/ method; lagged $PM_{2.5}$ source contribution for lag 0 through 5 days, left to right, are shown for each investigator/method.

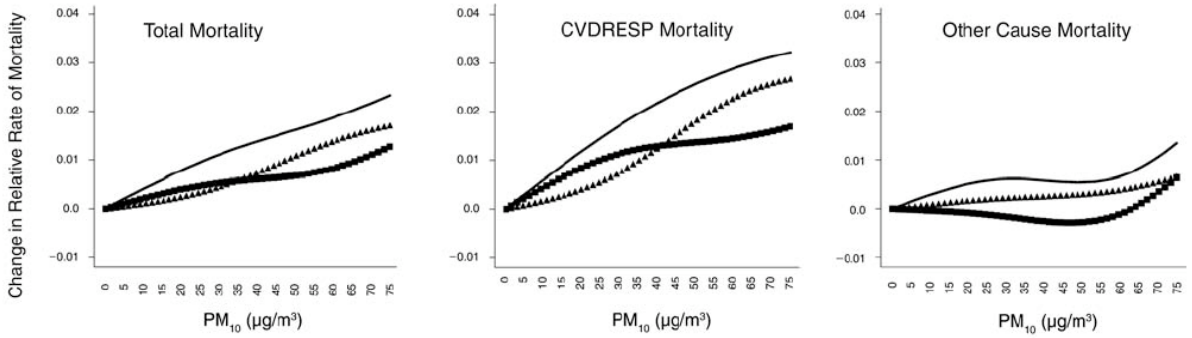
6.5.2.7. Investigation of Concentration-Response Relationship

The results from large multicity studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggested that strong evidence did not exist for a clear threshold for PM mortality effects. However, as discussed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), there are several challenges in determining and interpreting the shape of PM-mortality concentration-response functions and the presence of a threshold, including: (1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of susceptible populations; and (3)

the influence of measurement error. Regardless of these limitations, studies have continued to investigate the PM-mortality concentration-response relationship.

Daniels et al. (2004, 087343) evaluated three concentration-response models: (1) log-linear models (i.e., the most commonly used approach, from which the majority of risk estimates are derived); (2) spline models that allow data to fit possibly non-linear relationship; and (3) threshold models, using PM_{10} data in 20 cities from the 1987-1994 NMMAPS data. They reported that the spline model, combined across the cities, showed a linear relation without indicating a threshold for the relative risks of death for all-causes and for cardiovascular-respiratory causes in relation to PM_{10}, but "the other cause" deaths (i.e., all cause minus cardiovascular-respiratory) showed an apparent threshold at around 50 $\mu g/m^3$ PM_{10}, as shown in Figure 6-35. For all-cause and cardio-respiratory deaths, based on the Akaike's Information Criterion (AIC), a log-linear model without threshold was preferred to the threshold model and to the spline model.

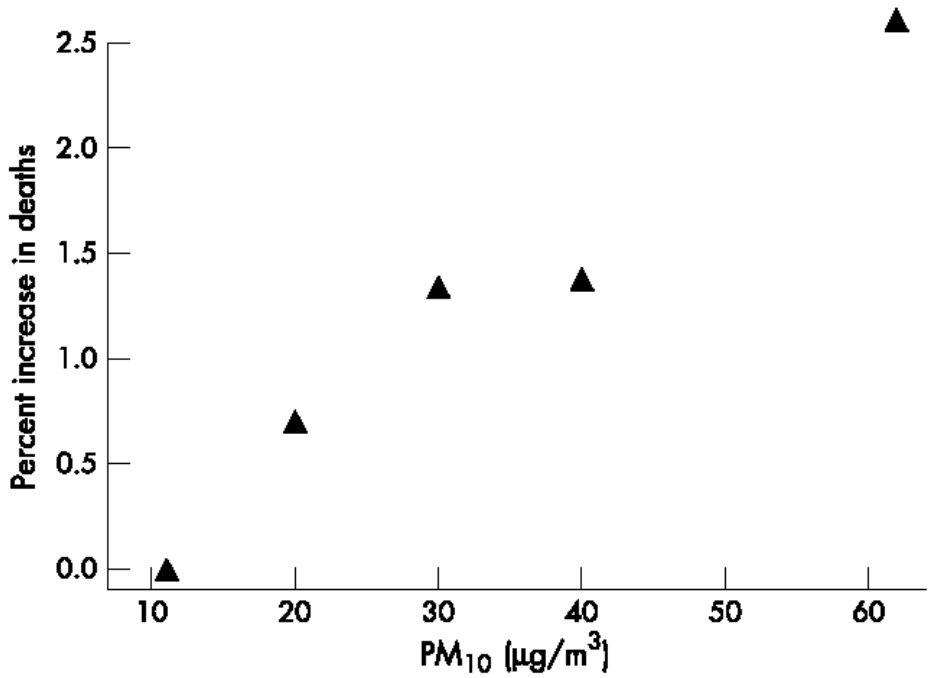
The HEI review committee commented that interpretation of these results required caution, because (1) the measurement error could obscure any threshold; (2) the city-specific concentration-response curves exhibited a variety of shapes; and (3) the use of AIC to choose among the models might not be appropriate due to the fact it was not designed to assess scientific theories of etiology. Note, however, that there has been no etiologically credible reason suggested thus far to choose one model over others for aggregate outcomes. Thus, at least statistically, the result of Daniels et al. (2004, 087343) suggests that the log-linear model is appropriate in describing the relationship between PM_{10} and mortality.



Source: Reprinted with Permission of HEI from Daniels et al. (2004, 087343)

Figure 6-35. Concentration-response curves (spline model) for all-cause, cardiovascular, respiratory and other cause mortality from the 20 NMMAPS cities. Estimates are posterior means under Bayesian random effects model. Solid line is mean lag, triangles are lag 0 (current day), and squares are lag 1 (previous day).

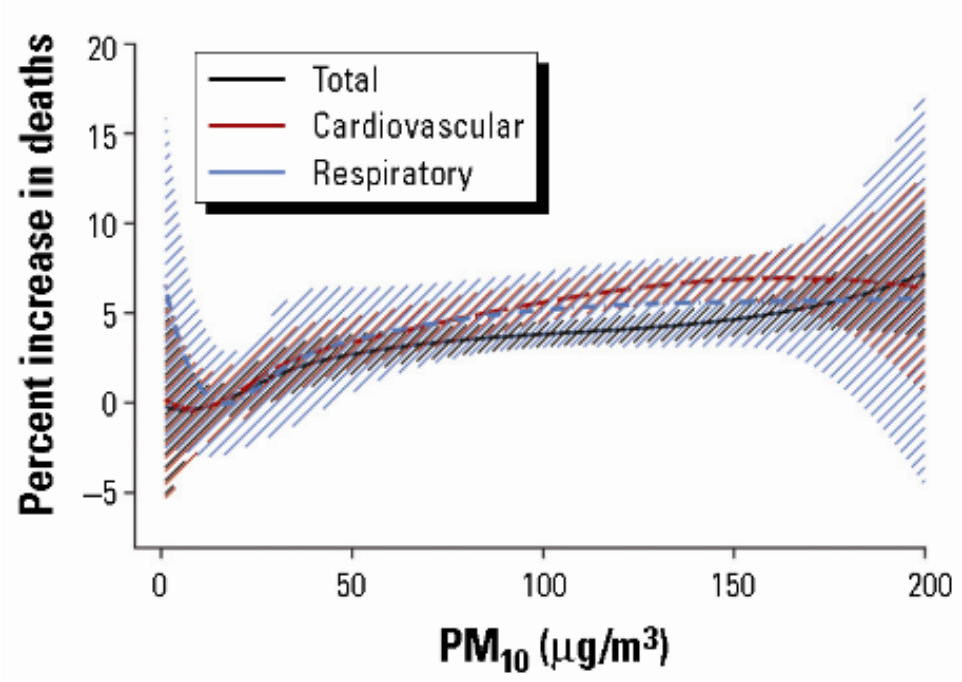
The Schwartz (2004, 078998) analysis of PM_{10} and mortality in 14 U.S. cities, described in Section 6.5.2.1, also examined the shape of the concentration-response relationship by including indicator variables for days when concentrations were between 15 and 25 $\mu g/m^3$, between 25 and 34 $\mu g/m^3$, between 35 and 44 $\mu g/m^3$, and 45 $\mu g/m^3$ and above. In the model, days with concentrations below 15 $\mu g/m^3$ served as the reference level. This model was fit using the single stage method, combining strata across all cities in the case-crossover design. Figure 6-36 shows the resulting relationship, which does not provide sufficient evidence to suggest that a threshold exists. The authors did not examine city-to-city variation in the concentration-response relationship in this study.



Source: Reprinted with Permission of BMJ Group from Schwartz (2004, 078998)

Figure 6-36. Percent increase in the risk of death on days with PM_{10} concentrations in the ranges of 15-24, 25-34, 35-44, and 45 µg/m^3 and greater, compared to a reference of days when concentrations were below 15 µg/m^3. Risk is plotted against the mean PM_{10} concentration within each category.

Samoli et al. (2005, 087436) investigated the concentration-response relationship between PM_{10} and mortality in 22 European cities (and BS in 15 of the cities) participating in the APHEA project. In nine of the 22 cities, PM_{10} levels were estimated using a regression model relating co-located PM_{10} to BS or TSP. They used regression spline models with two knots (30 and 50 µg/m^3) and then combined the individual city estimates of the splines across cities. The investigators concluded that the association between PM and mortality in these cities could be adequately estimated using the log-linear model. However, in an ancillary analysis of the concentration-response curves for the largest cities in each of the three distinct geographic areas (western, southern, and eastern European cities): London, England; Athens, Greece; and Cracow, Poland, Samoli et al. (2005, 087436) observed a difference in the shape of the concentration-response curve across cities. Thus, while the combined curves (Figure 6-37) appear to support no-threshold relationships between PM_{10} and mortality, the heterogeneity of the shapes across cities makes it difficult to interpret the biological relevance of the shape of the combined curves.



Source: Samoli et al. (2005, 087436)

Figure 6-37. Combined concentration-response curves (spline model) for all-cause, cardiovascular, and respiratory mortality from the 22 APHEA cities.

The results from the three multicity studies discussed above support no-threshold log-linear models, but issues such as the possible influence of exposure error and heterogeneity of shapes across cities remain to be resolved. Also, given the pattern of seasonal and regional differences in PM risk estimates depicted in recent multicity study results (e.g., Peng et al., 2005, 087463), the very concept of a concentration-response relationship estimated across cities and for all-year data may not be very informative.

6.5.3. Summary and Causal Determinations

6.5.3.1. $PM_{2.5}$

The 2004 PM AQCD (U.S. EPA, 2004, 056905) found that the strength of evidence from U.S.- and Canadian-based studies (both multi- and single-city) for $PM_{2.5}$ mortality associations varied across outcomes, with relatively stronger evidence for associations with cardiovascular compared to respiratory causes. The resulting effect estimates reported for these two endpoints ranged from 1.2 to 2.7% for cardiovascular-related mortality and 0.8 to 2.7% for respiratory-related mortality, per 10 µg/m^3 increase in $PM_{2.5}$ (U.S. EPA, 2004, 056905).

In the current review, $PM_{2.5}$ risk estimates were found to be consistently positive, and slightly larger than those reported for PM_{10} for all-cause, and respiratory- and cardiovascular-related mortality. The risk estimates for all-cause (nonaccidental) mortality ranged from 0.29% (Dominici et al., 2007, 097361) to 1.21% (Franklin et al., 2007, 091257) per 10 µg/m^3 increase in $PM_{2.5}$. These associations were consistently observed at lag 1 and lag 0-1, which have been confirmed through extensive analyses in PM_{10}-mortality studies. Cardiovascular-related mortality risk estimates were found to be similar to those for all-cause mortality; whereas, the risk estimates for respiratory-related mortality were consistently larger: 1.01% (Franklin et al., 2007, 091257) to 2.2% (Ostro et al., 2006, 087991) using the same lag (i.e., lag 1 and lag 0-1) and averaging indices. The studies evaluated that examined the relationship between short-term exposure to $PM_{2.5}$ and cardiovascular effects (section

6.2) provide coherence and biological plausibility for $PM_{2.5}$-induced cardiovascular mortality, which represents the largest component of total (nonaccidental) mortality (~ 35%) (American Heart Association, 2009, 198920). However, as noted in section 6.3, there is limited coherence between some of the respiratory morbidity findings from epidemiologic and controlled human exposure studies for the specific health outcomes reported and the subpopulations in which those health outcomes occur, complicating the interpretation of the $PM_{2.5}$ respiratory mortality effects observed.

Regional and seasonal patterns in $PM_{2.5}$ risk estimates were observed with results similar to those presented for PM_{10} (Dominici et al., 2007, 097361; Peng et al., 2005, 087463; Zeka et al., 2006, 088749), with the greatest effects occurring in the eastern U.S. (Franklin et al., 2007, 091257; Franklin et al., 2008, 097426) and during the spring (Franklin et al., 2007, 091257; Zanobetti and Schwartz, 2009, 188462). Of the studies evaluated only Burnett et al. (2004, 086247), a Canadian multicity study, analyzed gaseous pollutants and found mixed results, with possible confounding of $PM_{2.5}$ risk estimates by NO_2. Although the recently evaluated U.S.-based multicity studies did not analyze potential confounding of $PM_{2.5}$ risk estimates by gaseous pollutants, evidence from single-city studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggest that gaseous copollutants do not confound the $PM_{2.5}$-mortality association, which is further supported by studies that examined the PM_{10}-mortality relationship. An examination of effect modifiers (e.g., demographic and socioeconomic factors), specifically AC use which is sometimes used as a surrogate for decreased pollutant penetration indoors, has suggested that $PM_{2.5}$ risk estimates increase as the percent of the population with access to AC decreases (Franklin et al., 2007, 091257; 2008, 097426). Collectively, the epidemiologic evidence is sufficient to conclude that **a causal relationship exists between short-term exposure to $PM_{2.5}$ and mortality.**

6.5.3.2. $PM_{10-2.5}$

The 2004 PM AQCD (U.S. EPA, 2004, 056905) found a limited body of evidence that was suggestive of associations between short-term exposure to ambient $PM_{10-2.5}$ and various mortality outcomes (e.g., 0.08 to 2.4% increase in total [nonaccidental] mortality per 10 $\mu g/m^3$ increase in $PM_{10-2.5}$). As a result, the AQCD concluded that $PM_{10-2.5}$, or some constituent component(s) (including those on the surface) of $PM_{10-2.5}$, may contribute, in certain circumstances, to increased human health risks.

The majority of studies evaluated in this review that examined the relationship between $PM_{10-2.5}$ and mortality reported consistent positive associations in areas with mean 24-h avg concentrations ranging from 6.1-16.4 $\mu g/m^3$. However, uncertainty surrounds the $PM_{10-2.5}$ associations reported due to the different methods used to estimate $PM_{10-2.5}$ concentrations across studies (e.g., direct measurement of $PM_{10-2.5}$ using dichotomous samplers, calculating the difference between PM_{10} and $PM_{2.5}$ concentrations).

A new study of 47 U.S. cities (Zanobetti and Schwartz, 2009, 188462), which estimated $PM_{10-2.5}$ by calculating the difference between the county-average PM_{10} and $PM_{2.5}$, found associations between $PM_{10-2.5}$ and mortality across the U.S., including regions where $PM_{10-2.5}$ levels are not high. In addition, one well conducted multicity Canadian study (Burnett et al., 2004, 086247) provided evidence for an association between short-term exposure to $PM_{10-2.5}$ and mortality. However, unlike $PM_{2.5}$ very few of the $PM_{10-2.5}$ studies have investigated confounding by gaseous copollutants or the influence of model specification on $PM_{10-2.5}$ risk estimates. Zanobetti and Schwartz (2009, 188462) did provide preliminary evidence for greater effects occurring during the warmer months (i.e., spring and summer), which is consistent with the results from PM_{10}-mortality studies (Peng et al., 2005, 087463; Zeka et al., 2006, 088749). Overall, although more data is needed to: adequately characterize the chemical and biological components that may modify the potential toxicity of $PM_{10-2.5}$ and compare the different methods used to estimate exposure, consistent positive associations between short-term exposure to $PM_{10-2.5}$ and mortality were observed in the U.S. and Canadian-based multicity studies evaluated, as well as the single-city studies conducted in these locations. Therefore, the epidemiologic evidence **is suggestive of a causal relationship between short-term exposure to $PM_{10-2.5}$ and mortality.**

6.5.3.3. UFPs

Limited evidence was available during the review of the 2004 PM AQCD (U.S. EPA, 2004, 056905) regarding the potential association between UFPs and mortality. The lone study evaluated was conducted in Germany and provided some evidence for an association, but this association was reduced upon the inclusion of gaseous pollutants in a two-pollutant model.

Only a few new studies, all of them from Europe, were identified during this review, which examined the association between short-term exposure to UFPs and mortality. Inconsistencies were observed in the lag structure of association reported by each study in terms of both the lag day with the greatest association and the number of lag days considered in the study. Overall the studies consistently found that UFPs were correlated with gaseous pollutants derived from local combustion sources and that one or more of the gaseous pollutants were also associated with mortality. The limited number of studies available and the discrepancy in results between studies further confirms the need for additional data to examine the UFP-mortality relationship. In conclusion, the epidemiologic evidence **is inadequate to infer a causal association between short-term exposure to UFPs and mortality**.

6.6. Attribution of Ambient PM Health Effects to Specific Constituents or Sources

From a mechanistic perspective, it is highly plausible that the chemical composition of PM would be a better predictor of health effects than particle size. The observed geographical gradients in a number of $PM_{2.5}$ constituents (e.g., EC, OC, nitrate, and SO_4^{2-}) and regional heterogeneity in PM-related health effects reported in epidemiologic studies are consistent with this hypothesis. Recent studies in epidemiology, controlled human exposure, and toxicology have begun using information on ambient PM composition, and apportionment of constituents into sources, in an attempt to identify those with links to health outcomes and endpoints.

This section focuses on short-term exposure studies that (1) assessed health effects for ambient PM sources or components; and (2) used quantitative methods to relate those sources and components to health effects. Epidemiologic, controlled human exposure, and toxicological studies that took into consideration a large set of PM constituents (typically minerals, metals, EC, OC, and ions such as SO_4^{2-}) and aimed to segregate which constituents or groups of constituents may be responsible for the PM-related health effects observed are included. Most of these studies were reviewed earlier in this chapter and evaluated the relationship between specific chemical constituents derived from ambient PM and health effects. However, there were many studies presented earlier, as well as others only included in the Annexes, which only selected one or a small number of PM constituents *a priori*. Several controlled human exposure and toxicological studies likewise used a single compound found in PM rather than ambient PM. Additionally, studies that presented ambient PM composition and health data without systematically and explicitly investigating relationships are not included in this section. The few epidemiologic studies of long-term exposure that examined potential relationships between composition and sources of PM with mortality are discussed in Section 7.6.2.

Prior to the 2004 PM AQCD (U.S. EPA, 2004, 056905), only a handful of epidemiologic studies had attempted to relate specific constituents or sources of ambient PM to health outcomes without selecting constituents *a priori*. In this review, approximately 40 new epidemiologic, controlled human exposure, and toxicological studies explore the health effects attributed to chemical constituents and sources of ambient PM. The following summary (Section 6.6.3) provides a synthesis of the findings, including discussions on the coherence and consistency of the results.

6.6.1. Evaluation Approach

Relating a large number of ambient PM constituents with a large number of health outcomes presents difficulties that are related to both the nature of PM and methods of quantitative analysis. First, the number of constituents that comprise PM is not only large, but the correlations between them can be high. Reducing the correlation between constituents has been accomplished in most of

the recent studies through various forms of factor analysis, which limits the correlations between constituents by grouping the most highly correlated ambient PM constituents into less correlated groups or factors. Some studies identify the resulting groups or factors with named sources of ambient PM, but many do not draw explicit links between factors and actual sources. The methods used in estimating source contributions to ambient PM are reviewed in Section 3.6.1.

Most studies reviewed herein, regardless of discipline, were based on data for between 7 and 20 ambient PM constituents, with EC, OC, SO_4, and NO_3 most commonly measured. Most studies first reduced the number of ambient PM constituents by grouping them with various factorization or source apportionment techniques and the majority labeled the constituent groupings according to their presumed source. A separate analysis was then used to examine the relationship between the grouped PM constituents and various health effects. A few performed these two steps simultaneously using Partial Least Squares (PLS) procedures or Structural Equation Modeling (SEM). A small number of controlled human exposure and toxicological studies did not apply any kind of grouping to the ambient PM speciation data.

There are some differences in the type of PM constituent data used in epidemiologic, controlled human exposure and toxicological studies. In epidemiologic studies, ambient PM speciation data is obtained from atmospheric monitors; for controlled human exposure and toxicological studies, the technique used in the experimental exposure determines the type of PM data. Thus, all epidemiologic studies relied on monitor data, while all of the controlled human exposure and the majority of the toxicological studies used CAPs (and analyzed the concentrations of constituents therein). The remaining toxicological studies used ambient PM samples collected on filters at various U.S. sites. Further details on the studies included can be found in Appendix F.

Some important limitations in interpreting these studies together is that few, if any of the results are easily comparable, due to: (1) differences in the sets of ambient PM constituents that make up each of the factors; (2) the subjectivity involved in labeling factors as sources; (3) the numerous potential health effects examined in these studies, including definitive outcomes (e.g., HAs) as well as physiological alterations (e.g., increased inflammatory response); and (4) the various statistical methods and analytical approaches used in the studies. There are no well-established, objective methods for conducting the various forms of factor analysis and source apportionment, leaving much of the model operation and factor assignment open to judgment by the individual investigator. For example, the Al/Si factor identified in one study may differ from the Al/Ca/Fe/Si factor from another study, and the "Resuspended Soil" factor from a third study. After factorization or apportionment of the ambient PM data, the methods used for analyzing the potential association between ambient PM constituents or sources and health effects also varied. Except for the studies that used PLS or SEM, controlled human exposure and toxicological studies all used univariate mixed model regression for every identified PM factor or source. A number of toxicological studies followed the univariate step with multivariate regression for all factors. Epidemiologic studies generally related short-term exposure to sources with health outcomes through various forms of Poisson regression.

6.6.2. Findings

The results that follow are organized by discipline, with epidemiologic studies followed by controlled human exposure and toxicological studies. This section ends with a summary table, Table 6-18. Table 6-18 is broken out by $PM_{2.5}$ sources, and includes those epidemiologic, controlled human exposure, and in vivo toxicological studies that either grouped ambient $PM_{2.5}$ constituents or used tracers for each source. The table does not include all factors or sources examined in the studies listed: those factors or sources for which no association with effects was found not included.

6.6.2.1. Epidemiologic Studies

Results from the 2004 PM AQCD

Three epidemiologic studies that examined the association between PM constituents or sources and specific health effects were evaluated in the 2004 PM AQCD (U.S. EPA, 2004, 056905). Of

these studies, one study associated daily mortality with a mobile sources PM factor in Knoxville, TN and St. Louis, MO and coal in Boston, MA, while the crustal factor was not found to be significant for any of the six cities studied (Laden et al., 2000, 012102; Schwartz, 2003, 042811). Another study demonstrated an association between a regional SO_4^{2-} factor and total mortality at lag 0 in Phoenix and factors for regional SO_4^{2-}, motor vehicles, and vegetative burning with cardiovascular mortality at lags of 0, 1, and 3, respectively (Mar et al., 2000, 001760; 2003, 042841). Negative associations were observed between total mortality and regional SO_4^{2-} at lag 3, along with local SO_2 and soil factors (Mar et al., 2000, 001760; 2003, 042841). Finally, Tsai et al. (2000, 006251) identified significant associations between PM_{15}-derived industrial sources and total daily deaths in Newark and Camden, NJ; SO_4^{2-} was also linked to cardiopulmonary deaths in both locations. Total mortality and cardiopulmonary deaths were also significantly associated with PM from oil burning in Camden (2000, 006251).

Comparative Analyses of Source Apportionment Methods

Hopke et al. (2006, 088390) conducted a comparative analysis of source apportionment techniques used by investigators at multiple institutions, and subsequently used in epidemiologic analyses (Ito et al., 2006, 088391; Mar et al., 2006, 086143). An overarching conclusion of this set of analyses, reported in Thurston et al. (2005, 097949), is that variation in the source apportionment methods was not a major source of uncertainty in the epidemiologic effect estimates. In the primary analyses, mortality was associated with secondary SO_4^{2-} in both Phoenix and Washington D.C., although lag times differed (0 and 3, respectively). The SO_4^{2-} effect was stronger for total mortality in Washington D.C. and for cardiovascular mortality in Phoenix (Ito et al., 2006, 088391; Mar et al., 2006, 086143). In addition, Ito et al. (2006, 088391) found some evidence for associations with primary coal and traffic with total mortality in Washington D.C. (Ito et al., 2006, 088391) while copper smelter, traffic, and sea salt were associated with cardiovascular mortality in Phoenix at various lag times (Mar et al., 2006, 086143). In contrast to Phoenix, sea salt and traffic were not associated with mortality in Washington D.C. (Ito et al., 2006, 088391), but in both locations no associations were observed between biomass/wood combustion and mortality (Ito et al., 2006, 088391; Mar et al., 2006, 086143). In an additional study that compared three source apportionment methods in Atlanta–PMF, modified CMB, and a single-species tracer approach–found that the epidemiologic results were robust to the choice of analytic method (Sarnat et al., 2008, 097972). There were consistent associations between ED visits for cardiovascular diseases with $PM_{2.5}$ from mobile sources (gasoline and diesel) and biomass combustion (primarily prescribed forest burning and residential wood combustion), whereas $PM_{2.5}$ from secondary SO_4^{2-} was associated with respiratory disease ED visits (Sarnat et al., 2008, 097972). Sarnat et al. (2008, 097972) also found that the primary power plant $PM_{2.5}$ source identified by the CMB approach was negatively associated with respiratory ED visits while no association was found for $PM_{2.5}$ from soil and secondary nitrates/ammonium nitrate. In these studies, effect estimates based on the different source apportionment methods were generally in close agreement.

Source Apportionment Studies

A study that examined associations with mortality in Santiago, Chile, identified a motor vehicle source of $PM_{2.5}$ as having the greatest association with total and cardiac mortality at lag 1 (Cakmak et al., 2009, 191995). There was effect modification by age, with the total mortality relative risks associated with $PM_{2.5}$ from motor vehicles being greatest for those >85 yr. Soil and combustion sources were also associated with cardiac mortality. Risk estimates for respiratory mortality were the greatest for the motor vehicle source, with combustion and soil source factors also demonstrating positive associations for lag 1 (Cakmak et al., 2009, 191995).

An epidemiologic study that evaluated respiratory ED visits was conducted in Spokane, WA and used tracers as indicators of ambient $PM_{2.5}$ sources (Schreuder et al., 2006, 097959). In this study, only $PM_{2.5}$ from vegetative burning (total carbon) was associated with increased respiratory ED visits for lag 1, while $PM_{2.5}$ indicators for motor vehicles (Zn) and soil (Si) were not associated with cardiac hospital or respiratory ED visits. Andersen et al. (2007, 093201) conducted a source apportionment analysis to identify the sources of ambient PM_{10} associated with cardiovascular and

respiratory hospital admissions in older adults and children (ages 5-18) in Copenhagen, including two-pollutant models with various sources of PM_{10}. Andersen et al. (2007, 093201) found that secondary and crustal sources of PM_{10} were associated with cardiovascular hospital admissions; biomass sources were associated with respiratory hospital admissions; and vehicle sources were associated with asthma hospital admissions.

Several panel epidemiologic studies have examined the association between PM sources and physiological alterations in cardiovascular function. Lanki et al. (2006, 089788) reported positive associations between $PM_{2.5}$ from local traffic (measured as absorbance, which is correlated with EC content) and long-range transported $PM_{2.5}$ with ST-segment depression in elderly adults in a study conducted in Helsinki, Finland. Positive associations with ST-segment depression were also reported with $PM_{2.5}$ from crustal and salt sources, but these associations were not statistically significant. In an additional study, Yue et al. (2007, 097968) found that adult males with coronary artery disease in Erfurt, Germany, demonstrated changes in repolarization parameters associated with traffic-related $PM_{2.5}$, with increased vWF linked to traffic and combustion-generated particles, although the source apportionment was based solely on particle size distribution. In addition, elevated CRP levels were associated with all sources of $PM_{2.5}$ (soil, local traffic, secondary aerosols from local fuel combustion, diesel, and secondary aerosols from multiple sources) (Yue et al., 2007, 097968). Reidiker et al. (2004, 056992), in a study of young male highway patrol officers, found that the most significant effects (HRV, supraventricular ectopic beats, hematological markers, vWF) were associated with a speed-change factor for $PM_{2.5}$ (2004, 056992). In addition, the authors observed an association between crustal factor and cardiovascular effects, but no health-related associations with steel wear or gasoline $PM_{2.5}$ source factors.

Two recent studies have examined the associations between ambient $PM_{2.5}$ sources and respiratory symptoms and lung function. Positive associations with $PM_{2.5}$ motor vehicle and road dust sources were reported for respiratory symptoms and inhaler use in asthmatic children in New Haven, CT, and negative associations with wheeze or inhaler use for biomass burning at lag 0-2 (Gent et al., 2009, 180399). These positive effects for motor vehicle and road dust sources were robust to the inclusion of a gaseous copollutant (NO_2, CO, SO_2, or O_3) in the regression model. Penttinen et al. (2006, 087988) in a study consisting of asthmatic adults living in Helsinki, Finland, found that decrements in PEF were associated with ambient $PM_{2.5}$ soil, long-range transport, and local combustion sources at lags from 0-5 days. In addition, negative associations with asthma symptoms and medication use were reported for $PM_{2.5}$ from sea salt and long-range transport sources (Penttinen et al., 2006, 087988).

PM Constituent Studies

Some studies considered large sets of ambient PM constituents and attempted to identify which were associated with various health effects, but without grouping them into factors, or identifying sources. The majority of these studies focused on health effects associated with short-term exposure to $PM_{2.5}$. Peng et al. (2009, 191998) examined the association between $PM_{2.5}$ constituents (i.e., EC, OC, SO_4^{2-}, NO_3^-, Si, Na, NH_4^+) and cardiovascular and respiratory hospital admissions in 119 U.S. cities. When including each constituent in a multipollutant model, they found that EC and OC were robust to the inclusion of the other constituents at lag 0 for cardiovascular and respiratory hospital admissions, respectively. Although this study did not include analyses to identify sources of the constituents examined, EC and OC are often attributed to motor vehicle emissions, particularly diesel engines, and wood burning (Peng et al., 2009, 191998). Ostro et al. (2007, 091354; 2008, 097971) conducted two studies in six California counties to examine the association between ambient PM constituents and mortality. In the 2007 analysis, Ostro et al. (2006, 087991) found associations between Cu and all-cause mortality; EC, K, and Zn and CVD mortality; and Cu and Ti and respiratory mortality at lags ranging from 0 to 3 days. Associations during the summer were only observed between K for both CVD and respiratory mortality; and Al, Cl, Cu, Pb, Ti, and Zn and respiratory mortality. Overall, the most consistent associations were observed during the cool season. In a subsequent analysis, Ostro et al. (2008, 097971) examined the association between ambient PM constituents and cardiovascular mortality in potentially susceptible subpopulations. The authors found positive associations between EC, OC, NO_3^-, SO_4^{2-}, K, Cu, Fe, and Zn and cardiovascular mortality. These associations were higher in individuals with lower educational

attainment and of Hispanic ethnicity. In addition, similar to the 2007 analysis, associations were observed at lags ranging from 0 to 3 days.

Evaluation of Effect Modification by PM Constituents

Several studies have conducted secondary analyses to examine whether the variation in associations between $PM_{2.5}$ and morbidity and mortality or PM_{10} and mortality reflects differences in $PM_{2.5}$ constituents. An assumption in these types of analyses, especially when examining the effects on PM_{10} mortality risk estimates, is that the relative contributions of $PM_{2.5}$ have remained the same over time; these studies used PM_{10} data for years prior to 2000, while $PM_{2.5}$ speciation data has only been routinely collected since about 2000. Bell et al. (2009, 191997) found statistically significant associations between the county average concentrations of V, Ni, and EC (106 counties) and effect estimates for both cardiovascular and respiratory hospital admissions with short-term exposure to $PM_{2.5}$. In this analysis the ambient $PM_{2.5}$ constituents that comprised the majority of $PM_{2.5}$ total mass in the study locations were NH_4^+, EC, OC, NO_3^-, and SO_4^{2-}. Bell et al. (2009, 191997) also conducted a similar analysis for PM_{10}-mortality risk estimates and found that only Ni increased the risk estimate. However, in a sensitivity analysis, when selectively dropping out the communities examined one at a time, removing New York City diminished the Ni association. Both Lippmann et al. (2006, 091165) and Dominici et al. (2007, 099135) conducted similar analyses, albeit using a smaller subset of cities and/or different years of PM_{10} data. In both studies, Ni and V were found to modify the PM_{10}-mortality risk estimates. Similar to Bell et al. (2009, 191997), Dominici et al. (2007, 099135) also found that excluding New York City as part of a sensitivity analysis resulted in a diminished association with Ni and V. In an additional study, Franklin et al. (2008, 097426) examined the potential modification of the $PM_{2.5}$-mortality relationship by PM constituents in 25 U.S. cities. In a second-stage analysis using the species-to-$PM_{2.5}$ mass proportion of multiple constituents, the authors found that Al, As, Ni, Si, and SO_4^{2-} significantly modified the association between $PM_{2.5}$ and nonaccidental mortality.

6.6.2.2. Controlled Human Exposure Studies

A few controlled human exposure studies employed PCA, although not all linked groupings of PM constituents to the measured physiological parameters. Huang et al. (2003, 087377) demonstrated associations between increased fibrinogen and Cu/Zn/V and increased BALF neutrophils and Fe/Se/SO_4 in young, healthy adults exposed to RTP, NC CAPs; however, only water-soluble constituents were analyzed. In the other study that examined physiological cardiovascular effects, Fe and EC were associated with changes in ST-segment, while SO_4^{2-} was associated with decreased SBP in asthmatic and healthy human volunteers exposed to Los Angeles CAPs (2003, 087377). In Gong et al. (2003, 087365) the majority of the PM was in the thoracic coarse fraction. In the other study that used Los Angeles CAPs, the only observed association was between SO_4^{2-} content and decreased lung function (FEV_1 and FVC) in elderly volunteers with and without COPD (Gong et al., 2005, 087921). Two additional controlled human exposure studies that did not perform grouping and employed Toronto CAPs plus O_3 demonstrated increased DBP and increased brachial artery vasoconstriction associated with carbon content (Urch et al., 2004, 055629; 2005, 081080).

6.6.2.3. Toxicological Studies

The only toxicological in vivo study that characterized PM sources corresponding to identified sources was conducted in Tuxedo, NY, over a 5-mo period. This study reported that all sources (regional SO_4^{2-}, resuspended soil, residual oil, traffic and other unknown sources) were linked to HR or HRV changes in mice at one time or another during or after daily exposure (Lippmann et al., 2005, 087453). In a simultaneous in vitro study using CAPs from the same location, NF-κB in BEAS-2B cells were correlated with the oil combustion factor ($r = 0.289$ and 0.302 for V and Ni, respectively) (Maciejczyk and Chen, 2005, 087456). The other in vitro toxicological study (Duvall et al., 2008, 097969) that named sources employed samples from 5 U.S. cities and found a good fit for the regression model with increased IL-8 release in primary human airway epithelium cells and coal combustion ($R^2 = 0.79$), secondary nitrate ($R^2 = 0.63$), and mobile sources ($R^2 = 0.39$). In addition, soil ($R^2 = 0.48$), residual oil combustion ($R^2 = 0.38$), and wood combustion ($R^2 = 0.33$) were

associated with COX-2 effects; whereas, secondary SO_4^{2-} ($R^2 = 0.51$) was correlated with HO-1. Wood combustion and soil were negatively associated with HO-1.

Several toxicological studies employed Boston CAPs and identified at least four groupings of ambient $PM_{2.5}$ constituents (V/Ni, S, Al/Si, and Br/Pb), but they named sources only partially and tentatively (Batalha et al., 2002, 088109; Clarke et al., 2000, 011806; Godleski et al., 2002, 156478; Nikolov et al., 2008, 156808; Saldiva et al., 2002, 025988; Wellenius et al., 2003, 055691). When examining cardiovascular effects these studies reported that Si was associated with changes in the ST-segment of dogs (Wellenius et al., 2003, 055691) and decreased L/W ratio in rat pulmonary arteries (Batalha et al., 2002, 088109) in multivariate analyses. In addition, blood hematological results were associated with V/Ni, Al/Si, Na/Cl, and S in dogs (Clarke et al., 2000, 011806). An examination of respiratory effects in the latter study found that V/Ni and Br/Pb were associated with increased inflammation in BALF for only the third day of exposure (Clarke et al., 2000, 011806). Decreased respiratory rate and increased airway irritation (Penh) in dogs were associated with road dust (Al) and motor vehicles (OC), respectively (Nikolov et al., 2008, 156808). Individual $PM_{2.5}$ constituents associated with elevated neutrophils in BALF were Br, EC, OC, Pb, and SO_4^{2-} (Godleski et al., 2002, 156478), which is consistent with the findings (Br, EC, OC, Pb, V, and Cl) of Saldiva et al. (2002, 025988).

The two toxicological studies that used PLS methodologies identified $PM_{2.5}$ constituents linked to respiratory parameters. Seagrave et al. (2006, 091291) demonstrated associations between cytotoxic responses and a gasoline plus nitrates source factor (OC, Pb, hopanes/steranes, nitrate, and As) along with inflammatory responses and a gasoline plus diesel source factor (including major metal oxides) in rats exposed via IT instillation. In the other study, Veranth et al. (2006, 087479) collected loose surface soil from 28 sites in the Western U.S. and exposed BEAS-2B cells to $PM_{2.5}$. OC_1, OC_3, OC_2, EC_2, Br, EC_1, and Ni correlated with IL-8 release, decreased IL-6 release, and decreased viability at low and high doses (10 and 80 μg/cm^2, respectively).

Table 6-18. Study-specific $PM_{2.5}$ factor/source categories associated with health effects.

Source Category	Location	Health Effects	Time	Type of Study[1]	Species	Reference
CRUSTAL/SOIL/ROAD DUST						
Al, Si, Fe	Phoenix, AZ	negative association with total mortality	Lag 2	E	Human	Mar et al. (2000, 001760)
Not provided	Washington, D.C.	↑CV mortality	Lag 4	E	Human	Ito et al.(2006, 088391)
Al, Ca, Fe, Si	Santiago, Chile	↑CV mortality ↑ respiratory mortality	Lag 1	E	Human	Cakmak et al. (2009, 191995)
Al, Si, Ca, K, Fe	Helsinki, Finland	ST-segment depression	Lag 3	E	Human	Lanki et al. (2006, 089788)
Al, Si, Ca, K, Fe	Los Angeles, CA	↓ ST-segment voltage	2 days post-exposure	H	Human	Gong et al. (2003, 042106)
Al, Si	Boston, MA	ST-segment change	Following exposure	T	Dog	Wellenius et al. (2003, 055691)
Al, Si, Ca	Boston, MA	↓ lumen/wall ratio	24 h post-exposure	T	Rat	Batalha et al. (2002, 088109)
Al, Si, Ti, Fe	Wake County, NC	↑ uric acid ↑ mean cycle length	Lag 15 h	E	Human	Riediker et al. (2004, 056992)
Al, Si, Ca, Fe	Tuxedo, NY	↓ HR ↑ HR ↑ SDNN, ↑ RMSSD	During exposure Afternoon post-exposure. Night post-exposure	T	Mouse	Lippmann et al. (2005, 087453)
Al, Si	Boston, MA	↑ blood PMN % ↓ blood lymphocytes % ↑ WBC	Following exposure	T	Dog	Clarke et al.(2000, 011806)
Si, Fe, Al, Ca, Ba, Ti	New Haven, CT	↑ respiratory symptoms and inhaler use	Lag 0-2	E	Human	Gent et al. (2009, 180399)

Source Category	Location	Health Effects	Time	Type of Study[1]	Species	Reference
Si, Al, Ca, Fe, Mn	Helsinki, Finland	↓ mean PEF	Lag 3	E	Human	Penttinen et al. (2006, 087988)
Al	Boston, MA	↓ airway irritation (penh)	During exposure	T	Dog	Nikolov et al. (2008, 156808)
SALT						
Not provided	Phoenix, AZ	↑CV mortality ↑total mortality negative association with total mortality	Lag 5 Lag 0	E	Human	Mar et al. (2006, 086143)
Na, Cl	Helsinki, Finland	ST-segment depression	Lag 3	E	Human	Lanki et al. (2006, 089788)
Na, Cl	Boston, MA	↑ blood lymphocyte %	Following exposure	T	Dog	Clarke et al.(2000, 011806)
Na, Cl	Helsinki, Finland	Negatively associated with bronchodilator use and corticosteroid use	Lag 0-5 avg	E	Human	Penttinen et al. (2006, 087988)
Na, Cl	Boston, MA	↑ lung PMN density	24 h post-exposure	T	Rat	Saldiva et al. (2002, 025988)
SECONDARY SO_4^{2-} / LONG-RANGE TRANSPORT						
S	Phoenix, AZ	↑ total mortality negative association with total mortality	Lag 0 Lag 5	E	Human	Mar et al. (2000, 001760)
Not provided	Washington, D.C.	↑ total mortality	Lag 3	E	Human	Ito et al. (2006, 088391)
Not provided	Phoenix, AZ	↑CV mortality	Lag 0	E	Human	Mar et al. (2006, 086143)
S, K, Zn, Pb	Helsinki, Finland	ST-segment depression	Lag 2	E	Human	Lanki et al. (2006, 089788)
SO_4^{2-}	Los Angeles, CA	↓ SBP	4 h post-exposure	H	Human	Gong et al. (2003, 042106)
S, Si, OC	Tuxedo, NY	↓ HR ↓ SDNN, ↓ RMSSD	Afternoon post-exposure Night post-exposure	T	Mouse	Lippmann et al. (2005, 087453)
S	Boston, MA	↓ RBC ↑ hemoglobin	Following exposure	T	Dog	Clarke et al. (2000, 011806)
SO_4^{2-}, NH_4^+, OC	Atlanta, GA	↑ respiratory ED visits	Lag 0	E	Human	Sarnat et al. (2008, 097972)
S, K, Zn, PM mass	Helsinki, Finland	↓ mean PEF. Negative association with asthma symptom prevalence	Lag 1 Lag 3	E	Human	Penttinen et al. (2006, 087988)
SO_4^{2-} (+NO_2)	Los Angeles, CA	↓ FEV_1 ↓ FVC	Following exposure	H	Human	Gong et al. (2005, 087921)
TRAFFIC						
Pb, Br, Cu	Harvard Six Cities	↑ total mortality	Lag 0-1	E	Human	Laden et al. (2000, 012102)
Not provided	Phoenix, AZ	↑CV mortality	Lag 1	E	Human	Mar et al. (2006, 086143)
Mn, Fe, Zn, Pb, OC, EC, CO, NO_2	Phoenix, AZ	↑ CV mortality	Lag 1	E	Human	Mar et al. (2000, 001760)
CO, NO_2, EC, OC	Santiago, Chile	↑CV mortality ↑ respiratory mortality	Lag 1	E	Human	Cakmak et al. (2009, 191995)
Gasoline (OC, NO_3^-, NH_4^+)	Atlanta, GA	↑ CVD ED visits	Lag 0	E	Human	Sarnat et al. (2008, 097972)
Diesel (EC, OC, NO_3^-)	Atlanta, GA	↑ CVD ED visits	Lag 0	E	Human	Sarnat et al. (2008, 097972)
NO_X, EC, ultrafine count	Helsinki, Finland	ST-segment depression	Lag 2	E	Human	Lanki et al. (2006, 089788)

Source Category	Location	Health Effects	Time	Type of Study[1]	Species	Reference
Speed-change factor (Cu, S, aldehydes)	Wake County, NC	↑ blood urea nitrogen ↑ mean red cell volume ↑ blood PMN % ↓ blood lymphocytes % ↑ von Willebrand factor (vWF) ↓ protein C ↑ mean cycle length ↑ SDNN ↑ PNN50 ↑ supraventricular ectopic beats	Lag 15 h	E	Human	Riediker et al. (2004, 056992)
Motor vehicle/other (Br, Pb, Se, Zn, NO_3-)	Tuxedo, NY	↓ RMSSD	Afternoon post-exposure	T	Mouse	Lippmann et al. (2005, 087453)
EC, Zn, Pb, Cu, Se	New Haven, CT	↑ respiratory symptoms	Lag 0-2	E	Human	Gent et al. (2009, 180399)
Local combustion (NO_X, ultrafine PM, Cu, Zn, Mn, Fe)	Helsinki, Finland	↓ mean PEF	Lag 0-5 avg	E	Human	Penttinen et al. (2006, 087988)
Gasoline+secondary nitrate*	Birmingham, AL; Atlanta, GA; Pensacola, FL; Centreville, AL	cytotoxic responses (potency)	24 h post-exposure	T	Rat	Seagrave et al. (2006, 091291)
Gasoline+diesel*	Birmingham, AL; Atlanta, GA; Pensacola, FL; Centreville, AL	inflammatory responses (potency)	24 h post-exposure	T	Rat	Seagrave et al. (2006, 091291)
OIL COMBUSTION						
V, Ni	Boston, MA	↑ blood PMN % ↓ blood lymphocytes % ↑ BALF AM %	Following exposure Following exposure 24 h post-exposure	T	Dog	Clarke et al. (2000, 011806)
V, Ni, Se	Tuxedo, NY	↓ SDNN ↓ RMSSD	Afternoon post-exposure	T	Mouse	Lippmann et al. (2005, 087453)
Ni	Boston, MA	↓ respiratory rate	During exposure	T	Dog	Nikolov et al. (2008, 156808)
V, Ni	Boston, MA	↑ lung PMN density	24 h post-exposure	T	Rat	Saldiva et al. (2002, 025988)
COAL COMBUSTION						
Se, SO_4^{2-}	Harvard Six Cities	↑ total mortality	Lag 0-1	E	Human	Laden et al. (2000, 012102)
Not provided	Washington, D.C.	↑ total mortality	Lag 3	E	Human	Ito et al. (2006, 088391)
OTHER METALS						
Cu smelter (not provided)	Phoenix, AZ	↑CV mortality ↑total mortality	Lag 0	E	Human	Mar et al. (2006, 086143)
Incinerator	Washington, D.C.	Negative association with total and CV mortality	Lag 0	E	Human	Ito et al. (2006, 088391)
Metal processing (SO_4^{2-}, Fe, NH_4^+, EC, OC)	Atlanta, GA	↑ CVD ED visits	Lag 0	E	Human	Sarnat et al. (2008, 097972)

Source Category	Location	Health Effects	Time	Type of Study[1]	Species	Reference
Combustion (Cr, Cu, Fe, Mn, Zn)	Santiago, Chile	↑CV mortality ↑ respiratory mortality	Lag 1	E	Human	Cakmak et al. (2009, 191995)
WOODSMOKE / VEGETATIVE BURNING						
OC, K	Phoenix, AZ	↑ CV mortality	Lag 3	E	Human	Mar et al. (2000, 001760)
OC, EC, K, NH_4^+	Atlanta, GA	↑ CVD ED visits	Lag 0	E	Human	Sarnat et al. (2008, 097972)
Total C	Spokane, WA	↑ respiratory ED visits	Lag 1	E	Human	Schreuder et al. (2006, 097959)
UNNAMED FACTORS						
Zn-Cu-V	Chapel Hill, NC	↑ blood fibrinogen	18 h post-exposure	H	Human	Huang et al. (2003, 087377)
Fe-Se-SO_4^{2-}	Chapel Hill, NC	↑ BALF PMN	18 h post-exposure	H	Human	Huang et al. (2003, 087377)
Br, Cl, Pb	Santiago, Chile	↑CV mortality ↑ respiratory mortality	Lag 1	E	Human	Cakmak et al. (2009, 191995)
Br, Pb	Boston, MA	↑ BALF PMN %	24 h post-exposure	T	Dog	Clarke et al.(2000, 011806)
Br, Pb	Boston, MA	↑ lung PMN density	24 h post-exposure	T	Rat	Saldiva et al. (2002, 025988)

*Constituents not provided.
[1] E = Epidemiologic study; H = Controlled human exposure study; T = Toxicological study

An in vitro toxicological study that employed Chapel Hill PM_{10} used PCA but did not name specific PM sources (Becker et al., 2005, 088590). In this study, the release of IL-6 from human alveolar macrophages and IL-8 from normal human bronchial epithelial cells was associated with a PM_{10} factor comprised of Cr, Al, Si, Ti, Fe, and Cu. No statistically significant effects were observed for a second PM_{10} factor (Zn, As, V, Ni, Pb, and Se).

Those toxicological studies that did not apply groupings to the ambient $PM_{2.5}$ speciation data demonstrated a variety of results. Two Boston CAPs studies demonstrated lung oxidative stress correlated with a number of individual $PM_{2.5}$ constituents including, Mn, Zn, Fe, Cu, and Ca (Gurgueira et al., 2002, 036535) and Al, Si, Fe, K, Pb, and Cu (Rhoden et al., 2004, 087969) in rats using univariate regression.

The remaining toxicological study that did not use ambient PM constituent groupings reported a correlation between Zn and plasma fibrinogen in SH rats when constituents were normalized per unit mass of CAPs (Kodavanti et al., 2002, 035344).

6.6.3. Summary by Health Effects

Recent epidemiologic, toxicological, and controlled human exposure studies have evaluated the health effects associated with ambient PM constituents and sources, using a variety of quantitative methods applied to a broad set of PM constituents, rather than selecting a few constituents a priori. As shown in Table 6-18, numerous ambient $PM_{2.5}$ source categories have been associated with health effects, including factors for PM from crustal and soil, traffic, secondary SO_4^{2-}, power plants, and oil combustion sources. There is some evidence for trends and patterns that link particular ambient PM constituents or sources with specific health outcomes, but there is insufficient evidence to determine whether these patterns are consistent or robust.

For cardiovascular effects, multiple outcomes have been linked to a PM crustal/soil/road dust source, including cardiovascular mortality in Washington D.C. (Ito et al., 2006, 088391)and Santiago, Chile, (Cakmak et al., 2009, 191995) and ST-segment changes in Helsinki (Lanki et al., 2006, 089788), Los Angeles (Gong et al., 2003, 042106), and Boston (Wellenius et al., 2003, 055691). Interestingly, the ST-segment changes have been observed in an epidemiologic panel study, a controlled human exposure study, and a toxicological study, although the majority of the CAPs in the controlled human exposure study was $PM_{10-2.5}$. Further support for a crustal/soil/road dust source associated with cardiovascular health effects comes from a PM_{10} source apportionment study in Copenhagen that reported increased cardiovascular hospital admissions (Andersen et al., 2007, 093201).

$PM_{2.5}$ traffic and wood smoke/vegetative burning sources have also been linked to cardiovascular effects. Cardiovascular mortality in Phoenix (Mar et al., 2000, 001760; 2006, 086143) and Santiago, Chile, (Cakmak et al., 2009, 191995) was associated with traffic at lag 1. Gasoline and diesel sources were associated with ED visits in Atlanta for cardiovascular disease at lag 0 (Sarnat et al., 2008, 097972). Cardiovascular mortality in Phoenix (Mar et al., 2000, 001760) and ED visits in Atlanta (Sarnat et al., 2008, 097972) were associated with wood smoke/vegetative burning.

Studies that only examined the effects of individual $PM_{2.5}$ constituents linked EC to cardiovascular hospital admissions in a multicity analysis (Peng et al., 2009, 191998) and cardiovascular mortality in California (Ostro et al., 2007, 091354; 2008, 097971).

These studies suggest that cardiovascular effects may be associated with $PM_{2.5}$ from motor vehicle emissions, wood or biomass burning, and PM (both $PM_{2.5}$ and $PM_{10-2.5}$) from crustal or road dust sources. In addition, there are many studies that observed associations between other sources (i.e., salt, secondary SO_4^{2-}/long-range transport, other metals) and cardiovascular effects, but at this time, there does not appear to be a consistent trend or pattern of effects for those factors.

There is less consistency in observed associations between PM sources and respiratory health effects, which may be partially due to the fact that fewer studies have been conducted that evaluated respiratory-related outcomes and measures. However, there is some evidence for associations with secondary SO_4^{2-} $PM_{2.5}$. Sarnat et al. (2008, 097972) found an increase in respiratory ED visits in Atlanta that was associated with a $PM_{2.5}$ secondary SO_4^{2-} factor. Decrements in lung function in Helsinki (Lanki et al., 2006, 089788) and Los Angeles (Gong et al., 2005, 087921) in asthmatic and healthy adults, respectively, were also linked to this factor. Health effects relating to the crustal/soil/road dust and traffic sources of PM included increased respiratory symptoms in asthmatic children (Gent et al., 2009, 180399) and decreased PEF in asthmatic adults (Penttinen et al., 2006, 087988). Inconsistent results were also observed in those $PM_{2.5}$ studies that use individual constituents to examine associations with respiratory morbidity and mortality, although Cu, Pb, OC, and Zn were related to respiratory health effects in two or more studies.

A few studies have identified $PM_{2.5}$ sources associated with total mortality. These studies found an association between mortality and a $PM_{2.5}$ coal combustion factor (Laden et al., 2000, 012102), while others linked mortality to a secondary SO_4^{2-}/long-range transport $PM_{2.5}$ source (Ito et al., 2006, 088391; Mar et al., 2006, 086143).

Recent studies have evaluated whether the variation in associations between $PM_{2.5}$ and morbidity and mortality or PM_{10} and mortality reflects differences in $PM_{2.5}$ constituents (Bell et al., 2009, 191997; Dominici et al., 2007, 099135; Lippmann et al., 2006, 091165). In three studies (Bell et al., 2009, 191997; Dominici et al., 2007, 099135; Lippmann et al., 2006, 091165) PM_{10}-mortality effect estimates were greater in areas with a higher proportion of Ni in $PM_{2.5}$, but the overall PM_{10}-mortality association was diminished when New York City was excluded in a sensitivity analysis in two of the studies. V was also found to modify PM_{10}-mortality effect estimates as well as those for $PM_{2.5}$ with respiratory and cardiovascular hospital admissions (Bell et al., 2009, 191997). When examining the effect of species-to-$PM_{2.5}$ mass proportion on $PM_{2.5}$-mortality effect estimates Ni was found to modify the association along with Al, As, Si, and SO_4^{2-}, but not V (Franklin et al., 2008, 097426).

6.6.4. Conclusion

Recent studies show that source apportionment methods have the potential to add useful insights into which sources and/or PM constituents may contribute to different health effects. Of particular interest are several epidemiologic studies that compared source apportionment methods and the associated results. One set of studies compared epidemiologic associations with $PM_{2.5}$ source factors using several methods - PCA, PMF, and UNMIX - independently analyzed by separate research groups (Hopke et al., 2006, 088390; Ito et al., 2006, 088391; Mar et al., 2006, 086143; Thurston et al., 2005, 097949). Schreuder et al. (2006, 097959) compared UPM and two versions of UNMIX to derive tracers and Sarnat et al. (2008, 097972) compared PMF, modified CMB, and a single-species tracer approach. In all analyses, epidemiologic results based on the different methods were generally in close agreement. The variation in risk estimates for daily mortality between source categories was significantly larger than the variation between research groups (Ito et al., 2006, 088391; Mar et al., 2006, 086143; Thurston et al., 2005, 097949). Additionally, the variation in risk estimates based on the source apportionment model used had a much smaller effect than the

variation caused by the different source constituents. Further, the most strongly associated source types were consistent across all groups. This supports the general validity of such approaches, though greater integration of results would be possible if the methods employed for grouping PM constituents were more consistent across studies and disciplines. Further research would aid understanding of the contribution of different factors, sources, or source tracers of PM to health effects by increasing the number of locations where similar health endpoints or outcomes are examined.

Overall, the results displayed in Table 6-18 indicate that many constituents of PM can be linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those constituents or sources that are more closely related to specific health outcomes. These findings are consistent with the conclusions of the 2004 PM AQCD (U.S. EPA, 2004, 056905), that a number of source types, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning, are associated with health effects. Although the crustal factor of fine particles was not associated with mortality in the 2004 PM AQCD (U.S. EPA, 2004, 056905), recent studies have suggested that PM (both $PM_{2.5}$ and $PM_{10-2.5}$) from crustal, soil or road dust sources or PM tracers linked to these sources are associated with cardiovascular effects. In addition, secondary SO_4^{2-} $PM_{2.5}$ has been associated with both cardiovascular and respiratory effects.

Chapter 6 References

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▪Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

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Chapter 7. Integrated Health Effects of Long-Term PM Exposure

7.1. Introduction

This chapter reviews, summarizes, and integrates the evidence on relationships between health effects and long-term exposures to various size fractions and sources of PM. Cardiopulmonary health effects of long-term exposure to PM have been examined in an extensive body of epidemiologic and toxicological studies. Both epidemiologic and toxicological studies provide a basis for examining reproductive and developmental and cancer health outcomes with regard to long-term exposure to PM. In addition, there is a large body of epidemiologic literature evaluating the relationship between mortality and long-term exposure to PM.

Conclusions from the 2004 PM AQCD are summarized briefly at the beginning of each section, and the evaluation of evidence from recent studies builds upon what was available during the previous review. For each health outcome (e.g., respiratory infections, lung function), results are summarized for studies from the specific scientific discipline, i.e., epidemiologic and toxicological studies. The major sections (i.e., cardiovascular, respiratory, reproductive/developmental, cancer) conclude with summaries of the evidence for the various health outcomes within that category and integration of the findings that lead to conclusions regarding causality based upon the framework described in Chapter 1. Determination of causality is made for the overall health effect category, such as cardiovascular effects, with coherence and plausibility being based upon the evidence from across disciplines and also across the suite of related health outcomes including cause-specific mortality. Section 7.6 provides detailed discussions on the epidemiologic literature for long-term exposure to PM and mortality. In each summary section (7.2.11, 7.3.9, 7.4.3, 7.5.4, and 7.6.5), the evidence is briefly reviewed and independent conclusions drawn for relationships with $PM_{2.5}$, $PM_{10-2.5}$, and UF particles (UFPs).

7.2. Cardiovascular and Systemic Effects

Studies examining associations between long-term exposure to ambient PM (over months to years) and CVD morbidity had not been conducted and thus were not included in the 1996 or 2004 PM Air Quality Criteria Documents (U.S. EPA, 1996, 079380; U.S. EPA, 2004, 056905). A number of studies were included in the 2004 PM AQCD that evaluated the effect of long-term $PM_{2.5}$ exposure on cardiovascular mortality and found consistent associations. No toxicological studies examined chronic atherosclerotic effects of PM exposure in animal models. However, a subchronic study that evaluated atherosclerosis progression in hyperlipidemic rabbits was discussed and this study provided the foundation for the subsequent work that has been conducted in this area (Suwa et al., 2002, 028588). No previous toxicological studies evaluated effects of subchronic or chronic PM exposure on diabetes measures, or HR or HRV changes, nor were there animal toxicological studies included in the 2004 PM AQCD that evaluated systemic inflammatory or blood coagulation markers following subchronic or chronic PM exposure.

Several new epidemiologic studies have examined the long-term PM-CVD association among U.S. and European populations. The studies investigate the association of both $PM_{2.5}$ and PM_{10} exposures with a variety of clinical and subclinical CVD outcomes. Epidemiologic and toxicological studies have provided evidence of the adverse effects of long-term exposure to $PM_{2.5}$ on

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

cardiovascular outcomes, including atherosclerosis, clinical and subclinical markers of cardiovascular morbidity, and cardiovascular mortality. The evidence of these effects from long-term exposure to $PM_{10-2.5}$ is weaker.

7.2.1. Atherosclerosis

Atherosclerosis is a progressive disease that contributes to several adverse outcomes, including acute coronary syndromes such as myocardial infarction, sudden cardiac death, stroke and vascular aneurysms. It is multifaceted, beginning with an early injury or inflammation that promotes the extravasation of inflammatory cells. Under conditions of oxidative or nitrosative stress and high lipid or cholesterol concentrations, the vessel wall undergoes a chronic remodeling that is characterized by the presence of foam cells, migrated and differentiated smooth muscle cells, and ultimately a fibrous cap. The advanced lesion that develops from this process can occlude perfusion to distal tissue, causing ischemia, and erode, degrade, or even rupture, revealing coagulant initiators (tissue factor) that promote thrombosis, stenosis, and infarction or stroke. Several detailed reviews of atherosclerosis pathology have been published elsewhere (Ross, 1999, 156926; Stocker and Keaney, 2004, 157013).

7.2.1.1. Epidemiologic Studies

Measures of Atherosclerosis

Although no study has examined the association between long-term PM exposure and longitudinal change in subclinical markers of atherosclerosis, several cross sectional studies have been conducted. Markers of atherosclerosis used in these studies include coronary artery calcium (CAC), carotid intima-media thickness (CIMT), ankle-brachial index (ABI), and abdominal aortic calcium (AAC). These measures are descried briefly below.

CAC represents the accumulation of calcium in coronary artery macrophages and represents an advanced stage of atherosclerosis. As such CAC is a measure of atherosclerosis assessed by non-contrast, cardiac-gated electron beam computed tomography (EBCT) or multidetector computed tomography (MDCT) of the coronary arteries in the heart (Greenland and Kizilbash, 2005, 156496; Hoffmann et al., 2005, 156556; Mollet et al., 2005, 155988). The prevalence of CAC is strongly related to age. Few people have detectable CAC in their second decade of life but the prevalence of CAC rises to approximately 100% by age 80 (Ardehali et al., 2007, 155662). Previous studies suggest that while the absence of CAC does not rule out atherosclerosis, it does imply a very low likelihood of significant arterial obstruction (Achenbach and Daniel, 2001, 156189; Arad et al., 1996, 155661; Shaw et al., 2003, 156083; Shemesh et al., 1996, 156085). Conversely, the presence of CAC confirms the existence of atherosclerotic plaque and the amount of calcification varies directly with the likelihood of obstructive disease (Ardehali et al., 2007, 155662). CAC is a quantified using the Agatston method (Agatston et al., 1990, 156197). Its repeatability depends on the laboratory and the method of calculation (O'Rourke et al., 2000, 192159). Agatston scores are frequently used to classify individuals into one of five groups (zero; mild; moderate; severe; extensive) or according to age- and sex-specific percentiles of the CAC distribution (Erbel et al., 2007, 155768).

CIMT is a measure of atherosclerosis assessed by high-resolution, B-mode ultrasonography of the carotid arteries in the neck, the walls of which have inner (intimal), middle (medial) and outer (adventitial) layers (Craven et al., 1990, 155740; O'Leary et al., 1999, 156826; Wendelhag et al., 1993, 157136). CIMT estimates the distance in mm or µm between the innermost (blood-intima) and outermost (media-adventitia) interfaces, often by averaging over three arterial segments in the common carotid, carotid bulb, and internal carotid artery (Amato et al., 2007, 155656). CIMT has been associated with atherosclerosis risk factors (Heiss et al., 1991, 156535; O'Leary et al., 1992, 156825; Salonen and Salonen, 1991, 156938), prevalent coronary heart disease (Chambless et al., 1997, 156329; Geroulakos et al., 1994, 155788), and incident coronary and cerebral events (O'Leary et al., 1999, 156826; van der Meer et al., 2004, 156129). Several studies have indicated that CIMT measurements are accurate (Girerd et al., 1994, 156474; Pignoli et al., 1986, 156026; Wendelhag et

al., 1991, 157135) and reproducible (Montauban et al., 1999, 156777; Smilde et al., 1997, 156988; Willekes et al., 1999, 157147), especially for the common carotid artery (Montauban et al., 1999, 156777).

ABI, which is also known as the ankle-arm or resting (blood) pressure index, is a measure of lower extremity arterial occlusive disease commonly caused by advanced atherosclerosis (Weitz et al., 1996, 156150). It is assessed by continuous wave Doppler and manual or automated oscillometric sphygmomanometry, the latter having been shown to have higher repeatability and validity (Weitz et al., 1996, 156150). ABI is defined as the unitless ratio of ankle to brachial systolic blood pressures measured in mmHg. As ankle pressure is normally equal to or slightly higher than arm pressure (resulting in an ABI $\geq$ 1.0), epidemiologic studies typically define the normal ABI range as 0.90 to 1.50 (Resnick et al., 2004, 156048). Low ABI has been associated with all-cause and CVD mortality (Newman et al., 1993, 156805; Vogt et al., 1993, 157100), as well as myocardial infarction and stroke (Karthikeyan and Lip, 2007, 156626).

AAC is a measure of atherosclerosis assessed by non-contrast, EBCT or MDCT of the abdominal aorta. It is scored much like CAC (Agatston et al., 1990, 156197), but the age-specific prevalence and extent of AAC is greater, particularly among women and at ages >50 yr. Although AAC has not been studied as extensively as CAC, it is associated with carotid and coronary atherosclerosis as well as cardiovascular morbidity and mortality (Allison et al., 2004, 156210; Allison et al., 2006, 155653; Hollander et al., 2003, 156562; Khoury et al., 1997, 156636; Oei et al., 2002, 156820; Walsh et al., 2002, 157103; Wilson et al., 2001, 156159; Witteman et al., 1986, 156161) and measurements are sufficiently reproducible to allow serial investigations over time (Budoff et al., 2005, 192105).

Study Findings

Diez Roux et al. (2008, 156401) conducted cross-sectional analyses of the association of three of these subclinical markers of atherosclerosis (CAC, CIMT and ABI), collected from 2000 to 2003 during baseline examinations of participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), with long-term exposure to $PM_{2.5}$ and PM_{10}. The study population included 5,172 ethnically diverse people (53% female) residing in Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN ranging in age from 45 to 84 yr old. Authors used spatio-temporal modeling of pollutant concentrations, weather and demographic data to impute 20-yr avg exposures to $PM_{2.5}$ and PM_{10}. They reported small increases in CIMT of 1% (95% CI: 0-1.4) and 0.5% (95% CI: 0-1), which correspond to absolute changes of 8 (95% CI: 0-12) and 7 (95% CI: 0-14) µm, per 10 µg/m^3 increase in 20-yr avg PM_{10} and $PM_{2.5}$ concentration, respectively. Evidence of age-, gender-, lipid- and smoking-related susceptibility was lacking. They also reported weak, non-significant increases in the relative prevalence of CAC of 1% (95% CI: -2 to 4) and 0.5% (95% CI: -2 to 3) per 10 µg/m^3 increase in PM_{10} and $PM_{2.5}$, respectively. Among the subset of 2,586 participants with EBCT-identified calcification, similarly weak associations were observed. There was little evidence of modification of the CAC associations by demographic, socioeconomic or clinical characteristics. Finally, the authors report no differences in mean ABI with PM_{10} or $PM_{2.5}$ concentrations. The null findings for ABI exhibited little heterogeneity among participant subgroups and were similarly null when ABI was modeled as a dichotomous outcome using a cutpoint of 0.9 units.

MESA investigators also examined the chronic $PM_{2.5}$-AAC association in a residentially stable subset of 1,147 participants (mean age = 66 yr; 50% female) randomly selected from all MESA centers, except Baltimore, MD for enrollment in its Aortic Calcium Ancillary Study(Allen et al., 2009, 156209). The authors used kriging and inverse residence-to-monitor distance-weighted averaging of EPA AQS data to estimate 2-yr mean exposures to $PM_{2.5}$. In cross-sectional analyses, the authors found a 6% (95% CI: -4 to 16) excess risk of a non-zero Agatston score and an 8% (95% CI: -30 to 46) increase in AAC, i.e., approximately 50 (95% CI: -251 to 385) Agatston units, per 10 µg/m^3 increase in $PM_{2.5}$ concentration. These associations were stronger among users than non-users of lipid lowering drugs.

Kunzli et al. (2005, 087387) used baseline data collected between 1998-2003 from two randomized placebo-controlled clinical trials, the Vitamin E Atherosclerosis Progression Study (VEAPS) and the B-Vitamin Atherosclerosis Intervention Trial (BVAIT), for their ancillary cross-sectional analyses of the effect of long-term $PM_{2.5}$ exposure on CIMT. The study population included 798 residents of the greater Los Angeles, CA area who were more than 40 yr old at baseline and 44% were female. The authors used universal kriging of $PM_{2.5}$ data from 23 state and local monitors

operating in 2000 to estimate 1-yr avg exposure to $PM_{2.5}$ at each participant's geocoded U.S. Postal Service ZIP code. They found a 4.2% (95% CI: -0.2 to 8.9) or approximately 32 (95% CI: -2 to 68) μm increase in CIMT per 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration. In contrast to findings from the relatively large, ethnically diverse, yet geographically overlapping MESA ancillary study described above, PM-related increases in CIMT were two- to three-fold larger among older and female participants taking lipid lowering drugs in this study. PM-related increases in CIMT were also higher in never smokers when compared with current or former smokers.

Hoffmann et al. (2007, 091163) conducted a cross-sectional analysis of data collected at baseline (2000-2003) for 4,494 residents of Essen, Mülheim and Bochum, Germany enrolled in the Heinz Nixdorf Recall Study from 2000 to 2003. The age of participants ranged from 45-74 yr and 51% were female. In this cross-sectional study the authors used dispersion and chemistry transport modeling of emissions, climate and topography data to estimate 1-yr avg exposure to $PM_{2.5}$ in 2002 (the midpoint of the baseline exam.) They reported an imprecise 43% (95% CI: -15 to 115) or 102 (95% CI: -77 to 273) Agatston unit increase in CAC per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Differences in strength of association between subgroups defined by demographic and clinical characteristics were small. The authors reported a more consistent association of CAC with traffic exposure (distance from a major roadway) than with $PM_{2.5}$ in this study.

In a subsequent analysis of these data, Hoffmann et al. (2009, 190376) examined the PM-ABI association in this population. In this cross-sectional study, no changes in ABI were observed in association with $PM_{2.5}$ concentration nor was evidence of effect modification by demographic and clinical characteristics apparent. As in the previous study (Hoffmann et al., 2007, 091163), residing near a major roadway was a stronger predictor of atherosclerotic changes. Absolute changes in ABI of -0.024 (95% CI: -0.047 to -0.001) were associated with living within 50 m of a major roadway compared to living more than 200 m away.

Each of the studies described above relied on cross-sectional analyses examining differences in long-term average $PM_{2.5}$ concentrations across space (as well as time to the extent baseline examinations were conducted over time). Such associations may reflect the effect of compositional differences in $PM_{2.5}$ as well as the effect of higher $PM_{2.5}$ concentrations. Most associations of $PM_{2.5}$ with CAC (Diez et al., 2008, 156401; Hoffmann et al., 2007, 091163), CIMT (Diez et al., 2008, 156401; Kunzli et al., 2005, 087387), ABI (Diez et al., 2008, 156401; Hoffmann et al., 2009, 190376) and AAC (Allen et al., 2009, 156209) reviewed in this section were weak and/or imprecise. However, several factors including exposure measurement error, variation in baseline measures atherosclerosis, as well as limited power may contribute to the insensitivity of these cross-sectional studies to detect small differences in CAC, CIMT, ABI and AAC. The study by Hoffmann et al. (2007, 091163), which reported large, imprecise and non-significant increases in CAC in association with $PM_{2.5}$, is not distinguished from the other studies reviewed by a superior study design or larger sample size. The several fold difference in the magnitude of CIMT associations reported by Kunzli et al. (2005, 087387) and Diez Roux et al. (2008, 156401) may be related to differences between the study populations. The ambient PM concentrations from these studies are characterized in Table 7-1.

7.2.1.2. Toxicological Studies

In the only study of this kind described in the 2004 PM AQCD, Suwa et al. (2002, 028588) demonstrated more advanced atherosclerotic lesions based on phenotype and volume fraction in the left main and right coronary arteries of rabbits exposed to PM_{10} (5 mg/kg, 2 times/wk×4 wk). Although this study was conducted using IT exposure methodology at a relatively high dose, it provided the first experimental evidence that PM exposure may result in progression of atherosclerosis. Recent toxicological studies conducted using inhalation exposures have replicated these findings at relevant concentrations and are discussed below.

CAPs

New studies have demonstrated increased atherosclerotic plaque area in aortas of $ApoE^{-/-}$ mice exposed to $PM_{2.5}$ CAPs for 4-6 mo (6 h/day×5 days/wk). Average CAPs concentrations ranged from 85 to 138 $\mu g/m^3$ and all of the studies were conducted in Tuxedo or Manhattan, NY. Chen and Nadziejko (2005, 087219) reported that the percentage of aortic intimal surface covered by atherosclerotic lesions in $ApoE^{-/-}$ mice was increased. In male $ApoE^{-/-}/LDLR^{-/-}$ mice, both lesion area

and cellularity in the aortic root were enhanced by Tuxedo, NY CAPs exposure, although there was no change in lipid content. Genetic profiles within plaques recovered from $ApoE^{-/-}$ mice included many of the molecular pathways known to contribute to atherosclerosis, including inflammation (Floyd et al., 2009, 190350). Sun (2005, 087952) similarly demonstrated an enhancement of atherosclerosis in $ApoE^{-/-}$ mice exposed Tuxedo, NY CAPs. Plaque area in the aortic arch and abdominal aorta was significantly increased in the PM-exposed, high fat-chow group compared to air-exposed, high fat-chow group. Macrophage infiltration in the abdominal aorta was also observed in the groups exposed to CAPs. A study conducted in Manhattan for 4 mo (May- September 2007) showed that $PM_{2.5}$ CAPs exposure increased atherosclerotic plaque area and led to higher levels of macrophage infiltration, collagen deposition, and lipid composition in thoracic aortas of $ApoE^{-/-}$ mice (Ying et al., 2009, 190111), which is consistent with the previous two studies described that were conducted in Tuxedo, NY.

Alteration of vasomotor function has been observed in aortic rings of $ApoE^{-/-}$ mice on a high fat diet with long-term exposure to CAPs (Sun et al., 2005, 087952; Ying et al., 2009, 190111). Sun (2005, 087952) reported that. $PM_{2.5}$-exposed animals exhibited increased vasoconstrictor responsiveness to serotonin and PE. Increased ROS and elevated iNOS protein expression in aortic sections of CAPs-exposed mice may have resulted alterations in the NO pathway and generation of peroxynitrite that could have affected vascular reactivity. In contrast, Ying, et al. (2009, 190111) demonstrated decreased maximum constriction induced by PE following Manhattan CAPs exposure. Pretreatment with the soluble guanylate cyclase (sGC) inhibitor ODQ attenuated the response, indicating that CAPs exposure resulted in abnormal NO/sGC signaling. Expression of iNOS mRNA and protein was increased in aortas of CAPs-exposed mice, further supporting a role for NO production. In conjunction with increased NO, aortic superoxide production was demonstrated that appeared to be partially driven by increased NADPH oxidase activity. The difference in vasoconstrictor responses between these two studies may be attributable to varying durations (6 versus 4 mo, respectively) or CAPs compositions.

Sun (2005, 087952) and Ying et al. (2009, 190111) reported similar relaxation responses to ACh for air- and CAPs-exposed mice. However, Manhattan CAPs-exposed mice had a markedly decreased response to A23187, indicating that NO release occurred via Ca^{2+}-dependent mechanisms (Ying et al., 2009, 190111). Abnormal eNOS function is likely responsible for the decreased relaxation response, as activation of eNOS (but not iNOS) is Ca^{2+}-dependent.

A recent study (Sun et al., 2008, 157033) that was part of the research described above (Sun et al., 2005, 087952) investigated tissue factor (TF) expression in aortas, which is a major regulator of hemostasis and thrombosis following vascular injury or plaque erosion. In $PM_{2.5}$-exposed $ApoE^{-/-}$ mice on a high-fat diet, TF was significantly elevated in the plaques of aortic sections compared to air-exposed mice on the high-fat diet. TF expression was generally detected in (1) the extracellular matrix surrounding macrophages and foam cell-rich areas; and (2) around smooth muscle cells.

One new study of CAPs $PM_{2.5}$ or UFPs derived from traffic was conducted. Araujo et al. (2008, 156222) compared the relative impact of UF (0.01-0.18 μm) and fine (0.01-2.5 μm) PM inhalation on aortic lesion development in $ApoE^{-/-}$ mice following a 40-day exposure (5 h/day×3 days/wk for 75 total h). Animals were on a normal chow diet and exposed to CAPs in a mobile inhalation laboratory parked 300 m from a freeway in downtown Los Angeles. Exposure concentrations were ~440 $\mu g/m^3$ for $PM_{2.5}$ and ~110 $\mu g/m^3$ for UFPs, and the number concentrations were roughly equivalent (4.56×10^5 and 5.59×10^5 particles/cm^3 for $PM_{2.5}$ and UFPs, respectively). Significant increases in plaque size (estimated by lesions at the aortic root) were reported for mice exposed to UFPs only. The lesions were largely comprised of macrophages with intracellular lipid accumulation. Increased total cholesterol measured at the end of the exposure protocol was observed only in the $PM_{2.5}$ group. HDL isolated from the UF PM-exposed mice demonstrated decreased anti-inflammatory protective capacity against LDL-induced monocyte chemotactic activity in an in vitro assay. The livers from the UFP-exposed mice demonstrated significant increases in lipid peroxidation and several stress-related gene products (catalase, glutathione S-transferase Y_a, NADPH-quinone oxidoreductase1, superoxide dismutase 2). Thus, UFPs in these exposures had a substantially greater impact on the systemic response than did $PM_{2.5}$.

Ambient Air

A study employing young BALB/c mice examined the effects of a 4-month exposure (24 h/day×7 days/wk) to ambient air on arterial histopathology (Lemos et al., 2006, 088594). Outdoor exposure chambers were located in downtown Sao Paulo, Brazil next to streets of high traffic density. In the control chamber, PM_{10} and NO_2 were filtered with 50% and 75% efficiency, respectively. The average pollutant concentrations were 2.06 ppm for CO (8-h mean), 104.75 $\mu g/m^3$ for NO_2 (24-h mean), 11.07 $\mu g/m^3$ for SO_2 (24-h mean), and 35.52 $\mu g/m^3$ for PM_{10} (24-h mean) at a monitoring site within 100 m of the inhalation chambers. The pulmonary and coronary arteries demonstrated significant decreases in L/W ratio for animals exposed to the entire ambient mixture compared to controls, indicating thicker walls in these vessels. There was no difference reported for the L/W ratio in renal arteries. Morphologic examination suggested that the increases in L/W ratio were due to muscular hypertrophy rather than fibrosis. The results of this study indicate vascular remodeling of the pulmonary and coronary arteries, as opposed to changes in tone.

To examine the role of systemic inflammation and recruitment of monocytes into plaque tissue as a possible pathway for accelerated atherosclerosis, Yatera et al. (2008, 157162) exposed female Watanabe heritable hyperlipidemic rabbits (42 week old) to Ottawa PM_{10} (EHC-93) via IT instillation (5 mg/rabbit; approximately 1.56 mg/kg) twice a week for 4 wk. Transfusion of whole blood harvested to from exposed and non-exposed animals to donor rabbits supplied labeled monocytes for assessment of monocyte recruitment from the blood to the aortic wall. The fraction of aortic surface and volume of aortic wall taken up by atherosclerotic plaque was increased and the number of labeled monocytes in the atherosclerotic plaques was elevated in rabbits exposed to PM_{10}. In addition, labeled monocytes were attached onto the endothelium overlying atherosclerotic plaques and the number that migrated into the smooth muscle underneath plaques in aortic vessel walls was greater with PM_{10} exposure compared to control. These responses were not observed in normal vessel walls. ICAM-1 and VCAM-1 expression was elevated in atherosclerotic lesions, likely indicating enhanced monocyte adhesion to endothelium and migration into plaques. Monocytes in plaque tissue stained with immunogold demonstrated foam cell characteristics, which were more numerous in the rabbits exposed to PM_{10}.

Gasoline Exhaust

Lund and colleagues (2007, 125741) used whole emissions from gasoline exhaust to investigate changes in the transcriptional regulation of several gene products with known roles in both the chronic promotion and acute degradation/destabilization of atheromatous plaques. These 50-day exposures (6 h/day×7 days/wk) employed $ApoE^{-/-}$ mice on high-fat chow and the concentrations of the high exposure group were 61 $\mu g/m^3$ for PM, 19 ppm for NO_X, 80 ppm for CO, and 12.0 ppm for total hydrocarbons. The average particle number median diameter was approximately 15 nm (McDonald et al., 2007, 156746). Dilutions of gasoline engine emissions induced a concentration-dependent increase in transcription of matrix metalloproteinase (MMP) isoform 9, ET-1, and HO-1 in aortas; MMP-3 and -9 mRNA levels were only increased in animals in the highest exposure group. Strong increases in oxidative stress markers (nitrotyrosine and TBARS) in the aortas were also observed. However, using a high-efficiency particle trap, they established that most of the effects were caused by the gaseous portion of the emissions and not the particles. This study did not directly address lesion area.

7.2.2. Venous Thromboembolism

One epidemiologic study examined the relationship between long term PM_{10} concentration, venous thromboembolism, and laboratory measures of hemostasis (prothrombin and activated partial thomboplastin times [PT; PTT]). PT and PTT measure the extrinsic and intrinsic blood coagulation pathways, the former activated in response to blood vessel injury, the latter, key to subsequent amplification of the coagulation cascade and propagation of thrombus (Mackman et al., 2007, 156723). Decreases in PT and PTT are consistent with a hypercoagulable, prothrombotic state.

7.2.2.1. Epidemiologic Studies

Baccarelli et al. (2008, 157984) studied 2,081 residents (56% female) of the Lombardy region of Italy whose ages ranged from 18 to 84 yr old. In this case-control study of 871 patients with ultrasonographically or venographically diagnosed lower extremity deep vein thrombosis (DVT) and 1,210 of their healthy friends or relatives (1995-2005), the authors used arithmetic averaging of PM_{10} data available at 53 monitors in nine geographic areas to estimate 1-yr avg residence-specific exposures. They found -0.06 (95% CI: -0.11 to 0) and -0.12 (95% CI: -0.23 to 0) decreases in standardized correlation coefficients for PT as well as 0.01 (95% CI: -0.03 to 0.04) and -0.09 (95% CI: -0.19 to 0.01) decreases in standardized correlation coefficients for PTT among cases and controls, respectively, per 10 $\mu g/m^3$ increase in PM_{10}. Patients with DVT who were taking heparin or coumarin anticoagulants were not asked to stop taking them before measurement of PT and aPTT. Of additional note, PT was neither adjusted for differences in reagents used to determine it nor conventionally reported as the International Normalized Ratio (INR). The ambient PM concentrations from this study are characterized in Table 7-1.

7.2.3. Metabolic Syndromes

7.2.3.1. Epidemiologic Studies

Chen and Schwartz (2008, 190106) studied 2,978 residentially stable participants in 33 U.S. communities (age range = 20-89 yr; 49% female) who were examined during phase 1 of the National Health and Nutrition Examination Survey III (1989-1991). In this cross-sectional study, the authors used inverse-distance weighted averaging of U.S. EPA AQS monitored data from participant and adjacent counties of residence to estimate 1-yr avg exposures to PM_{10}. They found that after adjustment, residents of communities with lower PM_{10} concentrations had fewer white blood cells than residents of communities with higher PM_{10} concentrations. This difference increased with increasing number of metabolic abnormalities (insulin resistance; hypertension; hypertriglyceridemia; low high-density lipoprotein cholesterol; abdominal obesity) reported by the participant. This observed difference across individuals with different degrees of metabolic abnormalities supports the concept that the presence of a metabolic syndrome may impart greater susceptibility to PM-associated long-term CVD effects.

7.2.3.2. Toxicological Studies

Diabetics as a potentially susceptible subpopulation have only recently been evaluated. A toxicological study of a diet-induced obesity mouse model (C57BL/6 fed high-fat chow for 10 wk) examined the effects of a 128-day $PM_{2.5}$ CAPs exposure (mean mass concentration 72.7 $\mu g/m^3$; Tuxedo, NY) on insulin resistance, adipose inflammation, and visceral adiposity (Sun et al., 2009, 190487). Elevated fasting glucose and insulin levels were observed in CAPs-exposed mice compared to air-exposed during the glucose tolerance test. Aortic rings of mice exposed to CAPs demonstrated decreased peak relaxation to ACh or insulin, which was associated with reduced NO bioavailability. Additionally, insulin signaling was impaired in aortic tissue via lowered endothelial Akt phosphorylation. Increases in adipokines and systemic inflammatory markers (i.e., TNF-α, IL-6, E-selectin, ICAM-1, PAI-1, resistin, leptin) were reported for CAPs-exposed mice. CAPs resulted in increased visceral and mesenteric fat mass, as well as greater adipose tissue macrophages in epididymal fat pads and larger adipocyte size compared to mice in the filtered air group. The results of this study demonstrate that $PM_{2.5}$ exposure can exaggerate insulin resistance, visceral adiposity, and inflammation in mice fed high-fat chow.

7.2.4. Systemic Inflammation, Immune Function, and Blood Coagulation

7.2.4.1. Epidemiologic Studies

As discussed in Section 7.2.3.1, Chen and Schwartz (2008, 190106) conducted a cross-sectional study in 33 U.S. communities and used inverse-distance weighted averaging of U.S. EPA AQS monitored data from participant and adjacent counties of residence to estimate 1-yr avg exposures to PM_{10} (median concentration within quartiles = 23.1, 31.2, 38.8 and 53.7 $\mu g/m^3$). They found that after adjustment, residents of communities in quartile 1 had 138 (95% CI: 2-273) fewer white blood cells ($\times 10^6$/L) than residents of communities in quartiles 2-4. This difference increased with increasing number of metabolic abnormalities.

Forbes et al. (2009, 190351) studied approximately 25,000 adults (age ≥ 16 yr; 53% female) who were representatively sampled from 720 English postcode sectors and participated in the Health Survey for England (1994, 1998 and 2003). In this fixed-effects meta-analysis of year-specific cross-sectional findings, the authors used dispersion modeling of emissions and weather data to estimate 2-yr avg exposures to PM_{10} at participant postcode sector centroids (median in 1994, 1998 and 2003 = 19.5, 17.9 and 16.2 $\mu g/m^3$, respectively). They found little evidence of a PM_{10}-inflammatory marker association, i.e., only a -0.08% (95% CI: -0.25 to 0.10) decrease in fibrinogen concentration and a 0.14% (95% CI: -1.00 to 1.30) increase in CRP concentration per 1 $\mu g/m^3$ increase in PM_{10}.

Calderon-Garciduenas et al. (2007, 091252) compared residentially stable, non-smoking healthy children (age range: 6-13 yr) living and attending school between 2003-2004 in Mexico City (historically high PM; altitude 2,250 m) and Polotitlán (historically low PM; altitude 2,380 m). In this ecologic study, residents of Mexico City (n = 59; 93% female) had fewer white blood cells and neutrophils ($\times 10^9$/L) than residents of Polotitlán (n = 22; 69% female): unadjusted mean 6.2 (95% CI: 5.7-6.6) versus 6.9 (95% CI: 6.3-7.5) and 2.9 (95% CI: 2.3-3.5) versus 3.8 (95% CI: 3.2-4.4), respectively.

Calderon-Garciduenas et al. (2009, 192107) subsequently compared 37 unadjusted mean measures of immune function and inflammation among an expanded number of these participants. They found that under a two-sided type I error rate (α) = 0.05, 16 (43%) of the measures were significantly different in residents of southwest Mexico City (n = 66; 48% female) than those in Polotitlán (n = 93; 57% female). However, only 8 measures were significantly different after Bon Ferroni-correction (α = 0.05 / 37 = 0.001) and even fewer would be after adjustment for reported correlation between the measures of immune function and inflammation, e.g., CRP and lipopolysaccharide binding protein (Pearson's r = 0.71).

Two cross-sectional analyses of PM_{10} concentration and markers of immune function or inflammation have been conducted with significant changes observed in the NHANES population (stronger effects among those with metabolic disorders) (Chen and Schwartz, 2008, 190106) but not in a relative large survey of adults, which was conducted in England (Forbes et al., 2009, 190351). Ecological analyses comparing children in high versus low pollution regions in Mexico show differences in unadjusted blood markers that may be related to PM concentration or other unmeasured risk factors that differs across the communities studied (Calderon-Garciduenas et al., 2007, 091252; Calderón-Garcidueñas et al., 2009, 192107).

7.2.4.2. Toxicological Studies

In addition to the $PM_{2.5}$ study mentioned previously that showed increased TF expression (an important initiator of thrombosis) in aortas of $ApoE^{-/-}$ mice following subchronic CAPs exposure (Sun et al., 2008, 157033), three recent studies examined hematology and clotting parameters in rats and mice exposed to DE, gasoline exhaust, or hardwood smoke for 1 week or 6 mo (Reed et al., 2004, 055625; Reed et al., 2006, 156043; Reed et al., 2008, 156903). In all studies, male and female F344 rats were exposed to the mixtures by whole-body inhalation for 6 h/day, 7 day/wk. Respiratory effects for these studies are presented in Section 7.3.3.

Diesel Exhaust

The target PM concentrations in the DE study was 30, 100, 300, and 1,000 μg/m^3 and the MMAD was 0.10-0.15 μm (Reed et al., 2004, 055625). Male and female rats exposed to DE at the highest concentration (NO concentration 45.3 ppm; NO_2 concentration 4.0 ppm; CO concentration 29.8 ppm; SO_2 concentration 365 ppb) for 6 mo demonstrated decreased serum Factor VII, but no change in plasma fibrinogen or thrombin anti-thrombin complex (TAT) (Reed et al., 2004, 055625). White blood cells were decreased only in female rats in the highest exposure group. Another DE study of shorter duration (4 wk, 4 h/day, 5day/wk; PM mass concentration 507 or 2201 μg/m^3, CO 1.3 and 4.8 ppm, NO <2.5 and 5.9 ppm, NO_2 <0.25 and 1.2 ppm, SO_2 0.2 and 0.3 ppm for low and high PM exposures, respectively) did not demonstrate changes in hematologic parameters or those related to coagulation (i.e., PT, PPT, plasma fibrinogen, D-dimer) or inflammation (i.e., CRP) in SH or WKY rats (Gottipolu et al., 2009, 190360). Together, these findings do not support a DE-related stimulation of blood coagulation following 1 or 6 mo of exposure.

Hardwood Smoke

The target PM concentrations in the hardwood smoke study was 30, 100, 300, and 1,000 μg/m^3 and the MMAD was 0.25-0.36 μm (Reed et al., 2006, 156043). In male rats exposed to hardwood smoke, the mid-low group (PM concentration 113 μg/m^3; NO, NO_2, SO_2 concentrations 0 ppm; CO concentration 1,832.3 ppm) had the greatest responses in hematology parameters, including increased hematocrit, hemoglobin, lymphocytes, and decreased segmented neutrophils (Reed et al., 2006, 156043). Platelets were elevated in male and female rats after 1 week of exposure, but this response returned to control values following the 6-month exposure. No changes were observed for any coagulation markers at 6 mo.

Gasoline Exhaust

PM mass in the gasoline exhaust study ranged from 6.6 to 59.1 μg/m^3, with the corresponding number concentration between 2.6×10^4 and 5.0×10^5 particles/cm^3; the dilutions for the gasoline exhaust were 1:10, 1:15 or 1:90 and filtered PM at the 1:10 dilution (Reed et al., 2008, 156903). Similar to the responses observed with hardwood smoke, male and female rats in the mid- and high-gasoline exhaust exposure groups (NO concentrations 11.9 and 18.4 ppm; NO_2 concentrations 0.5 and 0.9 ppm; CO concentration 73.2 and 107.3 ppm; SO_2 concentration 0.38 and 0.62 ppm, respectively) demonstrated elevated hematocrit and hemoglobin; RBC count was also elevated in these groups (Reed et al., 2008, 156903). The only response that appeared somewhat dependent on the presence of particles was increased RBC in female rats at 6 mo, although the authors attributed the observed increases to the high concentration of CO.

Collectively, these studies do not indicate robust systemic inflammation or coagulation responses in F344 rats following 6-month exposures to diesel, hardwood smoke, or gasoline exhaust. The limited effects that were observed could possibly be due to the varying gas concentrations in the exposure mixtures.

7.2.5. Renal and Vascular Function

Two recent epidemiologic studies have tested associations between PM exposure and indicators of renal and vascular function (urinary albumin to creatinine ratio [UACR] and blood pressure). UACR is a measure of urinary albumin excretion (National Kidney Foundation, 2008, 156796). When calculated as the ratio of albumin to creatinine concentrations in untimed ("spot") urine samples, UACR approximates 24-h urinary albumin excretion and can be used to identify albuminuria, a marker of generalized vascular endothelial damage (Xu et al., 2008, 157157). Values ≥ 30 mg/g (3.5 mg/mmol) and ≥ 300 mg/g (34 mg/mmol) usually define micro- and macroalbuminuria, both of which are associated with increases in CVD incidence and mortality (Bigazzi et al., 1998, 156272; Deckert et al., 1996, 156389; Dinneen and Gerstein, 1997, 156403; Gerstein et al., 2001, 156466; Mogensen, 1984, 156769). Several researchers have called the

dichotomization of albuminuria into question, observing that there is no threshold below which risk of cardiovascular and end-stage kidney disease disappears (Forman and Brenner, 2006, 156439; Knight and Curhan, 2003, 179900; Ruggenenti and Remuzzi, 2006, 156933).

Systolic, diastolic, pulse, and mean arterial blood pressures (SBP; DBP; PP; MAP) in mmHg have also been used as measures of cardiovascular disease. Franklin et al. (1997, 156446) suggested that SBP and PP were the only two measures predictive of carotid stenosis in a multivariable analysis considering all 4 measures, whereas Khattar et al. (2001, 155896) suggested that their prognostic significance in hypertensive populations may differ by age, with SBP and PP being most predictive among those ≥ 60 yr and DBP among those <60 yr old (Khattar et al., 2001, 155896).

7.2.5.1. Epidemiologic Studies

O'Neill et al. (2007, 156006) examined the association of UACR with $PM_{2.5}$ and PM_{10} among members of the MESA population described previously (Diez et al., 2008, 156401). For this study of UACR, which included cross-sectional and longitudinal analyses, the study population was restricted to a subset of 3,901 participants (mean age = 63 yr; 52% female) with complete covariate, outcome and exposure data at their first through third exams (2000-2004). In cross-sectional analyses, the authors found that after adjustment for demographic and clinical characteristics, 10 $\mu g/m^3$ increases in 20-yr imputed exposures to $PM_{2.5}$ and PM_{10} were associated with negligible 0.002 (95% CI: -0.048 to 0.052) and -0.002 (95% CI: -0.038 to 0.035) mean differences in baseline log UACR, respectively. Similarly, small statistically non-significant decreases in the prevalence of microalbuminuria (defined in this setting as ≥ 25 mg/g) provided little evidence of an effect on renal function. These largely null cross-sectional findings mirrored those based on the study's shorter-term (30- and 60-day) $PM_{2.5}$ and PM_{10} exposures. Moreover, longitudinal analyses revealed only a weak association between 3-yr change in log UACR and 20-yr PM_{10} exposure. Evidence of effect modification by demographic and geographic characteristics was not apparent in either the cross-sectional or longitudinal analyses.

Auchincloss et al. (2008, 156234) focused on automated, oscillometric, sphygmomanometric measures of blood pressures in mmHg (SBP; DBP; PP; MAP). Like O'Neill (2007, 156006), Diez et al. (2008, 156401) and Allen et al. (2007, 156006), Auchincloss et al. (2008, 156234) based their examination on the previously described MESA population. The authors included 5,112 study participants (age range = 45-84 yr; 52% female) who were free of clinically manifested CVD at their baseline exam in one of six primarily urban U.S. locations (2000-2002). In this cross-sectional study, they used arithmetic averaging of EPA AQS $PM_{2.5}$ data available at the monitor nearest to each participant's geocoded U.S. Postal Service ZIP code centroid to estimate 30- and 60-day avg exposures to $PM_{2.5}$. They found small nonsignificant increases of 1.5 (95% CI: -0.2 to 3.2), 0.2 (95% CI: -0.7 to 1.0), 1.3 (95% CI: 0.1 to 2.6), and 0.6 (95% CI: -0.4 to 1.7) mmHg increases in SBP, DBP, PP and MAP, respectively, per 10 $\mu g/m^3$ increase in 30-day avg $PM_{2.5}$ exposure, Associations were slightly weaker for 60-day avg $PM_{2.5}$ exposure and among participants without hypertension, during cooler weather, in the presence of low NO_2, residing >300 m from a highway, or surrounded by lower road density.

Finally, the Calderon-Garciduenas et al. (2007, 091252) ecologic study introduced in Section 7.2.3.1 also found that children residing in Mexico City had higher mean pulmonary artery pressure as assessed by Doppler echocardiography and fasting plasma endothelin-1 (ET-1) than residents in Polotitlán: unadjusted mean 17.5 (95% CI: 15.7-19.4) versus 14.6 (95% CI: 13.8-15.4) mmHg and 2.23 (95% CI: 1.93-2.53) versus 1.23 (95% CI: 1.11-1.35) pg/mL, respectively. Within Mexico City, ET-1 was higher in residents of the Northeast (historically higher $PM_{2.5}$) than those of the Southwest (historically lower $PM_{2.5}$).

The MESA analyses of UACR (O'Neill et al., 2007, 156006) and the ecologic study of children living in a highly polluted area of Mexico (Calderon-Garciduenas et al., 2007, 091252) provide little evidence that long-term exposure to $PM_{2.5}$ had an effect on renal and vascular function, respectively. Auchincloss et al. (2008, 156234) reports small nonsignificant associations of blood pressure with 30- and 60-day avg $PM_{2.5}$ concentrations. PM concentrations from the analyses are characterized in Table 7-1.

Table 7-1. Characterization of ambient PM concentrations from studies of subclinical measures of cardiovascular diseases and long-term exposure.

Study	Location	Mean Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
PM_{10}			
Diez Roux et al. (2008, 156401)	MESA: 6 Cities U.S.	20 yr imputed mean: 34	NR
O'Neill et al. (2007, 156006)	MESA: 6 Cities U.S.	Long-Term Exposure: 1982-2002: 34.7 1982-1987: 40.5 1988-1992: 38 1993-1997: 30.6 1998-2002: 29.7 Previous Month: 27.5	NR
Baccarelli et al. (2008, 157984)	Lombardy Region Italy	NR	NR
Rosenlund et al. (2006, 089796)	Stockholm, Sweden	30-y avg PM_{10} (traffic) Cases: 2.6 Controls: 2.4	5th-95th %: 0.5-6 0.6-5.9
Chen and Swartz (2008, 190106)	US Population (NHANES)	Annual avg: 36.8	NR
Forbes et al. (2009, 190351)	British Population	1994: 19.5 (median) 1998: 17.9 (median) 2003: 16.2 (median)	1994, Min-Max: 12.5-36.1 1998, Min-Max: 12.6-27.0 2003, Min-Max: 11.0-22.7
$PM_{2.5}$			
Hoffmann et al.(2007, 091163)	HNRS, 3 Cities Germany	Annual avg: 22.8	NR
Allen et al. (2009, 156209)	MESA: 5 Cities	Annual avg: 15.8	Min-Max: 10.6-24.7
Kunzli et al. (2005, 087387)	VEAPS BVAIT	Annual avg: 20.3	Min-Max: 5.2-26.9
Auchincloss et al. (2008, 156234)	MESA: 6 Cities	Prior 30 days: 16.8 Prior 60 days: 16.7	NR
O'Neill (2007, 156006)	MESA: 6 Cities U.S.	Previous Month: 16.5	NR
Diez Roux et al. (2008, 156401)	MESA: 6 Cities U.S.	20-y imputed mean: 21.7	NR
Hoffmann et al. (2009, 190376)	HNRS: 3 Cities Germany	Annual avg: 22.8	Min-max: 19.8-26.8
Calderon-Garciduenas et al. (2009, 192107)	Southwest Mexico (high pollution)	Annual avg: 25	NR
	Potitlan (low pollution)	Annual avg: <15	NR
Calderon-Garciduenas et al. (2007, 091252)	Southwest Mexico (high pollution)	NR	NR
	Potitlan (low pollution)	NR	NR

MESA: Multi-Ethnic Study of Atherosclerosis
HNRS: Heinz Nixdorf Recall Study
VEAPS: Vitamin E Atherosclerosis Progression Study
BVAIT: B-Vitamin Atherosclerosis Intervention Trial

7.2.5.2. Toxicological Studies

In a $PM_{2.5}$ CAPs study of 10 wk (6 h/day×5 days/wk) in Tuxedo, NY (mean mass concentration 79.1 μg/m^3), there was no difference in mean arterial pressure (MAP) in SD rats between groups (Sun et al., 2008, 157032). When angiotensin II (Ang II) was infused during the last week of exposure to induce systemic hypertension, the MAP slope was consistently greater in the CAPs-exposed rats compared to the filtered air group. Furthermore, thoracic aortic rings were more responsive to phenylephrine-induced constriction and less responsive to ACh-induced relaxation in the PM+Ang II vessels. In contrast to the latter findings, the relaxation response was exaggerated in the PM+Ang II aortic segments with a Rho-kinase (ROCK) inhibitor. Superoxide production in aortic rings increased in the PM+Ang II group compared to the filtered air group and the addition of

NAD(P)H oxidase inhibitor (apocynin) or a NOS inhibitor (L-NAME) attenuated the superoxide generation. The levels of tetrahydrobiopterin (BH_4) were decreased in mesenteric vasculature and the heart by 46% and 41% in the PM+Ang II group compared to controls, respectively; furthermore, levels of BH_4 in the liver were similarly reduced, which is consistent with a systemic effect of CAPs. Together, these findings indicate that CAPs potentiate Ang II-induced hypertension and alter vascular reactivity, perhaps through activated NADPH oxidase and eNOS uncoupling that result in oxidative stress generation and triggering of the Rho/ROCK signaling pathway.

7.2.6. Autonomic Function

7.2.6.1. Toxicological Studies

Hwang et al. (2005, 087957) and Chen and Hwang (2005, 087218) used radiotelemetry to examine the chronic changes in HR and HRV resulting from the same CAPs exposures described previously (Chen and Nadziejko, 2005, 087219). The overall average CAPs exposure concentration was 133 μg/m^3 and results indicate differing responses to CAPs between $ApoE^{-/-}$ mice and their genetic background strain, C57BL/6J mice (Hwang et al., 2005, 087957). Using the time period of 1:30-4:30 a.m., C57BL/6J mice showed a HR increase only over the last month of exposure. In contrast, $ApoE^{-/-}$ mice had chronic decreases of 33.8 beat/min for HR. Changes in HRV (SDNN and rMSSD) were somewhat more complicated, with biphasic responses in $ApoE^{-/-}$ mice over the 5-month period (initial increase over first 6 wk, decrease over next 12 wk, and slight upward turn for remainder of the study)(Chen and Hwang, 2005, 087218). Increasing linear trends were observed in C57BL/6J mice for SDNN and rMSSD. The average CAPs concentration for the HRV study was 110 μg/m^3. However, only three C57BL/6J mice in the exposure group were included in the analysis compared to ten $ApoE^{-/-}$ animals, thus making it difficult to interpret the C57BL/6J mice responses (Chen and Hwang, 2005, 087218; Hwang et al., 2005, 087957).

7.2.7. Cardiac changes

7.2.7.1. Toxicological studies

Two recent toxicological studies have evaluated the effects of PM on cardiac effects including pathology and gene expression. Cardiac mitochondrial function has also been evaluated following PM exposure in rats.

Diesel Exhaust

A recent study of DE exposure (PM mass concentration 507 or 2,201 μg/m^3, CO 1.3 or 4.8 ppm, NO <2.5 or 5.9 ppm, NO_2 <0.25 or 1.2 ppm, SO_2 0.2 or 0.3 ppm for low and high PM exposures, respectively; geometric median number diameter 85 nm) indicated a hypertensive-like cardiac gene expression in WKY rats that mimicked baseline patterns in air-exposed SH rats (Gottipolu et al., 2009, 190360). Exposure to the high concentration of DE for 4 wk (4 h/day, 5 day/wk) led to downregulation of genes involved in stress, antioxidant compensatory response, growth and extracellular matrix regulation, membrane transport of molecules, mitochondrial function, thrombosis regulation, and immune function. No genes were affected by DE in SH rats. A dose-dependent inhibition of mitochondrial aconitase activity in both rat strains was observed, indicating a DE effect on oxidative stress. It should be noted that while DE-related cardiovascular effects were found in WKY rats only, pulmonary inflammation and injury were observed in both strains (Sections 7.3.3.2 and 7.3.5.1).

Model Particles

Wallenborn et al. (2008, 191171) examined the subchronic (5 h/day, 3 day/wk, 16 wk) pulmonary, cardiac, and systemic effects of nose-only exposure to particulate $ZnSO_4$ (9, 35, or 120 μg/m^3) in WKY rats. Particle size was reported to be 31-44 nm measured as number median diameter. Although changes in pulmonary inflammation or injury and cardiac pathology were not observed, effects on cardiac mitochondrial protein and enzyme levels were noted (i.e., increased ferritin levels, decrease in succinate dehydrogenase activity), possibly indicating a small degree of mitochondrial dysfunction. Glutathione peroxidase, an antioxidant enzyme, was also decreased in the cardiac cytosol. Gene expression analysis identified alterations in cardiac genes involved in cell signaling events, ion channels regulation, and coagulation in animals exposed to the highest $ZnSO_4$ concentration only. This study demonstrates a possible direct effect of $ZnSO_4$ on extrapulmonary systems, as suggested by the lack of pulmonary effects (Section 7.3.3.2).

7.2.8. Left Ventricular Mass and Function

Van Hee et al. (2009, 192110) studied 3,827 participants (age range = 45-84 yr; 53% female) who underwent magnetic resonance imaging (MRI) of the heart at the baseline examination of the MESA cohort (2000-2002). This cross-sectional study focused on two MRI-based outcome measures: left ventricular mass index (LVMI, g/m^2) and ejection fraction (EF, %), the former estimated using the DuBois formula for body surface area, the latter as the ratio of stroke volume to end diastolic volume. The study also estimated annual mean exposures to $PM_{2.5}$ at participants' geocoded residential addresses in 2000 using ordinary kriging of U.S. EPA AQS concentration data. In fully adjusted models, it found 3.8 (95% CI: -6.1 to 13.7) g/m^2 and -3.0% (-8.0 to 2.0) differences in LVMI and EF per 10 μg/m^3 increment in $PM_{2.5}$. The findings were small and imprecise, albeit suggestive of a slight, PM-associated increase in the mass and decrease in the function of the left ventricle. The effect of living within 50 m of a major roadway on LVMI was greater than the effect of $PM_{2.5}$ (i.e., 1.4 g/m^2 [95% CI: 0.3-2.5] per 10 μg/m^3.)

7.2.9. Clinical Outcomes in Epidemiologic Studies

Several epidemiologic studies of U.S. and European populations have examined associations between long-term PM exposures and clinical CVD events (Baccarelli et al., 2008, 157984; Hoffmann et al., 2006, 091162; Hoffmann et al., 2009, 190376; Maheswaran et al., 2005, 088683; Maheswaran et al., 2005, 090769; Miller et al., 2007, 090130; Rosenlund et al., 2006, 089796; Solomon et al., 2003, 156994; Zanobetti and Schwartz, 2007, 091247). Results from these studies are summarized in Figure 7-1. The ambient PM concentrations from these studies are characterized in Table 7-2.

Coronary Heart Disease

Epidemiologic studies examining the association of coronary heart disease (CHD) with long-term PM exposure are discussed below (Hoffmann et al., 2006, 091162; Maheswaran et al., 2005, 090769; Miller et al., 2007, 090130; Puett et al., 2008, 156891; Rosenlund et al., 2006, 089796; Rosenlund et al., 2009, 190309; Zanobetti and Schwartz, 2007, 091247). Cases of CHD were variably defined in these studies to include history of angina pectoris, MI, coronary artery revascularization (bypass graft; angioplasty; stent; atherectomy), and congestive heart failure (CHF). Results pertaining to death from CHD are described in Section 7.6.

Miller et al. (2007, 090130) studied incident, validated MI, revascularization, and CHD death, both separately and collectively, among 58,610 post-menopausal female residents of 36 U.S. metropolitan areas (age range = 50-79 yr) enrolled in the Women's Health Initiative Observational Study (WHI OS, 1994-1998). In this prospective cohort study of participants free of CVD at baseline (median duration of follow-up = 6 yr), the authors used arithmetic averaging of year 2000 EPA AQS $PM_{2.5}$ data available at the monitor nearest to each participant's geocoded U.S. Postal Service five-digit ZIP code centroid to estimate 1-yr avg exposures. They found 6% (95% CI: -15 to 34), 20% (95% CI: 0-43) and 21% (95% CI: 4-42) increases in the overall risk of MI, revascularization, and

their combination with CHD death per 10 μg/m^3 increase in $PM_{2.5}$, respectively. Hazards were higher within than between cities and in the obese. For the combined CVD outcome (MI, revascularization, stroke, CHD death, cerebrovascular disease), authors reported a 24% (95% CI: 9-41) increase in risk that was higher among participants at higher than lower quintiles of body mass index, waist-to-hip ratio, and waist circumference. The $PM_{2.5}$-CVD association was stronger among non-diabetic than diabetic participants.

Table 7-2. Characterization of ambient PM concentrations from studies of clinical cardiovascular diseases and long-term exposure.

Study	Location	Mean Annual Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
PM_{10}			
Puett et al. (2008, 156891)	13 U.S. States	21.6	
Zanobetti and Schwartz (2007, 091247)	21 U.S. Cities	28.8	Overall range NR
Rosenlund et al. (2006, 089796)	Stockholm, Sweden	30 y avg PM_{10} (traffic) Cases: 2.6 Controls: 2.4	5th-95th Percentile 0.5-6.0 0.6-5.9
Rosenlund et al. (2009, 190309)	Stockholm, Sweden	5-yr avg PM_{10} from traffic: Cases: 2.4 (median) Controls: 2.2 (median)	
Maheswaran et al. (2005, 090769)	Sheffield, U.K.	Range of means in each quintile: 16-23.3	NR
Baccarelli et al. (2008, 157984)	Lombardia Region, Italy	NR	NR
$PM_{2.5}$			
Miller et al. (2007, 090130)	WHI: 36 Metropolitan areas	Citywide avg (yr 2000): 13.5	Min-max: 4-19.3
Hoffmann et al. (2006, 091162)	HNRS: 2 Cities Germany	23.3	NR
Hoffman et al. (2009, 190376)	HRNS: 2 Cities German	22.8	NR

WHI: Womens Health Initiative
HNRS: Hans Nixdorf Recall Study

Puett et al. (2008, 156891) studied incident, validated CHD, CHD death, and non-fatal MI among 66,250 female residents (mean age = 62 yr) of metropolitan statistical areas in thirteen northeastern U.S. states who were enrolled in the Nurses' Health Study (NHS, 1992-2002). In this prospective cohort study of women without a history of non-fatal MI at baseline (maximum duration of follow-up = 4 yr), the authors used two-stage, spatially smoothed, land use regression to estimate residence-specific, 1-yr ma PM_{10} exposures from U.S. EPA AQS and emissions, IMPROVE, and Harvard University monitor data. They found a 10% (95% CI: -6 to 29) increase in risk of first CHD event per 10 μ/m^3 increase in 1-yr avg PM_{10} exposure, while the association with MI was close to the null value. The association with fatal CHD event of 30% (95% CI: 0-71) was stronger. Furthermore, associations with CHD death were higher in the obese and in the never smokers.

Rosenlund et al. (2006, 089796) studied 2,938 residents of Stockholm County, Sweden (age range = 45-70 yr; 34% female). In this case-control study of 1,085 patients with their first, validated non-fatal MI and an age-, gender- and catchment-stratified random sample of 1,853 controls without MI (1992-1994), the authors used street canyon-adjusted dispersion modeling of emissions data to estimate 30-yr avg exposure to PM_{10} (median = 2.4 μg/m^3). They found that the OR for prevalent MI per 10 μg/m^3 increase in PM_{10} was 0.85 (95% CI: 0.50-1.42). The OR for fatal MI was elevated, but not statistically significant.

In a more recent study, Rosenlund et al. (2009, 190309) evaluated 554,340 residents (age range = 15-79 yr; 49% female) of Stockholm County, Sweden (1984-1996). In this population-based, case-control study of 43,275 cases of incident, validated MI, the authors used dispersion modeling of traffic emissions and land use data to estimate 5-yr avg exposure to PM_{10}. They found that after

adjustment for demographic, temporal, and socioeconomic characteristics, the OR for MI per 5 μg/m^3 increase in PM_{10} was 1.04 (95% CI: 1.00-1.09). ORs were higher after restriction to fatal cases, in- or out-of-hospital deaths, and participants who did not move between population censuses. Authors state that control for confounding was superior in their previous study (Rosenlund et al., 2006, 089796) although the size of the population was larger in this recent study (Rosenlund et al., 2009, 190309).

Zanobetti and Schwartz (2007, 091247) studied ICD-coded recurrent MI (ICD 9 410) and post-infarction CHF (ICD 9 428) among 196,131 Medicare recipients (age ≥ 65 yr; 50% female) discharged alive following MI hospitalization in 21 cities from 12 U.S. states (1985-1999). In this ecologic, open cohort study of re-hospitalization among MI survivors (mean duration of follow-up = 3.6 and 3.7 yr for MI and CHF, respectively), the authors used arithmetic averaging of EPA AQS PM_{10} data available in the county of hospitalization to estimate 1-yr avg exposures. They found 17% (95% CI: 5-31) and 11% (95% CI: 3-21) increases in the risk of recurrent MI and post-infarction CHF, respectively, per 10 μg/m^3 increase in PM_{10} exposure. Hazards were somewhat higher among persons aged >75 yr.

Hoffmann et al. (2006, 091162) studied self-reported CHD (MI or revascularization) among 3,399 residents of Essen and Mülheim, Germany (age range = 45-75 yr; 51% female) at the baseline exam of the Heinz Nixdorf Recall Study (2000-2003) introduced previously. In this cross-sectional ancillary study, the authors used dispersion modeling of emissions, climate and topography data to estimate 1-yr avg exposure to $PM_{2.5}$ (mean = 23.3 μg/m^3). They found little evidence of an association between $PM_{2.5}$ and CHD in these data. After adjustment for geographic, demographic and clinical characteristics, the OR for prevalent CHD per 10 μg/m^3 increase in exposure was 0.55 (95% CI: 0.14-2.11).

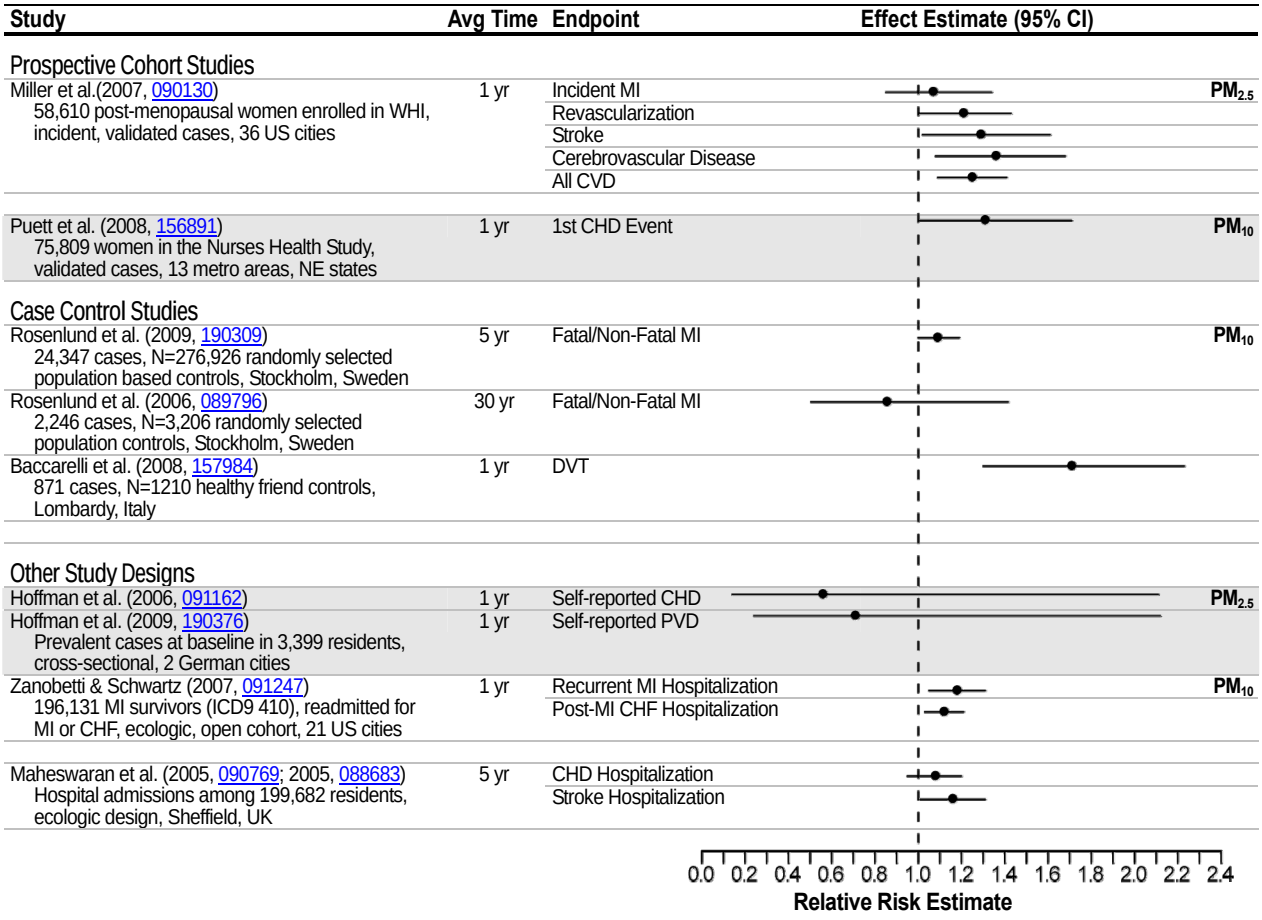


Figure 7-1. Risk estimates for the associations of clinical outcomes with long-term exposure to ambient $PM_{2.5}$ and PM_{10}.

In the study of 1,030 census enumeration districts in Sheffield, U.K. described previously, Maheswaran et al. (2005, 090769) studied 11,407 ICD-10-coded emergency hospitalizations for CHD (ICD10 I20-25) among 199,682 residents (age ≥ 45 yr; 45% female). In this ecologic study, the authors used dispersion modeling of emissions and climate data to estimate 5-yr avg exposure to PM_{10}. They found that after adjusting for smoking prevalence, controlling for socioeconomic factors, and smoothing, the age- and gender-standardized rate ratios for CHD admission were 1.01 (95% CI: 0.92-1.11), 1.04 (95% CI: 0.93-1.15), 0.97 (95% CI: 0.87-1.08), and 1.07 (95% CI: 0.95-1.20) across PM_{10} quintiles. The linear trend was somewhat stronger for CHD mortality (Section 7.3).

The study of post-menopausal women enrolled in the WHI OS by Miller et al. (2007, 090130) was the only U.S. study to examine the effect of $PM_{2.5}$ rather than PM_{10}. This study, which provides strong evidence of an association, was distinguished by its prospective cohort design, validation of incident cases and large population. Puett et al. (2008, 156891), the other U.S. study with comparable design features, provides evidence of an association of incident CHD with long- term PM_{10} exposure. Findings from Swedish case control studies of incident validated cases of MI were not consistent. A cross-sectional study of self-reported CHD did not provide evidence of an association with $PM_{2.5,}$ while findings from two ecologic studies of PM_{10} indicated positive associations of CHD hospitalizations with PM_{10} (Maheswaran et al., 2005, 088683; Zanobetti and Schwartz, 2007, 091247).

Stroke

Miller et al. (2007, 090130) found 28% (95% CI: 2-61) and 35% (95% CI: 8-68) increases in the overall risk of validated stroke and cerebrovascular disease, respectively, per 10 $\mu g/m^3$ increase in 1-yr avg $PM_{2.5}$ exposure. Risks were higher within than between cities. In the study of 1030 Census of enumeration districts in Sheffield, U.K. described previously, Maheswaran et al. (2005, 088683) studied 5,122 ICD-10-coded emergency hospital admissions for stroke (I60-69) among 199,682 residents (age ≥ 45 yr; 45% female) of 1,030 census enumeration districts in Sheffield, U.K. (1994-1999). In this ecologic study, the authors used dispersion modeling of emissions and climate data to estimate 5-yr avg exposure to PM_{10}. They found that the age- and gender-standardized rate ratios for stroke admission were 1.05 (95% CI: 0.94-1.17), 1.07 (95% CI: 0.95-1.20), 1.06 (95% CI: 0.94-1.20), and 1.15 (95% CI: 1.01-1.31) across PM_{10} quintiles. Linear trend was somewhat stronger for stroke mortality (Section 7.6).

These studies examining the long-term PM-stroke relationship provide evidence of association. Maheswaran et al. (2005, 088683) examined emergency room hospital admissions in Sheffield, U.K. using an ecologic design while results reported by Miller et al. (2007, 090130) are based on the prospective cohort study of the WHI OS population (both introduced previously).

Peripheral Arterial Disease

The German Heinz Nixdorf Recall cross-sectional study described in Section 7.2.1.1 (Hoffmann et al., 2009, 190376) also evaluated the association between 1-yr avg exposure to $PM_{2.5}$ and peripheral arterial disease (self-reported history of a surgical or procedural intervention or an ABI <0.9 in one or both legs). The authors found no evidence of an increase in risk. The OR for peripheral arterial disease was 0.87 (95% CI: 0.57-1.34) per 3.9 $\mu g/m^3$ increase in $PM_{2.5}$. However, evidence of an association with traffic exposure was present in these data. ORs of 1.77 (95% CI: 1.01-3.10), 1.02 (95% CI: 0.58-1.80), and 1.07 (95% CI: 0.68-1.68) for residing ≤ 50, 50-100, and 100-200 m of a major road (reference category: >200 m), respectively were observed. ORs were higher among participants with CAC scores ≤ 75th percentile, women, and smokers.

Deep Vein Thrombosis

The Italian case-control study (introduced in Section 7.2.1.2) also examined the chronic PM_{10}-DVT association (Baccarelli et al., 2008, 157984). The authors found a 70% (95% CI: 30-223) increase in the odds of DVT per 10 $\mu g/m^3$ increase in 1-yr avg PM_{10} exposure. This finding was consistent with the decreases in PT and PTT also observed among controls in this context as well as

the 47% (95% CI: 11-96) increase in the odds of DVT per inter-decile range (242 m) increase in the residence-to-major-roadway distance observed among a subset of cases and controls (Baccarelli et al., 2009, 188183). The PM_{10}-DVT and distance-DVT associations were both weaker among women and among users of oral contraceptives or hormone therapy.

7.2.10. Cardiovascular Mortality

New epidemiologic evidence reports a consistent association between long-term exposure to $PM_{2.5}$ and increased risk of cardiovascular mortality. There is little evidence for the long-term effects of $PM_{10-2.5}$ on cardiovascular mortality. This section focuses on cardiovascular mortality outcomes in response to long-term exposure to PM. The studies that investigate long-term exposure and mortality due to any specific or all (nonaccidental) causes are evaluated in Section 7.6. A summary of the mean PM concentrations reported for the studies characterized in this section is presented in Table 7-8, and the effect estimates are presented in Figure 7-7 and Figure 7-8.

A number of large, U.S. cohort studies have found consistent associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality. The American Cancer Society (ACS) (Pope et al. (2004, 055880) reported positive associations 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 $\mu g/m^3$ $PM_{2.5}$). In an additional reanalysis that extended the follow-up period for the ACS cohort to 18 yr (1982-2000) (Krewski et al., 2009, 191193), investigators found effect estimates that were similar, though generally higher, than those reported in previous ACS analyses.

A follow-up to the Harvard Six Cities study (Laden et al., 2006, 087605) used updated air pollution and mortality data and found positive associations between long-term exposure to $PM_{2.5}$ and mortality. Of special note is a statistically significant reduction in mortality risk reported with reduced long-term fine particle concentrations. This reduced mortality risk was observed for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths.

The WHI cohort study (Miller et al., 2007, 090130) (described previously) found that each 10 $\mu g/m^3$ increase of $PM_{2.5}$ was associated with a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76 [95% CI: 1.25-2.47]). The WHI study not only confirms the ACS and Six City Study associations with cardiovascular mortality in yet another well characterized cohort with detailed individual-level information, it also has been able to consider the individual medical records of the thousands of WHI subjects over the period of the study. This has allowed the researchers to examine not only mortality, but also related morbidity in the form of heart problems (cardiovascular events) experienced by the subjects during the study. These morbidity co-associations with $PM_{2.5}$ in the same population lend even greater support to the biological plausibility of the air pollution-mortality associations found in this study.

In an analysis for the Seventh-Day Adventist cohort in California (AHSMOG), a positive association with coronary heart disease mortality was reported among females (92 deaths; RR = 1.42 [95% CI: 1.06-1.90] per 10 $\mu g/m^3$ $PM_{2.5}$), but not among males (53 deaths; RR = 0.90 [95% CI: 0.76-1.05] per 10 $\mu g/m^3$ $PM_{2.5}$) (Chen et al., 2005, 087942). Associations were strongest in the subset of postmenopausal women (80 deaths; RR = 1.49 [95% CI: 1.17-1.89] per 10 $\mu g/m^3$ $PM_{2.5}$). 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. As was found with $PM_{2.5}$, a positive association with coronary heart disease mortality was reported for $PM_{10-2.5}$ and PM_{10} among females (RR = 1.38 [95% CI: 0.97-1.95] per 10 $\mu g/m^3$ $PM_{10-2.5}$; RR = 1.22 [95% CI: 1.01-1.47] per 10 $\mu g/m^3$ PM_{10}), but not for males (RR = 0.92 [95% CI: 0.66-1.29] per 10 $\mu g/m^3$ $PM_{10-2.5}$; RR = 0.94 [95% CI: 0.82-1.08] per 10 $\mu g/m^3$ PM_{10}); associations were strongest in the subset of postmenopausal women (80 deaths) (Chen et al., 2005, 087942).

Two additional studies explored the effects of PM_{10} on cardiovascular mortality. The Nurses' Health Study (Puett et al., 2008, 156891) is an ongoing prospective cohort study examining the relation of chronic PM_{10} exposures with all-cause mortality and incident and fatal coronary heart disease consisting of 66,250 female nurses in MSAs in the northeastern region of the U.S. The association with fatal CHD occurred with the greatest magnitude when compared with other specified causes of death (hazard ratio 1.42 [95% CI: 1.11-1.81]). The North Rhine-Westphalia State Environment Agency (LUA NRW) initiated a cohort of approximately 4,800 women, and assessed whether long-term exposure to air pollution originating from motorized traffic and industrial sources was associated with total and cause-specific mortality (Gehring et al., 2006, 089797). They found

that cardiopulmonary mortality was associated with PM_{10} (RR = 1.52 [95% CI: 1.09-2.15] per 10 $\mu g/m^3$ PM_{10}).

In summary, the 2004 PM AQCD concluded that there was strong evidence that long-term exposure to $PM_{2.5}$ was associated with increased cardiopulmonary mortality. Recent studies investigating cardiovascular mortality provide some of the strongest evidence for a cardiovascular effect of PM. A number of large cohort studies have been conducted throughout the U.S. and reported consistent increases in cardiovascular mortality related to $PM_{2.5}$ concentrations. The results of two of these studies have been replicated in independent reanalyses. These effects are coherent with short-term epidemiologic studies of CVD morbidity and mortality and with long-term epidemiologic studies of CVD morbidity. In addition, biological plausibility and coherence are provided by toxicological studies demonstrating short-term cardiovascular effects as well as $PM_{2.5}$-related plaque progression in chronically exposed mice.

7.2.11.Summary and Causal Determinations

7.2.11.1. $PM_{2.5}$

Epidemiologic studies examining associations between long-term exposure to ambient PM (over months to years) and CVD morbidity had not been conducted and thus were not included in the 1996 or 2004 PM AQCDs (U.S. EPA, 1996, 079380; U.S. EPA, 2006, 157071). A number of studies were included in the 2004 AQCD that evaluated the effect of long-term $PM_{2.5}$ exposure on cardiovascular mortality and found strong and consistent associations. No toxicological studies had evaluated the effects of subchronic or chronic PM exposure on CVD effects in the 2004 PM AQCD. Recently, epidemiologic and toxicological studies have provided evidence of the adverse effects of long-term exposure to $PM_{2.5}$ on cardiovascular outcomes and endpoints, including atherosclerosis and clinical and subclinical markers of cardiovascular morbidity.

The strongest evidence for a CVD health effect related to long-term $PM_{2.5}$ exposure comes from epidemiologic studies of cardiovascular mortality. A number of large, multicity U.S. studies (the ACS, Six Cities Study, WHI, and AHSMOG) provide consistent evidence of an effect between long-term exposure to $PM_{2.5}$ and cardiovascular mortality (Section 7.2.10). These studies were conducted in urban areas across the U.S. where mean concentrations ranged from 10.2-29.0 $\mu g/m^3$ (Table 7-8). An epidemiologic study investigating the relationship between $PM_{2.5}$ and clinical CVD morbidity among post-menopausal women (Miller et al., 2007, 090130) provides evidence of an effect that is coherent with the cardiovascular mortality studies. This large, prospective cohort study of incident, validated cases found large increases in the adjusted risk of MI, revascularization, and stroke using a 1-yr avg $PM_{2.5}$ concentration (mean = 13.5 $\mu g/m^3$). A cross-sectional analyses of self-reported prevalence of CHD and peripheral arterial disease found no such increase in the odds of CVD morbidity (Hoffmann et al., 2006, 091162); the inconsistency of these findings with Miller et al. (2007, 090130) may be explained by differences in study design or location.

The effect of long-term $PM_{2.5}$ exposure on pre-clinical measures of atherosclerosis (CIMT, CAC, AAC or ABI) has been studied in several populations using a cross-sectional study design. The magnitude of the $PM_{2.5}$ effects and their consistency across different measures of atherosclerosis in these studies varies widely, and they may be limited in their ability to discern small changes in these measures. Kunzli et al. (2005, 087387) observed a non-significant 4.2% increase in CIMT associated with long-term $PM_{2.5}$ exposure among participants of a clinical trial in greater Los Angeles, which was several fold higher than the 0.5% increase observed by Diez-Roux et al. (2008, 156401) in their analyses of MESA baseline data. The associations in MESA of CAC and ABI with long-term $PM_{2.5}$ exposure were largely null (Diez et al., 2008, 156401), while an increase in AAC with long-term $PM_{2.5}$ exposure was reported (Chang et al., 2008, 180393). By contrast, a 43% increase in CAC was associated with long-term $PM_{2.5}$ exposure in a German study, but no similar association with ABI was observed (Hoffmann et al., 2009, 190376). Although the number of studies examining these relationships is limited, effect modification by use of lipid lowering drugs and smoking status was reported in more than one study of long-term $PM_{2.5}$ and PM_{10} exposure.

Evidence of enhanced atherosclerosis development was demonstrated in new toxicological studies that report increased plaque and lesion areas, lipid deposition, and TF in aortas of $ApoE^{-/-}$ mice exposed to CAPs (Section7.2.1.2). In addition, alterations in vasoreactivity were observed,

suggesting an impaired NO pathway. Additional toxicological studies of PM_{10} are consistent with these results. Further support is provided by a study that reported decreased L/W ratio in the pulmonary and coronary arteries of mice exposed to ambient air. However, $PM_{2.5}$ CAPs derived from traffic in Los Angeles did not affect plaque size (Araujo et al., 2008, 156222). Collectively, these toxicological studies provide biological plausibility for the associations reported in epidemiologic studies.

There is limited evidence for the effects of $PM_{2.5}$ on renal or vascular function. Cross-sectional and longitudinal epidemiologic analyses of $PM_{2.5}$ and UACR revealed no evidence of an effect (O'Neill et al., 2007, 156006), while small non-statistically significant increases in BP with 30- and 60-day avg $PM_{2.5}$ concentrations were reported (Auchincloss et al., 2008, 156234). A toxicological study did not show changes in MAP with CAPs, but indicated a CAPs-related potentiation of experimentally-induced hypertension (Sun et al., 2008, 157032). In addition, CAPs has induced changes in insulin resistance, visceral adiposity, and inflammation in a diet-induced obesity mouse model (Sun et al., 2009, 190487), indicating that diabetics may be a potentially susceptible population to PM exposure.

In summary, a number of large U.S. cohort studies report associations of long-term $PM_{2.5}$ concentration with cardiovascular mortality. These studies provide the strongest evidence for an effect of long-term $PM_{2.5}$ exposure on CVD effects. Additional evidence comes from a methodologically rigorous epidemiology study that demonstrates coherent associations between long-term $PM_{2.5}$ exposure and CVD morbidity among post-menopausal women. Toxicological studies demonstrate that this effect is biologically plausible and the effect is coherent with studies of short-term $PM_{2.5}$ exposure and CVD morbidity and mortality, and with long-term exposure to $PM_{2.5}$ and CVD mortality. Associations between $PM_{2.5}$ and subclinical measures of atherosclerosis are inconsistent, but cross-sectional studies may be limited in their ability to discern small changes in these measures. In addition, potential modification of the $PM_{2.5}$-CVD association by smoking status and the use of lipid lowering drugs has been demonstrated in epidemiologic studies that used individual-level data. Toxicological studies provide evidence for accelerated development of atherosclerosis in $ApoE^{-/-}$ mice exposed to CAPs and show effects on coagulation factors, experimentally-induced hypertension, and vascular reactivity. Available studies of clinical cardiovascular disease outcomes report inconsistent results. Based on the above findings, the epidemiologic and toxicological evidence is **sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposures and cardiovascular effects.**

7.2.11.2. $PM_{10-2.5}$

One epidemiologic study evaluated the relationship between long-term exposure to $PM_{10-2.5}$ and cardiovascular mortality and found a positive association with coronary heart disease mortality among females, but not for males; associations were strongest in the subset of post-menopausal women (Chen et al., 2005, 087942). No toxicological studies of long-term exposure to ambient $PM_{10-2.5}$ and cardiovascular effects have been conducted to date. Evidence is **inadequate to infer the presence or absence of a causal relationship.**

7.2.11.3. UFPs

A few toxicological studies of long-term exposure to UFPs have been conducted. Increased plaque size was reported in mice exposed to UF CAPs derived from traffic (Araujo et al., 2008, 156222). Studies of diesel and gasoline exhaust reported relatively few changes in hematologic or coagulation parameters (Section 7.2.4.2) and one DE study demonstrated altered cardiac gene expression in normotensive rats that reflected the development of hypertension (Gottipolu et al., 2009, 190360). Whole and filtered gasoline exhaust induced increases in gene products involved in atheromatous plaque formation and/or degradation, but these effects were largely due to the gaseous emissions (Lund et al., 2007, 125741). Evidence from these studies alone is **inadequate to infer the presence or absence of a causal relationship**.

7.3. Respiratory Effects

Several cohort studies reviewed in the 2004 PM AQCD provided evidence for relationships between long-term PM exposure and effects on the respiratory system, though it did not rule out the possibility that the observed respiratory effects may have been confounded by other pollutants. In 12 southern California communities in the Children's Health Study (CHS), Gauderman et al. (2000, 012531; 2002, 026013) found that decreases in lung function growth among schoolchildren were associated with long-term exposure to PM. Declines in pulmonary function were reported with all three major PM size classes – PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ – though the three PM measures were highly correlated. In another analysis of data from the CHS cohort, McConnell et al. (1999, 007028), reported an increased risk of bronchitis symptoms in children living in communities with higher PM_{10} and $PM_{2.5}$ concentrations. These results were found to be consistent with results of cross-sectional analyses of the 24-city study by Dockery et al. (1996, 046219) and Raizenne et al. (1996, 077268), that were assessed in the 1996 PM AQCD. These studies reported associations between increased bronchitis rates and decreased peak flow with fine particle sulfate and fine particle acidity. However, the high correlation of PM_{10}, acid vapor and NO_2 precluded clear attribution of the bronchitis effects reported by McConnell et al. (1999, 007028) to PM alone. In a prospective cohort study among a subset of children in the CHS (n = 110) who moved to other locations during the study period, Avol et al. (2001, 020552) reported that those subjects who moved to areas of lower PM_{10} showed increased growth in lung function compared with subjects who moved to communities with higher PM_{10} concentrations. Finally, the 2004 PM AQCD concluded that there was strong epidemiologic evidence for associations between long-term exposures to $PM_{2.5}$ and cardiopulmonary mortality, though the respiratory effects were not separated from the cardiovascular effects in this conclusion.

The 2004 PM AQCD (U.S. EPA, 2004, 056905) concluded that the evidence for an association between long-term exposure to PM and respiratory effects may be confounded by other pollutants. Gauderman et al. (2002, 026013) reported declines for FEV_1 and McConnell et al. (1999, 007028) reported increased ORs for bronchitic symptoms in asthmatics for PM_{10} and $PM_{2.5}$. Recent epidemiologic literature includes results from several prospective cohort studies, which found consistent, positive associations between long-term exposure to PM and respiratory morbidity. Associations were reported with $PM_{2.5}$ and PM_{10}, and the studies showing associations only with PM_{10} were conducted in locations where the PM consisted predominantly of fine particles, providing support for associations with long-term exposure to fine particles. These results are summarized below; further details of these studies are summarized in Annex E.

Very few subchronic and chronic toxicological studies investigating respiratory effects were available in the 2004 PM AQCD. However, the 2002 EPA Health Assessment Document for DE reported that chronic exposure to DE was associated with histopathology including alveolar histiocytosis, aggregation of alveolar macrophages, tissue inflammation, increased polymorphonuclear leukocytes, hyperplasia of bronchiolar and Type 2 epithelial cells, thickened alveolar septa, edema, fibrosis, emphysema and lesions of the trachea and bronchi. Since then a number of animal toxicological studies have been conducted involving inhalation exposure to CAPs, urban air, DE, gasoline exhaust, and wood smoke. These subchronic and chronic studies provide evidence of altered pulmonary function, inflammation, histopathological changes and oxidative and allergic responses following $PM_{2.5}$ exposures. These results are summarized below; further details of these studies are summarized in Annex D.

7.3.1. Respiratory Symptoms and Disease Incidence

7.3.1.1. Epidemiologic Studies

New longitudinal cohort studies provide the best evidence to evaluate the relationship between long-term exposure to ambient PM and increased incidence of respiratory symptoms or disease. A summary of the mean PM concentrations reported for the long-term exposure studies characterized in this section is presented in Table 7-3.

Bayer-Oglesby et al. (2005, 086245) examined the decline of ambient pollution levels and improved respiratory health demonstrated by a reduction in respiratory symptoms and diseases in school children (n = 9,591) in Switzerland. Reduced air pollution exposure resulted in improved respiratory health of children. Further, the average reduction of symptom prevalence was more pronounced in areas with stronger reduction of air pollution levels. The average decline of PM_{10} between 1993 and 2000 across the nine study regions was 9.8 $\mu g/m^3$ (29%). Declining levels of PM_{10} were associated with declining prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis symptoms, but no significant associations were reported for wheezing, sneezing, asthma, and hay fever, as shown in Figure 7-2. In Figure 7-2, Panel (B) illustrates that on an aggregate level across regions, the mean change in adjusted prevalence of chronic cough is associated with the mean change in PM_{10} levels ($r = 0.78$; $p = 0.02$). Similar associations were seen for nocturnal dry cough and conjunctivitis symptoms and PM_{10} levels. Röösli et al. (2000, 010296; 2001, 108738; 2005, 156923) have demonstrated that PM_{10} levels are homogeneously distributed within regions of Basel, Switzerland and are not substantially affected by local traffic, justifying the single-monitor approach for assignment of PM_{10} exposures. Based on parallel measurements of $PM_{2.5}$ and PM_{10} at seven sites in Switzerland, $PM_{2.5}$ and PM_{10} at all sites are generally highly correlated (r^2 ranging from 0.85 to 0.98) (Gehrig and Buchmann, 2003, 139678), indicating that PM_{10} consists predominantly of fine particles in these locations.

Schindler et al. (2009, 191950) reported that sustained reduction in ambient PM_{10} concentrations can lead to decreases in respiratory symptoms among Swiss adults in the SAPALDIA study. They compared baseline data in 1991 to a follow-up interview in 2002 after a substantial decline in PM_{10} concentrations served as a natural experiment. Each subject was assigned model-based estimates of PM_{10} concentrations averaged over the 12 mo preceding each health assessment with mean decline in PM_{10} levels of 6.2 $\mu g/m^3$ (SD = 3.9 $\mu g/m^3$). When the authors tested the joint hypothesis of no association between the PM_{10} difference and symptom incidence or persistence, positive results were obtained for regular cough, chronic cough or phlegm and wheezing but not regular phlegm or wheezing without a cold.

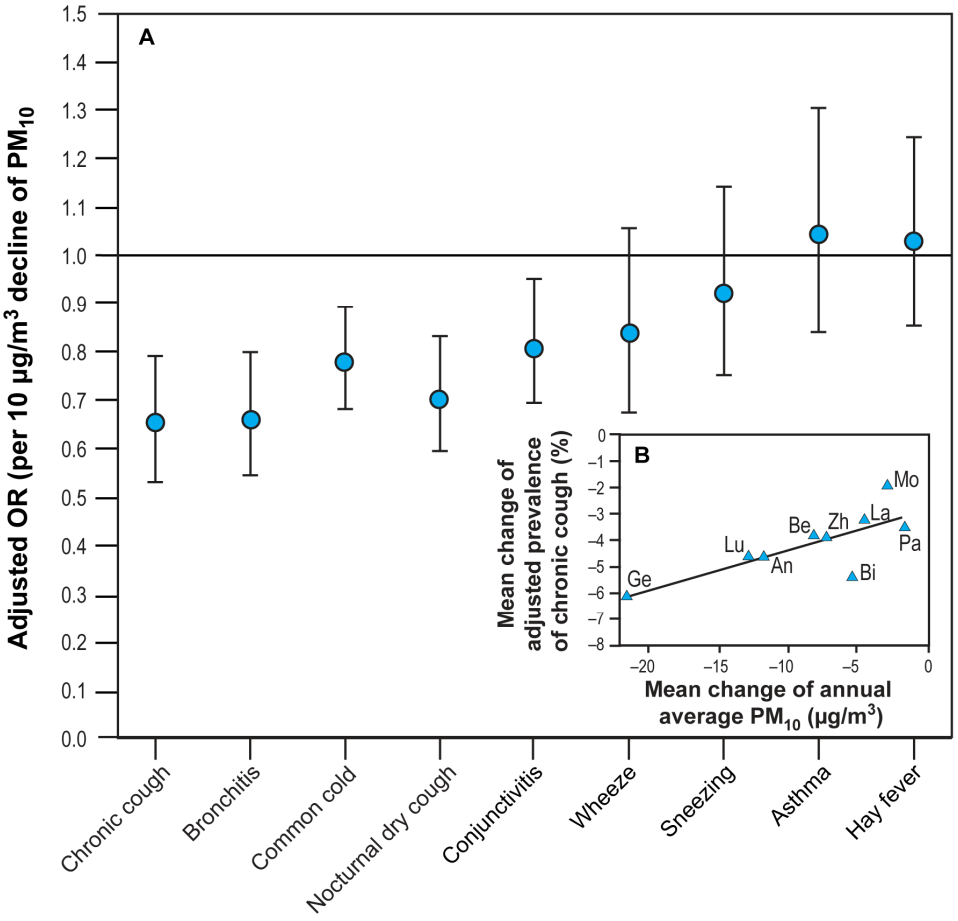
Pierse et al. (2006, 088757) studied the association between primary PM_{10} (particles directly emitted from local sources/traffic) and the prevalence and incidence of respiratory symptoms in a randomly sampled cohort of 4,400 children (aged 1-5 yr) in Leicestershire, England surveyed in 1998 and again in 2001. Annual exposure to primary PM_{10} was calculated for the home address using the Airviro statistical dispersion model. After adjusting for confounders, mean annual exposure to locally generated PM_{10} was associated with an increased prevalence of cough without a cold in both the 1998 (OR 1.21 [95% CI: 1.07-1.38], n = 2,164) and 2001 surveys (OR 1.56 [95% CI: 1.32-1.84], n = 1,756).

Nordling et al. (2008, 097998) examined the relationship between estimated PM exposure levels and respiratory health effects in a Swedish birth cohort of preschool children (n = 4,089). The spatial distributions of PM from traffic in the study area were estimated with emission databases and statistical dispersion modeling. Children were examined at 2 mo and 1, 2, and 4 yr of age. Using GIS methods, the average contribution of traffic-generated PM_{10} above regional background to the children's residential outdoor air pollution levels was determined. To evaluate the exposure assessment, the authors compared the estimated levels of traffic-generated PM_{10} with $PM_{2.5}$ measurements from 42 locations (Hoek et al., 2002, 042364) and reported modeled traffic-generated PM_{10} correlated reasonably well with measured $PM_{2.5}$ ($r = 0.61$). Persistent wheezing (cumulative incidence up to age 4 yr) was associated with exposure to traffic-generated PM_{10} (OR 2.28 [95% CI: 0.84-6.24] per 10 $\mu g/m^3$ increase) while transient and late onset wheezing was not associated. This study demonstrates that respiratory effects may be present in preschool children.

Table 7-3. Characterization of ambient PM concentrations from studies of respiratory symptoms/disease and long-term exposures.

Study	Location	Mean Annual Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
$PM_{2.5}$			
Annesi-Maesano et al. (2007, 093180)	6 French Cities	Range of means across sites: 8.7-23.0 Avg of means across sites: 15.5	
Brauer et al. (2007, 090691)	The Netherlands	16.9	75th: 18.1 90th: 19.0 Max: 25.2
Goss et al. (2004, 055624)	U.S.	13.7	75th: 15.9
Islam et al. (2007, 090697)	12 CHS/CA communities		Max: 29.5
Janssen et al. (2003, 133555)	The Netherlands	20.5	75th: 22.1 Max: 24.4
Kim et al. (2004, 087383)	San Francisco, CA	Range of means across sites: 11-15 Avg of means across sites: 12	
McConnell et al. (2003, 049490)	12 CHS/CA communities	13.8	Max: 28.5
Morgenstern et al. (2008, 156782)	Munich, Germany	11.1	
PM_{10}			
Bayer-Oglesby et al. (2005, 086245)	Nine study regions in Switzerland		Max: 46
Kunzli et al. (2009, 191949)	Switzerland	21.5	
Nordling et al. (2008, 097998)	Sweden	4*	
Schindler et al. (2009, 191950)	Switzerland	**	
McConnell et al. (2003, 049490)	12 CHS/CA communities	30.8	Max: 63.5
Pierse et al. (2006, 088757)	Leicestershire, U.K.	1.33	75th: 1.84

*Source specific; PM_{10} from traffic
**Only reported change in PM concentration



Source: Bayer-Oglesby et al. (2005, 086245)

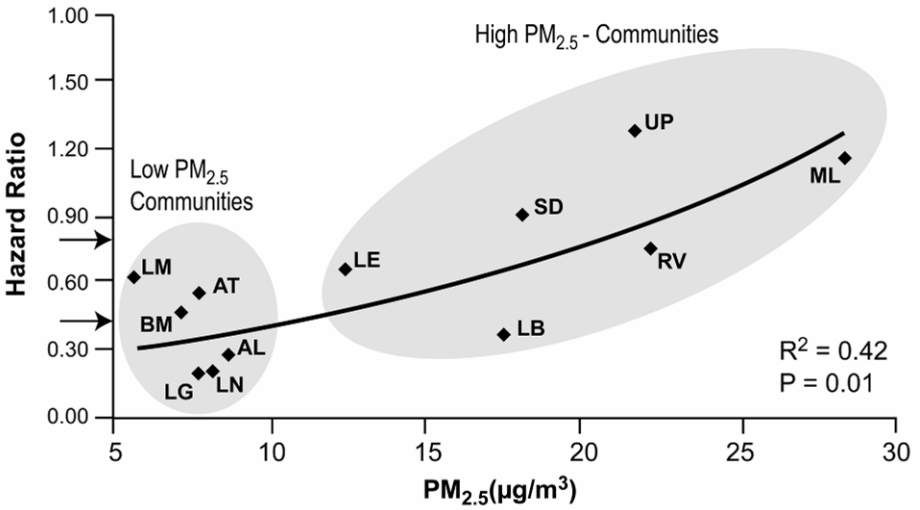
Figure 7-2. Adjusted ORs and 95% CIs of symptoms and respiratory diseases associated with a decline of 10 µg/m^3 PM_{10} levels in Swiss Surveillance Program of Childhood Allergy and Respiratory Symptoms[1]. Inset: Mean change in adjusted prevalence (1998-2001 to 1992-1993) versus mean change in regional annual averages of PM_{10} (1997-2000 to 1993) for chronic cough, across nine SCARPOL regions (An: Anières. Be: Bern. Bi: Biel. Ge: Geneva. La:, Langnau. Lu: Lugano. Mo: Montana. Pa: Payerne. Zh: Zürich).

McConnell et al. (2003, 049490) conducted a prospective study examining the association between air pollution and bronchitic symptoms in 475 school children with asthma in 12 Southern California communities as part of the CHS from 1996 to 1999. They investigated both the differences between- communities with 4-yr avg and within-communities yearly variation in PM (i.e., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, and OC). Based on a 10 µg/m^3 change in $PM_{2.5}$, within-communities effects were larger (OR 1.90 [95% CI: 1.10-2.70]) than those for between-communities (OR 1.30 [95% CI: 1.10-1.50]). The OR for the 10 µg/m^3 range in 4-yr avg $PM_{2.5}$ concentrations across the 12 communities was 1.29 (95% CI: 1.06-1.58). Similar results were reported for PM_{10} and $PM_{10-2.5}$ but the effect estimates were smaller in magnitude and generally not statistically significant. Within-community associations were not confounded by any time-fixed personal covariates. In two-

[1] Adjusted for age, sex, nationality, parental education, number of siblings; farming status, low birth weight, breastfeeding, child who smokes, family history of asthma, bronchitis, and/or atopy, mother who smokes, indoor humidity, mode of heating and cooking, carpeting, pets allowed in bedroom, removal of carpet and/or pets for health reasons, person who completed questionnaire, month when questionnaire was completed, number of days with the maximum temperature <0°C, and belief of mother that there is an association between environmental exposures and children's respiratory health

pollutant models, the within-community effect estimates for $PM_{2.5}$ and OC were significant in the presence of several other pollutants. While the within-community single-pollutant effect of $PM_{2.5}$ (ß = 0.085/μg/m^3) was only modestly attenuated after adjusting for some pollutants, it was markedly reduced after adjusting for NO_2 or OC. The between-community effect estimates generally were not significant in the presence of other pollutants in copollutant models.

In the CHS, Islam et al. (2007, 090697) examined the hypothesis that ambient air pollution attenuates the reduced risk for childhood asthma that is associated with higher lung function (n = 2,057). At each age a distribution of pulmonary functions exists. Haland et al. (2006, 156511) found evidence that children with high lung function have a reduced risk for asthma. Islam et al. (2007, 090697) used the CHS data to study how the association of asthma incidence with lung function is modified by long-term PM exposure. The incidence rate (IR) of newly diagnosed asthma increased from 9.5/1,000 person-years for children with percent-predicted FEF_{25-75} values ≥ 120% to 20.4/1,000 person-years for children with FEF_{25-75} value ≤ 100%. Over the 10th-90th percentile range for FEF_{25-75} (57.1%), the hazard ratio of new onset asthma was 0.50 (95% CI: 0.35-0.71). The IR of asthma for FEF_{25-75} ≥ 120% in the "high" $PM_{2.5}$ (13.7-29.5 μg/m^3) communities was 15.9/1,000 person-years compared to 6.4/1,000 person-years in "low" $PM_{2.5}$ (5.7-8.5 μg/m^3) communities. Loss of protection by high lung function against new onset asthma in the "high" $PM_{2.5}$ communities was observed for all the lung function measures. Figure 7-3 shows the effect of $PM_{2.5}$ on the association of lung function with asthma. Of all the pollutants examined (NO_2, PM_{10}, $PM_{2.5}$, acid vapor, O_3, EC, and OC), $PM_{2.5}$ appeared to have the strongest modifying effect on the association between lung function with asthma as it had the highest R^2 value (0.42). Over the 10th-90th percentile range of FEF_{25-75}, the hazard ratio of new onset asthma was 0.34 (95% CI: 0.21-0.56) in a community with low $PM_{2.5}$ (<13.7 μg/m^3) and 0.76 (95% CI: 0.45-1.26) in a community with high $PM_{2.5}$ (≥ 13.7 μg/m^3). The data do not indicate that PM exposure increased rates of incident asthma among children with poor lung function at study entry because rates among those with poor lung function were similar in both low and high pollution communities.



Source: Reprinted with Permission of BMJ Publishing Group Ltd & British Thoracic Society from Islam et al. (2007, 090697)

Figure 7-3. Effect of $PM_{2.5}$ on the association of lung function with asthma. Community-specific hazard ratio of newly diagnosed asthma over 10-90th percentile range (57.1%) of $FEF_{25-75\%}$ by level of ambient $PM_{2.5}$ (μg/m^3). The 12 CHS communities are shown.

In a prospective birth cohort study (n = 4,000) in The Netherlands, Brauer et al. (2007, 090691) assessed the development of asthma, allergic symptoms, and respiratory infection during the first 4 yr of life in relation to long-term $PM_{2.5}$ concentration at the home address with a validated model using GIS. $PM_{2.5}$ was associated with doctor-diagnosed asthma (OR = 1.32 [95% CI:

1.04-1.69]) for a cumulative lifetime indicator. These findings extend observations made at 2 yr of age in the same cohort (Brauer et al., 2002, 035192) providing greater confidence in the association. No associations were observed for bronchitis.

Kunzli et al. (2009, 191949) used the SAPALDIA cohort study discussed previously in this section to evaluate the relationship between the 11-yr change (1991-2002) in traffic-related PM_{10} and asthma incidence-adult onset asthma. In a cohort of 2,725 never-smokers without asthma at baseline (age: 18-60 yr in 1991), subjects reporting doctor-diagnosed asthma at follow-up were considered incident cases. Modeled traffic-related PM_{10} levels were used. Cox proportional hazard models for time to asthma onset were used with adjustments for cofounders. The study findings suggest that PM contributes to asthma development and that reductions in PM decrease asthma risk. A strong feature of SAPALDIA is the ability to assign space, time, and source-specific pollution to each subject. Further, Kunzli et al. (2008, 129258) discusses the impact of attributable health risk models for exposures that are assumed to cause both chronic disease and its exacerbations. The added impact of causing disease increases the risk compared to only exacerbations.

A matched case-control study of infant bronchiolitis (ICD 9 code 466.1) hospitalization and two measures of long-term exposure – the month prior to hospitalization (subchronic) and the lifetime average (chronic) – to $PM_{2.5}$ and gaseous air pollutants in the South Coast Air Basin of southern California was conducted by Karr et al. (2007, 090719) among 18,595 infants born between 1995-2000. For each case, 10 controls matched on date were randomly selected from birth records. Exposure was based on $PM_{2.5}$ measurements collected every third day. The mean distance between the subjects' residential ZIP code and the assigned monitor was generally 4-6 mi with a maximum distance of 30 mi. For 10 $\mu g/m^3$ increases in both sub-chronic and chronic $PM_{2.5}$ exposure, an adjusted OR of 1.09 (95% CI: 1.04-1.14) was observed. In multipollutant model analyses, the association with $PM_{2.5}$ was robust to the inclusion of gaseous pollutants. Also, in a cohort of children in Germany, Morgenstern et al. (2008, 156782) modeled $PM_{2.5}$ data at birth addresses found statistically significant effects for asthmatic bronchitis, hay fever, and allergic sensitization to pollen.

Goss et al. (2004, 055624) conducted a national study examining the relationship between air pollutants and health effects in a cohort of cystic fibrosis (CF) patients (n = 11,484) over the age of 6 yr (mean age = 18.4, SD = 10) enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Exposure was assessed by linking air pollution values from the closest population monitor from the Air Quality System (AQS) with the centroid of the patient's home ZIP code that was within 30 mi. The mean distance from the patient's ZIP code to monitors for $PM_{2.5}$ and PM_{10} was 10.8 mi (SD 7.8) and 11.5 mi (SD 7.9), respectively. $PM_{2.5}$ and PM_{10} 24-h avg were collected every 1 to 12 days. CF diagnosis involves genetic screening panels and a common severe mutation used is the loss of phenylalanine at the 508th position. Genotyping was available in 74% of the population and of those genotyped, 66% carried one or more delta F508 deletions. After adjusting for confounders, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ or PM_{10} was associated with a 21% (95% CI: 7-33) or 8% (95% CI: 2-15) increase in the odds of two or more exacerbations, respectively. The exacerbations were defined as a CF-related pulmonary condition requiring admission to the hospital or use of home intravenous antibiotics. The estimate for the associations between pulmonary exacerbations and $PM_{2.5}$ and PM_{10} were attenuated when the models were adjusted for lung function. Brown et al. (2001, 012307) found that particle deposition was increased in CF and that particle distribution in the lungs was enhanced in poorly ventilated tracheobronchial regions in CF patients. Such focal deposition may partially explain the association of PM and CF exacerbation.

Annesi-Maesano (2007, 093180) relate individual data on asthma and allergy from 5,338 school children (10.4 ± 0.7 yr) attending 108 randomly chosen schools in 6 French cities to the concentration of $PM_{2.5}$ monitored in school yards. Atopic asthma was related to $PM_{2.5}$ (OR 1.43 [95% CI: 1.07-1.91]) when high $PM_{2.5}$ concentrations (20.7 $\mu g/m^3$) were compared to low $PM_{2.5}$ concentrations (8.7 $\mu g/m^3$). The report is consistent with the results in an earlier paper (Penard-Morand et al., 2005, 087951) in the same sample of children that related the findings to PM_{10}.

Kim et al. (2004, 087383) conducted a school-based cross-sectional study in the San Francisco metropolitan area in 2001 comprised of 10 neighborhoods to examine the relationship between traffic-related pollutants and current bronchitic symptoms and asthma obtained by parental questionnaire (n = 1,109). They related traffic-related pollutants (PM) and bronchitic and asthma symptoms in the past 12 mo. No multipollutant models were evaluated because of the high interpollutant correlations. $PM_{2.5}$ levels ranged across the school sites from 11 to 15 $\mu g/m^3$.

Schikowski et al. (2005, 088637) examined the relationship between both long-term air pollution exposure and living close to busy roads and COPD in the Rhine-Ruhr Basin of Germany

from 1985 to 1994 using consecutive cross-sectional studies. Seven monitoring stations that were <8 km to a woman's home address provided TSP data that PM_{10} was estimated from using a conversion factor (obtained from parallel measurement of TSP and PM_{10} conducted at 7 sites in the Ruhr area). Distance to a major road was determined using GIS. The results of the study suggest that long-term exposure to air pollution from PM_{10} and living near a major road might increase the risk of developing COPD and can have a detrimental effect on lung function. All ORs for 5-yr exposures were stronger than those for 1-yr exposures.

In summary, the 2004 PM AQCD evaluated the available studies which primarily related effects to bronchitic symptoms in school-age children. New studies are using several different methods to include individual estimates of exposure to ambient PM that may reduce the impact of exposure error. The strength and consistency of the outcomes is enhanced by results being reported by several different researchers in different countries using different designs. Most recent studies have focused on children, but a few studies have also reported associations in adults.

The CHS (McConnell et al., 2003, 049490) provides evidence in a prospective longitudinal cohort study that relates $PM_{2.5}$ and bronchitic symptoms and reports larger associations for within-community effects that are less subject to confounding than between-community effects. Several new studies report similar findings with long-term exposure to PM_{10} in areas where fine particles are the predominant fraction of PM_{10}. In England, in a cohort of 4,400 children (aged 1-5 yr), an association is seen with an increased prevalence of cough without a cold. Further evidence includes a reduction of respiratory symptoms corresponding to decreasing PM levels in "natural experiments" in both a cohort of Swiss school children (Bayer-Oglesby et al., 2005, 086245) and adults (Schindler et al., 2009, 191950).

In a separate analysis of the CHS, Islam et al. (2007, 090697) showed that $PM_{2.5}$ had the strongest modifying effect on the association between lung function with asthma such that loss of protection by high lung function against new onset asthma in high $PM_{2.5}$ communities was observed for all the lung function measures from 10 to 18 yr of age. This relates new onset asthma to long-term PM exposure. In the Netherlands, Brauer et al. (2007, 090691) augments the literature with data examining the first 4 yr of life in a birth cohort showing an association with doctor-diagnosed asthma. Further, in an adult cohort in the SALPALDIA study, Kunzli et al. (2009, 191949) relate PM to asthma incidence.

7.3.2. Pulmonary Function

Several cohort studies reviewed in the 2004 PM AQCD provided evidence for relationships between long-term PM exposure and effects on the respiratory system. In 12 southern California communities in the Children's Health Study (CHS), Gauderman et al. (2000, 012531; 2002, 026013) found that decreases in lung function growth among school children were associated with long-term exposure to PM. Declines in pulmonary function were reported with all three major PM size classes – PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ – though the three PM measures were highly correlated. These results were found to be consistent with results of cross-sectional analyses of Raizenne et al. (1996, 077268), that was assessed in the 1996 PM AQCD. That study reported associations between decreased peak flow with fine particle sulfate and fine particle acidity. Finally, in a prospective cohort study among a subset of children in the CHS (n = 110) who moved to other locations during the study period, Avol et al. (2001, 020552) reported that those subjects who moved to areas of lower PM_{10} showed increased growth in lung function compared with subjects who moved to communities with higher PM_{10} concentrations who showed decrease growth in lung function.

7.3.2.1. Epidemiologic Studies

New longitudinal cohort studies have evaluated the relationship between long-term exposure to PM and changes in measures of pulmonary function (FVC, FEV_1, and measures of expiratory flow). Cross-sectional studies also offer supportive information (Annex E) and may provide insights derived from within community analysis. Lung function increases continue through early adulthood with growth and development, then declines with aging (Stanojevic et al., 2008, 157007; Thurlbeck, 1982, 093260; Zeman and Bennett, 2006, 157178). A summary of the mean PM concentrations reported for the long-term exposure studies characterized in this section is presented in Table 7-4.

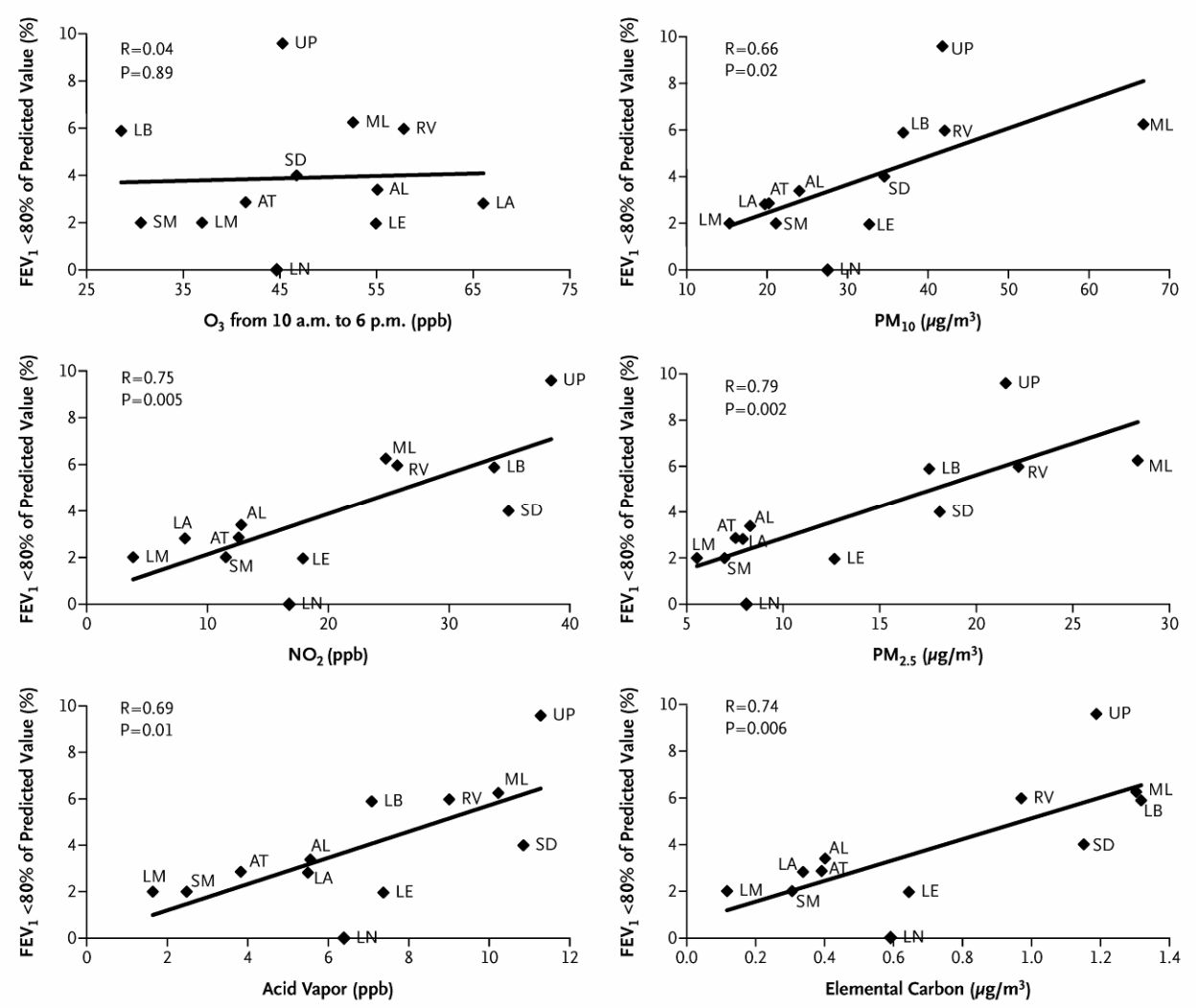
Table 7-4. Characterization of ambient PM concentrations from studies of FEV_1 and long-term exposures.

Study	Location	Mean Annual Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Gauderman et al. (2002, 026013)	12 CHS/CA communities	5-30	
Gauderman et al. (2004, 056569)	12 CHS/CA communities	6-27	
Goss et al. (2004, 055624)	U.S.	13.7	75th: 15.9
Gotschi et al. (2008, 180364)	21 European cities	Range of means across sites: 3.7-44.7 Avg of mean across sites: 16.8	
PM_{10}			
Downs et al. (2007, 092853)	8 cities in Switzerland	Range of means across sites: 9-46 Avg of mean across sites: 21.6	
Gauderman et al. (2002, 026013)	12 CHS/CA communities	Range of means across sites: 13-78 Avg of mean across sites: NR	
Gauderman et al. (2004, 056569)	12 CHS/CA communities	Range of means across sites: 18-68 Avg of mean across sites: NR	
Nordling et al. (2008, 097998)	Sweden	Modeled exposure	
Avol et al. (2001, 020552)	Southern CA/CHS	Range of means across sites: 15.0-66.2	
Rojas-Martinez et al. (2007, 091064)	Mexico City, Mexico	75.6	75th: 92.2 90th: 112.7

The CHS prospectively examined the relationship between air pollutants and lung function (FVC, FEV_1, MMEF) in a cohort (n = 1,759) of children between the ages of 10 and 18 yr, a period of rapid lung development (Gauderman et al., 2004, 056569). Air pollution monitoring stations provided data in each of the 12 study communities from 1994-2000. The results for O_3, PM_{10}, NO_2, $PM_{2.5}$, acid vapor, and EC are depicted in Figure 7-4. In general, copollutant models for any pair of pollutants did not provide a substantially better fit to the data than the corresponding single-pollutant models due to the strong correlation between most pollutants. The pollution-related deficits in the average growth in lung function over the 8-yr period resulted in clinically important deficits in attained lung function at the age of 18.

Downs et al. (2007, 092853) prospectively examined 9,651 randomly selected adults (18-60 yr of age) in eight cities in Switzerland (see alsoAckermann-Liebrich et al., 1997, 077537) to ascertain the relationship between reduced exposure to PM_{10} and age-related decline in lung function (FVC, FEV_1, and FEF_{25-50}). An evaluated statistical dispersion model (Liu et al., 2007, 093093) provided spatially resolved concentrations of PM_{10} that enabled assignment to residential addresses for the participant examinations in 1991 and 2002 that yielded a median decline of 5.3 $\mu g/m^3$ (IQR 4.1-7.5). Decreasing PM_{10} concentrations attenuated the decline in lung function. Effects were greater in tests reflecting small airway function. No other pollutant relationships were evaluated, though a related study indicated that levels of NO_2 also declined over the same period (Ackermann-Liebrich et al., 2005, 087826). Generalized cross-validation essentially chose a linear fit for the concentration-response curve for age-related decline in lung function.

These data show that improvement in air quality may slow the annual rate of decline in lung function in adulthood indicating positive consequences for public health. Further evidence on improvement in respiratory health with reduction in air pollution levels is provided from studies conducted in East Germany related to dramatic emissions reductions after the reunification in 1990 (Fryer and Collins, 2003, 156454; Heinrich et al., 2002, 034825; Sugiri et al., 2006, 088760). This type of "natural experiment" provides additional support for epidemiologic findings that relatively low levels of airborne particles have respiratory effects.



Source: Adapted from Gauderman et al. (2004, 056569)

Figure 7-4. Proportion of 18-yr olds with an FEV_1 below 80% of the predicted value plotted against the average levels of pollutants from 1994 through 2000 in the 12 southern California communities of the Children's Health Study. AL = Alpine; AT = Atascadero; LA = Lake Arrowhead; LB = Long Beach; LE = Lake Elsinore; LM = Lompoc; LN = Lancaster; ML = Mira Loma; RV = Riverside; SD = San Dimas; SM = Santa Maria; UP = Upland.

In a prospective cohort study consisting of school-age children (n = 3,170) who were 8 yr of age at the beginning of the study, had not been diagnosed with asthma, and were located in Mexico City, Rojas-Martinez et al. (2007, 091064) evaluated the association between long-term exposure to PM_{10}, O_3 and NO_2 and lung function growth every 6 mo from April 1996 through May 1999. Exposure data were provided by 10 air quality monitor stations located within 2 km of each child's school. The multipollutant model effect of PM_{10} over the age of 8-10 yr of life in this cohort on FVC, FEV_1, and FEF_{25-75} showed an association. Single pollutant models showed an association between ambient pollutants (O_3, PM_{10} and NO_2) and deficits in lung function growth. The association between PM_{10} and FEF_{25-75} was not statistically significant. While the estimates from copollutant models were not substantially different than single pollutant models, independent effects for pollutants could not be estimated accurately because the traffic-related pollutants were correlated.

Although no $PM_{2.5}$ data were presented in this study, in a separate study Chow et al. (2002) report that during the winter of 1997 approximately 50% of PM_{10} was in the $PM_{2.5}$ fraction in Mexico City.

Gotschi et al. (2008, 156485) examined the relationship between air pollution and lung function in adults in the European Community Respiratory Health Survey (ECRHS). FEV_1 and FVC were assessed at baseline and after 9 yr of follow-up from 21 European centers (followed-up sample n = 5,610). No statistically significant associations were found between city-specific annual mean $PM_{2.5}$ and average lung function levels which is in contrast to the results seen by Ackermann-Liebrich (1997, 077537) (SAPALDIA) and Schikowski et al. (2005, 088637) (SALIA) which compared across far more homogenous populations than for the population assessed in the ECRHS. Misclassification and confounding may partially explain the discrepancy in findings.

In a birth cohort (n = 2,170) in Oslo, Norway, Oftedal et al. (2008, 093202) examined effects of exposure to $PM_{2.5}$ and PM_{10} on lung function (FVC, FEV_1, $FEF_{50\%}$). Spirometry was performed in 2,307 children aged 9-10 yr in 2001-2002. Residential air pollution levels over the time period 1992-2002 were calculated using EPISODE dispersion models to provide three time scales of exposure: (1) first year of life; (2) lifetime exposure; and (3) just before the lung function test. Only single pollutant models were evaluated because air pollutants were highly correlated (r = 0.83-0.95). PM exposure was associated with changes in adjusted peak respiratory flow, especially in girls. No effect was found for forced volumes. Adjusting for contextual socioeconomic factors diminished associations. Results for PM_{10} were similar to those for $PM_{2.5}$.

In an exploratory study, Mortimer et al. (2008, 187280) examined the association of prenatal and lifetime exposure to air pollutants using geocoded monthly average PM_{10} levels with pulmonary function in a San Joaquin Valley, California cohort of 232 children (ages 6-11 yr) with asthma. First and second trimester PM_{10} exposures (based on monthly average concentrations) had a negative effect on pulmonary function and may relate to prenatal exposures affecting the lungs as they begin to develop at 6-wk gestation.

Dales et al. (2008, 156378) in a cross-sectional prevalence study examined the relationship of pulmonary function and PM measures, other pollutants, and indicators of motor vehicle emissions in Windsor, Ontario, in a cohort of 2,402 school children. $PM_{2.5}$ and PM_{10} concentrations were estimated for each child's residence at the postal code level. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7.0% decrease in FVC expressed in a percentage of predicted.

In Leicester, England, investigators examined the carbon content of airway macrophages in induced sputum in 64 of 114 healthy 8-15 year-old children (Grigg et al., 2008, 156499; Kulkarni et al., 2006, 089257). The carbon content of airway macrophages (Finch et al., 2002, 054603; Strom et al., 1990, 157020) was used as a marker of individual exposure to PM_{10}. Near each child's home, exposure to PM_{10} was estimated using a statistical dispersion model (Pierse et al., 2006, 088757). The authors reported a dose-dependent inverse association between the carbon content of airway macrophages and lung function in children and found no evidence that reduced lung function itself causes an increase in carbon content. Consistent results were obtained for both FVC and FEF_{25-75}. Caution should be used when interpreting these results as the accuracy of the estimates on individual PM_{10} exposures were not validated; there is potential for confounding by ethnic origin; and there is concern that the magnitude of the changes in pulmonary function associated with increased particle area appear large (Boushey et al., 2008, 192162).

Nordling et al. (2008, 097998) discussed above in the respiratory symptoms section, also reported that lower PEF at age 4 was associated with exposure to traffic-related PM_{10} (-8.93 L/min [95% CI: -17.78 to -0.088]). Goss et al. (2004, 055624), discussed in Section 7.3.1.1, found strong inverse relationships between FEV_1 and $PM_{2.5}$ concentrations in both cross-sectional and longitudinal analyses.

In summary, recent studies have greatly expanded the evidence available for the 2004 PM AQCD. The earlier CHS studies followed young children for 2-4 yr. New analyses have been conducted that include longer follow-up periods of this cohort through 18 yr of age (considered early adulthood for lung development (Stanojevic et al., 2008, 157007) and provide evidence that effects from exposure to $PM_{2.5}$ persist into early adulthood. Longitudinal studies follow effects over time and are considered to provide the best evidence as opposed to studies across communities as in cross-sectional studies. The longitudinal cohort studies in the 2004 PM AQCD provided data for children in one location in one study and new longitudinal studies have been conducted in other locations.

Gauderman et al. (2004, 056569) reported that $PM_{2.5}$ exposure was associated with clinically and statistically significant deficits in FEV_1 attained at the age of 18 yr. Clinical significance was

defined as a FEV_1 below 80% of the predicted value, a criterion commonly used in clinical settings to identify persons at increased risk for adverse respiratory conditions. This clinical aspect is an important enhancement over the earlier results reported in the 2004 PM AQCD. Further, the association reported in this study that evaluated the 8-yr time period into early adulthood not only provided evidence for the persistence of the effect, but in addition the strength and robustness of the outcomes were more positive, larger, and more certain than previous CHS studies of shorter follow-up.

Supporting this result are new longitudinal cohort studies conducted by other researchers in other locations with different methods. Though these studies report results for PM_{10}, available data discussed above indicate that the majority of PM_{10} is composed of $PM_{2.5}$ in these areas. New studies provide positive results from Mexico City, Sweden, and a national cystic fibrosis cohort in the U.S. One study reported null results in a European cohort described as having potential misclassification and confounding concerns as well as lacking a homogenous population potentially rendering the outcome as non-informative. A natural experiment in Switzerland, where PM levels had decreased, reported that improvement in air quality may slow the annual rate of decline in lung function in adulthood, indicating positive consequences for public health. These natural experiments are considered especially supportive.

The relationship between long-term PM exposure and decreased lung function is thus seen during lung growth and lung development in school-age children into adulthood. At adult ages studies continue to show a relationship between decreased lung function and long-term PM exposure. Some newer studies attempting to study the relationship of long-term PM exposure from birth through preschool are reporting a relationship. Thus, the impact of long-term PM exposure is seen over the time period of lung function growth and development and the decline of lung function with aging.

Overall, effect estimates from these studies are negative (i.e., indicating decreasing lung function) and the pattern of effects are similar between the studies for FVC and FEV_1. Thus, the data are consistent and coherent across several designs, locations, and researchers. With cautions noted, the results relating carbon content of airway macrophages to decreased measures of pulmonary function add plausibility to the epidemiologic findings. Some new studies are using individual estimates of exposure to ambient PM to reduce the impact of exposure error (Downs et al., 2007, 092853; Jerrett et al., 2005, 087381).

As was found in the 2004 PM AQCD, the studies report associations with $PM_{2.5}$ and PM_{10}, while most did not evaluate $PM_{10-2.5}$. Associations have been reported with fine particle components, particularly EC and OC. Source apportionment methods generally have not been used in these long-term exposure studies. However, numerous studies have evaluated exposures to PM related to traffic or motor vehicle sources. For example, Meng et al. (2007, 093275) investigated the associations between traffic and outdoor pollution levels and poorly controlled asthma among adults who were respondents to the California Health Interview Survey and found associations for traffic density and PM_{10}, but not $PM_{2.5}$.

7.3.2.2. Toxicological Studies

Urban Air

One new study evaluated the effects of chronic exposure to ambient levels of urban particles on lung development in the mouse (Mauad et al., 2008, 156743). Both functional and anatomical indices of lung development were measured. Male and female BALB/c mice were continuously exposed to ambient or filtered Sao Paolo air for 8 mo. Concentrations in the "polluted chamber" versus "clean chamber" were 16.8 versus 2.9 $\mu g/m^3$ $PM_{2.5}$. Thus PM levels were reduced by filtration but not entirely eliminated. Ambient concentrations of CO, NO_2 and SO_2 were 1.7 ppm, 89.4 $\mu g/m^3$ and 8.1 $\mu g/m^3$, respectively. Concentrations of gaseous pollutants were assumed to be similar to ambient levels in both chambers. After 4 mo, the animals were mated and the offspring were divided into 4 groups to provide for a prenatal exposure group, a postnatal exposure group, a pre and postnatal exposure group and a control group. Animals were sacrificed at 15 and 90 days of age for histological analysis of lungs. Pulmonary pressure-volume measurements were also conducted in the 90-day-old offspring. Statistically significant reductions in inspiratory and

expiratory volumes were found in the group receiving both prenatal and postnatal exposure, but not in the groups receiving only prenatal exposure or only postnatal exposure, compared with controls. These changes in pulmonary function correlated with anatomical changes which are discussed in Section 7.3.5.1.

Diesel Exhaust

Li et al. (2007, 155929) exposed BALB/c and C56BL/6 mice to clean air or to low-dose DE (at a PM concentration of 100 $\mu g/m^3$) for 7 h/day and 5 days/week for 1, 4 and 8 wk. Average gas concentrations were reported to be 3.5 ppm CO, 2.2 ppm NO_2, and less than 0.01 ppm SO_2. Airway hyperresponsiveness (AHR) was evaluated by whole-body plethysmography at Day 0 and after 1, 4 and 8 wk of exposure. Short-term exposure responses are discussed in Section 6.3.2.3, 6.3.3.3 and 6.3.4.2. The increased sensitivity of airways to methacholine (measured as Penh) seen in C57BL/6 but not BALB/c mice at 1 week was also seen at 4 wk but not at 8 wk. This study suggests that adaptation occurs during prolonged DE exposure. Influx of inflammatory cells, markers of oxidative stress and effects of antioxidant intervention were also evaluated (Sections 7.3.3.2 and 7.3.4.1). Although no attempt was made in this study to determine the effects of gaseous components of DE on the measured responses, concentrations of gases were very low suggesting that PM may have been responsible for the observed effects.

In many animal studies changes in ventilatory patterns are assessed using whole-body plethysmography, for which measurements are reported as enhanced pause (Penh). Some investigators report increased Penh as an indicator of AHR, but these are inconsistently correlated and many investigators consider Penh solely an indicator of altered ventilatory timing in the absence of other measurements to confirm AHR. Therefore use of the terms AHR or airway responsiveness has been limited to instances in which the terminology has been similarly applied by the study investigators.

Gottipolu et al. (2009, 190360) exposed WKY and SH rats to filtered air or DE (particulate concentration 500 and 2,000 $\mu g/m^3$) for 4 h/day and 5 days/wk over a 4-wk period. Concentrations of gases were 1.3 and 4.8 ppm CO, NO <2.5 and 5.9 ppm NO, <0.25 and 1.2 ppm NO_2, 0.2 and 0.3 ppm SO_2 for low and high PM exposures, respectively. Particle size, measured as geometric median number and volume diameters, was 85 and 220 nm, respectively. No DE-related effects were found for breathing parameters measured by whole-body plethysmography. Other pulmonary effects are described in Sections 7.3.3.2 and 7.3.5.1.

Woodsmoke

One study evaluated the effects of subchronic woodsmoke exposure on pulmonary function in Brown Norway rats. Rats were exposed 3 h/day and 5 days/week for 4 and 12 wk to air or to concentrated wood smoke from the pinyon pine which is native to the U.S. Southwest (Tesfaigzi et al., 2002, 025575). PM concentrations in the woodsmoke were 1,000 and 10,000 $\mu g/m^3$. The particles in this woodsmoke had a bimodal size distribution with the smaller size fraction (74%) characterized by a MMAD of 0.405 µm and the larger size fraction (26%) characterized by a MMAD of 6.7-11.7 µm. Many of these larger particles would not be inhalable by the rat since 8 µm MMAD particles are about 50% inhalable (Ménache et al., 1995, 006533). Concentrations of gases were reported to be 15-106.4 ppm CO, 2.2-18.9 ppm NO, 2.4-19.7 ppm NO_X and 3.5-13.8 ppm total hydrocarbon in these exposures. Respiratory function measured by whole-body plethysmography demonstrated a statistically significant increase in total pulmonary resistance in rats exposed to 1000 $\mu g/m^3$ woodsmoke. Additional effects were found at 10,000 $\mu g/m^3$. Inflammatory and histopathological responses were also evaluated (Sections 7.3.3.2 and 7.3.5.1).

7.3.3. Pulmonary Inflammation

7.3.3.1. Epidemiologic Studies

One epidemiologic study examined the relationship of airway inflammation (eNO) and PM measures, other pollutants, and indicators of motor vehicle emissions in Windsor, Ontario (Dales et al., 2008, 156378). This cohort of 2,402 school children estimated $PM_{2.5}$ and $PM_{10-2.5}$ for each child's residence at the postal code level with an evaluated statistical model (Wheeler et al., 2006, 103905). Each 10 μg/m^3 increase in 1-yr $PM_{2.5}$ was associated with a 39% increase in eNO ($p = 0.058$). Associations between eNO and $PM_{10-2.5}$ were positive but not statistically significant.

7.3.3.2. Toxicological Studies

CAPs Studies

A set of subchronic studies involved exposure of normal (C57BL1/6) mice, ApoE$^{-/-}$ and the double-knockout ApoE$^{-/-}$/LDLR$^{-/-}$ mice to Tuxedo, NY CAPs for 5-6 month (March, April or May through September 2003 (Lippmann et al., 2005, 087452). The average $PM_{2.5}$ exposure concentration was 110 μg/m^3. Animals were fed a normal chow diet during the CAPs exposure period. No pulmonary inflammation was observed in response to CAPs exposure as measured by BALF cell counts and histology. The lack of a persistent pulmonary response may have been due to adaptation of the lung following repeated exposures. In fact, a parallel study examined CAPs-related gene expression in the double-knockout animals and found upregulation of numerous genes in lung tissue (Gunnison and Chen, 2005, 087956). An in vitro study conducted simultaneously found daily variations in CAPs-mediated NF-κB activation in cultured human bronchial epithelial cells, suggesting that transcription factor-mediated gene upregulation could occur in response to CAPs (Maciejczyk and Chen, 2005, 087456). It should be noted that significant cardiovascular effects were observed in these subchronic studies which are discussed in Section 7.2.1.2.

Araujo et al. (2008, 156222) compared the relative impact of UF (0.01-0.18 μm) versus fine (0.01-2.5 μm) PM inhalation in ApoE$^{-/-}$ mice following a 40 day exposure (5 h/day×3 days/wk for 75 total hours). Animals were fed a normal chow diet and exposed to PM from November 3 -December 12, 2005 in a mobile inhalation laboratory that was parked 300 m from the 110 Freeway in downtown Los Angeles. Particles were concentrated to ~440 μg/m^3 for $PM_{2.5}$ exposures and ~110 μg/m^3 for the UF exposures, representing a roughly 15-fold increase in concentration from ambient levels; the number concentration of PM in the fine and UF chambers were roughly equivalent (4.56×10^5 and 5.59×10^5 particles/cm^3, respectively). Over 50% of the UFPs were comprised of OC compared to only 25% for $PM_{2.5}$. No major increase in BALF inflammatory cells was found in response to PM. However UFP exposure resulted in significant cardiovascular and systemic effects (Section 7.2.1.2).

Diesel Exhaust

Gottipolu et al. (2009, 190360) exposed WKY and SH rats to filtered air or DE for 4 wk as described in Section 7.3.2.2. Previous studies from this laboratory have shown enhanced effects of PM in SH compared with WKY rats. Although the main focus of this recent study was on DE-induced mitochondrial oxidative stress and hypertensive gene expression in the heart (Section 7.2.7.1), some pulmonary effects were also found. Subchronic exposure to DE resulted in a dose-dependent increase in BALF neutrophils in both rat strains although levels of measured cytokines were not altered. Histological analysis of lung tissue from rats exposed to the higher concentration of DE demonstrated accumulation of particle-laden macrophages as well as focal alveolar hyperplasia and inflammation. Effect on indices of injury are discussed in Section 7.3.5.1.

Ishihara and Kagawa (2003, 096404) exposed Wistar rats to filtered air and DE containing 200, 1,000 and 3,000 μg/m^3 PM for 16 h/day and 6 days/wk for 6, 12, 18 or 24 mo. The mass median particle diameter was reported to be between 0.3 and 0.5 μm. Concentrations of gases ranged from

2.93-35.67 ppm NO_X, 0.23-4.57 ppm SO_2, 1.8-21.9 ppm CO in the DE exposures. Statistically significant increases in total numbers of inflammatory cells and neutrophils in BALF were observed beginning at 6-12 mo of exposure to DE containing 1,000 and 3,000 µg/m^3 PM. When rats were exposed to DE containing 1,000 µg/m^3 PM, which was filtered to remove PM, the inflammatory cell response was significantly diminished. These results implicate the PM fraction of DE as a key determinant of the inflammation. The PM fraction was also found to mediate the increase in protein levels, the decrease in PGE_2 levels and alterations in mucus and surfactant components observed in BALF (Section 7.3.5.1).

Li et al. (2007, 155929) exposed BALB/c and C56BL/6 mice to low dose DE as described in Section 7.3.2.2. for 1, 4 and 8 wk. Increases in numbers of BALF macrophages and total inflammatory cells were observed in BALB/c mice at 8 wk but not 4 wk of DE exposure. Persistent increases in numbers of BALF neutrophils and lymphocytes were observed in both strains at 4 and 8 wk of DE exposure. Corresponding increases in BALF cytokines differed between the two strains. These results should be interpreted with caution since comparisons were made with Day 0 controls rather than age-matched controls. No histopathological changes in the lungs were seen at any time point after DE exposure. This study demonstrated differences in pulmonary responses to low dose DE between two mouse strains. AHR, pulmonary inflammation, markers of oxidative stress and effects of antioxidant intervention were also evaluated (Sections 7.3.2.2 and 7.3.4.1). Although no attempt was made in this study to determine the effects of gaseous components of DE on the measured responses, concentrations of gases were very low suggesting that PM may have been responsible for the observed effects.

In a study by Hiramatsu et al. (2003, 155846), BALB/c and C57BL/6 mice were exposed to DE (PM concentrations 100 and 3,000 µg/m^3) for 1 or 3 mo. Concentrations of gases were reported to be 3.5-9.5 ppm CO, 2.2-14.8 ppm NO_X, and less than 0.01 ppm SO_2. Modest increases in BALF neutrophils and lymphocytes were observed in response to DE in both mouse strains at 1 and 3 mo. Histological analysis demonstrated diesel exposure particle-laden alveolar macrophages in alveoli and peribronchial tissues at both time points. Bronchus-associated lymphoid tissue developed after 3-month exposure to the higher concentration of DE in both mouse strains. Mac-1 positive cells (a marker of phagocytic activation of alveolar macrophages) were also increased in BALF of BALB/c mice exposed to the higher concentration of DE for 1 and 3 mo. Increased expression of several cytokines and decreased expression of iNOS mRNA was observed in DE-exposed mice at 1 and 3 mo. NF-κB activation was also noted following 1-month exposure to the lower concentration of DE. No attempt was made in this study to determine the responses to gaseous components of the DE.

In a study by Reed et al. (2004, 055625), healthy Fisher 344 rats and A/J mice were exposed to DE (PM concentration = 30, 100, 300 and 1,000 µg/m^3) by whole body inhalation for 6 h/day, 7 days/wk for either 1 week or 6 mo. Concentrations of gases were reported to be 2.0-45.3 ppm NO, 0.2-4.0 ppm NO_2, 1.5-29.8 ppm CO and 8-365 ppb SO_2. Short-term responses are discussed in Section 6.3.3.3 and 6.3.7.2, and sub-chronic systemic effects are presented in Section 7.2.4.1. Six months of exposure resulted in no measurable effects on pulmonary inflammation. However numerous black particles were observed within alveolar macrophages after 6 mo of exposure.

Seagrave et al. (2005, 088000) evaluated pulmonary responses in male and female CDF (F-344)/CrlBR rats exposed 6 h/day for 6 mo to filtered air or DE at concentrations ranging from 30-1000 µg/m^3 PM. Concentrations of gases were reported for the highest exposure as 45.3 ppm NO, 4.0 ppm NO_2, 29.8 ppm CO and 2.2 ppm total vapor hydrocarbon. No changes in BALF cells were noted. A small decrease in TNF-α was seen in BALF of female rats exposed to the highest concentration of DE for 6 mo. Pulmonary injury also was evaluated (Section 7.3.5.1). Thus changes in BALF markers were modest and gender-specific.

Woodsmoke

Seagrave et al. (2005, 088000) also evaluated pulmonary responses in male and female CDF (F344)/CrlBR rats exposed 6 h/day for 6 mo to filtered air or hardwood smoke concentrations ranging from 30-1,000 µg/m^3 PM. Concentrations of gases were reported for the highest exposure as 3.0 ppm CO and 3.1 ppm total vapor hydrocarbon. A small increase in BALF neutrophils was observed in male rats exposed to the lowest concentration of hardwood smoke. Female rats exhibited a decrease in BALF macrophage inflammatory protein-2 (MIP-2) at the highest concentration of hardwood smoke. Pulmonary injury also was evaluated (Section 7.3.5.1). In general, responses to

hardwood smoke were more remarkable than responses to DE seen in a parallel study. However these gender-specific responses were modest and difficult to interpret.

In a study by Reed et al. (2006, 156043), Fisher 344 rats, SHR rats, A/J mice and C57BL/6 mice were exposed to clean air or hardwood smoke (PM concentrations 30, 100, 300 and 1,000 $\mu g/m^3$) by whole body inhalation for 6 h/day, 7 days/wk for either 1 week or 6 mo. Concentrations of gases ranged from 229.0-14887.6 mg/m^3 for CO, 54.9-139.3 $\mu g/m^3$ for ammonia, and 177.6- 3455.0 $\mu g/m^3$ nonmethane VOC in these exposures. Short-term responses are discussed in Section 6.3.7.2 and sub-chronic effects are presented in Section 7.2.4.1. Histological analysis of lung tissue showed minimal increases in alveolar macrophages. The effects of hardwood smoke on bacterial clearance are discussed below (Section 7.3.7.2).

Another study evaluated the effects of subchronic woodsmoke exposure in Brown Norway rats and is described in detail in Section 7.3.2.2 (Tesfaigzi et al., 2002, 025575). Numbers of alveolar macrophages in BALF were significantly increased in rats exposed to 1,000 $\mu g/m^3$ woodsmoke for 12 wk, but no changes were seen in numbers of other inflammatory cells. A large percent of BALF macrophages contained carbonaceous material. Histological analysis of lung tissue showed minimal to mild inflammation in the epiglottis of the larynx in rats exposed to both concentrations of woodsmoke.

Ramos et al. (2009, 190116) examined the effects of subchronic woodsmoke exposure on the development of emphysema in guinea pigs. Inflammation is thought to be involved in the pathogenesis of this form of COPD. Statistically significant increases in total numbers of BALF cells were observed in guinea pigs exposed to smoke for 1-7 mo, with numbers of macrophages increased at 1-4 mo and numbers of neutrophils increased at 4-7 mo. At 4 mo, alveolar mononuclear phagocytic and lymphocytic peribronchiolar inflammation were observed by histological analysis of lung tissue. This study is discussed in depth in Section 7.2.5.1.

Model Particles

Wallenborn et al. (2008, 191171) examined the pulmonary, cardiac and systemic effects of subchronic exposure to particulate $ZnSO_4$. WKY rats were exposed nose-only to 10, 30, or 100 $\mu g/m^3$ UFP of $ZnSO_4$ for 5 h/day and 3 day/wk over a 16-wk period. Particle size was reported to be 31-44 nm measured as number median diameter. No changes in pulmonary inflammation or injury were observed although cardiac effects were noted (Section 7.2.7.1). This study possibly demonstrates a direct effect of $ZnSO_4$ on extrapulmonary systems, as suggested by the lack of pulmonary effects.

7.3.4. Pulmonary Oxidative Response

7.3.4.1. Toxicological Studies

Urban Air

One new study evaluated the effects of subchronic exposure to ambient levels of urban particles on the development of emphysema in papain-treated mice (Lopes et al., 2009, 190430). Since oxidative stress is thought to contribute to the development of emphysema, 8-isoprostane levels were measured in lung tissue from the four groups of mice used in this study. A statistically significant increase in 8-isoprostane, a marker of oxidative stress, was observed in lungs from mice treated with papain and exposed to ambient air compared with the other groups of mice. This study is described in greater depth in Section 7.3.5.1.

Diesel Exhaust

Li et al. (2007, 155929) exposed mice to low dose DE for 1, 4 and 8 wk as described in Section 7.3.2.2. Markers of oxidative stress and effects of antioxidant intervention were evaluated in this model. While HO-1 mRNA and protein were increased in lung tissues of both mouse strains after 1 week of DE exposure (Section 6.3.4.2), at 8 wk of DE exposure, HO-1 protein levels remained high in C57BL/6 mice but returned to control values in BALB/c mice. This study demonstrates differences in pulmonary responses to low dose DE between two mouse strains. Furthermore, this study suggests that adaptation occurs in BALB/c mice during prolonged DE exposure since the increase in HO-1 protein seen in both strains at 1 week of exposure was only seen in C57BL/6 mice at 8 wk. AHR (Section 7.3.2.2) and pulmonary inflammation (Section 7.3.3.2) were also evaluated. Although no attempt was made in this study to determine the effects of gaseous components of DE on the measured responses, concentrations of gases were very low. This suggests that PM may have been responsible for the observed effects.

7.3.5. Pulmonary Injury

7.3.5.1. Toxicological Studies

Urban Air

One new study evaluated the effects of chronic exposure to ambient levels of urban particles on lung development in the mouse (Mauad et al., 2008, 156743). Both functional and anatomical indices of lung development were measured in mice exposed prenatally and/or postnatally as described in Section 7.3.2.2. Animals were sacrificed at 15 and 90 days of age for histological analysis of lungs. Histological analysis demonstrated the presence of mild foci of macrophages containing black dots of carbon pigment in the prenatal and postnatal exposure group at 90 days. In addition, the alveolar spaces of 15-day old mice in the prenatal and postnatal exposure group were enlarged compared with controls. Morphometric analysis demonstrated statistically significant decreases in surface to volume ratio at 15 and 90 days in the prenatal and postnatal exposure group compared with controls. Since alveolarization is normally complete by 15 days of age, these results suggest incomplete alveolarization in the 15-day-old group and an enlargement of air spaces in the 90-day-old group. These anatomical changes correlated with decrements in pulmonary function which are discussed in Section 7.3.2.2.

Prolonged exposure to low levels of ambient air pollution beginning in early life has been linked to secretory changes in the nasal cavity of mice, specifically increased production of acidic mucosubstances (Pires-Neto et al., 2006, 096734). Six-day-old Swiss mice were continuously chamber exposed to ambient or filtered São Paulo air for 5 mo. Concentrations in the "polluted chamber" versus "clean chamber" were (in $\mu g/m^3$) 59.52 versus 37.08 for NO_2, 12.52 versus 0 for BC, and 46.49 versus 18.62 for $PM_{2.5}$. Thus, pollutant levels were reduced by filtration but not entirely eliminated. Compared to filtered air, exposure to ambient air resulted in increased total mucus and acidic mucus in the epithelium lining the nasal septum, but no statistically significant differences in other parameters (amount of neutral mucus, volume proportions of neutral mucus, total mucus, or nonsecretory epithelium, epithelial thickness, or ratio between neutral and acidic mucus). The physicochemical properties of mucus glycoproteins are critical to the protective function of the airway mucus layer. Acidified mucus is more viscous, and is associated with a decrease in mucociliary transport. Thus acidic mucosubstances may represent impaired defense mechanisms in the respiratory tract.

One new study evaluated the effects of subchronic exposure to ambient levels of urban particles on the development of emphysema in papain-treated mice (Lopes et al., 2009, 190430). Emphysema is a form of COPD caused by the destruction of extracellular matrix in the alveolar region of the lung which results in airspace enlargement, airflow limitation and a reduction of the gas-exchange area of the lung. Inflammation, oxidative stress, protease imbalance and apoptosis are thought to contribute to the development of emphysema. In this study, male BALB/c mice were

continuously exposed to ambient or filtered Sao Paulo air for 2 mo. Concentrations of $PM_{2.5}$ in the "polluted chamber" versus "clean chamber" were 33.86 ± 2.09 versus 2.68 ± 0.38 μg/m^3. Thus filtration reduced PM levels considerably. Ambient concentrations of CO and SO_2 were 1.7 ppm and 16.2 μg/m^3 respectively. No significant difference was observed in the concentrations of NO_2 in the "polluted chamber" versus "clean chamber" (60-80 μg/m^3). Half of the mice were pre-treated with papain by intranasal instillation in order to induce emphysema. Morphometric analysis of lung tissue demonstrated a statistically significant increase in mean linear intercept, a measure of airspace enlargement, in papain-treated mice compared with saline-treated controls exposed to filtered air. While exposure to ambient air failed to increase mean linear intercept values in saline-treated mice, mean linear intercept values were significantly increased in papain-treated mice exposed to ambient air compared with papain-treated mice exposed to filtered air. A similar pattern of responses was observed for the volume proportion of collagen and elastin fibers in alveolar tissue, which are markers of alveolar wall remodeling. Lung immunohistochemical analysis demonstrated an effect of papain, but not ambient air, on macrophage cell density and matrix metalloproteinase 12-positive cell density. No differences in caspase-3 positive cells, a marker of apoptosis, were observed between the four groups of mice. Oxidative stress was evaluated in this model as described in Section 7.3.4.1. Taken together, results of this study demonstrate that urban levels of PM, mainly from traffic sources, worsen protease-induced emphysema in an animal model.

Pulmonary vascular remodeling, measured by a decrease in the lumen to wall ratio, was observed in mice exposed to ambient São Paulo air for 4 mo (Lemos et al., 2006, 088594). This study is described in greater detail in Section 7.2.1.2.

Kato and Kagawa (2003, 089563) exposed Wistar rats to roadside air contaminated mainly with automobile emissions (55.7-65.2 ppb NO_2 and 63-65 μg/m^3 suspended PM [SPM]) and examined the effects on respiratory tissue after 24, 48, or 60 wk of exposure. The surface of the lungs was light gray in color after all durations of exposure, and BC particle deposits accumulated with prolonged exposure. These characteristics were not evident in filtered air-exposed control animals, although filtered air contained low levels of air pollutants (≤ 6.2 ppb NO_2 and 15 μg/m^3 SPM). The most common change observed using transmission electron microscopy was the presence of particle laden (anthracotic) alveolar macrophages, or anthracosis, in a wide range of pulmonary tissues, including the submucosa, tracheal- and bronchiole-associated lymph nodes, alveolar wall and space, pleura, and perivascular connective tissue. These changes were evident after 24 wk and increased with duration of exposure. Other changes included increases in the number of mucus granules in goblet cells, mast cell infiltration (but no degranulation) after 24 wk, increased lysosomes in ciliated cells, some altered morphology of Clara cells, and hypertrophy of the alveolar walls after 48 wk. No goblet cell proliferation was observed, but slight, variable acidification of mucus granules appeared after 24 and 48 wk and disappeared after 60 wk. Anthracotic macrophages were seen in contact with plasma cells and lymphocytes in the lymphoid tissue, suggesting immune cell interaction in the immediate vicinity of particles. Even after 60 wk, no lymph node anthracosis was observed in the filtered air group.

In a post-mortem study of lung tissues from 20 female lifelong residents of Mexico City, a high PM locale, histology demonstrated significantly greater amounts of fibrous tissue and muscle in the airway walls compared to subjects from Vancouver (Churg et al., 2003, 087899), a city with relatively low PM levels. Electron microscopy showed carbonaceous aggregates of UFPs, which the authors conclude penetrate into and are retained in the walls of small airways. The study shows an association between retained particles and airway remodeling in the form of excess muscle and fibrotic walls. The subjects were deemed suitable for examination based on never-smoker status, no use of biomass fuels for cooking, no known occupational particle/dust exposure, death by cause other than respiratory disease, and extended residence in each locale (lifelong for Mexico City and >20 yr for Vancouver). However, subjects from the two locales were not matched with respect to ethnicity, sex (20 females from Mexico City versus 13 females and 7 males from Vancouver), or mean age at death (66 ± 9 versus 76 ± 11), and other possibly influential factors such as exercise or diet were not considered.

Diesel Exhaust

Gottipolu et al. (2009, 190360) exposed WKY and SH rats to filtered air or DE as described in Section 7.3.2.2. Previous studies from this laboratory have shown enhanced effects of PM in SH

compared with WKY rats. Although the main focus of this recent study was on DE-induced mitochondrial oxidative stress and hypertensive gene expression in the heart (Section 7.2.7.1), some pulmonary effects were found. Inflammatory effects are described in Section 7.3.3.2. GGT activity in BALF was increased in both strains in response to the higher concentration of DE. No DE-related changes were observed in BALF protein or albumin. Histological analysis of lung tissue from rats exposed to the higher concentration of DE demonstrated accumulation of particle-laden macrophages as well as focal alveolar hyperplasia and inflammation. No effects on indices of pulmonary function were observed (Section 7.3.2.2.)

Ishihara and Kagawa (2003, 096404) exposed rats to DE for up to 24 mo as described in Section 7.3.3.2. A statistically significant increase in BALF protein was observed at 12 mo of exposure to DE containing 1,000 $\mu g/m^3$ PM. This response was attenuated when the DE was filtered to remove PM. Pulmonary inflammation was noted and is described in Section 7.3.3.2.

Seagrave et al. (2005, 088000) evaluated pulmonary responses in rats exposed to DE for up to 6 mo as described in Section 7.3.3.2. A small increase in LDH was seen in BALF of female rats exposed to the highest concentration of DE for 6 mo. Pulmonary inflammation was also evaluated (Section 7.3.3.2). The changes in BALF markers in this study were modest and gender-specific.

Gasoline Exhaust

Reed et al. (2008, 156903) examined a variety of health effects following subchronic inhalation exposure to gasoline engine exhaust. Male and female CDF (F344)/CrlBR rats, SHR rats and male C57BL/6 mice were exposed for 6 h/day and 7 days/wk for a period of 3 days-6 mo. The dilutions for the gasoline exhaust were 1:10, 1:15 and 1:90; filtered PM was at the 1:10 dilution. PM mass ranged from 6.6 to 59.1 $\mu g/m^3$, with the corresponding number concentration between 2.6×10^4 and 5.0×10^5 particles/cm^3. Concentrations of gases ranged from 12.8-107.3 ppm CO, 2.0-17.9 ppm NO, 0.1-0.9 ppm NO_2, 0.09-0.62 ppm SO_2 and 0.38-3.37 ppm NH_3. Other effects are described in Sections 7.2.4.1 and 7.3.6.1. No pulmonary inflammation or histopathological changes were noted in the F344 rats and A/J mice, except for a time-dependent increase in the number of macrophages containing PM. However statistically significant increases of 47% and 29% in BALF LDH were observed in female and male F344 rats, respectively, after 6 mo of exposure to the highest concentration of engine exhaust. This response was absent when gasoline exhaust was filtered, implicating PM as a key determinant of this response. In addition, exposure to the highest concentration of gasoline exhaust resulted in statistically significant decreases in hydrogen peroxide and superoxide production in unstimulated and stimulated BALF macrophages. Hypermethylation of lung DNA was observed in male F344 rats following 6 mo of exposure to gasoline exhaust containing 30 $\mu g/m^3$ PM. This response was PM-dependent since it was absent in mice exposed to filtered gasoline exhaust. The significance of this epigenetic change in terms of respiratory health effects is not known. However, altered patterns of DNA methylation can affect gene expression and are sometimes associated with altered immune responses and/or the development of cancer.

Woodsmoke

Seagrave et al. (2005, 088000) also evaluated pulmonary responses in rats exposed to hardwood smoke for 6 mo as described in Section 7.3.3.2. Increases in BALF LDH and protein were seen in male but not female rats. Female rats exhibited a decrease in BALF glutathione at the highest concentration of hardwood smoke. Decreases in BALF alkaline phosphatase were found in both males and females exposed to 1,000 $\mu g/m^3$ hardwood smoke. Male rats exposed to 100 and 300 $\mu g/m^3$ hardwood smoke exhibited a decrease in BALF β-glucuronidase activity. Pulmonary inflammation was also evaluated (Section 7.3.3.2). These changes in BALF markers in this study were modest and gender-specific.

Another study evaluated the effects of subchronic woodsmoke exposure in Brown Norway rats as described in Section 7.3.2.2. (Tesfaigzi et al., 2002, 025575). Exposure to 1,000 $\mu g/m^3$ woodsmoke for12 wk resulted in a statistically significant increase in Alcian Blue- (AB) and Periodic Acid Schiff- (PAS) positive airway epithelial cells compared to controls, indicating an increase in mucous secretory cells containing neutral and acid mucus, respectively. More significant histopathological responses were found following exposure to 10,000 $\mu g/m^3$ of DE. Pulmonary

function and inflammation were evaluated also but are not discussed here due to the extremely high exposure level (Sections 7.3.2.2. and 7.3.3.2).

Ramos et al. (2009, 190116) examined the effects of subchronic woodsmoke exposure on the development of emphysema in guinea pigs. In particular, the involvement of macrophages and macrophage-derived MMP in woodsmoke-related responses was investigated. Guinea pigs were exposed to ambient air or to whole smoke from pine wood for 3 h/day and 5 days/wk over a 7-month period. PM_{10} and $PM_{2.5}$ concentrations in the exposure chambers were reported to be 502 ± 34 and 363 ± 23 $\mu g/m^3$, respectively, while the concentration of CO was less than 80 ppm. COHb levels were reported to be 6% in controls and 15-20% in smoke-exposed guinea pigs. Statistically significant decreases in body weight were observed in guinea pigs exposed to smoke for 4 or more months compared with controls. Statistically significant increases in total numbers of BALF cells were observed in guinea pigs exposed to smoke for 1-7 mo, with numbers of macrophages increased at 1-4 month and numbers of neutrophils increased at 4-7 mo. At 4 mo, alveolar mononuclear phagocytic and lymphocytic peribronchiolar inflammation, as well as bronchiolar epithelial and smooth muscle hyperplasia, were observed by histological analysis of lung tissue. Emphysematous lesions, smooth muscle hyperplasia and pulmonary arterial hypertension were noted at 7 mo. Morphometric analysis of lung tissue demonstrated statistically significant increases in mean linear intercept values, a measure of airspace enlargement, in guinea pigs at 6 and 7 mo of exposure. Statistically significant increases in elastolytic activity was observed in BALF macrophages and lung tissue homogenates at 1-7 mo of exposure. Lung collagenolytic activity was also increased at 4-7 mo of exposure and corresponded in time with the presence of active forms of MMP-2 and MMP-9 in lung tissue homogenates and BALF. Furthermore, MMP-1 and MMP-9 immunoreactivity was detected in macrophages, epithelial and interstitial cells in smoke-exposed animals at 7 mo. Increased levels of MMP-2 and MMP-9 mRNA were also found in smoke-exposed guinea pigs after 3-7 mo. Apoptosis was found in BALF macrophages (TUNEL assay) from guinea pigs exposed to smoke for 3-7 mo and in alveolar epithelial cells (caspase-3 immunoreactivity) after 7 mo. Taken together, these results provide evidence that subchronic exposure to woodsmoke leads to the development of emphysematous lesions accompanied by the accumulation of alveolar macrophages, increased levels and activation of MMPs, connective tissue remodeling and apoptosis. However, the high levels of CO and COHb reported in this study make it difficult to conclude that woodsmoke PM alone is responsible for these dramatic effects.

7.3.6. Allergic Responses

7.3.6.1. Epidemiologic Studies

A number of epidemiologic studies have found associations between PM and allergic (or atopic) indicators. Allergy is a major driver of asthma, which has been associated with PM in studies discussed in previous sections. In a study by Annesi-Maesano (2007, 093180) (described in Section 7.3.1.1) atopic asthma was related to $PM_{2.5}$ (OR 1.43 [95% CI: 1.07-1.91]) and positive skin prick test to common allergens was also increased with higher PM levels. This report is consistent with the results from an earlier study (Penard-Morand et al., 2005, 087951) in the same sample of children that associated allergic rhinitis and atopic dermatitis with PM_{10}. Also, Morgenstern et al. (2008, 156782) found statistically significant effects for asthmatic bronchitis, hay fever, and allergic sensitization to pollen in a cohort of children in Germany examining modeled $PM_{2.5}$ data at birth addresses. Distance to a main road had a dose-response relationship with sensitization to outdoor allergens. Nordling et al. (2008, 097998) (discussed above in Section 7.3.2.1) reported a positive association of PM_{10} exposure during the first year of life with allergenic sensitization (IgE antibodies) to inhaled allergens, especially pollen. In a study by Brauer et al. (2007, 090691) (discussed above in Section 7.3.1.1) an interquartile range increase in $PM_{2.5}$ was associated with an increased risk of sensitization to food allergens (OR 1.75 [95% CI 1.23-2.47]). A significant association was found for sensitization to any allergen, but none was found for sensitization to specific indoor or outdoor aeroallergens or atopic dermatitis (eczema). In a study by Janssen et al. (2003, 133555), $PM_{2.5}$ was associated with allergic indicators such as hay fever (ever), skin prick test reactivity to outdoor allergens, current itchy rash, and conjunctivitis in Dutch children. These same outcomes were also associated with proximity of the school to truck traffic but not car traffic,

suggesting a role for diesel-related pollution. Consistent with the aforementioned Dutch study by Brauer et al. (2007, 090691), $PM_{2.5}$ was not associated with eczema.

Mortimer et al. (2008, 187280) examined the association between prenatal and early-life exposures to air pollutants with allergic sensitization in a cohort of 170 children with asthma, ages 6-11 yr, living in central California. Sensitization to at least one allergen was associated with higher levels of PM_{10} and CO during the entire pregnancy and 2nd trimester and higher PM_{10} during the first 2 yr of life. Sensitization to at least one indoor allergen was associated with higher exposures to PM_{10} and CO in during the entire pregnancy and during the 2nd trimester. However, no significant associations remained for PM_{10} after adjustment for copollutants, effect modifiers, or potential cofounders in addition to year of birth. The authors advise that the large number of comparisons may be of concern and this study should be viewed as an exploratory, hypothesis-generating undertaking. In examining the National Health Interview Survey for the years 1997-2006, Bhattacharyya et al. (2009, 180154) found relationships between air quality and the prevalence of hay fever and sinusitis. However, the air quality data were not clearly defined and as such caution is required in interpretation of these results. In contrast, Bayer-Oglesby et al. (2005, 086245) found no significant association between declining levels of PM_{10} and hay fever in Switzerland. In a study by Oftedal et al. (2007, 191948) conducted in Oslo, Norway, early-life exposure to PM_{10} or $PM_{2.5}$ was generally not associated with sensitization to allergens in 9- to 10-yr-old children; lifetime exposures to PM_{10} and $PM_{2.5}$ were associated with dust mite allergy, but the association was diminished by adjustment for socioeconomic factors . In Norway, wood burning in the wintertime is thought to account for about half of the $PM_{2.5}$ levels. Although associations between PM and reactivity to specific allergens have been reported in long-term studies, there is a consistent lack of correlation between PM and total IgE levels, indicating a selective enhancement of allergic responses.

7.3.6.2. Toxicological Studies

Diesel Exhaust

Exposure to relatively low doses of DE has been shown to exacerbate asthmatic responses in ovalbumin (OVA) sensitized and challenged BALB/c mice (Matsumoto et al., 2006, 098017). Mice were intraperitoneally sensitized and intranasally challenged 1 day prior to inhalation exposure to DE (PM concentration 100 $\mu g/m^3$; CO, 3.5 ppm; NO_2, 2.2 ppm; SO_2 <0.01 ppm) for 1 day or 1, 4, or 8 wk (7/h/day, 5 days/wk, endpoints 12 h post DE exposure). Results from the 1- and 4-wk exposures are described in Section 6.3.6.3. It should be noted that control mice were left in a clean room as opposed to undergoing chamber exposure to filtered air. The significant increases in AHR and airway sensitivity observed following shorter exposure periods did not persist at 8 wk. BALF cytokines were altered by DE exposure with only RANTES significantly elevated after 8 wk. DE had no effect on OVA challenge-induced peribronchial inflammatory or mucin positive cells. These results suggest that adaptive processes may have occurred during prolonged exposure to DE.

Gasoline Exhaust

In a study by Reed et al. (2008, 156903), BALB/c mice were exposed to whole gasoline exhaust diluted 1:10 (H), 1:15 (M), or 1:90 (L), filtered exhaust at the 1:10 (HF), or clean air for 6 h/day (atmospheric characterization described in Section 6.3.6.3). GEE exposure from conception through 4 wk of age induced slight but non-significant increases in OVA-specific IgG1 in offspring but had no significant effect on airway reactivity, BALF cytokine or cell concentrations, although there were non-significant increases in lung neutrophils and eosinophils. Significant increases in total serum IgE were observed, but this effect persisted after filtration of particles and was thus attributed to gas phase components.

Woodsmoke

In a study by Tesfaigzi et al. (2005, 156116), Brown Norway rats were sensitized and challenged with OVA. Rats were exposed for 70 days to filtered air or to 1,000 µg/m^3 hardwood smoke. Particles were characterized by a MMAD of 0.36 µm. Concentrations of gases were reported to be 13.0 ppm CO and 3.1 ppm total vapor hydrocarbon with negligible NO_X. Respiratory function was measured in anesthetized animals by whole-body plethysmography and demonstrated a significant increase in functional residual capacity as well as a significant increase in dynamic lung compliance in hardwood smoke-exposed animals compared to controls. No change in total pulmonary resistance or airway responsiveness to methacholine was observed. BALF inflammatory cells were not increased, although histological analysis demonstrated focal inflammation including granulomatous lesion and eosinophilic infiltrations in hardwood smoke-exposed rats. Alterations of several cytokines in BALF and plasma were noted. Changes in airway epithelial mucus cells and intraepithelial stored mucosubstances were modest and did not achieve statistical significance. Results of this study demonstrate that subchronic exposure to hardwood smoke had minimal effects on pulmonary responses in a rat model of allergen sensitization and challenge.

7.3.7. Host Defense

7.3.7.1. Epidemiologic Studies

Epidemiologic studies of respiratory infections indicate an association with PM. This is more evident when considering short-term exposures (Chapter 6), but studies of long-term exposures have observed associations with general respiratory symptoms often caused by infection, such as bronchitis. In a birth cohort study of approximately 4,000 Dutch children, Brauer et al. (2007, 090691)(described in Section 7.3.1.1) found significant positive associations for $PM_{2.5}$ with ear/nose/throat infections and doctor-diagnosed flu/serious cold in the first 4 yr of life. These results are consistent with an earlier study by Brauer et al. (2006, 090757), which found that an increase of 10 µg/m^3 $PM_{2.5}$ was associated with increased risk for ear infections in the Netherlands [OR 1.50 (95% CI, 1.00-2.22)]. A Swiss study by Bayer-Oglesby et al. (2005, 086245), discussed in Section 7.3.1.1 above, demonstrated that declining levels of PM_{10} were associated with declining prevalence of common cold and conjunctivitis. Because traffic-related pollutants such as UFPs are high near major roadways and then decay exponentially over a short distance, Williams, et al. (2009, 191945) assessed exposure according to residential proximity to major roads in a Seattle area study of postmenopausal women. Proximity to major roads was associated with a 21% decrease in natural killer cell function, which is an important defense against viral infection and tumors. This finding was limited to women who reported exercising near traffic; other markers of inflammation and lymphocyte proliferation did not consistently differ according to proximity to major roads. In the Puget Sound region of Washington, Karr et al. (2009, 191946) reported that there may be a modest increased risk of bronchiolitis related to $PM_{2.5}$ exposure for infants born just before the peak respiratory syncytial virus (RSV) season. Risk estimates were stronger when restricted to cases specifically attributed to RSV and for infants residing closer to highways. Emerging evidence suggests that respiratory infections, particularly infection by viruses such as RSV, can cause asthma or trigger asthma attacks.

7.3.7.2. Toxicological Studies

Diesel Exhaust

DE may affect systemic immunity. The proliferative response of A/J mouse spleen cells following stimulation with T cell mitogens was suppressed by 6 mo of daily exposure to DE at concentrations at or above 300 µg/m^3 PM (Burchiel et al., 2004, 055557). B cell proliferation was increased at 300 µg/m^3 but unaffected at higher concentrations (up to 1,000 µg/m^3). Concentrations of gases and were reported in the parallel study by Reed et al. (2004, 055625), described in

Section 7.3.3.2. The Reed study reported a decrease in spleen weight in male mice (27% reduction in the 300 μg/m^3 exposure group). The immunosuppressive effects of DE were not due to PAHs or benzo(a)pyrene (BaP)-quinones (BPQs) since there were little, if any, of these compounds present in the chamber atmosphere. It should be noted that sentinel animals were negative for mouse parvovirus at the start of the study, but seroconverted by the end of the study, indicating possible infection. Parvovirus can interfere with the modulation of lymphocyte mitogenic responses (Baker, 1998, 156245). A 6-month exposure (6h/day, 7d/wk) to 30, 100, 300 or 1,000 μg/m^3 of PM in DE did not significantly affect bacterial clearance in C57BL/6 mice infected with *Pseudomonas aeruginosa*, although all levels reduced bacterial clearance when the exposure only lasted a week (Harrod et al., 2005, 088144). Characterization of the exposure atmosphere was given by Reed et al. (2004, 055625) (Section 7.3.3.2.).

Gasoline Exhaust

In a study by Reed et al. (2008, 156903) (described in Section 6.3.7.2) long-term exposure to fresh gasoline exhaust (6h/day, 7d/wk for 6 mo) did not affect clearance of *P. aeruginosa* from the lungs of C57BL/6 mice.

Hardwood Smoke

One study demonstrated immunosuppressive effects of hardwood smoke (Burchiel et al., 2005, 088090). Exposure to hardwood smoke increased proliferation of T cells from A/J mice exposed daily to 100 μg/m^3 PM for 6 mo, but produced a concentration-dependent suppression of proliferation at PM concentrations >300 μg/m^3. No effects on B cell proliferation were observed. Concentrations of NO and NO_2 were not detectable or <40 ppb for all exposure levels. CO was reported to be 2, 4, and 13 ppm for the 100, 300 and 1,000 μg/m^3 PM concentrations, respectively. Exposure atmospheres contained significant levels of naphthalene and methylated napthalenes, fluorene, phenanthrene, and anthracene, as well as low concentrations of several metals (K, Ca, and Fe) (Burchiel et al., 2005, 088090). It should be noted that serologic analysis of study sentinel animals indicated infection with parvovirus , which can interfere with the modulation of lymphocyte mitogenic responses (Baker, 1998, 156245). In another study by Reed et al. (2006, 156043) C57BL/6 mice were exposed to 30-1,000 μg/m^3 hardwood smoke by whole-body inhalation for 6 mo prior to instillation of *P. aeruginosa*. Exposure characterizations are described in Section 7.3.3.2. Although there was a trend toward increased clearance with increasing exposure concentrations, there was no statistically significant effect of hardwood smoke exposure on bacterial clearance.

7.3.8. Respiratory Mortality

Two large U.S. cohort studies examined the effect of long-term exposure to $PM_{2.5}$ on respiratory mortality with mixed results. In the ACS study, Pope et al. (2004, 055880) reported positive associations with deaths from specific cardiovascular diseases, but no $PM_{2.5}$ associations were found with respiratory mortality. A follow-up to the Harvard Six Cities study (Laden et al., 2006, 087605) used updated air pollution and mortality data and found positive associations between long-term exposure to $PM_{2.5}$ and mortality. Of special note is a statistically significant reduction in mortality risk reported with reduced long-term fine particle concentrations observed for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths. There is some evidence for an association between $PM_{2.5}$ and respiratory mortality among post-neonatal infants (ages 1 month-1 year) (Section 7.4.1). In summary, when deaths due to respiratory causes are separated from all-cause (nonaccidental) and cardiopulmonary deaths, there is limited and inconsistent evidence for an effect of $PM_{2.5}$ on respiratory mortality, with one large cohort study finding a reduction in deaths due to respiratory causes associated with reduced $PM_{2.5}$ concentrations, and another large cohort study finding no $PM_{2.5}$ associations with respiratory mortality.

7.3.9. Summary and Causal Determinations

7.3.9.1. $PM_{2.5}$

The epidemiologic studies reviewed in the 2004 PM AQCD suggested relationships between long-term PM_{10} and $PM_{2.5}$ (or $PM_{2.1}$) exposures and increased incidence of respiratory symptoms and disease. One of these studies indicated associations with bronchitis in the 24-city cohort (Dockery et al., 1996, 046219). They also suggested relationships between long-term exposure to $PM_{2.5}$ and pulmonary function decrements in the CHS (Gauderman et al., 2000, 012531; Gauderman et al., 2002, 026013). These findings added to the database of the earlier 22-city study of $PM_{2.1}$ (Raizenne et al., 1996, 077268) that found an association between exposure to ambient particle strong acidity and impairment of lung function in children. No long-term exposure toxicological studies were reported in the 2004 PM AQCD.

Recent studies have greatly expanded the evidence available since the 2004 PM AQCD. New analyses have been conducted that include longer follow-up periods of the CHS cohort through 18 yr of age and provide evidence that effects from exposure to $PM_{2.5}$ persist into early adulthood. Gauderman et al. (2004, 056569) reported that $PM_{2.5}$ exposure was associated with clinically and statistically significant deficits in FEV_1 attained at the age of 18 yr. In addition, the strength and robustness of the outcomes were larger in magnitude, and more precise than previous CHS studies with shorter follow-up periods. Supporting this result are new longitudinal cohort studies conducted by other researchers in other locations with different methods. These studies report results for PM_{10} that is dominated by $PM_{2.5}$. New studies provide positive associations from Mexico City, Sweden, and a national cystic fibrosis cohort in the U.S. A natural experiment in Switzerland, where PM levels had decreased, reported that improvement in air quality may slow the annual rate of decline in lung function in adulthood, indicating positive consequences for public health. Thus, the data are consistent and coherent across several study designs, locations and researchers. As was found in the 2004 PM AQCD, the studies report associations with $PM_{2.5}$ and PM_{10}, while most did not evaluate $PM_{10-2.5}$. Associations have been reported with fine particle components, particularly EC and OC. Source apportionment methods generally have not been used in these long-term exposure studies.

Coherence and biological plausibility for the observed associations with lung function decrements is provided by toxicological studies (Section7.3.2.2). A recent study demonstrated that pre- and postnatal exposure to ambient levels of urban particles affected mouse lung development, as measured by anatomical and functional indices (Mauad et al., 2008, 156743). Another study suggested that the developing lung may be susceptible to PM since acute exposure to UF iron-soot decreased cell proliferation in the proximal alveolar region of neonatal rats (Pinkerton et al., 2004, 087465) (Section 6.3.5.3). Impaired lung development is a viable mechanism by which PM may reduce lung function growth in children. Other animal toxicological studies have demonstrated alterations in pulmonary function following exposure to DE and wood smoke (Section 7.3.2.2).

An expanded body of epidemiologic evidence for the effect of $PM_{2.5}$ on respiratory symptoms and asthma incidence now includes prospective cohort studies conducted by different researchers in different locations, both within and outside the U.S. with different methods. The CHS provides evidence in a prospective longitudinal cohort study that relates $PM_{2.5}$ and bronchitic symptoms and reports larger associations for within-community effects that are less subject to confounding than between-community effects (McConnell et al., 2003, 049490). Several new studies report similar findings with long-term exposure to PM_{10} in areas where fine particles predominate. In England, an association was seen with an increased prevalence of cough without a cold. Further evidence includes a reduction of respiratory symptoms corresponding to decreasing PM levels in natural experiments in cohorts of Swiss school children (Bayer-Oglesby et al., 2005, 086245) and adults (Schindler et al., 2009, 191950).

New studies examined the relationship between long-term $PM_{2.5}$ exposure and asthma incidence. $PM_{2.5}$ had the strongest modifying effect on the association between lung function with asthma in an analysis of the CHS (Islam et al., 2007, 090697). The loss of protection by high lung function against new onset asthma in high $PM_{2.5}$ communities was observed for all the lung function measures. In the Netherlands, an association with doctor-diagnosed asthma was found in a birth cohort examining the first 4 yr of life (Brauer et al., 2007, 090691) Further, findings from an adult cohort suggest that traffic-related PM_{10} contributes to asthma development and that reductions in PM decrease asthma risk (Kunzli et al., 2009, 191949).

A large proportion of asthma is driven by allergy, and the majority of recent epidemiologic studies examining allergic (or atopic) indicators found positive associations with $PM_{2.5}$ or PM_{10} (Section 7.3.6.1) . Limited evidence for PM-mediated allergic responses is provided by toxicological studies of DE and woodsmoke, while effects of gasoline exhaust were attributed to gaseous components (Section 7.3.6.2).

Long-term $PM_{2.5}$ exposure is associated with pulmonary inflammation and oxidative responses. An epidemiologic study found a relationship between $PM_{2.5}$ and increased inflammatory marker eNO among school children (Dales et al., 2008, 156378). Toxicological studies of pulmonary inflammation have demonstrated mixed results, with subchronic DE exposures generating increases and CAPs and wood smoke inducing little or no response (Section 7.3.3.2). The pulmonary inflammation observed with DE was attributable to the particle fraction. Toxicological studies also reported evidence of oxidative responses (Section 7.3.4.1). Adaptation to prolonged DE was observed for some oxidative responses in addition to some allergic and pulmonary function responses (Section 7.3.2.2 and 7.3.6.2).

Additional support for the relationship between long-term $PM_{2.5}$ exposures and respiratory outcomes is provided by pulmonary injury responses observed in toxicological studies (Section 7.3.5.1). Markers of pulmonary injury were increased in rats exposed to DE and gasoline exhaust; and these changes were attributable to PM. Further, lung DNA methylation was observed in the gasoline exhaust study. Histopathological changes have also been reported following exposure to heavily-trafficked urban air and woodsmoke. Findings include nasal and airway mucous cell hyperplasia accompanied by alterations in mucus production which can lead to a loss of mucus–mediated protective functions; exacerbation of protease-induced emphysema; and mast cell infiltration and hypertrophy of alveolar walls. These results provide biological plausibility for adverse respiratory outcomes following long-term PM exposure.

Limited information is available on host defense responses (Section 7.3.7) and respiratory mortality (Section 7.3.8) resulting from $PM_{2.5}$ exposure. Several recent epidemiologic studies suggest a relationship between long-term exposure to $PM_{2.5}$ or PM_{10} and infection in children and infants (Section 7.3.7.1). A few toxicological studies suggest that DE exposure affects systemic immunity, and although impaired bacterial clearance is associated with short-term exposures to DE, neither DE or gasoline exhaust seems to have this effect after longer exposures (Section 7.3.7.2).

In summary, the strongest evidence for a relationship between long-term exposure to $PM_{2.5}$ and respiratory morbidity is provided by epidemiologic studies demonstrating associations with decrements in lung function growth in children and with respiratory symptoms and disease incidence in adults. Mean $PM_{2.5}$ concentrations in these study locations ranged from 13.8 to 30 $\mu g/m^3$ during the study periods. These studies provide evidence for associations in areas where PM is predominantly fine particles. A major challenge to interpreting the results of these studies is that the PM size fractions and concentrations of other air pollutants are often correlated; however, the consistency of findings across different locations supports an independent effect of $PM_{2.5}$. Recent toxicological studies provide support for the associations with $PM_{2.5}$ and decreases in lung function growth in children. Pre- and postnatal exposure to ambient levels of urban particles was found to affect mouse lung development, which provides biological plausibility for the epidemiologic findings. Recent subchronic and chronic toxicological studies also demonstrate altered pulmonary function, mild inflammation, oxidative responses, histopathological changes including mucus cell hyperplasia and enhanced allergic responses in response to CAPs, DE, urban air and woodsmoke and provide further coherence and biological plausibility. Exacerbation of emphysematous lesions was noted in one study involving exposure to urban air in a heavily-trafficked area. **Collectively, the evidence is sufficient to conclude that the relationship between long-term $PM_{2.5}$ exposure and respiratory effects is likely to be causal.**

7.3.9.2. $PM_{10-2.5}$

The 2004 PM AQCD did not report long-term exposure studies for $PM_{10-2.5}$. The only recent study to evaluate long-term exposure to $PM_{10-2.5}$ found positive, but not statistically significant associations with eNO (Dales et al., 2008, 156378). The evidence is **inadequate to determine if a causal relationship exists between long-term $PM_{10-2.5}$ exposures and respiratory effects**.

7.3.9.3. UFPs

The 2004 PM AQCD did not report long-term exposure studies for UFPs. The current evidence for long-term UFP effects is limited to toxicological studies. Generally, subchronic exposure to DE induced pulmonary inflammation, which was in contrast to UF CAPs exposure (Section 7.3.3.2) It appeared that the PM fraction was responsible for the inflammatory response with DE exposure. Long-term exposure to DE also resulted in oxidative and allergic responses, although lung injury was not remarkable (Sections 7.3.4.1 and 7.3.6.2). The evidence is **inadequate to determine if a causal relationship exists between long-term UFP exposures and respiratory effects**.

7.4. Reproductive, Developmental, Prenatal and Neonatal Outcomes

7.4.1. Epidemiologic Studies

This section evaluates and summarizes the scientific evidence on PM and developmental and pregnancy outcomes and infant mortality. Infants and fetal development processes may be particularly vulnerable to PM exposure, and although the physical mechanisms are not fully understood, several hypotheses have been proposed involving direct effects on fetal health, altered placenta function, or indirect effects on the mother's health (Bracken et al., 2003, 156288; Clifton et al., 2001, 156360; Maisonet et al., 2004, 156725; Schatz et al., 1990, 156073; Sram et al., 2005, 087442). Study of these outcomes can be difficult given the need for detailed data and potential residential movement of mothers during pregnancy. Two recent articles have reviewed methodological issues relating to the study of outdoor air pollution and adverse birth outcomes (Ritz and Wilhelm, 2008, 156914; Slama et al., 2008, 156985). Some of the key challenges to interpretation of these study results include the difficulty in assessing exposure as most studies use existing monitoring networks to estimate individual exposure to ambient PM; the inability to control for potential confounders such as other risk factors that affect birth outcomes (e.g., smoking); evaluating the exposure window (e.g., trimester) of importance; and limited evidence on the physiological mechanism of these effects (Ritz and Wilhelm, 2008, 156914; Slama et al., 2008, 156985). Another uncertainty is whether PM effects differ by the child's sex. A review of preterm birth and low birth weight studies found limited indication that effects may differ by gender, however sample size was limited (Ghosh et al., 2007, 091233).

Previous summaries of the association between PM concentrations and pregnancy outcomes and infant mortality were presented in previous PM AQCDs. The 1996 PM AQCD concluded that although few studies had been conducted on the link between PM and infant mortality, the research "suggested an association," particularly for post-neonates (U.S. EPA, 1996, 079380). In the 2004 PM AQCD, additional evidence was available on PM's effect on fetal and early postnatal development and mortality (U.S. EPA, 2004, 056905) and although some studies indicated a relationship between PM and pregnancy outcomes, others did not. Studies identifying associations found that exposure to PM_{10} early during pregnancy (first month of pregnancy) or late in the pregnancy (6 wk prior to birth) were linked with higher risk of preterm birth, including models adjusted for other pollutants, and that $PM_{2.5}$ during the first month of pregnancy was associated with intrauterine growth restriction. However, other work did not identify relationships between PM_{10} exposure and low birth weight. The state of the science at that time, as indicated in the 2004 PM AQCD, was that the research provided mixed results based on studies from multiple countries, and that additional research was required to better understand the impact of PM on pregnancy outcomes and infant mortality. Considering evidence from recent studies discussed below, along with previous AQCD conclusions, epidemiologic studies consistently report associations between PM_{10} and $PM_{2.5}$ exposure and low birth weight and infant mortality, especially during the post-neonatal period. Animal toxicological evidence supports these associations with $PM_{2.5}$, but provides little mechanistic information or biological plausibility. Information on the ambient concentrations of PM_{10} and $PM_{2.5}$ in these study locations can be found in Table 7-5.

7.4.1.1. Low Birth Weight

A large number of studies have investigated exposure to ambient PM and low birth weight at term, including a U.S. national study, as well as two studies in the northeast U.S., and four in California. Parker and Woodruff (2008, 156846) linked U.S. birth records for singletons delivered at 40-wk gestation in 2001-2003 during the months of March, June, September and December to quarterly estimates of PM exposure by county of residence and month of birth. They found an association between $PM_{10-2.5}$ and birthweight (-13 g [95% CI: -18.3 to -7.6]) per 10 $\mu g/m^3$ increase), but no such association for $PM_{2.5}$.

Maisonet et al. (2001, 016624) analyzed 89,557 births (1994-96) in six northeastern cities (Boston and Springfield MA; Hartford CT; Philadelphia and Pittsburgh PA; and Washington DC). Each city had three PM_{10} monitors measuring every sixth day. Results from multiple monitors were averaged in each city. Exposure was determined for each trimester of pregnancy and categorized by quartiles (<25, 25-30, 31-35, 36-43 $\mu g/m^3$) and 95th percentile (>43$\mu g/m^3$). There was no increased risk for low birth weight at term associated with PM_{10} exposure during any trimester of pregnancy. When birth weight was considered as a continuous outcome, exposure to PM_{10} was not associated with a reduction in mean birth weight.

In contrast, Bell et al. (2007, 093256) reported positive associations for both $PM_{2.5}$ and PM_{10} with birth weight in a study of births (n = 358,504) in Connecticut and Massachusetts (1999-2002). Birth data indicated county, not street address or ZIP code, so women were assigned exposure based on county residence at delivery. The difference in birth weight per 10 $\mu g/m^3$ associated with $PM_{2.5}$ was -66.8 (95% CI: -77.7 to -55.9) g. For PM_{10} it was -11.1 (95% CI: -15.0 to -7.2) g. The increased risk for low birth weight was OR = 1.054 (95% CI: 1.022-1.087) for $PM_{2.5}$ and OR = 1.027 (95% CI: 0.991-1.064) for PM_{10}, based on average exposure during pregnancy. Reductions in birth weight were also associated with third trimester exposure to PM_{10} and second and third trimester exposure to $PM_{2.5}$. Comparing this study to Maisonet et al. (2001, 016624), a larger sample size was able to detect a small increase in risk. In addition, birth weight was reduced more by exposure to $PM_{2.5}$ than by exposure to PM_{10}. Measured $PM_{2.5}$ concentrations were not available in the earlier study.

The Children's Health Study is a population based cohort of children living in 12 southern California communities, selected on the basis of differing levels of air pollution (Salam et al., 2005, 087885), as previously discussed in Section 7.3. The children in grades 4, 7 and 10 were recruited through schools. A subset of this cohort (n = 6,259) were born in California from 1975-1987. Of these, birth certificates were located for 4,842, including 3,901 infants born at term and 72 cases of low birth weight at term. Using the mother's ZIP code at the time of birth, exposure was determined by inverse distance weighting of up to three PM_{10} monitors within 50 km of the ZIP code centroid. If there was a PM_{10} monitor within 5 km of the ZIP code centroid (40% of data), exposure from that monitor was used. Exposure was calculated for the entire pregnancy, and for each trimester of pregnancy. A 10 $\mu g/m^3$ increase in PM_{10} during the third trimester reduced mean birth weight -10.9 g (95% CI: -21.1 to -0.6) in single pollutant models, but became non-significant in copollutant models controlling for the effects of O_3. Increased risks of low birth weight (<2,500 g) were not statistically significant (OR = 1.3 [95% CI: 0.9-1.9]). A strength of this study was the cohort data available included information on SES and smoking during pregnancy. A limitation is the assignment of exposure based on monitoring stations up to 50 km distant; this may have introduced substantial exposure misclassification obscuring some associations.

Table 7-5. Characterization of ambient PM concentrations from studies of reproductive, developmental, prenatal and neonatal outcomes and long-term exposure.

Study	Location	Mean Annual Concentration (µg/m^3)	Upper Percentile Concentrations (µg/m^3)
$PM_{2.5}$			
Basu et al. (2004, 087896)	CA	Range of means across sites: 14.5-18.2 Avg of means across sites: 16.2	Max: 26.3-34.1
Bell et al. (2007, 091059)	CT & MA	22.3	
Brauer et al. (2008, 156292)	Vancouver, Canada	5.3	Max: 37.0
Huynh et al. (2006, 091240)	CA	Range of means across trimesters: 17.5-18.8 Avg of means across trimesters: 18.2	
Jalaludin et al. (2007, 156601)	Sydney, Australia	9.0	
Liu (2007, 090429)	Multicity, Canada	12.2	75th: 15
Loomis et al. (1999, 087288)	Mexico City	27.4	Max: 85
Mannes et al. (2005, 087895)	Sydney, Australia	9.4	75th: 11.2; Max: 82.1
Parker et al. (2005, 087462)	CA	15.4	
Ritz et al. (2007, 096146)	Los Angeles, CA	20.0	
Wilhelm and Ritz (2005, 088668)	Los Angeles, CA	21.0	Max: 38.9-48.5
Woodruff et al. (2006, 088758)	CA	19.2[a]	75th: 22.7
Woodruff et al. (2008, 098386)	U.S.	Range of means across effects: 14.5-14.9[a] Avg of means across effects: 14.8[a]	75th: 18.5-18.7
$PM_{10-2.5}$			
Parker et al. (2008, 156013)	U.S.	13.2	75th: 17.5
PM_{10}			
Bell et al. (2007, 093256)	CT & MA	22.3	
Brauer et al. (2008, 156292)	Vancouver, Canada	12.7	Max: 35.4
Chen et al. (2002, 024945)`	Washoe County, NV	31.53	75th: 39.35; Max: 157.32
Gilboa et al. (2005, 087892)	TX	23.8[a]	75th: 29
Ha et al. (2003, 042552)	Seoul, South Korea	69.2	75th: 87.7; Max: 245.4
Hansen et al. (2006, 089818)	Brisbane, Australia	19.6	Max: 171.7
Hansen et al. (2007, 090703)	Brisbane, Australia	19.6	75th: 22.7; Max: 171.7
Jalaludin et al. (2007, 156601)	Sydney, Australia	16.3	
Kim et al. (2007, 156642)	Seoul, Korea	Range of means across time: 88.7-89.7 Avg of means across time: 89.2	
Lee et al. (2003, 043202)	Seoul, Korea	71.1	75th: 89.3; Max: 236.9
Leem et al. (2006, 089828)	Incheon, Korea	53.8[a]	75th: 64.6; Max: 106.39
Lipfert et al. (2000, 004103)	U.S.	33.1	Max: 59
Maisonet et al. (2001, 016624)	NE U.S.	31.0[a]	75th: 36.1; Max: 46.5
Mannes et al. (2005, 087895)	Sydney, Australia	16.8	75th: 19.9; Max: 104.0
Pereira et al. (1998, 007264)	Sao Paulo, Brazil	65.04	Max: 192.8
Ritz et al. (2000, 012068)	CA	49.3	Max: 178.8
Ritz et al. (2006, 089819)	CA	46.3	Max: 83.5

Study	Location	Mean Annual Concentration (μg/m^3)	Upper Percentile Concentrations (μg/m^3)
Rogers and Dunlop (2006, 091232)	GA	3.75	75th: 15.07
Romieu et al. (2004, 093074)	Ciudad Juarez, Mexico	33.0-45.9	
Sagiv et al. (2005, 087468)	PA	Range of means across time: 25.3-27.1 Avg of means across time: 26.2	Max: 68.9-156.3
Salam et al. (2005, 087885)	CA	Range of means across trimesters: 45.4-46.6 Avg of means across trimesters: 45.8	
Suh et al. (2008, 192077)	Seoul, Korea	Range of means across trimesters: 54.6-61.1 Avg of means across trimesters: 58.27	75th: 62.8-67.8 Max: 85.1-107.36
Tsai et al. (2006, 090709)	Kaohsiung, Taiwan	81.5	75th: 111.5; Max: 232.0
Wilhelm and Ritz (2005, 088668)	Los Angeles, CA	38.1	Max: 74.6-103.7
Woodruff et al. (2008, 098386)	U.S.	Range of means across effects: 28.6-29.8[a] Avg of means across effects: 29.1[a]	75th: 33.8-36.5
Yang et al. (2006, 090760)	Taipei, Taiwan	53.2	75th: 64.9; Max: 234.9

[a]Median concentration

Parker et al. (2005, 087462) examined births in California within 5 miles of a monitoring station (n = 18,247). Only infants born at 40 wk gestation were included. Thus all infants were the same gestational age, and had been exposed in the same year. Exposure to $PM_{2.5}$ in quartiles (<11.9, 11.9-13.9, 14.0-18.4, >18.4) was associated with decrements in birth weight. Infants exposed to >13.9 μg/m^3 experienced reductions in birth weight (third quartile -13.7 g (95% CI: -34.2 to 6.9), fourth quartile -36.1 g (95% CI: -55.8 to -16.5). These are larger reductions than have been seen in some other studies. However, this study reduced misclassification by including only women living within 5 miles of a monitoring station, and only included births at 40 wk gestation. Reducing misclassification should lead to a stronger association, if the association is causal.

The effects of spatial variation in exposure were also investigated by Wilhelm and Ritz (2005, 088668). Their study included all women living in ZIP codes where 60% of the ZIP code was within two miles of a monitoring station in the Southern California Basin, and women with known addresses in Los Angeles County within 4 miles of a monitoring station. Exposure to average PM_{10} in the third trimester was analyzed for increased risk of low birth weight at term (≥ 37-wk gestation). Analysis at the ZIP code level did not detect increased risk (per 10 μg/m^3 PM_{10}, OR = 1.03 [95% CI: 0.97-1.09]). However the analysis based on geocoded addresses indicated that increasing exposure to PM_{10} was associated with increased risk of low birth weight for women living within 1 mile of the station where PM_{10} was measured. For these women (n = 247 cases, 10,981 non-cases), each 10 μg/m^3 increase in PM_{10} was associated with a 22% increase in risk of term low birth weight (OR = 1.22 [95% CI: 1.05-1.41]). In the categorical analysis, exposure to PM_{10} >44.4 μg/m^3 was associated with a 48% increase in risk (OR = 1.48 [95% CI: 1.00-2.19]). Increased risk of low birth weight also was associated with exposure to CO in single pollutant models. However, when multipollutant models were considered, the effects of CO were attenuated but the effects of PM_{10} increased. Controlling for CO, NO_2, and O_3, each 10 μg/m^3 increase in exposure to PM_{10} increased risk of low birth weight 36% (OR = 1.36 [95% CI: 1.12-1.65]).

Spatial variation in $PM_{2.5}$ exposure was investigated by Basu et al. (2004, 087896). They included only mothers who lived within 5 miles of a $PM_{2.5}$ monitor and within a California county with at least 1 monitor. To minimize potential confounding, they included only white (n = 8,597) or Hispanic (n = 8,114) women, who were married, between 20 and 30 yr of age, completed at least high school and were having their first child. Consistently, $PM_{2.5}$ exposure measured by the county monitor was more strongly associated with reductions in birth weight than exposure measured by the neighborhood monitor. The results were replicated in both the white and the Hispanic samples. Reductions in birth weight ranged from 15.2 to 43.5 g per 10 μg/m^3 increase in $PM_{2.5}$.

In the remaining U.S. study, Chen et al. (2002, 024945) analyzed 33,859 birth certificates of residents of Washoe County in northern Nevada (1991-1999). There were four sites monitoring PM_{10} during the study period, it appears (not stated) that exposure was averaged over the county. A

10 μg/m^3 increase in exposure to PM_{10} during the third trimester of pregnancy was associated with an 11 g reduction in birth weight (95% CI: -2.3 to -19.8). Effects on risk of low birth weight were not statistically significant. For exposure in the third trimester of 19.77 to 44.74 μg/m^3 compared to <19.74 μg/m^3 the odds ratio for low birth weight was 1.05 (95% CI: 0.81-1.36). Comparing exposure >44.74 to the same reference category, the odds ratio was 1.10 (95% CI: 0.71-1.71). Misclassification of exposure may have occurred when exposure was averaged over a large geographic area (16,968 km^2).

Recent international studies investigating effects of particles on low birth weight include one in Munich (Slama et al., 2007, 093216), two in Canada (Brauer et al., 2008, 156292; Dugandzic et al., 2006, 088681), two in Australia (Hansen et al., 2007, 090703; Mannes et al., 2005, 087895), two in Taiwan (Lin et al., 2004, 089827; Yang et al., 2003, 087886) one in Korea (Ha et al., 2003, 042552) and two in Sao Paulo, Brazil (Gouveia et al., 2004, 055613; Medeiros and Gouveia, 2005, 089824). The majority of these studies found that PM concentrations were associated with low birth weight, though two studies (Hansen et al., 2007, 090703; Lin et al., 2004, 089827) found no associations. The effect estimates were similar in magnitude to those reported in the U.S. studies.

Considerations in Interpreting Results of Low Birth Weight Studies

Studies included subjects at distances from monitoring stations varying from as close as 1 mile or 2 km, to as far as 50 km or the size of the county. Studies that only included subjects living within a short distance (1 mile, 2 km) of the monitoring station (thus likely reducing exposure measurement error) were more likely to find that PM exposure was associated with increased risk of low birth weight. However, Basu et al. (2004, 087896) reported a stronger association between $PM_{2.5}$ exposure and birth weight when exposure was estimated based on the county monitor, rather than the monitor within 5 miles of the residence. They suggest that county level exposure may be more representative of where women spend their time, including not only home, but also other time spent away from home. Other pollutants also appeared to influence the risk associated with particle exposure. In one study, exposure to PM_{10} in a single pollutant model reduced birth weight by 11 g, but became non-significant in copollutant models with O_3 (Salam et al., 2005, 087885). In another study the risk associated with PM_{10} exposure increased from 22% to 36% when other pollutants were included in the model (Wilhelm and Ritz, 2005, 088668). All but one study in the U.S. found some association between particle exposure and reduced birth weight (Maisonet et al., 2001, 016624). The results of international studies were inconsistent. This might be related to the chemical composition of particles in the U.S., or to differences in the pollutant mixture. Studies with null results must be interpreted with caution when the comparison groups have significant exposure. This was certainly the situation in studies in Taiwan and Korea (Lee et al., 2003, 043202; Lin et al., 2004, 089827; Yang et al., 2003, 087886). Differences in geographical locations, study samples and linkage decisions may contribute to the diverse findings in the literature on the association between PM and birthweight, even within the U.S. (Parker and Woodruff, 2008, 156846).

7.4.1.2. Preterm Birth

A potential association of exposure to airborne particles and preterm birth has been investigated in numerous epidemiologic studies, including some conducted in the U.S. and others in foreign countries. Three U.S. studies have been carried out by the same group of investigators in California.

A natural experiment occurred when an open-hearth steel mill in Utah Valley was closed from August 1986 through September 1987. Parker et al. (2008, 156013) compared birth outcomes for Utah mothers within and outside of the Utah Valley, before, during, and after the mill closure. They report that mothers who were pregnant around the time of the closure of the mill were less likely to deliver prematurely than mothers who were pregnant before or after. The strongest effect estimates were observed for exposure during the second trimester (14% decrease in risk of preterm birth during mill closure). Preterm birth outside of the Utah Valley did not change during the time of the mill closure.

In 2000, Ritz et al. (2000, 012068) published the first study investigating the association of preterm birth with PM in the U.S. The study population was women living in the southern California Basin. There were eight monitoring stations measuring PM_{10} every 6th day during the study period.

Birth certificates (1989-1993) were analyzed for women living in ZIP codes within 2 miles of a monitoring station. Women with multiple gestations, chronic disease prior to pregnancy and women who delivered by cesarean section were excluded resulting in a study population of 48,904 women. The risk of preterm birth increased by 4% (RR = 1.04 [95% CI: 1.02-1.6]) per 10 μg/m^3 increase in PM_{10} averaged in the 6 wk before birth. Exposure to PM_{10} in the first month of pregnancy resulted in a 3% increase in risk (RR = 1.03 [95% CI: 1.01-1.05]). These results were robust in multipollutant models.

Wilhelm and Ritz (2005, 088668) reinvestigated this association among women in the same area in 2005, when air pollution had declined from a mean level near 50 μg/m^3 to a mean level near 40 μg/m^3. Birth certificate data from 1994-2000 was analyzed for women living in ZIP codes within 2 miles of a monitoring station, or with addresses within 5 miles of a monitoring station. No significant effects of exposure to PM_{10} were reported. Exposure to $PM_{2.5}$ 6 wk before birth resulted in an increase in preterm birth (RR = 1.19 [95% CI: 1.02-1.40]) for the highest quartile of exposure ($PM_{2.5}$ >24.3 μg/m^3). Using a continuous measure of $PM_{2.5}$, there was a 10% increase in risk for each 10 μg/m^3 increase in $PM_{2.5}$ (RR = 1.10 [95% CI: 1.00-1.21]).

There have been two major criticisms of air pollution studies using birth certificate data. First, that birth certificates only indicate the address at birth and the exposure of women who moved during pregnancy may be misclassified; second, that information about some important confounders may not be available (e.g., smoking). To obtain more precise information about these variables, Ritz et al. (2007, 096146) conducted a case-control study nested within a cohort of birth certificates (Jan 2003-Dec 2003) in Los Angeles County. Births to women residing in ZIP codes (n = 24) close to monitoring stations or major population centers or roadways (n = 87) were eligible (n = 58,316 births). All cases of low birth weight or preterm birth and an equal number of randomly sampled controls in the 24 ZIP codes close to monitors were selected. In the other 87 ZIP codes, 30% of cases and an equal number of controls were randomly sampled. Of 6,374 women selected for the case control study, 2,543 (40%) were interviewed. The association of preterm birth with exposure to $PM_{2.5}$ differed between women responding to the survey and women who did not respond. Among responders, exposure to each 10 μg/m^3 increase in $PM_{2.5}$ concentration in the first trimester increased risk to preterm birth by 23% (RR = 1.23 [95% CI: 1.02-1.48]). There was no increase in risk among non-responders (RR = 0.95 [95% CI: 0.82-1.10]), or in the entire birth cohort (RR = 1.00 [95% CI: 0.94-1.07]).

An additional case control study of preterm birth and $PM_{2.5}$ exposure (Huynh et al., 2006, 091240) used California birth certificate data. Singleton preterm infants (24-36-wk gestation) born in California (1999-2000) whose mothers lived within 5 miles of a $PM_{2.5}$ monitor were eligible. Each of these 10,673 preterm infants were matched to three term (39- to 44-wk gestation) controls (having a last menstrual period within 2 wk of the case infant), resulting in a study population of 42,692. Controlling for maternal race/ethnicity, education, marital status, parity and CO exposure, exposure to $PM_{2.5}$ >17.7 μg/m^3 increased the risk of preterm birth by 14% (OR = 1.14 [95% CI: 1.07-1.23]). Averaging $PM_{2.5}$ exposure over the first month of pregnancy, the last 2 wk before birth, or the entire pregnancy did not substantially change the risk estimate.

Two additional studies of preterm birth and exposure to particulate air pollution have been conducted in the U.S. Each has used a unique methodology. Sagiv et al. (2005, 087468) used time series to analyze births in four Pennsylvania counties between January 1997 and December 2001. In this analysis, exposure to PM_{10} is compared to the rate of preterm births each day. Both acute exposure (on the day of birth) and longer term exposure (average exposure for the preceding 6 wk) were considered in the analysis. An advantage of this analysis is that days, rather than individuals are compared, so confounding by individual risk factors is minimized. For exposure averaged over the 6 wk prior to birth, there was an increase in risk (RR = 1.07 [95% CI: 0.98-1.18]), which persisted for acute exposure with a 2-day lag (RR = 1.10 [95% CI: 1.00-1.21]) and 5-day lag (RR = 1.07 95% CI: 0.98-1.18]).

Rogers and Dunlop (2006, 091232) examined exposure to particles and risk of delivery of an infant weighing less than 1,500 g (all of which were preterm) from 24 counties in Georgia. The study included 69 preterm, small for gestational age (SGA) infants, 59 preterm appropriate for gestational age (AGA) infants and 197 term AGA controls. Exposure was estimated using an environmental transport model that considered PM_{10} emissions from 32 geographically located industrial point sources, meteorological factors, and geographic location of the birth home. Exposure was categorized by quartiles. Comparing women who delivered a preterm AGA infant to those who

delivered a term AGA infant, exposure to PM_{10}>15.07 μg/m^3 tripled the risk (OR = 3.68 [95% CI: 1.44-9.44]).

Brauer et al. (2008, 156292) evaluated the impacts of $PM_{2.5}$ on preterm birth using spatiotemporal exposure metrics in Vancouver, Canada. The authors found similar results when they used a land-use regression model or inverse distance weighting as the exposure metric. For preterm births <37 wk, they reported an OR of 1.06 (95% CI: 1.01-1.11), and for preterm births <35 wk the OR increased to 1.12 (95% CI: 1.02-1.24). There were no consistent trends for early or late gestational period to be more strongly associated with preterm births.

Suh et al. (2008, 192077) conducted a study to determine if the effects of exposure to PM_{10} during pregnancy on preterm delivery are modified by maternal polymorphisms in metabolic genes. They analyzed the effects of the gene-environment interaction between the GSTM1, GSTT1, CYP1a1-T6235C and -1462V polymorphisms and exposure to PM_{10} during pregnancy on preterm birth in a case-control study in Seoul, Korea. PM_{10} concentration ≥ 75th percentile alone was significant in the third trimester of pregnancy (OR = 2.33 [95% CI: 1.33-4.80]), but not in the first or second trimester. The risk of preterm delivery conferred by the GSTM1 null genotype was increased, and the highest risk was found during the third trimester of pregnancy (OR = 2.58 [95% CI: 1.34-4.97]). There were no statistical associations with the GSTT1 or CYP1A1 genotypes. When the gene-environment interaction was analyzed, the risk for preterm birth was substantially higher for women who carried the GSTM1 null genotype and were exposed to high levels of PM_{10} (≥ 75th percentile) than for those who carried the GSTM1 positive genotype but were only exposed to low levels of PM_{10} (<75th percentile) during the third trimester of pregnancy (OR = 6.22, 95% CI: 2.14-18.08).

In Incheon, Korea, Leem et al. (2006, 089828) estimated PM_{10} exposure spatially as well as temporally. Exposure was based on 26 monitors and kriging was used to determine exposure for 120 dongs (administrative districts, mean area 7.82 km^2, median area 1.42 km^3). The sample included 52,113 births, from 2001-2002. PM_{10} was very weakly correlated with other pollutants. Exposure was compared in quartiles for the first and third trimester of pregnancy. In the first trimester, relative risks for the second, third and fourth quartiles were RR = 1.14 (95% CI: 0.97-1.34), RR = 1.07 (95% CI: 0.94-1.37), and RR = 1.24 (95% CI: 1.09-1.41), respectively. Exposure to PM_{10} in quartile one (reference group) was 26.9-45.9 μg/m^3; fourth quartile exposure equaled 64.6-106.4 μg/m^3. The p-value for trend was 0.02. Exposure in the third trimester was not related to preterm birth, however no information was provided to determine how exposure in the third trimester was adjusted for women who delivered preterm.

Two studies investigating risks of preterm birth related to particle exposure have been reported from Australia. In Brisbane, Hansen et al. (2006, 089818) studied 28,200 births (2000-2003) in an area of low PM_{10} concentrations. Exposure to an interquartile range increase in PM_{10} exposure in the first trimester resulted in a 15% increased risk of preterm birth (OR = 1.15 [95% CI: 1.06-1.25]). This result was strongly influenced by the effect of PM_{10} exposure in the first month of pregnancy (OR = 1.19 [95% CI: 1.13-1.26]). PM_{10} was correlated with O_3 (r = 0.77) in this study and O_3 also increased risk in the first trimester. No effects were associated with exposure to PM_{10} in the third trimester.

In Sydney, associations between exposure to particles and preterm birth varied by season. Jalaludin et al. (2007, 156601) obtained information on all births in metropolitan Sydney (1998-2000). Exposure to $PM_{2.5}$ in the 3 mo preceding birth was associated with an increased risk of preterm birth (OR = 1.11 [95% CI: 1.04-1.19]). Additional effects were dependent on season of conception. Both PM_{10} (OR = 1.3 [95% CI: 1.2-1.5]) and $PM_{2.5}$ (OR = 1.4 [95% CI: 1.3-1.6]) were associated with increased risk for conceptions in the winter. Conceptions in summer were associated with reductions in risk (PM_{10} OR = 0.91 [95% CI: 0.88-0.93]) ($PM_{2.5}$ OR = 0.87 [95% CI: 0.84-0.92]). Due to both positive and negative findings, the authors recommend caution in interpreting their results.

Considerations in Analyzing Environmental Exposures and Preterm Birth

A major issue in studying environmental exposures and preterm birth is selecting the relevant exposure period, since the biological mechanisms leading to preterm birth and the critical periods of vulnerability are poorly understood (Bobak, 2000, 011448). Exposures proximate to the birth may be most relevant if exposure causes an acute effect. However, exposure occurring in early gestation

might affect placentation, with results observable later in pregnancy, or cumulative exposure during pregnancy may be the most important determinant. The studies reviewed have dealt with this issue in different ways. Many have considered several exposure metrics based on different periods of exposure.

Often the time periods used are the first month (or first trimester) of pregnancy and the last month (or 6 wk) prior to delivery. Using a time interval prior to delivery introduces an additional problem since cases and controls are not in the same stage of development when they are compared. For example, a preterm infant delivered at 36 wk is a 32-week fetus 4 wk prior to birth, while an infant born at term (40 wk) is a 36-week fetus 4 wk prior to birth. Only one study (Huynh et al., 2006, 091240) adjusted for this in the design.

Many of these studies compare exposure in quartiles, using the lowest quartile as the reference (or control) group. No studies use a truly unexposed control group. If exposure in the lowest quartile confers risk, than it may be difficult to demonstrate additional risk associated with a higher quartile. Thus negative studies must be interpreted with caution.

Preterm birth occurs both naturally (*idiopathic preterm*), and as a result of medical intervention (*iatrogenic preterm*). Ritz et al. (2000, 012068; 2007, 096146) excluded all births by Cesarean section, to limit their studies to idiopathic preterm. No other studies attempted to distinguish the type of preterm birth, although PM exposure maybe associated with only one type. This is a source of potential effect misclassification.

7.4.1.3. Growth Restriction

Low birth weight has often been used as an outcome measure because it is easily available and accurately recorded on birth certificates. However, low birth weight may result from either short gestation, or inadequate growth in utero. Most of the studies investigating air pollution exposure and low birth weight, limited their analysis to term infants to focus on inadequate growth. A number of studies were identified that specifically addressed growth restriction in utero by identifying infants who failed to meet specific growth standards. Usually these infants had birth weights less than the 10th percentile for gestational age, using an external standard. Many of these studies have been previously discussed, since they also examined other reproductive outcomes (low birth weight or preterm delivery).

Three studies in the U.S. examined intrauterine growth. A recent study (Rich et al., 2009, 180122) investigated very small for gestational age (defined as a fetal growth ratio <0.75), small for gestational age (defined as ≥ 75 and <85) and "reference" births (≥ 85) to women residing in New Jersey and mean air pollutant concentrations during the first, second and third trimesters. They reported an increased risk of SGA associated with first and third trimester $PM_{2.5}$ concentrations (1.116 [95% CI: 1.012, 1.232], and 1.106 [1.008-1.212], per 10 μg/m^3 $PM_{2.5}$, respectively). Parker et al. (2005, 087462) reported a positive association between exposure to $PM_{2.5}$. Since this study only included singleton live births at 40-wk gestation, birth weights less than 2,872 g for girls and 2,986 g for boys were designated SGA, based on births in California. Infants exposed to the highest quartile $PM_{2.5}$ (>18.4 μg/m^3) compared to the lowest quartile $PM_{2.5}$ (<11.9 μg/m^3) were 23% more likely to be small for gestational age (OR = 1.23 [95% CI: 1.03-1.50]). Very similar results were found for exposure in each of the three trimesters respectively (OR = 1.26 [95% CI: 1.04-1.51], OR = 1.24 [95% CI: 1.04-1.49], OR = 1.21 [95% CI: 1.02-1.43]). These results controlled for exposure to CO, which did not increase risk for SGA.

In contrast, Salam et al. (2005, 087885) found no association between exposure to PM_{10} and intrauterine growth retardation (IUGR) in the California Children's Health Study. IUGR was defined as less than the 15th percentile of predicted birth weight based on gestational age and sex in term infants. Apparently no external standard was used since 15% of infants in the study were designated as IUGR. An IQR increase in PM_{10} exposure was not significantly associated with IUGR for the whole pregnancy (OR = 1.1 [95% CI: 0.9-1.3]) or for any specific trimester. Differences between this study and the study by Parker et al. (2005, 087462) include measurement of PM_{10} versus $PM_{2.5}$, a less stringent definition of IUGR, and exposures determined by monitors located much farther away from the subjects' residences (up to 50 km versus within 5 mi). All of these factors could lead to misclassification.

Two studies investigating particle exposure and SGA were conducted in Australia, with differing results (Hansen et al., 2007, 090703; Mannes et al., 2005, 087895). Mannes et al. (2005, 087895) defined SGA as birth weight less than two standard deviations below the national mean

birth weight for gestational age. In this study there was a statistically significant effect of exposure to both PM_{10} (OR = 1.10 [95% CI: 1.00-1.48], per 10 μg/m^3 increase) and $PM_{2.5}$ (OR = 1.34 [95% CI: 1.10-1.63], per 10 μg/m^3 increase) for exposure during the second trimester. When analysis was restricted to births within 5 km of the monitoring station, the association for PM_{10} became slightly stronger (OR = 1.22 [95% CI: 1.10-1.34]). Exposure during other trimesters of pregnancy was not associated with IUGR.

In Brisbane, Hansen et al. (2007, 090703) examined head circumference (HC), crown heel length (CHL) and risk of SGA, defined as less than the tenth percentile of weight for gestational age and gender based on an Australian national standard. There was no consistent relationship between PM_{10} exposure and SGA, HC or CHL in any trimester of pregnancy. PM_{10} exposure was determined by averaging values from the five monitoring stations. Due to the sample size and limited number of monitoring stations, it was not possible to analyze the data for women living within 5 km of a monitoring station, as was done in Sydney.

In Canada, Liu et al. (2007, 090429) investigated the effect of $PM_{2.5}$ exposure on fetal growth in three cities, Calgary, Edmonton and Montreal. IUGR was defined as birth weight below the tenth percentile, by sex and gestational week (37-42) for all singleton live births in Canada between 1986 and 2000. Models were adjusted for maternal age, parity, infant sex, season of birth, city of residence, and year of birth. A 10 μg/m^3 increase in $PM_{2.5}$ was associated with an increased risk for IUGR (OR = 1.07 [95% CI: 1.03-1.10]) in the first trimester, and similar risks were associated with exposure in the second or third trimesters. The effect of $PM_{2.5}$ was reduced in multipollutant models including CO and NO_2.

Brauer et al. (2008, 156292) observed consistent increased risks of SGA for $PM_{2.5}$, PM_{10}, NO_2, NO and CO in Vancouver, Canada (20% increase in risk in $PM_{2.5}$ and PM_{10} per 10 μg/m^3 increase). The effects were similar for exposure estimates based on nearest monitor, inverse distance weighting, and land-use regression modeling. ORs for early or late pregnancy exposure windows were remarkably similar to those for the full duration of pregnancy.

7.4.1.4. Birth Defects

Four recent studies examined PM and birth defects. The Seoul, Korea study discussed above also considered congenital anomalies, defined as a defect in the child's body structure (Kim et al., 2007, 156642). PM_{10} levels were associated with higher risk of birth defects for the second trimester, with a 16% (95% CI: 0-34) increase in risk per 10 μg/m^3 in PM_{10}.

Two U.S. studies examined air pollution and risk of birth defects. Data were collected from the California Birth Defects Monitoring Program for four counties in Southern California (Los Angeles, Riverside, San Bernardino, and Orange) for the period 1987-1993, although each county included a subset of this period (Ritz et al., 2002, 023227). Cases (i.e., infants with birth defects) were identified as live birth infants and fetal deaths from 20-wk gestation to 1 yr post-birth, with isolated, multiple, syndrome, or chromosomal cardiac or orofacial cleft defects. Cases were restricted to those with registry data for gestational age and residence ZIP code, and those with residences <10 miles from an air pollution monitor. Six types of categories were included: aortic defects; atrium and atrium septum defects; endocrinal and mitral value defects; pulmonary artery and valve defects; conotruncal defects; and ventricular septal defects not part of the conotruncal category. PM_{10} measurements were available every 6 days. While results indicated increased risk of birth defects for higher levels of CO or O_3, the authors determined that results for PM_{10} were inconclusive, finding no consistent trend of effect after adjustment for CO and O_3.

The other U.S. study examined birth defects through a case-control design in seven Texas counties for the period 1997-2000 (Gilboa et al., 2005, 087892). Births were excluded for parents <18 yr and several non-air pollution risk factors known to be associated with birth defects (e.g., maternal diabetes, holoprosencephaly in addition to oral clef). Comparison of the highest (≥ 29.0 μg/m^3) and lowest (<19.521 μg/m^3) quartiles of PM_{10} for exposure defined as the third to eighth week of pregnancy generated an OR of 2.27 (95% CI: 1.43-3.60) for risk of isolated atrial septal defects and 1.26 (95% CI: 1.03-1.55) for individual atrial septal defects. Including other pollutants (CO, NO_2, O_3, SO_2) in the model did not greatly alter results; numerical results for copollutant analysis were not provided. Strong evidence was not observed for a relationship between PM_{10} and the other birth defect categories. Review articles have concluded that the scientific literature is not sufficient to conclude a relationship between air pollution and birth defects (Sram et al., 2005, 087442).

A recent study of oral clefts conducted in Taiwan found no association between this birth defect and concentrations of PM_{10} during the first or second gestational month (Hwang and Jaakkola, 2008, 193794). This population-based case-control study included 653 cases and a random sample of 6,530 controls born in Taiwan between 2001 and 2003.

7.4.1.5. Infant Mortality

Many studies have identified strong associations between exposure to particles and increased risk of mortality in adults or the general population, including for short- and long-term exposure (Sections 6.5 and 7.6). Less evidence is available for the potential impact on infant mortality, although studies have been conducted in several countries. The results of these infant mortality studies are presented here with the other reproductive and developmental outcomes because it is likely that in vitro exposures contribute to this outcome. Both long-term and short-term exposure studies of infant mortality are included in this section. Results on PM and infant mortality includes a range of findings, with some studies finding associations and many statistically non-significant or null effects. Yet, more consistency is observed when results are divided into the type of health outcome based on the age of infant and cause of death.

An important question regarding the association between PM and infant mortality is the critical window of exposure during development for which infants are susceptible. Several age intervals have been explored: neonatal (<1 mo); infants (<1 yr); and postneonatal (1 mo-1 yr). Within these various age categories, multiple causes of deaths have been investigated, particularly total deaths and respiratory-related deaths. The studies reflect a variety of study designs, particle size ranges, exposure periods, regions, and adjustment for confounders.

Stillbirth

Only one study of stillbirths and PM was identified. A prospective cohort of pregnant women in Seoul, Korea from 2001 to 2004 was examined with respect to exposure to PM_{10} (Kim et al., 2007, 156642). Gestational age was estimated by the last menstrual period or by ultrasound. Whereas many of the previously discussed studies of PM and pregnancy outcomes were based on national registries, this study examined medical records and gathered individual information through interviews on socioeconomic condition, medical history, pregnancy complications, smoking, second-hand smoke exposure, and alcohol use. Mother's exposure to PM_{10} was based on residence for each month of pregnancy, each trimester defined as a three month period, and the 6 wk prior to death. Exposure was assigned by the nearest monitor. A 10 $\mu g/m^3$ increase in PM_{10} in the third trimester was associated with an 8% (95% CI: 2-14) increase in risk of stillbirth.

In São Paulo, Brazil, Poisson regression of stillbirth counts for the period 1991-1992 found that a 10 $\mu g/m^3$ increase in PM_{10} was associated with a 0.8% increase in stillbirth rates (Pereira et al., 1998, 007264). When other pollutants (NO_2, SO_2, CO, O_3) were included simultaneously in the model, the association did not remain. Stillbirths were defined as fetal loss at >28 wk of pregnancy age, weight >1,000 g, or length of fetus >35 cm.

Neonatal Mortality and Neonatal Respiratory Mortality, <1 Month

Studies on PM and neonatal mortality (<1 month) included a time-series analysis of PM_{10} for 4 yr of data (1998-2000) for São Paulo, Brazil (Lin et al., 2004, 095787). The analysis used daily counts of deaths from government registries and adjusted for temporal trend, day of the week, weather, and holidays. Findings indicated that a 10 $\mu g/m^3$ increase in PM_{10} was associated with a 1.71% (95% CI: 0.31-3.32) increase in risk of neonatal death.

A case-crossover study of 11 yr (1989-2000) in Southern California did not find an association between PM_{10} and neonatal deaths (Ritz et al., 2006, 089819). Quantitative results were not provided. The authors considered adjustment for season, county, parity, gender, prenatal care, and maternal age, education, and race/ethnicity.

These results add to previous work on PM and neonatal death, including studies identifying higher risk of neonatal mortality with higher TSP in the Czech Republic in an ecological analysis (Bobak and Leon, 1992, 044415) and case-crossover study (Bobak and Leon, 1999, 007678), and a

Poisson model study in Kagoshima City, Japan (Shinkura et al., 1999, 090050). An ecological study evaluated U.S. PM_{10} data for the year 1990 using long-term pollution levels in 180 U.S. counties (Lipfert et al., 2000, 004103). Analysis considered birth weight, sex, month of birth, location by state and county, prenatal care, and mother's race, age, educational level, marital status, and smoking status. County-level variables were included for socioeconomic status, altitude, and climate. Results indicate a 13.1% increase in neonatal mortality (95% CI: 4.4-22.6) per 10 $\mu g/m^3$ PM_{10} for non-low birth weight infants. Statistically significant associations were also observed considering all infants or low birth weight infants. However, higher levels of SO_2 were associated with lower risk of infant mortality. When sulfate and an estimate of non-sulfate particles were included in the regression simultaneously, associations were observed with non-sulfate particles and an inverse relationship with sulfate particles. Respiratory neonatal mortality was not associated with higher TSP in the Czech Republic case-control study (Bobak and Leon, 1999, 007678).

Infant Mortality and Infant Respiratory Mortality, <1Year

A literature search did not reveal new studies on PM and infant mortality (<1 year) since the previous PM AQCD. Previously conducted studies include a case-control study that reported associations between infant mortality and TSP levels over the period between birth and death for infants in the Czech Republic (Bobak and Leon, 1999, 007678). An ecological study evaluated U.S. PM_{10} data for the year 1990 using long-term pollution levels in 180 U.S. counties (Lipfert et al., 2000, 004103). The authors found a 9.64% (95% CI: 4.60-14.9) increase in risk of infant mortality for non-low birth weight infants per 10 $\mu g/m^3$ increase in PM_{10}, a 13.4% (95% CI: -10.3 to 43.5) increase in non-low birth weight respiratory-disease related deaths (ICD 9 460-519) and a 19.5% (95% CI: 0.07-42.8) increase in all non-low birth weight respiratory-related infant deaths (ICD 9 460-519, 769, 770).

Postneonatal Mortality and Postneonatal Respiratory Mortality, 1 Month–1 Year

Several studies have been conducted on PM and postneonatal mortality since the previous PM AQCD, including three from the U.S., one from Mexico, and three from Asia. Two case-control studies examined the risk of PM to postneonatal death in California. Research focused on Southern California for the period 1989-2000 linked birth and death certificates and considered PM_{10} 2 mo prior to death with adjustment for prenatal care, gender, parity, county, season, and mother's age, race/ethnicity, and education (Ritz et al., 2006, 089819). As previously noted, this study did not find an association between PM_{10} and neonatal mortality (<1 month), however an association was observed for post-neonatal mortality, with a 10 $\mu g/m^3$ increase in PM_{10} associated with a 4% (95% CI: 1-6) increase in risk. The exposure period of 2 wk before death was also considered, producing effect estimates of 5% (95% CI: 1-10) for the same PM_{10} increment. Even larger effect estimates were observed for those who died at ages 4-12 mo. When CO, NO_2, and O_3 were simultaneously included with PM_{10} in the model, the central estimate reduced to 2% for the 2-wk exposure period and 4% for the 2-mo exposure period, and both estimates lost statistical significance. The other case-control study of California considered $PM_{2.5}$ from 1999 to 2000 for infants born to mothers within five miles of a $PM_{2.5}$ monitoring station (Woodruff et al., 2006, 088758). Infants who died during the postneonatal period were matched to infants with date of birth within 2 wk and birth weight category. Exposure was estimated from the time of birth to death. Models considered parity and maternal race, education, age, and martial status. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7% (95% CI: -7 to 24) increase in postneonatal death

County-level PM_{10} and $PM_{2.5}$ for the first 2 mo of life for births in urban U.S. counties ($\geq$ 250,000 residents) from 1999 to 2002 were evaluated in relation to postneonatal mortality with GEE models (Woodruff et al., 2008, 098386). Births were restricted to singleton births with gestational age $\leq$ 44 wk, same county of residence at birth and death, and non-missing data on birth order, birth weight, and maternal race, education, and martial status. Higher levels of either PM metric were associated with higher risk of postneonatal mortality, with 4% (95% CI: -1 to 10) increase in mortality risk per 10 $\mu g/m^3$ in PM_{10} and 4% (95% CI: -2 to 11) increase in mortality risk for the same increment of $PM_{2.5}$. This work builds on a previous study of 86 U.S. urban areas from

1989 to 1991, finding a 4% (95% CI: 2-7) increase in postneonatal mortality per 10 μg/m^3 county-level PM_{10} over the first 2 mo of life (Woodruff et al., 1997, 084271).

In Ciudad Juarez, Mexico, a case-crossover approach was applied to data from 1997 to 2001 based on death certificates and the cumulative PM_{10} for the day of death and previous two days (Romieu et al., 2004, 093074). A case-crossover study of Kaohsiung, Taiwan from 1994 to 2000 compared the average of PM_{10} on the day of death and two previous days to PM_{10} in control periods a week before and week after death (Tsai et al., 2006, 090709). A similar approach was also applied to 1994-2000 data from Taipei, Taiwan, also using case-crossover methods for the lag 0-2 PM_{10} with referent periods the week before and after death (Yang et al., 2006, 090760). In these case-crossover studies, season was addressed through matching in the study design. A 10 μg/m^3 increase in PM_{10} was associated with a 2.0% (95% CI: -2.8 to 7.0) increase in the Mexico study, a 0.59 (95% CI: -15.0 to 18.8) increase in postneonatal death in the Kaohsiung study, and a 1.02% (95% CI: -13.2 to 17.6) increase in the Taipei study. A study in Seoul, South Korea from 1995 to 1999 used time-series approaches adjusted for temporal trend and weather, based on national death registries excluding accidental deaths (Ha et al., 2003, 042552). A 10 μg/m^3 increase in PM_{10} was associated with a 3.14% (95% CI: 2.16-4.14) increase in risk of death for postneonates.

A subset of the studies examining postneonatal mortality also considered the subset of postneonatal deaths from respiratory causes. These include the time-series study in South Korea, finding a 17.8% (95% CI: 14.4-21.2) increase in respiratory-mortality per 10 μg/m^3 increase in PM_{10} (Ha et al., 2003, 042552) and the case-crossover study in Mexico, for which the same increment in PM_{10} was associated with a 1.5% (95% CI: -14.1 to 13.0) decrease in risk (Romieu et al., 2004, 093074). Both California case-control studies identified associations, with a 5% (95% CI: 1-10) increase in risk in Southern California (Ritz et al., 2006, 089819) and 57.4% (95% CI: 7.0-132) increase in California per 10 μg/m^3 PM_{10} (Woodruff et al., 2006, 088758). The U.S. study found this increment in PM_{10} to be linked with a 16% (95% CI: 6.0-28.0) increase in respiratory postneonatal mortality, although effect estimates for $PM_{2.5}$ were not statistically significant (Woodruff et al., 2008, 098386). Earlier studies on respiratory-related postneonatal mortality include the study of 86 U.S. urban areas, finding statistically significant effects (Woodruff et al., 1997, 084271).

Sudden Infant Death Syndrome

Three studies examining the relationship between PM and sudden infant death syndrome (SIDS) have been published from 2002 onward. These studies examined infant mortality and were thereby discussed in this section previously. A case-control study over a 12-year period (1989 to 2000) matched 10 controls to deaths (cases) in Southern California (Ritz et al., 2006, 089819). A 10 μg/m^3 increase in PM_{10} the 2 mo prior to death was associated with a 3% (95% CI: -1 to 8) increase in SIDS. Adjusted for other pollutants (CO, NO_2, and O_3), the effect estimate reduced to 1% (95% CI: -5 to 7).

A case-control study, also based in California, found an OR of 1.008 (95% CI: 1.006-1.012) per 10 μg/m^3 increase in $PM_{2.5}$, considering a SIDS definition of ICD 10 R95 (Woodruff et al., 2006, 088758). Due to changes in SIDS diagnosis, another SIDS definition was explored for ICD 10 R99 in addition to ICD 10 R95. Under this SIDS definition, the effect estimate changed to 1.03 (95% CI: 0.79-1.35). The authors also examined whether the relationship between $PM_{2.5}$ and SIDS differed by season, finding no significant difference. PM_{10} and $PM_{10-2.5}$ were not associated with risk of SIDS; numerical results were not provided for these PM metrics. The third recent study of PM and SIDS examined U.S. urban counties from 1999 to 2002 (Woodruff et al., 2008, 098386). Statistically non-significant relationships were observed between SIDS and PM_{10} or $PM_{2.5}$ in the first 2 mo of life.

These studies add to earlier work, such as a U.S. study that found higher risk of SIDS with higher annual $PM_{2.5}$ levels, including in a separate analysis of normal birth weight infants (Lipfert et al., 2000, 004103), and a U.S. study identifying a 12% (95% CI: 7-17) increase in SIDS risk per 10 μg/m^3 in PM_{10} for the first 2 mo of life for normal weight births (Woodruff et al., 1997, 084271). A study based on Taiwan found higher SIDS risk with lower visibility (Knöbel et al., 1995, 155905), whereas a 12-city Canadian time-series study identified no significant associations (Dales et al., 2004, 087342).

Deaths by SIDS were identified by different methods in the studies, partly due to transition from ICD 9 to ICD 10 codes, but also due to different choices within the research design. Two studies examined multiple approaches (ICD 10 R95, ICD 10 R95 and R99) (Woodruff et al., 2006,

088758; Woodruff et al., 2008, 098386), and other studies investigated ICD 9 798.0 and ICD 10 R95 (Ritz and Wilhelm, 2008, 156914), ICD 9 798.0 (Woodruff et al., 1997, 084271), ICD 9 798.0 and 799.0 (Knöbel et al., 1995, 155905), as well as a sudden unexplained death of infant <1 year for which an autopsy did not identify a specific cause of death (Dales et al., 2004, 087342). These variations in the definition of health outcomes add to differences in populations and study designs.

Although some findings indicate a potential effect of PM on risk of SIDS, with the strongest evidence perhaps from the case-control study in California (Woodruff et al., 2006, 088758), others do not find an effect or observe an uncertain association. For the relationship between PM and SIDS, a 2004 review article concluded consistent evidence exists compared to evidence for other infant mortality effects (Glinianaia et al., 2004, 087898), whereas other reviews found weaker or insufficient evidence (Heinrich and Slama, 2007, 156534). Another review concluded that the scientific literature on air pollution and SIDS suggests an effect, but that further research is needed to draw a conclusion (Tong and Colditz, 2004, 087883).

Considerations for Comparisons across Studies

Comparison of results across studies can be challenging due to several issues, including differences in methodologies, populations and study areas, pollution levels, and the exposure timeframes used. Given the large variation in study designs, the methods to address potential confounders vary. For example, weather and season were addressed in the case-control studies by matching, in the time-series study through non-linear functions of temperature and temporal trend, and in the ecological study through county-level variables. All studies included consideration of seasonality and weather. Researchers used different definitions of respiratory-related deaths, including ICD 9 460-519 (Bobak and Leon, 1999, 007678; Lipfert et al., 2000, 004103); ICD 9 460-519, 769-770 (Lipfert et al., 2000, 004103); ICD 9 460-519, 769, 770.4, 770.7, 770.8, 770.9, and ICD 10 J00-J98, P22.0, P22.9, P27.1, P27.9, P28.0, P28.4, P28.5, and P28.9 (Ritz et al., 2006, 089819); and ICD 9 460-519 and ICD 10 J00-J99 for any cause on death certificate (Romieu et al., 2004, 093074); ICD 10 J00-99 and P27.1 excluding J69.0 (Woodruff et al., 2006, 088758; Woodruff et al., 2008, 098386); and ICD 9 460-519 (Woodruff et al., 1997, 084271).

Socioeconomic conditions were included at the individual level, typically maternal education, in many studies (e.g., Bobak and Leon, 1999, 007678; Ritz and Wilhelm, 2008, 156914; Ritz et al., 2006, 089819; Woodruff et al., 1997, 084271; Woodruff et al., 2006, 088758) and at the community-level in others (e.g., Bobak and Leon, 1992, 044415; Penna and Duchiade, 1991, 073325) or for both individual and community-level data (e.g., Lipfert et al., 2000, 004103). The time-series approach is unlikely to be confounded by socioeconomic and other variables that do not exhibit day-to-day variation. Similarly, case-crossover methods use each case as his/her own control, thereby negating the need for individual-level confounders such as socioeconomic status (e.g., Romieu et al., 2004, 093074; Tsai et al., 2006, 090709; Yang et al., 2006, 090760). All studies published after 2001 incorporated individual-level socioeconomic data or were of case-crossover or time-series design. One study specifically examined whether socioeconomic status modified the PM and mortality relationship, dividing subjects into three socioeconomic strata based on the ZIP code of residence at death (Romieu et al., 2004, 093074). This work, based in Mexico, found that at lower socio-economic levels the association between PM_{10} and postneonatal mortality increased. Although the overall association showed higher risk of death with higher PM_{10} with statistical uncertainty, for the lowest socio-economic group, a 10 $\mu g/m^3$ increment in cumulative PM_{10} over the 2 days before death was associated with a 60% (95% CI: 3-149) increase in postneonatal death. A trend of higher effect for lower socio-economic condition is observed in all 3 lag structures.

Studies differ in terms of the time frame of pregnancy that was used to estimate exposure. Exposure to PM for infant mortality (<1 yr) was estimated as the levels between birth and death (Bobak and Leon, 1999, 007678), annual community levels (Lipfert et al., 2000, 004103; Penna and Duchiade, 1991, 073325) and the 3-5 days prior to death (Loomis et al., 1999, 087288). For neonatal deaths, exposure timeframes considered were the time between birth and death (Bobak and Leon, 1992, 044415; Bobak and Leon, 1999, 007678), annual levels (Bobak and Leon, 1999, 007678; Lipfert et al., 2000, 004103), monthly levels (Shinkura et al., 1999, 090050), the same day concentrations (Lin et al., 2004, 095787), and the 2 mo or 2 wk prior to death (Ritz et al., 2006, 089819). Postneonatal mortality was associated with PM concentrations based on annual levels (Bobak and Leon, 1992, 044415; Lipfert et al., 2000, 004103), between birth and death (Bobak and

Leon, 1999, 007678; Woodruff et al., 2006, 088758), 2 mo before death (Ritz et al., 2006, 089819), the first 2 mo of life (Woodruff et al., 1997, 084271; Woodruff et al., 2006, 088758), the day of death (Ha et al., 2003, 042552), and the average of the same day as death and previous 2 days (Romieu et al., 2004, 093074; Tsai et al., 2006, 090709; Yang et al., 2006, 090760). Thus, no consistent window of exposure was identified across the studies.

PM_{10} concentrations were highest in South Korea (69.2 $\mu g/m^3$) (Ha et al., 2003, 042552) and Taiwan (81.45 $\mu g/m^3$) (Tsai et al., 2006, 090709), and lowest in the U.S. (29.1 $\mu g/m^3$) (Woodruff et al., 2008, 098386) and Japan (21.6 $\mu g/m^3$) (Shinkura et al., 1999, 090050). All studies used community-level exposure information based on ambient monitors, as opposed to exposure measured at the individual level (e.g., subject's home) or personal monitoring.

Given similar sources for multiple pollutants (e.g., traffic), disentangling the health responses of copollutants is a challenge in the study of ambient air pollution. Several studies examined multiple pollutants, most by estimating the effect of different pollutants through several univariate models. Some studies noted the difficulty of separating PM effects from those of other pollutants, but noted stronger evidence for particles than other pollutants (Bobak and Leon, 1999, 007678). A few studies applied copollutant models by including multiple pollutants simultaneously in the same model. Effect estimates for the relationship between PM_{10} and neonatal deaths in São Paulo were reduced to a null effect when SO_2 was incorporated (Lin et al., 2004, 095787). Associations between PM_{10} and postneonatal mortality or respiratory postneonatal mortality remained but lost statistical significance in a multiple pollutant model with CO, NO_2, and O_3 (Ritz et al., 2006, 089819).

Several review articles in recent years have examined whether exposure to PM affects risk of infant mortality, generally concluding that more consistent evidence has been observed for postneonatal mortality, particularly from respiratory causes (Bobak and Leon, 1999, 007678; Heinrich and Slama, 2007, 156534; Lacasaña et al., 2005, 155914; Sram et al., 2005, 087442). In one review authors identified 14 studies on infant mortality and air pollution and determined that studies on PM and infant mortality do not provide consistent results, although more evidence was present for an association for some subsets of infant mortality such as postneonatal respiratory-related mortality (Bobak and Leon, 1999, 007678). The relationship between PM and postneonatal respiratory mortality was concluded to be causal in one review (Sram et al., 2005, 087442), and strong and consistent in another (Heinrich and Slama, 2007, 156534). Meta-analysis using inverse-variance weighting of PM_{10} studies found that a 10 $\mu g/m^3$ increase in acute PM_{10} exposure was associated with 3.3% (95% CI: 2.4-4.3) increase in risk of postneonatal mortality, whereas the same increment of chronic PM_{10} exposure was linked with a 4.8% (95% CI: 2.2-7.2) increase in postneonatal mortality and a 21.6% (95% CI: 10.2-34.2) increase for respiratory postneonatal mortality (Lacasaña et al., 2005, 155914).

Studies that examined multiple outcomes and ages of death allow a direct comparison based on the same study population and methodologies, thereby negating the concern that inconsistent results are due to underlying variation in population, approaches, etc. In this review, one study, based in Southern California identified no association for neonatal effects (numerical results not provided) but statistically significant results for postneonatal mortality (Ritz et al., 2006, 089819). Figure 7-5compares risk for the postneonatal period for respiratory and total mortality. In six of the seven studies, higher effect estimates were observed for respiratory-related mortality. Results from the neonatal period found higher effects for total mortality compared to respiratory mortality (Bobak and Leon, 1999, 007678) and the reverse for a study examining infant mortality (Lipfert et al., 2000, 004103). Thus, there exists evidence for a stronger effect at the postneonatal period and for respiratory-related mortality, although this trend is not consistent across all studies.

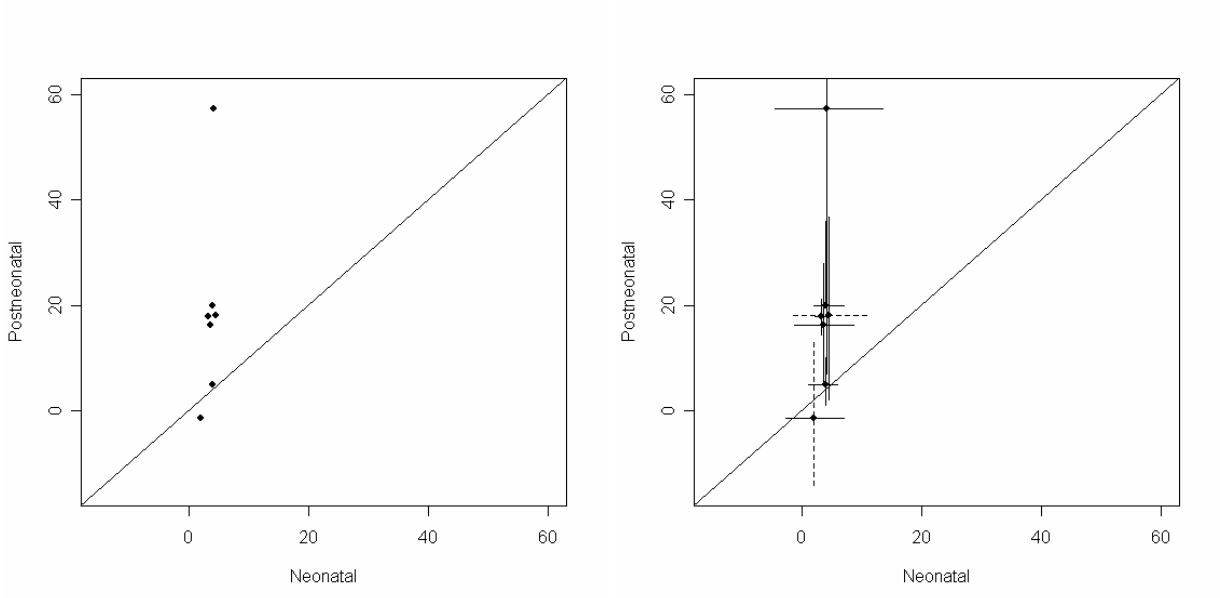


Figure 7-5. Percent increase in postneonatal mortality per 10 µg/m^3 in PM_{10}, comparing risk for total and respiratory mortality. Panel a (left) provides central estimates; panel b (right) also adds the 95% intervals. The points reflect central estimates and the lines the 95% intervals. Solid lines represent statistically significant effect estimates; dashed lines represent non-statistically significant estimates.[1]

7.4.1.6. Decrements in Sperm Quality

Limited research conducted in the Czech Republic on the effect of ambient air pollution on sperm production has found associations between elevated air pollution and decrements in proportionately fewer motile sperm, proportionately fewer sperm with normal morphology or normal head shape, proportionately more sperm with abnormal chromatin (Selevan et al., 2000, 012578), and an increase in the percentage of sperm with DNA fragmentation (Rubes et al., 2005, 078091). These results were not specific to PM, but for exposure to a high-, medium- or low-polluted air mixture. Similarly, in Salt Lake City, Utah, $PM_{2.5}$ was associated with decreased sperm motility and morphology (Hammoud et al., 2009, 192156). Research in Los Angeles, California examined 5,134 semen samples from 48 donors in relation to ambient air pollution measured 0-9, 10-14, 70-90 days before semen collection over a 2-yr period (1996-1998). Ambient O_3 during all exposure periods had a significant negative correlation with average sperm concentration, and no other pollutant measures were significantly associated with sperm quality parameters, or presented quantitatively (Sokol et al., 2006, 098539).

7.4.2. Toxicological Studies

This section summarizes recent evidence on reproductive health effects reported with exposure to ambient PM; no evidence was presented in this area in the 2004 PM AQCD. Studies from different toxicological rodent models allow for investigation of specific mechanisms and modes of

[1] Studies included are Bobak and Leon (1999, 007678), Ha et al. (2003, 042552), Ritz et al. (2006, 089819), Romieu et al. (2004, 093074), Romieu et al. (2008, 156922), Woodruff et al. (1997, 084271), Woodruff et al. (2006, 088758). Findings from Bobak and Leon (1999, 007678) were based on TSP and were converted to PM_{10} estimates assuming $PM_{10}/TSP = 0.8$ as per summary data in the original article (Bobak and Leon, 1999, 007678). Findings from Woodruff et al. (1997, 084271) for respiratory-related mortality were based on non-low birth weight infants. Results for Woodruff et al. (2006, 088758) were based on $PM_{2.5}$ and were converted to PM_{10} assuming $PM_{2.5}/PM_{10} = 0.6$.

action for reproductive changes. Emphasis is placed here on results from different windows of development, i.e., exposure in utero, neonatally or as an adult can affect reproductive outcomes as an adult. In addition, studies evaluating whether fertility is affected in female and/or male animals by a similar exposure, and how exposures are transmitted to the fertility of the F_1 offspring, are summarized. Hormonal changes which can lead to decreased sperm count or changes in the estrous cycle are also of interest. Studies of pregnancy losses and placental sufficiency are also reported. Most recently, the role of environmental chemicals in shifting sex ratios (also seen in epidemiologic studies) and in affecting heritable DNA changes have become outcomes of interest.

7.4.2.1. Female Reproductive Effects

Urban Air

Windows of exposure are important in determining reproductive success as an adult. Exposure as a neonate may have a drastically different impact than does a similar adult exposure. To test this, female BALB/C mice were exposed to ambient air in Sao Paulo as neonates or as adults and then were bred to non-exposed males (Mohallem et al., 2005, 088657). Ambient concentrations of the pollutants CO, NO_2, PM_{10}, and SO_2 were 2.2 ± 1.0 ppm, 107.8 ± 42.3 μg/m^3 , 35.5 ± 12.8 μg/m^3, and 11.2 ± 5.3 μg/m^3, respectively. They reported decreased fertility in animals exposed as newborns, but not in adult-exposed female BALB/c mice. There were a significantly higher number of liveborn pups from dams housed in filtered chambers (PM and gaseous components removed) versus animals exposed to ambient air as newborns. There was also a higher incidence of implantation failures in dams reared as newborns in polluted chambers. Sex ratio, number of pregnancies per group, resorptions, fetal deaths, and fetal placental weights did not differ significantly by exposure group. Thus, in these studies, exposure to ambient air pollution affected future reproductive success of females if they were exposed as neonates and not if exposed as adults.

Diesel Exhaust

Significant work has been done in male rodent models to determine the effect of PM exposure on reproductive outcomes, with fewer studies conducted using female rodents. Tsukue et al. (2004, 096643) exposed pregnant C57-BL mice to DE (0.1 mg/m^3) or to clean air (controls) for 8 h/day from GD2-13. The concentration of the gaseous materials including NO, NO_X, NO_2, CO and SO_2 are 2.2 ± 0.34 ppm, 2.5 ± 0.34 ppm, 0.0 ppm, 9.8 ± 0.69 ppm, and <0.1 ppm (not detectable), respectively. At GD14 female fetuses were collected for analysis of mRNA for two genes involved in sexual differentiation (Ad4BP-1/SF-1 and MIS), and found no significant changes. Work by Yoshida et al. (2006, 097015) showed changes in these two transcripts in male ICR fetuses exposed to similar concentrations of DE, albeit with different daily durations of exposure. Further work by Yoshida et al. (2006, 097015) showed that of three mouse strains tested, ICR male fetuses were the most sensitive to DE-dependent changes in these two genes. Nonetheless, strain sensitivity to DE particles may also differ by sex. Thus, it appears that female mice exposed in utero to DE show a lack of response at the mRNA level of MIS or Ad4bP-1/SF-1, important genes in male sexual differentiation that showed DE-dependent changes in male pups from dams exposed in utero. Female fetuses have shown a decrease in BMP-15, which is related to oocyte development (Tsukue et al., 2004, 096643).

A sensitive measure of androgenic activity in male rodents is anogenital distance (AGD), i.e., decreased AGD is seen with exposure to anti-androgenic environmental chemicals, the phthalates (Foster et al., 1980, 094701; Foster et al., 2001, 156442). To assess the role of DE exposure on reproductive success and anti-androgenic effects on offspring, Tsukue et al. (2002, 030593) exposed 6 week-old female C57-Bl mice to 4 mo of DE (0.3, 1.0, or 3.0 mg/m^3; PM MMAD of 0.4 μm) or filtered air. DE-exposed estrous females had significantly decreased uterine weight (1.0 mg/m^3). Some of the DE-exposed females were bred to unexposed males and DE-exposure led to increased, albeit not significantly increased, rates of pregnancy loss in mated females (up to 25%). Offspring were weighed after birth and decreases in body weight were observed at 6 and 8 wk (males and females, 1.0 and 3.0 mg/m^3) and 9 wk (females, 1.0 and 3.0 mg/m^3). Anogenital distance was decreased in 70-day old DE-exposed male offspring (0.3 mg/m^3). In female offspring at 70 days of

age, lower organ weights (adrenals, liver, and thymus) were observed (1.0 mg/m^3) compared to controls; thymus weight of the 0.3 mg/m^3 females was also lower at 70 days. Crown to rump length in females from dams exposed to DE (1.0 and 3.0 mg/m^3) was less than the control group. In conclusion, adult exposure to DE led to maternal-dependent reproductive changes that affected outcomes in offspring that manifested as decreased pup body weight, anti-androgenic effects like decreased AGD and decreased organ weight (which may have been confounded by changes in body weight because weights were not reported as relative organ weights).

7.4.2.2. Male Reproductive Effects

Diesel Exhaust

Studies were performed to determine PM-dependent strain sensitivity of the male reproductive tract using male steroidogenic enzymes as the model pathway. Three strains of pregnant mice (ICR, C57Bl/6J or ddY mice) were continuously exposed to DE at 0.1 mg/m^3 via inhalation or clean air over gestational days 2-13 (Yoshida et al., 2006, 156170). At GD14, dams were euthanized and fetuses were collected. Male fetuses were collected from each dam for mRNA analysis of genes related to male gonad development including Mullerian inhibiting substance (MIS; crucial for sexual differentiation including Mullerian duct regression in males), steroid transgenic factor (Ad4BP/SF-1, an enzyme in the testosterone synthesis pathway), cytochrome P450 cholesterol side chain cleavage enzyme (P450scc), and other steroidogenic enzymes [17β-hydroxysteroid dehydrogenase (HSD), cytochrome P450 17-α-hydroxylase (P450c17), and 3-βhydroxysteroid dehydrogenase (3βHSD)]. There were significant decreases in MIS (ICR and C57BL/6 mice) and Ad4BP/SF-1 (ICR mice) compared to the control groups. The ddY strain demonstrated no changes in Ad4BP/SF-1 or MIS, which may be due to marked changes in 3β-hD expression compared to non-DE exposed controls. From these studies, it appears that mouse strains with in utero exposure to DE show differential sensitivity in gonadal differentiation genes (mRNA) expression in male offspring; ICR are the most sensitive, followed by C57BL/6, with ddY mice being the least sensitive.

Yoshida et al. (2006, 097015) also monitored changes in the male reproductive tract after in utero exposure to DE. Timed-pregnant ICR dams were exposed during gestation (2 days post-coitus [dpc]-16 dpc) to continuous DE (0.3, 1.0 or 3.0 mg/m^3) or clean air. The reproductive tracts of male offspring were monitored at 4 wk postnatally. These pups received possible continued exposure through lactation as dams were exposed to DE during gestation and nursed pups. Exposure to 0.3 mg/m^3 of DE had no effect on male reproductive organ weight or serum testosterone. The intermediate concentration of 1.0 mg/m^3 induced increases in serum testosterone. Exposure to the higher concentration (1.0 and 3.0 mg/m^3) of DE led to significant increases in reproductive gland weight (testis, prostate, and coagulating gland). The organ weights are presented as absolute numbers and not adjusted for body weight, which is sometimes problematic for complete representation of hormonal changes, as body weight may confound absolute organ weight changes. Transcripts relating to male sexual differentiation (MIS and AD4BP/SF-1, 1.0 and 3.0 mg/m^3) were also significantly decreased. Sexual differentiation is a tightly regulated process and these changes in transcription may lead to changes that can affect genitalia development.

The effects of DE exposure on male spermatogenesis have also been demonstrated. Exposure of pregnant ICR mice to DE (2-16 dpc continuous inhalation exposure to 1.0 mg/m^3 or filtered clean air) led to impaired spermatogenesis in offspring (Ono et al., 2007, 156007). Male offspring were followed at PND 8, 16, 21 (3 wk), 35 (5 wk) and 84 (12 wk). After 16 dpc, but before termination of the study, all of the animals were transferred to a regular animal care facility and received clean air exposure until the termination of the study. No cross fostering was performed in this experiment, so pups that were born to DE-exposed dams were also nursed on these dams and may have received lactational exposure to DE. The gaseous components of the diluted DE included NO, NO_2, SO_2, and CO_2 at concentrations of 11.75 ± 1.18, 4.62 ± 0.36, 0.21 ± 0.01, and 4922 ± 244 ppm, respectively. Body weight was significantly depressed at PNDs 8 and 35. Accessory gland relative weight was significantly increased at PND8 and PND16 only. Serum testosterone was significantly decreased at 3 wk and was significantly increased at 12 wk. At 5 and 12 wk, daily sperm production (DSP) was significantly decreased. FSH receptor and StAR mRNA levels were significantly increased at 5 and 12 wk, respectively. Relative testis weight and relative epididymal weight were unchanged at all

time points. Histological changes showed sertoli cells with partial vacuolization and a significant increase in testicular multinucleated giant cells in the seminiferous tubules of DE-exposed animals compared to control. This study indicates that in utero exposure to DE had effects on spermatogenesis in offspring at the histological, hormonal and functional levels.

In utero exposure to DE and its effect on adult body weight, sex ratio, and male reproductive gland weight was measured by Yoshida et al. (2006, 097015). Pregnant ICR mice were exposed by inhalation to DE (0.3, 1.0 or 3.0 mg/m^3) or clean air from 2 dpc to 16 dpc. Pups were allowed to nurse in clean air on exposed dams until weaning and at PND28, male pups were sacrificed. At this time, serum testosterone and pup reproductive gland weight was determined. Significant increases in relative reproductive organ weights were reported at 1.0 and 3.0 mg/m^3 for the seminal vesicle, testis, epididymis, coagulating gland, prostate and liver. Male pup serum testosterone was significantly increased at 1.0 mg/m^3. Mean testosterone positively correlated with testis weight, DSP, aromatase and steroidogenic enzyme message levels (P450cc, c17 lyase, and P450 aromatase). Sex ratio did not differ in DE-exposed animals versus control. Male pup body weight of DE-exposed animals was significantly increased at PND28 (1.0 and 3.0 mg/m^3). These studies show that in utero DE-exposure led to increased serum testosterone and increased reproductive gland weight in male offspring early in life.

The effects of DE on murine adult male reproductive function were studied by exposing ICR male mice (6 wk of age) to DE (clean air control, 0.3, 1.0 or 3.0 mg/m^3) for 12 h/day for 6 mo with another group receiving a 1-mo recovery of clean air post-exposure (Yoshida and Takedab, 2004, 097760). After 6 mo of DE exposure, there was a concentration-dependent increase in degeneration of seminiferous tubules and a decrease in DSP/g of testis tissue. After 6 mo exposure to DE particles plus 1 mo of recovery in clean air, significant decreases remained in DSP at the two highest concentrations. The effect of ingestion of deposited PM on the fur with grooming cannot be ruled out as a possible exposure pathway in this experiment.

To expand on PM-dependent changes in spermatogenesis, an eloquent DE-exposure model was designed to determine if PM or the gaseous phase of DE was responsible for changes in sperm production in rodents (Watanabe, 2005, 087985). Pregnant dams (F344/DuCrj rats) exposed to DE (6 h/day exposure to 0.17 or 1.71 mg/m^3; <90% of PM less than 0.5 μm; NO_2 concentrations 0.10 and 0.79 ppm, respectively) or filtered air (removing PM only, low concentration filtered air and high concentration filtered air) from GD7 to parturition produced adult male offspring with a decreased number of sertoli cells and decreased DSP (PND 96) when compared to control mice exposed to clean air. The concentrations of NO_2 for the low and high filtered exposure groups were 0.1 and 0.8 ppm, respectively. Because both PM-filtered and DE-exposure groups showed the same outcomes, the effects are likely due to gaseous components of DE.

Motorcycle Exhaust

Adult male (8-wk old) Wistar rats were exposed to motorcycle exhaust (ME) for 1 h in the morning and 1 h in the afternoon (5 day/wk) at 1:50 dilution for 4 wk (group A), 1:10 dilution for 2 wk (group B) or 4 wk (group C), or to clean air (Huang et al., 2008, 156574). After 4 wk of exposure, both exposed groups had significantly decreased body weight compared to the control group. All three ME exposure groups showed a decreased number of spermatids in the testis. Both 1:10 exposure groups also demonstrated decreased caudal epididymal sperm counts. Group C had significant decreased testicular weight, decreased mRNA expression for the cytochrome P450 substrate 7-ehtoxycoumarin O-de-ethylase, and increased IL-6, IL-1β, and COX-2 mRNA levels. Decreased protein levels of the antioxidant, superoxide dismutase, and increased IL-6 protein were reported for group C when compared to control. In addition, serum testosterone was significantly decreased in group C. Co-treatment with the antioxidant vitamin E resulted in partial attenuation of serum testosterone levels and caudal epididymal sperm counts, and returned IL-6, IL-1β, and COX-2 ME exposure-dependent message levels to baseline. The glutathione antioxidant system and lipid peroxidation were unchanged. In conclusion, male animals exposed to ME showed significant decrements in body weight, spermatid number, and serum testosterone with an increase in inflammatory cytokines. Vitamin E co-treatment with ME-exposure led to an attenuation of inflammation and a partial rescue of testosterone levels and sperm numbers.

Summary of Toxicological Study Findings for Male Reproductive Effects

In summary, laboratory animals exposed to DE in utero or as adults manifest with abnormal effects on the male reproductive system. In utero exposure to DE induced increased reproductive gland weight and increased serum testosterone in early life (PND28), which may lead to early puberty (albeit not measured in this study). With similar in utero DE exposures, later life outcomes include decreased DSP, aberrant sperm morphology, and hormonal changes (testosterone and FSHr decrements). Chronic exposure of adult mice to DE also induced decreased DSP and seminiferous tubule degeneration. DE-dependent effects on male reproductive function have been reported in multiple animal models, with only one model separating exposure based on particulate versus gaseous components. DE and filtered air (gaseous phase only) exposure in utero induced sertoli cell and DSP decrements in both groups, indicating that the gaseous phase of DE was causative. Adult male rats exposed to ME manifested with decreased spermatid number, serum testosterone, and an increase in inflammatory cytokines. Significant effects on the male reproductive system have been demonstrated after exposure to ambient PM sources (DE or ME). Nonetheless, these models often include a complex mixture of gaseous component and PM exposure, which makes interpreting the contribution from PM alone difficult.

7.4.2.3. Multiple Generation Effects

Urban Air

Veras et al. (2009, 190496) investigated pregnancy and female reproductive outcomes in BALB/c female mice exposed to ambient air or PM-filtered ambient air at one of two different time periods (before conception and during pregnancy) near an area of high traffic density in Sao Paulo, Brazil. Exposures were 27.5 and 6.5 $\mu g/m^3$ $PM_{2.5}$ for ambient and PM-filtered air chambers, respectively, with 101 $\mu g/m^3$ NO_2, 1.81 $\mu g/m^3$ CO, and 7.66 ppm SO_2 in both chambers. Two groups of 2nd generation (G2) nulliparous female mice were continuously exposed from birth. Estrous cyclicity and ovarian follicle classification were followed at PND60 (reproductive maturation) in one group. A further group was subdivided into four groups by exposures during pregnancy following reproductive capability and pregnancy outcomes of the G2 mice. Animals exposed to ambient air versus PM-filtered air had an extended time in estrous and thus, a reduction in the number of cycles during the study period. The number of antral follicles was significantly decreased in the ambient air versus the PM-filtered air animals. Other follicular quantification (number of small, growing or preovulatory follicles) showed no differences between the two chambers. There was an increase in the time necessary for mating, a decrease in the fertility index, and an increase in the pregnancy index in the ambient air group versus the PM-filtered group. Specifically, in the ambient air groups, there was a significant increase in rate of the post-implantation loss in G1 and G2 groups. However, there was no statistically significant change in number of pups in the litter. Fetal weight was decreased in all treatment groups (ambient air groups G1 and G2, and PM-filtered G2) when compared to the PM-filtered G1 group or animals raised entirely in filtered air, showing that fetal weight was affected by both pre-gestational and gestational PM exposure.

PM exposure prior to conception is associated with increased time in estrous, which in other animal models can be related to ovarian hormone dysfunction and ovulatory problems. These estrous alterations can contribute to fecundity issues. There was no significant difference in number of preovulatory follicles in the above model, but there was a statistically significant decrease in the number of antral follicles (Veras et al., 2009, 190496). Antral follicles are the last stage in follicle development prior to ovulation, and a decrease in antral follicle number can be related to premature reproductive senescence, premature ovarian failure, or early menopause, which were not followed in this study.

In this study (Veras et al., 2009, 190496), the males that were used to generate the G1 and G2 groups were also exposed to ambient air or PM-filtered ambient air, and thus the reproductive contribution of these males to the overall fertility and mating changes in the females cannot be totally eliminated as a possible confounder to the observed effects. Thus, these effects are hard to differentiate as male- or female-dependent and likely indicate a general loss of reproductive fitness. Interestingly, both pre- and gestational exposure to ambient air induced a significant loss in post-

implantation of fetuses and this may be related to placental insufficiency as has been described in other work by this lab (Veras et al., 2008, 190493).

7.4.2.4. Receptor Mediated Effects

Arylhydrocarbon Receptor (AhR)

Diesel Exhaust Particles

The AhR is often activated by chemicals classified as endocrine disrupting compounds (EDCs), exogenous chemicals that behave as hormonally active agents, disrupting the physiological function of endogenous hormones. DE particles are known to activate the AhR. A recent study by Izawa et al. (2007, 190387) showed that certain polyphenols (quercetin from the onion) and food extracts (Ginkgo biloba extract) are able to attenuate DE particle-dependent AhR activation when measured with the Ah-Immunoassay, thus possibly attenuating the EDC activity of DE particles.

7.4.2.5. Developmental Effects

Sex Ratio

Urban Air

A correlation between PM_{10} exposure and a decrease in standardized sex ratios (SSRs) has been reported in humans exposed to air pollution (Lichtenfels et al., 2007, 097041; Wilson et al., 2000, 010288), with fewer numbers of male births reported. To understand this shift, two groups (control and exposed) of male Swiss mice were housed concurrently in Sao Paulo and received either ambient air exposure or filtered air (chemical and particulate filtering) from PND10 for 4 mo (Lichtenfels et al., 2007, 097041). Filtration efficiency for $PM_{2.5}$, CB, and NO_2 inside the chamber was found to be 55%, 100%, and 35%, respectively. After this exposure, non-exposed females were placed in either chamber to mate. After mating, the males were sacrificed and testes collected; males exposed to ambient air showed decreased testicular and epididymal sperm counts, decreased total number of germ cells, and decreased elongated spermatids, but no significant change in litter size. Females were housed in the chambers and sacrificed on GD19 when the number of pups born alive and the sex ratio were obtained. There was a significant decrease in the SSR for pups born after living in the ambient air-exposed chamber compared to the filtered chamber. In this study, a shift in SSR has been shown for both humans and rodents exposed to air pollution, but other studies with DE exposure (Yoshida et al., 2006, 156170) or ambient air in Sao Paulo (Mohallem et al., 2005, 088657) showed no changes in rodent sex ratio. Possible exposure to PM and other components of ambient air via ingestion during grooming cannot be ruled out in this rodent model.

Immunological Effects: Placenta

Diesel Exhaust

Placental insufficiency can lead to the loss of a pregnancy or to adverse fetal outcomes. DE-exposure has been shown to induce inflammation in various models. Fujimoto et al. (2005, 096556) assessed cytokine/immunological changes of DE-dependent inhalation exposure on the placenta during pregnancy. Pregnant Slc:CR mice were exposed to DE (0.3, 1.0, or 3.0 mg/m^3; PM MMAD of 0.4 µm) or clean air from 2 to 13 dpc and dams, placenta, and pups were collected at 14 dpc. There was a significant increase in the number of absorbed placentas in DE-exposed animals (0.3

and 3.0 mg/m^3) with a significant decrease in the number of absorbed placentas in DE-exposed animals at the middle concentration (1.0 mg/m^3). Absorbed placentas from DE exposed mice had undetectable levels of CYP1A1 and twofold increases in TNF-α; CYP1A1 placental mRNA from healthy placentas of DE-exposed mice was unchanged versus control. IL-2, IL-5, IL-12α, IL-12β and GM-CSF mRNA significantly increased in placentas of DE-exposed animals (0.3 and 3.0 mg/m^3). Fujimoto et al. (2005, 096556) reported DE-induced significant increases in multiple inflammatory markers in the placenta with significant increases in the number of absorbed placentas.

Immunological Effects: Asthma

Model Particles

In utero exposure may confer susceptibility to PM-induced asthmatic responses in offspring. Exposure of pregnant BALB/c mice to aerosolized ROFA leachate by inhalation or to DE particles intranasally increases asthma susceptibility to their offspring (Fedulov et al., 2008, 097482; Hamada et al., 2007, 091235). The offspring from dams exposed for 30 min to 50 mg/mL ROFA 1, 3, or 5 days prior to delivery responded to OVA immunization and aerosol challenge with airway hyperreactivity and increased antigen-specific IgE and IgG1 antibodies (Hamada et al., 2007, 091235). Airway hyperreactivity was also observed in the offspring of dams intranasally instilled with 50 µg of DE particles or TiO_2, or 250 µg CB, indicating that the same effect could be demonstrated using relatively "inert" particles (Fedulov et al., 2008, 097482). Pregnant mice were particularly sensitive to exposure to DE or TiO_2 particles, and genetic analysis indicated differential expression of 80 genes in response to TiO_2 in pregnant dams. Thus pregnancy and in utero exposure may enhance responses to PM, and exposure to even relatively inert particles may result in offspring predisposed to asthma.

Placental Morphology

Urban Air

Exposure to ambient air pollution during pregnancy is associated with reduced fetal weight in both human and animal models. The effect of particulate urban air pollution on the functional morphology of the mouse placenta was explored by exposing second generation mice in one of four groups to urban Sao Paulo air (PM was 67% $PM_{2.5}$, mainly of vehicular origin) or filtered air (Veras et al., 2008, 190493). Experimental design was: group F-F comprised of mice that were raised in filtered air chambers and completed pregnancy in filtered air chambers; group F-nF raised in filtered air and pregnant in ambient air; group nF-nF raised and completed pregnancy in non-filtered air chambers; and group nF-F mice raised in ambient air and received filtered air during pregnancy. Mean $PM_{2.5}$ concentrations in the F and nF chambers were 6.5 and 27.5 µg/m^3, respectively. Exposure was from PND20-PND60. After this exposure, the animals were mated and then maintained in their respective chambers during pregnancy. Pregnancy was terminated at GD8 (near term) with placentas and fetuses collected for analysis.

Exposure to ambient PM pre-gestationally or gestationally led to significantly smaller fetal weight (total litter weight). Pregestational exposure to ambient air induced significant increases in fetal capillary surface area and total mass-specific conductance, but this may be explained by reduced maternal/dam blood space and diameters. Gestational exposure to non-filtered air was associated with reduced volume, diameter (caliber) and surface area of maternal blood space with compensatory greater fetal capillary surface and oxygen diffusion conduction rates. Intravascular barrier thickness, a quantitative relationship between trophoblast volume and the combined surfaces of maternal blood spaces and fetal capillaries, was not reduced with ambient air exposure. This study provides evidence that fetal/placental circulatory adaptation to maternal blood deficits after ambient PM exposure may not be sufficient to overcome PM-dependent birth weight deficits in mice exposed to ambient air, with the magnitude of this effect greater in the gestationally-exposed groups.

Placental Weights and Birth Outcomes

Urban Air

Pregnant female Swiss mice were exposed to ambient air (Sao Paulo) or filtered air over various portions of gestation to determine if there was an association between fetal or placental weight or birth outcomes with exposure to air pollution (Rocha et al., 2008, 096685). The reported ambient concentrations of PM_{10} (42 ± 17 μg/m^3), NO_2 (97 ± 39 μg/m^3), and SO_2 (9 ± 4 μg/m^3) were measured 100 m away from the rodent exposure chambers. By using six time windows of exposure that covered 1-3 wk of gestation (the entire gestation period in a mouse), a significant decrease in near-term fetal weight (GD19) was induced by ambient air-exposure during the first week of gestation. Decreased placental weight could be induced by ambient air exposure during any of the 3 wk of gestation. This study points to possible windows of exposure that may be important in evaluating epidemiologic study results.

Neurodevelopmental Effects

Diesel Exhaust

The diagnosis of autism is on the rise in the Western world with its etiology mostly unknown. Autism-associated cell loss is brain region-specific and hypothesized to be developmental in origin. Sugamata et al. (2006, 097166) exposed pregnant ICR mice to DE (0.3 mg/m^3) continuously from 2 dpc to 16 dpc. Pups with in utero exposure to DE were nursed in clean air chambers, but may have received gastro-intestinal exposure via lactational transfer of various components of DE. At 11 wk of age, cerebellar brain tissue was collected. Earlier work has shown that DE particles (<0.1 μm) have been detected in the brains (cerebral cortex and hippocampus) of newborn pups who were born to dams exposed to DE during pregnancy (Sugamata et al., 2006, 097166). Histological analysis of DE-exposed pup cerebella revealed significant increases in caspase-3 (c-3) positive cells compared to control and significant decreases in cerebella Purkinje cell numbers in DE-exposed animals versus control. The ratio of cells positive for apoptosis (c-3 positive) showed a nearly significant sex difference with males displaying increased apoptosis versus females ($p = 0.09$). In humans with autism, the cerebellum has a decreased number of Purkinje cells, which is thought to be fetal and developmental in origin; further, these authors speculate that humans may be more sensitive to DE-dependent neuronal brain changes, as the human placenta is two-layers thick compared to the mouse placenta that is four layers thick.

Behavioral Effects

Diesel Exhaust Particles

Body weight decrements at birth have recently been associated through the Barker hypothesis with adverse adult outcomes. Thus, many publications have begun to focus on decreased birth weight for gestational age and associated adult changes. Hougaard et al. (2008, 156570) exposed 40 timed-pregnant C57BL/6 dams to DE particles reference materials (SRM 2975) via inhalation over GD7-GD19 of pregnancy. They found significantly decreased pup weight at weaning, albeit not at birth. PM-dependent liver changes were monitored by following various inflammatory and genotoxicity-related mRNA transcripts and there were no significant differences in pups at PND2. The comet assay from PND2 pup livers showed no significant differences in DNA damage between DE particle-exposed and control animals. The prohormone, thyroxine, was unchanged in control and DE particle-exposed dams and offspring at weaning. At 2 mo, female DE particle-exposed pups required less time than controls to locate the platform in its new location during the first trial of the spatial reversal learning task in the Morris water maze. Thus, DE particle exposure during in utero development led to behavioral changes without body weight at weaning or changes in inflammatory markers or thyroid hormone levels.

Diesel Exhaust

The effect of in utero DE exposure on CNS motor function was evaluated in male pups (ICR mice) after dams received DE exposure (8h/d×5d/wk) from GD2-GD17 (Yokota et al., 2009, 190518). The exposure atmosphere contained concentrations of 1.0 mg/m^3 for particle mass, 2.67 ppm CO, 0.23 ppm NO_2, and <0.01 ppm SO_2. Spontaneous motor activity was significantly decreased in pups (PND35), as was the dopamine metabolite homovanillic acid measured in the striatum and nucleus accumbens, indicating decreased dopamine (DA) turnover. However, DA levels were unchanged in the same areas of the brain. The authors conclude that these data demonstrate that maternal exposure to DE induced hypolocomotion, similar to earlier studies with adult and neonatal DE particle exposure (Peters et al., 2000, 001756), with decreased extracellular DA release.

Lactation

Diesel Exhaust

Tozuka et al. (2004, 090864) monitored the transfer of PAHs to fetuses and breast milk of F344 rats exposed to DE (6h/day) for 2 wk from GD7-GD 20 (minus 4 days for the weekend when no exposure occurred) with PM_{10} concentration of 1.73 mg/m^3. At PND 14, breast milk was collected. Fifteen PAHs were monitored in the DE exposure chamber and seven were quantified in dam blood with levels of phenanthrene (Phe), anthracene (Ant) and benz[a]anthracene (BaA) in the DE group being significantly higher than the control group. In breast milk, Ant, fluoranthene (Flu), pyrene (Pyr), and chrysene (Chr) showed significant increases in the DE group compared to the control group. BaA tended to be about fourfold higher than the control group in breast milk, but the increase was not significant. PAHs in dam livers of DE versus control were not significantly different. The results of this study demonstrate that PAHs derived from DE are transferred across the placenta from the DE-exposed dam to the fetus. Lactational transfer through the breast milk is also likely as PAHs were detected in dam breast milk, but this should be confirmed in future studies that cross foster control and exposed dams and pups. The lipophilicity of the PAH based on its structure likely affected its uptake in the dam, as PAHs with 3 or 4 rings were found in maternal blood and PAHs with 5 or 6 rings were not detected.

Heritable DNA Changes and Epigenetic Changes

Ambient Air

To address the role of ambient air exposure on heritable changes, Somers et al. (2004, 078098) exposed mice to ambient air in at a rural Canadian site or at an urban site near a steel mill. They showed that offspring of mice exposed to ambient air in urban regions inherited paternal-origin expanded simple tandem repeat (ESTR) mutations 1.9-2.1 times more frequently than offspring of mice exposed to HEPA filtered air or those exposed to rural ambient air. Mouse expanded simple tandem repeat (ESTR) DNA is composed of short base pair repeats which are unstable in the germline and tend to mutate by insertion or deletion of repeat units. In vivo and in situ studies have shown that murine ESTR loci are susceptible to ionizing radiation, and other environmental mutatgen-dependent germline mutations, and are thus good markers of exposure to environmental contaminants.

Expanding upon the above work and to determine if PM or the gaseous phase of the urban air was responsible for heritable mutations, Yauk et al. (2008, 157164) exposed mature male C57Bl×CBA F1 hybrid mice to either HEPA-filtered air or to ambient air in Hamilton, Ontario, Canada for 3 or 10 wk, or 10 wk plus 6 wk of clean air exposure (16 wk). Sperm DNA was monitored for expanded simple tandem repeat (ESTR) mutations. In addition, male-germ line (spermatogonial stem cell) DNA methylation was monitored post-exposure. This area in Hamilton is near two steel mills and a major highway. Air quality data provided by the Ontario Ministry of the Environment showed the highest concentrations of TSP and metals at week 4 (93.8 ± 17 and 3.6 ± 0.7 μg/m^3, respectively) and PAH at week 3 (8.3 ± 1.7 ng/m^3). Mutation frequency at ESTR

Ms6-hm locus in sperm DNA from mice exposed 3 or 10 wk did not show elevated ESTR mutation frequencies, but there was a significant increase in ESTR mutation frequency at 16 wk in ambient air-exposed males versus HEPA filter-exposed animals, pointing to a PM-dependent mechanism of action. When compared to HEPA filter air-exposed males, ambient air-exposed males manifested with hypermethylation of germ-line DNA at 10 and 16 wk. These PM-dependent epigenetic modifications (hypermethylation) were not seen in the halploid stage (3 wk) of spermatogenesis, but were nonetheless seen in early stages of spermatogenesis (10 wk) and remained significantly elevated in mature sperm even after removal of the mouse from the environmental exposure (16 wk). Thus, these studies indicate that the ambient PM phase and not the gaseous phase is responsible for the increased frequency of heritable DNA mutations and epigenetic modifications.

7.4.3. Summary and Causal Determinations

7.4.3.1. $PM_{2.5}$

The 1996 PM AQCD concluded that while few studies had been conducted on the link between PM and infant mortality, the research "suggested an association," particularly for post-neonates (U.S. EPA, 1996, 079380). In the 2004 PM AQCD, additional evidence was available on PM's effect on fetal and early postnatal development and mortality and while some studies indicated a relationship between PM and pregnancy outcomes, others did not (U.S. EPA, 2004, 056905). Studies identifying associations found that exposure to PM_{10} early during pregnancy (first month of pregnancy) or late in the pregnancy (6 wk prior to birth) were linked with higher risk of preterm birth, including models adjusted for other pollutants, and that $PM_{2.5}$ during the first month of pregnancy was associated with IUGR. However, other work did not identify relationships between PM_{10} exposure and low birth weight. The state of the science at that time, as indicated in the 2004 PM AQCD, was that the research provided mixed results based on studies from multiple countries.

Building on the evidence characterized in the previous AQCDs, recent epidemiologic studies conducted in the U.S. and Europe were able to examine the effects of $PM_{2.5}$, and all found an increased risk of low birth weight (Section 7.4.1). Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth weight than exposure to PM_{10}. All of the studies that examined the relationship between $PM_{2.5}$ and preterm birth report positive associations, and most were statistically significant. The studies evaluating the association between $PM_{2.5}$ and growth restriction all found positive associations, with the strongest evidence coming when exposure was assessed during the first or second trimester (Section 7.4.1). For infant mortality (<1 yr), several studies examined $PM_{2.5}$ and found positive associations (Section 7.4.1).

Animal toxicological studies reported effects including decreased uterine weight, limited evidence of male reproductive effects, and conflicting reports of reproductive outcomes in male offspring, particularly in studies of DE (Section 7.4.2). Toxicological studies also reported effects for several development outcomes, including immunological effects (placental and related to asthma), neurodevelopmental and behavioral effects (Section 7.4.2).

In summary evidence is accumulating from epidemiologic studies for effects on low birth weight and infant mortality, especially due to respiratory causes during the post-neonatal period. The mean $PM_{2.5}$ concentrations during the study periods ranged from 5.3-27.4 $\mu g/m^3$. Exposure to $PM_{2.5}$ was usually associated with greater reductions in birth weight than exposure to PM_{10}. Several U.S. studies of PM_{10} investigating fetal growth reported 11-g decrements in birth weight associated with PM_{10} exposure. Most of these studies were conducted in California, where $PM_{2.5}$ and $PM_{10-2.5}$ contribute almost equally to the PM_{10} mass concentration. So while these results can not be attributed to one size fraction or the other, the consistency of the results strengthens the interpretation that particle exposure may be causally related to reductions in birth weight. Similarly, animal evidence supported an association between $PM_{2.5}$ and PM_{10} exposure and adverse reproductive and developmental outcomes, but provided little mechanistic information or biological plausibility for an association between long-term PM exposure and adverse birth outcomes, including low birth weight, or infant mortality. Epidemiologic studies do not consistently report associations between PM exposure and preterm birth, growth restriction, birth defects or decreased sperm quality. New evidence from animal toxicological studies on heritable mutations is of great interest, and warrants further investigation. Overall, the epidemiologic and toxicological evidence is **suggestive of a**

causal relationship between long-term exposures to $PM_{2.5}$ and reproductive and developmental outcomes.

7.4.3.2. $PM_{10-2.5}$

Evidence is **inadequate to determine if a causal relationship exists between long-term exposure to $PM_{10-2.5}$ and developmental and reproductive outcomes** because studies have not been conducted in sufficient quantity or quality to draw any conclusion. A single study found an association between $PM_{10-2.5}$ and birthweight (-13 g [95% CI: -18.3 to -7.6] per 10 $\mu g/m^3$ increase), but no such association for $PM_{2.5}$ (Parker et al., 2008, 156013).

7.4.3.3. UFPs

The 2004 PM AQCD did not report long-term exposure studies for UFPs. No epidemiologic or animal toxicology studies have been conducted to evaluate the effects of long-term UFP exposure and reproductive and developmental effects. Ambient air exposures, which likely include UFPs, are reported in this ISA but there is no delineation of the separate contribution from UFPs. The evidence is **inadequate to determine if a causal relationship exists between long-term UFP exposures and reproductive and developmental effects**.

7.5. Cancer, Mutagenicity, and Genotoxicity

Evidence from epidemiologic and animal toxicological studies has been accumulating for more than three decades regarding the mutagenicity and carcinogenicity of PM in the ambient air. DE has been identified as one source of PM in ambient air, and has been extensively studied for its carcinogenic potential. In 1989, the International Agency for Research on Cancer (IARC) found that there was sufficient evidence that extracts of DE particles were carcinogenic in experimental animals and that there was limited evidence for the carcinogenic effect of DE in humans (IARC, 1989, 002958). This conclusion was based on studies in which organic extracts of DE particles were used to evaluate the effects of concentrates of the organic compounds associated with carbonaceous soot particles. These extracts were applied to the skin or administered by IT instillation or intrapulmonary implantation to mice, rats, or Syrian hamsters and an excess of tumors on the skin, lung or at the site of injection were observed.

In 2002, the U.S. EPA reviewed over 30 epidemiologic studies that investigated the potential carcinogenicity of DE. These studies, on average, found that long-term occupational exposures to DE were associated with a 40% increase in the relative risk of lung cancer (U.S. EPA, 2002, 042866). In the same report the U.S. EPA concluded that extensive studies with salmonella had unequivocally demonstrated mutagenic activity in both particulate and gaseous fractions of DE. They further concluded that DE may present a lung cancer hazard to humans (U.S. EPA, 2002, 042866). The particulate phase appeared to have the greatest contribution to the carcinogenic effect. Both the particle core and the associated organic compounds demonstrated carcinogenic properties, although a role for the gas-phase components of DE could not be ruled out. Almost the entire diesel particle mass is $\leq$ 10 μm in diameter (PM_{10}), with approximately 94% of the mass of these particles <2.5 μm in diameter ($PM_{2.5}$), including a subgroup with a large number of UFPs (U.S. EPA, 2002, 042866). U.S. EPA considered the weight of evidence for potential human carcinogenicity for DE to be strong, even though inferences were involved in the overall assessment, and concluded that DE is "likely to be carcinogenic to humans by inhalation" and that this hazard applies to environmental exposures (U.S. EPA, 2002, 042866).

Two recent reviews of the mutagenicity (Claxton et al., 2004, 089008) and carcinogenicity (Claxton and Woodall, 2007, 180391) of ambient air have characterized the animal toxicological literature on ambient air pollution and cancer. The majority of these toxicological studies have been conducted using IT instillation or dermal routes of exposure. Generally, the toxicological evidence reviewed in this ISA has been limited to inhalation studies conducted with lower concentrations of

PM (<2 mg/m^3), relevant to current ambient concentrations and the current regulatory standard (Section 1.3). Because this ISA focuses on toxicological studies which use the inhalation route of exposure, it is possible that important evidence for the role of PM in mutagenicity, tumorigenicity, and/or carcinogenicity may be missed. In order to accurately characterize the relationship between PM and cancer and be consistent with the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005, 086237), these reviews (that include studies that employ IT instillation and dermal routes of exposure) are summarized briefly.

Claxton et al. (2004, 089008) reviewed the mutagenicity of air in the Salmonella (Ames) assay, and showed that hundreds of compounds identified in ambient air from varying chemical classes are mutagenic and that the commonly monitored PAHs could not account for the majority of mutagenicity associated with most airborne particles. They concluded that the smallest particles have the highest toxicity per particulate mass, with the $PM_{2.5}$ size fraction having greater mutagenic and cytotoxic potential than the PM_{10} size fraction, which had a higher mutagenic potential than the TSP size fraction. One study reviewed by Claxton et al. (2004, 089008) found that the cytotoxic potential of $PM_{2.5}$ was higher in wintertime samples than in summertime samples. A series of studies on source apportionment for ambient particle mutagenic activity reviewed by Claxton et al. (2004, 089008) indicate that mobile sources (cars and diesel trucks) account for most of the mutagenic activity.

Claxton and Woodall (2007, 180391) reviewed many studies that examined the rodent carcinogenicity of extracts of ambient PM samples; the PM was of various size classes, often from TSP samples. Among a variety of mouse and rat strains, application methods, and samples employed, the authors found no pattern that would suggest the routine use of a particular strain or protocol would be more informative than another. The primary conclusion that comes from the analysis of rodent carcinogenicity studies is that the most polluted urban air samples tested to date are carcinogenic; the contribution of PM and different size classes of PM to the carcinogenic effects of ambient air has not been delineated. The differences in response by the various strains of inbred mice indicate that the genetic background of an individual can influence tumorigenic response. Studies examining different components of ambient PM (e.g., PAHs) confirm that ambient air contains multiple carcinogens, and that the carcinogenic potential of particles from different airsheds can be quite different. Therefore, one would expect the incidence of cancers related to ambient air exposure in different metropolitan areas to differ.

Numerous epidemiologic and animal toxicological studies of ambient PM and their contributing sources have been conducted to assess the relative mutagenic or genotoxic potential. Studies previously reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide evidence that ambient PM as well as PM from specific combustion sources (e.g., fossil fuels) is mutagenic in vivo and in vitro. Building on these results, data from recent epidemiologic and animal toxicological studies that evaluated the carcinogenic, mutagenic and/or genotoxic effects of PM, PM-constituents, and combustion emission source particles are reviewed in this section.

7.5.1. Epidemiologic Studies

The 2004 PM AQCD reported on original and follow-up analyses for three prospective cohort studies that examined the relationship between PM and lung cancer incidence and mortality. Based on these findings, as well as on the results from case-control and ecologic studies, the 2004 PM AQCD concluded that long-term PM exposure may increase the risk of lung cancer incidence and mortality. The largest of the three prospective cohort studies included in the 2004 PM AQCD was the ACS study (Pope et al., 2002, 024689). This study was the follow-up to the original ACS study (Pope et al., 1995, 045159), and included a longer follow-up period and reported a statistically significant association between $PM_{2.5}$ exposure and lung cancer mortality.

A 14- to 16-yr prospective study conducted using the Six Cities Study cohort reported a slightly elevated risk of lung cancer mortality for individuals living in the most polluted city (mean PM_{10}: 46.5 µg/m^3; mean $PM_{2.5}$ 29.6 µg/m^3) as compared to the least polluted city (mean PM_{10}: 18.2 µg/m^3; mean $PM_{2.5}$ 11.0 µg/m^3) but the association was not statistically significant (Dockery et al., 1993, 044457).

Re-analysis of the AHSMOG cohort, a study of non-smoking whites living in California, concluded that elevated long-term exposure to PM_{10} was associated with lung cancer incidence among both men and women (Beeson et al., 1998, 048890). The original study had reported an excess of incident lung cancers only among women (Abbey et al., 1991, 042668). Further reanalysis

of this cohort revealed an association between PM_{10} and lung cancer mortality among men but no association among women (Abbey et al., 1999, 047559). In addition, McDonnell et al. (2000, 010319) reported increases in lung cancer mortality with long-term exposure to $PM_{2.5}$ in the AHSMOG cohort; no association was seen for $PM_{10-2.5}$.

7.5.1.1. Lung Cancer Mortality and Incidence

The following sections will examine extensions of the above mentioned cohort studies and new studies published since the 2004 PM AQCD. The section includes discussion of both lung cancer incidence and mortality, as well as markers of exposure/susceptibility. A summary of the mean PM concentrations reported for the new studies is presented in Table 7-6. In addition, a summary of the associations for lung cancer mortality and incidence are presented in Table 7-7 and Figure 7-7 (Section 7.6) Further discussion of all-cause and cause-specific mortality is presented in Section 7.6.

Table 7-6. Characterization of ambient PM concentrations from recent studies of cancer and long-term exposures to PM.

Study	Location	Pollutant	Mean Annual Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
Brunekreef et al. (2009, 191947)	The Netherlands	$PM_{2.5}$	28.3	Max: 36.8
Bonner et al. (2005, 088993)	Western NY State	TSP	44	
Jerret et al. (2005, 087600)	Los Angeles, California	$PM_{2.5}$		Max:27.1
Laden et al. (2006, 087605)	6 U.S. cities	$PM_{2.5}$	Range of means across sites: 10.2-29.0 Avg of means across sites: 16.4	
Naess et al. (2007, 090736)	Oslo, Norway	$PM_{2.5}$	15	Max: 22
		PM_{10}	19	Max: 30
Palli et al. (2008, 156837)	Florence, Italy	PM_{10}	NR	
Pedersen et al. (2006, 156848)	Czech Republic	$PM_{2.5}$		Max: 46-120
		PM_{10}		Max: 120-238.6
Sorensen et al. (2005, 083053)	Copenhagen, Denmark	$PM_{2.5}$	Range of means across sites: 12.6-20.7 Avg of means across sites: 16.7	75th: 24.3-27.7
Sram et al. (2007, 188457)	Czech Republic	PM_{10}		Max: 55
		$PM_{2.5}$		Max: 38
Sram et al. (2007, 192084)	Czech Republic	PM_{10}	Range of means across sites: 36.4-55.6 Avg of means across sites: 46.0	
		$PM_{2.5}$	Range of means across sites: 24.8-44.4 Avg of means across sites: 34.6	
Vineis et al. (2006, 192089)	Multi-city, Europe	PM_{10}	Range of means across sites: 19.9-73.4 Avg of means across sites: 35.4	
Vinzents et al. (2005, 087482)	Copenhagen, Denmark	PM_{10}	Range of means across sites: 16.9-23.5 Avg of means across sites: 20.2	

A subset of the ACS cohort study from 1982 to 2000 that included only residents of Los Angeles, California was used to examine the association between $PM_{2.5}$ and lung cancer mortality while adjusting for both individual and neighborhood covariates (Jerrett et al., 2005, 087600). There was a positive association between $PM_{2.5}$ and lung cancer mortality when adjusting for 44 individual covariates (RR 1.44 [95% CI: 0.98-2.11] per 10 $\mu g/m^3$ increase in $PM_{2.5}$). However, including all potential individual and neighborhood covariates associated with mortality reduced the association

(RR 1.20 [95% CI: 0.79-1.82] per 10 μg/m^3 increase in $PM_{2.5}$). A recent re-analysis of the full ACS cohort also demonstrated a positive association between $PM_{2.5}$ and lung cancer mortality (RR 1.11 [95% CI: 1.04-1.18]) (Krewski et al., 2009, 191193). The authors observed modification of this risk by educational attainment, with those completing a high school degree or less having greater risk. In addition to utilizing the ACS cohort for a nationwide analysis, this same study conducted two regional assessments, one in the New York City area and the other in the Los Angeles area. No association was detected between $PM_{2.5}$ and lung cancer mortality in the analysis of the region included in the New York City analysis. A positive association was observed in the Los Angeles-area analysis using an unadjusted model, but this association did not persist after control for individual, ecologic, and copollutant covariates.

The Six Cities Study was extended to include data from 1990-1998, a period including 1,368 deaths and 54,735 person-years (Laden et al., 2006, 087605). An elevated risk ratio for lung cancer mortality was reported when the entire follow-up period (1974-1998) was included in the analysis (RR 1.27 [95% CI 0.96-1.69] per 10 μg/m^3 increase in average annual $PM_{2.5}$). However, estimated decreases in $PM_{2.5}$ were not associated with reduced lung cancer mortality (RR 1.06 (95% CI: 0.43-2.62] for every 10 μg/m^3 reduction in $PM_{2.5}$).

Naess et al. (2007, 090736) studied individuals aged 51-90 yr living in Oslo, Norway in 1992. Death certificate data were obtained for 1992-1998 and information on PM was collected from 1992-1995. Women had a larger association of lung cancer mortality with $PM_{2.5}$ compared to men. Similar results were reported for PM_{10}.

Most recently, Brunekreef et al. (2009, 191947) used the Netherlands cohort study (NLCS) on diet and cancer to conduct a re-analysis of the research performed by Beelen et al. (2008, 156263) examining the association between PM and both lung cancer mortality and incidence. After 10 yr of follow-up, there was no association between $PM_{2.5}$ and lung cancer mortality for either the analysis of the full cohort (n = 105,296) (RR 1.06 [95% CI: 0.82-1.38] per 10 μg/m^3 increase in $PM_{2.5}$) or the case-cohort (n = 4,075) (RR 0.87 [95% CI: 0.52-1.47]). There was also no association with black smoke or traffic density variables, although living near a major roadway was associated with an elevated relative risk for lung cancer in the full cohort analysis (RR 1.20 [95% CI: 0.98-1.47]). The association was not present in the case-cohort analysis (RR 1.07 [95% CI: 0.70-1.64]).

In addition to lung cancer mortality, Brunekreef et al. (2009, 191947) also examined the association with lung cancer incidence using 11.3 yr of follow-up data. In both the full cohort and the case-cohort analyses no association was reported between $PM_{2.5}$ and lung cancer incidence (full cohort: RR 0.81 [95% CI: 0.63-1.04]; case-cohort: RR 0.67 [95% CI: 0.41-1.10] per 10 μg/m^3 increase in $PM_{2.5}$). The same was true for analyses of BS and traffic density variables.

The association between PM and incident lung cancers was examined in the European Prospective Investigation into Cancer and Nutrition study (EPIC) (Vineis et al., 2006, 192089). Within this cohort, a nested case-control study, the GenAir study, included cases of incident cancer and controls matched on age, gender, smoking status, country of recruitment, and time between recruitment and diagnosis. Only non-smokers and former smokers who had quit smoking at least 10 yr prior were included. The study included 113 cases and 312 controls. No association was seen between PM_{10} and lung cancer (OR 0.91 [95% CI: 0.70-1.18] per 10 μg/m^3). The OR was elevated when cotinine, a marker for cigarette exposure, was included in the model but the authors state that this is probably due to small study size (OR 2.85 [95% CI: 0.97-8.33] comparing ≥ 11 μg/m^3 to <11 μg/m^3). Control for other potential confounders, such as BMI, education level, and intake of fruit and vegetables, did not have a large impact on the estimate.

Table 7-7. Associations* between ambient PM concentrations from select studies of lung cancer mortality and incidence.

Study	Cohort	Location	Years	Analysis subgroup	Effect Estimate (95% CI)
MORTALITY - $PM_{2.5}$					
Dockery et al. (1993, 044457)‡	Six-Cities	Six cities across the U.S.	1974-1991		1.18 (0.89-1.57)
Krewski et al. (2000, 012281)‡	Six-Cities-Re-analysis	Six cities across the U.S.	1974-1991		1.16 (0.86-1.23)
Laden et al. (2006, 087605)	Six-Cities	Six cities across the U.S.	1974-1998		1.27 (0.96-1.69)
Beelen et al. (2008, 156263)	NLCS	Netherlands	1987-1996	Full Cohort	1.06 (0.82-1.38)
Beelen et al. (2008, 156263)	NLCS	Netherlands	1987-1996	Case Cohort	0.87 (0.52-1.47)
Brunekreef et al. (2009, 191947)	NLCS-Re-analysis	Netherlands	1987-1996	Full Cohort	1.06 (0.82-1.38)
Brunekreef et al. (2009, 191947)	NLCS-Re-analysis	Netherlands	1987-1996	Case Cohort	0.87 (0.52-1.47)
Pope et al. (1995, 045159)‡	ACS	U.S.	1982-1989		1.01 (0.91-1.12)
Pope et al. (2002, 024689)‡	ACS	U.S.	1982-2000		1.13 (1.04-1.22)
Jerret et al. (2005, 087600)	ACS-LA	Los Angeles	1982-2000	Intra-metro Los Angeles	1.44 (0.98-2.11)
Krewski et al. (2009, 191193)	ACS-Re-analysis	U.S.	1982-2000		1.11 (1.04-1.18)
Krewski et al. (2009, 191193)	ACS-Re-analysis	New York City	1982-2000	Intra-metro New York City	0.90 (0.29-2.78)
Krewski et al. (2009, 191193)	ACS-Re-analysis	Los Angeles	1982-2000	Intra-metro Los Angeles	1.31 (0.90-1.92)
McDonnell et al. (2000, 010319) †	AHSMOG	California	1973-1977	Men	1.39 (0.79-2.46)
Naess et al. (2007, 090736)		Oslo, Norway	1992-1998	Men, 51-70 yrs	1.18 (0.93-1.52)
Naess et al. (2007, 090736)		Oslo, Norway	1992-1998	Men, 71-90 yrs	1.18 (0.93-1.52)
Naess et al. (2007, 090736)		Oslo, Norway	1992-1998	Women, 51-70 yrs	1.83 (1.36-2.47)
Naess et al. (2007, 090736)		Oslo, Norway	1992-1998	Women, 71-90 yrs	1.45 (1.05-2.02)
MORTALITY - PM_{10}					
McDonnell et al. (2000, 010319) †	AHSMOG	California	1973-1977	Men	1.23 (0.84-1.80)
Naess et al. (2007, 090736) †		Oslo, Norway	1992-1998	Men, 51-70 yrs	1.12 (0.95-1.33)
Naess et al. (2007, 090736)		Oslo, Norway	1992-1998	Men, 71-90 yrs	1.14 (0.97-1.36)
Naess et al. (2007, 090736) †		Oslo, Norway	1992-1998	Women, 51-70 yrs	1.50 (1.23-1.84)
Naess et al. (2007, 090736) †		Oslo, Norway	1992-1998	Women, 71-90 yrs	1.29 (1.03-1.60)
INCIDENCE - $PM_{2.5}$					
Beelen et al. (2008, 155681)	NLCS	Netherlands	1987-1996	Full Cohort	0.81 (0.63-1.04)
Beelen et al. (2008, 155681)	NLCS	Netherlands	1987-1996	Case Cohort	0.65 (0.41-1.04)
Brunekreef et al. (2009, 191947)	NLCS-Re-analysis	Netherlands	1987-1996	Full Cohort	0.81 (0.63-1.04)
Brunekreef et al. (2009, 191947)	NLCS-Re-analysis	Netherlands	1987-1996	Case Cohort	0.67 (0.41-1.10)
INCIDENCE – PM_{10}					
Beeson et al. (1998, 048890)	AHSMOG	California	1977-1992	Men	1.99 (1.32-3.00)
Vineis et al. (2006, 192089)	GenAir	Europe	1993-1999	Case-Control	0.91 (0.70-1.18)

*per 10 $\mu g/m^3$ increase

†Results from the paper were standardized to10 $\mu g/m^3$ [For McDonnell et al. (2000, 010319) the non-standardized results were reported based on IQR increments (24.3 $\mu g/m^3$ for $PM_{2.5}$ and 29.5 $\mu g/m^3$ for PM_{10}). For Naess et al. (2007, 090736) the original hazard ratios were calculated based on quartiles of PM exposure. The results were converted to10 $\mu g/m^3$ using the mean range of the four quartiles (3.95 $\mu g/m^3$ for $PM_{2.5}$ and 5.88 $\mu g/m^3$ for PM_{10})].

‡Study was included in the 2004 PM AQCD

7.5.1.2. Other Cancers

Bonner et al. (2005, 088993) conducted a population-based, case-control study of the association between ambient exposure to PAHs in early life and breast cancer incidence among women living in Erie and Niagara counties in the state of New York. Cases (n = 1,166 of which 841 were post-menopausal) were women with primary breast cancer, and controls (n = 2,105 of which 1,495 were post-menopausal) were frequency matched to the cases by age, race, and county of residence. TSP was used as a proxy for PAH exposure. Annual average TSP concentrations (1959-1997) were obtained from the New York State Department of Environmental Conservation for Erie and Niagara Counties. Among postmenopausal women, exposure to high concentrations of TSP (>140 $\mu g/m^3$) at birth was associated with an OR of 2.42 for breast cancer (95% CI: 0.97-6.09) relative to low concentrations of TSP (<84 $\mu g/m^3$). ORs were elevated for pollution exposures at age of menarche (OR: 1.45 [95% CI: 0.74-2.87]) and age at first birth (OR: 1.33 [95% CI: 0.87-2.06]) among postmenopausal women. Among premenopausal women, exposure to high concentrations of TSP at birth was associated with an OR for breast cancer incidence of 1.79 (95% CI: 0.62-5.10) relative to low exposure levels, exposure at age of menarche was associated with an OR of 0.66 (95% CI: 0.38-1.16), and exposure at age of first birth was associated with an OR of 0.52 (95% CI: 0.22-1.20).

7.5.1.3. Markers of Exposure or Susceptibility

Several studies looked at markers of exposure or susceptibility as the outcome associated with short-term exposure. These studies are included here because they may be relevant to the mechanism that leads to cancer associated with long-term exposures. For example, inflammation can contribute to carcinogenesis by inducing genomic instability, which can then lead to altered gene expression, enhanced proliferation, and resistance to apoptotic signals. Reactive oxygen and nitrogen species, provided by PM components or inflammation pathways, can cause molecular damage leading to cellular transformation. Elevated inflammatory cytokines, chemokines, and prostaglandins promote tumor growth and angiogenesis, which in turn promotes metastasis and malignant invasion. In particular, IL-6, IL-8, IL-1β, COX-2, and TNF-α have been implicated in these processes (Kundu and Surh, 2008, 198840). Several lines of evidence support the involvement of COX-2 in the pathogenesis of lung cancer (Lee et al., 2008, 198811). Both short- and long-term exposure studies demonstrate relationships between various forms of PM and increased production of these inflammatory mediators, both in the lungs and circulation. Additionally, limited evidence suggests that exposure to PM (Chen and Schwartz, 2008, 190106), or traffic (Williams et al., 2009, 191945), or residence in a polluted airshed (Calderon-Garciduenas et al., 2007, 091252; Calderón-Garcidueñas et al., 2009, 192107) are associated with decreases in the number or function of natural killer cells or other white blood cells, indicating suppression of anti-tumor defenses.

A study performed in the Czech Republic compared 53 male policemen working at least 8 hours per day outdoors in urban air with age- and sex-matched controls who spent at least 90% of their day indoors (n = 52) (Sram et al., 2007, 188457). During the sampling period, two monitors from downtown and suburban areas detected levels of air pollutants in the following ranges: PM_{10} 32-55 $\mu g/m^3$, $PM_{2.5}$ 27-38 $\mu g/m^3$, c-PAHs 18-22 ng/m^3, and B[a]P 2.5-3.1 ng/m^3 using a VAPS monitor (measurements taken with a HiVol monitor, which has a lower flow rate, had a mean for PM_{10} of 62.6 $\mu g/m^3$). c-PAHs detected on personal monitors during sampling days had a mean of 12.04 ng/m^3 among the policemen and 6.17 ng/m^3 among the controls. No difference in percent of chromosomal aberrations was observed between the policemen and control group using conventional cytogenetic analysis. However, using fluorescent in situ hybridization (FISH), a difference in chromosomal aberrations between the policemen and control group was reported. For example, the percentage of aberrant cells, as well as the genomic frequency of translocations per 100 cells, was about 1.4-fold greater in the policemen. This was largely driven by a difference in chromosomal aberrations between nonsmoking policemen and nonsmoking controls. A similar study that included only the policemen (n = 60), reported that the mean exposure to c-PAHs and B[a]P for 40-50 days before sampling was associated with chromosomal aberrations when analyzed with FISH (Sram et al., 2007, 192084). However, when included in a model with other covariates, the association with these variables was null. No association was present with use of conventional cytogenetic analysis.

Palli et al. (2008, 156837) investigated the correlation between ambient PM_{10} concentrations and individual levels of DNA bulky adducts. Study participants were 214 healthy adults aged

35-64 yr at enrollment who resided in the city of Florence, Italy. This study was conducted between 1993 and 1998. PM_{10} exposure levels were based on daily environmental measures provided by two types of urban monitoring stations (high-traffic and low-traffic). The researchers assessed correlation between DNA bulky adducts measured in blood samples and PM_{10} concentrations prior to blood sample collection. Time windows of PM_{10} exposure evaluated in this study were 0-5 days, 0-10 days, 0-15 days, 0-30 days, 0-60 days, and 0-90 days prior to blood sample collection. Overall, average PM_{10} concentrations decreased during the study period, with some fluctuations. Quantitative values were not reported, but PM_{10} appeared to range between approximately 30 and 100 $\mu g/m^3$ for high-traffic stations, and between approximately 20 and 50 $\mu g/m^3$ for low-traffic stations. This study found that levels of DNA bulky adducts among non-smoking workers with occupational traffic exposure were positively correlated with cumulative PM_{10} levels from high-traffic stations during approximately 2 wk preceding blood sample collection (0-5 days: $r = 0.55$, $p = 0.03$; 0-10 days: $r = 0.58$, $p = 0.02$; 0-15 days: $r = 0.56$, $p = 0.02$). DNA bulky adducts were not associated with PM_{10} levels among Florence residents with no occupational exposure to vehicle emissions or among smokers. DNA bulky adducts were not associated with PM_{10} levels assessed by low-traffic urban monitoring stations.

The association between personal exposure to water-soluble transition metals in $PM_{2.5}$ and oxidative stress-induced DNA damage was investigated among 49 students from Central Copenhagen, Denmark (Sorensen et al., 2005, 083053). Researchers assessed $PM_{2.5}$ exposure by personal sampling over two weekday periods twice in one year (November 1999 and August 2000), and determined the concentration of water-soluble transition metals (V, Cr, Fe, Ni, Cu and Pt) in these samples. In addition, lymphocyte and 24-h urine samples were analyzed for DNA damage by measuring 7-hydro-8-oxo-2'-deoxyguanosine (8-oxodG). Mean concentrations and corresponding IQR of these metals differed between months of sample collection. This study found that 8-oxodG concentration in lymphocytes was significantly associated with V and Cr concentrations, with a 1.9% increase in 8-oxodG per 1 µg/L increase in V concentration and a 2.2% increase in 8-oxodG per 1 µg/L increase in Cr concentration; these associations were independent of the $PM_{2.5}$ mass concentration. The other transition metals were not significantly associated with the 8-oxodG concentration in lymphocytes, and none of the six measured transition metals was associated with the 8-oxodG concentration in urine.

Vinzents et al. (2005, 087482) investigated the association between UFP and PM_{10} concentrations with levels of purine oxidation and strand breaks in DNA using a crossover design in Copenhagen, Denmark. Study participants were 15 healthy nonsmoking individuals with a mean age of 25 yr. UFP exposure was evaluated using number concentration obtained in the breathing zone by portable instruments in six 18-h weekday periods from March to June 2003. Ambient concentrations for PM_{10} and UFP were also measured on all exposure days at curbside street stations and at one urban background station. Oxidative DNA damage was assessed by evaluating strand breaks and oxidized purines in mononuclear cells isolated from venous blood the morning after exposure measurement. Mean number concentration of UFPs (street station) was 30.4×10^3 UFPs/mL (standard deviation [SD]: 1.38), mean mass concentration of PM_{10} at a background monitoring station was 16.9 $\mu g/m^3$ (SD: 1.53), and mean mass concentration of PM_{10} at a street station was 23.5 $\mu g/m^3$ (SD: 1.48). Mean personal exposure to UFPs was 32.4×10^3 UFPs/mL (SD: 1.49) while bicycling (5 occasions), 19.6×10^3 UFPs/mL (SD: 1.78) during other outdoor activities (6 occasions), and 13.4×10^3 UFPs/mL (SD: 1.96) while indoors (6 occasions). The regression coefficients of the mixed-effects models looking at level of purine oxidation were estimated as 1.50×10^{-3} (95% CI: 0.59×10^{-3} to 2.42×10^{-3}; $p = 0.002$) for cumulative outdoor exposure and 1.07×10^{-3} (95% CI: 0.37×10^{-3} to 1.77×10^{-3}; $p = 0.003$) for cumulative indoor exposure. Neither cumulative outdoor nor cumulative indoor exposures to UFPs were associated with strand breaks. Neither ambient air concentrations of PM_{10} nor number concentrations of UFPs at monitoring stations were significant predictors of DNA damage.

Additionally, a number of studies employed ecologic study designs, comparing the prevalence of biomarkers in populations from more polluted locations to those in less polluted locations. In a pilot study conducted in the Czech Republic (Pedersen et al., 2006, 156848), children age 5-11 yr provided 5 mL blood samples and the frequency of micronuclei (MN) in peripheral blood lymphocytes was analyzed as a measure of cytogenetic effects. Significantly higher frequencies of MN were found in younger children living in Teplice ($PM_{2.5}$ concentration = 120 $\mu g/m^3$) than in Prachatice ($PM_{2.5}$ concentration = 46 $\mu g/m^3$). The levels of c-PAHs were also much higher in Teplice (nearly 30 ng/m^3 in Teplice and about 15 ng/m^3 in Prachatice). The difference in MN frequencies

observed in the children from the two locations may be attributable to differences in exposure to air pollution, but could also be due to differences in diet or other environmental exposures. This finding is noteworthy considering MN formation in peripheral blood lymphocytes is thought to be biologically relevant for carcinogenesis.

Avogbe et al. (2005, 087811) showed a correlation between the level of oxidative DNA damage in individuals and exposure to ambient UFPs. Formamidopyrimidine DNA glycosylase sensitive sites and the presence of DNA strand breaks were assessed in blood and urine samples obtained from healthy, non-smoking male volunteers that lived and worked in different areas of Cotonou, Benin. Exposure to benzene was assessed by urinary excretion of S-phenylmercapturic acid. There was a high degree of correlation between exposure to benzene and UFPs and the presence of DNA strand breaks and formamidopyrimidine DNA glycosylase sensitive sites (rural subjects < suburban subjects < residents living near high traffic roads < taxi drivers). Genotyping studies showed that the magnitude of the effects of benzene and UFPs may be modified by polymorphisms in GSTP1 and NQO1 genes.

Tovalin et al. (2006, 091322) evaluated the association between exposure to air pollutants and the level of DNA damage using the single cell gel electrophoresis (comet) assay. Mononuclear lymphocytes from outdoor and indoor workers from two areas in Mexico, Mexico City (large city) and Puebla (medium size city), were evaluated. The outcomes showed that the outdoor workers in Mexico City exhibited greater DNA damage than indoor workers in the same region. Similar levels of DNA damage were observed between indoor and outdoor workers in Puebla. The level of observed DNA damage was correlated with exposure to O_3 and $PM_{2.5}$.

In summary, several recent studies have reported an association between lung cancer mortality and long-term $PM_{2.5}$ exposure. Although many of the estimates include the null in the confidence interval, overall the results have shown a positive relationship. The two recent studies that looked at lung cancer incidence did not report an association with $PM_{2.5}$ (Brunekreef et al., 2009, 191947) or PM_{10} (Vineis et al., 2006, 192089). Studies of exposure/susceptibility markers have reported inconsistent outcomes, with some markers being associated with PM and others not.

7.5.2. Toxicological Studies

Over the past 30 yr numerous mutagenicity and genotoxicity studies of ambient PM and their contributing sources have been conducted to assess the relative mutagenic or genotoxic potential. Studies previously reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) provide compelling evidence that ambient PM and PM from specific combustion sources (e.g., fossil fuels) are mutagenic in vivo and in vitro. Research cited in the 2004 AQCD demonstrated mutagenic activity of ambient PM from urban centers in California, Germany and the Netherlands. These studies suggested that ubiquitous emission sources, particularly motor vehicle emissions, rather than isolated point sources were largely responsible for the mutagenic effects. In addition, the mutagenicity was dependent upon the chemical composition of the PM with unsubstituted polyaromatic compounds and semi-polar compounds being highly mutagenic. Mutagenicity was also dependent on size, with the fine fraction of urban PM having greater effects than the coarse fraction. Genotoxic activity was demonstrated for ambient PM from two high traffic areas (one upwind and one downwind) and a rural site. In addition, the 2004 AQCD reported that exhausts from gasoline and diesel engines were mutagenic and that DE was more potent. More mutagenicity was observed for exhaust from cold starts than starts at room temperature. Both gaseous and particulate fractions of DE were found to be mutagenic. Sequential fractionation of extracts from gasoline and DE implicated the polar fractions, especially nitrated polynuclear aromatic compounds, as contributing greatly to mutagenicity. Among some of the other mutagenically active compounds found in the gas phase of DE are ethylene, benzene, 1,3-butadiene, acrolein and several PAHs, all of which are also present in gasoline exhaust. Also cited in the 2004 AQCD were studies demonstrating mutagenic effects of emissions from wood/biomass burning, which were primarily attributable to the organic fraction and not the condensate. It was noted that wood smoke induced both frameshift mutations and base pair substitution but not DNA adducts. Further, emissions from coal combustion in China were found to be mutagenic, with both polar and aromatic fractions contributing to effects. Little data were available on the mutagenicity of coal fly ash emissions from U.S. conventional combustion plants. In conclusion, these studies provide evidence that ambient PM and combustion-derived PM are mutagenic/genotoxic. The 2004 AQCD noted that there is not a simple relationship between

mutagenic potential and carcinogenic potential in animals or humans. No studies evaluating carcinogenic effects of PM were reported in the 2004 AQCD.

Building on results of earlier studies in the 2004 PM AQCD, data from newly published studies that evaluated the mutagenic, genotoxic and carcinogenic effects of PM, PM-constituents, and combustion emission source particles are reviewed. Pertinent studies are described briefly in the following paragraphs. A summary table is provided in Annex D, Tables D7 and D8).

7.5.2.1. Mutagenesis and Genotoxicity

In Vitro Studies

In general, studies have focused on PM and PM extracts for mutagenicity testing using bacteria and mammalian cell lines. PM and/or PM extracts from ambient air samples, wood smoke, and coal, diesel, or gasoline combustion have all been reported to induce mutation in *S. typhimurium* and in cultured human cells (Abou et al., 2007, 098819; Gabelová et al., 2007, 156457; Gabelová et al., 2007, 156458; Hannigan et al., 1997, 083598; Hornberg et al., 1998, 095741). In addition, effects associated with PM and PM-associated constituents include induction of MN formation, DNA adduct formation, SCE, DNA strand breaks, frameshifts and inhibition of gap-junction intercellular communication (Alink et al., 1998, 087159; Arlt et al., 2007, 097257; Avogbe et al., 2005, 087811; Gabelová et al., 2007, 156457; Gabelová et al., 2007, 156458; Healey et al., 2006, 156532; Hornberg et al., 1996, 087164; Hornberg et al., 1998, 095741; Sevastyanova et al., 2007, 156969).

Constituents adsorbed onto individual particles play a large role in the genotoxic potential of PM. Poma et al. (2006, 096903) showed that fine CB particles were consistently less genotoxic than similar concentrations of $PM_{2.5}$ extracts, suggesting that the adsorbed components play a role in the genotoxic potential of PM. Total PAH and carcinogenic PAH content were correlated with the genotoxic effects of PM (De Kok et al., 2005, 088656; Sevastyanova et al., 2007, 156969). Comparison of different extracts (water-soluble versus organic) by Gutierrez-Castillo et al. (2006, 089030) indicated that water-soluble extracts were more genotoxic than the corresponding organic extracts. Sharma et al. (2007, 156975) reported that mutagenic activity of extracted PM samples collected in and around a waste incineration plant was attributed to the moderately polar and polar fractions. The polar and crude fractions were mutagenic without metabolic activation, suggesting a direct mutagenic effect. No mutagenic activity was observed from any of the nonpolar samples evaluated. Arlt and colleagues (2007, 097257) have shown that the PM constituents 2-nitrobenzanthrone (2-NB) and 3-nitrobenzanthrone were genotoxic in a variety of bacterial and mammalian cell systems.

Conflicting data have been reported on the role of metabolic enzymes in the genotoxicity of PM and their adsorbed constituents. Arlt et al. (2007, 097257) reported that the PM constituent 2-NB was genotoxic in bacterial and mammalian cells. However, metabolic activation with the human N-acetyltransferase 2 or sulfotransferase (SULT1A1) enzyme was needed for the effect to be observed in human cells. Erdinger et al. (2005, 156423) demonstrated that mutagenic activity was not affected when metabolism was induced. de Kok et al. (2005, 088656) evaluated the relationship between the physical, chemical, and genotoxic effects of ambient PM. TSP, PM_{10}, and $PM_{2.5}$ were sampled at different locations and the extracts were assessed for mutagenicity and induction of DNA adducts in cells. Overall, induction of rat liver S9 metabolism generally reduced the mutagenic potential via the Ames assay of the particle fractions and DNA reactivity (induction of DNA adducts) was generally higher after metabolic activation. Binková et al. (2003, 156274) found that the addition of S9 increased PM_{10}-dependent DNA adduct formation.

Ambient Air

A limited number of studies evaluated the impact of the season on the genotoxic effects of ambient PM. A few studies have indicated that greater genotoxic effects were associated with samples collected during the winter months compared to those collected in the summer (Abou et al., 2007, 098819; Gabelová et al., 2007, 156457; Gabelová et al., 2007, 156458). In contrast, Hannigan et al. (1997, 083598) indicated that no seasonal variation was observed. Studies have also shown that greater genotoxic effects were associated with smaller particle size extracts (e.g., $PM_{2.5}$>PM_{10}) and

from samples collected in urban areas or closer to higher trafficked areas (Abou et al., 2007, 098819; Hornberg et al., 1998, 095741).

de Kok et al. (2005, 088656) found the direct mutagenicity (Ames assay) and the direct DNA reactivity (DNA adduct formation) of the $PM_{2.5}$ size fraction was significantly higher than that of the larger size fractions (TSP, PM_{10}) at most locations.

DNA damage was assessed by the Comet assay in A549 cells exposed to PM collected from a high traffic area in Copenhagen, Denmark (TSP approximately 30 µg/m^3) and compared to the results from exposure of A549 cells to standard reference materials (SRM1650 or SRM2975) at the same concentrations (2.5-250 µg/ml) (Danielsen et al., 2008, 192092). All three particles induced strand breaks and oxidized purines in a dose-dependent manner and there were no obvious differences in potency. In contrast, only the ambient PM formed 8-oxodG when incubated with calf thymus DNA , which may be due to the concentration of transition metals.

Diesel and Gasoline Exhaust

Automobile DE particles (A-DE particles) was tested in *S. typhimurium* strains TA98, TA100, and its derivatives (e.g., TA98NR and YG1021) and found to be more mutagenic than forklift DE particles (f-DE particles, derivative SRM2975), based on PM mass. A-DE particles had 227 times more PAH-type mutagenic activity and 8-45 times more nitroarene-type mutagenic activity (DeMarini et al., 2004, 066329). Using a diesel engine without an oxidation catalytic converter (OCC), the diesel engine exhaust particle extract produced the highest number of revertant colonies in strains TA98 and TA100 with and without S9 at several tested loads when compared to extracts from low-sulfur diesel fuel (LSDF), rapeseed oil methyl ester (RME), and soybean oil methyl ester (SME). When an OCC was installed in the exhaust pipe of the engine, all extracts reduced the number of revertant colonies in both strains with and without S9 at partial loads but increased the number of revertant colonies without S9 at rated power. At idling, DE particles extracts increased the number of revertant colonies with and without S9 (Bunger et al., 2006, 156303). In a separate study, engine emissions (particle extracts and condensates) from rapeseed (canola) oil were found to produce greater mutagenic effects in *S typhimurium* strains TA98 and TA100 than DE particles (Bunger et al., 2007, 156304). Additionally, DE extract (DEE) from diesel fuel containing various percentages of ethanol was also observed to induce mutational response in two Salmonella strains. Base diesel fuel DEE and DEE from fuel with 20% ethanol caused more significant DNA damage in rat fibrocytes L-929 cells than extracts containing 5, 10, or 15% ethanol (Song et al., 2007, 155306).

DE and gasoline engine exhaust particles, as well as their semi-volatile organic compound (SVOC) extracts, induced mutations in the two *S. typhimurium* strains YG1024 and YG1029 in the absence and presence of S9; the PM extracts were more mutagenic than the SVOC extracts. Additionally, all extracts except the DE extract induced DNA damage and MN formation in Chinese hamster lung V79 cells (Liu et al., 2005, 097019). Another study demonstrated that gasoline engine exhaust significantly increased colony formation in TA98 with and without S9 (Zhang et al., 2007, 157186).

Jacobsen et al. (2008, 156597) used the FE1-Muta™ Mouse lung epithelial cell line to investigate putative mechanisms of DE particle-induced mutagenicity. Mutation ion frequencies and ROS were determined after cells were incubated with 37.5 or 75 µg/ml DE particles (SRM1650) for 72-h (n = 8). The mutation frequency at the 75 µg/ml dose was significantly increased (1.55-fold; $p<0.001$) in contrast to cells treated with 37.5 µg/ml DE particles. DE particles-induced ROS generation 1.6- to 1.9-fold in the epithelial cell cultures after 3 h of exposure compared with the 3- to 10-fold increase in ROS production previously reported for CB. The authors concluded that the mutagenic activity of DE particles is likely attributable to activity from the organic fraction that both contains reactive species and can generate ROS.

In human A549 and CHO-K1 cells, the organic fraction of DE particles significantly increased the amount of Comet and MN formation, respectively, in the presence and absence of SKF-525A (a CYP450 inhibitor) and S9, respectively (Oh and Chung, 2006, 088296). The organic base and neutral fractions of DE particles also significantly induced DNA damage but only without SKF-525A, and all fractions but the moderately polar fraction (phthalates and PAH oxyderivatives) induced MN formation with and without S9 (Bao et al., 2007, 097258). Gasoline engine exhaust significantly induced DNA damage as measured in the Comet assay and increased the frequency of MN in human A549 cells (Zhang et al., 2007, 157186). In human-hamster hybrid (A_L) cells, DE particles (SRM 2975) dose-dependently increased the mutation yield at the *CD59* locus; this was

significantly reduced by simultaneous treatment with phagocytosis inhibitors (Bao et al., 2007, 097258).

Wood Smoke

The mutagenicity of wood smoke and cigarette smoke (CS) extracts was assayed in *S. typhimurium* strains TA98 and TA100 (Ames assay) using the pre-incubation assay with exogenous metabolic activation (rat liver S-9). Extracts of both samples (62.5 or 125 µg total PM equivalent/ml) were equally mutagenic to strain TA98 but the wood smoke extract was less mutagenic than the CS extracts in strain TA100 (Iba et al., 2006, 156582).

In Vivo studies

Ambient Air

The contribution of ambient urban roadside air exposure (4, 12, 24, 48 or 60 wk) to DNA damage was examined in the lungs, nasal mucosa, and livers of adult male Wistar rats in Kawasaki, Japan (Sato et al., 2003, 096615). Messenger RNA levels of CYP450 enzymes that catalyze the transformation of PAHs to reactive metabolites were also evaluated. Concentrations of gases were reported to be 12-182 ppb NO and 0-9 ppb NO_2 in the filtered air chamber and 33-280 ppb NO and 42-81 ppb NO_2 in the experimental group chamber. Suspended PM concentrations were 11-19 µg/m^3 in the filtered air chamber and 42-100 µg/m^3 (average 63 µg/m^3) in the experimental group chamber. Body weight significantly decreased in exposed animals at 24, 48 and 60 wk. A 4-wk exposure to urban roadside air resulted in significant increases in multiple DNA adducts (lung, nasal, and liver DNA adducts). With longer exposures, there were significant increases in lung (48 wk), nasal (60 wk), and liver DNA adducts (60 wk). Changes were seen in CYP1A2 mRNA at 4 wk with a 2.3-fold increase in exposed animals compared to the control group with no change observed at 60 wk; CYP1A1 mRNA was unchanged. These results indicate that exposure to ambient air in this roadside area could induce DNA adduct formation, which may be important for carcinogenicity. Earlier studies (Ichinose et al., 1997, 053264) have shown that 8-oxodG, a DNA adduct, is elevated along with tumor formation in a dose-dependent manner in mice administered DE particles. The finding of adducts in the liver indicated that deposition of PM and its associated PAHs in the lung can have indirect effects on extrapulmonary organs. It should be noted that PM deposition on the fur and ingestion during grooming cannot be ruled out as a possible exposure route.

Another animal toxicological study employed "non-carcinogenic" particles obtained from pooled non-cancerous lung tissue collected during surgical lung resection from three non-smoking male patients diagnosed with lung adenocarcinomas (Tokiwa et al., 2005, 191952). Particles were partially purified to remove organic compounds. Morphologically the particles were similar to DE or ambient air PM and the organic extracts from the particles were directly mutagenic in S. typhimurium tester strains TA98, YG1021 and YG1024. BALB/c and ICR mice were intratracheally instilled with particles at doses of 0.25, 0.5, 1.0, or 2.0 mg/mouse. After 24 h, 8-oxodG was measured in lung DNA and found to be increased in ICR mice in a dose-dependent manner, reaching a maximum of ~2.75 8-oxodG/10^5 dG at the 2.0 mg dose. The response was statistically significant at doses of 0.5, 1.0, and 2.0 mg. The increased 8-oxodG levels observed in vivo was reported to be likely due to hydroxyl radicals presumed to be involved in phagocytosis of non-mutagenic particles by inflammatory cells that could induce hydroxylation of guanine residue on DNA.

Diesel Exhaust

An in vivo study employed *gtp* delta transgenic mice carrying the lambda EG10 on each Chromosome 17 from a C57BL/6J background to investigate the effects of DE particles on mutation frequency (Hashimoto et al., 2007, 097261). Mice were exposed via inhalation to DE particles or via IT instillation to DE particles or DE particle extract and lambda EG10 phages were rescued; *E. coli YG6020* was infected with the phage and screened for 6-thioguanine resistance. The mutagenic potency (mutation frequency per mg) caused by DE particle extract was twice that of DE particles, suggesting that the mutagenicity of DE particles is attributed primarily to compounds in the extract,

since ≈50% of the weight of DE particles was provided by the extract. There was no difference in mutation frequency between the 1 and 3 mg/m^3 DE particle groups after 12 wk of exposure.

Wood Smoke

One recent study measured the effect of freshly generated hardwood smoke on CYP1A1 activity based on ethoxyresorufin O-deethylase in pulmonary microsomes recovered from male Sprague-Dawley rats exposed to hardwood smoke by nose-only inhalation exposure (Iba et al., 2006, 156582). CYP1A1 activity in rat lung explants treated with extracts of the total PM (TPM) from hardwood smoke samples and from freshly generated cigarette smoke (CS) was also evaluated. Unlike CS, hardwood smoke did not induce pulmonary CYP1A1 activity or mRNA (assessed by northern blot analysis) nor did extracts of hardwood smoke TPM induce CYP1A1 protein (assessed by western blot analysis) in cultured rat lung explants. The results suggest that unique constituents that are activated by CYP1A1 may be present in CS but not hardwood smoke.

7.5.2.2. Carcinogenesis

Studies published prior to the 2004 AQCD that evaluated the carcinogenicity of ambient air were reviewed by Claxton and Woodall (2007, 180391). Five studies involved chronic inhalation exposures in rodents. No statistically significant increase in tumorigenesis was observed following chronic exposure to urban air pollution in Los Angeles (Gardner, 1966, 015129; Gardner et al., 1969, 015130; Wayne and Chambers, 1968, 038537). However in a study conducted in Brazil, urban air pollution was found to enhance the formation of urethane-induced lung tumors in mice (Cury et al., 2000, 192100; Reymao et al., 1997, 084653).

Two recent studies evaluated the carcinogenic potential of chronic inhalation exposures to DE (Reed et al., 2004, 055625) and hardwood smoke (Reed et al., 2006, 156043). Two indicators of carcinogenic potential, formation of MN and tumorigenesis were measured in strain A/J mice, which is a mouse model that spontaneously develops lung tumors. Exposure to DE or hardwood smoke at concentrations of 1,000 μg/m^3 and below did not cause increased formation of MN or an increased rate of lung tumors in this cancer-prone rodent model. These studies are described below.

Diesel Exhaust

A/J mice were exposed to 30, 100, 300 and 1000 μg/m^3 DE for 6 h/day and 7 days/wk for 6 mo (Reed et al., 2004, 055625). The concentration of gases in this including NO_X, NO_2, CO, SO_2, NH_3, methane, non-methane VOC, and FID total hydrocarbon ranged from control to high dose group values of 0 to 50.4 ± 0.6 ppm, 0.2 ± 0.2 to 6.9 ± 3.3 ppm, 0.3 ± 0.1 to 30.9 ± 4.5 ppm, not detectable to 955.2 ± 58.4 ppb, 176.5 ± 8.8 to 9.1 ± 0.2 μg/m^3, 1406.5 ± 253.2 to 2642.1 ± 455.9 μg/m^3, 134.0 ± 52.1 to 1578.6 ± 256.2 μg/m^3, 0.1 ± 0.1 to 2.2 ± 0.2 ppm, respectively. Particle sizes in the four exposure groups ranged from 0.10-0.15 μm MMAD with geometric standard deviations of 1.4-1.8. Following the 6-mo exposure and a 6-mo recovery period, mice were collected and MN formation in blood and tumor multiplicity and tumor incidence were measured in lungs. No increases in formation of MN or numbers of lung adenomas were observed in DE-exposed mice compared with controls.

Wood Smoke

A/J mice were exposed to 30, 100, 300 and 1,000 μg/m^3 hardwood smoke or to 30, 100, 300 and 1,000 μg/m^3 DE for 6 h/day and 7 days/wk for 6 mo (Reed et al., 2006, 156043). Gaseous components of the hardwood smoke included CO, NH_3, and non-methane VOC with concentrations from control levels to high dose hardwood smoke exposure ranging from 229 ± 31 to 14887.6 ± 832.3 ppm, 139.3 ± 2.3 to 54.9 ± 1.2 μg/m^3 and 177.6 ± 10.4 to 3455.0 ± 557.2 μg/m^3, respectively. Concentrations of NO_X, NO_2 and SO_2 were reported to be null. Particle sizes in the four exposure groups ranged from 0.25-0.36 μm MMAD with geometric standard deviations of 2.0-3.3. Following the 6-mo exposure and a 6-mo recovery period, mice were collected and MN formation in blood and tumor multiplicity and tumor incidence were measured in lungs. No increases in formation of MN or

numbers of lung adenomas were observed in hardwood smoke-exposed mice compared with controls. However, hardwood smoke from this study was mutagenic in the Ames reverse mutation assay.

7.5.2.3. Summary of Toxicological Studies

In summary, numerous new in vitro studies confirm and extend findings reported in the 2004 AQCD that ambient PM from urban sites and combustion-derived PM are mutagenic and genotoxic. A small number of new studies were conducted in vivo. One of these studies demonstrated increased mutagenic potency in mice exposed to DE particles and DE particle extract. Another study found increased formation of 8-oxodG, a DNA adduct, following IT instillation of PM in mice. A chronic inhalation study of rats exposed to urban roadside air reported increased formation of DNA adducts in nose, lung, and liver and induction of CYP1A2. Inhalation exposure of rats to hardwood smoke failed to induce CYP1A1 in another study. Finally, two chronic inhalation studies found no evidence of carcinogenic potential for DE and hardwood smoke in a cancer-prone mouse model. Collectively, these results provide some evidence, mainly from in vitro studies, to support the biological plausibility of ambient PM-lung cancer relationships observed in epidemiology studies.

7.5.3. Epigenetic Studies and Other Heritable DNA mutations

Two epidemiologic epigenetic studies examined the effect of PM on DNA methylation. Both studies examined methylation of Alu and long interspersed nuclear element-1 (LINE-1) sequences, which are located in repetitive elements. In previous studies, methylation of these sequences has been linked to global genomic DNA methylation content (Weisenberger et al., 2005, 192101; Yang et al., 2004, 192102).

The first study included men age 55 and older who were part of the Normative Aging Study in the Boston area (Baccarelli et al., 2009, 192155). A stationary monitoring site located 1 km from the examination site was used to estimate ambient $PM_{2.5}$ exposure for the duration of the study (1999-2007). During the study period, the median level of $PM_{2.5}$, averaged over 7-day periods, was 9.8 $\mu g/m^3$ (interquartile range 8.0-12.0 $\mu g/m^3$). There was no association between $PM_{2.5}$ and Alu methylation. LINE-1 methylation was associated with $PM_{2.5}$ measured over the 7 days before the examinations.

The second study included 63 healthy men aged 27-55 yr working at an electric furnace steel plant (Tarantini et al., 2009, 192010). Blood samples were taken twice, once in the morning after 2 days of not working and once in the morning after 3 full days of work. PM_{10} was measured in 11 work areas and individuals completed daily logs about the amount of time spent in each area. On average, individuals had an estimated exposure of 233.4 $\mu g/m^3$ PM_{10} (range 73.4-1220.2 $\mu g/m^3$). Short-term exposure did not alter the methylation of Alu and LINE-1. To examine effects of long-term exposure, both blood samples were considered independent of time, and Alu and LINE-1 were examined with respect to overall estimated PM_{10} exposure using mixed effects models. There was a negative association between increasing levels of PM_{10} exposure and Alu and LINE-1 methylation, indicating that PM_{10} causes epigenetic changes to occur with long-term exposure. This study also looked at levels of iNOS gene, which is a gene suppressed by DNA methylation. iNOS expression was not associated with long term exposure to PM_{10} but was affected by methylation in the short term.

Animal toxicology studies evaluating the effect of PM exposure on changes in the epigenome and other non-epigenetic heritable DNA changes have only recently been conducted. After earlier work showed increased germline mutation rates in herring gulls nesting near steel mills on Lake Ontario (Yauk and Quinn, 1996, 089093) further work was conducted to address air-dependent contribution to germline mutations by housing male and female Swiss Webster mice in the same area and comparing mutation rates in those animals with mutation rates of animals housed in a rural setting with less air pollution (Somers et al., 2002, 078100). To determine if PM or the gaseous phase of the urban air was responsible for heritable mutations, Yauk et al. (2008, 157164) exposed mature male C57Bl×CBA F1 hybrid mice to either HEPA-filtered air or to ambient air in Hamilton, Ontario, Canada for 3 or 10 wk, or 10 wk plus 6 wk of clean air exposure (16 wk) (also discussed in Section 7.4.2.5). Sperm DNA was monitored for ESTR mutations, testicular sample bulky DNA adducts, and DNA single or double strand breaks. In addition, male-germ line (spermatogonial stem

cell) DNA methylation was monitored post-exposure. This area in Hamilton is near two steel mills and a major highway. Air composition showed mean concentrations for TSP of 93.8 ± 17 μg/m^3, PAH of 8.3 ± 1.7 ng/m^3, and metal of 3.6 ± 0.7 μg/m^3. Mutation frequency at ESTR Ms6-hm locus in sperm DNA from mice exposed 3 or 10 wk did not show elevated ESTR mutation frequencies, but there was a significant increase in ESTR mutation frequency at 16 wk compared to HEPA-filter control animals, pointing to a PM-dependent mechanism of action. No detectable DNA adducts were observed in testes samples at any of the time points monitored. To verify inhalation exposure to particles, DNA adducts were reported in the lungs of mice exposed for 3 wk to ambient air; no other time points showed detectable DNA adduct formation. Hypermethylation of germ-line DNA was also observed in mice exposed to ambient air for 10 and 16 wk. These PM-dependent epigenetic modifications (hypermethylation) were not seen in the halploid stage (3 wk) of spermatogenesis, but were nonetheless seen in early stages of spermatogenesis (10 wk) and remained significantly elevated in mature sperm even after removal of the mouse from the environmental exposure (16 wk). Thus, these studies indicate that the ambient PM phase and not the gaseous phase is responsible for the increased frequency of heritable DNA mutations and epigenetic modifications.

Based on the limited evidence from these epigenetics studies, long-term exposure to PM_{10} may result in epigenetic changes. $PM_{2.5}$ also potentially affects some DNA methylation content. As epigenetic research progresses, future studies examining the relationship between PM and DNA methylation will be important in more thoroughly characterizing these associations.

The effect of ambient PM on heritable DNA mutations and the epigenome has been well characterized in a Canadian steel mill area. Mice exposed to ambient PM plus gases developed paternally-derived heritable DNA mutations and epigenetic changes in sperm DNA that were not observed in mice exposed to ambient air that was HEPA-filtered. This is the first animal toxicology study showing heritable effects of PM exposure on DNA mutation and the epigenome. Because the epigenetics field is so new, further work in this emerging area will expand on these PM-dependent methylation changes to determine if the results can be recapitulated at other urban sites.

7.5.4. Summary and Causal Determinations

7.5.4.1. $PM_{2.5}$

The 2004 PM AQCD reported on original and follow-up analyses for three prospective cohort studies that reported positive relationships between $PM_{2.5}$ and lung cancer mortality. Several recent, well-conducted epidemiologic studies have extended the evidence for a positive association between $PM_{2.5}$ and lung cancer mortality (Section 7.5.1.1). Generally, studies have not reported associations between long-term exposure to $PM_{2.5}$ or PM_{10} and lung cancer incidence (Section 7.5.1.1). Animal toxicological studies did not focus on specific size fractions of PM, but rather examined ambient PM, wood smoke, and DE particles (Section 7.5.2). A number of recent studies indicate that ambient urban PM, emissions from wood/biomass burning, emissions from coal combustion, and gasoline and DE are mutagenic and that PAHs are genotoxic (Section 7.5.2). These findings are consistent with earlier studies that concluded that ambient PM and PM from specific combustion sources are mutagenic and genotoxic and provide biological plausibility for the results observed in the epidemiologic studies. A limited number of epidemiologic and toxicological studies on the epigenome demonstrate that PM induces changes in methylation (Section 7.5.3), a new area of research that will likely be expanded in the future. However, it has yet to be determined how these alterations in the genome could influence the initiation and promotion of cancer. Overall, the evidence is **suggestive of a causal relationship between relevant $PM_{2.5}$ exposures and cancer, with the strongest evidence from the epidemiologic studies of lung cancer mortality.** This evidence is limited by the non-specific measure of PM size fraction in some of the epidemiologic studies and most of the animal toxicological studies, and the inconsistency in evidence with recent epidemiologic studies for an effect on cancer incidence. There is no epidemiologic evidence for cancer related to long-term exposure to PM in organs or systems other than the lung.

7.5.4.2. $PM_{10-2.5}$

The 2004 PM AQCD did not report long-term exposure studies for $PM_{10-2.5}$. No epidemiologic studies have been conducted to evaluate the effects of long-term $PM_{10-2.5}$ exposure and cancer. The evidence is **inadequate to assess the association between $PM_{10-2.5}$ and UFP exposures and cancer.**

7.5.4.3. UFPs

The 2004 PM AQCD did not report long-term exposure studies for UFPs. No epidemiologic studies have been conducted to evaluate the effects of long-term UFP and cancer. The evidence is **inadequate to determine if a causal relationship exists between long-term UFP exposures and cancer**.

7.6. Mortality

In the 1996 PM AQCD, results were presented for three prospective cohort studies of adult populations: the Six Cities Study (Dockery et al., 1993, 044457); the ACS Study (Pope et al., 1995, 045159); and the AHSMOG Study (Abbey et al., 1995, 000669). The 1996 AQCD concluded that the chronic exposure studies, taken together, suggested associations between increases in mortality and long-term exposure to $PM_{2.5}$, though there was no evidence to support an association with $PM_{10-2.5}$ (U.S. EPA, 1996, 079380).

Discussions of mortality and long-term exposure to PM in the 2004 PM AQCD emphasized the results of four U.S. prospective cohort studies, but the greatest weight was placed on the findings of the ACS and the Harvard Six Cities studies, which had each undergone extensive independent reanalysis, and which were based on cohorts that were broadly representative of the U.S. population. The 2004 PM AQCD concluded that the results from the Seventh-Day Adventist (AHSMOG) cohort provided some suggestive (but less conclusive) evidence for associations, while results from the Veterans Cohort provided inconsistent evidence for associations between long-term exposures to $PM_{2.5}$ and mortality. Collectively, the 2004 PM AQCD found that these studies provided strong evidence that long-term exposure to $PM_{2.5}$ was associated with increased risk of human mortality. Effect estimates for all-cause mortality ranged from 6 to 13% increased risk per 10 $\mu g/m^3$ $PM_{2.5}$, while effect estimates for cardiopulmonary mortality ranged from 6 to 19% per 10 $\mu g/m^3$ $PM_{2.5}$. For lung cancer mortality, the effect estimate was a 13% increase per 10 $\mu g/m^3$ $PM_{2.5}$, based upon the results of the extended analysis from the ACS cohort (Pope et al., 2002, 024689). With regard to $PM_{10-2.5}$, the 2004 PM AQCD reported that no association was observed between mortality and long-term exposure to $PM_{10-2.5}$ in the ACS study (Pope et al., 2002, 024689), while a positive but statistically non-significant association was reported in males in the AHSMOG cohort (McDonnell et al., 2000, 010319). Thus, the 2004 PM AQCD concluded that there was insufficient evidence for associations between long-term exposure to $PM_{10-2.5}$ 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 excess all-cause and cardiopulmonary mortality.

At the time of the 2004 PM AQCD, only a limited number of the chronic-exposure cohort studies had considered direct measurements of constituents of PM, other than sulfates. With regard to source-oriented evaluations of mortality associations with long-term exposure, the 2004 PM AQCD noted only the study by Hoek et al. (2002, 042364), in which the authors concluded that long-term exposure to traffic-related air pollution may shorten life expectancy. However, Hoek et al. (2002, 042364) also noted that living near a major road might include other factors that contribute to mortality associations. There was not sufficient evidence at the time of the 2004 PM AQCD to draw conclusions on effects associated with specific components or sources of PM.

New epidemiologic evidence reports a consistent association between long-term exposure to $PM_{2.5}$ and increased risk of mortality. There is little evidence for the long-term effects of $PM_{10-2.5}$ on mortality. Although this section focuses on mortality outcomes in response to long-term exposure to PM, it does not evaluate studies that examine the association between PM and infant mortality.

These studies are evaluated in Section 7.5 because it is possible that in utero exposures contribute to infant mortality. A summary of the mean PM concentrations reported for the studies characterized in this section is presented in Table 7-8.

Table 7-8. Characterization of ambient PM concentrations from studies of mortality and long-term exposures to PM.

Study	Location	Mean Concentration ($\mu g/m^3$)	Upper Percentile Concentrations ($\mu g/m^3$)
$PM_{2.5}$			
Brunekreef et al. (2009, 191947)	The Netherlands	28	95th: 32 99th: 33 Max: 37
Chen et al. (2005, 087942)	Multicity, CA	29.0	
Eftim et al. (2008, 099104)	U.S.	13.6-14.1	Max: 19.1-25.1
Enstrom (2005, 087356)	CA	23.4	Max: 36.1
Goss et al. (2004, 055624)	U.S.	13.7	75th: 15.9
Janes et al. (2007, 090927)	U.S.	14.0	
Jerrett et al. (2005, 087600)	Los Angeles, CA		Max: 27.1
Krewski et al. (2009, 191193)	U.S.	14.02	75^{th}: 16.00 90th: 26.75 95th: 27.89 Max: 30.01
Laden et al. (2006, 087605)	Multicity, U.S.	10.2-29.0	
Lipfert et al. (2006, 088218)	U.S.	14.3	
Miller et al. (2007, 090130)	U.S.	13.5	75th: 18.3 Max: 28.3
Pope et al. (2004, 055880)	U.S.	17.1	
Schwartz et al. (2008, 156963)	Multicity, U.S.	17.5	Max: 40
Zeger et al. (2007, 157176)	U.S.		17.0
Zeger et al. (2008, 191951)	U.S.	13.2	75th: 14.9
$PM_{10-2.5}$			
Chen et al. (2005, 087942)	Multicity, CA	25.4	
Lipfert et al. (2006, 088218)	U.S.	16.0	
PM_{10}			
Chen et al. (2005, 087942)	Multicity, CA	52.6	
Gehring et al. (2006, 089797)	North Rhine, Germany	43.7-48.0	Max: 52.5-56.1
Goss et al. (2004, 055624)	U.S.	24.8	75th: 28.9
Puett et al. (2008, 156891)	NE U.S.	21.6	
Zanobetti et al. (2008, 156177)	U.S.	29.4	

7.6.1. Recent Studies of Long-Term Exposure to PM and Mortality

Studies since the last PM AQCD include results of new analyses and insights for the ACS and Harvard Six Cities studies, further analyses from the AHSMOG and Veterans study cohorts, as well as analyses of a Cystic Fibrosis cohort and subsets of the ACS from Los Angeles and New York City. 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, and the extended and follow-up analyses did not evaluate associations with $PM_{10-2.5}$. The historical and more recent results for $PM_{2.5}$ of both the ACS and the Harvard Six Cities studies are compiled in Figure 7-6. Moreover, since the last PM AQCD, there is a major new cohort that investigates the effects of $PM_{2.5}$ on cardiovascular mortality in the literature: the WHI study (Miller et al., 2007, 090130). Most recently, an ecologic cohort study of the nation's Medicare population has been completed (Eftim et al., 2008, 099104). These new findings further strengthen the evidence linking long-term exposure to $PM_{2.5}$ and mortality, while providing indications that the magnitude of the $PM_{2.5}$-mortality association is larger than previously estimated (Figure 7-7). Two recent reports from the AHSMOG and Veterans study cohorts have provided some limited evidence for associations between long-term exposure to $PM_{10-2.5}$ and mortality. The original analyses of the AHSMOG cohort study found positive associations between long-term concentrations of PM_{10} and 15-yr mortality due to natural causes and lung cancer (Abbey et al., 1999, 047559). McDonnell et al. (2000, 010319) reanalyzed these data and concluded that previously observed association of long-term ambient PM_{10} concentrations with mortality for males were best explained by a relationship of mortality with the fine fraction of PM_{10} rather than the thoracic coarse fraction of PM_{10}. Recent reports from the AHSMOG study cohort, as well as the Nurses' Health Study and a cohort of women in Germany have provided some evidence for associations between long-term exposure to PM_{10} and mortality among women.

Harvard Six Cities: A follow-up study has used updated air pollution and mortality data; an additional 1,368 deaths occurred during the follow-up period (1990-1998) versus 1,364 deaths in the original study period (1974-1989) (Laden et al., 2006, 087605). 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 special note is a statistically significant reduction in mortality risk reported with reduced long-term $PM_{2.5}$ 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 risks with reduced long-term $PM_{2.5}$ concentrations. This reduced mortality risk was observed for deaths due to cardiovascular and respiratory causes, but not for lung cancer deaths. The $PM_{2.5}$ concentrations for recent years were estimated from visibility data, which introduces some uncertainty in the interpretation of the results from this study. Coupled with the results of the original analysis (Dockery et al., 1993, 044457), this study strongly suggests that a reduction in $PM_{2.5}$ pollution yields positive health benefits.

ACS Extended Analyses/Reanalysis II: Two new analyses further evaluated the associations of long-term $PM_{2.5}$ exposures with risk of mortality in 50 U.S. cities reported by Pope and colleagues (2002, 024689), adding new details about deaths from specific cardiovascular and respiratory causes (Krewski, 2009, 190075; Pope et al., 2004, 055880). Pope et al. (2004, 055880) reported positive associations with deaths from specific cardiovascular diseases, particularly ischemic heart disease (IHD), 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 $\mu g/m^3$ $PM_{2.5}$), but no PM associations were found with respiratory mortality.

In an additional reanalysis that extended the follow-up period for the ACS cohort to 18 yr (1982-2000) (Krewski et al., 2009, 191193), investigators found effect estimates that were similar, though generally higher, than those reported in previous ACS analyses. This reanalysis also included data for seven ecologic (neighborhood-level) contextual (i.e., not individual-level) covariates, each of which represents local factors known or suspected to influence mortality, such as poverty level, educational attainment, and unemployment. The effect estimate for all cause mortality, based on $PM_{2.5}$ concentrations measured in 1999-2000 was 1.03 (95% CI: 1.01-1.05). The corresponding effect estimates for deaths due to IHD and lung cancer were 1.15 (95% CI: 1.04-1.18) and 1.11 (95% CI: 1.04-1.18), respectively. In earlier analyses of this cohort, investigators found that increasing education levels appeared to reduce the effect of $PM_{2.5}$ exposure on mortality. Results from this reanalysis show a similar pattern, although with somewhat less certainty, for all causes of death except IHD, for which the pattern was reversed. Overall, although the addition of random effects modeling and contextual covariates to the ACS model made most effect estimates higher (but

some lower), they were not statistically different from the earlier ACS effect estimates. Thus, these new analyses, with their more extensive consideration of potentially confounding factors, confirm the published ACS $PM_{2.5}$-mortality results to be robust.

California Cancer Prevention Study: In a cohort of elderly people in 11 California counties (mean age 73 yr in 1983), an association was reported for long-term $PM_{2.5}$ exposure with all-cause deaths from 1973-1982 (RR = 1.04 [95% CI: 1.01-1.07] per 10 $\mu g/m^3$ $PM_{2.5}$) (Enstrom, 2005, 087356). However, no significant associations were reported with deaths in later time periods when $PM_{2.5}$ levels had decreased in the most polluted counties (1983-2002) (RR = 1.00 [95% CI: 0.98-1.02] per 10 $\mu g/m^3$ $PM_{2.5}$). The $PM_{2.5}$ data were obtained from the EPA's Inhalation Particle Network (collected 1979-1983), and the locations represented a subset of data used in the 50-city ACS study (Pope et al., 1995, 045159). However, 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.

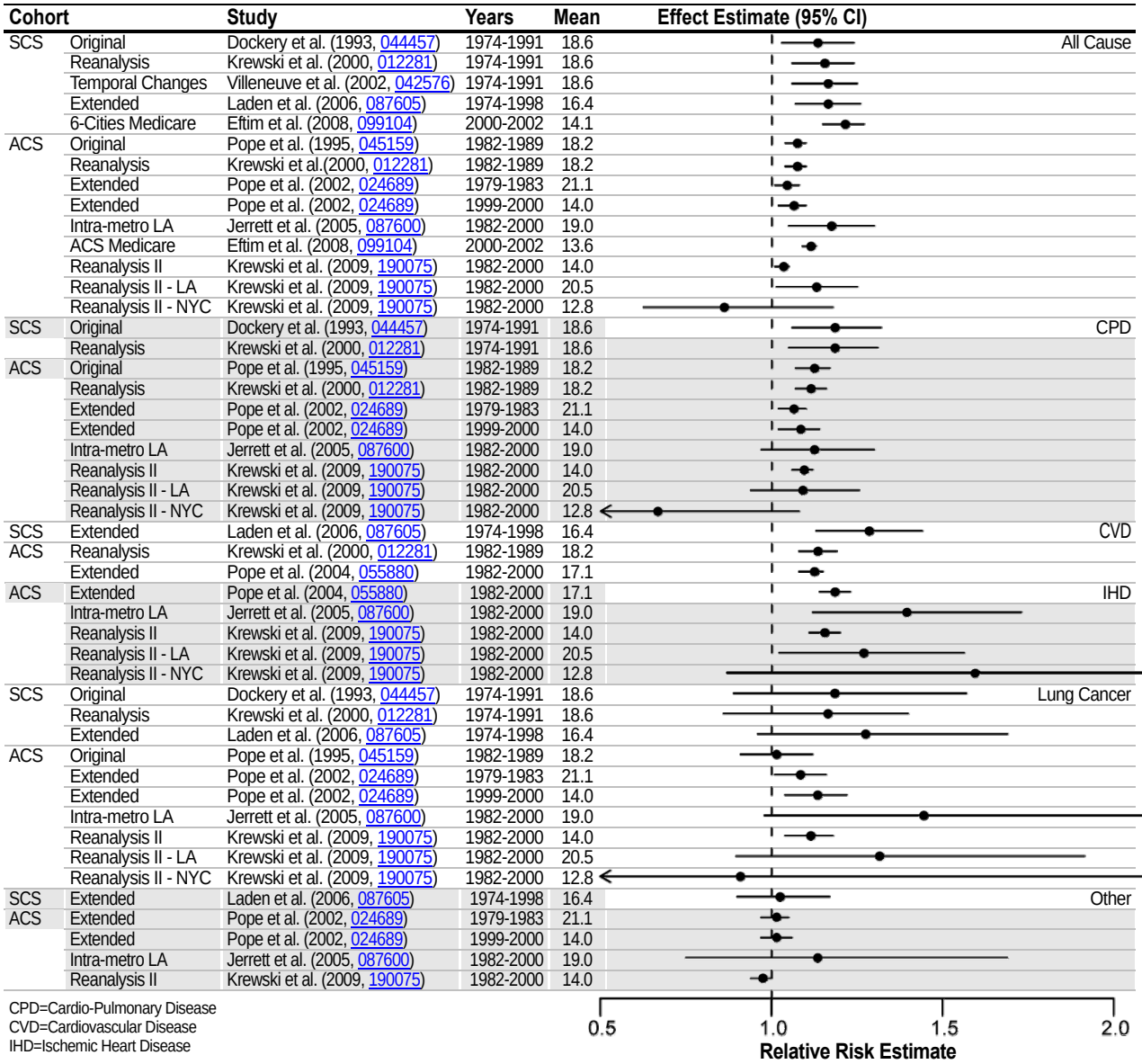
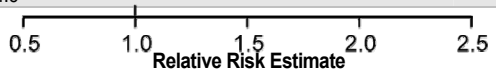


Figure 7-6. Mortality risk estimates associated with long-term exposure to $PM_{2.5}$ from the Harvard Six Cities Study (SCS) and the American Cancer Society Study (ACS).

Study	Cohort	Subset	Mean	Effect Estimate (95% CI)	
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		All Cause
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		
		Case Cohort	28.3		
Enstrom (2005, 087356)	CA Cancer Prevention	1973-1982	23.4		
		1983-2002	23.4*		
		1973-2002	23.4*		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Lipfert et al. (2006, 088218)	Veterans Cohort		14.3		
			14.3		
Eftim et al. (2008, 099104)	Medicare Cohort	ACS Sites	13.6		
		6-Cities sites	14.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
Goss et al. (2004, 055624)	U.S. Cystic Fibrosis		13.7		
Zeger et al. (2008, 191951)	MCAPS	65+, Eastern	14.0		
		65+, Central	10.7		
		65+, Western	13.1		
		65-74, Eastern	14.0		
		65-74, Central	10.7		
		65-74, Western	13.1		
		65+, Eastern	14.0		
		75-84, Central	10.7		
		75-84, Western	13.1		
		85+, Eastern	14.0		
		85+, Central	10.7		
		85+, Western	13.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		CV
		Case Cohort	28.3		
Pope et al. (2004, 055880)	ACS		17.1		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Naess et al. (2007, 090736)	Oslo, Norway	Males, 51-70 yrs	14.3		
		Males, 71-90 yrs	14.3		
		Females, 51-70 yrs	14.3		
		Females 71-90 yrs	14.3		
Miller et al. (2007, 090130)	WHI	Females	13.5		
Chen et al. (2005, 087942)	AHSMOG	Females	29.0		CHD
		Males	29.0		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		IHD
Krewski et al. (2009, 190075)	ACS Reanalysis II-LA		20.5		
Pope et al. (2004, 055880)	ACS		17.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		CPD
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		Respiratory
		Case Cohort	28.3		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		Lung Cancer
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		
		Case Cohort	28.3		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Naess et al. (2007, 090736)	Oslo, Norway	Males, 51-70 yrs	14.3		
		Males 71-90 yrs	14.3		
		Females, 51-70 yrs	14.3		
		Females, 71-90 yrs	14.3		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		Other
		Case Cohort	28.3		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		



CV=Cardiovascular; CHD= Coronary Heart Disease
IHD=Ischemic Heart Disease; CPD=Cardio-Pulmonary Disease
* $PM_{2.5}$ data from 1973-1982 applied to all subsequent time periods

Figure 7-7. Mortality risk estimates, long-term exposure to $PM_{2.5}$ in recent cohort studies.

AHSMOG: In this analysis for the Seventh-Day Adventist cohort in California, a positive, statistically significant, association with coronary heart disease mortality was reported among females (92 deaths; RR = 1.42 [95% CI: 1.06-1.90] per 10 $\mu g/m^3$ $PM_{2.5}$), but not among males (53 deaths; RR = 0.90 [95% CI: 0.76-1.05] per 10 $\mu g/m^3$ $PM_{2.5}$) (Chen et al., 2005, 087942). Associations were strongest in the subset of postmenopausal women (80 deaths; RR = 1.49 [95% CI: 1.17-1.89] per 10 $\mu g/m^3$ $PM_{2.5}$). 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. As was found with $PM_{2.5}$, a positive association with coronary heart disease mortality was reported for PM_{10-25} and PM_{10} among females (RR = 1.38 [95% CI: 0.97-1.95] per 10 $\mu g/m^3$ $PM_{10-2.5}$; RR = 1.22 [95% CI: 1.01-1.47] per 10 $\mu g/m^3$ PM_{10}), but not for males (RR = 0.92 [95% CI: 0.66-1.29] per 10 $\mu g/m^3$ $PM_{10-2.5}$; RR = 0.94 [95% CI: 0.82-1.08] per 10 $\mu g/m^3$ PM_{10}); associations were strongest in the subset of postmenopausal women (80 deaths) (Chen et al., 2005, 087942).

U.S. Cystic Fibrosis cohort: A positive, but not statistically significant, association was reported for $PM_{2.5}$ in this study (RR = 1.32 [95% CI: 0.91-1.93] per 10 $\mu g/m^3$ $PM_{2.5}$) that primarily focused on evidence of exacerbation of respiratory symptoms (Goss et al., 2004, 055624). No clear association was reported for PM_{10}. However, only 200 deaths had occurred in the cohort of over 11,000 people (average age in cohort was 18.4 yr), so the power of this study to detect associations was relatively low.

Women's Health Initiative (WHI) Study: This nationwide cohort study considered 65,893 post-menopausal women with no history of cardiovascular disease who lived in 36 U.S. metropolitan areas from 1994 to 1998 (Miller et al., 2007, 090130). The study had a median subject follow-up time of 6 years. Miller and colleagues assessed each woman's exposure to air pollutants using the monitor located nearest to their residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Overall, this study concludes that "long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women." In terms of effect size, the study found that each increase of 10 $\mu g/m^3$ of $PM_{2.5}$ was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24 [95% CI: 1.09-1.41]) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76 [95% CI: 1.25-2.47]). While this study found results confirmatory to the ACS and Six Cities Study, it reports much larger relative risk estimates per $\mu g/m^3$ $PM_{2.5}$. In addition, since the study included only women without pre-existing cardiovascular disease, it could potentially be a healthier cohort population than that considered by the ACS and Six Cities Study. Indeed, the WHI Study reported only 216 cardiovascular deaths in 349,643 women-yr of follow-up, or a rate of 0.075% deaths per year (Miller et al., 2007, 090130), while the ACS Study reported that 10% of subjects died of cardiovascular disease over a 16-yr follow-up period, yielding a rate of 0.625% per year, or approximately 8 times the cardiovascular mortality rate of the WHI population (Pope et al., 2004, 055880). Thus, $PM_{2.5}$ impacts may yield higher relative risk estimates in the WHI population because the $PM_{2.5}$ risk is being compared to a much lower prevailing risk of cardiovascular death in this select study population.

The WHI study not only confirms the ACS and Six City Study associations with mortality in yet another well characterized cohort with detailed individual-level information, it also has been able to consider the individual medical records of the thousands of WHI subjects over the period of the study. This has allowed the researchers to examine not only mortality, but also related morbidity in the form of heart problems (cardiovascular events) experienced by the subjects during the study. As reported in this paper, this examination confirmed that there is an increased risk of cardiovascular morbidity, as well (Section 7.2.9). These morbidity co-associations with $PM_{2.5}$ in the same population lend even greater support to the biological plausibility of the air pollution-mortality associations found in this study.

Medicare Cohort Studies: Using Medicare data, Eftim and co-authors (2008, 099104) assessed the association of $PM_{2.5}$ with mortality for the same locations included in the ACS and Six City Study. For these locations, they estimated the chronic effects of $PM_{2.5}$ on mortality for the period 2000-2002 using mortality data for cohorts of Medicare participants and average $PM_{2.5}$ levels from monitors in the same counties included in the two studies. Using aggregate counts of mortality by county for three age groups, they estimated mortality risk associated with air pollution adjusting for age and sex and area-level covariates (education, income level, poverty, and employment), and controlled for potential confounding by cigarette smoking by including standardized mortality ratios

for lung cancer and COPD. This study is, therefore, an ecological analysis, similar to past published cross-sectional analyses, in that area-level covariates (education, income level, poverty, and employment) are employed as controlling variables, since individual level information is not available from the Medicare database (other than age and sex), which includes virtually all Americans aged 65 or greater. Exposures are also ecological in nature, as central site data are used as indices of exposure. These results indicated that a 10 $\mu g/m^3$ increase in the yearly average $PM_{2.5}$ concentration is associated with 10.9% (95% CI: 9.0-12.8) and with 20.8% (95% CI: 14.8-27.1) increases in all-cause mortality for the ACS and Six Cities Study counties, respectively. The estimates are somewhat higher than those reported by the original investigators, and there may be several possible explanations for this apparent increase, especially that this is an older population than the ACS cohort. Perhaps the most likely explanation is that the lack of personal confounder information (e.g., past personal smoking information) led to an insufficient control for the effects of these other variables' effects on mortality, inflating the pollution effect estimates somewhat, similar to what has been found in the ACS analyses when only ecological-level control variables were included. The ability of the Eftim et al. (2008, 099104) study results to qualitatively replicate the original individual-level cohort study (e.g., ACS and Six Cities Study) results suggests that past ecological cross-sectional mortality study results may also provide useful insights into the nature of the association, especially when used for consideration of time trends, or for comparisons of the relative (rather than absolute) sizes of risks between different pollutants or PM components in health effects associations.

Janes et al. (2007, 090927) used the same nationwide Medicare mortality data to examine the association between monthly averages of $PM_{2.5}$ over the preceding 12 mo and monthly mortality rates in 113 U.S. counties from 2000 to 2002. They decomposed the association between $PM_{2.5}$ and mortality into two components: (1) the association between "national trends" in $PM_{2.5}$ and mortality; and (2) the association between "local trends," defined as county-specific deviations from national trends. This second component is posited to provide evidence as to whether counties having steeper declines in $PM_{2.5}$ also have steeper declines in mortality relative to the national trend. They report that the exposure effect estimates are different at these two spatiotemporal scales, raising concerns about confounding bias in these analyses. The authors assert that the association between trends in $PM_{2.5}$ and mortality at the national scale is more likely to be confounded than is the association between trends in $PM_{2.5}$ and mortality at the local scale and, if the association at the national scale is set aside, that there is little evidence of an association between 12-month exposure to $PM_{2.5}$ and mortality in this analysis. However, in response, Pope and Burnett (2007, 090928) point out that such use of long-term time trends as the primary source of exposure variability has been avoided in most other air pollution epidemiology studies because of such concerns about potential confounding of such time-trend associations.

By linking monitoring data to the U.S. Medicare system by county of residence, Zeger et al. (2007, 157176) analyzed Medicare mortality records, comprising over 20 million enrollees in the 250 largest counties during 2000-2002. The authors estimated log-linear regression models having age-specific county level mortality rates as the outcome and, as the main predictor, the average $PM_{2.5}$ pollution level in each county during 2000. Area-level covariates were used to adjust for socio-economic status and smoking. The authors reported results under several degrees of adjustment for spatial confounding and with stratification into eastern, central and western U.S. counties. A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7.6% increase in mortality (95% CI: 4.4-10.8). When adjusted for spatial confounding, the estimated log-relative risks dropped by 50%. Zeger et al. (2007, 157176) found a stronger association in the eastern counties than nationally, with no evidence of an association in western counties.

In a subsequent report, Zeger et al. (2008, 191951) created a new retrospective cohort, the Medicare Cohort Air Pollution Study (MCAPS), consisting of 13.2 million persons residing in 4,568 ZIP codes in urban areas having geographic centroids within 6 miles of a $PM_{2.5}$ monitor. Using this cohort, they investigated the relationship between 6-yr avg exposure to $PM_{2.5}$ and mortality risk over the period 2000-2005. When divided by region, the associations between long-term exposure to $PM_{2.5}$ and mortality for the eastern and central ZIP codes were qualitatively similar to those reported in the ACS and Six Cities Study, with 11.4% (95% CI: 8.8-14.1) and 20.4% (95% CI: 15.0-25.8) increases per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in the eastern and central regions, respectively. The MCAPS results included evidence of differing $PM_{2.5}$ relative risks by age and geographic location, where risk declines with increasing age category until there is no evidence of an association among persons

≥ 85 yr of age, and there is no evidence of a positive association for the 640 urban ZIP codes in the western region of the U.S.

Using hospital discharge data, Zanobetti et al. (2008, 156177) constructed a cohort of persons discharged with COPD using Medicare data between 1985 and 1999. Positive associations in the survival analyses were reported for single year and multiple-year lag exposures, with a hazard ratio for total mortality of 1.22 (95% CI: 1.17-1.27) per 10 $\mu g/m^3$ increase in PM_{10} over the previous 4 years.

Veterans Cohort: A recent reanalysis 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 (Lipfert et al., 2006, 088218). 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 $\mu g/m^3$ $PM_{2.5}$). This risk estimate is larger than results reported in a previous study of this cohort. In multipollutant 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 multipollutant model results should be interpreted with caution. In a companion study, Lipfert et al. (2006, 088218) used data from EPA's fine particle speciation network, and reported findings for $PM_{2.5}$ which were similar to those reported by Lipfert et al. (2006, 088218). In this study (Lipfert et al., 2006, 088218), 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 $\mu g/m^3$ $PM_{10-2.5}$). However, 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 the $PM_{10-2.5}$ concentrations, it is difficult to interpret the results of these multipollutant analyses.

Nurses' Health Study Cohort: The Nurses' Health Study (Puett et al., 2008, 156891) is an ongoing prospective cohort study examining the relation of chronic PM_{10} exposures with all-cause mortality and incident and fatal CHD consisting of 66,250 female nurses in MSAs in the northeastern region of the U.S. All cause mortality was statistically significantly associated with average PM_{10} exposures in the time period 3-48 mo preceding death. The association was strongest with average PM_{10} exposure in the 24 mo prior to death (hazard ratio 1.16 [95% CI: 1.05-1.28]) and weakest with exposure in the month prior to death (hazard ratio 1.04 [95% CI: 0.98-1.11]). The association with fatal CHD occurred with the greatest magnitude with mean exposure in the 24 mo prior to death (hazard ratio 1.42 [95% CI: 1.11-1.81]).

Netherlands Cohort Study (NLCS): The Netherlands Cohort Study (Brunekreef et al., 2009, 191947) estimates the effects of traffic-related air pollution on cause specific mortality in a cohort of approximately 120,000 subjects aged 55-69 yr at enrollment. For a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration, the relative risk for natural-cause mortality in the full cohort was 1.06 (95% CI: 0.97-1.16), similar in magnitude to the results reported by the ACS. In a case-cohort analysis adjusted for additional potential confounders, there were no associations between air pollution and mortality.

German Cohort: The North Rhine-Westphalia State Environment Agency (LUA NRW) initiated a cohort of approximately 4,800 women, and assessed whether long-term exposure to air pollution originating from motorized traffic and industrial sources was associated with total and cause-specific mortality (Gehring et al., 2006, 089797). They found that cardiopulmonary mortality was associated with PM_{10} (RR = 1.52 [95% CI: 1.09-2.15] per 10 $\mu g/m^3$ PM_{10}).

7.6.2. Composition and Source-Oriented Analyses of PM

As discussed in the 2004 PM AQCD, only a very limited number of the chronic exposure cohort studies have included direct measurements of chemical-specific PM constituents other than sulfates, or assessments of source-oriented effects, in their analyses. One exception is the Veterans Cohort Study, which looked at associations with some constituents, and traffic.

Veterans Cohort: Using data from EPA's fine particle speciation network, Lipfert et al. (2006, 088756) reported a positive association for mortality with sulfates. Using 2002 data from the fine particle speciation network, positive associations were found between mortality and long-term exposures to nitrates, EC, Ni and V, as well as traffic density and peak O_3 concentrations. In

multipollutant models, associations with traffic density remained significant, as did nitrates, Ni and V in some models.

Netherlands Cohort Study: Beelen et al. (2008, 156263) studied the association between long-term exposure to traffic-related air pollution and mortality in a Dutch cohort. They used data from an ongoing cohort study on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. Exposure to BS, NO_2, SO_2, and $PM_{2.5}$, as well as various exposure variables related to traffic, were estimated at the home address. Traffic intensity on the nearest road was independently associated with mortality. Relative risks (CI) for a 10 $\mu g/m^3$ increase in BS concentrations (difference between 5th and 95th percentile) were 1.05 (95% CI: 1.00-1.11) for natural cause, 1.04 (95% CI: 0.95-1.13) for cardiovascular, 1.22 (95% CI: 0.99-1.50) for respiratory, 1.03 (95% CI: 0.88-1.20) for lung cancer, and 1.04 (95% CI: 0.97-1.12) for mortality other than cardiovascular, respiratory, or lung cancer. Results were similar for NO_2 and $PM_{2.5}$, but no associations were found for SO_2. Traffic-related air pollution and several traffic exposure variables were associated with mortality in the full cohort, although the relative risks were generally small. Associations between natural-cause and respiratory mortality were statistically significant for NO_2 and BS. These results add to the evidence that long-term exposure to traffic-related particulate air pollution is associated with increased mortality.

Given the general dearth of published source-oriented studies of the mortality impacts of long-term PM exposure components, and given that the recent Medicare Cohort study now indicates that such ecological cross-sectional studies can be useful for evaluating time trends and/or comparisons across pollution components, it may well be that examining past cross-sectional studies comparing source-oriented components of PM may be informative. In particular, Ozkaynak and Thurston (1987, 072960), utilized the chemical speciation conducted in the Inhalable Particle (IP) Network to conduct a chemical constituent and source-oriented evaluation on long-term PM exposure and mortality in the U.S. They analyzed the 1980 U.S. vital statistics and available ambient air pollution data bases for sulfates and fine, inhalable, and TSP mass. Using multiple regression analyses, they conducted a cross-sectional analysis of the association between various particle measures and total mortality. Results from the various analyses indicated the importance of considering particle size, composition, and source information in modeling of particle pollution health effects. Of the independent mortality predictors considered, particle exposure measures most related to the respirable fraction of the aerosols, such as fine particles and sulfates, were most consistently and significantly associated with the reported SMSA-specific total annual mortality rates. On the other hand, particle mass measures that included $PM_{10-2.5}$ (e.g., total suspended particles and inhalable particles) were often found to be non-significant predictors of total mortality. Furthermore, based on the application of $PM_{2.5}$ source apportionment, particles from industrial sources and from coal combustion were indicated to be more significant contributors to human mortality than fine soil-derived particles.

7.6.3. Within-City Effects of PM Exposure

Much of the exposure gradient in the national-scale cohort studies was due to city-to-city differences in regional air pollution, raising the possibility that some or all of the original PM-survival associations may have been driven instead by city-to-city differences in some unknown (non-pollution) confounder variable. This has been evaluated by three recent studies.

ACS, Los Angeles: To investigate this issue, two new analyses using ACS data focused on neighborhood-to-neighborhood differences in urban air pollutants, using data from 23 $PM_{2.5}$ monitoring stations in the Los Angeles area, and applying interpolation methods (Jerrett et al., 2005, 087600) or land use regression methods (Krewski et al., 2009, 191193) to assign exposure levels to study individuals. This resulted in both improved exposure assessment and an increased focus on local sources of $PM_{2.5}$. 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. In general, the associations for $PM_{2.5}$ and mortality using these two methods for exposure assessment were similar, though the use of land use regression resulted in somewhat smaller hazard ratios and tighter CIs (see Table 7-9). This indicates that city-to-city confounding was not the cause of the associations found in the earlier ACS Cohort studies. This provides evidence 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.

Table 7-9. Comparison of results from ACS intra-urban analysis of Los Angeles and New York City using kriging or land use regression to estimate exposure.

Cause of Death	Los Angeles: Hazard Ratio[1] and 95% Confidence Interval Using Kriging[2] (Jerrett et al., 2005, 087600)	Los Angeles: Hazard Ratio[1] and 95% Confidence Interval Using Land Use Regression[3] (Krewski et al., 2009, 191193)	New York City: Hazard Ratio[1] and 95% Confidence Interval Using Land Use Regression[4] (Krewski et al., 2009, 191193)
All Cause	1.11 (0.99-1.25)	1.13 (1.01-1.25)	0.86 (0.63-1.18)
IHD	1.25 (0.99-1.59)	1.26 (1.02-1.56)	1.56 (0.87-2.88)
CPD	1.07 (0.91-1.26)	1.09 (0.94-1.26)	0.66 (0.41-1.08)
Lung Cancer	1.20 (0.79-1.82)	1.31 (0.90-1.92)	0.90 (0.29-2.78)

[1]Hazard ratios presented per 10 μg/m^3 increase in $PM_{2.5}$
[2]Model included parsimonious contextual covariates
[3]Model included parsimonious individual level (23) and ecologic (4) covariates
[4]Model included all 44 individual level and 7 ecologic covariates.

ACS, New York: Krewski et al. (2009, 191193) applied the same techniques used in the land use regression analysis of Los Angeles to an investigation conducted in New York City. Annual average concentrations were calculated for each of 62 monitors from 3 yr of daily monitoring data for 1999-2001. Those data were combined with land-use data collected from traffic counting systems, roadway network maps, satellite photos of the study area, and local government planning and tax-assessment maps to assign estimated exposures to the ACS participants. The investigators did not observe elevated effect estimates for all cause, CPD or lung cancer deaths, but IHD did show a positive association with $PM_{2.5}$ concentration. The difference between the 90th and 10th percentiles of the 3-yr avg $PM_{2.5}$ concentration was 1.5 μg/m^3 and the difference between the minimum and maximum values of the 3-yr avg $PM_{2.5}$ concentration was 7.8 μg/m^3. This narrow range in $PM_{2.5}$ exposure contrasts across the New York City metropolitan area and may well account for the inconclusive results in this city-specific analysis. Relatively uniform exposures would reduce the power of the statistical models to detect patterns of mortality relative to exposure and estimate the association with precision.

WHI Study: This study also investigated the within- versus between-city effects in its cities. As shown in Figure 7-8, similar effects for both the within and between-city analyses demonstrate that this association is not due to some other (non-pollution) confounder differing between the various cities, strengthening confidence in the overall pollution-effect estimates.

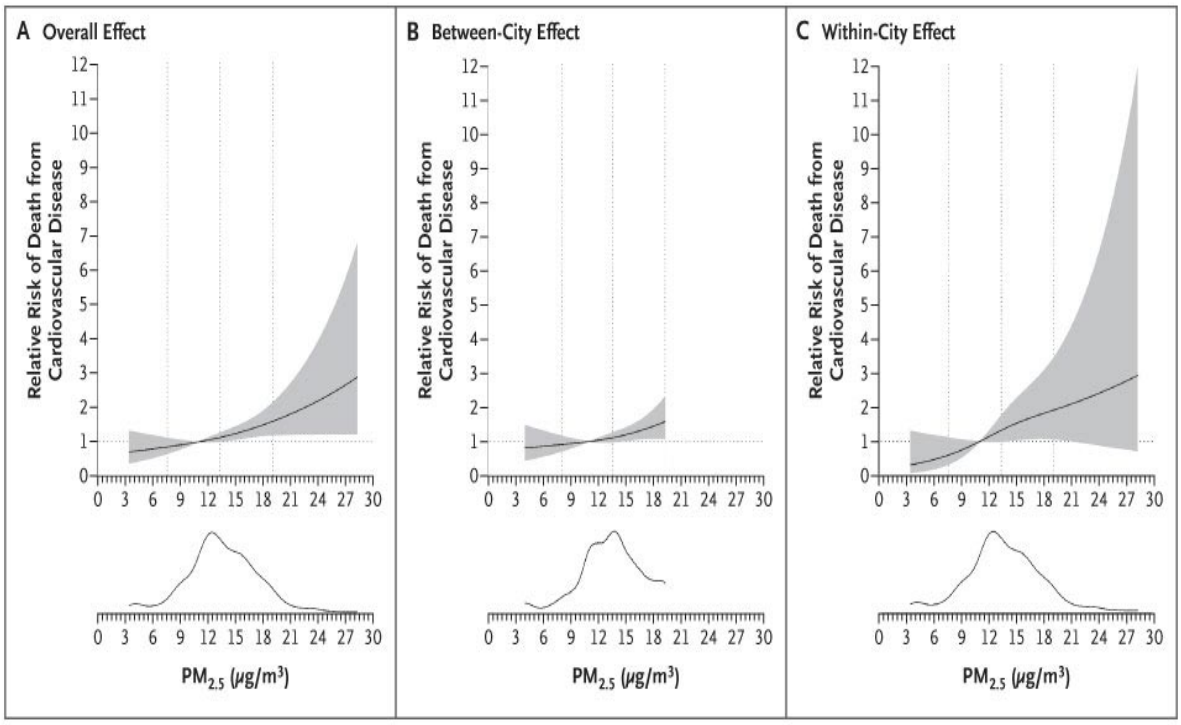
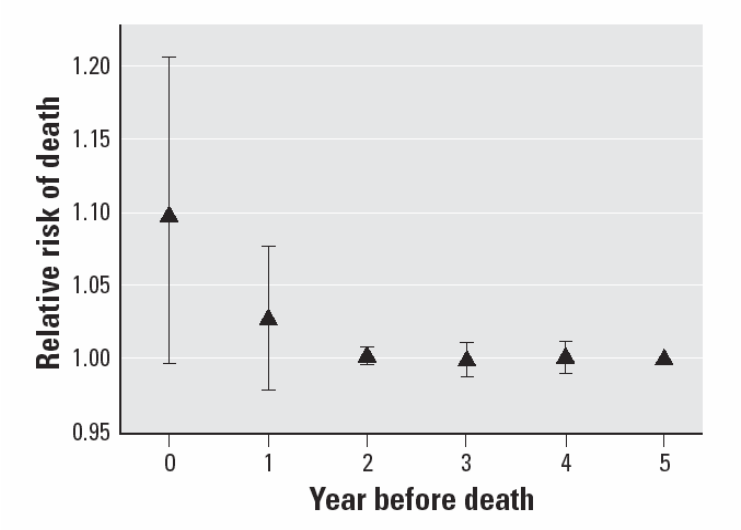


Figure 7-8. Plots of the relative risk of death from cardiovascular disease from the Women's Health Initiative study displaying the between-city and within-city contributions to the overall association between $PM_{2.5}$ and cardiovascular mortality windows of exposure-effects.

7.6.4. Effects of Different Long-term Exposure Windows

The delay between changes in exposure and changes in health has important policy implications. Schwartz et al. (2008, 156963) investigated this issue using an extended follow-up of the Harvard Six Cities Study. Cox proportional hazards models were fit to control for smoking, body mass index, and other covariates. Penalized splines were fit in a flexible functional form to the concentration response to examine its shape, and the degrees of freedom for the curve were selected based on Akaike's information criterion (AIC). The researchers also used model averaging as an alternative approach, where multiple models are fit explicitly and averaged, weighted by their probability of being correct given the data. The lag relationship by model was averaged across a range of unconstrained distributed lag models (i.e., same year, 1 yr prior, 2 yr prior, etc.). Results of the lag comparison are shown in Figure 7-9 indicating that the effects of changes in exposure on mortality are seen within 2 yr. The authors also noted that the concentration-response curve was linear, clearly continuing below the level of the current U.S. air quality standard of 15 $\mu g/m^3$.

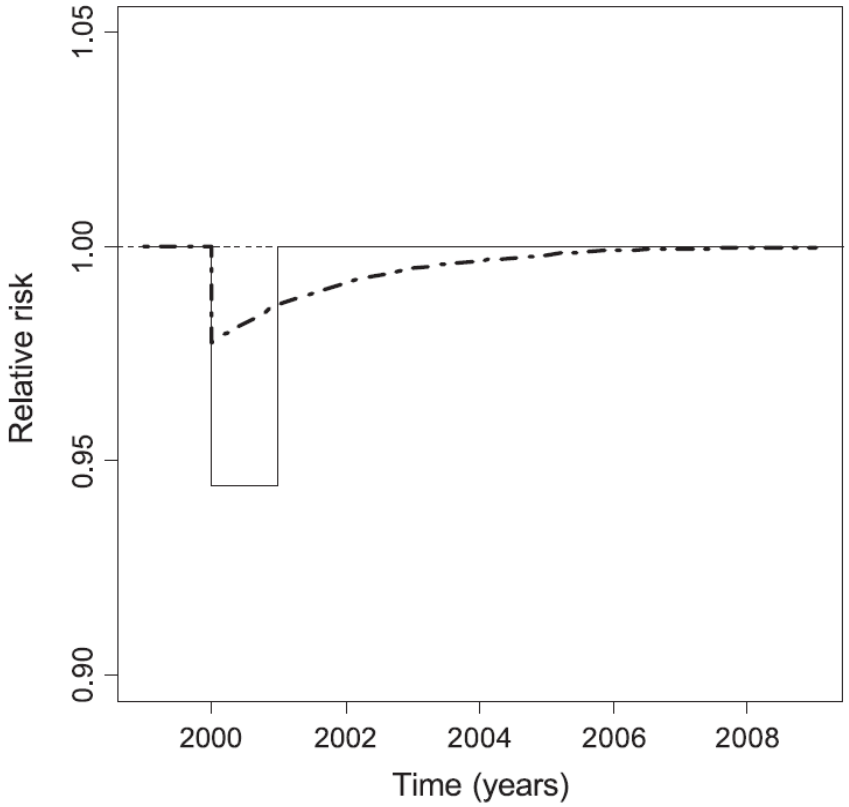


Source: Schwartz et al. (2008, 156963)

Figure 7-9. The model-averaged estimated effect of a 10-μg/m^3 increase in $PM_{2.5}$ on all-cause mortality at different lags (in years) between exposure and death. Each lag is estimated independently of the others. Also shown are the pointwise 95% CIs for each lag, based on jackknife estimates.

Similarly, the effect of long-term exposure to PM_{10} on the risk of death in a large multicity study of elderly subjects discharged alive following an admission for COPD found the effect was not limited to the exposure in each year of follow-up, and had larger cumulative effects spread over the follow-up year and three preceding years (Zanobetti et al., 2008, 156177).

Röösli et al. (2005, 156923) took an alternative approach to determining the window over which the mortality effects of long-term pollution exposures occurred. They fit the model shown in Figure 7-10 using k = 0.5 based on the Utah Steel Strike (Pope, 1989, 044461) and the Ireland coal ban study (Clancy et al., 2002, 035270). They found that roughly 75% of health benefits are observed in the first 5 years, as shown in Table 7-10. These results are consistent with the findings of Schwartz et al. (2008, 156963). Puett et al. (2008, 156891) also compared different long-term exposure lags, with exposure periods ranging from 1 month to 48 mo prior to death. They found statistically significant associations with average PM_{10} exposures in the time period 3-48 mo prior to death, with the strongest associations in the 24 mo prior to death and the weakest with exposure in the 1 mo prior to death.



Source: Reprinted with Permission from Oxford University Press & the International Epidemiological Society from Röösli et al. (2005, 156923)

Figure 7-10. Time course of relative risk of death after a sudden decrease in air pollution exposure during the year 2000, assuming a steady state model (solid line) and a dynamic model (bold dashed line). The thin dashed line refers to the reference scenario.

Table 7-10. Distribution of the effect of a hypothetical reduction of 10 µg/m^3 PM_{10} in 2000 on all-cause mortality 2000-2009 in Switzerland.

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Proportion of total effect (%)	-	39.3	23.9	14.5	8.8	5.3	3.2	2.0	1.2	0.7	0.4
Relative risk (per 10 µg/m^3 reduction in PM_{10})	1.0	0.9775	0.9863	0.9917	0.9950	0.9969	0.9981	0.9989	0.9993	0.9996	0.9997

Relative risk and proportion of total effect in each year are shown, assuming a time constant k of 0.5

Source: Röösli et al. (2005, 156923)

In the reanalysis of the ACS cohort, the investigators calculated time windows of exposure as average concentrations during successive 5-yr periods preceding the date of death (Krewski et al., 2009, 191193). The investigators considered the time window with the best-fitting model (judged by the AIC statistic) to be the period during which pollution had the strongest influence on mortality. Overall, the differences between the time periods were small and demonstrated no definitive patterns. High correlations between exposure levels in the three periods may have reduced the ability of this analysis to detect any differences in the relative importance of the time windows. The investigators did not analyze any time periods smaller than 5 yr, so the results are not directly comparable to those reported by Schwartz et al. (2008, 156963), Röösli et al. (2005, 156923), and Puett et al. (2008, 156891).

Generally, these results indicate a developing coherence of the air pollution mortality literature, suggesting that the health benefits from reducing air pollution do not require a long latency period and would be expected within a few years of intervention.

7.6.5. Summary and Causal Determinations

7.6.5.1. $PM_{2.5}$

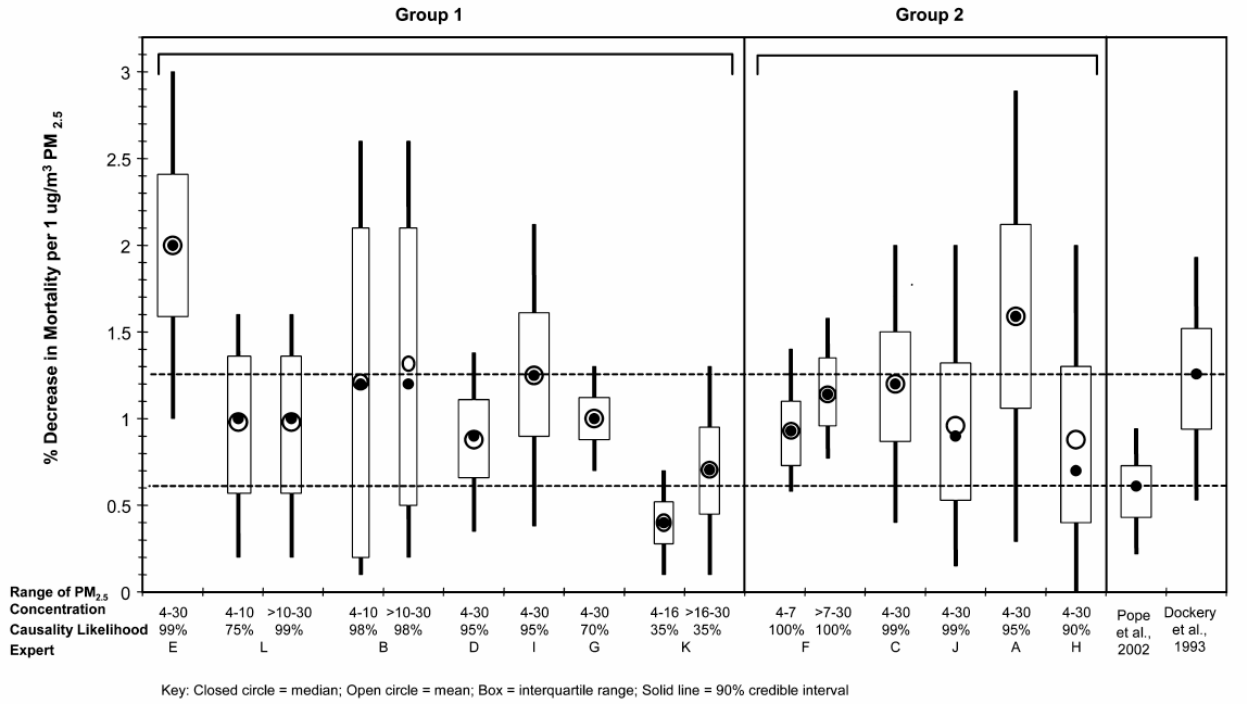
In the 1996 PM AQCD (U.S. EPA, 1996, 079380), results were presented for three prospective cohort studies of adult populations: the Six Cities Study (Dockery et al., 1993, 044457); the ACS Study (Pope et al., 1995, 045159); and the AHSMOG Study (Abbey et al., 1995, 000669). The 1996 AQCD concluded that the chronic exposure studies, taken together, suggested associations between increases in mortality and long-term exposure to $PM_{2.5}$, though there was no evidence to support an association with $PM_{10-2.5}$ (U.S. EPA, 1996, 079380). Discussions of mortality and long-term exposure to PM in the 2004 PM AQCD emphasized the results of four U.S. prospective cohort studies, but the greatest weight was placed on the findings of the ACS and the Harvard Six Cities studies, which had undergone extensive independent reanalysis, and which were based on cohorts that were broadly representative of the U.S. population. Collectively, the 2004 PM AQCD found that these studies provided strong evidence that long-term exposure to $PM_{2.5}$ was associated with increased risk of human mortality.

The recent evidence is largely consistent with past studies, further supporting the evidence of associations between long-term $PM_{2.5}$ exposure and increased risk of human mortality (Section 7.6) in areas with mean concentrations from 13.2 to 29 $\mu g/m^3$ (Figure 7-7). New evidence from the Six Cities cohort study shows a relatively large risk estimate for reduced mortality risk with decreases in $PM_{2.5}$ (Laden et al., 2006, 087605). The results of new analyses from the Six Cities cohort and the ACS study in Los Angeles suggest that previous and current studies may have underestimated the magnitude of the association (Jerrett et al., 2005, 087600). With regard to mortality by cause-of-death, recent ACS analyses indicate that cardiovascular mortality primarily accounts for the total mortality association with $PM_{2.5}$ among adults, and not respiratory mortality. The recent WHI cohort study shows even higher cardiovascular risks per $\mu g/m^3$ than found in the ACS study, but this is likely due to the fact that the study included only post-menopausal women without pre-existing cardiovascular disease (Miller et al., 2007, 090130). There is additional evidence for an association between $PM_{2.5}$ exposure and lung cancer mortality (Section 7.5.1.1). The WHI study also considered within versus between city mortality, as well as morbidity co-associations with $PM_{2.5}$ in the same population. The first showed that the results are not due to between city confounding, and the morbidity analyses show the coherence of the mortality association across health endpoints, supporting the biological plausibility of the air pollution-mortality associations found in these studies.

Results from a new study examining the relationship between life expectancy and $PM_{2.5}$ and the findings from a multiyear expert judgment study that comprehensively characterizes the size and uncertainty in estimates of mortality reductions associated with decreases in $PM_{2.5}$ in the U.S draw conclusions that are consistent with an association between long-term exposure to $PM_{2.5}$ and mortality (Pope et al., 2009, 190107; Roman et al., 2008, 156921). Pope et al. (2009, 190107) report that a decrease of 10 $\mu g/m^3$ in the concentration of $PM_{2.5}$ is associated with an estimated increase in mean (± SE) life expectancy of 0.61 ± 0.20 year. For the approximate period of 1980-2000, the average increase in life expectancy was 2.72 yr among the 211 counties in the analysis. The authors note that reduced air pollution was only one factor contributing to increased life expectancies, with its effects overlapping with those of other factors.

Roman et al. (2008, 156921) applied state-of-the-art expert judgment elicitation techniques to develop probabilistic uncertainty distributions that reflect the broader array of uncertainties in the concentration-response relationship. This study followed best standard practices for expert elicitations based on the body of literature accumulated over the past two decades. The resulting $PM_{2.5}$ effect estimate distributions, elicited from 12 of the world's leading experts on this issue, are shown in Figure 7-11. They indicate both larger central estimates of mortality reductions for decreases in long-term $PM_{2.5}$ exposure in the U.S. (averaging almost 1% per $\mu g/m^3$ $PM_{2.5}$) than reported (for example) by the ACS Study (i.e., 0.6% per $\mu g/m^3$ $PM_{2.5}$ in Pope et al. (2002, 024689),

and a wider distribution of uncertainty by each expert than provided by any one of the $PM_{2.5}$ epidemiologic studies. However, a composite uncertainty range of the overall mean effect estimate (i.e., based upon all 12 experts' estimates, but not provided in Figure 7-11) would be much narrower, and closer to that derived from the ACS study than indicated for any one expert shown in Figure 7-11.



Source: Reprinted with Permission of ACS from Roman et al. (2008, 156921)

Figure 7-11. Experts' mean effect estimates and uncertainty distributions for the $PM_{2.5}$ mortality concentration-response coefficient for a 1 µg/m^3 change in annual average $PM_{2.5}$.

Overall, recent evidence supports the strong evidence reported in the 2004 PM AQCD (U.S. EPA, 2004, 056905) that long-term exposure to $PM_{2.5}$ is associated with an increased risk of human mortality. When looking at the cause of death, the strongest evidence comes from mortality due to cardiovascular disease, with additional evidence supporting an association between $PM_{2.5}$ and lung cancer mortality (Figure 7-7). Fewer studies evaluate the respiratory component of cardiopulmonary mortality, and the evidence to support an association with long-term exposure to $PM_{2.5}$ and respiratory mortality is weak (Figure 7-7). Together these findings are consistent and coherent with the evidence from epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short- and long-term exposure to PM on cardiovascular effects presented in Sections 6.2 and 7.2, respectively. Evidence of short- and long-term exposure to $PM_{2.5}$ and respiratory effects (Sections 6.3 and 7.3, respectively) and infant mortality (Section 7.4) are coherent with the weak respiratory mortality effects. Additionally, the evidence for short- and long-term cardiovascular and respiratory morbidity provides biological plausibility for mortality due to cardiovascular or respiratory disease. The most recent evidence for the association between long-term exposure to $PM_{2.5}$ and mortality is particularly strong for women. Collectively, the evidence is **sufficient to conclude that the relationship between long-term $PM_{2.5}$ exposures and mortality is causal.**

7.6.5.2. $PM_{10-2.5}$

In the 2004 PM AQCD, results from the ACS and Six Cities study analyses indicated that $PM_{10-2.5}$ was not associated with mortality. Evidence is still limited to adequately characterize the association between $PM_{10-2.5}$ and PM sources and/or components. The new findings from AHSMOG and Veterans cohort studies provide limited 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 evidence **for $PM_{10-2.5}$ is inadequate to determine if a causal relationship exists between long-term exposures and mortality**.

7.6.5.3. UFPs

The 2004 PM AQCD did not report long-term exposure studies for UFPs. No epidemiologic studies have been conducted to evaluate the effects of long-term UFP exposure and mortality. The evidence is **inadequate to determine if a causal relationship exists between long-term UFP exposures and mortality**.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

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