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Second External Review Draft

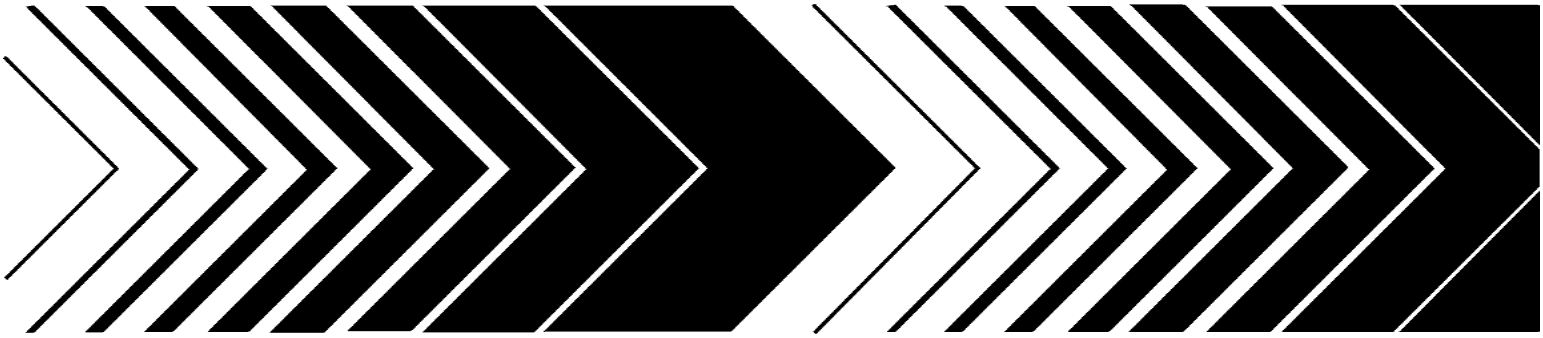
EPA

Air Quality Criteria for Particulate Matter

Volume II

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



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This document is an external review draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Preface

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act (CAA). Sections 108 and 109 require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria for them that assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set "primary" NAAQS to protect human health with adequate margin of safety and to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (5) to periodically (every 5 years) review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

The original NAAQS for particulate matter (PM), issued in 1971 as "total suspended particulate" (TSP) standards, were revised in 1987 to focus on protecting against human health effects associated with exposure to ambient PM less than 10 microns (≤ 10 μm) that are capable of being deposited in thoracic (tracheobronchial and alveolar) portions of the lower respiratory tract. Later periodic reevaluation of newly available scientific information, as presented in the last previous version of this "Air Quality Criteria for Particulate Matter" document published in 1996, provided key scientific bases for PM NAAQS decisions published in July 1997. More specifically, the PM_{10} NAAQS set in 1987 (150 $\mu g/m^3$, 24-h; 50 $\mu g/m^3$, annual average) were retained in modified form and new standards (65 $\mu g/m^3$, 24-h; 15 $\mu g/m^3$, annual average) for particles ≤ 2.5 μm ($PM_{2.5}$) were promulgated in July 1997.

This Second External Review Draft of revised Air Quality Criteria for Particulate Matter assesses new scientific information that has become available mainly between early 1996 through December 2000. The present draft is being released for public comment and review by the Clean Air Scientific Advisory Committee (CASAC) to obtain comments on the organization and structure of the document, the issues addressed, the approaches employed in assessing and interpreting the newly available information on PM exposures and effects, and the key findings and conclusions arrived at as a consequence of this assessment. Extensive additional pertinent information is expected to be published during the next 6 to 9 mo (including results from a vastly expanded EPA PM Research program and from other federal and state agencies, as well as other

partners in the general scientific community) and, as such, the findings and conclusions presented in this draft document must be considered only provisional at this time. Public comments and CASAC review recommendations will be taken into account, along with any pertinent newly available information published or accepted for peer-reviewed publication by May/June 2001, in making any appropriate further revisions to this document for incorporation into a Third External Review Draft. That draft is expected to be released in September/October, 2001 for further public comment and CASAC review (December 2001) in time for a final version to be completed by early 2002. Evaluations contained in the present document will be drawn on to provide inputs to associated PM Staff Paper analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose options for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision of the current PM NAAQS.

Preparation of this document was coordinated by staff of EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from other EPA/ORD laboratories and academia, contributed to writing of document chapters, and earlier drafts of this document were reviewed by experts from federal and state government agencies, academia, industry, and NGO's for use by EPA in support of decision making on potential public health and environmental risks of ambient PM. The document describes the nature, sources, distribution, measurement, and concentrations of PM in outdoor (ambient) and indoor environments. It also evaluates the latest data on human exposures to ambient PM and consequent health effects in exposed human populations (to support decision making regarding primary, health-related PM NAAQS). The document also evaluates ambient PM environmental effects on vegetation and ecosystems, visibility, and man-made materials, as well as atmospheric PM effects on climate change processes associated with alterations in atmospheric transmission of solar radiation or its reflectance from the Earth's surface or atmosphere (to support decision making on secondary PM NAAQS).

The NCEA of EPA acknowledges the contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

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6. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS FROM AMBIENT PARTICULATE MATTER

6.1 INTRODUCTION

Epidemiology studies linking community ambient PM concentrations to adverse health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD), and continue to play an important role. Those studies are indicative of measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations being associated with ambient levels of $PM_{2.5}$, PM_{10}, and other indicators of PM exposure. The numerous more recent epidemiologic studies reviewed in this chapter generally identify more cities where ambient PM-relationships with morbidity and mortality have been found and, thereby, both extend the earlier findings and provide an expanded evidence base that substantiates health effects being associated with exposures to PM at concentrations currently encountered in the United States.

The epidemiology studies presented here should be considered in combination with the ambient concentration information presented in Chapter 3, the human exposure studies in Chapter 5, and the dosimetry and toxicology studies in Chapters 7 and 8. The contribution of the epidemiology studies is to evaluate associations between health effects and exposures of human populations to ambient PM and to help identify susceptible subgroups and associated risk factors. Chapter 9 provides a more detailed interpretive synthesis of information.

This chapter opens with a brief overview of key general features of the several types of epidemiologic studies assessed in the chapter and a discussion of important general methodological issues that must be considered in their critical assessment. After this brief introduction, Section 6.2 assesses studies of PM effects on mortality. Section 6.3 evaluates studies of morbidity as a health endpoint. Section 6.4 then provides an interpretive assessment of the overall PM epidemiologic data base in relation to a variety of key issues and potential inferences associated with studies reviewed in Sections 6.2 and 6.3. The overall key findings and conclusions for this chapter are then summarized in Section 6.5.

6.1.1 Types of Epidemiology Studies Reviewed

Definitions of various types of epidemiology studies used here were provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) and are briefly summarized here. Briefly, the epidemiology studies are divided into *mortality* studies and *morbidity* studies. *Mortality* studies evaluating PM effects on total (non-accidental) mortality and cause-specific mortality have provided the most unambiguous evidence of a clearly adverse endpoint. The *morbidity* studies further substantiate PM effects on a wide range of health endpoints, such as: cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory symptoms, self-medication in asthmatics, changes in pulmonary function tests (PFT), low birthweight infants, etc.

The epidemiology strategies most commonly used in PM health studies are of four types, in order of increasing inferential strength as delineated by Rothman and Greenland (1998): (1) *ecologic studies;* (2) *time-series semi-ecologic studies;* (3) *longitudinal panel and prospective cohort studies;* and (4) *case-control studies*. All of these are observational studies rather than experimental studies, since participants are not assigned at random to air pollution exposures. In general, the exposure of the participant is not directly observed, and the concentration of airborne particles and other air pollutants at one or more stationary air monitors is used as a proxy for individual exposure to ambient air pollution.

In *ecologic studies*, the responses are at a community level (for example, annual mortality rates), as are the exposure indices (for example, annual average particulate matter concentrations) and covariates (for example, the percentage of the population greater than 65 years of age). No individual data is used in the analysis, therefore the relation between health effect and exposure calculated across different communities may not reflect individual-level associations between health outcome and exposure. The use of proxy measures for individual exposure and covariates or effects modifiers may also bias the results, and within-city or within-unit confounding may be overlooked.

Time series studies are more informative because they allow study of associations between *changes* in outcomes and *changes* in exposure indicators preceding or simultaneous with the outcome. The temporal relationship supports a conclusion of a causal relation, even when both the outcome (for example, the number of non-accidental deaths in a city during a day) and the exposure (for example, daily air pollution concentration) are community indices.

Prospective cohort (or panel) studies use data from individuals, including health status, individual exposure, and individual covariates or risk factors, observed over time. The participants in a prospective cohort study are ideally recruited independently of prior health status or exposure, using a simple or stratified random sample so as to represent a target population, so that exposure of the participants is known before the health endpoint occurs. The use of individual-level data is believed to give prospective cohort studies greater inferential strength than other epidemiology strategies, but the use of community-level or estimated exposure data may weaken this advantage, as in time-series studies.

Case-control studies are retrospective studies in that exposure is determined after the health endpoint occurs (this is common in occupational health studies). As Rothman and Greenland (1998) describe it, "Case-control studies are best understood by defining a source population, which represents a hypothetical study population in which a cohort study might have been conducted . . . In a case-control study, the cases are identified and their exposure status is determined just as in a cohort study . . . [and] a control group of study subjects is sampled from the entire source population that gives rise to the cases . . . the cardinal requirement of control selection is that the controls must be sampled independently of their exposure status."

6.1.2 Confounding and Effect Modification

A pervasive problem in the analysis of epidemiology data, no matter what design or strategy, is the unique attribution of the health outcome to the nominal causal agent–airborne particles in this document. The health outcomes attributed to particles are not very specific (for example, mortality in a broad range of ICD-9 categories) and may also be attributable to high or low temperatures, influenza and other diseases, and/or exposure to gaseous criteria air pollutants. Many of the other factors can be measured, directly or by proxies. Some of these co-variables are *confounders*, others are *effects modifiers*. The distinctions are important.

Confounding is " . . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)." (Rothman and Greenland, 1998, p. 120). These authors list three criteria for a confounding factor:

(1) A confounding factor must be a risk factor for the disease [health effect].

(2) A confounding factor must be associated with the exposure under study in the source population (the population at risk from which the cases are derived).

(3) A confounding factor must not be affected by the exposure or the disease, i.e., it cannot be an intermediate step in the causal path between the exposure and the disease.

Gaseous criteria pollutants (CO, NO_2, SO_2, O_3) are candidates for confounders since: (1) all of these have adverse health effects, with CO more often identified with cardiovascular effects and the others with respiratory effects (including symptoms and hospital admissions), as part of the wide spectrum of cardiopulmonary disease also associated with particles; (2) the gaseous criteria pollutants may be associated with particles for several reasons, including (a) common sources, (b) correlated changes in response to wind and weather, and (c) SO_2 and NO_2 may be precursors to sulfate and nitrate components of ambient particle mixes.

A common source, such as combustion of gasoline in motor vehicles emitting CO, NO_2, and primary particles, may play an important role in confounding among these pollutants, as does weather and seasonal effects. Even though O_3 is a secondary pollutant also associated with emission of NO_2, it is often less highly associated with particles. Levels of SO_2 in the western U.S. are often quite low, so that secondary formation of particle sulfates plays a much smaller role and there is usually relatively little confounding of SO_2 with PM mass concentration in the west. On the other hand, in the industrial midwest and northeastern states, SO_2 and sulfate levels during many of the epidemiology studies were relatively high, and highly correlated with fine particle mass concentrations, so that criterion 3 (no causal path leading from confounder to exposure, or exposure to confounder to health effect) may not be strictly true for SO_2 vs sulfate or overall fine particle mass. If there is a causal pathway, then it is not clear whether the observed relation of exposure to health effect is a direct effect of the exposure, an indirect effect mediated by the confounder, or a mixture of these.

Most extraneous variables fall into the category of *effects modifiers*. "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification." (Rothman and Greenland, 1998, p. 254). Examples of effects modifiers in some

of the studies evaluated in this chapter include environmental variables (such as temperature or humidity in time-series studies), individual risk factors (such as education, cigarette smoking status, age in a prospective cohort study), and community factors (such as percent of population > 65 years old). It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables.

6.1.3 Selection of Studies for Review

Numerous PM epidemiology papers have been published since the 1996 PM AQCD. An ongoing medline search has been and is continuing to be conducted in conjunction with other strategies to identify PM literature pertinent to developing criteria for PM NAAQS. Those epidemiologic studies that relate measures of ambient PM to human health outcomes are assessed in this chapter, but occupational exposures studies are not. Some of the criteria used for selecting relevant literature for consideration here include whether a given study presents: (1) pertinent ambient PM indices: e.g., PM_{10}, fine or coarse fractions of PM_{10}, etc.; (2) analyses of health effects of specific PM chemical constituents (e.g., metals, sulfates, nitrates or ultrafines, etc.); (3) health endpoints not previously extensively researched; (4) multiple pollutant analyses; and/or (5) for long-term effects, mortality displacement information. The publication of pertinent new studies has been and is proceeding at a prodigious rate; and the review and evaluation of pertinent literature in this PM AQCD development process is an ongoing process which continues to obtain and assess new evidence. Efforts have been made to assess here pertinent new studies published mainly through December, 2000.

In the sections that follow on PM mortality and morbidity effects, key points derived from the 1996 PM AQCD assessment of then-available information are first concisely highlighted. The numerous individual new studies that have become available since that prior PM AQCD are then summarized in tabular form, in which important methodological features and results are presented. The tables have a uniform general organization with four divisions: (1) information about study location and ambient PM levels, (2) study description of methods employed, (3) results and comments and (4) quantitative outcomes for PM measures. For consistency with the prior PM AQCD (U. S. Environmental Protection Agency, 1996), the pollutant increments utilized here to report Relative Risks (RR's) or Odds Ratio for various health effects are:

for PM_{10}, 50 $\mu g/m^3$; for $PM_{2.5}$, 25 $\mu g/m^3$; for $SO_4^=$, 155 nmoles/m^3 (=15 $\mu g/m^3$); and, for H^+, 75 nmoles/m^3 (=3.6 $\mu g/m^3$, if as H_2SO_4).

Greater emphasis is placed in text discussions on integrating and interpreting findings from the body of evidence provided by the newer studies (as well as relating them to those reviewed in the 1999 PM AQCD), rather than detailed evaluation of each of the numerous newly available studies. Particular emphasis is focused in the text on those studies and analyses thought to provide the most pertinent information for U.S. standard setting purposes. For example, North American studies conducted in the U.S. or Canada are generally accorded more text discussion than those from other geographic regions; and analyses using gravimetric (mass) measurements are generally accorded more text attention than those using non-gravimetric ambient PM measures, e.g., black smoke (BS) or coefficient of haze (COH). Also, more emphasis is placed on text discussion of new multi-city studies that employ standardized methodological analyses for evaluating PM effects across several or numerous cities and often provide overall effects estimates based on combined analyses of information pooled across multiple cities.

6.2 MORTALITY EFFECTS OF PARTICULATE MATTER EXPOSURE

6.2.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been intensively studied and has played an important role in previous PM health assessments (U.S. Environmental Protection Agency, 1986, 1996). Mortality is the most severe adverse health endpoint and, in some ways, the easiest to study. Excellent death records are maintained at every level of government in most all nations and are typically made available to researchers. Also, from a narrowly technical point of view, individual deaths are more amenable to statistical analyses, since individual deaths from natural causes (typically respiratory and cardiovascular diagnoses) are statistically independent except in rare extremely infectious instances. Individual deaths are also non-recurring events, unlike hospital admissions or respiratory symptoms.

Recent findings are evaluated here for the two most important epidemiology designs by which mortality is studied: time-series mortality studies (Section 6.2.2); and prospective cohort studies (Section 6.2.3). The time-series studies mostly assess acute responses to short-term PM

exposure, although some recent work suggests that time-series data sets are also useful to examine responses to exposures over a longer time scale. Time-series studies use community-level air pollution measurements to index exposure and community-level response (i.e., the total number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully complement time-series studies; they use individual health records, with survival lifetimes or hazard rates adjusted for individual risk factors, and typically evaluate human health impacts of long-term PM exposures indexed by community-level measurements.

6.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

6.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

The time-series mortality studies reviewed in the 1996 and other past PM AQCD's provided much evidence that ambient PM air pollution is associated with increases in daily mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published between 1988 and 1996. Information derived from those studies was consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution.

The PM_{10} relative risk estimates derived from short-term PM_{10} exposure studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is most clearly associated with an increased risk of premature total nonaccidental mortality (total deaths minus those from accident/injury) on the order of relative risk (RR) = 1.025 to 1.05 in the general population or, in other words, 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increase, with all statistically significant RR estimates ranging more broadly from 1.015 to 1.085 (i.e., 1.5 to 8.5% excess risk). Higher relative risks were indicated for the elderly and for those with pre-existing cardiopulmonary conditions. Also, based on the then recently published Schwartz et al. (1996a) analysis of Harvard Six City data, the 1996 PM AQCD found the RR for excess total mortality in relation to 24-h fine particle concentrations to be in the range of RR = 1.026 to 1.055 per 25 $\mu g/m^3$ $PM_{2.5}$ (i.e., 2.6 to 5.5% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$).

While numerous studies reported PM-mortality associations, important issues needed to be addressed in interpreting their findings. The 1996 PM AQCD extensively discussed most critical issues, including: (1) seasonal confounding and effect modification; (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold; (6) harvesting and life shortening; and (7) the role of PM components. As important issues

related to model specification became further clarified, more studies began to address the most critical issues, with some having been at least partially resolved, whereas others required still further investigation. The next several paragraphs summarize the status of these issues at the 1996 PM AQCD publication time.

One of the most important components in time-series model specification is adjustment for seasonal cycles and other longer-term temporal trends. Residual over-dispersion and autocorrelation result from inadequate control for these temporal trends, and not adequately adjusting for them could result in biased RRs. Modern smoothing methods allow efficient fits of temporal trends and minimize such statistical problems. Thus, most recent studies controlled for seasonal and other temporal trends, and it was unlikely that inadequate control for such trends seriously biased estimated PM coefficients. Effect modification by season was examined in several studies. Season-specific analyses are often not feasible in small-sized studies (due to marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season. It was not fully resolved, however, if these results represent real seasonal effect modifications or may be due to varying extent of correlation between PM and co-pollutants or weather variables by season.

While most available studies included control for weather variables, some reported sensitivity of PM coefficients to weather model specification, leading some investigators to speculate that inadequate weather model specifications may still have erroneously ascribed residual weather effects to PM. Two PM studies (Samet et al., 1996, 1998; Pope and Kalkstein, 1996) involved collaboration with a meteorologist and utilized more elaborate weather modeling, e.g., use of synoptic weather categories. These studies found that estimated PM effects were essentially unaffected by the synoptic weather variables and also indicated that the synoptic weather model did not provide better model fits in predicting mortality when compared to other weather model specifications used in previous PM-mortality studies. Thus, these results suggested that the reported PM effects were not explained by weather effects.

Many earlier PM studies considered at least one co-pollutant in the mortality regression, and some also examined several co-pollutants. In most cases, when PM indices were significant in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate the PM associations. When multiple pollutant models were performed by

season, the PM coefficients became less stable, again, possibly due to PM's varying correlation with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM indices showed the highest significance (versus gaseous co-pollutants) in single and multiple pollutant models. Thus, it was concluded that PM-mortality associations were not seriously distorted by co-pollutants, but interpretation of the relative significance of each pollutant in mortality regression as relative causal strength was difficult because of limited quantitative information on relative exposure measurement/characterization errors among air pollutants.

Measurement error can influence the size and significance of air pollution coefficients in time-series regression analyses and is also important in assessing confounding among multiple pollutants, as varying the extent of such error among the pollutants could also influence the corresponding relative significance. The 1996 PM AQCD discussed several types of such exposure measurement or characterization errors, including site-to-site variability and site-to-person variability—errors thought to bias the estimated PM coefficients downward in most cases. However, there was not sufficient quantitative information available to estimate such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Several studies indicated that associations were seen monotonically below the existing PM standards. It was considered difficult, however, to statistically identify a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models was considered adequate and appropriate.

The extent of prematurity of death (i.e., mortality displacement, or harvesting) in observed PM-mortality associations has important public health policy implications. At the time of the 1996 PM AQCD review, only a few studies had investigated this issue. While one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalized because this estimate was obtained for identifiable PM episodes. There was not sufficient evidence to suggest the extent of prematurity for non-episodic periods, from which most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

> "In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence prevent quantification of years of life lost to such mortality in the population. Life

shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized." (p. 13-45)

Only a limited number of PM-mortality studies analyzed fine particles and chemically specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+). The results suggested that $PM_{2.5}$ was most significantly associated with mortality among the components of PM. While H^+ was not significantly associated with mortality in this and an earlier analysis (Dockery et al., 1992), the smaller sample size for H^+ than for other PM components made a direct comparison difficult. The 1996 PM AQCD also noted that mortality associations with BS or COH reported in earlier studies in Europe and the U.S. during the 1950s to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50% cut-off diameters ($\approx 4.5\mu$m). Furthermore, certain respiratory morbidity studies showed associations between hospital admissions/visits with components of PM in the fine particle range. Thus, the U.S. EPA 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Overall, then, the status of key issues raised in the 1996 PM AQCD can be summarized as follows: (1) the observed PM effects are unlikely to be seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) the observed PM effects are unlikely to be significantly confounded by weather; (3) the observed PM effects may be to some extent confounded or modified by co-pollutants, and such extent may vary from season to season; (4) determining the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement characterization error among pollutants (there was not sufficient information on this); (5) no clear evidence for any threshold for PM-mortality associations was reported (statistically identifying a threshold from existing data was also considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was conducted to investigate harvesting in non-episodic U.S. data); (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in the light of historical data, biological plausibility, and the results from morbidity studies, a greater role for fine particles than coarse particles was suggested in the 1996 PM AQCD as being likely. The AQCD concluded:

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

6.2.2.2 Introduction to Newly Available Information

Since the 1996 PM AQCD, numerous new studies have examined short-term associations between PM indices and mortality. The newly available studies on relationships between short-term PM exposure and daily mortality are summarized in Table 6-1. The table describes the location, study period, levels of PM, outcomes, methods, results, and reported risk estimates and lags. This table does not include review papers and simulation-only studies that did not include analyses of real data. In addition to the table, discussion in the text below highlights findings from several multi-city studies. Discussion of implications of new study results for types of issues identified in foregoing text is mainly deferred to Section 6.4.

The summarization of studies in Table 6-1 (and in subsequent tables) is not meant to imply that all listed studies should be accorded equal weight in the overall interpretive assessment of evidence regarding PM-associated health effects. In general, increasing scientific weight should be accorded to those studies (i.e., those not clearly flawed and which have adequate control for confounding) in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally produce less precise estimates than large studies with an adequate exposure gradient. Therefore, the range of exposures (e.g., as indicated by the IQR), the size of the study as indexed by the total number of observations (e.g., days) and total number of events (i.e., total deaths), and the inverse variance for the principal effect estimate are all important indices useful in determining the likely precision of health effects estimates and in according relative scientific weight to the findings of a given study.

TABLE 6-1. SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States			
Samet et al. (2000a,b). 90 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 15.3 (Honolulu) to 52.0 (Riverside).	Non-accidental total deaths and cause-specific (cardiac, respiratory, and the other remaining) deaths, stratified in three age groups (<65, 65-75, 75+), were examined for their associations with PM_{10}, O_3, SO_2, NO_2, and CO (single, two, and three pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for the pollutants for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled within region. The third stage modeled between-region variation (7 regions). Two alternative assumptions were made regarding the prior distribution: one with possibly substantial heterogeneity and the other with less or no heterogeneity within region. The weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate; (3) socio-demographic variables; (4) urbanization; (5) variables related to measurement error.	The estimated city-specific coefficients were mostly positive at lag 0, 1, and 2 days (estimated overall effect size was largest at lag 1, with the estimated percent excess death rate per 10 $\mu g/m^3$ PM_{10} being about 0.5%). The posterior probabilities that the overall effects are greater than 0 at these lags were 0.99, 1.00, and 0.98, respectively. None of the county-specific variables (effect modifiers) in the second-stage regression significantly explained the heterogeneity of PM_{10} effects across cities. In the 3-stage regression model with the index for 7 geographical regions, the effect of PM_{10} varied somewhat across the 7 regions, with the effect in the Northeast being the greatest. Adding O_3 and other gaseous pollutants did not markedly change the posterior distributions of PM_{10} effects. O_3 effects, as examined by season, were associated with mortality in summer ($\approx$0.5 percent per 10 ppb increase), but not in all season data (negative in winter).	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 2.3% (0.1, 4.5) for "more heterogeneity" across-city assumption; 2.2% (0.5, 4.0) for "less or no heterogeneity" across cities assumption. The largest PM_{10} effect estimated for 7 U.S. regions was for the Northeast: 4.6% (2.7, 6.5) excess deaths per 50 $\mu g/m^3$ PM_{10} increment.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Dominici et al. (2000). 20 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 23.8 $\mu g/m^3$ (San Antonio) to 52.0 $\mu g/m^3$ (Riverside).	Non-accidental total deaths (stratified in three age groups: <65, 65-75, 75+) were examined for their associations with PM_{10} and O_3 (single, 2, and 3 pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for PM_{10} and O_3 for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled as a function of city-specific covariates including mean PM_{10} and O_3 levels, percent poverty, and percent of population with age 65 and over. The prior distribution assumed heterogeneity across cities. To approximate the posterior distribution, a Markov Chain Monte Carlo (MCMC) algorithm with a block Gibbs sampler was implemented. The second stage also considered spatial model, in which RRs in closer cities were assumed to be more correlated.	The lag 1 day PM_{10} concentration was positively associated with total mortality in most locations (only 2 out of 20 coefficients were negative), though the estimates ranged from 2.1% to –0.4% per 10 $\mu g/m^3$ increase in PM_{10}. PM_{10}-mortality associations changed little with the addition of O_3 to the model, or with the addition of a third pollutant in the model. The pattern of PM_{10} effects with respiratory and cardiovascular was similar to that of total mortality. The PM_{10} effect was smaller (and weaker) with other causes of deaths. The pooled analysis of 20 cities data confirmed the overall effect on total and cardio-respiratory mortality, with lag 1 day showing the largest effect estimates. The posterior distributions for PM_{10} were generally not influenced by addition of other pollutants. In the data for which the distributed lags could be examined (i.e., nearly daily data), the sum of the 7-day distributed lag coefficients was greater than each of single day coefficients. The city-specific covariates did not predict the heterogeneity across cities. Regional model results suggested that PM_{10} effects in the West U.S. was larger than in the East and South U.S.	Total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10}: 1.8 (−0.5, 4.1) for lag 0; 1.9 (−0.4, 4.3) for lag 1; 1.2 (−1.0, 3.4) for lag 2. Cardiovascular disease excess deaths per 50 $\mu g/m^3$ PM_{10}: 3.4 (1.0, 5.9).
Braga et al. (2000). Five U.S. cities: Pittsburgh, PA; Detroit, MI; Chicago, IL; Minneapolis-St. Paul, MN; Seattle, WA. 1986-1993. PM_{10} means were 35, 37, 37, 28, and 33 $\mu g/m^3$, respectively in these cities.	Potential confounding caused by respiratory epidemics on PM-total mortality associations was investigated in a subset of the 10 cities evaluated by Schwartz (2000a,b), as summarized below. GAM Poisson models were used to estimate city-specific PM_{10} effects, adjusting for temperature, dewpoint, barometric pressure, time-trend and day-of-week. A cubic polynomial was used to for each epidemic period, and a dummy variable was used to control for isolated epidemic days. Average of 0 and 1 day lags were used.	When respiratory epidemics were adjusted for, small decreases in the PM_{10} effect were observed (9% in Chicago, 11% in Detroit, 3% in Minneapolis, 5% in Pittsburgh, and 15% in Seattle).	The overall estimated percent excess deaths per 50 $\mu g/m^3$ increase in PM_{10} was 4.3% (3.0, 5.6) before controlling for epidemics and 4.0% (2.6, 5.3) after. Average of 0 and 1 day lags.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000a). Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	Daily total (non-accidental) deaths (20, 19, 63, 60, 10, 133, 32, 6, 9, and 29, respectively in these cities in the order shown left). Deaths stratified by location of death (in or outside hospital) were also examined. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. The data were also analyzed by season (November through April as heating season). In the second stage, the PM_{10} coefficients were modeled as a function of city-dependent covariates including copollutant to PM_{10} regression coefficient (to test confounding), unemployment rate, education, poverty level, and percent non-white. Threshold effects were also examined. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	PM_{10} was significantly associated with total deaths, and the effect size estimates were the same in summer and winter. Adjusting for other pollutants did not substantially change PM_{10} effect size estimates. Also, socioeconomic variables did not modify the estimates. The effect size estimate for the deaths that occurred outside hospitals was substantially greater than that for inside hospitals. The effect size estimate was larger for subset with PM_{10} less than 50 $\mu g/m^3$.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.4 (2.7, 4.1); summer 3.4 (2.4, 4.4); winter 3.3 (2.3, 4.4); in-hospital 2.5 (1.5, 3.4); out-of-hospital 4.5 (3.4, 5.6); days < 50 $\mu g/m^3$ 4.4 (3.1, 5.7); with SO_2 2.9 (1.2, 4.6); with CO 4.6 (3.2, 6.0); with O_3 3.5 (1.6, 5.3).
Schwartz (2000b). Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	The issue of distributed lag effects was the focus of this study. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were examined using four models: (1) 1-day mean at lag 0 day; (2) 2-day mean at lag 0 and 1 day; (3) second-degree distributed lag model using lags 0 through 5 days; (4) unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	The effect size estimates for the quadratic distributed model and unconstrained distributed lag model were similar. Both distributed lag models resulted in substantially larger effect size estimates than the single day lag, and moderately larger effect size estimates than the two-day average models.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 3.3 (2.5, 4.1) for 1-day mean at lag 0; 5.4 (4.4, 6.3) 2-day mean of lag 0 and 1; 7.3 (5.9, 8.6) for quadratic distributed lag; and 6.6 (5.3, 8.0) for unconstrained distributed lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz and Zanobetti (2000). Ten U.S. cities. Same as above.	The issue of a threshold in PM-mortality exposure-response curve was the focus of this study. First, a simulation was conducted to show that the "meta-smoothing" could produce unbiased exposure-response curves. Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were used to generate mortality series in 10 cities, and GAM Poisson models were used to estimate exposure response curve. Effects of measurement errors were also simulated. In the analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature, dewpoint, and barometric pressure, and day-of-week. Smooth function of PM_{10} with the same span (0.7) in each of the cities. The predicted values of the log relative risks were computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the predicted values were combined across cities using inverse-variance weighting.	The simulation results indicated that the "meta-smoothing" approach did not bias the underlying relationships for the linear and threshold models, but did result in a slight downward bias for the logarithmic model. Measurement error (additive or multiplicative) in the simulations did not cause upward bias in the relationship below threshold. The threshold detection in the simulation was not very sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.	The combined exposure-response curve indicates that an increase of 50 $\mu g/m^3$ is associated with about a 4% increase in daily deaths. Avg. of 0 and 1 day lags.
Zanobetti and Schwartz (2000). Four U.S. cities: Chicago, IL; Detroit, MI; Minneapolis-St. Paul, MN; Pittsburgh, PA. 1986-1993. PM_{10} median = 33, 33, 25, and 31 respectively for these cities.	Separate daily counts of total non-accidental deaths, stratified by sex, race (black and white), and education (education > 12yrs or not), were examined to test hypothesis that people in each of these groups had higher risk of PM_{10}. GAM Poisson models adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were used. The mean of 0- and 1-day lag PM_{10} was used. The inverse variance weighted averages of the four cities' estimates were used to combine results.	The differences in the effect size estimates among the various strata were modest. The results suggest effect modification with the slope in female deaths one third larger than in male deaths. Potential interaction of these strata (e.g., black and female) were not investigated.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: white 5.0 (4.0, 6.0); black 3.9 (2.3, 5.4); male 3.8 (2.7, 4.9); female 5.5 (4.3, 6.7); education <12y 4.7 (3.3, 6.0); education > 12y 3.6 (1.0, 6.3).

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar (2000a) Cook County, Illinois Los Angeles County, CA Maricopa County, AZ 1987-1995 PM_{10}, CO, O_3, NO_2, SO_2 in all three locations. $PM_{2.5}$ in Los Angeles County. Cook Co: PM_{10} Median = 47 $\mu g/m^3$. Maricopa Co: PM_{10} Median = 41. Los Angeles Co: PM_{10} Median = 44; $PM_{2.5}$ Median = 22.	Associations between air pollution and time-series of daily deaths evaluated for three U.S. metropolitan areas with different pollutant mixes and climatic conditions. Daily total non-accidental deaths and deaths from cardiovascular disease (CVD), cerebrovascular (CrD), and chronic obstructive lung disease and associated conditions (COPD) were analyzed by generalized additive Poisson models in relation to 24-h readings for each of the air pollutants averaged over all monitors in each county. All models included an intercept term for day-of-week and a spline smoother for temporal trends. Effects of weather were first evaluated by regressing daily deaths (for each mortality endpoint) against temp and rel. humidity with lag times of 0 to 5 days. Then lags that minimized deviance for temp and rel. humidity were kept fixed for subsequent pollutant effect analyses. Each pollutant entered linearly into the regression and lags of between 0 to 5 days examined. Effects of two or more pollutants were then evaluated in multipollutant models. Sensitivity analyses were used to evaluate effect of degree of smoothing on results.	In general, the gases, especially CO (but not O_3) were much more strongly associated with mortality than PM. Specified pattern of results found for each county were as follows. For Cook Co., in single pollutant analyses PM_{10}, CO, and O_3 were all associated (PM_{10} most strongly on lag 0-2 days) with total mortality, as were SO_2 and NO_2 (strongest association on lag 1 day for the latter two). In joint analyses with one of gases, the coefficients for both PM_{10} and the gas were somewhat attenuated, but remained stat. sig. for some lags. With 3-pollutant models, PM_{10} coefficient became small and non-sig. (except at lag 0), whereas the gases dominated. For Los Angeles, PM_{10}, $PM_{2.5}$, CO, NO_2, and SO_2, (but not O_3), were all associated with total mortality. In joint analyses with CO or SO_2 and either PM_{10} or $PM_{2.5}$, PM metrics were markedly reduced and non-sig., whereas estimates for gases remained robust. In Maricopa Co. single-pollutant analyses, PM_{10} and each of the gases, (except O_3), were associated with total morality; in 2-pollutant models, coefficients for CO, NO_2, SO_2, were more robust than for PM_{10}. Analogous patterns of more robust gaseous pollutant effects were generally found for cause-specific (CVD, CrD, COPD) mortality analyses. Author concluded that while direct effect of individual components of air pollution cannot be ruled out, individual components best thought of as indices of overall pollutant mix.	In single pollutant models, estimated daily total mortality % excess deaths per 50 $\mu g/m^3$ PM_{10} was mainly in range of: 0.5-1.0% lags 0-2 Cook Co.; 0.25-1.0% lags 0-2 LA; 2.0% lag 2 Maricopa. Percent per 25 $\mu g/m^3$ $PM_{2.5}$ 0.5% lags 0, 1 for Los Angeles. Maximum estimated COPD % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 5.4 (0.3,10.7), lag 2; with O_3, 3.0 (−1.8, 8.1) lag 2; LA 5.9 (−1.6, 14.0) lag 1; Maricopa 8.2 (−4.2, 22.3) lag 1; per 25 μg $PM_{2.5}$ in LA 2.7 (−3.4, 9.1). CVD % per 50 $\mu g/m^3$ PM_{10}: Cook 2.2 (0.4, 4.1) lag 3; with O_3, SO_2 1.99 (−0.06, 4.1) lag 3; LA 4.5 (1.7, 7.4) lag 2; with CO −0.56 (−3.8, 2.8) lag 2; Maricopa 8.9 (2.7, 15.4) lag 1; with NO_2 7.4 (−0.95, 16.3) lag 1. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1; with CO 0.60 (−2.1, 3.4). CrD % per 50 $\mu g/m^3$ PM_{10}: Cook 3.3 (−0.12, 6.8) lag 2; LA 2.9 (−2.3, 8.4) lag 3; Maricopa 11.1 (0.54, 22.8) lag 5. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 3.6 (−0.6, 7.9) lag 3.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ostro et al. (1999a). Coachella Valley, CA. 1989-1992. PM_{10} (beta-attenuation) Mean = 56.8 $\mu g/m^3$.	Study evaluated total, respiratory, cardiovascular, non-cardiorespiratory and age >50 yr deaths (mean = 5.4, 0.6, 1.8, 3.0, and 4.8 per day, respectively). The valley is a desert area where 50-60% of PM_{10} estimated to be coarse particles. Correlation between gravimetric and beta-attenuation, separated by 25 miles, was high (r = 0.93). Beta-attenuation data were used for analysis. GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used. Seasonally stratified analyses were also conducted. Lags 0-3 days (separately) of PM_{10} along with moving averages of 3 and 5 days examined, as were O_3, NO_2, and CO.	Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined, except non-cardiorespiratory series. The effect size estimates for total and cardiovascular deaths were larger for warm season (May through October) than for all year period. NO_2 and CO were significant predictor of mortality in single pollutant models, but in multi-pollutant models, none of the gaseous pollutants were significant (coefficients reduced), whereas PM_{10} coefficients remained the same and significant.	Total mortality percent excess deaths per 50 $\mu g/ m^3$ PM_{10} at 2-day lag= 4.6 (0.6, 8.8). Cardiac deaths: 8.33 (2.14, 14.9) Respiratory deaths: 13.9 (3.25, 25.6)
Ostro et al. (2000). Coachella Valley, CA. 1989-1998. $PM_{2.5}$ = 16.8; $PM_{10-2.5}$ = 25.8 in Indio; $PM_{2.5}$ = 12.7; $PM_{10-2.5}$ = 17.9 in Palm Springs.	A follow-up study of the Coachella Valley data, with $PM_{2.5}$ and $PM_{10-2.5}$ data in the last 2.5 years. Both $PM_{2.5}$ and $PM_{10-2.5}$ were estimated for the remaining years to increase power of analyses.	Several pollutants were associated with all-cause mortality, including $PM_{2.5}$, CO, and NO_2. More consistent results were found for cardiovascular mortality, for which significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not $PM_{2.5}$ (possibly due to low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data).	Total percent excess deaths: PM_{10} = 2.0 (−1.0, 5.1) per 50 $\mu g/m^3$ $PM_{2.5}$ = 11.5 (0.2, 24.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 1.3 (−0.6, 3.5) per 25 $\mu g/m^3$ Cardio deaths: PM_{10} = 6.1 (2.0, 10.3) per 50 $\mu g/m^3$ $PM_{2.5}$ = 8.6 (−6.4, 25.8) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 2.6 (0.7, 4.5) per 25 $\mu g/m^3$ Respiratory deaths: PM_{10} = −2.0 (−11.4, 8.4) per 50 $\mu g/m^3$ $PM_{2.5}$ = 13.3 (−43.1, 32.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ = −1.3 (−6.2, 4.0) per 25 $\mu g/m^3$

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Fairley (1999). Santa Clara County, CA 1989-1996.$PM_{2.5}$ (13); PM_{10} (34); $PM_{10-2.5}$ (11); COH (0.5 unit); NO_3 (3.0); SO_4 (1.8)	Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, COH, nitrate, sulfate, O_3, CO, NO_2, adjusting for trend, season, and min and max temperature, using Poisson GAM model. Season-specific analysis was also conducted. The same approach was also used to re-analyze 1980-1986 data (previously analyzed by Fairley, 1990).	$PM_{2.5}$ and nitrate were most significantly associated with mortality, but all the pollutants (except $PM_{10-2.5}$) were significantly associated in single poll. models. In 2 and 4 poll. models with $PM_{2.5}$ or nitrate, other pollutants were not significant. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that COH was very significantly associated with mortality.	Total mortality per 25 $\mu g/m^3$ $PM_{2.5}$ at 0 d lag: 8% in one pollutant model; 9-12% in 2 pollutant model; 12% in 4-pollutant model. Also, 8% per 50 $\mu g/m^3$ PM_{10} in one pollutant model and 2% per 25 $\mu g/m^3$ $PM_{10-2.5}$. Cardiovascular mortality: PM_{10} = 9% per 50 $\mu g/m^3$ $PM_{2.5}$ = 13% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 3% per 25 $\mu g/m^3$ Respiratory mortality: PM_{10} = 11% per 50 $\mu g/m^3$ $PM_{2.5}$ = 7% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 16% per 25 $\mu g/m^3$
Schwartz et al. (1999). Spokane, WA 1989-1995 PM_{10}: "control" days: 42 $\mu g/m^3$; dust-storm days: 263	Effects of high concentration of coarse crustal particles were investigated by comparing death counts on 17 dust storm episodes to those on non-episode days on the same day of the years in other years, adjusting for temperature, dewpoint, and day-of-week, using Poisson regression.	No association was found between the mortality and dust storm days on the same day or the following day.	0% (−4.5, 4.7) for dust storm days at 0 day lag (50 $\mu g/m^3$ PM_{10}) (lagged days also reported to have no associations).
Pope et al. (1999a). Ogden, Salt Lake City, and Provo/Orem, UT 1985-1995 PM_{10} (32 for Ogden; 41 for SLC; 38 for P/O)	Associations between PM_{10} and total, cardiovascular, and respiratory deaths studied in three urban areas in Utah's Wasatch Front, using Poisson GAM model and adjusting for seasonality, temperature, humidity, and barometric pressure. Analysis was conducted with or without dust (crustal coarse particles) storm episodes, as identified on the high "clearing index" days, an index of air stagnation.	Salt Lake City (SLC), where past studies reported little PM_{10}-mortality associations, had substantially more dust storm episodes. When the dust storm days were screened out from analysis and PM_{10} data from multiple monitors were used, comparable RRs were estimated for SLC and Provo/Orem (P/O).	Ogden PM_{10} Total (0 d) = 12.0% (4.5, 20.1) CVD (0-4 d) = 1.4% (−8.3, 12.2) Resp. (0-4 d) = 23.8 (2.8, 49.1) SLC PM_{10} Total (0 d) = 2.3% (0.47) CVD (0-4 d) = 6.5% (2.2, 11.0) Resp. (0-4 d) = 8.2 (2.4, 15.2) Provo/Ovem PM_{10} Total (0 d) = 1.9% (−2.1, 6.0) CVD (0-4 d) = 8.6% (2.4, 15.2) Resp. (0-4 d) = 2.2% (−9.8, 15.9) Note: Above % for $PM_{2.5}$ and $PM_{10-2.5}$ all per 25 $\mu g/m^3$; all PM_{10} % per 50 $\mu g/m^3$.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz and Zanobetti (2000). Chicago 1988-1993. PM_{10}. Median = 36 $\mu g/m^3$.	Total (non-accidental), in-hospital, out-of-hospital deaths (median = 132, 79, and 53 per day, respectively), as well as heart disease, COPD, and pneumonia elderly hospital admissions (115, 7, and 25 per day, respectively) were analyzed to investigate possible "harvesting" effect of PM_{10}. GAM Poisson models adjusting for temperature, relative humidity, day-of-week, and season were applied in baseline models using the average of the same day and previous day's PM_{10}. The seasonal and trend decomposition techniques called STL was applied to the health outcome and exposure data to decompose them into different time-scales (i.e, short-term to long-term), excluding the long, seasonal cycles (120 day window). The associations were examined with smoothing windows of 15, 30, 45, and 60 days.	The effect size estimate for deaths outside of the hospital is larger than for deaths inside the hospital. All cause mortality shows an increase in effect size at longer time scales. The effect size for deaths outside of hospital increases more steeply with increasing time scale than the effect size for deaths inside of hospitals.	Mortality RR estimates per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: total deaths 4.5 (3.1, 6.0); in-hospital 3.9 (2.1, 5.8); out-of-hospital 6.3 (4.1, 8.6). For total deaths, the RR approximately doubles as the time scale changes from 15 days to 60 days. For out-of-hospital deaths, it triples from15 days to 60 days time scale.
Lippmann et al. (2000). Detroit, MI.1992-1994. PM_{10} = 31; $PM_{2.5}$ = 18; $PM_{10-2.5}$ = 13.	For 1992-1994 study period, total (non-accidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO.	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ effect size estimates were comparable per same distributional increment (5^{th} to 95^{th} percentile).	Total mortality percent excess deaths: PM_{10} (1 d) = 4.4% (−1.0, 10.1) $PM_{2.5}$ (0 d) = 3.1% (−0.6, 7.0) $PM_{10-2.5}$ (1 d) = 4.0% (−1.2, 9.4) PM_{10} (1 d) = 6.9% (−1.3, 15.7) $PM_{2.5}$ (1 d) = 3.2% (−2.3, 8.9) $PM_{10-2.5}$ (1 d) = 7.8% (0.0, 16.2) Respiratory mortality: PM_{10} (0 d) = 7.8% (−10.2, 29.5) Circulatory mortality: $PM_{2.5}$ (o d) = 2.3% (−10.3, 16,6) PM_{10-25} (2 d) = 7.4% (−9.1, 26.9) Note: All above PM_{10} per 50 $\mu g/m^3$; all $PM_{2.5}$ and $PM_{10-2.5}$ % per 25 $\mu g/m^3$.
For 1985-1990 period TSP, PM_{10}, TSP-PM_{10}, Sulfate from TSP (TSP-$SO_4^=$)	For earlier 1985-1990 study period, total non-accidental, circulatory, respiratory, and "other" (non-circulatory or respiratory non-accidental) mortality were evaluated versus noted PM indices and gaseous pollutants.	Both PM_{10} (lag 1 and 2 day) and TSP (lag 1 day) but not TSP-PM_{10} or TSP-$SO_4^=$ significantly associated with respiratory mortality for 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM_{10} or TSP reduced PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.	

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Chock et al. (2000). 1989-1991 Pittsburgh, PA PM_{10} (daily) $PM_{2.5}$ (every 2 days)	Study evaluated associations between daily mortality and several air pollution variables (PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2) in two age groups (<75 yr., ≥75 yr.) in Pittsburgh, PA, during 3-yr. period. Poisson regression used, including filtering of data based on cubic B-spline basis functions, with adjustments for seasonal trends, day-of-week effects, temp., dew point. Single- and multi-pollutant models run for 0, 1, 2, and 3 day lags. $PM_{2.5}/PM_{10} \approx 0.67$.	Issues of seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients emphasized. Single- and multi-pollutant non-seasonal models show significant positive association between PM_{10} and daily mortality, but seasonal models showed much multi-collinearity, masking association of any pollutant with mortality. Also, based on data set half the size for PM_{10}, the $PM_{2.5}$ coefficients were highly unstable and, since no consistently significant associations found in this small data set stratified by age group and season, no conclusions drawn on relative role of $PM_{2.5}$ vs. $PM_{10-2.5}$.	Total mortality percent increase per 25 $\mu g/m^3$ for aged <75 yrs: $PM_{2.5}$ = 2.6% (2.0, 7.3) $PM1_{0-2.5}$ = 0.7% (−1.7, 3.7) Total mortality percent increase per 25 $\mu g/m^3$ for aged >75 yrs: $PM_{2.5}$ = 1.5% (−3.0, 6.3) $PM1_{0-2.5}$ = 1.3% (−1.3, 3.8)
Klemm and Mason (2000). Atlanta, GA 1998-1999 $PM_{2.5}$ mean=19.9; $PM_{2.5}/PM_{10}$ =0.65. Nitrate, EC, OC, and oxygenated HC.	Reported "interim" results for 1 yr period of observations regarding total mortality in Atlanta, GA during 1998-1999. Generalized additive model used to assess effects of $PM_{2.5}$ vs $PM_{10-2.5}$, and for nitrate, EC, OC and oxygenated HC components.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.	Total mortality percent increase per 25 $\mu g/m^3$ for: $PM_{2.5}$ = 4.8% (−3.2, 13.4) $PM1_{0-2.5}$ = 1.4% (−11.3, 15.9)
Gwynn et al. (2000). Buffalo, NY. 1988-1990. PM_{10} (24); COH (0.2 /1000ft); SO_4= (62 nmoles/m3)	Total, circulatory, and respiratory mortality and unscheduled hospital admissions were analyzed for their associations with H+, SO_4=, PM_{10}, COH, O_3, CO, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, humidity, using. Poisson and negative binomial GAM models.	For total mortality, all the PM components were significantly associated, with H+ being the most significant, and COH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality.	12% (2.6, 22.7) per 50 $\mu g/m^3$ PM_{10} at 2-day lag.
Schwartz (2000c). Boston, MA. 1979-1986. $PM_{2.5}$ mean = 15.6.	Non-accidental total, pneumonia, COPD, and ischemic heart disease mortality were examined for possible "harvesting" effects of PM. The mortality, air pollution, and weather time-series were separated into seasonal cycles (longer than 2-month period), midscale, and short-term fluctuations using STL algorithm. Four different midscale components were used (15, 30, 45, and 60 days) to examine the extent of harvesting. GAM Poisson regression analysis was performed using deaths, pollution, and weather for each of the four midscale periods.	For COPD deaths, the results suggest that most of the mortality was displaced by only a few months. For pneumonia, ischemic heart disease, and total mortality, the effect size increased with longer time scales.	Total mortality percent increase per 25 $\mu g/m^3$ increase in $PM_{2.5}$: 5.3 (1.8, 9.0) for short-term fluctuations; 9.6 (8.1, 11.1) for the 60 day window.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Lipfert et al. (2000a). Philadelphia (7 county Metropolitan area), 1992-1995. Harvard PM measurements: $PM_{2.5}$ (17.3); PM_{10} (24.1); $PM_{10-2.5}$ (6.8), sulfate (53.1 nmol/m3); H^+ (8.0 nmol/m3).	12 mortality variables, as categorized by area, age, and cause, were regressed on 29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by sub-areas), yielding 348 regression results. Both dependent and explanatory variables were pre-filtered using the19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for hot and cold days and day-of-week using stepwise procedure. The average of current and previous days' pollution levels were used.	Significant associations were found for a wide variety gaseous and particulate pollutants, especially for peak O_3. No systematic differences were seen according particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.	The fractional Philadelphia mortality risk attributed to the pollutant levels: "average risk" was 0.0423 for 25 $\mu g/m^3$ $PM_{2.5}$; 0.0517 for 25 $\mu g/m^3$ $PM_{10-2.5}$; 0.0609 for 50 $\mu g/m^3$ PM_{10}, using the Harvard PM indices at avg. of 0 and 1 d lags.
Laden et. al. (2000) Six Cities (means): Watertown, MA (16.5); Kingston-Harriman, TN (21.1); St. Louis, MO (19.2); Steubenville, OH (30.5); Portage, WI (11.3); Topeka, KS (12.2). 1979-1988?. 15 trace elements in the dichot $PM_{2.5}$: Si, S, Cl, K, Ca, V, Mn, Al, Ni, Zn, Se, Br, Pb, Cu, and Fe.	Total (non-accidental), ischemic heart disease, pneumonia, and COPD (mean daily total deaths for the six cities: 59, 12, 55, 3, 11, and 3, respectively in the order shown left). A factor analysis was conducted on the 15 elements in the fine fraction of dichot samplers to obtain five common factors; factors were rotated to maximize the projection of the single "tracer" element (as in part identified from the past studies conducted on these data) for each factor; $PM_{2.5}$ was regressed on the identified factors scores so that the factor scores could be expressed in the mass scale. Using GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time, mortality was regressed on the factor scores in the mass scale. The mean of the same-day and previous day (increasing the sample size from 6,211 to 9,108 days) mass values were used. The city-specific regression coefficients were combined using inverse variance weights.	Three sources of fine particles were defined in all six cities with a representative element for each source type: Si for soil and crustal material; Pb for motor vehicle exhaust; and Se for coal combustion sources. In city-specific analysis, additional sources (V for fuel oil combustion, Cl for salt, etc.) were considered. Five source factors were considered for each city, except Topeka with the three sources. Coal and mobile sources account for the majority of fine particles in each city. In all of the metropolitan areas combined, 46% of the total fine particle mass was attributed to coal combustion and 19% to mobile sources. The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality.	Total mortality percent excess overall: 4.0 (2.8, 5.3), 2.7 (0.6, 5.0) with each 25 $\mu g/m^3$ increase in the two-day mean of coal combustion fine PM factor; 8.7 (4.2, 13.4) with each 25 $\mu g/m^3$ increase in the two-day mean of mobile source fine PM factor; −5.7 (−13.7, 3.2) with each 25 $\mu g/m^3$ increase in the two-day mean of the crustal source fine PM factor.
Levy (1998). King County, WA. 1990-1994. PM_{10} Nephelometer (30); (0.59 bsp unit)	Out-of-hospital deaths (total, respiratory, COPD, ischemic heart disease, heart failure, sudden cardiac death screening codes, and stroke) were related to PM_{10}, nephelometer (0.2 - 1.0 μm fine particles), SO_2, and CO, adjusting for day-of-week, month of the year, temperature and dewpoint, using Poisson regression.	Nephelometer data were not associated with mortality. Cause-specific death analyses suggest PM associations with ischemic heart disease deaths. Associations of mortality with SO_2 and CO not mentioned. Mean daily death counts were small (e.g., 7.7 for total; 1.6 for ischemic heart disease). This is an apparently preliminary analysis.	Total mortality percent excess: 5.6% (−2.4, 1.43) per 50 $\mu g/m^3$ PM_{10} at avg. of 2 to 4 d lag; 7.2% (−6.3, 22.8) with SO_2 CO. 1.8% (−3.5, 7.3) per 25 $\mu g/m^3$ PM_1; −1.0 (−8.7,. 7.7) with SO_2 and CO.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Mar et al. (2000). Phoenix, AZ. 1995-1997. PM_{10}, and $PM_{2.5}$, and $PM_{10\text{-}2.5}$ (TEOM), with means = 46.5, 13.0, and 33.5, respectively; and $PM_{2.5}$ (DFPSS), mean = 12.0.	Total (non-accidental) and cardiovascular deaths (mean = 8.6 and 3.9, respectively) for only those who resided in the zip codes located near the air pollution monitor were included. GAM Poisson models were used, adjusting for season, temperature, and relative humidity. Air pollution variables evaluated included: O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10\text{-}2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days evaluated. Factor analysis also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores included in mortality regression.	Total mortality was significantly associated with CO and NO_2 and weakly associated with SO_2, PM_{10}, $PM_{10\text{-}2.5}$, and EC. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$, OC and EC. Combustion-related factors and secondary aerosol factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality.	Total mortality percent excess: 5.4 (0.1, 11.1) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 3.0 (−0.5, 6.6) for $PM_{(10\text{-}2.5)}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d; 3.0 (−0.7, 6.9) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d. Cardiovascular mortality RRs: 9.9 (1.9, 18.4) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 18.7 (5.7, 33.2) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 1 d; and 6.4 (1.4, 11.7) PM_{10} (TEOM) 25 $\mu g/m^3$ $PM_{(10\text{-}2.5)}$ at lag 0 d.
Clyde et al. (2000). Phoenix, AZ. 1995-1998. PM_{10}, and $PM_{2.5}$, (from TEOM), with means = 45.4, and 13.8. $PM_{10\text{-}2.5}$ computed as PM_{10}-$PM_{2.5}$.	Elderly (age ≥65 years) non-accidental mortality for three regions of increasing size in Phoenix urban area analyzed to evaluate influence of spatial uniformity of PM_{10} and $PM_{2.5}$. All-age accidental deaths for the metropolitan area also examined as a "control". GAM Poisson models adjusting for season (smoothing splines of days), temperature, specific humidity, and lags 0- to 3-d of weather variables. PM indices for lags 0-3 d considered. Bayesian Model Averaging (BMA) produces posterior mean relative risks by weighting each model (out of all possible model specifications examined) based on support received from the data.	The BMA results suggest that a weak association was found only for the mortality variable defined over the region with uniform $PM_{2.5}$, with a 0.91 probability that RR is greater than 1. The other elderly mortality variables, including the accidental deaths ("control"), had such probabilities in the range between 0.46 to 0.77. Within the results for the mortality defined over the region with uniform $PM_{2.5}$, the results suggested that effect was primarily due to coarse particles rather than fine; only the lag 1 coarse PM was consistently included in the highly ranked models.	Posterior mean RRs and 90% probability intervals per changes of 25 $\mu g/m^3$ in all lags of fine and coarse PM for elderly mortality for uniform PM_{10} region: 1.06 (1+, 1.11).

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Smith et al. (2000). Phoenix, AZ. 1995-1997	Study evaluated effects of daily and 2- to 5-day average coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$) particles from an EPA-operated central monitoring site on nonaccidental mortality among elderly (65+ years), using time-series analyses for residents within city of Phoenix and, separately, for region of circa 50 mi around Phoenix. Initial model selected to represent long-term trends and weather variables (e.g., ave. daily temp., max daily temp., daily mean specific humidity, etc.); then PM variables added to model one at a time to ascertain which had strongest effect. Piecewise linear analysis and spline analysis used to evaluate possible nonlinear PM-mortality relationship and to evaluate threshold possibilities. Data analyzed most likely same as Clyde's or Mar's Phoenix data.	In linear PM effect model, a statistically significant mortality association found with $PM_{10-2.5}$, but not with $PM_{2.5}$. In the model allowing for a threshold, evidence suggestive of possible threshold for $PM_{2.5}$ (in the range of 20-25 $\mu g/m^3$) found, but not for $PM_{10-2.5}$. A seasonal interaction in the $PM_{10-2.5}$ effect was also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10-2.5}$ is lowest.	—
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983. PM_{15}: 55.5, 47.0, 47.5; and $PM_{2.5}$: 42.1, 37.1, 39.9, for Newark, Elizabeth, and Camden, respectively.	Factor analysis-derived source type components were examined for their associations with mortality in this study. Non-accidental total deaths and cardiorespiratory deaths were examined for their associations with PM_{15}, $PM_{2.5}$ sulfate, trace metals from PM_{15}, three fractions of extractable organic matter, and CO. Data were analyzed with Poisson GEE regression models with autoregressive correlation structure, adjusting for temperature, time-of-week, and season indicator variables. Individual pollution lag days from 0 to 3, as well as the average concentrations of current and preceding 3 days were considered. Factor analysis of the trace elements, sulfate, and CO data was conducted, and mortality series were regressed on these factor scores.	Factor analysis identified several source types with tracer elements. In Newark, oil burning factor, industrial source factor, and sulfate factor were positively associated with total mortality; and sulfate was associated with cardio-respiratory mortality. In Camden, oil burning and motor vehicle factors were positively associated with total mortality; and, oil burning, motor vehicles, and sulfate were associated with cardio-respiratory mortality. In Elizabeth, resuspended dust was not associated with total mortality; and industrial source (traced by Cd) showed positive associations with cardio-respiratory mortality. On the mass basis (source-contributed mass), the RRs estimates per 10 $\mu g/m^3$ were larger for specific sources (e.g., oil burning, industry, etc.) than for total mass. The choice of lag/averaging reported to be not important.	Percent excess deaths per 50 $\mu g/m^3$ increase in current day PM_{15}: in Newark, 5.7 (4.6, 6.7) for total mortality, 7.8 (3.6, 12.1) for cardioresp. mortality; in Camden, 11.1 (0.7, 22.5) and 15.0 (4.3, 26.9); and in Elizabeth, −4.9 (−17.9, 10.9) and 3.0 (−11.0, 19.4), respectively. Percent excess deaths per 25 $\mu g/m^3$ $PM_{2.5}$; in Newark, 4.3 (2.8, 5.9) for total and 5.1 (3.1, 7.2) for cardiorespiratory mortality; in Camden, 5.7 (0.1, 11.5) and 6.2 (0.6, 12.1); in Elizabeth, 1.8 (−5.4, 9.5) and 2.3 (−5.0, 10.1), respectively.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Gamble (1998). Dallas, TX. 1990-1994. PM_{10} (25)	Relationships of total, respiratory, cardiovascular, cancer, and remaining non-accidental deaths to PM_{10}, O_3, NO_2, SO_2, and CO evaluated, adjusting for temperature, dewpoint, day-of-week, and seasonal cycles (trigonometric terms) using Poisson regression.	O_3 (avg. of 1-2 day lags), NO_2 (avg.. 4 -5 day lags), and CO (avg. of lags 5- 6 days) were significantly positively associated with total mortality. PM_{10} and SO_2 were not significantly associated with any deaths.	−3.6% (−12.7, 6.6) per 50 $\mu g/m^3$ PM_{10} at 0 lag (other lags also reported to have no associations)
Ostro (1995). San Bernardino and Riverside Counties, CA, 1980-1986. $PM_{2.5}$ (estimated from visual range). Mean = 32.5.	Study evaluated total, respiratory, cardiovascular, and age > = 65 deaths (mean = 40.7, 3.8, 18.7, and 36.4 per day, respectively). $PM_{2.5}$ estimated based on airport visual range and previously published empirical formula. Autoregressive OLS (for total) and Poisson (for sub-categories) regressions used, adjusting for season (sine/cosine with cycles from 1 yr to 0.75 mo; prefiltering with 15-day moving ave.; dichotomous variables for each year and month; smooth function of day and temp.), day-of-week, temp. and dewpoint. Evaluated lags 0, 1, and 2 of estimated $PM_{2.5}$, as well as moving averages of 2, 3, and 4 days and O_3.	The results were dependent on season. No $PM_{2.5}$ – mortality association found for the full year-round period. Associations between estimated $PM_{2.5}$ (same-day) and total and respiratory deaths found during summer quarters (April - Sept.). Correlation between the estimated $PM_{2.5}$ and daily max temp. was low (r = 0.08) during the summer quarters. Ozone was also associated with mortality, but was also relatively highly correlated with temp. r = 0.73). Moving averages of $PM_{2.5}$ did not improve the associations.	Percent excess deaths per 25 $\mu g/m3$ of estimated $PM_{2.5}$, lag 0: Full year: 0.3 (−0.6, 1.2) for total; 2.1 (−0.3, 4.5) for respiratory; and 0.7 (−0.3, 1.7) for circulatory. Summer quarters: 1.6 (0.03, 3.2) for total; 5.5 (1.1, 10.0) for respiratory; and 0 (−1.0, 1.0) for circulatory.
Kelsall et al. (1997). Philadelphia, PA 1974-1988. TSP (67)	Total, cardiovascular, respiratory, and by-age mortality regressed on TSP, SO_2, NO_2, O_3, and CO, adjusting for temporal trends and weather, using Poisson GAM model.	TSP, SO_2, O_3, and 1-day lagged CO individually showed statistically significant associations with total mortality. No NO_2 associations unless SO_2 or TSP was also considered. The effects of TSP and SO_2 were diminished when both pollutants were included.	Total mortality excess risk: 3.2% (0, 6.1) per 100 $\mu g/m^3$ TSP at 0 day lag.
Moolgavkar and Leubeck (1996). Philadelphia, PA. 1973-1988. TSP (68)	A critical review paper, with an analysis of total daily mortality for its association with TSP, SO_2, NO_2, and O_3, adjusting for temporal trends, temperature, and also conducting analysis by season, using Poisson GAM model.	RR results presented as figures, and seasonal difference noted. TSP, SO_2, O_3 - mortality associations varied across season. TSP associations were stronger in summer and fall. NO_2 was the most significant predictor.	Total mortality excess risk: ranged ≈ 0 (winter) to ≈4% (summer) per 100 $\mu g/m^3$ TSP at 1 day lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Neas et. al. (1999). Philadelphia. 1973-1980. TSP mean = 77.2.	Total, age over 65, cancer, and cardiovascular deaths analyzed for association with TSP. Conditional logistic regression analysis with case-crossover design conducted. Average values of current and previous days' TSP used. Case period is the 48-hr period ending at midnight on day of death. Control periods are 7, 14, and 21 days before and after the case period. Other covariates included temperature on the previous day, dewpoint on the same day, an indicator for hot days (> 80°F), an indicator for humid days (dewpoint > 66°F), and interaction of same-day temp. and winter season.	In each set of the six control periods, TSP was associated with total mortality. A model with four symmetric reference periods 7 and 14 days around the case period produced a similar result. A model with only two symmetric reference periods of 7 days around the case produced a larger estimate. A larger effect was seen for deaths in persons ≥ 65 years of age and for deaths due to pneumonia and to cardiovascular disease. Cancer mortality was not associated with TSP.	Odds Ratio (OR) for all cause mortality per 100 $\mu g/m^3$ increase in 48-hr mean TSP was 1.056 (1.027, 1.086). The corresponding number for those aged 65 and over was 1.074 (1.037, 1.111), and 1.063 (1.021, 1.107) for cardiovascular disease.
Schwartz (2000d). Philadelphia. 1974-1988. TSP. Mean = 70 $\mu g/m^3$ for warm season (April through August) and 64 $\mu g/m^3$ for cold season.	Total (non-accidental) deaths analyzed. GAM Poisson models adjusting for temperature, dewpoint, day-of-week, and season applied to each of 15 warm and cold seasons. Humidity-corrected extinction coefficient, derived from airport visual range, also considered as explanatory variable. In the second stage, resulting 30 coefficients were regressed on regression coefficients of TSP on SO_2. Results of first stage analysis combined using inverse variance weighting.	When TSP controlled for, no significant association between SO_2 and daily deaths. SO_2 had no association with daily mortality when it was poorly correlated with TSP. In contrast, when SO_2 was controlled for, TSP was more strongly associated with mortality than when it was less correlated with SO_2. However, all of the association between TSP and mortality was explained by its correlation with extinction coefficient.	Total mortality excess risk estimates combined across seasons/years: 9.0 (5.7, 12.5) per 100 $\mu g/m^3$ TSP.
Canada			
Burnett et al. (1998a). 11 Canadian cities. 1980-1991. No PM index data available on consistent daily basis.	Total non-accidental deaths were linked to gaseous air pollutants (NO_2, O_3, SO_2, and CO) using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather (selected from spline-smoothed functions of temperature, dewpoint, relative humidity with 0, 1, and 2 day lags using forward stepwise procedure). Pollution variables evaluated at 0, 1, 2, and up to 3-day lag averages thereof. No PM index included in analyses because daily PM measurements not available. City-specific models containing all four gaseous pollutants examined. Overall risks computed by averaging risks across cities.	NO_2 had 4.1% increased risk per mean concentration; O_3 had 1.8%; SO_2 had 1.4%, and CO had 0.9% in multiple pollutant regression models. A 0.4% reduction in excess mortality was attributed to achieving a sulfur content of gasoline of 30 ppm in five Canadian cities. Daily PM data for fine and coarse mass and sulfates available on varying (not daily) schedules allowed ecologic comparison of gaseous pollutant risks by mean fine particle indicators mass concentrations.	Found suggestion of weak negative confounding of NO_2 and SO_2 effects with fine particles and weak positive confounding of particle effects with O_3. No quantitative RR or ER estimates reported for PM indicators.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Burnett et al. (2000). 8 largest Canadian cities. 1986-1996. All city mean PM_{10} 25.9; $PM_{2.5}$ 13.3; $PM_{10-2.5}$ 12.6; sulfate 2.6.	Total non-accidental deaths linked to PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO). Each city's mortality, pollution, and weather variables separately filtered for seasonal trends and day-of-week patterns. The residual series from all the cities then analyzed in a GAM Poisson model. The weather model was selected from spline-smoothed functions of temperature, relative humidity, and maximum change in barometric pressure within a day, with 0 and 1 day lags using forward stepwise procedure. Pollution effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-pollutant models, principal components were also used as predictors in the regression models.	O_3 was weakly correlated with other pollutants and other pollutants were "moderately" correlated with each other (the highest was r = 0.65 for NO_2 and CO). The strongest association with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger predictor of mortality than $PM_{10-2.5}$. The estimated gaseous pollutant effects were generally reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10-2.5}$. Sulfate, Fe, Ni, and Zn were most strongly associated with mortality. Total effect of these four components was greater than that for $PM_{2.5}$ mass alone.	Percentage increase in daily filtered non-accidental deaths associated with increases of 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{(10-2.5)}$ at lag 1 day: 3.5 (1.0, 6.0) for PM_{10}; 3.0 (1.1, 5.0) for $PM_{2.5}$; and 1.8 (−0.7, 4.4) for $PM_{10-2.5}$. In the multiple pollutant model with $PM_{2.5}$, $PM_{10-2.5}$, and the 4 gaseous pollutants, 1.9 (0.6, 3.2) for $PM_{2.5}$; and 1.2 (−1.3, 3.8) for $PM_{(10-2.5)}$.
Burnett et al. (1998b). Toronto, 1980-1994. TSP (60); COH (0.42); SO4= (9.2 $\mu g/m^3$); PM_{10} (30, estimated); $PM_{2.5}$ (18, estimated)	Total, cardiac, and other nonaccidental deaths (and by age groups) were regressed on TSP, COH, SO_4=, CO, NO_2, SO_2, O_3, estimated PM_{10} and $PM_{2.5}$ (based on the relationship between the existing every-6th-day data and SO_4=, TSP and COH), adjusting for seasonal cycles, day-of-week, temperature, and dewpoint using Poisson GAM model.	Essentially all pollutants were significant predictors of total deaths in single pollutant models, but in two pollutant models with CO, most pollutants' estimated RRs reduced (all PM indices remained significant). Based on results from the co-pollutant models and various stepwise regressions, authors noted that effects of the complex mixture of air pollutants could be almost completely explained by the levels of CO and TSP.	Total mortality percent excess: 2.3% (0.8, 3.8) per 100 $\mu g/m^3$ TSP; 3.5% (1..8, 5.3) per 50 $\mu g/m^3$ PM_{10}; 4.8% (3.3, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$. 0 day lag for TSP and PM_{10}; Avg. of 0 and 1 day for $PM_{2.5}$.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Goldberg et al. (2000) Montreal, Quebec 1984-95 Mean TSP = 53.1 (14.6 - 211.1) $\mu g/m^3$ PM_{10} = 32.2 (6.5 - 120.5) $\mu g/m^3$ $PM_{2.5}$ = 3.3 (0.0 - 30.0) $\mu g/m^3$	Study aimed to shed light on population subgroups that my be susceptible to PM effects. Linked data on daily deaths with other health data (physician visits, pharmaceutical R_x, etc.) to identify individuals with presenting health conditions. PM_{10} and $PM_{2.5}$ measured by dichotomous sampler 1 in 6 days until 1992 (2 stations), then daily through 1993. PM missing days interpolated from COH, ext. coefficient, sulfates. Used quasi likelihood estimation in GAM's to assess PM associations with total and cause-specific mortality; and, also, in subgroups by age and/or preexisting health conditions. Adjusted for CO, NO_2, NO, O_3 and SO_2 in 2-pollutant and all-pollutant models.	Significant associations found for all-cause (total non-accidental) and cause-specific (cancer, CAD, respiratory disease, diabetes) with PM measures. Results reported for $PM_{2.5}$, COH and sulfates. All three PM measures associated with increases in total, resp., and "other nonaccidental", and diabetes-related mortality. No PM associations found with digestive, accidental, renal or neurologic causes of death. Also, mainly in 65+ yr group, found consistent associations with increased total mortality among persons who had cancer, acute lower resp. diseases, any cardiovascular disease, chronic CAD and congestive heart failure (CHF).	Percent excess mortality per 25 $\mu g/m^3$ estimated $PM_{2.5}$: Total deaths (3 d ave.) = 4.4% (2.5, 6.3) CV deaths (3 d ave.) = 2.6% (−0.1, 5.5) Resp deaths (3 d ave.) = 16.0% (9.7, 22.8) Coronary artery (3 d ave.) = 3.4% (−0.2, 7.1) Diabetes (3 d ave.) = 15.7% (4.8, 27.9) Lower Resp Disease (3 d ave.) = 9.7% (4.5, 15.1) Airways disease (3 d ave.) = 2.7% (−0.9, 6.4) CHF (3 d ave.) = 8.2% (3.3, 13.4)
Özkaynak et al. (1996). Toronto, 1970-1991. TSP (80); COH (0.42 /1000ft).	Total, cardiovascular, COPD, pneumonia, respiratory, cancer, and the remaining mortality series were related to TSP, SO_2, COH, NO_2, O_3, and CO, adjusting for seasonal cycles (by high-pass filtering each series) temperature, humidity, day-of-week, using OLS regression. Factor analysis of multiple pollutants was also conducted to extract automobile related pollution, and mortality series were regressed on the resulting automobile factor scores.	TSP (0 day lag) was significantly associated with total and cardiovascular deaths. NO_2 (0-day lag) was a significant predictor for respiratory and COPD deaths. 2-day lagged O_3 was associated with total, respiratory, and pneumonia deaths. Factor analysis showed factor with high loadings for NO_2, COH, and CO (apparently representing automobile factor) as significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.	Total mortality excess risk: 2.8% per 100 $\mu g/m^3$ TSP at 0 day lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe			
Katsouyanni et al. (1997). 12 European (APHEA) cities. 1975-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Athens and Kracow.	Total daily deaths regressed on BS or SO_2 using Poisson models, adjusting for seasonal cycles, day-of-week, influenza epidemic, holidays, temp., humidity. Final analysis done with autoregressive Poisson models to allow for overdispersion and autocorrelation. Pollution effects examined at 0 through 3 day lags and multi-day averages thereof. When city-specific coefficients tested to be homogeneous, overall estimates obtained by computing variance-weighted means of city-specific estimates (fixed effects model). When significant heterogeneity present, source of heterogeneity sought by examining a predefined list of city-specific variables, including annual and seasonal means of pollution and weather variables, number of monitoring sites, correlation between measurements from different sites, age-standardized mortality, proportion of elderly people, smoking prevalence, and geographic difference (north-south, east-west). A random effects model was fit when heterogeneity could not be explained.	Substantial variation in pollution levels (winter mean SO_2 ranged from 30 to 330 $\mu g/m^3$), climate, and seasonal patterns were observed across cities. Significant heterogeneity was found for the effects of BS and SO_2, but only the separation between western and central eastern European cities resulted in more homogeneous subgroups. Significant heterogeneity for SO_2 remained in western cities. Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both SO_2 and BS were stronger during the summer and were independent.	Total mortality excess deaths per 25 $\mu g/m^3$ increase in single day BS for western European cities: 1.4 (1.0, 1.8); and 2 (1, 3) per 50 $\mu g/m^3$ PM_{10} increase. In central/eastern Europe cities, corresponding figure was 0.3 (0.05, 0.5) per 25 $\mu g/m^3$ BS.
Touloumi et al. (1997). 6 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 14.6 in London to 84.4 in Athens.	The results of the short-term effects of ambient NO_2 and/or O_3 on daily deaths from all causes (excluding accidents) were discussed to provide a basis of comparison with estimated SO_2 or BS effects in the APHEA cities. Poisson models, lag/averaging of pollution, and the computation of combined effects across the cities were done in the same way as done by Katsouyanni et al. (1997), as described above.	Significant positive associations found between daily deaths and both NO_2 and O_3. Tendency for larger effects of NO_2 in cities with higher levels of BS. When BS included in the model, pooled estimate for O_3 effect only slightly reduced, but coefficient for NO_2 reduced by half. Authors speculated that short-term effects of NO_2 on mortality confounded by other vehicle-derived pollutants.	NO_2 and/or O_3 estimates only.
Zmirou et al. (1998). 10 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Kracow.	Cardiovascular, respiratory, and digestive mortality series in10 European cities analyzed to examine cause-specificity of air pollution. The mortality series were analyzed for associations with PM (BS, except TSP in Milan and Bratislava; PM_{13} in Lyon), NO_2, O_3, and SO_2. Poisson models, lag/averaging of pollution, and computation of combined effects across the cities done in the same way as by Katsouyanni et al. (1997), above.	The cardiovascular and respiratory mortality series were associated with BS and SO_2 in western European cities, but not in the five central European cities. NO_2 did not show consistent mortality associations. RRs for respiratory causes were at least equal to, or greater than those for cardiovascular causes. No pollutant exhibited any association with digestive mortality.	Pooled cardiovascular mortality percent excess deaths per 25 $\mu g/m^3$ increase in BS for western European cities: 1.0 (0.3, 1.7); for respiratory mortality, it was 2.0 (0.8, 3.2) in single lag day models (the lags apparently varied across cities).

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Bremner et al. (1999). London, UK, 1992-1994. BS (13), PM_{10} (29).	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tend to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	1.9% (0.0, 3.8) per 25 $\mu g/m^3$ BS at lag 1 day; 1.3% (-1.0, 3.6) per 50 $\mu g/m^3$ PM_{10} at lag 1 d for total deaths. Resp. deaths (3 d) = 4.9% (0.5, 9.4). CVD deaths (1 d) = 3.0% (0.3, 5.7).
Prescott et al. (1998). Edinburgh, UK, 1981-1995. PM_{10} (21, by TEOM only for 1992-1995); BS (8.7).	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and >= 65), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	3.8 (1.3, 6.4) per 25 $\mu g/m^3$ increase in BS for all cause mortality in age 65+ group, avg. of 1-3 day lags.
Rooney et al. (1998). England and Wales, and Greater London, UK PM_{10} (56, during the worst heat wave; 39, July-August mean)	Excess deaths, by age, sex , and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-94 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987-1992 study (Anderson et al., 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave.
Wordley et al. (1997). Birmingham, UK, 1992-1994. PM_{10} (apparently beta-attenuation, 26)	Mortality data were analyzed for COPD, pneumonia, all respiratory diseases, all circulatory diseases, and all causes. Mortality associations with PM_{10} , NO_2, SO_2, and O_3 were examined using OLS (with some health outcomes log- or square-root transformed), adjusting for day-of-week, month, linear trend, temperature and relative humidity. The study also analyzed hospital admission data.	Total, circulatory, and COPD deaths were significantly associated with 1-day lag PM_{10}. The gaseous pollutants "did not have significant associations independent from that of PM_{10}", and the results for gaseous pollutants were not presented. The impact of reducing PM_{10} to below 70 $\mu g/m^3$ was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70 $\mu g/m^3$ occurred only once during the study period.	5.6% (0.5, 11.0) per 50 $\mu g/m^3$ PM_{10} at 1 d lag for total deaths. COPD (1 d lag) deaths = 27.6 (5.1, 54.9). Circulatory (1 d) deaths = 8.8 (1.9, 17.1)

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (2000). The Netherlands, 1986-1994. PM_{10} (median 34); BS (median 10).	Total, cardiovascular, COPD, and pneumonia mortality series were regressed on PM_{10}, BS, sulfate, nitrate, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model. Deaths occurring inside and outside hospitals were also examined.	Particulate air pollution was not more consistently associated with mortality than were the gaseous pollutants SO_2 and NO_2. Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}. The RRs for all pollutants were larger in the summer months than in the winter months.	0.9 (0.1, 1.7) per 50 $\mu g/m^3$ PM_{10}; 1.0 (0.5, 1.5) per 25 $\mu g/m^3$ BS; 3.2 (0.6, 5.9) per 25 $\mu g/m^3$ sulfate; and 4.1 (1.4, 6.9) per 25 $\mu g/m^3$ nitrate, all at 1 day lag.
Pönkä et al. (1998). Helsinki, Finland, 1987-1993. TSP (median 64); PM_{10} (median 28)	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant significantly associated with mortality from all cardiovascular or CVD causes in 65+ year age group. Only in age <65 year group, PM_{10} associated with total and CVD deaths with 4 and 5 d lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with CVD mortality <65 yr. group with inconsistent signs and late and spiky lags (neg. on d 5 and pos. on d 6).	18.8% (5.6, 33.2) per 50 $\mu g/m^3$ PM_{10} 4 day lag (other lags negative or zero).
Peters et al. (1999a). A highly polluted coal basin area in the Czech Republic and a rural area in Germany, northeast Bavaria districts. 1982-1994. TSP: mean = 121.1 and 51.6, respectively, for these two regions. PM_{10} and $PM_{2.5}$ were also measured in the coal basin during 1993-1994 (mean = 65.9 and 51.0, respectively).	Non-accidental total and cardiovascular deaths (mean = 18.2 and 12.0 per day, for the Czech and Bavaria areas, respectively). The APHEA approach (Poisson model with sine/cosine, temperature as a quadratic function, relative humidity, influenza, day-of-week as covariates), as well as GAM Poisson models were considered. Logarithm of TSP, SO_2, NO_2, O_3, and CO (and PM_{10} and $PM_{2.5}$ for 1993-1994) were examined at lags 0 through 3 days.	In the coal basin (i.e., the Czech Republic polluted area), on the average, 68% of the TSP was PM_{10}, and most of PM_{10} was $PM_{2.5}$ (75%). For the coal basin, associations were found between the logarithm of TSP and all-cause mortality at lag 1 or 2 days. SO_2 was also associated with all-cause mortality with slightly lower significance. PM_{10} and $PM_{2.5}$ were both associated with all-cause mortality in 1993-1994 with a lag of 1-day. NO_2, O_3 and CO were positively but more weakly associated with mortality than PM indices or SO_2. In the Bavarian region, neither TSP nor SO_2 was associated with mortality, but CO (at lag 1-day) and O_3 (at lag 0-day) were associated with all-cause mortality.	Total mortality excess deaths per 100 $\mu g/m^3$ increase in TSP for the Czech region: 3.8 (0.8, 6.9) at lag 2-day for 1982-1994 period. For period 1993-1994, 9.5 (1.2, 18.5) per 100 $\mu g/m^3$ increase in TSP at lag 1-day, and 4.8 (0.7, 9.0) per 50 $\mu g/m^3$ increase in PM_{10}; and 1.4 (−0.5, 3.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (1997). Rotterdam, the Netherlands, 1983-1991. TSP (median 42); BS (median 13).	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	5.5 (1.1, 9.9) per 100 $\mu g/m^3$ TSP at 1 day lag.
Kotěšovec et al. (2000). Northern Bohemia, Czech Republic, 1982-1994. TSP (121.3).	Total (excluding accidents and children younger than 1 yr), cause specific (cardiovascular and cancer), age (65 and less vs. otherwise), and gender specific mortality series were examined for their associations with TSP and SO_2 using logistic model, adjusting for seasonal cycles, influenza epidemics, linear and quadratic temperature terms. Lags 0 through 6 days, as well as a 7 day mean values were examined.	For the total mortality, TSP, but not SO_2, was associated. There were apparent differences in associations were found between men and women. For example, for age below 65 cardiovascular mortality was associated with TSP for men but not for women.	Total mortality percent excess deaths per 100 $\mu g/m^3$ increase in TSP at 2 day lag was 3.4 (0.5, 6.4).
Zanobetti et al. (2000a). Milan, Italy. 1980-1989. TSP mean = 142.	The focus of this study was to quantify mortality displacement using GAM distributed lag models. Non-accidental total deaths were regressed on smooth function of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect.	TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45^{th} day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.	Total mortality percent increase estimates per IQR increase in TSP: 2.2 (1.4, 3.1) for single-day model; 6.7 (3.8, 9.6) for distributed lag model.
Anderson et al. (1996). London, UK, 1987-1992. BS (15)	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson model.	Both O_3 (0 day lag) and BS (1 day lag) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	2.8% (1.4, 4.3) per 25 $\mu g/m^3$ BS at 1-d lag for total deaths. CVD (1 d) = 1.0 (−1.1, 3.1). Resp. (1 d) = 1.1 (−2.7, 5.0).

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Michelozzi et al. (1998). Rome, Italy, 1992-1995. TSP ("PM_{13}" beta attenuation, 84).	Total mortality was related to PM_{13}, SO_2, NO_2, CO, and O_3, using Poisson GAM model , adjusting for seasonal cycles, temperature, humidity, day-of-week, and holiday. Analysis of mortality by place of residence, by season, age, place of death (in or out of hospital), and cause was also conducted.	PM_{13} and NO_2 were most consistently associated with mortality. CO and O_3 coefficients were positive, SO_2 coefficients negative. RR estimates higher in the warmer season. RRs similar for in- and out-of hospital deaths.	1.9% (0.5, 3.4) per 50 $\mu g/m^3$ PM_{13} at 0 day lag.
Garcia-Aymerich et al. (2000). Barcelona, Spain. 1985-1989. Black Smoke no data distribution was reported).	Daily total (mean = 1.8/day), respiratory, and cardiovascular mortality counts of a cohort (9,987 people) with COPD or asthma were associated with black smoke (24-hr), SO_2 (24-hr and 1-hr max), NO_2 (24-hr and 1-hr max), O_3 (1-hr max), temperature, and relative humidity. Poisson regression models using APHEA protocol were used. The resulting RRs were compared with those of the general population.	Daily mortality in COPD patients was associated with all six pollution indices. This association was stronger than in the general population only for daily 1-hr max of SO_2, daily 1-hr max and daily means of NO_2. BS and daily means of SO_2 showed similar or weaker associations for COPD patients than for the general population.	Total mortality percent increase per 25 $\mu g/m^3$ increase in avg. of 0-3 day lags of BS: 2.76 (1.31, 4.23) in general population, and 1.14 (−4.4, 6.98) in the COPD cohort.
Rahlenbeck and Kahl (1996). East Berlin, 1981-1989. "SP" (beta attenuation, 97)	Total mortality (as well as deviations from long-wave cycles) was regressed on SP and SO_2, adjusting for day-of-week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 $\mu g/m^3$.	Both SP and SO_2 were significantly associated with total mortality with 2 day lag in single pollutant model. When both pollutants were included, their coefficients were reduced by 33% and 46% for SP and SO_2, respectively.	6.1% per 100 $\mu g/m^3$ "SP" at 2 day lag.
Rossi et al. (1999). Milan, Italy, 1980-1989 TSP ("PM_{13}" beta attenuation, 142)	Specific causes of death (respiratory, respiratory infections, COPD, circulatory, cardiac, heart failure, and myocardial infarction) were related to TSP, SO_2, and NO_2, adjusting for seasonal cycles, temperature, and humidity, using Poisson GAM model.	All three pollutants were associated with all cause mortality. Cause-specific analysis was conducted for TSP only. Respiratory infection and heart failure deaths were both associated with TSP on the concurrent day, whereas the associations for myocardial infarction and COPD deaths were found for the average of 3 to 4 day prior TSP.	3.3% (2.4, 4.3) per 100 $\mu g/m^3$ TSP at 0 day lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Sunyer et al. (2000). Barcelona, Spain. 1990-1995. BS means: 43.9 for case period, and 43.1 for control period.	Those who were over age 35 and sought emergency room services for COPD exacerbation between 1985 and 1989 and had died during 1990-1995 were included in analysis. Total, respiratory, and cardiovascular deaths were analyzed using a conditional logistic regression analysis with a case-crossover design, adjusting for temperature, relative humidity, and influenza epidemics. Bi-directional control period at 7 days was used. Average of the same and previous 2 days used for pollution exposure period. Data also stratified by potential effect modifiers (e.g., age, gender, severity of ER visits, number of ER visits, etc.).	BS levels were associated with all cause deaths. The association was stronger for respiratory causes. Older women, patients admitted to intensive care units, and patients with a higher rate of ER visits were at greater risk of deaths associated with BS.	Percent increase per 25 $\mu g/m^3$ increase in 3-day average BS: 14.2 (1.6, 28.4) for all causes; 9.7 (−10.2, 34.1) for cardiovascular deaths; 23.2 (3.0, 47.4) for respiratory deaths.
Tobias and Campbell (1999). Barcelona, Spain. 1991-1995. Black Smoke (BS) (no data distribution was reported).	Study examined the sensitivity of estimated total mortality effects of BS to different approaches to modeling influenza epidemics: (1) with a single dummy variable; (2) with three dummy variables; (3) using daily number of cases of influenza. Poisson regression used to model total daily mortality, adjusting for weather, long-term trend, and season, apparently following APHEA protocol.	Using the reported daily number of influenza cases resulted in a better fit (i.e., a lower AIC) than those using dummy variables. In the "better" model, the black smoke coefficient was about 10% smaller than those in the models with dummy influenza variables, but remained significant. Lags not reported.	Total mortality excess deaths per 25 $\mu g/m^3$ increase in BS: 1.37 (0.20, 2.56) for model using the daily case of influenza; 1.71 (0.53, 2.91) for model with three influenza dummy variables.
Alberdi Odriozola et al. (1998). Madrid, Spain, 1986-1992. "TSP" (beta attenuation, 47 for average of 2 stations)	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (1-day lag) and SO_2 (3-day lagged) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 $\mu g/m^3$ TSP at lag 1 day.
Díaz et al. (1999). Madrid, Spain. 1990-1992. TSP (no data distribution was reported).	Non-accidental, respiratory, and cardiovascular deaths (mean = 62.4, 6.3, and 23.8 per day, respectively). Auto-regressive Integrated Moving Average (ARIMA) models fit to both depend. and independ. variables first to remove auto-correlation and seasonality (i.e., pre-whitening"), followed by examining cross-correlation to find optimal lags. Multivariate OLS models thus included ARIMA components, seasonal cycles (sine/cosine), V-shaped temp., and optimal lags found for pollution and weather variables. TSP, SO_2, NO_2, and O_3 examined. Season-specific analyses also conducted.	TSP was significantly associated with non-accidental mortality at lag 0 for year around and winter, but with a 1-day lag in summer. A similar pattern was seen for circulatory deaths. For respiratory mortality, a significant association with TSP was found only in summer (0-day lag). SO_2, NOx, and NO_2 showed similar associations with non-accidental deaths at lag 0 day. O_3' associations with non-accidental mortality was U-shaped, with inconsistent lags (1, 4, and 10).	For non-accidental mortality, excess deaths was 7.4% (confidence bands not reported; $p < 0.05$) per 100 $\mu g/m^3$ TSP at 0 day lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Wichmann et al., (2000). Erfurt, Germany. 1995-1998. Number counts (NC) & mass concentrations (MC) of ultrafine particles in three size classes, 0.01 to 0.1 μm, and fine particles in three size classes from 0.1 to 2.5 μm diameter, using Spectrometryll Mobile Aerosol Spectrometry (MAS). MAS MC PM2.5-0.01 (mean 25.8, median 18.8, IQR 19.9). Filter measurements of PM_{10} (mean 38.2, median 31.0, IQR 27.7) and $PM_{2.5}$ (mean 26.3, median 20.2, IQR 18.5). MAS NC2.5-0.01 (mean 17,966 per cu.cm, median 14,769, IQR 13,269).	Total non-accidental, cardiovascular, and respiratory deaths (mean 4.88, 2.87, 1.08 per day, respectively) were related to particle mass concentration and number counts in each size class, and to mass concentrations of gaseous co-pollutants NO_2, CO, SO_2, using GAM regression models adjusted for temporal trends, day of week, weekly national influenza rates, temperature and relative humidity. Data were analyzed by season, age group, and cause of death separately. Single-day lags and polynomial distributed lag models (PDL) were used. Particle indices and pollutants were fitted using linear, log-transformed, and LOESS transformations. Two-pollutant models with a particle index and a gaseous pollutant were fitted. The "best" model as used by Wichmann et al. (2000) was that having the highest t-statistic, since other criteria such as log-likelihood for nested models and AIC for non-nested models could not be applied due to different numbers of observations in each model. There should be little difference between these approaches and resulting differences in results should be small in practice. Sensitivity analyses included stratifying data by season, winter year, age, cause of death, or transformation of the pollution variable (none, logarithmic, non-parametric smooth).	Loss of stat. power by using a small city with a small number of deaths was offset by advantage of having good exposure representation from single monitoring site. Since ultrafine particles can coagulate into larger aggregates in a few hours, ultrafine particle size and numbers can increase into the fine particle category, resulting in some ambiguity. Significant associations were found between mortality and ultrafine particle number concentration (NC), ultrafine particle mass concentration (MC), fine particle mass concentration, or SO_2 concentration. The correlation between MC0.01-2.5 and NC0.01-0.1 is only moderate, suggesting it may be possible to partially separate effects of ultrafine and fine particles. The most predictive single-day effects are either immediate (lag 0 or 1) or delayed (lag 4 or 5 days), but cumulative effects characterized by PDL are larger than single-day effects. The significance of SO_2 is robust, but hard to explain as a true causal factor since its concentrations are very low. Age is an important modifying factor, with larger effects at ages < 70 than $\geq$ 70 years. Respiratory mortality has a higher RR than cardio-vascular mortality. A large number of models were fitted, with some significant findings of association between mortality and particle mass or number indices.	Total mortality excess deaths: Filter PM_{10} (0-4 d lag) = 6.6 (0.7, 12.8) per 50 $\mu g/m^3$. Filter $PM_{2.5}$ (0-1 d) = 3.0 (−1.7, 7.9). MC for $PM_{0.01-2.5}$ 6.2% (1.4, 11.2) for all year; by season, Winter = 9.2% (3.0, 15.7) Spring = 5.2% (−2.0, 12.8) Summer = −4.7% (−18.7, 11.7) Fall = 9.7% (1.9, 18.1) For ultrafine PM, NC 0.01-0.1 (0-4 d lag): All Year = 8.2% (0.3, 16.9) Winter = 9.7% (0.3, 19.9) Spring = 10.5% (−1.4, 23.9) Summer = −13.9% (−29.8, 5.7) Fall = 12.0% (2.1, 22.7)
Latin America			
Cifuentes et al. (2000). Santiago, Chile. 1988-1996. $PM_{2.5}$ (64.0), and $PM_{10-2.5}$ (47.3).	Non-accidental total deaths (56.6 per day) were examined for associations with $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, SO_2, and NO_2. Data analyzed using GAM Poisson regression models, adjusting for temperature, seasonal cycles. Single and two pollutant models with lag days from 0 to 5, as well as the 2- to 5-day average concentrations evaluated.	Both PM size fractions associated with mortality, but different effects found for warmer and colder months. $PM_{2.5}$ and $PM_{10-2.5}$ both important in whole year, winter, and summer. In summer, $PM_{10-2.5}$ had largest effect size estimate. NO_2 and CO also associated with mortality, as was O_3 in warmer months. No consistent SO_2-mortality associations.	Percent excess total deaths per 25 $\mu g/m^3$ increase in the average of previous two days for the whole year: 1.8 (1.3, 2.4) for $PM_{2.5}$ and 2.3 (1.4, 3.2) for $PM_{(10-2.5)}$ in single pollutant models.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America (cont'd)			
Castillejos et al. (2000). Mexico City. 1992-1995. PM_{10} (44.6), $PM_{2.5}$ (27.4), and $PM_{10-2.5}$ (17.2).	Non-accidental total deaths, deaths for age 65 and over, and cause-specific (cardiac, respiratory, and the other remaining) deaths were examined for their associations with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, and NO_2. Data were analyzed using GAM Poisson regression models, adjusting for temperature (average of 1-3 day lags) and seasonal cycles. Individual pollution lag days from 0 to 5, and average concentrations of previous 5 days were considered.	All three particle size fractions were associated individually with mortality. The effect size estimate was largest for $PM_{10-2.5}$. The effect size estimate was stronger for respiratory causes than for total, cardiovascular, or other causes of death. The results were not sensitive to additions of O_3 and NO_2. In the model with simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$, the effect size for $PM_{10-2.5}$ remained about the same, but the effect size for $PM_{2.5}$ became negligible.	Total mortality percent increase estimates per increase for average of previous 5 days: 9.5 (5.0, 14.2) for 50 $\mu g/m^3$ PM_{10}; 3.7 (0, 7.6) for 25 $\mu g/m^3$ $PM_{2.5}$; and 10.5 (6.4, 14.8) for 25 $\mu g/m^3$ $PM_{(10-2.5)}$.
Borja-Aburto et al. (1998). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27)	Total, respiratory, cardiovascular, other deaths, and age-specific (age >= 65) deaths were related to $PM_{2.5}$, O_3, and NO_2, adjusting for 3-day lagged temperature and periodic cycles, using Poisson GAM model.	$PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 avg.; 1-5 avg., respectively). $PM_{2.5}$ associations were most consistently significant. SO_2 was available, but not analyzed because of its "low" levels.	For total excess deaths, 3.4% (0.4, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$ for both 0 and 4 d lags. For respiratory (4 d) = 6.4 (−2.6, 16.2); for CVD (4 d) = 5.6 (−0.1, 11.5)
Borja-Aburto et al. (1997). Mexico-City, 1990-1992. TSP (median: 204)	Total, respiratory, cardiovascular, and age-specific (age >= 65) deaths were related to O_3, TSP, and CO, adjusting for minimum temperature (temperature also fitted seasonal cycles) using Poisson models. The final models were estimated using the iteratively weighted and filtered least squares method to account for overdispersion and autocorrelation.	O_3, SO_2, and TSP were all associated with total mortality in separate models, but in multiple pollutant model, only TSP remained associated with mortality. CO association weak.	Total deaths: 6% (3.3, 8.3) per 100 $\mu g/m^3$ TSP at 0 d lag. CVD deaths: 5.2% (0.9, 9.9). Resp. deaths: 9.5% (1.3, 18.4).
Loomis et al. (1999). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27.4 $\mu g/m^3$)	Infant mortality (avg. ≈ 3/day) related to $PM_{2.5}$, O_3, and NO_2, adjusting for temperature and smoothed time, using Poisson GAM model.	Excess infant mortality associated with $PM_{2.5}$, NO_2, and O_3 in the same average/lags. NO_2 and O_3 associations less consistent in multi-pollutant models.	Infant mortality excess risk: 18.2% (6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$ at avg. 3-5 lag days.
Pereira et al. (1998). Sao Paulo, Brazil, 1991-1992. PM_{10} (beta-attenuation, 65)	Intrauterine mortality associations with PM_{10}, NO_2, SO_2, CO, and O_3 investigated using Poisson regression adjusting for season and weather. Ambient CO association with blood carboxyhemoglobin sampled from umbilical cords of non-smoking pregnant mothers studied in separate time period.	NO_2, SO_2, and CO were all individually significant predictor of the intrauterine mortality. NO_2 was most significant in multi-pollutant model. PM_{10} and O_3 were not significantly associated with the mortality. Ambient CO levels were associated with and carboxyhemoglobin of blood sampled from the umbilical cords.	Intrauterine mortality excess risk: 4.1% (−1.8, 10.4) per 50 $\mu g/m^3$ PM_{10} at 0 day lag.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Australia			
Morgan et al. (1998). Sydney, 1989-1993. Nephelometer (0.30 bscat/104m). Site-specific conversion: $PM_{2.5} \approx 9$; $PM_{10} \approx 18$	Total, cardiovascular, and respiratory deaths were related to PM (nephelometer), O_3, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation.	PM, O_3, and NO_2 all showed significant associations with total mortality in single pollutant models. In multiple pollutant models, the PM and O_3 effect estimates for total and cardiovascular deaths were marginally reduced, but the PM effect estimate for respiratory deaths was substantially reduced.	4.7% (1.6, 8.0) per 25 $\mu g/m^3$ estimated $PM_{2.5}$ or 50 $\mu g/m^3$ estimated PM_{10} at avg. of 0 and 1 day lags. (Note: converted from nephelometry data)
Simpson et al. (1997). Brisbane, 1987-1993. PM_{10} (27, not used in analysis). Nephelometer (0.26 bscat/104m, size range: 0.01-2 μm).	Total, cardiovascular, and respiratory deaths (also by age group) were related to PM (nephelometer), O_3, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE to adjust for autocorrelation. Season-specific (warm and cold) analyses were also conducted.	Same-day PM and O_3 were associated most significantly with total deaths. The O_3 effect size estimates for cardiovascular and respiratory deaths were consistently positive (though not significant), and larger in summer. PM's effect size estimates were comparable for warm and cold season for cardiovascular deaths, but larger in warm season for respiratory deaths. NO_2 and SO_2 were not associated with mortality.	3.4% (0.4, 6.4) per 25 $\mu g/m^3$ 1-h $PM_{2.5}$ increment at 0 d lag; and 7.8% (2.5, 13.2) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.
Asia			
Hong et al. (1999). Inchon, South Korea, 1995-1996 (20 months). PM_{10} mean = 71.2.	Non-accidental total deaths, cardiovascular, and respiratory deaths were examined for their associations with PM_{10}, O_3, SO_2, CO, and NO_2. Data were analyzed using GAM Poisson regression models, adjusting for temperature, relative humidity, and seasonal cycles. Individual pollution lag days from 0 to 5, as well as the average concentrations of previous 5 days were considered.	A greater association with mortality was seen with the 5-day moving average and the previous day's exposure than other lag/averaging time. In the models that included a 5-day moving average of one or multiple pollutants, PM_{10} was a significant predictor of total mortality, but gaseous pollutants were not significant. PM_{10} was also a significant predictor of cardiovascular and respiratory mortality.	Percent excess deaths (t-ratio) per 50 $\mu g/m^3$ increase in the 5-day moving average of PM_{10}: 4.1 (0.1, 8.2) for total deaths; 5.1 (0.1, 10.4) for cardiovascular deaths; 14.4 (−3.2, 35.2) for respiratory deaths.
Lee et al. (1999). Seoul and Ulsan, Korea, 1991-1995. TSP (beta attenuation, 93 for Seoul and 72 for Ulsan)	Total mortality series was examined for its association with TSP, SO_2, and O_3, in Poisson GEE (exchangeable correlation for days in the same year), adjusting for season, temperature, and humidity.	All the pollutants were significant predictors of mortality in single pollutant models. TSP was not significant in multiple pollutant models, but SO_2 and O_3 remained significant.	5.1% (3.1, 7.2) for Seoul, and -0.1% (-3.9, 3.9) for Ulsan, per 100$\mu g/m^3$ TSP at avg. of 0, 1, and 2 day lags.

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Lee and Schwartz (1999). Seoul, Korea. 1991-1995. TSP mean = $9_{2.5}$.	Total deaths were analyzed for their association with TSP, SO_2, and O_3. A conditional logistic regression analysis with a case-crossover design was conducted. Three-day moving average values (current and two past days) of TSP and SO_2, and 1-hr max O_3 were analyzed separately. The control periods are 7 and 14 days before and/or after the case period. Both unidirectional and bi-directional controls (7 or 7 and 14 days) were examined, resulting in six sets of control selection schemes. Other covariates included temperature and relative humidity.	Among the six control periods, the two unidirectional retrospective control schemes resulted in odds ratios less than 1; the two unidirectional prospective control schemes resulted in larger odds ratios (e.g., 1.4 for 50 ppb increase in SO_2); and bi-directional control schemes resulted in odds ratios between those for uni-directional schemes. SO_2 was more significantly associated with mortality than TSP.	OR for non-accidental mortality per 100 $\mu g/m^3$ increase in 3-day average TSP was 1.010 (0.988, 1.032).
Xu et al. (2000). Shenyang, China, 1992. TSP (430).	Total (non-accidental), CVD, COPD, cancer and other deaths examined for their associations with TSP and SO_2,using Poisson (GAM, and Markov approach to adjust for mortality serial dependence) models, adjusting for seasonal cycles, Sunday indicator, quintiles of temp. and humidity. Ave. pollution values of concurrent and 3 preceding days used.	Total deaths were associated with TSP and SO_2 in both single and two pollutant models. TSP was significantly associated with CVD deaths, but not with COPD. SO_2 significantly associated with COPD, but not with CVD deaths. Cancer deaths not associated with TSP or SO_2.	Percent total excess deaths per 100 $\mu g/m^3$ increase in 0-3 day ave. of TSP = 1.75 (0.65, 2.85); with SO_2 = 1.31 (0.14, 2.49) COPD TSP = 2.6 (−0.58, 5.89); with SO_2 = 0.76 (−2.46, 4.10). CVD TSP = 2.15 (0.56, 3.71); with SO_2 = 1.95 (1.19, 3.74). Cancer TSP = 0.87 (−1.14, 2.53); with SO_2 = 1.07 (−1.05, 3.23). Other deaths TSP = 3.52 (0.82, 6.30); with SO_2 = 2.40 (−0.51, 5.89).
Ostro et al. (1998). Bangkok, Thailand, 1992-1995 PM_{10} (beta attenuation, 65)	Total (non-accidental), cardiovascular, respiratory deaths examined for associations with PM_{10} (separate measurements showed ≈50% of PM_{10} was $PM_{2.5}$),using Poisson GAM model adjusting for seasonal cycles, day-of-week, temp., humidity.	All the mortality series were associated with PM_{10} at various lags. The effects appear across all age groups. No other pollutants were examined.	Total mortality excess risk: 5.1% (2.1, 8.3) per 50 $\mu g/m^3$ PM_{10} at 3 d lag (0 and 2 d lags also significant). CVD (3 d ave.) = 8.3 (3.1, 13.8) Resp. (3 d ave.) = 3.0 (−8.4, 15.9)

TABLE 6-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Cropper et al. (1997). Delhi, India, 1991-1994 TSP (375)	Total (by age group), respiratory and CVD deaths related to TSP, SO_2, and NOx, using GEE Poisson model (to control for autocorrelation), adjusting for seasonal cycles (trigonometric terms), temperature, and humidity. 70% deaths occur before age 65 (in U.S., 70% occur after age 65).	TSP was significantly associated with all mortality series except with the very young (age 0-4) and the "very old" (age >=65). The results were reported to be unaffected by addition of SO_2 to the model. The authors note that, because those who are affected are younger (than Western cities), more life-years are likely to be lost per person from air pollution impacts.	2.3% (significant at 0.05, but SE of estimate not reported) per 100 $\mu g/m^3$ TSP at 2 day lag.

As can be seen in Table 6-1, with a few exceptions, most all of the newly reported analyses continue to show statistically significant associations between short-term (24-h) PM exposures indexed by a variety of ambient PM measurements and increases in daily mortality in numerous U.S. and Canadian cities, as well as elsewhere around the world. Also, the effects estimates from the newly reported studies generally comport well with those derived from the earlier 1996 PM AQCD assessment, with the newly reported PM risk estimates generally falling within the range of ca. 1 to 8% increase in excess deaths per 50 $\mu g/m^3$ PM_{10} and ca. 2 to 6% increase per 25 $\mu g/m^3$ $PM_{2.5}$. Several newly available PM epidemiology studies which conducted time-series analyses in multiple cities are of particular interest, as discussed below.

6.2.2.3 New Multi-City Studies

The new multi-city studies are of particular interest here due to their evaluation of a wide range of PM exposures and large numbers of observations holding promise of providing more precise effects estimates then most smaller scale independent studies of single cities. Another major advantage of the multi-city studies, over meta-analyses for multiple "independent" studies, is the consistency in data handling and model specifications, which eliminates variation due to study design. Further, unlike regular meta-analysis, they clearly do not suffer from potential omission of negative studies due to "publication bias". Furthermore, geographic patterns of air pollution effects can be systematically evaluated in multiple-city analyses. Thus, the results from multi-city studies can provide especially valuable evidence regarding the consistency and/or heterogeneity, if any, of PM-health effects relationships across geographic locations. Also, many of the cities included in these multi-city studies were ones for which no time-series analyses had been previously reported.

6.2.2.3.1 U.S. Multi-City Studies

U.S. PM_{10} 20-Cities and 90-Cities NMMAPS Analyses

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-series analyses of PM_{10} effects on mortality during 1987-1994 in the 90 largest U.S. cities (Samet et al., 2000a,b), in the 20 largest U.S. cities in more detail (Dominici et al., 2000), and PM_{10} effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b). These NMMAPS analyses are marked by extremely sophisticated statistical approaches addressing

issues of measurement error biases, co-pollutant evaluations, regional spatial correlation, and synthesis of results from multiple cities by hierarchical Bayesian meta-regressions and meta-analyses. These analyses provide extensive new information of much importance in being among that most highly relevant to the setting of U.S. PM standards, because no other study has examined as many U.S. cities in such a consistent manner. NMMAPS used only one consistent PM index (PM_{10}) across all cities; death records were collected in a uniform manner; and demographic variables were uniformly addressed. Both the 20 and 90 cities analyses studies employ multi-stage models (see Table 6-1) in which heterogeneity in individual cities' coefficients in the first stage GAM Poisson models were evaluated in the second stage models with city or region specific explanatory variables.

In both the 20 and 90 cities studies, the combined estimates of PM_{10} coefficients were positively associated with mortality at all the lags examined (0, 1, and 2 day lags), although the 1-day lag PM_{10} resulted in the largest overall combined estimate. Figure 6-1 shows the estimated percent excess total deaths per 10 $\mu g/m^3$ PM_{10} at lag 1 day in the 90 largest cities, as well as (weighted average) combined estimates for U.S. geographic regions depicted in Figure 6-2. The majority of the coefficients were positive for the various cities listed along the left axis of Figure 6-1. See Appendix 6-A for names of cities designated by the abbreviations, e.g., seat = Seattle. The estimates for the individual cities were first made independently, without borrowing information from other cities. The cities were then grouped into the 7 regions seen in Figure 6-2 (based on characteristics of the ambient PM mix typical of each region, as delineated in the 1996 PM AQCD). The bolded segments represent the posterior means and 95% posterior intervals of the pooled regional effects under the more conservative prior A for the heterogeneity across both regions and cities within regions. The solid circles and squares denote, respectively, the overall regional means without and with borrowing information from other regions, ("overall 1" = the regional mean without other regions, "overall 2" = with information from other regions). The triangles and bolded segments at the bottom of Figure 6-1 display combined estimates of nationwide overall effects of PM_{10} for all cities overall, and for all cities minus those in the Northeast (overall-north).

Note that there appears to be some regional-specific variation in the overall combined estimates, shown as "overall 1" and "overall 2" for the two sets of modeling assumptions and specifications used in analyses combining data from all the cities in a given region. This can be

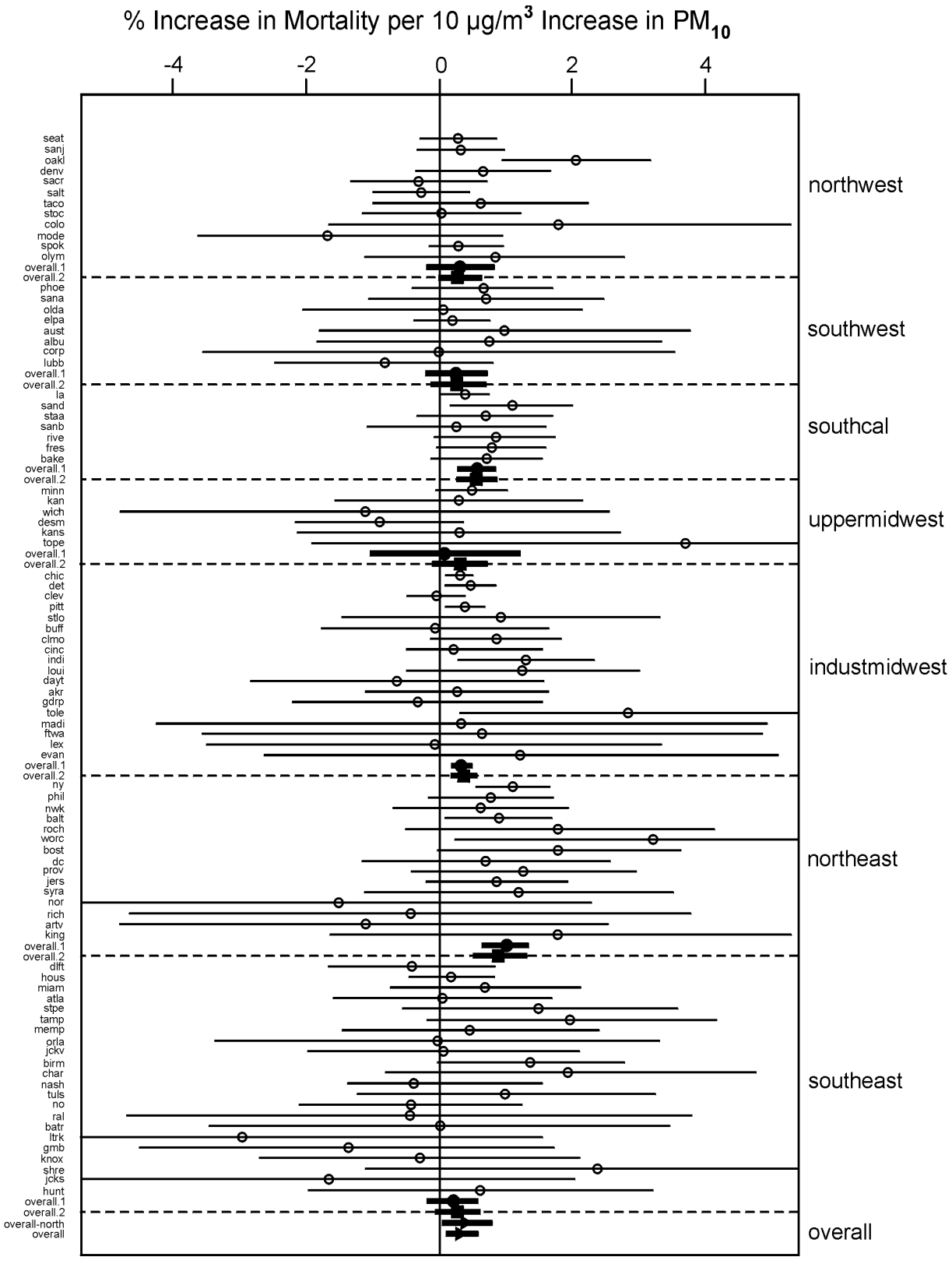

Figure 6-1. Estimated excess risks for PM mortality (1 day lag) for the 90 largest U.S. cities as shown in the original NMAPS report. From Samet et al. (2000a,b).

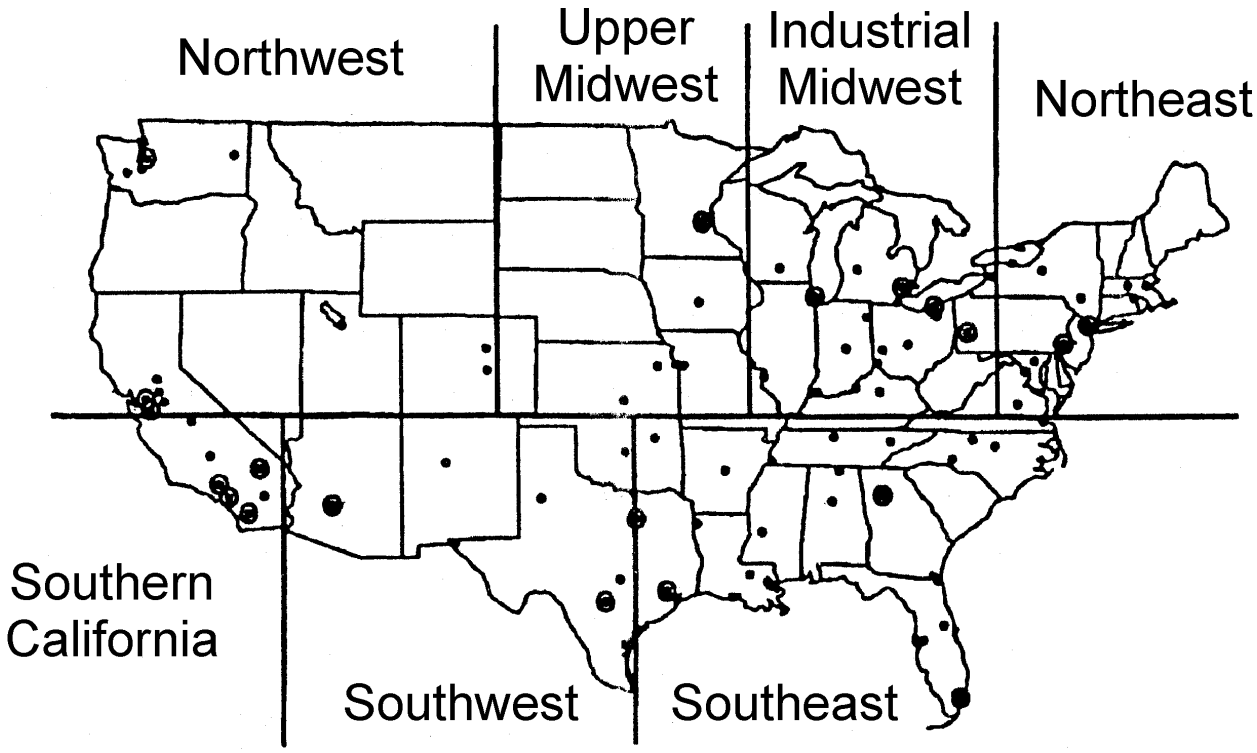

Figure 6-2. Map of the United States showing the 90 cities (the 20 cities are circled) and the seven regions considered in the NMMAPS geographic analyses. Regions: Northwestern; Southern California; Southwest; Upper Midwest; Industrial Midwest; Northeast; Southeast.

discerned more readily in Figure 6-3 (which depicts overall region-specific excess risk estimates for day 0 and 2 day lags, as well as for lag 1 day). For example, the coefficients for the Northeast are generally higher than for other regions (the Northeast combined estimate, 4.5% excess total deaths per 50 $\mu g/m^3$ increase in PM_{10}, was about twice that for the 90-cities overall). The overall national combined estimate (i.e., at lag 1 day, 2.3% excess total deaths per 50 $\mu g/m^3$ increase in PM_{10}) for the 90 cities is consistent with the range of estimates reported in the 1996 PM AQCD.

In the 90 cities study, the weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude mortality rate); (3) socio-demographic variables (% not graduating from high school and median household income); (4) urbanization (public transportation); (5) variables related to measurement error (median of all pair-wise correlations between monitors). Some of these variables were apparently correlated (e.g., mean PM_{10} and NO_2, household income and education) so that the

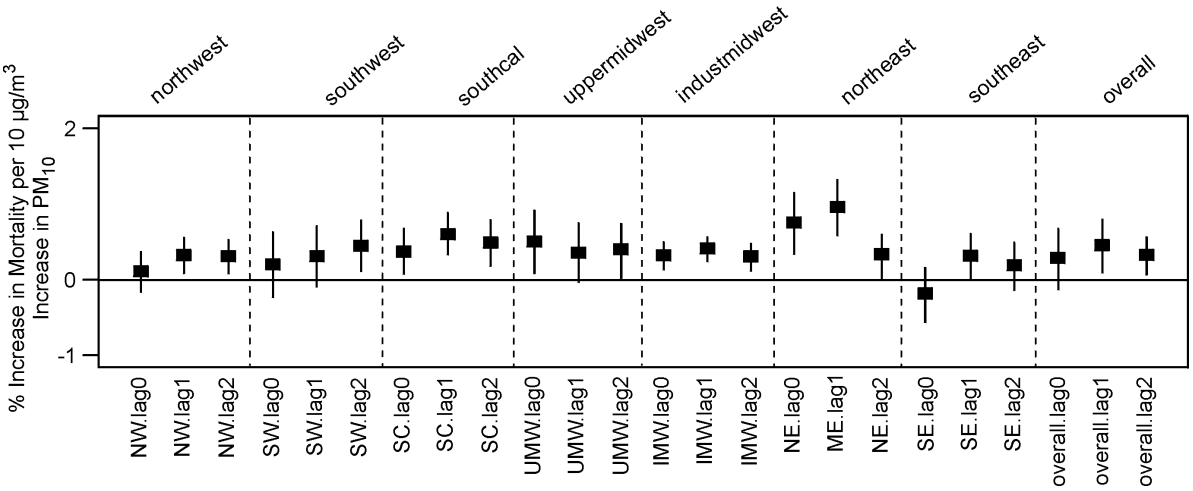

Figure 6-3. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-μg/m^3 increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 6-2.

sign of coefficients in the regression changed when correlated variables were included in the model. Thus, while some of the county specific variables were statistically significant (e.g., mean NO_2 levels), interpreting the role of these county specific variables may require caution. Regarding the heterogeneity of PM_{10} coefficients, the investigators concluded that they "did not identify any factor or factors that might explain these differences".

Another important finding from Samet and coworkers' analyses was the weak influence of gaseous co-pollutants on the PM_{10} effect size estimates. In both the 20 and 90 cities analyses, PM_{10} coefficients changed little when O_3 was added to regression models. Additions of a third pollutant (i.e., PM_{10} + O_3 + another gaseous pollutant) did reduce PM_{10} coefficients somewhat (e.g., from $\approx$2.2 to $\approx$1.7 per 50 μg/m^3 PM_{10} at lag 1 day in the combined 90 cities analysis), but the PM_{10} coefficients remained statistically significant at $p < 0.05$. The gaseous pollutants themselves in single-, two-, and three-pollutant models were less consistently associated with mortality than PM_{10}. O_3 was not associated with mortality using year-round data; but, in season specific analyses, it was associated with mortality negatively in winter and positively in summer. SO_2, NO_2, and CO were weakly associated with mortality, but additions of PM_{10} and other gaseous pollutants did not always reduce their coefficients, possibly suggesting their independent effects. As noted in Section 6.1, CO and NO_2 from motor vehicles are likely confounders of

$PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the coarse particle fraction. The investigators concluded that the PM_{10} effect on mortality "did not appear to be affected by other pollutants in the model".

U.S. 10-Cities Studies

In another set of multi-city analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000), Zanobetti and Schwartz (2000), and Braga et al. (2000) analyzed 1987-1995 air pollution and mortality data from ten U.S. cities (New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of these cities was based on the availability of daily (or near daily) PM_{10} data. The main results of the study were presented in the Schwartz (2000a) paper and the other studies noted above focused on each of several specific issues, including: potential confounding, effect modification, distributed lag, and threshold. In this section, the results for the Schwartz (2000a) main analyses and that of Braga et al. (2000) on confounding are discussed, and results for analyses of other specific issues are discussed later in appropriate sections. For each of the 10 cities, daily total (non-accidental) mortality was fitted using a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time. Deaths stratified by location of death (in or outside hospital) were also examined. The data were also analyzed by season (November through April as heating season). In the second stage, the PM_{10} coefficients were modeled as a function of city-dependent covariates including co-pollutant to PM_{10} regression coefficient (to test potential confounding), education, unemployment rate, poverty level, and percent non-white. Threshold effects were also examined. The inverse variance weighted averages of the ten cities' estimates were used to combine results. PM_{10} was significantly associated with total deaths, and the effect size estimates were the same in summer and winter. Adjusting for other pollutants did not substantially change the PM_{10} effect size estimates. The socioeconomic variables did not modify the estimates. The effect size estimates for the deaths outside hospital were substantially greater than for inside hospital. The combined percent excess death estimate for total mortality was 3.4% (95% CI: 2.7-4.1) per 50 $\mu g/m^3$ increase in PM_{10}, but was larger for days with $PM_{10} < 50$ $\mu g/m^3$.

Braga et al. (2000) evaluated potential confounding of the reported PM-mortality associations by effects of respiratory epidemics, using data from a subset of 5 of the 10 cities

evaluated by Schwartz (2000a). When adjustments were made for respiratory epidemics, small decreases in PM_{10} effects were seen in the cities evaluated. The overall estimated percent excess deaths per 50 $\mu g/m^3$ PM_{10} for the five cities was 4.3% (CI 3.0, 5.6) without control for respiratory epidemics, but slightly decreased to 4.0% (CI 2.6, 5.3) with control for epidemics.

U.S. 3-Cities Study

Moolgavkar (2000a) evaluated associations between short-term measures of major air pollutants and daily deaths in three large U.S. metropolitan areas (Cook Co., IL, encompassing Chicago; Los Angeles Co., CA; and Maricopa Co., AZ, encompassing Phoenix) during a 9-year period (1987-1995). Generalized additive models (GAM) were used in a standard manner to conduct time-series Poisson regression analyses independently for each of the three cities (allowing comparison of results across them not due to methodological differences), but no combined analyses were attempted to derive overall PM effects estimates. Total non-accidental deaths and cause-specific deaths from cardiovascular disease (CVD), cerebrovascular disease (CrD), and chronic obstructive lung disease (COPD), and associated conditions were analyzed in relation to 24-h readings for PM, O_3, CO, NO_2, SO_2 averaged over all monitors in a given county. Daily readings were available for each of the gaseous pollutants in all three countries, as were PM_{10} values for Cook County. However, PM_{10} values were only available every sixth day in Maricopa and Los Angeles Counties; as were $PM_{2.5}$ values in Los Angeles Co. PM values were highest in the winter and fall in Los Angeles Co., in the fall in Maricopa Co., and in summer in Cook Co., whereas the gases (except for O_3) were highest in winter in all three counties (O_3 was highest in summer in all three). The PM indices were moderately correlated ($r = 0.30$ to 0.73) with CO, NO_2, and SO_2 in Cook Co. and Los Angeles Co., but poorly correlated ($r < 0.22$) with those gases in Maricopa Co. Ozone was very poorly ($r < 0.20$) or negatively correlated with PM or the other gases in each location (except for Cook Co., $r = 0.36$ for O_3 vs PM_{10}). Total non-accidental, CVD, and COPD deaths were all highest during winter in all three counties, but CrD deaths were relatively constant from season to season (no season-specific analyses reported).

Controlling for temperature and relative humidity effects in separate analyses for each mortality endpoint for each of the three countries, varying patterns of results were found from one location to another, as noted in Table 6-1. In general, although PM_{10} in each of the three counties (and $PM_{2.5}$ in Los Angeles) and each of the gaseous pollutants (except O_3) were all

statistically significantly associated with total non-accidental mortality at one or more lag times (0 to 5 days) in single pollutant models, the PM effect estimates tended to be reduced and non-significant in many of the multi-pollutant (PM plus one other gas or PM plus all others) analyses. In contrast, effect estimates for several of the gases (CO, SO_2, and NO_2) tended to be more robust than those for PM in multi-pollutant models, with their estimates remaining statistically significant (although usually somewhat attenuated) at one or more lag times when included in multi-pollutant models with PM_{10} or $PM_{2.5}$. Similarly, a somewhat analogous varying pattern of results was observed for the cause-specific mortality analyses (discussed further below in Section 6.2.2.5). That is, although PM_{10} or $PM_{2.5}$ were statistically significantly related to CVD and COPD-related (and to CrD only in Maricopa Co., lag 5) mortality in single pollutant models, their coefficients were typically markedly reduced and became non-significant in multi-pollutant analyses with one or more of the gases included in the model. Moolgavkar (2000a) concluded that, while direct effects of individual components of air pollution cannot be ruled out, individual components can best be thought of as indices of the overall air pollution mix; and he noted considerable heterogeneity of air pollution effects across the three geographic areas evaluated.

6.2.2.3.2 Canadian Multi-City Study Analyses

Urban Air Pollution Mix and Daily Mortality in 11 Canadian Cities

The number of daily deaths for non-accidental causes during 1980-1991 were obtained for 11 Canadian cities and linked to concentrations of ambient gaseous air pollutants using relative risk regression models for longitudinal count data (Burnett et al., 1998a). The GAM Poisson models used evaluated daily mortality versus O_3, NO_2, SO_2 and CO (including adjustments for seasonal cycles, day-of-week effects, and weather effects), but no PM indices were included in their analyses because daily PM measurements were not available. However, data were available for fine and coarse PM mass from dichot samples, and sulfates, on variable schedules somewhat more frequently than once per six days in Montreal, Toronto, and Windsor (with smaller numbers in the other cities). This allowed an ecologic comparisons of gaseous pollutant risks by mean fine particle concentration (their Figure 1). These comparisons suggested a weak negative confounding of NO_2 and SO_2 effects with fine particles, and a weak positive confounding of particle effects with O_3.

Eight Largest Canadian Cities Study

Burnett et al. (2000) analyzed various PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, COH, and 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO) for association with total mortality in the 8 largest Canadian cities: Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This study differs from (Burnett et al., 1998a), including fewer cities but more recent years of data (1986-1996 vs. 1980-1991) and detailed analyses of particle mass components by size and elemental composition. Each city's mortality, pollution, and weather variables were separately filtered for seasonal trends and day-of-week patterns. The residual series from all cities were then combined and analyzed in a GAM Poisson model. The weather model was selected from spline-smoothed functions of temperature, relative humidity, and maximum change in barometric pressure within a day and with 0 and 1 day lags, using forward stepwise procedures. Pollution effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-pollutant models, principal components were also used as predictors in the regression models.

Ozone was weakly correlated with other pollutants, and other pollutants were "moderately" correlated with each other (the highest was $r = 0.65$ for NO_2 and CO). The strongest association with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger predictor of mortality than $PM_{10-2.5}$. The gaseous pollutant effects estimates were generally reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10-2.5}$, where strength of prediction is measured by the t value or statistical significance of the excess risk. In addition to the results implicating the fine particle fraction ($PM_{2.5}$) most clearly, other findings on fine particle components were also of interest. Specifically, sulfate, Fe, Ni, and Zn were most strongly associated with mortality. The total effect of these four components was greater than that for $PM_{2.5}$ mass alone, the authors suggesting that the characteristics of the complex chemical mixture in the fine fraction may be a better predictor of mortality than the mass index alone.

6.2.2.3.3 European Multi-City APHEA Study Analyses

The Air Pollution and Health: a European Approach (APHEA) project is a multi-center study of short-term effects of air pollution on mortality and hospital admissions during the period 1975-1992, using data from 15 European cities with a wide range of geographic, climatic, sociodemographic, and air quality patterns. The obvious strength of this approach is to be able to

evaluate potential effect modifiers in a consistent manner. It should be noted that PM indices measured in those cities were mostly black smoke (BS), except for: Paris, Lyon (PM_{13}); Bratislava, Cologne, and Milan (TSP); and Barcelnoa (BS and TSP). As discussed below, there have been three papers published that presented either a meta-analysis or pooled summary estimates of these multi-city mortality results: (1) Katsouyanni et al. (1997)-SO_2 and PM results from 12 cities; (2) Touloumi et al. (1997)-ambient oxidants (O_3 and NO_2) results from six cities; and (3) Zmirou et al. (1998)- cause-specific mortality results from 10 cities (see Section 6.2.2.5).

APHEA Sulfur Dioxide and Particulate Matter Results for 12 Cities

The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens, Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyons, Milan, Paris, Poznan, and Wroclaw. In the western European cities, an increase of 50 $\mu g/m^3$ in SO_2 or BS was associated with a 3% (95% CI = 2.0, 4.0) increase in daily mortality; and the corresponding figure was 2% (95% CI = 1.0, 3.0) for estimated PM_{10} (they used conversion: PM_{10} = TSP*0.55). In the central/eastern European cities, the increase in mortality associated with a 50 $\mu g/m^3$ change was 0.8% (CI = −0.1, 2.4) for SO_2 and 0.6% (CI = 0.1, 1.1) per 50 $\mu g/m^3$ change in BS. Estimates of cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to those for one day effects. The effects of both pollutants (BS, SO_2) were stronger during the summer and were mutually independent. Regarding the contrast between the western and central/eastern Europe results, the authors speculated that this could be due to: difference in exposure representativeness; difference in pollution toxicity or mix; difference in proportion of sensitive sub-population; and model fit for seasonal control. Bobak and Roberts (1997) commented that the heterogeneity between central/eastern and western Europe could be due to the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted that, having examined the source of heterogeneity, other factors could apparently explain the difference in estimates as well as or better than temperature.

APHEA Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities

Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents), and (b) impacts on effect estimates for NO_2 and O_3 of including a PM measure (BS) in

multi-pollutant models. Six cities in central and western Europe provided data on daily deaths and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were fitted. Significant positive associations were found between daily deaths and both NO_2 and O_3. Increases of 50 $\mu g/m^3$ in NO_2 (1-hour maximum) or O_3 (1-hour maximum) were associated with a 1.3% (95% CI 0.9-1.8) and 2.9% (95% CI 1.0-4.9) increase in the daily mortality, respectively. There was a tendency for larger effects of NO_2 in cities with higher levels of BS: when BS was included in the model, the pooled estimate for the O_3 effect was only slightly reduced, but the coefficient for NO_2 was reduced by half (but remained significant). The authors speculated that the short-term effects of NO_2 on mortality might be confounded by other vehicle-derived pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study reports only relative risk levels for NO_2 and O_3 (but not for BS), it illustrates the importance of confounding of NO_2 and PM effects and the relative limited confounding of O_3 and PM effects.

6.2.2.3.4 Comparison of Effects Estimates from Multi-City Studies

In summary, based on pooled analyses of data combined across multiple cities, the percent excess (total, non-accidental) deaths estimated per 50 $\mu g/m^3$ increase in PM_{10} in the above multi-city studies were: (1) 2.3% in the 90 largest U.S. cities (4.5% in the Northeast region); (2) 3.4% in 10 U.S. cities; (3) 3.5% in the 8 largest Canadian cities; and (4) 2.0% in western European cities (using PM_{10} = TSP*0.55). These combined estimates are all consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD.

6.2.2.4 The Role of Particulate Matter Components

Delineation of the roles of specific ambient PM components in contributing to associations between short-term PM exposures and mortality requires evaluation of several factors, e.g., size, chemical composition, surface characteristics, and presence of gaseous co-pollutants. While possible combinations of interactions among these factors can in theory be limitless, the actual data tend to cover definable ranges of aerosol characteristics and co-pollutant environments due to typical source characteristics (e.g., fine particles tend to be combustion products in most cities). Newly available studies conducted in the last few years have begun to provide more extensive information on the issue of PM component roles; their results are discussed below in

relation to three topics: (1) PM particle size (e.g., $PM_{2.5}$ vs. $PM_{10-2.5}$); (2) chemical components; and (3) source oriented evaluations.

6.2.2.4.1 Particulate Matter Particle Size Evaluations

Numerous new studies published since the 1996 PM AQCD substantiate associations between $PM_{2.5}$ and increased total mortality. Consistent with the 1996 PM AQCD findings, effect size estimates from the new studies generally fall within the range of 2 to 6% excess total mortality per 25 $\mu g/m^3$ $PM_{2.5}$, with many being statistically significant at $p<0.05$.

With regard to the relative importance of fine and coarse particles, at the time of the 1996 PM AQCD, there was only one acute mortality study (Schwartz et al., 1996a), in which this issue was examined. That study suggested that fine particles, but not coarse particles, were associated with daily mortality. A recent study (Klemm and Mason 2000) to reconstruct the data and to replicate the analyses essentially reproduced the original investigators' results. Since the 1996 PM AQCD, several new studies used size-fractionated PM data to investigate the relative importance of fine ($PM_{2.5}$) vs. coarse ($PM_{10-2.5}$) particles.

In Table 6-2, synopses of these studies with regard to the relative importance of the two size fractions, as well as some characteristics of the data, are provided. The average levels of $PM_{2.5}$ ranged from about 13 to 20 $\mu g/m^3$ in the U.S. cities, but much higher average levels were measured in Mexico City (27.4 $\mu g/m^3$) and Santiago, Chile (64.0 $\mu g/m^3$). As can be seen in Table 6-2, in the northeastern U.S. cities (Pittsburgh, Philadelphia, and Detroit) and Atlanta, GA, there was more $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average, whereas in the western U.S. (Phoenix, AZ; Coachella Valley, CA; Santa Clara County, CA) the average $PM_{10-2.5}$ levels were higher than $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 6-2 use much the same data set, with fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal differences in PM component levels should also be noted. For example, in Santa Clara County and in Santiago, Chile, the winter $PM_{2.5}$ levels averaged twice those during summer. The temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$ ranged between 0.30 and 0.65. Such differences in ambient PM mix characteristics from season to season or from location to location complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

To facilitate a quantitative overview of the effect size estimates and their corresponding uncertainties from these studies, the percent excess risks are plotted in Figure 6-4. These

TABLE 6-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ VERSUS $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10-2.5}$.	Results regarding relative importance of $PM_{2.5}$ vs. $PM_{10-2.5}$ and comments.
Fairley (1999). Santa Clara County, CA	$PM_{2.5}$ mean = 13; $PM_{2.5}/PM_{10}$ = 0.38; r = 0.51.	Of the various pollutants including PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, COH, CO, NO_2, and O_3, strongest associations were found for ammonium nitrate and $PM_{2.5}$. $PM_{2.5}$ was significantly associated with mortality, but $PM_{10-2.5}$ was not, separately and together in the model. Sulfate was a significant predictor of mortality in single pollutant model, but not when $PM_{2.5}$ was included simultaneously. Winter $PM_{2.5}$ level is more than twice that in summer.
Ostro et al. (2000). Coachella Valley, CA	$PM_{2.5}$ (Palm Springs and Indio, respectively) mean = 12.7, 16.8; $PM_{2.5}/PM_{10}$ = 0.43, 0.35; r = 0.46, 0.28.	Total mortality was more significantly associated with $PM_{2.5}$ than with $PM_{10-2.5}$. Cardiovascular mortality was associated with $PM_{10-2.5}$ more significantly than with $PM_{2.5}$, but their effect size estimates per IQR were similar.
Clyde et al. (2000). Phoenix, AZ	$PM_{2.5}$ mean = 13.8; $PM_{2.5}/PM_{10}$ = 0.30; r = 0.65.	Using Bayesian Model Averaging that incorporates model selection uncertainty, with 29 covariates (lags 0- to 3-day), effects of coarse particles (most consistent at lag 1 day) were found to be stronger than that for fine particles. The association was for mortality confined to the region where fine particles ($PM_{2.5}$) are expected to be uniform.
Mar et al. (2000). Phoenix, AZ 1995-1997.	$PM_{2.5}$ (TEOM) mean = 13; $PM_{2.5}/PM_{10}$ = 0.28; r = 0.42.	Total mortality was weakly ($p < 0.10$) associated with $PM_{10-2.5}$. It was less strongly ($p > 0.10$) associated with $PM_{2.5}$. Cardiovascular mortality was both significantly associated with $PM_{2.5}$ (lags 1, 3, 4) and $PM_{10-2.5}$ (lag 0), with similar effect size estimates.
Smith et al. (2000). Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, a statistically significant mortality association found with $PM_{10-2.5}$, but not with $PM_{2.5}$. In models allowing for a threshold, evidence of a threshold for $PM_{2.5}$ (in the range of 20-25 $\mu g/m^3$) suggested, but not for $PM_{10-2.5}$. Seasonal interaction in the $PM_{10-2.5}$ effect also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10-2.5}$ is lowest.
Lippmann et al. (2000). Detroit, MI 1992-1994.	$PM_{2.5}$ mean=18; $PM_{2.5}/PM_{10}$ =0.58; r = 0.42.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were positively associated with mortality outcomes to a similar extent. Simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$ also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a). Philadelphia, PA 1992-1995.	$PM_{2.5}$ mean=17.3; $PM_{2.5}/PM_{10}$ =0.72.	The authors conclude that no systematic differences were seen according to particle size or chemistry. However, when $PM_{2.5}$ and $PM_{10-2.5}$ were compared, $PM_{2.5}$ (at lag 1 or average of lag 0 and 1) was more significantly (with larger attributable risk estimates) associated with cardiovascular mortality than $PM_{10-2.5}$.

TABLE 6-2 (cont'd). SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ VS. $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10-2.5}$.	Results regarding relative importance of $PM_{2.5}$ vs. $PM_{10-2.5}$ and comments.
Klemm and Mason (2000). Atlanta, GA	$PM_{2.5}$ mean = 19.9; $PM_{2.5}/PM_{10}$ =0.65.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.
Chock et al. (2000). Pittsburgh, PA	Data distribution not reported. $PM_{2.5}/PM_{10} \approx$ 0.67.	Seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and small size of dataset stratified by age group and season limit confidence in results finding no consistently significant associations for any size fraction.
Burnett et al. (2000) 8 Canadian cities 1986-1996	$PM_{2.5}$ mean=13.3; $PM_{2.5}/PM_{10}$ =0.51; r = 0.37.	$PM_{2.5}$ was a stronger predictor of mortality than $PM_{10-2.5}$. For chemical species, sulfate ion, nickel, and zinc from the fine fraction were most strongly associated with mortality.
Castillejos et al. (2000). Mexico City. 1992-1995	$PM_{2.5}$ mean=27.4; $PM_{2.5}/PM_{10}$ =0.61; r = 0.52.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were associated individually with mortality, but the $PM_{10-2.5}$ effect size was larger and more significant. When both were included in the model, the effect size of $PM_{10-2.5}$ remained the same but that of $PM_{2.5}$ was virtually eliminated.
Cifuentes et al. (2000). Santiago, Chile 1988-1996.	$PM_{2.5}$ mean=64.0; $PM_{2.5}/PM_{10}$ =0.58; r = 0.52.	Results were different for warmer and colder months. $PM_{2.5}$ was more important than $PM_{10-2.5}$ in the whole year and in winter, but not in summer. The mean of $PM_{2.5}$ was more than twice higher in winter (82.4 $\mu g/m^3$) than in summer (32.8), whereas the mean of $PM_{10-2.5}$ was more comparable for winter (49.9 $\mu g/m^3$) and for summer (42.9).

excluded the Clyde et al. study, in which the model specification did not obtain RRs for $PM_{2.5}$ and $PM_{10-2.5}$ separately, and the Smith et al. study, which did not present linear term RRs for $PM_{2.5}$ and $PM_{10-2.5}$. Note that, in most of the original studies, the RRs were computed for comparable distributional features (e.g., inter quartile range, mean, 5^{th}-to-95^{th} percentile, etc.). However, the increments derived and their absolute values varied across studies; and therefore, the RRs used in deriving the excess risk estimates delineated in Figure 6-4 were re-computed for consistent increments of 25 $\mu g/m^3$ for both $PM_{2.5}$ and $PM_{10-2.5}$. Note also that re-computing the RRs per 25 $\mu g/m^3$ in some cases changed the relative effect size between $PM_{2.5}$ and $PM_{10-2.5}$, but it did not affect the relative significance.

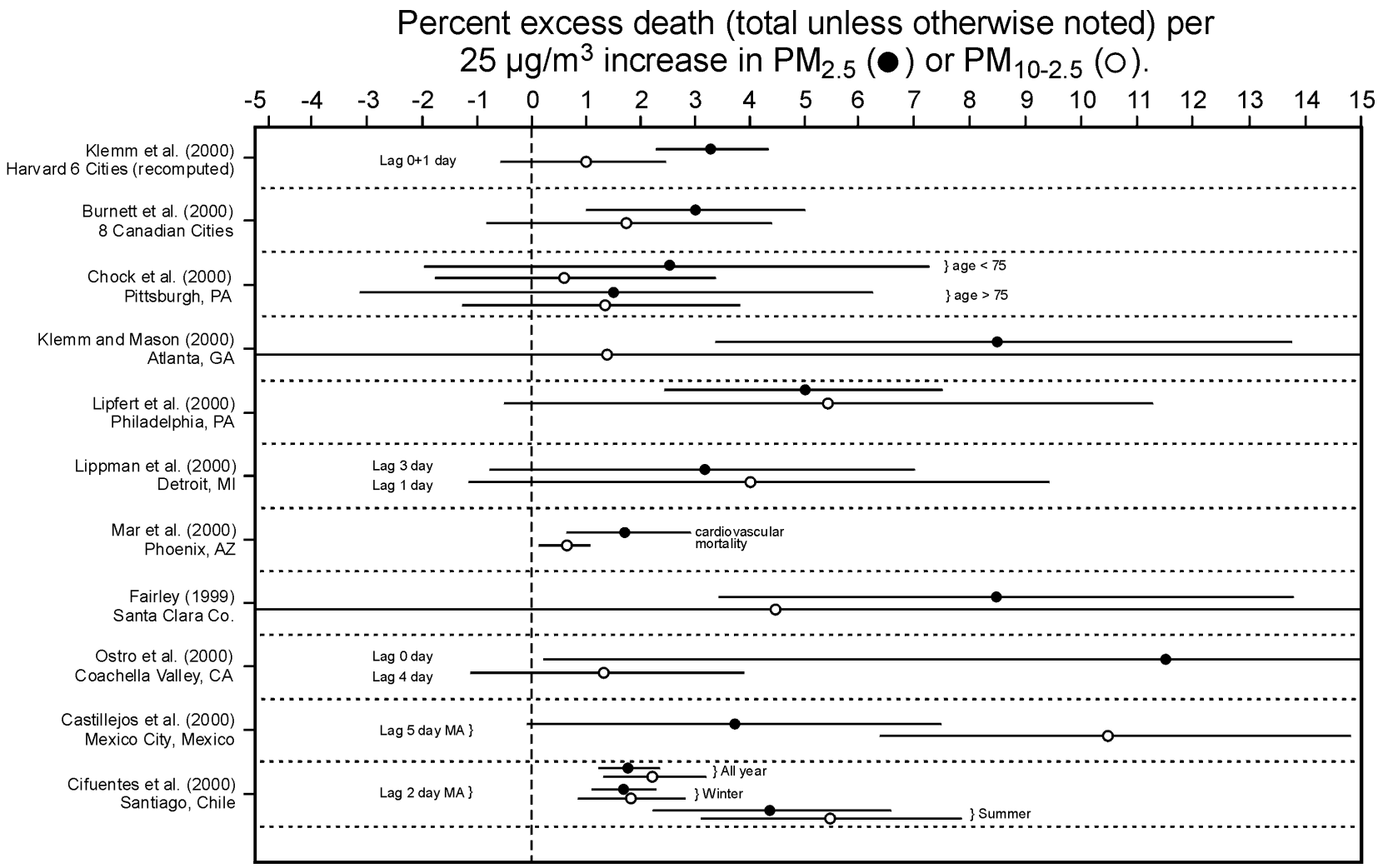

Figure 6-4. Percent excess risks estimated per 25 μg/m^3 increase in $PM_{2.5}$ or $PM_{10\text{-}2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10\text{-}2.5}$ data for multiple years. All lags = 1 day, unless indicated otherwise.

All of the studies found positive associations between both the fine and coarse PM indices and increased mortality risk, with most for $PM_{2.5}$ and a few for $PM_{10-2.5}$ being statistically significant (at $p < 0.05$). Unfortunately, most of the studies did not have large enough sample sizes to separate out what often appear to be relatively small differences in effect size estimates; but several do show statistical distinctly larger and significant mortality associations with $PM_{2.5}$ than for non-significant $PM_{10-2.5}$ effects. For example, the Klemm et al. (2000) recomputation of the Harvard Six Cities time-series study reconfirmed the original Schwartz et al. (1996a) finding of $PM_{2.5}$ being significantly associated (at $p < 0.05$) with excess mortality, whereas $PM_{10-2.5}$ was not. Similar results were obtained by the other multi-city study, i.e., the 8 largest Canadian cities study by Burnett et al. (2000), and by the Atlanta (Klemm et al. 2000), Santa Clara (Fairley et al., 1999), and the Coachella Valley (Ostra et al., 2000) studies. There were two studies in which the importance of $PM_{2.5}$ and $PM_{10-2.5}$ were considered to be similar or, at least, not distinguishable: Philadelphia, PA (Lipfert et al., 2000a) and Detroit, MI (Lippmann et al., 2000). The three Phoenix studies obtained "mixed" results, in that the Smith et al. (2000) and Clyde et al. (2000) analyses found $PM_{10-2.5}$ to appear to be more important in explaining mortality than $PM_{2.5}$ but Mar et al. found both to be significant, as depicted in Figure 6-4. Also, the Mexico City analysis by Castillejos et al. (2000) implicated $PM_{10-2.5}$ as the apparent more important fraction of PM_{10}. However, the Santiago, Chile study (Cifuentes et al., 2000) found significant associations with both fine and coarse fractions and interesting seasonal differences, as well. In Chock et al.'s (2000) analysis of Pittsburgh, PA data, the authors emphasized the lack of significant PM associations; and no specific comments were made regarding the relative importance of $PM_{2.5}$ vs. $PM_{10-2.5}$.

The Canadian 8-city study (Burnett et al., 2000) is noteworthy for a variety of reasons, including the use of elemental composition and principal components analyses to provide additional information about the relative importance of fine and coarse particles. The $PM_{2.5}$ effect on mortality is greater than the $PM_{10-2.5}$ effect for all gaseous-pollutant models in Table 5 of Burnett et al. (2000) and in the principal component model 1 in their Table 8, where both PM size fractions and the four gaseous co-pollutants are used simultaneously. PM component models from this study are discussed further below, in Section 6.2.2.4.2.

The Lippmann et al. (2000) results for Detroit are also noteworthy in that additional PM indices were evaluated besides those depicted in Figure 6-4 and the overall results obtained may

be helpful in comparing fine- versus coarse-mode PM effects. In analyses of 1985 to 1990 data, PM-mortality relative risks and their statistical significance were generally in descending order: PM_{10}, TSP-$SO_4^=$, and TSP-PM_{10}. For the 1992-1994 period, relative risks for equivalent distributional increment (e.g., IQR) were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for both mortality and hospital admissions categories; and $SO_4^=$ was more strongly associated with most outcomes than H^+. Consideration of the overall pattern of results led the authors to state that the mass of smaller size index could explain a substantial portion of the variation in the larger size indices. In these data, on average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some days) and PM_{10} for 66% of TSP mass. Also, the temporal correlation between TSP and $PM_{2.5}$ was r = 0.63, and for $PM_{2.5}$ vs. PM_{10} r = 0.90, suggesting that much of the apparent larger particle effects may well be mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger associations for sulfates than H^+, suggestive of non-acid fine particle effects, must be caveated by noting the very low H^+ levels present (often circa non-detection limit).

Three research groups have examined the same Phoenix, AZ data set using different methods. While these groups used somewhat different approaches, there is some consistency among their results in that $PM_{10-2.5}$ appeared to emerge as possibly the more important predictor of mortality versus $PM_{2.5}$. In the Clyde et al. (2000) analysis, PM-mortality associations were found only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the association was with $PM_{10-2.5}$, not $PM_{2.5}$. Based on the Bayes Information Criterion, the highly ranked models consistently included 1-day lagged $PM_{10-2.5}$. In the Mar et al. (2000) analysis, total mortality was significantly associated with CO and NO_2 and weakly ($p < 0.1$) associated with PM_{10} and $PM_{10-2.5}$ (and $PM_{2.5}$ was more weakly associated), although cardiovascular mortality was significantly associated with both $PM_{2.5}$ and $PM_{10-2.5}$ at $p<0.05$. Smith et al.'s (2000) analyses found that, based on a linear PM effect, $PM_{10-2.5}$ was significantly associated with total mortality, but $PM_{2.5}$ was not. The $PM_{2.5}$ in Phoenix is mostly generated from motor vehicles, whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles from natural (wind blown dust) and anthropogenic (construction and road dust) processes, and (b) organic particles from natural biogenic processes (endotoxin and molds) and anthropogenic (sewage aeration) processes. Thus, the associations with $PM_{10-2.5}$ are not necessarily indicative of crustal particle effects.

The Castillejos et al. (2000) and Cifuentes et al. (2000) analyses also appear to implicate $PM_{10-2.5}$, as well as $PM_{2.5}$, as importantly contributing to mortality in two non-U.S. locations, Mexico City and Santiago, Chile. The latter study also suggests possible seasonal differences in Santiago, the PM effects in summer being more than double those in winter at that South American location.

Crustal Particle Effects

Since the 1996 PM AQCD, several studies have yielded interesting new information concerning possible roles of crustal wind-blown particles or crustal particles within the fine particle fraction (i.e., $PM_{2.5}$) in contributing to observed PM-mortality effects.

Schwartz et al. (1999), for example, investigated the association of coarse particle concentrations with non-accidental deaths in Spokane, Washington, where dust storms elevate coarse particle concentrations. During the 1990-1997 period, 17 dust storm days were identified. The PM_{10} levels during those storms averaged 263 $\mu g/m^3$, compared to 39 $\mu g/m^3$ for the entire period. The coarse particle domination of PM_{10} data on those dust storm days was confirmed by a separate measurement of PM_{10} and PM_1 during a dust storm in August, 1996: the PM_{10} level was 187 $\mu g/m^3$, while PM_1 was only 9.5 $\mu g/m^3$. The deaths on the day of a dust storm were contrasted with deaths on control days (n=95 days in the main analysis and 171 days in the sensitivity analysis), which are defined as the same day of the year in other years when dust storms did not occur. The relative risk for dust storm exposure was estimated using Poisson regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity analyses considering different seasonal adjustment, year effects, and lags, were conducted. The expected relative risk for these storm days with an increment of 221 $\mu g/m^3$ would be about 1.04, based on PM_{10} relative risk from past studies, but the estimated RR for high PM_{10} days was found to be only 1.00 (95% CI=0.95-1.05 for 50 $\mu g/m^3$ change) in this study. Schwartz et al. concluded that there was no evidence to suggest that coarse (presumably crustal) particles were associated with daily mortality.

Pope et al. (1999a) investigated PM_{10}-mortality associations in three metropolitan areas (Ogden, Salt Lake City, and Provo/Orem) in Utah's Wasatch Front mountain region during 1985-1995 period. While the three metropolitan areas shared common weather patterns, pollution levels and patterns among the three areas were different due to different emission

sources. The authors ingeniously utilized an index of air stagnation (the clearing index which the National Weather Service computes from temperature, moisture and wind), to identify and screen obvious windblown dust days, days clearly identified as with low stagnation index but high PM_{10}. They found that Salt Lake City experienced substantially more episodes of wind-blown dust. They therefore conducted Poisson regression of mortality series using both unscreened and screened PM_{10} data. The effects of screening were most apparent in Salt Lake City results. Before screening no significant relationships were observed. After screening, the RRs per 50 $\mu g/m^3$ increase in PM_{10} for mortality in the three metropolitan areas were 1.12 (1.045 - 1.20), 1.023 (1.00 - 1.047), and 1.019 (0.979 - 1.06) for Ogden, Salt Lake City, and Provo/Orem, respectively. These results suggest that the pollution episodes of wind-blown (crustal-derived) dusts were less associated with mortality than were the episodes of (presumably) combustion-related particles.

Ostro et al. (1999a) analyzed the Coachella Valley, CA data for 1989-1992. This desert valley, where coarse particles of geologic origin comprise circa 50-60% of annual-average PM_{10} (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and Indio, CA. Total, respiratory, cardiovascular, non-cardiorespiratory and age-over-50 deaths were analyzed. The correlation between gravimetric and beta-attenuation measurements, separated by 25 miles, was high (r = 0.93); and the beta-attenuation data were used for analysis. GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used. Seasonally stratified analyses were also conducted. Lags 0 through 3 days (separately) of PM_{10}, along with moving averages of 3 and 5 days, were evaluated, as were O_3, NO_2, and CO. Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined, except non-cardiorespiratory. Effect size estimates for total and cardiovascular deaths were larger for warm season (May through October) than for all year (analogous to Cifuentes et al. (2000) findings for Santiago, Chile). NO_2 and CO were statistically significant predictors of mortality in single pollutant models; but in multi-pollutant models, all gaseous pollutants coefficients were reduced and non-significant, whereas PM_{10} coefficients remained the same and significant. Ostro et al. (2000) also conducted a follow-up study of the Coachella Valley data for 1989-1998, using actual $PM_{2.5}$ and $PM_{10-2.5}$ data for the last 2.5 years but $PM_{2.5}$ and $PM_{10-2.5}$ concentrations estimated for the other, earlier years. $PM_{2.5}$, CO, and NO_2 were significantly associated with all-cause mortality, and PM_{10} and $PM_{10-2.5}$ with cardiovascular mortality (but not

$PM_{2.5}$, possibly due to the low range of concentrations and reduced sample size for $PM_{2.5}$ data versus PM_{10} data). Thus, although the cardiovascular mortality results hint at crustal particle effects possibly being important in this desert situation, the ability to discern more clearly the role of fine particles would likely be improved by analyses of more years of actual data for $PM_{2.5}$.

Laden et al. (2000) analyzed Harvard Six Cities study data and Mar et al. the Phoenix data to investigate the role of crustal particles in $PM_{2.5}$ samples on daily mortality. More detailed discussion of this study is provided below in Section 6.2.2.4.3 on the source-oriented evaluation of PM, and only the basic result regarding crustal particles is mentioned here. The elemental abundance data (from X-ray fluorescence spectroscopy analysis of daily filters) were analyzed to estimate the concentration of crustal particles in $PM_{2.5}$ using factor analysis. Then, they estimated the association of mortality with fine crustal mass using Poisson regression (regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather. Neither found a positive association between fine crustal mass factor and mortality.

The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are not likely associated with daily mortality. However, as noted in the previous section, three analyses of Phoenix, AZ data suggested that $PM_{10-2.5}$ may be associated with mortality. The results from one of the three studies (Smith et al., 2000) suggest that coarse particle mortality associations are stronger in spring and summer, when the anthropogenic portion of $PM_{10-2.5}$ is lowest as determined by factor analysis. However, during spring and summer, biogenic processes (e.g., wind-blown endotoxins and molds) may contribute more to the $PM_{10-2.5}$ fraction in the Phoenix area, clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles, per se. Disentangling potential contributions of biogenically-derived organic particle components from those of crustal materials in the $PM_{10-2.5}$ fraction in Mexico City and Santiago poses further interesting challenges.

Ultrafine Particle Effects

The Wichmann et al. (2000) study evaluated the attribution of PM effects to specific size fractions, including both the number concentration (NC) and mass concentration (MC) of particles in a given size range. The study was carried out in the small German city of Erfurt (pop. 200,000) in the former German Democratic Republic, by a team of scientists at the Gessellschaft fur Strahlenforschung (GSF) and Ludwig Maximilian University in Germany.

Erfurt was heavily polluted by particles and SO_2 in the 1980s, and excess mortality was attributed to high levels of TSP by Spix et al. (1993). Concentrations of PM and SO_2 have markedly dropped since then. The present study provides a much more detailed look at the health effects of ultrafine particles (diameter < 0.1 μm) than earlier studies, and allows examination of effects related to number counts for fine and ultrafine particles, as well as to their mass.

The Mobile Aerosol Spectrometer (MAS), developed by GSF, produces number and mass concentrations in three size classes of ultrafines (0.01 to 0.1 μm) and three size classes of larger fine particles (0.1 μm to 2.5 μm). The mass concentration MC0.01-2.5 is well correlated with gravimetric $PM_{2.5}$, and the number concentration NC0.01-2.5 is well correlated with total particle counts from a condensation particle counter (CPC). Mortality data were coded by cause of death, with some discrimination between underlying causes and prevalent conditions of the deceased. Some analyses looked at cardiovascular causes without respiratory, respiratory without cardiovascular, and both causes together as separate groups. Age was used as a modifying factor, as was weekly data for all of Germany on influenza and similar diseases. Daily mortality data were fitted using a Poisson Generalized Additive Model (GAM) with adjustments for weather variables, time trends, day of week, and particle indices. Two types of models were fitted, one using the best single-day lag for air pollution, and a second using the best polynomial distributed lag (PDL) model for air pollution.

Winter PM generally had the most significant positive effects on mortality, and fall PM effects were similar in magnitude, but less significant because of the smaller NC and MC in fall than in winter. Summer PM effects were consistently lower and not significant. PDL models generally had larger and more significant PM effects than single-day lag models. Log-transformed pollution models occasionally provided better fits than untransformed pollutant models, particularly for number concentration indices in single-day lag models. However, there were some nonlinear relationships that could not be adequately described by either parametric model, as shown by use of LOESS models. The results cited in Table 6-1 are all for linear PDL models, to facilitate comparison.

Mass concentration was most often significantly associated with excess mortality in one-pollutant models, with excess risks for MAS MC0.1-2.5 being about 6.2% (CI 1.4, 11.2) per 25 $\mu g/m^3$. The non-significant estimate from filter $PM_{2.5}$ was about 3% (CI -1.7, 7.9) per

25 $\mu g/m^3$. Filter PM_{10} estimates were also significant predictors of mortality overall, about 6.6% excess risk per 50 $\mu g/m^3$ (CI 0.7 to 12.8) in PDL models.

Mass concentrations for smaller fine particles were also often significant, with excess risk for MC0.01-1.0 being ca. 5.1% (CI 0.2, 10.2) per 25 $\mu g/m^3$ in a linear PDL model. Smaller-size components of MC0.01-1.0 were also significantly associated, or nearly so, with excess mortality. The intermodal fraction MC1.0-2.5 was also significant in a PDL logarithmic model, 4.7% (CI 1.05, 8.5) per IQR in log concentration. No results were reported for the effects of ultrafine mass concentrations in classes 0.01-0.3, 0.03-0.05, 0.05-0.1 $\mu g/m^3$.

Number concentrations of ultrafine particles were also associated with excess mortality, significantly or nearly so in smaller size classes. The results for linear models are shown in Table 6-3. The table also shows how much the estimated excess risks are reduced, sometimes drastically, when co-pollutants (especially SO_2 and NO_2) are included in a two-pollutant model. Number and mass concentrations of various ultrafine and fine particles in all size ranges are rather well correlated with gaseous co-pollutants except for the intermodal size range MC1.0-2.5. The correlations range from 0.44 to 0.62 with SO_2, from 0.58 to 0.66 with NO_2, and from 0.53 to 0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2, from 0.48 to 0.60 with NO_2, and from 0.56 to 0.62 with CO. The large decreases in excess risk for number concentration, particularly when NO_2 is a co-pollutant with NC0.01-0.1, clearly involves a more complex structure than simple correlation. The large decrease in excess risk when SO_2 is a co-pollutant with MC0.01-2.5 is not readily explained, and is discussed in some detail in Wichmann et al. (2000).

SO_2 is a strong predictor of excess mortality in this study; and its estimated effect is little changed when different particle indicators are included in a two-pollutant model. The authors noted: "... the [LOESS] smoothed dose response curve showed most of the association at the left end, below 15 $\mu g/m^3$, a level at which effects were considered biologically implausible ...". Replacement of sulfur-rich surface coal has reduced mean SO_2 levels in Erfurt from 456 $\mu g/m^3$ in 1988 to 16.8 $\mu g/m^3$ during 1995 to 1998 and to 6 $\mu g/m^3$ in 1998. The estimated concentration-response functions for SO_2 are very different in these time periods, comparing Spix et al. (1993) with Wichmann et al. (2000) results. Wichmann et al. concluded "These inconsistent results for SO_2 strongly suggested that SO_2 was not the causal agent but an indicator for something else." The authors offered no specific suggestions as to what the "something else" might be, but they

TABLE 6-3. EXCESS TOTAL MORTALITY RISKS ESTIMATED TO BE ASSOCIATED WITH VARIOUS AMBIENT PARTICLE SIZE-RELATED INDICES

		Single-Pollutant Models		
PM Index	Co-Pollutant	Excess Risk, %	Lower 95% CL	Upper 95% CL
NC0.01-0.03	None	3.00[a]	−0.342	6.455
NC0.03-0.05	None	3.80[a]	0.021	7.722
NC0.05-0.1	None	4.00[a]	−0.307	8.493
NC0.01-2.5	None	6.891[b]	0.662	13.504
NC0.01-0.1	None	8.238[b]	0.252	16.860
	SO_2	4.758[b]	−0.451	10.239
	NO_2	0.739[b]	−3.951	5.658
	CO	3.594[b]	−2.312	9.856
	MC0.01-2.5	4.123[b]	−1.437	9.996
MC0.01-2.5	None	6.194[c]	1.409	11.205
	SO_2	2.014[c]	−2.304	6.523

[a]Risks estimates for mortality associated with number concentrations (NC) in specified ranges. At actual interquartile range, respectively 8888, 2524, and 1525 particles/cm^3.
[b]At standard increment 25,000 particles/cm^3; winter IQR is 22,211 particles/cm^3, annual IQR is 12,690 particles/cm^3.
[c]At standard increment 25 $\mu g/m^3$.

Source: Based on Wichman et al. (2000), as calculated by U.S. EPA.

did finally conclude that their studies from Germany strongly supported particulate air pollution as more relevant than SO_2 to observed mortality impacts.

The authors also found that ultrafine particles, NO_2 and CO form a group of pollutants strongly identified with motor vehicle traffic. Immediate and delayed effects seemed to be independent in two-pollutant models, with single-day lags of 0 to 1 days and 4 to 5 days giving 'best fits' to data. The delayed effect of ultrafines was stronger than that for NO_2 or CO.

Another finding of interest is that the excess risk in Erfurt is larger and more significantly associated with ages < 70 years than with older ages. This is consistent for PDL models for NC0.01-0.1, MC0.01-2.5, and PM_{10}. None of the single lag day models were significant.

Examination of prevalent disease categories found larger and more significant risks for respiratory disease mortality than for cardiovascular mortality in almost all models. Combined

cardiovascular or combined respiratory diseases were generally the next highest category. Other natural causes (i.e., neither respiratory nor cardiovascular) almost always had the lowest risk.

6.2.2.4.2 Chemical Components

Nine new studies from U.S. and Canada examined specific chemical components of PM. Table 6-3 shows the chemical components examined in these studies, the mean concentrations for Coefficient of Haze (COH), sulfate, and H^+, as well as the list of those that were found to be associated with increased mortality. There are several chemical components of PM whose associations with mortality can be compared across studies, including COH, sulfate, and H^+.

Coefficient of Haze, Elemental Carbon, and Organic Carbon

COH is highly correlated with elemental carbon (EC) and is often considered as a good PM index for motor vehicle sources (especially diesel), although other combustion processes such as space heating likely also contribute to COH levels. Five studies (Table 6-4) examined COH; and, in most cases, positive and significant associations with mortality outcomes were reported. In terms of relative significance of COH in comparison to other PM components, COH was not the most significant PM component in any of these studies. The average level of COH in these studies ranged from 0.2 (Buffalo, NY) to 0.5 (Santa Clara County, CA) 1000 linear feet. The correlation between COH and NO_2 or CO in these studies (8 largest Canadian cities; Santa Clara County, CA; and Buffalo, NY) were moderately high ($r \approx 0.7$ to 0.8), suggesting a likely motor vehicle contribution. Some of the inconsistencies in the results across cities may be in part due to the differences in COH levels. For example, in Buffalo, NY (where COH was lowest), no significant association were found for any pollutant, possibly due to small sample size ($\approx$ 1 year of data). However, both EC and OC were significant predictors of cardiovascular mortality in the Phoenix study, with their effect sizes per IQR being comparable to those for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$; there, EC and OC represented major mass fractions of $PM_{2.5}$ (11% and 38%, respectively) and correlated highly with $PM_{2.5}$ ($r = 0.84$ and 0.89, respectively). They were also highly correlated with CO and NO_2 ($r \approx 0.8$ to 0.9), indicating their associations with an "automobile" factor. Thus, the COH and EC/OC results from the Mar et al. (2000) study suggest that PM components from motor vehicle sources are likely associated with mortality.

TABLE 6-4. SUMMARY OF PARTICULATE MATTER CHEMICAL COMPONENTS ANALYZED IN RECENT STUDIES

Author, City	Mean COH (1000ft)	Mean $SO_4^=$ ($\mu g/m^3$)	Mean H^+ ($nmol/m^3$)	Other PM components analyzed	PM components associated with mortality. Comments.
Burnett et al. (1998b) Toronto, Canada. 1980-1994.	0.42	9.2		TSP, estimated PM_{10} and $PM_{2.5}$,	TSP, COH, sulfate, estimated PM_{10} and $PM_{2.5}$. However, CO together with TSP explained most of the association.
Burnett et al. (2000). 8 largest Canadian cities 1986-1996.	0.26	2.6		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and 47 trace elements	PM_{10}, $PM_{2.5}$, COH, sulfate, Zn, Ni, and Fe significantly associated with total mortality.
Fairley (1999). Santa Clara County, CA	0.5	1.8		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and nitrate	COH, sulfate, nitrate, PM_{10}, and $PM_{2.5}$ were associated with mortality. $PM_{2.5}$ and nitrate most significant.
Gwynn et al. (2000). Buffalo, NY 1988-1990	0.2	5.9	36.4	PM_{10}	Sulfate, H^+, PM_{10}, and COH were associated with total mortality. COH was least significant predictor.
Lipfert et al. (2000a). Philadelphia, PA 1992-1995	0.28	5.1	8.0	Nephelometry, NH_4^+, TSP, PM_{10} $PM_{2.5}$, and $PM_{10-2.5}$	Essentially all PM components were associated with mortality.
Lippmann et al. (2000). Detroit, MI 1992-1994		5.2	8.8	PM_{10} $PM_{2.5}$, and $PM_{10-2.5}$	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more strongly associated with mortality outcomes than sulfate or H^+.
Klemm and Mason (2000). Atlanta, GA 1998-1999		5.2	0.0	Nitrate, EC, OC, oxygenated HC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	"Interim" results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were: H^+, PM_{10}, and $PM_{2.5}$,

TABLE 6-4 (cont'd). SUMMARY OF PARTICULATE MATTER CHEMICAL COMPONENTS ANALYZED IN RECENT STUDIES

Author, City	Mean COH (1000ft)	Mean $SO_4^=$ ($\mu g/m^3$)	Mean H^+ ($nmol/m^3$)	Other PM components analyzed	PM components associated with mortality. Comments.
Mar et al. (2000). Phoenix, AZ 1995-1997				S, Zn, Pb, soil-corrected K, reconstructed soil, EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	S, Pb, and soil were negatively associated with total mortality. PM_{10} and $PM_{10-2.5}$ were positively associated with total mortality. Soil-corrected K, non-soil $PM_{2.5}$, EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ 1981-1983		12.7		PM_{15}, $PM_{2.5}$, sulfates cyclohexane-solubles (CX), dichloromethane-solubles (DCM), and acetone-solubles (ACE).	PM_{15}, $PM_{2.5}$, sulfate, CX and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek et al. (2000). The Netherlands 1986-1994		3.8 (median)		PM_{10}, BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than PM_{10}.

Sulfate and Hydrogen Ion

Sulfate and H^+, markers of acidic components of PM, have been hypothesized to be especially harmful components of PM (Lippmann and Thurston, 1996). The newly available studies that examined sulfate are shown in Table 6-4; four of them also analyzed H^+ data. The sulfate concentrations ranged from 1.8 $\mu g/m^3$ (Santa Clara County, CA) to 12.7 $\mu g/m^3$ (three NJ cities). Aside from the west versus east coast contrast, the higher levels observed in Toronto and the three NJ cities are likely due to their study period coverage of the early 1980's, when sulfate levels were higher. Sulfate explained 25 to 30% of $PM_{2.5}$ mass in eastern U.S. and Canadian cities, but it was only 14% of $PM_{2.5}$ mass in Santa Clara County, CA. The mean H^+ level in the Buffalo, NY study (36.4 $nmol/m^3$) was much higher than the levels in Philadelphia, Detroit, or Atlanta, in part because the Buffalo study covered the 1988 summer when summer-haze episodes

occurred. The H^+ levels measured in the other three cities were low, especially in Atlanta, GA (where the mean concentration was reported to be 0.0 $\mu g/m^3$). Even the mean H^+ concentration for Detroit, MI (the H^+ was actually measured in Windsor, a Canadian city a few miles from downtown Detroit), 8.8 $nmol/m^3$, was low compared to the reported detection limit of 15.1 $nmol/m^3$ (Brook et al., 1997) for the measurement system used in the study. Note that the corresponding detection limit for sulfate was 3.6 $nmol/m^3$ (or 0.34 $\mu g/m^3$) and the mean sulfate level for Detroit was 54 $nmol/m^3$ (or 5.2 $\mu g/m^3$), so that the signal-to-noise ratio is expected to be higher for sulfate than for H^+. Thus, the ambient levels and possible relative measurement errors for these data should be considered in interpreting the results of the studies listed in Table 6-4.

Sulfate was a statistically significant (at $p \leq 0.05$) predictor of mortality, at least in single pollutant models, in: Toronto, CN; the 8 largest Canadian cities; Santa Clara County, CA; Buffalo, NY; Philadelphia, PA; Newark, NJ; and Camden, NJ; but not in Detroit, MI, Elizabeth, NJ, or Atlanta, GA. However, it should be noted that the relative significance across the cities is influenced by the sample size (both the daily mean death counts and number of days available), as well as the range of sulfate levels, and therefore should be interpreted with caution. Figure 6-5 shows the excess risks (± 95% CI) estimated per 5 $\mu g/m^3$ increase in 24-h sulfate reported in these studies. The largest estimate was seen for Santa Clara County, CA, but the very wide confidence band (possibly due to the small variance of the sulfate, since its levels were low) should be taken into account. Also, in the Santa Clara County analysis, the sulfate effect was eliminated once $PM_{2.5}$ was included in the model, perhaps being indicative of sulfate mainly serving as a surrogate for fine particles in general there. In any case, more weight should be ascribed to estimates from other studies with narrower confidence bands. In the rest of the studies, the effect size estimates mostly ranged from about 1 to 4% per 5 $\mu g/m^3$ increase in 24-h sulfate.

The relative significance of sulfate and H^+ compared to other PM components varied from city to city, as seen in Table 6-4. Because each study included different combinations of co-pollutants that had different extents of correlation with sulfate, and because multiple mortality outcomes were analyzed, it is difficult to assess the overall importance of sulfate across the available studies. However, it can generally be seen that the associations were stronger in cities where the sulfate and H^+ levels were relatively high. For example, the Gwynn et al., 2000 finding for Buffalo, NY data that H^+ and sulfate were most significantly associated with total

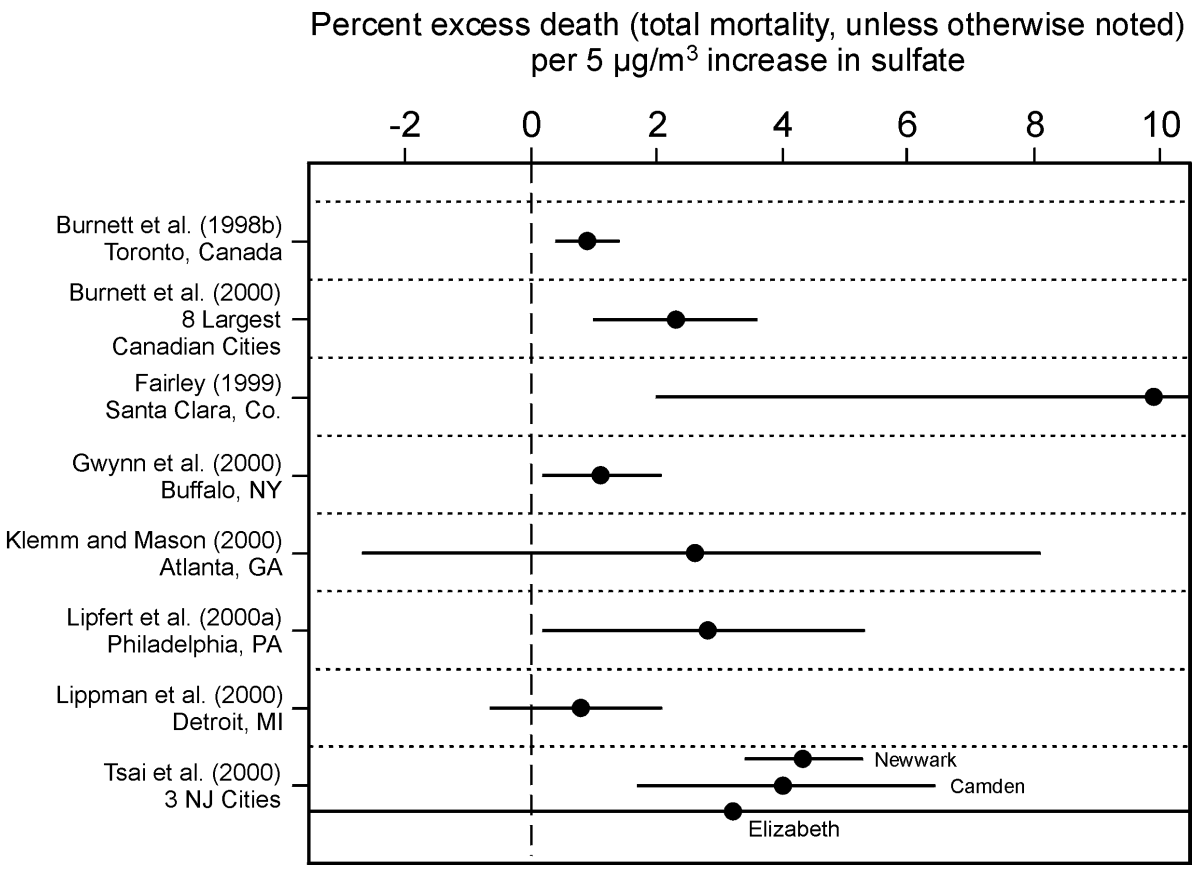

Figure 6-5. Excess risks estimated for sulfate per 5 μg/m^3 increase from the studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

mortality may be in part due to the high acid aerosol levels in that data. Also, the fact that the Lippmann et al. (2000) finding for Detroit, MI data on H^+ and sulfate being less significantly associated with mortality than the size-fractionated PM mass indices may be due to acidic aerosols levels being mostly below the detection limit in that data. In this case, it appears that the Detroit PM components show mortality effects even without much acidic input.

In summary, assessment of new study results for individual chemical components of PM suggest that an array of PM components (mainly fine particle constituents) were associated with mortality outcomes, including: COH, EC, OC, sulfate, H^+, and nitrate. The discrepancies seen with regard to the relative significance of these PM components across studies may be in part due to the difference in their concentrations. This issue is further discussed below as part of the assessment of new studies involving source-oriented evaluation of PM components.

6.2.2.4.3 Source-Oriented Evaluations

Several new studies have conducted source-oriented evaluation of PM components. In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous co-pollutants were analyzed using factor analysis to estimate daily concentrations due to underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear combinations of associated individual variables. The mortality outcomes were then regressed on those factors (factor scores) to estimate the impact of source types, rather than just individual variables. These studies differ in terms of: specific objectives/focus, the size fractions from which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The main findings from these studies regarding the source-types identified (or suggested) and their associations with mortality outcomes are summarized in Table 6-5.

The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 aimed to identify distinct source-related fractions of $PM_{2.5}$ and to examine each fraction's association with mortality. Fifteen elements in the fine fraction samples were routinely found above their detection limits and included in the data analyses. For each of the six cities, up to 5 common factors were identified from among the 15 elements, using specific rotation factor analysis. Using the Procrustes rotation (a type of oblique rotation), the projection of the single tracer for each factor was maximized. This specification of the tracer element was based on: (1) knowledge from previous source apportionment research; (2) the condition that regression of total fine mass on that element must result in a positive coefficient; and (3) identifications of additional local source factors that positively contributed to total fine mass regression. Three source factors were identified in all six cities: (1) a soil and crustal material factor with Si as a tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and, (3) a coal combustion factor with Se as a tracer. City-specific analyses also identified a fuel combustion factor (V), a salt factor (Cl), and selected metal factors (Ni, Zn, or Mn). For each city, a GAM Poisson regression model, adjusting for trend/season, day-of-week, smooth function of temperature and dewpoint, was used to estimate impacts of each source type (using absolute factor scores) simultaneously. Summary estimates across cities were obtained by combining the city-specific estimates, using inverse variance weights. The identified factors and their tracers are listed in Table 6-5. The results from mortality regression analysis including these factors indicated that the strongest increase in daily mortality was associated with the mobile source factor. Also, the coal

TABLE 6-5. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PARTICULATE MATTER COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality. Comments.
Laden et. al., (2000) Harvard Six Cities 1979-1988	*Soil and crustal material*: Si *Motor vehicle emissions*: Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality associated with mobile source factor. Coal combustion factor was positively associated with mortality in all metropolitan areas, with exception of Topeka. Crustal factor from fine particles not associated with mortality. Coal and mobile sources account for majority of fine particles in each city.
Mar et al. (2000). Phoenix, AZ 1995-1997	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust*: Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and K_S (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S --- ***$PM_{10-2.5}$ (from dichot) trace elements:*** *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	$PM_{2.5}$ factors results: Soil factor and local SO_2 factor were negatively associated with total mortality. Regional sulfate was positively associated with total mortality on the same day, but negatively associated on the lag 3 day. Motor vehicle factor, vegetative burning factor, and regional sulfate factor were significantly positively associated with cardiovascular mortality. Factors from dichot $PM_{10-2.5}$ trace elements not analyzed for associations with mortality because of small sample size (every-3rd day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions*: Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicles factors were associated with mortality.
Özkaynak et al. (1996). Toronto, Canada.	*Motor vehicle emissions*: CO, COH, and NO_2	Motor vehicle factor was a significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.

combustion factor was positively associated with mortality in all metropolitan areas, except for Topeka. Lastly, S, Ni, and Pb were specific elements individually associated with mortality, but the crustal factor from fine particles was not.

Mar et al. (2000) analyzed PM_{10}, $PM_{10-2.5}$, two measurements of $PM_{2.5}$, and various sub-components of $PM_{2.5}$ for their associations with total (non-accidental) and cardiovascular deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor analysis-derived factor scores. GAM Poisson models were used, adjusting for season, temperature, and relative humidity. The evaluated air pollution variables included: O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (K_S), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. As earlier noted, individual PM component results indicated that $PM_{10-2.5}$ was more significantly associated with total mortality than $PM_{2.5}$, although both TEOM $PM_{2.5}$ and $PM_{10-2.5}$ were significantly associated with cardiovascular mortality. A factor analysis conducted on the chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, K_S, OC, and EC) identified factors for: motor vehicle emissions/re-suspended road dust; soil; vegetative burning; local SO_2 sources; and regional sulfate (see Table 6-5). The results of mortality regression with these factors suggested that the soil factor and local SO_2 factor were negatively associated with total mortality. Regional sulfate was positively associated with total mortality on the same day, but negatively associated on the lag 3 day. The motor vehicle factor, vegetative burning factor, and regional sulfate factor were each significantly positively associated with cardiovascular mortality. The authors also analyzed elements from dichot $PM_{10-2.5}$ samples, and identified soil, a source of coarse fraction metals (industry), and marine influence factors. However, these factors were not analyzed for their associations with mortality outcomes due to the short measurement period (starting in June 1996 with every-3rd-day sampling).

It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included factor analysis on the elements from the coarse fraction and identified essentially the same factors ("a source of coarse fraction metals" factor in Mar et al.'s study was called "the anthropogenic elements" in Smith et al.'s study). While Smith et al. did not relate these factors to mortality (due to a small sample size), they did show that the anthropogenic elements were low in summer and spring, when the $PM_{10-2.5}$ effect was largest. These results suggest that the $PM_{10-2.5}$ effects were not necessarily due to anthropogenic components of the coarse particles,

with biogenically-generated coarse particles perhaps being key during the warmer months (as noted earlier above).

Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis - Poisson regression techniques. During the three-year study period (1981-1983), extensive chemical speciation data were available, including nine trace elements, sulfate, and particulate organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory mortality were analyzed. Tsai et al. first conducted a factor analysis of trace elements and sulfate, identifying major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson regression of mortality on these factors, they also used an alternative approach in which the inhalable particle mass (IPM, $D_{50} < 15\ \mu m$) was first regressed on the factor scores of each of the source types to apportion the PM mass; and then the estimated daily PM mass for each source type was included in Poisson regression, so that RR could be calculated per mass concentration basis for each PM source type. They found that oil burning (V, Ni), various industrial sources (Zn, Cd), motor vehicle (Pb, CO), and the secondary aerosols, as well as the individual PM indices IPM, FPM ($D_{50} < 3.5\ \mu m$), and sulfates, were all associated with total and/or cardiorespiratory mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were higher (≈ 1.10) than those for individual PM indices (≈ 1.02).

Özkaynak et al. (1996) analyzed 21 years of mortality and air pollution data in Toronto, Canada. In addition to the usual simultaneous inclusion of multiple pollutants in mortality regressions, they also conducted a factor analysis of all the air pollution and weather variables, including TSP, SO_2, COH, NO_2, O_3, CO, relative humidity and temperature. The factor with the largest variance contribution ($\approx$ 50%) had the highest factor loadings for CO, COH, and NO_2, which they considered to be representative of motor vehicle emissions, since this pollution grouping was also consistent with the emission inventory information for that city. They then regressed mortality on the factor scores (a linear combination of standardized scores for the covariates), after filtering out seasonal cycles and adjusting for temperature and day-of-week effects. The estimated impacts on mortality from motor vehicle pollution ranged from 1 to 6%, depending on the outcomes.

In summary, these studies suggest that a number of source-types are associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with mortality in the Harvard Six Cities data. In Phoenix data, where coarse particles were reported to be associated with mortality, the associations between the factors related to coarse particles (soil, marine influence, and anthropogenic elements) and mortality could not be evaluated due to the small sample size. However, the soil (i.e., crustal) factor from fine particles in the Phoenix data was negatively associated with mortality. Thus, although some unresolved issues remain, mainly due to the lack of sufficient data, the source-oriented evaluation approach, using factor analysis, thus far seems to implicate fine particles of anthropogenic origin as being most important (versus crustal particles of geologic origin) in contributing to observed increased mortality risks.

6.2.2.5 New Assessments of Cause-Specific Mortality

Consistent with similar findings described in the 1996 PM AQCD, most of the newly available studies summarized in Table 6-1 that examined non-accidental total, circulatory, and respiratory mortality categories (e.g., Samet et al., 2000a,b; Dominici et al., 2000; Moolgavkar, 2000a; Gwynn et al., 2000; Lippmann et al., 2000; Ostro et al., 1999a; Schwartz, 2000c) found significant PM associations with both cardiovascular and/or respiratory-cause mortality. Several (e.g., Ostro et al., 1998; Fairley, 1999; Gwynn et al., 2000; Borja-Aburto et al., 1997; Wordley et al., 1997; Borja-Aburto et al., 1998; Prescott et al., 1998;) reported estimated PM effects that were generally higher for respiratory deaths than for circulatory or total deaths. Once again, the NMMAPS results for U.S. cities are among those of particular note here due to the large study size and the combined, pooled estimates derived for various U.S. regions.

The Samet et al. (2000a,b) NMMAPS 90-cities analyses not only examined all-cause mortality (excluding accidents), but also evaluated cardiovascular, respiratory, and other remaining causes of deaths. Results were presented for all-cause, cardio-respiratory, and "other" mortality for lag 0, 1, and 2 days. The investigators commented that, compared to the result for cardio-respiratory deaths showing 3.5% (CI 1.0, 5.9) increase per 50 $\mu g/m^3$ PM_{10}, there was less evidence for non-cardio-respiratory deaths. However, the estimates for "other" mortality, though half those for cardio-respiratory mortality, were nevertheless positive, with fairly high posterior probability (e.g., 0.84 at lag 0 day) that the overall effects were greater than 0 (estimated percent

excess "other" deaths being ≈ 1.3 per 50 $\mu g/m^3$ PM_{10} at lag 0). Dominici et al. (2000) evaluated the 20 largest U. S. cities, a subset of the cities included in Samet et al.'s NMMAPS analyses. The pattern of PM_{10} effects on cardiovascular and respiratory mortality was similar to that discussed earlier for total mortality, with lag day 1 showing the largest estimates. In this case, the PM_{10} effect in these analyses was smaller and weaker for "other" causes. Regional model results suggested that PM_{10} effects in the western U.S. were larger than in the eastern or southern U.S. The PM coefficients were little affected by including gaseous pollutants in the model.

The Lippmann et al. (2000) analyses of cause-specific mortality in Detroit also evaluated such mortality at various lags (0-3 days) in relation to several PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+) and various gaseous pollutants (O_3, SO_2, NO_2 and CO), with appropriate adjustment for season, temperature, relative humidity, etc. Significant effects for both cardiovascular and respiratory mortality were more consistently found for the first three PM indices than for H^+ or sulfate. Effect size estimates tended to be highest for lag 1 day. It is notable here that, in the Lippmann et al. (2000) analysis of Detroit mortality data, the "other" mortality category, also showed statistically significant effect size estimates. The authors noted, however, that the "other" (non-circulatory and non-respiratory) mortality showed seasonal cycles and apparent influenza peaks, suggesting that this series may have also been influenced by respiratory contributing causes.

Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-specific mortality across a broad range of lag (0-5 days) times. Moolgavkar reported that in Poisson regression GAM analyses, controlling for temperature and relative humidity, varying patterns of results were obtained for PM indices in evaluations of daily deaths related to cardiovascular disease (CVD), cerebrovascular disease (CrD), and chronic obstructive lung disease (COPD) in three large U.S. metropolitan areas. In Cook County (Chicago area), the association of PM_{10} with CVD mortality was statistically significant at a lag of 3 days based on a single-pollutant analysis and remained significantly associated with CVD deaths with a 3-day lag in two pollutant models including one or another of CO, NO_2, SO_2, or O_3. In joint analyses with both O_3 and SO_2, however, the PM_{10} association became markedly reduced and non-significant. Also, in Los Angeles single-pollutant analyses, PM_{10} and $PM_{2.5}$ were significantly associated with CVD mortality with lags of 2 and 1 days, respectively; but their coefficients were not robust to inclusion of one or more gaseous pollutants. In Maricopa Co., AZ, PM_{10} coefficients were large

for several lags and significantly associated with CVD mortality lagged 1 day, as were each of the gaseous pollutants tested (except O_3) at several different lag times; and PM_{10} coefficients seemed to be robust in 2-pollutant models including PM_{10} and NO_2. As for cerebrovascular disease, Moolgavkar (2000a) reported that there was little evidence of association for PM with CrD deaths at any lag in any of the three counties analyzed. With regard to COPD deaths, PM_{10} was significantly associated with COPD mortality (lag 2 days) in Cook County.

As for European findings of particular interest, Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the 12 APHEA European cities. Using Poisson autoregressive models adjusting for trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated in each city, and "meta-analyses" of city specific estimates was conducted. The pooled excess risk estimates for cardiovascular mortality were 1.0% (0.3, 1.7) per 25 $\mu g/m^3$ increase in BS and 2.0% (0.5, 3.0) per 50 $\mu g/m^3$ increase in SO_2 in western European cities. The pooled risk estimates for respiratory mortality in the same cities were: 2.0% (0.8, 3.2) and 2.5% (1.5, 3.4) for BS and SO_2, respectively. However, significant associations were not found for the central/eastern European cities. Again, the investigators noted: (a) potential explanations for differences between the western and central/eastern European cities (smaller fraction of elderly population and likely larger measurement error related to exposure representativeness in the central/eastern European cities), and (b) lack of consistency in NO_2- mortality associations. Also of note, Wichmann et al. (2000) found significant associations of elevated cardiovascular and respiratory disease mortality with various fine (and ultrafine) particle indices evaluated in Erfurt, Germany. "Other" natural causes (neither cardio- or respiratory-related) almost always had the lowest risk in those models evaluating cause-specific mortality.

Seeking unique cause-specificity of effects associated with various pollutants has been difficult because the "cause specific" categories examined are typically rather broad (usually cardiovascular and respiratory) and overlap; also cardiovascular and respiratory conditions tend to cooccur. Examinations of more specific cardiovascular and respiratory sub-categories may be necessary to test hypotheses about any specific mechanisms, but smaller sample sizes for more specific sub-categories may make a meaningful analysis difficult. The study by Rossi et al. (1999), however, examined associations between TSP and detailed cardio-vascular and respiratory cause-specific mortality in Milan, Italy for a 9-year period (1980-1989). They found

significant associations for respiratory infections (11% increase per 100 $\mu g/m^3$ increase in TSP; 95%CI: 5, 17) and for heart failure (7%; 95%CI: 3, 11), both on the same day TSP. The associations with myocardial infarction (10%; 95%CI: 3, 18) and COPD (12%; 95%CI: 6, 17) were found for the average of 3 and 4 day TSP levels. They noted the difference in lags between temperature effects (i.e., cold temp. at lag 1 day for respiratory infections; hot temp. at lag 0 for heart failure and myocardial infarction) and air pollution (TSP) effects. The immediate hot temperature effects and the lagged cold temperature effects for total and cardiovascular mortality have been reported in many of the past studies (e.g., Philadelphia, Chicago), but investigations of the differences in lags of PM effects for specific cardiovascular or respiratory categories have rarely been conducted in time-series mortality studies.

A very recently published HEI report on an epidemiologic study conducted by Goldberg et al. (2000) in Montreal, Canada also provides interesting new information regarding types of medical conditions putting susceptible individuals at increased risk for PM-associated mortality effects, and it highlights the potential importance of evaluating "contributing causes" in cause-specific mortality analyses. First, the immediate causes of death, as listed on death certificates, were evaluated in relation to various ambient PM indices (TSP, PM_{10}, $PM_{2.5}$, COH, sulfates, extinction coefficients) lagged for 0 to 4 days, with results reported emphasizing effects at 3 day lags for three main PM measures (COH, sulfate, estimated $PM_{2.5}$). Significant associations were observed between all three measures and total nonaccidental deaths, respiratory diseases, and diabetes, with an approximate 2% increase in excess nonaccidental mortality being observed per 9.5 $\mu g/m^3$ interquartile increase in 3-day mean estimated $PM_{2.5}$ exposure.

When underlying clinical conditions identified in decedents' medical records were then evaluated in relation to ambient PM measures, all three measures (COH, sulfate, estimated $PM_{2.5}$) were associated with acute lower respiratory disease, congestive heart failure, and any cardiovascular disease. Estimated $PM_{2.5}$ and COH were also reported to be associated with chronic coronary artery disease, any coronary artery disease, and cancer; whereas, sulfate was associated with acute and chronic upper respiratory disease. None of the three PM measures were related to airways disease, acute coronary artery disease, or hypertension. These results both tend to support previous findings identifying individuals with preexisting cardiopulmonary diseases as being at increased risk for ambient PM effects and appear to implicate another risk

factor, diabetes (which typically also involves cardiovascular complications as it progresses), as a possible susceptibility condition putting individuals at increased risk for ambient PM effects.

Overall, then, the above assessment of newly available information provides interesting additional new information (beyond that in the 1996 PM AQCD) with regard to cause-specific mortality related to ambient PM. That is, a growing number of studies continue to report increased cardiovascular- and respiratory-related mortality risks as being significantly associated with ambient PM measures at one or another varying lag times. Largest effects estimates are most usually reported for 0-1 day lags (with some studies also now noting a second peak at 3-4 day lags). A few of the newer studies also report associations of PM metrics with "other" (i.e., non-cardiorespiratory) causes, as well. However, at least some of these "other" associations may also be due to seasonal cycles that include relationships to peaks in influenza epidemics that may imply respiratory complications as a "contributing" cause to the "other" deaths. Or, the "other" category may include sufficient numbers of deaths due to diabetes or other diseases which may also involve cardiovascular complications as contributing causes. Varying degrees of robustness of PM effects are seen in the newer studies, as typified by estimates in multiple pollutant models containing gaseous co-pollutants; many show little effect of gaseous pollutant inclusion on estimated PM effect sizes, some show larger reductions in PM effects to non-significant levels upon such inclusion, and a growing number also report significant associations of cardiovascular and respiratory effects with one or more gaseous co-pollutants. Thus, the newer studies both further substantiate PM effects on cardiovascular- and respiratory-related mortality, while also pointing toward possible significant contributions of gaseous pollutants to such cause-specific mortality, as well. The magnitudes of the PM effect size estimates are consistent with the range of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

6.2.2.6 Salient Points Derived from Summarization of Studies of Short-Term Particulate Matter Exposure Effects on Mortality

The most salient key points to be extracted from the above discussion of newly available information on short-term PM exposures mortality relationships can be summarized as follow:

- ***PM_{10} effects estimates***. Since the 1996 PM AQCD, thus far, there have been more than 70 new time-series PM-mortality analyses published. Estimated mortality relative risks in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. Of particular importance are several studies which evaluated multiple cities using consistent data analytical approaches. The NMMAPS analyses for the largest 90 U.S. cities ([Samet et al., 2000a,b] thought to probably provide the most precise estimates for PM_{10} effects applicable to the U.S.) derived a combined nationwide excess risk estimate of about 2.3% increase in total (non-accidental) mortality per 50 $\mu g/m^3$ increase in PM_{10}. The other multi-city analyses, as well as various single city analyses, also obtained PM_{10} effect sizes generally in the range of 1.5 to 8.5% per 50 $\mu g/m^3$ increase in PM_{10}, consistent with the broader range of statistically significant estimates given in the 1996 PM AQCD. However, more geographic heterogeneity is evident among the newer multi-city study results than was the case among the fewer studies assessed in the 1996 PM AQCD. In particular, in the NMMAPS analysis of the 90 largest U.S. cities data, the risk estimates varied somewhat by U.S. geographic region, with the estimate for the Northeast being the largest (4.6% per 50 $\mu g/m^3$ PM_{10} increase). The observed heterogeneity in the estimated PM risks across cities/regions could not be explained with the city-specific explanatory variables, such as the mean levels of pollution and weather, mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error. Notable apparent heterogeneity was also seen among effects estimates for PM (and SO_2) indices in the multi-city APHEA study conducted in European cities. The issue of heterogeneity of effects estimates is discussed further below in Section 6.4.

- ***Confounding and effect modification by other pollutants***. Numerous new short-term PM exposure studies not only continue to report significant associations between various PM indices and mortality, but also between gaseous pollutants (O_3, SO_2, NO_2, and CO) and mortality as well. In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models did not meaningfully affect the PM effect size estimates. This was the case for the NMMAPS 90 cities study with regard to the overall combined U.S. regional and nationwide risk estimates derived for that study. On the other hand, some other non-multicity studies found significant PM-mortality associations at one or more lag times to be reduced by

inclusion of one or another gaseous pollutants (e.g., CO, NO_2, SO_2, but not typically O_3). Thus, there appears to be independent effects of short-term PM and gaseous pollutant exposures on mortality and/or significant confounding between PM and gaseous pollutants derived from common sources. There is not sufficient evidence to clearly establish modifications of PM effects by other gaseous co-pollutants. The issue of confounding is discussed further in Section 6.4.

- ***Fine and coarse particle effects***. Newly available studies provide generally statistically significant $PM_{2.5}$ associations with mortality, with effect size estimates falling in the range reported in the 1996 PM AQCD. New results from Germany appear to implicate both ultrafine (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as being important contributors to increased mortality risks. As to the relative importance of fine and coarse particles, in the 1996 PM AQCD there was only one acute mortality study in which examined this issue. In that study, the authors suggested that fine particles ($PM_{2.5}$), but not coarse particles ($PM_{10-2.5}$), were associated with daily mortality. Now, more than ten studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality. While the results from some of these new studies (e.g., Santa Clara County, CA analysis [Fairley, 1999] and the largest 8 Canadian cities analysis [Burnett et al., 2000]) did suggest that $PM_{2.5}$ was more important than $PM_{10-2.5}$ in predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses [Clyde et al., 2000; Mar et al., 2000; Smith et al., 2000]; Mexico City and Santiago, Chile studies [Castillejos et al., 2000; Cifuentes et al., 2000]) suggest that $PM_{10-2.5}$ may also be important in at least some locations. Seasonal dependence of size-related PM component effects observed in some of the studies complicates interpretations. At least some of the reported coarse ($PM_{10-2.5}$) fraction particle effects seen most clearly during warmer seasons may be hypothesized to be due to biogenically-derived particles (molds, endotoxins, etc.) that tend to be elevated during such seasons.

- ***Chemical components of PM***. Several new studies have examined the role of specific chemical components of PM. The studies conducted in U.S. and Canadian cities showed mortality associations with specific fine particle components of PM including H^+, sulfate, nitrate, as well as COH, but their relative importance varied from city to city, likely depending

on their levels (e.g., no clear associations in those cities where H^+ and sulfate levels were very low, i.e., circa non-detection limits). The results of several studies that investigated the role of crustal particles, although somewhat mixed, do not appear overall to support associations between crustal particles and mortality (see also source-oriented evaluations below).

- ***Source-oriented evaluations***. Several studies conducted source-oriented evaluations of PM components using factor analysis. The results from these studies generally indicate that several combustion-related source-types are likely associated with mortality, including: motor vehicle emissions; coal combustion; oil burning; and vegetative burning. The crustal factor from fine particles was not associated with mortality in the Harvard Six Cities data, and the soil (i.e., crustal) factor from fine particles in the Phoenix data was negatively associated with mortality. Thus, the source-oriented evaluations seem to implicate fine particles of anthropogenic origin as being most important as contributing to increased mortality and are thus far generally non-supportive of increased mortality risks being related to short-term exposures to crustal materials in U.S. ambient environments examined to date.

- ***Cause-specific mortality.*** Findings for new results concerning cause-specific mortality comport well with those for total (non-accidental) mortality, the former showing generally larger effect size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess risks than for total mortality risks.

- ***Lags.*** In general, maximum effect sizes for total mortality appear to be obtained with 0-1 day lags, with some studies finding a second peak for 3-4 days lags. There is also some evidence that, if effects distributed over multiple lag days are considered, the effect size may be larger than for any single maximum effect size lag day.

- ***Threshold***. Few new short-term mortality studies explicitly address the issue of thresholds. One study that analyzed Phoenix, AZ data did report some limited evidence suggestive of a possible threshold for $PM_{2.5}$ there. However, several different analyses of larger PM_{10} data sets across multiple cities generally provide little or no support to indicate a threshold for PM_{10} mortality effects. Threshold issues are discussed further in Section 6.4.

6.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter

6.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document

6.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies

Mortality effects associated with chronic, long-term exposure to ambient PM have been assessed in cross-sectional studies and, more recently, in prospective cohort studies. A number of older cross-sectional studies from the 1970s provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM, especially with respect to fine mass or sulfate ($SO_4^=$) concentrations. However, questions unresolved at that time regarding the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996) on such purely "ecological" studies or on quantitative estimates of PM effects derived from these studies. Evidence comparing the toxicities of specific PM components was relatively limited. The sulfate and acid components had already been discussed in detail in the previous PM AQCD (U.S. Environmental Protection Agency, 1986).

6.2.3.1.2 Semi-Individual (Prospective Cohort) Chronic Exposure Studies

Semi-individual cohort studies using subject-specific information about relevant covariates (such as cigarette smoking, occupation, etc.) have provided more certain findings of long-term PM exposure effects than past purely "ecological studies" (Künzli and Tager, 1997). At the same time, these better designed cohort studies have largely confirmed the magnitude of PM effect estimates from past cross-sectional study results.

Prospective cohort semi-individual studies of mortality associated with chronic exposures to air pollution of outdoor origins have yielded especially valuable insights into the adverse health effects of long-term PM exposures. The extensive Harvard Six-Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS study did not evaluate the possible contributions of other air pollutants. Neither study considered multi-pollutant models, although the Six-City study did examine various gaseous and particulate matter indices (including total particles, $PM_{2.5}$, $SO_4^=$, H^+,

SO_2, and ozone), finding that sulfate and $PM_{2.5}$ fine particles were best associated with mortality. The RR estimates for total mortality in the Six-Cities study (and 95 percent confidence intervals, CI) per increments in PM indicator levels were: RR=1.42 (CI=1.16-2.01) for 50 $\mu g/m^3$ PM_{10}; RR=1.31 (CI=1.11-1.68) for 25 $\mu g/m^3$ $PM_{2.5}$; and RR=1.46 (CI=1.16-2.16) for 15 $\mu g/m^3$ $SO_4^=$. The estimates for total mortality derived from the ACS study were RR=1.17 (CI=1.09-1.26) for 25 $\mu g/m^3$ $PM_{2.5}$ and 1.11 (CI=1.06-1.16) for 15 $\mu g/m^3$ $SO_4^=$. The ACS pollutant RR estimates are smaller than those from the Six-Cities study, although their 95% confidence intervals overlap. In some cases in these studies, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in cities with historically higher PM levels (e.g., Steubenville, OH); but more current PM measurements were used to estimate the chronic PM exposures. In the ACS study, the pollutant exposure estimates were based on concentrations at the start of the study (during 1979-1983). Also, the average age of the ACS cohort was 56, which could overestimate the pollutant RR estimates and perhaps underestimate the life-shortening associated with PM associated mortality. Still, although caution must be exercised regarding the use of the reported quantitative risk estimates, the Six-Cities and ACS semi-individual studies provided consistent evidence of a significant mortality association with long-term exposure to PM of ambient origins.

In contrast to the Six-Cities and ACS studies, early results from the Adventist Health Study on Smog (AHSMOG) of California nonsmokers by Abbey et al. (1991) and Abbey et al. (1995a) found no significant mortality effects of previous PM exposure in a relatively young cohort. However, these analyses used TSP as the PM exposure metric, rather than more health relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study, and considered a shorter follow-up time than the Six-Cities study (ten years vs. 15 years for the Six-Cities study). Moreover, the AHSMOG study included only non-smokers, indicated by the Six-Cities Study as having lower pollutant RR's than smokers, suggesting that a longer follow-up time than considered in the past (10 years) might be required to have sufficient power to detect significant pollution effects than is required in studies that include smokers (such as the Six-Cities and ACS studies). Thus, greater emphasis has been placed thus far on the Six-Cities and ACS studies.

Overall, the past chronic PM exposure studies collectively indicated that increases in mortality are associated with long-term exposure to ambient airborne particles. Also, effect size estimates for total mortality associated with chronic PM exposure indices are much larger than

those reported from daily mortality PM studies. This suggests that a major fraction of the reported mortality relative risk estimates associated with chronic PM exposure likely reflects cumulative PM impacts above and beyond those exerted by the sum of acute exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM AQCD (Chapter 12) reached several conclusions concerning four key questions about the prospective cohort studies, as directly quoted below:

(1) Have potentially important confounding variables been omitted?

"While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as individual and community risk factors are included in the analyses." These include individual variables such as education, occupational exposure to dust and fumes, and physical activity, as well as ecological (community) variables such as regional location, migration, and income distribution. Further refinement of the effects of smoking status may also prove useful."

(2) Can the most important pollutant species be identified?

"The issue of confounding with co-pollutants has not been resolved for the prospective cohort studies . . . Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies." The ability to separate the effects of different pollutants, each measured as a long-term average on a community basis, was clearly most limited in the Six Cities study. The ACS study offered a much larger number of cities, but did not examine differences attributable to the spatial and temporal differences in the mix of particles and gaseous pollutants across the cities. The AHSMOG study constructed time- and location-dependent pollution metrics for most of its subjects that might have allowed such analyses, but no results were reported.

(3) Can the time scales for long-term exposure effects be evaluated?

"Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. This potential was greater in the Six Cities and AHSMOG studies because of the greater length of the historical air pollution data for the cohort. The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure."

(4) Is it possible to identify pollutant thresholds that might be helpful in health assessments?

"Model specification searches for thresholds have not been reported for prospective cohort studies. . . . Measurement error in pollution variables also complicates the search for potential threshold effects. . . . The problems that complicate threshold detection in the population-based studies have a somewhat different character for the long-term studies."

6.2.3.2 Prospective Cohort Analyses of Chronic Particulate Matter Exposure Mortality Effects Published Since the 1996 Particulate Matter Air Quality Criteria Document

Considerable progress has been made towards addressing further the above issues. For example, extensive reanalyses (Krewski et al., 2000) of the ACS and Six-Cities Study conducted under sponsorship by the Health Effects Institute (HEI) indicate that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses. The HEI reanalysis project has demonstrated that small corrections in input data have very little effect on the findings and that alternative model specifications further substantiate the robustness of the originally reported findings. In addition, some of the above key questions have been further investigated by Krewski et al. (2000) via sensitivity analyses for the Six City and ACS studies data sets, including consideration of a much wider range of confounding variables. Recently published analyses of AHSMOG data (Abbey et al., 1999; Beeson et al., 1998) also extend the ASHMOG findings showing some

analytic outcomes different from earlier analyses reported out from the study. Additional new studies suggestive of possible effects of sub-chronic PM exposures on infant mortality (Woodruff et al., 1997; Bobak and Leon, 1998), are also discussed below.

6.2.3.2.1 Health Effects Institute Reanalyses of the Six-Cities and ACS Studies

The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) Studies of air pollution and mortality. The following description of approach, key results, and conclusions is largely extracted from the Executive Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort was approached in two steps:

- Part I: Replication and Validation. The Reanalysis Team sought to test: (a) if the original studies could be replicated via a quality assurance audit of a sample of the original data and; (b) if the original numeric results could be validated.
- Part II: Sensitivity Analyses. The Reanalysis Team tested the robustness of the original analyses to alternate risk models and analytic approaches.

The Part I audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed the data to be of generally high quality with few exceptions. In both studies, a few errors were found in the data coding for and exclusion of certain subjects; when those subjects were included in the analyses, they did not materially change the results from those originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses in Part II.

The Reanalysis Team was able to replicate the original results for both studies using the same data and statistical methods as used by the Original Investigators. The Reanalysis Team confirmed the original point estimates, as shown in Table 6-6. For the Six Cities Study, they reported the relative risk of mortality from all causes associated with an increase in fine particles of 20.0 $\mu g/m^3$ as 1.28, the same as the 1.28 per 20 $\mu g/m^3$ reported by the Original Investigators. For the ACS Study, the relative risk of all-cause mortality associated with a 20 $\mu g/m^3$ increase in fine particles was 1.19 in the reanalysis, very close to the original 1.14 value.

TABLE 6-6. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM[a]	
Original Investigators' Findings		Total mortality Relative Risk (95% CI)	Cardiopulmonary mortality Relative Risk (95% CI)
Six City[b]	$PM_{2.5}$	*1.28 (1.09-1.51)*	*1.40 (1.12-2.01)*
Six City[b]	$PM_{15/10}$	*1.18 (1.06-1.32)*	*e*
ACS Study[c]	$PM_{2.5}$	*1.14 (1.07-1.21)*	*1.25 (1.14-1.36)*
HEI reanalysis Phase I: Replication		Relative Risk (95% CI)	
Six City Reanalysis[d]	$PM_{2.5}$	*1.28 (1.09-1.51)*	*1.41 (1.13-1.76)*
	PM_{15}	*1.19 (1.06-1.34)*	*1.20 (1.02-1.41)*
ACS Study Reanalysis[d]	$PM_{2.5}$	*1.19 (1.08-1.21)*	*1.33 (1.19-1.47)*
	PM_{15} *(dichot)*	*1.04 (1.01-1.07)*	*1.07 (1.02-1.12)*
	PM_{15} *(SSI)*	*1.02 (0.99-1.04)*	*1.06 (1.03-1.09)*

[a] *Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, using increments of 20* $\mu g/m^3$ *increase for* PM_{10}, PM_{15} *and* $PM_{2.5}$
[b] *Dockery et al. (1993)*
[c] *Pope et al. (1995)*
[d] *Krewski et al. (2000)*
[e] *Data presented only by smoking subgroup*

The Part II sensitivity analysis applied an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions and model specifications. The Reanalysis Team first applied the standard Cox model used by the Original Investigators and included variables in the model for which data were available from both original studies, but had not been used in the published analyses (e.g. physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.

Next, for both the Six Cities and ACS Studies, the Reanalysis Team investigated the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. These analyses did not find differences in PM-mortality associations among subgroups based on various personal characteristics (e.g., including gender, smoking status, exposure to occupational dusts and fumes, and marital status). However, estimated effects of fine particles did vary with educational level; the association between an increase in fine particles

and mortality tended to be higher for individuals without a high school education than for those with more education. The Reanalysis Team postulated that this finding could be attributable to some unidentified socioeconomic effect modifier. The authors concluded, "The Reanalysis Team found little evidence that questionnaire variables had led to confounding in either study, thereby strengthening the conclusion that the observed association between fine particle air pollution and mortality was not the result of a critical covariate that had been neglected by the Original Investigators." (Krewski et al., 2000, pp. 219-220).

In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes of the concentration-response relationships warrant additional research in the future.

One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In the Six Cities Study, for which such data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality was reduced (RR = 1.22, CI 1.03, 1.45). This would be expected, since the most polluted cities would be expected to have the greatest decline as pollution controls were applied. Despite this adjustment, the $PM_{2.5}$ effect estimate continued to be positive and statistically significant.

To test the validity of the original ACS air quality data, the Reanalysis Team constructed and applied its own air quality dataset from available historical data. In particular, sulfate levels with and without adjustment were found to differ by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed dataset contained sulfate levels inflated by approximately 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data, while the relative risk of mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis

Team found essentially the same results as the original Harvard Six-Cities and ACS studies, even after using independently developed pollution datasets and after adjusting for sulfate artifact.

Because of the limited statistical power to conduct most model specification sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study dataset that considered 151 cities. When a range of city-level (ecologic) variables (e.g., population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. The only exception was that associations with fine particles and sulfate were reduced when city-level measures of population change or SO_2 were included in the model.

A major product of the Reanalysis Project is the determination that both pollutant variables and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for addressing this, each of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved, and were noted to be an important subject for future research.

When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and variation from the spatial correlation between cities, associations were still found between mortality and sulfates or fine particles. In results of various models using alternative methods to address spatial autocorrelation and including different ecologic covariates, fine particle-mortality associations ranged from 1.11 to 1.29 (RR reported by original investigators was 1.17) for a 24.5 $\mu g/m^3$ increase in $PM_{2.5}$. With the exception of sulfur dioxide, consideration of other pollutants in these models did not alter the associations found with sulfates. The authors reported associations that were stronger for SO_2 than for sulfate, which may indicate that the sulfate with artifact was "picking up" some of the SO_2 association, perhaps because the artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977). It should be recognized that the Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate. The Reanalysis Team concluded: "it suggests that uncontrolled spatial autocorrelation accounts for

24% to 64% of the observed relation. Nonetheless, all our models continued to show an association between elevated risks of mortality and exposure to airborne sulfate." (Krewski et al., 2000, p. 230)

In summary, the reanalyses generally confirmed the original investigator's findings of associations between mortality and long-term exposure to PM, while recognizing that increased mortality may be attributable to more than one ambient air pollution component. Regarding the validity of the published Harvard Six-Cities and ACS Studies, the HEI Reanalysis Report concluded that: "Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

6.2.3.2.2 AHSMOG Analyses

The Adventist Health Study of Smog (AHSMOG) represents a third major U.S. prospective cohort study of chronic PM exposure-mortality effects. The study enrolled 6,338 non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to 95 years, in 1977. The participants had resided for at least 10 years within 5 miles (8 km) of their then-current residence locations, either within the 3 major California air basins (San Diego, Los Angeles, or San Francisco) or else were part of a random 10% sample of Adventist Health Study participants in the rest of California. The study has been extensively described and initial results reported elsewhere (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991). In the latest AHSMOG analyses (Abbey et al., 1999), mortality status of the subjects after ca. 15-years of follow-up (1977-1992) was determined by various tracing methods, finding 1,628 deaths (989 female, 639 male) in the cohort. This is a 50% percent increase in the follow-up period vs. previous AHSMOG reports, which increases the power of the latest analyses over past published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029 were cardiopulmonary, 135 were non-malignant respiratory (ICD9 codes 460-529), and 30 were lung cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category, contributing respiratory causes (CRC). CRC included any mention of nonmalignant respiratory disease as either an underlying or a "contributing cause" on the death certificate. Numerous analyses were done for the CRC category, due to the large numbers and relative specificity of respiratory causes as a factor in the

deaths. Education was used to index socio-economic status, rather than income. Physical activity and occupational exposure to dust were also used as covariates.

Cox proportional hazard models adjusted for a variety of covariates, or stratified by sex, were used. The "time" variable used in most of the models was survival time from date of enrollment, except that age on study was used for lung cancer effects due to the expected lack of short-term effects. A large number of covariate adjustments were evaluated, yielding results for all non-external mortality as shown in Table 6-7 and described by Abbey et al. (1999). Essentially no statistically significant PM related effects were observed for either males or females, except RR = 1.08 for males in relation to $PM_{10} > 100\ \mu g/m^3$, d/yr.

TABLE 6-7. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

		Females			Males		
Pollution Index	Pollution Incr.	RR	LCL	UCL	RR	LCL	UCL
PM_{10}>100, d/yr.	30 days/yr.	0.958	0.899	1.021	1.082	1.008	1.162
PM_{10} mean	50 $\mu g/m^3$	0.879	0.713	1.085	1.242	0.955	1.616
SO_4 mean	15 $\mu g/m^3$	0.732	0.484	1.105	1.279	0.774	2.116
O_3>100 ppb, h/yr.	551 h/yr. (IQR)	0.90	0.80	1.02	1.140	0.98	1.32
SO_2 mean	3.72 (IQR)	1.00	0.91	1.10	1.05	0.94	1.18

LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

An analogous pattern of results was found for cause-specific mortality analyses of the AHSMOG data. That is, positive and statistically significant effects on cardiopulmonary deaths were found in models that included both sexes and adjustment for age, pack-years of smoking, and body-mass index (BMI) (RR = 1.14, 95% CI 1.03-1.56 for 30 day/yr > 100 $\mu g/m^3$ PM_{10}). Subsets of the cohort had elevated risks: (a) former smokers had higher RR's than never-smokers (RR for PM_{10} exceedances for never-smokers was marginally significant by itself); (b) subjects with low intake of anti-oxidant vitamins A, C, E had significantly elevated risk of

response to PM_{10}, whereas those with adequate intake did not (suggesting that dietary factors or, possibly, other socio-economic or life style factors for which they are a surrogate may be important covariates); and (c) there also appeared to be a gradient of PM_{10} risk with respect to time spent outdoors, with those who had spent at least 16 h/wk outside at greater risk from PM_{10} exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal variation in exposure to ambient air pollution is not certain. For example, if the males spent much more time outdoors than females, outdoor exposure time could be confounded with gender. When the cardiopulmonary analyses are broken down by gender (Table 6-8), the RR's for female deaths were generally smaller than that for males, although none of the risks for PM indices or gaseous pollutants were statistically significant.

TABLE 6-8. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL

		Females			Males		
Pollution Index	Pollution Incr.	RR	LCL	UCL	RR	LCL	UCL
PM_{10}>100, d/yr.	30 days/yr.	0.929	0.857	1.007	1.062	0.971	1.162
PM_{10} mean	50 $\mu g/m^3$	0.841	0.639	1.107	1.219	0.862	1.616
SO_4 mean	15 $\mu g/m^3$	0.857	0.498	1.475	1.279	0.002	1.018
O_3>100 ppb, h/yr.	551 h/yr. (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O_3 mean	10 ppb	0.975	0.865	1.099	1.066	0.920	1.236
SO_2 mean	3.72 (IQR)	1.02	0.90	1.15	1.01	0.86	1.18

LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

The AHSMOG cancer analyses showed a confusing array of results for lung cancer mortality (Table 6-9). For example, RR's for lung cancer deaths were statistically significant for males for PM_{10} and O_3 metrics, but not for females. In contrast, such cancer deaths were significant for mean NO_2 only for females (but not for males), but lung cancer metrics for mean SO_2 were significant for both males and females. This pattern is not readily interpretable, but is

TABLE 6-9. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

			Females			Males		
Pollution Index	Pollution Incr.	Smoking Category	RR	LCL	UCL	RR	LCL	UCL
PM_{10}>100, d/yr.	30 days/yr.	All[1]	1.055	0.657	1.695	1.831	1.281	2.617
PM_{10} mean	50 $\mu g/m^3$	All	1.808	0.343	9.519	12.38	2.552	60.107
NO_2 mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
O_3>100 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.50	12.07
O_3 mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO_2 mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.20
		never smokers	2.99	1.66	5.40			

[1]All = both never smokers and past smokers.
LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

reasonably attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males), resulting in wide RR confidence intervals and very imprecise effects estimates.

The analyses reported by Abbey et al. (1999) attempted to separate PM_{10} effects from those of other pollutants by use of two-pollutant models, but no quantitative findings from such models were reported. Abbey et al. mentioned that the PM_{10} coefficient for CRC remained stable or increased when other pollutants were added to the model. Lung cancer mortality models for males evaluated co-pollutant effects in detail and indicated that NO_2 was non-significant in all two-pollutant models but the other pollutant coefficients were stable. The PM_{10} and O_3 effects remained stable when SO_2 was added, suggesting possible independent effects, but PM_{10} and O_3 effects were hard to separate because these pollutants were highly correlated in this study. Again, however, the very small number of lung cancer observations and likely great imprecision of reported effects estimates markedly diminish the credibility of these results.

Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey et al. (1999), but focused on lung cancer incidence (1977-1992). There were only 20 female and 16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be specifically relevant to cancer, being the annual average of monthly exposure indices from January, 1973 through the following months, but ending 3 years before date of diagnosis of the case (i.e., representing a 3-year lag between exposure and diagnosis of lung cancer). The covariates in the Cox proportional hazards model were pack-years of smoking and education, and the time variable was attained age. Many additional covariates were evaluated for inclusion, but only 'current use of alcohol' met criteria for inclusion in the final model. Pollutants evaluated were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant, including outdoor exposure times. The RR estimates for male lung cancer cases were: (a) positive and statistically significant for all PM_{10} indicators; (b) positive and predominantly significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in former smokers; (c) positive and significant for mean SO_2, except when restricted to proximate monitors; and (d) positive but not significant for mean NO_2. A very high non-credible RR found for mean PM_{10} for males (31.1, CI = 3.98, 243.9) may be attributable to the small number of cases (N = 16) and the large standard increment (50 $\mu g/m^3$) used. When analyses are restricted to use of air quality data within 32 km of the residences of subjects, the RR is reduced to 9.26 over 50 $\mu g/m^3$ and the RR over the IQR of 24 $\mu g/m^3$ in the full data set is 5.21. The female RR's were all much smaller than for males, not being statistically significant for any indicator of PM_{10} or O_3, but being significant for mean SO_2.

The AHSMOG investigators also attempted to compare effects of fine vs. coarse particles (McDonnell et al, 2000). For AHSMOG participants living near an airport (n=3,769), daily $PM_{2.5}$ concentrations were estimated from airport visibility using previously-described methods (Abbey et al, 1995b). Table 6-10 shows the results of this analysis for the male subset near airports (n=1266). Given the smaller numbers of subjects in these subset analyses, it is not necessarily surprising that no pollutants are statistically significant in these regressions. It is important, however, to caveat that the $PM_{2.5}$ exposures were estimated from visibility measurements (increasing exposure measurement error), and a very uneven and clustered distribution of exposures was presented by the authors. Also, the $PM_{10-2.5}$ values were calculated

TABLE 6-10. COMPARISON OF REPORTED PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ IQR RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN A MALE SUBSET OF THE AHSMOG STUDY FOR ONE-POLLUTANT MODELS [and for $PM_{2.5}$ & $PM_{10-2.5}$ Simultaneous Models]

	$PM_{2.5}$ (Range = 24.3 $\mu g/m^3$)			PM_{10} (Range = 29.5 $\mu g/m^3$)			$PM_{10-2.5}$ (Range = 9.7 $\mu g/m^3$)		
Underlying Mortality Cause	Rel. Risk	RR 95% CI	RR t-Stat.	Rel. Risk	RR 95% CI	RR t-Stat.	Rel. Risk	RR 95% CI	RR t-Stat
All Cause [Two Pollutants]	1.22 [1.24]	(0.95,1.58) [0.91,1.67]	1.37 [1.24]	1.15	(0.94,1.41)	1.25	1.05 [0.99]	(0.92,1.20) [0.84,1.16]	0.70 [-.12]
Non-Malignant Respiratory	1.64 [1.55]	(0.93,2.90) [0.80,3.03]	1.27 [0.97]	1.48	(0.93,2.34)	1.33	1.19 [1.06]	(0.88,1.62) [0.74,1.52]	1.00 [.30]
Lung Cancer [Two Pollutants]	2.23 [2.10]	(0.56,8.94) [0.45,9.90]	0.58 [.46]	1.84	(0.59,5.67)	0.65	1.25 [1.07]	(0.63,2.49) [0.49,2.31]	0.52 [.15]

Source: McDonnell et al., 2000.

from the differencing of PM_{10} and $PM_{2.5}$, likely contributing to additional measurement error for the coarse particle ($PM_{10-2.5}$) variable used in the analyses.

6.2.3.2.3 Relationship of AHSMOG to Six Cities and ACS Study Findings

The results of the recent AHSMOG mortality analyses (Abbey et al., 1999; McDonnell et al., 2000) are compared here with findings from the earlier Six Cities study (Dockery et al., 1993), the ACS study (Pope et al., 1995), and the recent HEI reanalyses of the latter two studies. Table 6-11 compares the estimated RR for total and cardiopulmonary mortality respectively among the studies. The number of subjects in these studies varies greatly (8,111 subjects in the Six-Cities Study; 295,223 subjects in the 50 fine particle cities and 552,138 subjects in the 151 sulfate cities of the ACS Study; and 6,338 in the California Seventh-day Adventist AHSMOG Study) and may partially account for differences among their results.

As shown in Table 6-11, the Six Cities study found significant associations with all PM indicators. In the Krewski et al. (2000) reanalysis of the ACS study data, stronger associations were found for $PM_{2.5}$ than PM_{15} (RR's of 1.14 and 1.04 for a 20 $\mu g/m^3$ change in $PM_{2.5}$ and PM_{15}, respectively), though both associations were significant. Most recently, McDonnell et al. (2000) reported evidence from the AHSMOG analyses suggestive of somewhat stronger associations

TABLE 6-11. COMPARISON OF AHSMOG, SIX CITIES, AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM[a]		
		Total mortality Relative Risk (95% CI)	Total mortality - Males Relative Risk (95% CI)	Total mortality - Females Relative Risk (95% CI)
Six City[b]	$PM_{2.5}$	*1.28 (1.09-1.51)*	*no results presented*	*no results presented*
Six City Reanalysis[e]	$PM_{2.5}$	*1.28 (1.09-1.51)*	*1.36 (1.09-1.70)*	*1.22 (0.94-1.58)*
Six City[b]	$PM_{15/10}$	*1.18 (1.06-1.32)*	*no results presented*	*no results presented*
ACS Study[d]	$PM_{2.5}$	*1.14 (1.07-1.21)*	*1.14 (1.06-1.24)*	*1.13 (1.02-1.25)*
ACS Study Reanalysis[e]	PM_{15} *(dichot)*	*1.04 (1.01-1.19)*	*no results presented*	*no results presented*
ACS Study Reanalysis[e]	PM_{15} *(SSI)*	*1.02 (0.99-1.04)*	*no results presented*	*no results presented*
AHSMOG[f]	PM_{10}	*1.02 (0.95-1.09)**	*1.09 (0.98-1.21)*	*0.95 (0.87-1.04)*
AHSMOG[f] *(30 d >100 ug/m^3)*	PM_{10}	*1.02 (0.97-1.07) **	*1.08 (1.01-1.16)*	*0.96 (0.90-1.02)*
AHSMOG[g]	$PM_{2.5}$	*no results presented*	*1.18 (0.96-1.46)*	*no results presented*
		Cardiopulmonary mortality Relative Risk (95% CI)	Cardiopulmonary mortality - Males Relative Risk (95% CI)	Cardiopulmonary mortality - Females Relative Risk (95% CI)
Six City[b]	$PM_{2.5}$	*1.40 (1.12-1.75)*	*no results presented*	*no results presented*
Six City Reanalysis[e]	PM_{15}	*1.20 (1.02-1.41)*	*no results presented*	*no results presented*
ACS Study[d]	$PM_{2.5}$	*1.25 (1.14-1.36)*	*1.19 (1.07-1.33)*	*1.35 (1.15-1.59)*
ACS Study Reanalysis[e]	PM_{15} *(dichot)*	*1.07 (1.03-1.12)*	*no results presented*	*no results presented*
ACS Study Reanalysis[e]	PM_{15} *(SSI)*	*1.06 (1.03-1.09)*	*no results presented*	*no results presented*
AHSMOG[f]	PM_{10}	*1.01 (0.92-1.10) **	*1.08 (0.95-1.24)*	*0.93 (0.83-1.04)*
AHSMOG[f] *(30 d >100 ug/m^3)*	PM_{10}	*0.99 (0.93-1.06) **	*1.06 (0.97-1.17)*	*0.93 (0.87-1.01)*
AHSMOG[f] *CRC*[h] *(30 d >100 ug/m^3)*	PM_{10}	*1.14 (1.03-1.56) **	*1.19 (1.03-1.38)*	*1.05 (0.66-1.69)*
AHSMOG[g]	$PM_{2.5}$	*no results presented*	*1.50 (0.62-2.40)*	*no results presented*

[a] Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, using PM increments of a 20 $\mu g/m^3$ increase for all indicators
[b]Dockery et al. (1993)
[c]Data presented only by smoking subgroup
[d]Pope et al. (1995)
[e]Krewski et al. (2000)
[f]Abbey et al. (1999)
[g]McDonnell et al. (2000)
[h]CRC= contributing respiratory cause
** represents pooled estimates for males and females, using inverse weighted variances*

with fine particles than coarse particles, though the associations were only reported for males and none reached statistical significance.

Overall, the results most recently reported for the AHSMOG study (Abbey et al., 1999; McDonnell et al., 2000) do not find consistent, statistically significant associations between mortality and long-term PM exposure, though the authors conclude that some evidence was suggestive of associations with fine particles. However, the lack of consistent findings in the AHSMOG study does not cast doubt on the findings of the Six Cities and ACS studies, which both had larger study populations (especially the ACS study), were based on measured PM data (in contrast with AHSMOG PM estimates based on TSP or visibility measurements), and have been validated through an exhaustive reanalysis. When considering the results of these three studies, along with the results of the reanalysis of the Six Cities and ACS studies, it can be concluded that there is evidence for an association between long-term exposure to PM (especially fine particles) and mortality.

There is no obvious statistically significant relationship between PM effect sizes, gender, and smoking status across these studies. The AHSMOG analyses show no significant relationships between PM_{10} and total mortality or cardiovascular mortality for either sex, and only for male lung cancer incidence and lung cancer deaths in a predominantly non-smoking sample. The ACS results, in contrast, show similar and significant associations with total mortality for both "never smokers" and "ever smokers", although the ACS cohort may include a substantial number of long-term former smokers with much lower risk than current smokers. The Six Cities study cohort shows the strongest evidence of a higher PM effect in current smokers than in non-smokers, with female former smokers having a higher risk than male former smokers. This study suggests that smoking status may be viewed as an "effect modifier" for ambient PM, just as smoking may be a health effect modifier for ambient O_3 (Cassino et al., 1999).

When the ACS study results are compared with the AHSMOG study results for $SO_4^=$ (PM_{10} was not considered in the ACS study), the total mortality effect sizes per 15 $\mu g/m^3$ $SO_4^=$ for the males in the AHSMOG population are seen to fall between the Six-Cities and the ACS effect estimates for males: RR=1.28 for AHSMOG male participants; RR=1.61 for Six-Cities Study male non-smokers; and RR=1.10 for never smoker males in the ACS study. The AHSMOG study 95% confidence intervals encompass both of those other studies' sulfate RR's.

6.2.3.3 Studies by Particulate Matter Size-Fraction and Composition

6.2.3.3.1 Six Cites, ACS, and AHSMOG Study Results

Ambient PM consists of a mixture that may vary in composition over time and from place to place. This should logically affect the relative toxicity of PM indexed by mass at different times or locations. Some semi-individual chronic exposure studies have investigated relative roles of various PM components in contributing to observed air pollution associations with mortality. Unfortunately, only a limited number of the chronic exposure studies have included direct measurements of chemical-specific constituents of the PM mixes indexed by mass measurements used in their analyses. As shown in Table 6-12, the Harvard Six-Cities study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and $SO_4^=$ RR associations (as indicated by their respective 95% CI's and t-statistics) were more consistent than those for the coarser mass components. However, the effects of sulfate and non-sulfate $PM_{2.5}$ are indicated to be quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities; so, the Six-Cities results were much less conclusive for the acidic component of PM than for the other PM metrics measured over many years during the study. The Six-Cities study also yielded total mortality RR estimates for the reported range across those cities of $PM_{2.5}$ and $SO_4^=$ concentrations that, although not statistically different, were roughly double the analogous RR's for the TSP-PM_{15} and $PM_{15-2.5}$ mass components.

TABLE 6-12. COMPARISON OF ESTIMATED RELATIVE RISKS FOR ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH THE REPORTED INTER-CITY RANGE OF CONCENTRATIONS OF VARIOUS PARTICULATE MATTER METRICS

PM Species	Concentration Range ($\mu g/m^3$)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
$SO_4=$	8.5	1.29	(1.06-1.56)	3.67
$PM_{2.5}$ - $SO_4=$	8.4	1.24	(1.16-1.32)	8.79
$PM_{2.5}$	18.6	1.27	(1.06-1.51)	3.73
$PM_{15-2.5}$	9.7	1.19	(0.91-1.55)	1.81
TSP-PM_{15}	27.5	1.12	(0.88-1.43)	1.31

Source: Dockery et al. (1993); U.S. Environmental Protection Agency (1996).

Table 6-13 presents comparative $PM_{2.5}$ and $SO_4^=$ results from the ACS study, which indicate that both had substantial, statistically significant impacts in all-cause and cardiopulmonary mortality. On the other hand, RR for lung cancer was notably larger (and substantially significant) for $SO_4^=$ than $PM_{2.5}$ (not significant).

TABLE 6-13. COMPARISON OF REPORTED $SO_4^=$ AND $PM_{2.5}$ RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN THE AMERICAN CANCER SOCIETY STUDY

Mortality Cause	$SO_4^=$ (Range = 19.9 $\mu g/m^3$)			$PM_{2.5}$ (Range = 24.5 $\mu g/m^3$)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

The most recent AHSMOG study analysis reported by Abbey et al. (1999) employed PM_{10} as its PM mass index, finding some significant associations with total and by-cause mortality, even after controlling for potentially confounding factors (including other pollutants). This analysis also considered $SO_4^=$ as a PM index for all health outcomes studied except lung cancer, but $SO_4^=$ was not as strongly associated as PM_{10} with mortality and was not statistically significant for any mortality category.

Overall, the semi-individual long-term PM exposure studies conducted to-date collectively confirm earlier cross-sectional study indications that the fine mass component of PM_{10} (and usually especially its sulfate constituent) are more strongly correlated with mortality than is the coarse $PM_{10-2.5}$ component. However, the greater precision of $PM_{2.5}$ population exposure measurement (both analytical and spatial) relative to $PM_{10-2.5}$ makes conclusions regarding their relative contributions to observed PM_{10}-related associations less certain than if the effect of their relative errors of measurement could be addressed.

Single-pollutant results about PM components are informative, as shown in Table 6-14 for total mortality and in Table 6-15 for cardiopulmonary causes. The t-statistics are compared for studies where appropriate: mean PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and sulfate for the Six Cities (Dockery et al., 1993); mean $PM_{2.5}$ and sulfate for ACS (Pope et al., 1995); mean PM_{10} and sulfate, and PM_{10} exceedances of 100 $\mu g/m^3$ for AHSMOG (Abbey et al., 1999).

TABLE 6-14. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.504[a]; 1.530[b]	**2.94**[a]; **3.27**[b]
		Male Nonsmoker	1.280[a]	0.81[a]
	AHSMOG	Male Nonsmoker	1.242	1.616
$PM_{2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.364[a]; 1.379[b]	**2.94**[a]; **3.73**[b]
		Male Nonsmoker	1.207[a]	0.81[a]
	ACS (50 cities)	All	1.174	**4.35**
		Male Nonsmoker	1.245	**1.960**
SO_4= (15 $\mu g/m^3$)	Six Cities	All	1.504[a]; 1.567[b]	**2.94**[a]; **3.67**[b]
		Male Nonsmoker	1.359	0.81[a]
	ACS (151 cities)	All	1.111	**5.107**
		Male Nonsmoker	1.104	1.586
	AHSMOG	Male Nonsmoker	1.279	0.960
Days/yr. with PM_{10}>100 $\mu g/m^3$ (30 days)	AHSMOG	Male Nonsmoker	1.082	**2.183**
$PM_{10-2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.814[a]; 1.560[b]	**2.94**[a,c] 1.816[b]
		Male Nonsmoker	1.434[a]	0.81[a]

[a]Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
[b]Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996).
[c]Method 1 not recommended for $PM_{10-2.5}$ analysis, due to high concentration in Topeka.

TABLE 6-15. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 $\mu g/m^3$)	Six Cities	All	1.744[a]	**2.94**[a]
	AHSMOG	Male Nonsmoker	1.219	1.120
		Male Non. - CRC[c]	1.537	**2.369**
$PM_{2.5}$ (25 $\mu g/m^3$)	Six Cities	All	1.527[a]	**2.94**[a]
	ACS (50 cities)	All	1.317	**4.699**
		Male	1.245	**3.061**
		Male Nonsmoker	1.245	1.466
SO_4= (15 $\mu g/m^3$)	Six Cities	All	1.743[a]	**2.94**[a]
	ACS (151 cities)	All	1.190	**5.470**
		Male	1.147	**3.412**
		Male Nonsmoker	1.205	**2.233**
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non. - CRC[c]	1.219	0.357
Days/yr. with PM_{10}>100 (30 days)	AHSMOG	Male Nonsmoker	1.082	1.310
		Male Non. - CRC[c]	1.188	**2.370**
$PM_{10-2.5}$ (25 $\mu g/m^3$)	Six Cities	All	2.251[a]	**2.94**[a,b]

[a]Method 1 compares Portage vs. Steubenville (Table 3, Dockery et al., 1993).
[b]Method 1 not recommended for $PM_{10-2.5}$ analysis due to high concentration in Topeka.
[c]Male non. - CRC = AHSMOG subjects who died of any contributing non-malignant respiratory cause.

Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the most versus least polluted city in Table 3 of Dockery et al. (1993) adjusted to standard increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection Agency (1996). The Six Cities study of eastern and mid-western U.S. cities suggests a strong and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly significant relationship to PM_{10}, and a marginal relationship to $PM_{10-2.5}$. The ACS study looked at

a broader spatial representation of cities, and found a stronger statistically significant relationship to $PM_{2.5}$ than to sulfate (no other pollutants were examined). The AHSMOG study at California sites (where sulfate levels are typically low) found significant effects in males for PM_{10} 100 $\mu g/m^3$ exceedances, and a marginal effect of mean PM_{10}, but no PM effects for females or with sulfates. On balance, the overall results shown in Tables 6-14 and 6-15 suggest statistically significant relationships between long-term exposures to PM_{10}, $PM_{2.5}$, and/or sulfates and excess total and cause-specific cardiopulmonary mortality.

6.2.3.3.2 The Washington University-EPRI Veterans' Cohort Mortality Study

Lipfert et al. (2000b) recently reported preliminary results from new large-scale mortality analyses using a prospective cohort of up to 70,000 men assembled by the U.S. Veterans Administration (VA) in the mid 1970s. Like the ACS cohort, this cohort was not originally designed to study air pollution, but was linked to air pollution data collected separately, much of it subsequent to the start of the study. The study cohort was male, middle-aged (51 $\pm$ 12 years) and included a larger proportion of African-Americans (35%) than the U.S. population as a whole and a large percentage of current or former smokers (81%). The cohort was selected at the time of recruitment as being mildly to moderately hypertensive, with screening diastolic blood pressure (DBP) in the range 90 to 114 mm Hg (mean 96, about 7 mm more than the U.S. population average) and average systolic blood pressure (SBP) of 148 mm Hg. Also, although the subjects had all been healthy enough to be in the U.S. armed forces at one time, their pre-existing health status at time of study recruitment should be noted: 12% had a pulmonary abnormality on physical examination, 9% were diabetic, 19% had a history of heart disease, 7% had a history of stroke, and 56% had a positive cardio-renal family history.

The subjects received all or most of their medical care at a VA facility, perhaps suggesting relatively low socioeconomic status. The medical care was presumably similar for the entire cohort since it was standardized in the Hypertension, Screening, and Treatment Program (HSTP) clinics. Long records of patient treatment allowed comparison of the health of the mortality cohort with the U.S. population at large, showing about the same proportion of heart attacks, but slightly higher percentages of lung cancer and stroke. Apart from treatment records and determination of vital status, there appeared to be no further follow-up on other individual risk factors; for example, it is likely that the veterans enrolled in the HTSP received medication or

other interventions during subsequent visits to VA clinics if they were found to have elevated blood pressure, whereas no such regular diagnosis or treatment can be assumed for comparable individuals outside this VA cohort. Pollutant levels of the county of residence at the time of entry into the study were used for analyses versus levels at the VA hospital area. Contextual socioeconomic variables were also assembled at the ZIP-code and county levels. The ZIP-code level variables were average education, income, and racial mix. County-level variables included altitude, average annual heating-degree days, percentage Hispanic, and socioeconomic indices. Census tract variables included poverty rate and racial mix. County-wide air pollution variables included TSP, PM_{10}, $PM_{2.5}$, PM_{15}, $PM_{15\text{-}2.5}$, SO_4, O_3, CO, and NO_2 levels at each of the 32 VA clinics where veterans were enrolled. The study that led to the development of this clinical cohort (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970; 1967) was a "landmark" VA cooperative study demonstrating that anti-hypertensive treatment markedly decreased morbidity and mortality. The clinical cohort itself involves actual clinical rather than research settings. Thus, there was no single protocol, no matched control or placebo groups, and no extensive data collection forms to provide systemic information on such things as the presence of other risk factors (for hypertension) (Perry et al., 1982).

Three sequential mortality follow-up periods (1976-81, 1982-88, 1989-96) were considered separately in statistical analyses, which evaluated relationships of mortality in each of those periods to air pollution in different preceding, concurrent, or subsequent periods (i.e., up to 1975, 1975-81, 1982-88, and 1989-86, for TSP in the first three periods, PM_{10} for the last, and NO_2, 95 percentile O_3, and 95 percentile CO for all four periods). Mortality in the above-noted periods was also evaluated in relation to SO_4 in each of the same four periods noted for NO_2, O_3, and CO, and to $PM_{2.5}$, PM_{15}, and $PM_{15\text{-}2.5}$ in 1979-81 and 1982-84. The preliminary screening models used proportional hazards regression models to identify age, SBP, DBP, body mass index (BMI, nonlinear), age and race interaction terms, and present or former smoking as baseline predictors, with one or two pollution variables added. In the final model using 233 terms (of which 162 were interactions of categorized SBP, DBP, and BMI variables with age), the most significant non-pollution variables were SBP, DBP, BMI, and their interactions with age, smoking status, average ZIP education, race, poverty, height, and a clinic-specific effect. Many of the particle effects were not statistically significant, or were significantly negative. The most consistently positive effects were found for O_3 and NO_2 exposures in the immediately preceding years.

It is difficult to assess the methodological soundness of this study or to interpret its preliminary results. These findings may reflect one or more unintentional forms of confounding (e.g., use of SBP and DBP as mortality predictors). Elevated SBP and DBP are generally accepted as risk factors in mortality. However, elevated blood pressure may also be an important intermediate step in a causal pathway from PM exposure to cardiopulmonary disease states and/or related mortality, although the mechanisms involved are not fully understood. Possible mechanisms may include inducing irregularities in heart rate or rhythms, decreased heart rate variability, increasing blood viscosity, and so on (as discussed elsewhere), with elevated blood pressure possibly serving as a marker for such pathophysiological changes. Rothman and Greenland (1998, p. 255) warn that, "In order to avoid bias due to the inappropriate control of variables, the following criterion is usually added to the list: 3. It [the variable] must *not* be affected by exposure or disease (although it may affect exposure). ... The third criterion excludes variables that are intermediate on the causal pathway from exposure to disease. This exclusion can be relaxed under certain conditions, but in doing so special analytic techniques must be applied . . ." Such techniques apparently have not been applied in this case. Data reanalysis, omitting SBP and DBP as predictors of mortality, might clarify the situation.

Also complicating interpretation of the study is the choice of the study population. The restricted range of DBP at the time of recruitment limits the comparability of these findings to more general populations, including both veterans and civilians with lower DBP or with more highly elevated DBP (not necessarily medically treated). Even if the veterans were disproportionately of low SES, their enrollment in the HTSP by reason of national service likely allowed them more regular treatment (e.g., by medication) of their identified hypertension than the general public. Such medication would presumably considerably narrow the range of blood pressure values downward in subsequent years of the study compared to the SBP and DBP values at time of recruitment into the study, thus making it more difficult to detect PM effects on mortality related to blood pressure or other associated cardiovascular pathophysiology.

6.2.3.4 Population-Based Mortality Studies in Children

Older cross-sectional mortality studies suggest that the very young may represent an especially susceptible sub-population for PM-related mortality. For example, Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP.

More recently, Bobak and Leon (1992) studied neonatal (ages less than one month) and post-neonatal mortality (ages 1-12 months) in the Czech Republic and reported significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. The exposure duration was longer than a few days, but shorter than in the adult prospective cohort studies. Thus, the limited available studies reviewed in the 1996 PM AQCD were highly suggestive of an association between ambient PM concentrations and infant mortality, especially among post-neonatal infants.

More recent studies since the 1996 PM AQCD have focused specifically on ambient PM relationships to (a) intrauterine mortality (Pereira et al., 1998) and morbidity (Dejmek et al., 1999) and (b) early post neonatal mortality (Woodruff et al., 1997; Bobak and Leon, 1999; Loomis et al., 1999; Lipfert et al., 2000c). In the case of the Pereira study of intrauterine (pre-natal) mortality during one year (1991-1992) in Brazil, PM_{10} was not found to be a significant predictor, but CO's involvement was suggested by the association between increased carboxyhemoglobin (COHb) in fetal blood and ambient CO levels on the day of delivery measured in a separate study. Another study (Dejmek et al., 1999) evaluated possible impacts of ambient PM_{10} and $PM_{2.5}$ exposure (monitored by EPA-developed VAPS methods) during pregnancy on intrauterine growth retardation (IUGR) risk in the highly polluted Teplice District of Northern Bohemia in the Czech Republic during three years (1993-1996). Mean levels of pollutants (PM, NO_2, SO_2) were calculated for each month of gestation and three concentration intervals (low, medium, high) derived for each pollutant. Preliminary analyses of data found no significant associations of IUGR with NO_2, but SO_2 and PM_{10} early in pregnancy were significantly associated with IUGR. Odds ratios for IUGR for PM_{10} and $PM_{2.5}$ levels were determined by logistic regressions for each month during gestation, after adjusting for potential confounding factors (e.g., smoking, alcohol consumption during pregnancy, etc.). Definition of an IUGR birth was any one for which the birth weight fell below the 10th percentile by gender and age for live births in the Czech Republic (1992-93). The OR's for IUGR were significantly related to PM_{10} during the first month of gestation: that is, as compared to low PM_{10}, the medium level PM_{10} OR = 1.47 (CI 0.99-2.16), and the high level PM_{10} OR = 1.85 (CI 1.29-2.66). $PM_{2.5}$ levels were highly correlated with PM_{10} (r = 0.98) and manifested similar patterns (OR = 1.16, CI

0.08-0.69 for medium $PM_{2.5}$ level; OR = 1.68, CI 1.18-2.40 for high $PM_{2.5}$ level). These results suggest effects of PM exposures (probably including fine particles such as sulfates, acid aerosols, and PAHs in the Teplice ambient mix) early in pregnancy (circa embryo implantation) on subsequent fetal growth and development.

More consistent results indicating likely early post-natal PM exposure effects on neonatal infant mortality have emerged from other new studies. Woodruff et al. (1997), for example, used cross-sectional methods to evaluate possible association of post-neonatal mortality with ambient PM_{10} pollution. This study involved an analysis of a cohort of circa 4 million infants born during 1989 - 1991 in 86 U.S. metropolitan statistical areas (MSAs). Data from the National Center for Health Statistics-linked birth/infant death records were combined at the MSA level with PM_{10} data from EPA's Aerometric database. Infants were categorized as having high, medium, or low exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Relationships between this early neonatal PM_{10} exposure and total and cause-specific post-neonatal mortality rates (from 1 mo. to 1 yr of age) were examined using logistic regression analyses, adjusting for demographic and environmental factors. Overall post-neonatal mortality rates per 1,000 live births were 3.1 among infants in areas with low PM_{10} exposures, 3.5 among infants with medium PM_{10} exposures, and 3.7 among highly PM exposed infants. After adjustment for other covariates, the odds ratio (OR) and 95% confidence intervals for total post-neonatal mortality for the high versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85) and sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies, high PM_{10} exposure was positively (but not significantly) associated with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61). However, other pollutants (e.g., CO) were not considered as possible confounders. This study provides results consistent with some earlier reports indicating that outdoor PM air pollution may be associated with increased risk of post-neonatal mortality (e.g., Bobak and Leon, 1992), but lack of consideration of other air pollutants as potential confounders in this new study reduces the certainty that PM is the specific causal outdoor air pollutant in this case.

Recently, Lipfert et al. (2000c) reported replicating the basic findings of Woodruff et al. (1997) using a similar modeling approach but annual average PM_{10} air quality data for one year (1990) instead of PM_{10} averaged over the first two post natal months during 1989-1991. The

quantitative relationship between the individual risk of infant mortality did not differ among infant categories (by age, by birthweight, or by cause), but PM_{10} risks for SIDs deaths were higher for babies of smoking mothers. $SO_4^=$ was a strong negative predictor of SIDs mortality for all age and birth weight categories. The authors (a) noted difficulties in ascribing the reported PM_{10} and $SO_4^=$ associations to effects of the PM pollutants per se versus the results possibly reflecting interrelationships between the air pollution indices, a strong well-established East-West gradient in U.S. SIDS cases, and/or underlying sociodemographic factors (e.g., the socioeconomic or education level of parents) and (b) hypothesized that a parallel gradient in use of wood burning in fireplaces or woodstoves and consequent indoor wood smoke exposure might explain the observed cross-sectional study results.

The basic findings from Woodruff et al. (1997) also appear to be bolstered by a more recent follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles and nitrogen oxides on risk of death in the neonatal and early post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and specific for respiratory causes. Only PM showed a consistent association when all pollutants were entered in one model. Thus, in this study, it appears that long-term exposure to PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995 adds additional interesting information pointing towards likely fine particle impacts on infant mortality. That is, in Mexico City (where mean 24-h $PM_{2.5}$ = 27.4 $\mu g/m^3$), infant mortality was found to be associated with $PM_{2.5}$, NO_2, and O_3 in single pollutant GAM Poisson models, but much less consistently with NO_2, and O_3 than $PM_{2.5}$ in multipollutant models. The estimated excess risk for $PM_{2.5}$-related infant mortality lagged 3-5 days was 18.2% (95% CI 6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$. It is not clear, however, the extent to which such a notable increased risk for infant mortality might be extrapolated to U.S. situations, due to (a) possible differences in prenatal maternal or early post natal infant nutritional status and/or (b) possible enhancement of PM-related risks associated with exposure to PM under higher altitude conditions in Mexico City versus most U.S. cities.

6.2.3.5 Shortening-of-Life Associated With Long-Term Ambient Particulate Matter Exposure

The public health burden of mortality associated with exposure to ambient PM depends not only on the increased risk of death, but also on the length of life shortening that is attributable to those deaths. However, the 1996 PM AQCD concluded that confident quantitive determination of years of life lost to ambient PM exposure is not yet possible; life shortening may range from days to years (U.S. Environmental Protection Agency, 1996). A newly published analysis has now attempted to estimate life-shortening associated with chronic PM exposures.

6.2.3.5.1 Life-Shortening Estimates Based on Semi-Individual Cohort Study Results

Brunekreef (1997) reviewed the available evidence of the mortality effects of long-term exposure to PM air pollution and, using life table methods, derived an estimate of the reduction in life expectancy implied by those effect estimates. Based on the results of Pope et al. (1995) and Dockery et al. (1993), a relative risk of 1.1 per 10 $\mu g/m^3$ exposure over 15 years was assumed for the effect of PM air pollution on men 25-75 years of age. A 1992 life table for men in the Netherlands was developed for 10 successive five-year categories that make up the 25-75 year old age range. Life expectancy of a 25 year old was then calculated for this base case and compared with the calculated life expectancy for the PM exposed case where the death rates were increased in each age group by a factor of 1.1. A difference of 1.11 years was found between the "exposed" and "clean air" cohorts' overall life expectancy at age 25. Looked at another way, this implies that the expectation of the lifespan of persons who actually died from air pollution was reduced by more than 10 years, since they represent a small percentage of the entire cohort population. A similar calculation by the authors for the 1969-71 life table for U.S. white males yielded an even larger reduction of 1.31 years for the entire population's life expectancy at age 25. Thus, these calculations imply that relatively small differences in long-term exposure to ambient PM can have substantial effects on life expectancy.

6.2.3.5.2 Potential Effects of Infant Mortality on Life-Shortening Estimates

Deaths among children can logically have the greatest influence on a population's overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible long-term air pollution exposure effects on the population aged <25 years. As discussed above,

some of the older cross-sectional studies and the more recent studies by Bobak and Leon (1992), Woodruff et al. (1997), Bobak and Leon (1999), and Loomis et al. (1999) suggest that infants may be among sub-populations notably affected by long-term PM exposure. Thus, although it is difficult to quantify, any premature PM associated mortality that does occur among children due to long-term PM exposure, as suggested by these studies, would significantly increase the overall population life shortening over and above that estimated by Brunekreef (1997) for long-term PM exposure of adults aged 25 years and older.

6.2.3.6 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects

A review of the studies summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996) indicates that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins. The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events.

The recent HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) "replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality." Several questions, including the questions (1-4) posed at the outset of this Section (6.2.3) were investigated by the Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies data sets. Key results emerging from the HEI reanalyses and other new chronic PM mortality studies are as follow:

(1) A much larger number of confounding variables and effects modifiers were considered in the Reanalysis Study than in the original Six City and ACS studies. The only significant air pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2, which greatly decreased the $PM_{2.5}$ and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38). A similar reduction in particle effects occurred in any multi-pollutant model with SO_2. The most important new effects modifier was education. The AHSMOG study suggested that other metrics for air pollution, and other personal covariates such as time spent outdoors and consumption of

anti- oxidant vitamins, might be useful. Both individual- level covariates and ecological-level covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated.

(2) Specific attribution of excess long-term mortality to any specific particle component or gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$and sulfate were significantly associated with excess total mortality and cardiopulmonary mortality and to about the same extent whether the air pollution data were mean or median long-term concentrations or whether based on Original Investigator or Reanalysis Team data. The association of mortality with PM_{15} was much smaller, though still significant, and the associations with the coarse fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was significant only for sulfate with the original investigator data, or for new investigators with regional sulfate artifact adjustment for the 1980-1981 data (Krewski et al., 2000, Part II, Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous co-pollutants were generally non-significant except for SO_2 (Krewski et al., 2000, Part II, Tables 32, 34-38) which was highly significant, and for cardiopulmonary disease with warm-season ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very high, and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000, p. 234) concluded that, "Collectively, our reanalyses suggest that mortality may be associated with more than one component of the complex mix of ambient air pollutants in urban areas of the United States."

(3) The extensive temporal data on air pollution concentrations over time in the Six City Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure to a much greater extent than reported in Dockery et al. (1993). The first approach was to estimate the log- hazard ratio as a function of follow up time using a flexible spline-function model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4 and $PM_{2.5}$ suggest very similar relationships, with larger risk after initial exposure decreasing to 0 after about 4 or 5 years, and a large increase in risk at about 10 years follow-up time.

The analyses of the ACS Study proceeded somewhat differently, with less temporal data but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of estimated cumulative exposure (not defined) were very nonlinear and showed quite different relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the mortality log-hazard ratio increasing up to about 15 $\mu g/m^3$ and relatively flat above about

22 $\mu g/m^3$, then increasing again. The sulfate relationship is almost piecewise linear, with a low near- zero slope below about 11 $\mu g/m^3$ and a steep increase above that concentration.

A third approach evaluated several time-dependent $PM_{2.5}$ exposure indicators in the Six City study. They are: (a) constant (at the mean) over the entire follow-up period; (b) annual mean within each of the 13 years of the study; (c) city-specific mean concentration for the earliest years of the study, i.e., very long-term effect; (d) exposure estimate in 2 years preceding death; (e) exposure estimate in 3 to 5 years preceding death; (f) exposure estimate > 5 years preceding death. The time-dependent estimates (a-e) for mortality risk are generally similar and statistically significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per 24.5 $\mu g/m^3$ being much lower than the risk of 1.31 estimated for exposure at the constant mean for the period. Thus, it is highly likely the duration and time patterns of long-term exposure affect the risk of mortality, and further study of this question (along with that of mortality displacement from short-term exposures) would improve estimates of life-years lost from PM exposure.

(4) The Reanalysis Study also advanced our understanding of the shape of the relationship between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II, Figure 6) found a visually near linear relationship between all cause and cardiopulmonary mortality residuals and mean sulfate concentrations, near linear between cardiopulmonary mortality and mean $PM_{2.5}$, but a somewhat nonlinear relationship between all cause mortality residuals and mean $PM_{2.5}$ concentrations that flattens above about 20 $\mu g/m^3$. The relationship with lung cancer is much weaker, as noted above. The confidence bands around the fitted curves are very wide, however, neither requiring a linear relationship nor precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality relationship for other indicators may be useful in identifying a threshold, if one exists, for chronic PM exposures.

(5) With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies have generally found that the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with mortality. While the relative measurement errors of the various PM constituents must be further evaluated as a possible source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective semi-individual studies both indicate that the fine mass components of PM are more strongly associated with the mortality effects of chronic PM exposure than are coarse PM components.

(6) Recent investigations of the public health implications of such chronic PM exposure-mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne PM of ambient origin can have substantial effects on life expectancy. For example, a calculation for the 1969-71 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25. Also, new evidence of associations of PM exposure with infant mortality (Bobak and Leon, 1992, 1999; Woodruff et al., 1997; Loomis et al., 1999) and/or intrauterine growth retardation (Dejmek et al., 1999) and consequent increase risk for many serious health conditions associated with low birth weight, if further substantiated, would imply that life shortening in the entire population from long-term PM exposure could well be significantly larger than that estimated by Brunekreef (1997).

6.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE

This morbidity discussion is presented below in several subsections, dealing with: (a) acute cardiovascular morbidity effects of ambient PM exposure; (b) effects of short-term PM exposure on the incidence of respiratory and other medical visits and hospital admissions; and (c) short- and long-term PM exposure effects on lung function and respiratory symptoms in asthmatics and non-asthmatics.

6.3.1 Cardiovascular Effects Associated with Acute Ambient Particulate Matter Exposure

6.3.1.1 Introduction

Very little information specifically addressing acute cardiovascular morbidity effects of PM existed at the time of the 1996 PM AQCD. While the literature still remains relatively sparse, an important new body of data now exists that both extends the available quantitative information on the ecologic relationship between ambient pollution and hospital admissions and which, more intriguingly, illuminates some of the physiological changes that may occur on the mechanistic pathway leading from PM exposure to adverse cardiac outcomes.

This section begins with a brief summary of the conclusions that were reached in the 1996 PM AQCD regarding acute cardiovascular impacts of PM. Next, new studies are reviewed which fall into two general classes: ecologic time series studies of daily hospitalizations in relation to ambient PM and other pollutants; and individual-level studies of temporal changes in physiological measures of cardiac function as they relate to ambient pollution. This review is followed by discussion of several issues that are important in interpreting the available data, including the identification of potentially susceptible sub-populations, the roles of environmental co-factors such as weather and other air pollutants, temporal lags in the relationship between exposure and outcome, and the relative importance of various size-classified PM components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$).

6.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air quality Criteria Document

Just two studies were available for review in the 1996 PM AQCD that provided data on acute cardiovascular morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time series design, using standard statistical methods. Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett and colleagues (1995) reported significant associations between fine particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that, "There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints" (U.S. Environmental Protection Agency, 1996 p. 12-100). The PM AQCD went on to state that acute impacts on CVD admissions had been demonstrated for elderly populations (i.e., ≥ 65), but that insufficient data existed to assess relative impacts on younger populations.

Also relevant to an evaluation of the acute impacts of particles on cardiovascular endpoints are insights gained from time series studies of daily mortality, which, aside from the outcome studied, are nearly identical in design and analysis to time series studies of hospitalizations. It is

also probable that acute effects of air pollution on cardiovascular hospitalizations and mortality follow qualitatively similar etiologic mechanisms.

Several acute mortality studies reviewed in the 1996 PM AQCD analyzed cause-specific deaths (usually total cardiovascular and total respiratory) in relation to ambient particle concentrations. The PM AQCD noted that, in general, cause-specific analyses "reported higher estimated relative risks for respiratory and cardiovascular categories than for total or other categories" (U.S. Environmental Protection Agency, 1996 p. 12-349). It was noted that these findings were consistent with analyses of case reports from historic air pollution episodes, like the December, 1952 London episode, in which the mortality impacts were greatest among the elderly and those with pre-existing respiratory and/or cardiovascular disease. A comparative analysis of age- and cause-specific mortality effects of particles in modern-day Philadelphia with those observed in the 1952 London episode concluded that the patterns of mortality were largely consistent, once the order of magnitude difference in exposure levels was taken into account (Schwartz, 1994a).

Viewed as a group, the acute morbidity and mortality studies reviewed in the 1996 PM AQCD were thus consistent with the notion that acute health risks of PM are larger for cardiovascular and respiratory causes than for other causes. Given the tendency for end-stage disease states to include both respiratory and cardiovascular impairment, and the associated diagnostic overlap that often exists, it was not possible on the basis of these studies alone to determine which of the two organ systems, if either, was more critically impacted.

6.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies

6.3.1.3.1 Acute Hospital Admission Studies

Numerous new studies have reported associations between daily measures of ambient PM and daily hospital admissions for cardiovascular disease (see Table 6-16). Again, of particular interest are results from multi-city studies, as discussed most extensively below, which likely yield more precise effect estimates than those derived from smaller independent studies of individual cities with fewer overall study observations. Results from several new multi-city studies (Schwartz, 1999; Samet et al., 2000a,b; Zanobetti et al., 2000b), that provide combined estimates of PM-CVD effects across numerous U.S. cities and regions, provide evidence substantiating significant PM effects on cardiovascular-related hospital admissions and visits.

TABLE 6-16. ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States			
Samet et al. (2000a,b) 14 US cities 1985-1994, but range of years varied by city PM_{10} ($\mu g/m^3$) mean, median, IQR: Birmingham, AL: 34.8, 30.6, 26.3 Boulder, CO: 24.4, 22.0, 14.0 Canton, OH: 28.4, 25.6, 15.3 Chicago, Il: 36.4, 32.6, 22.4 Colorado Springs, CO: 26.9, 22.9, 11.9 Detroit, MI: 36.8, 32.0, 28.2 Minneapolis/St. Paul, MN: 27.4, 24.1, 17.9 Nashville, TN: 31.6, 29.2, 17.9 New Haven, CT: 29.3, 26.0, 20.2 Pittsburgh, PA: 36.0, 30.5, 27.4 Provo/Orem, UT: 38.9, 30.3, 22.8 Seattle, WA: 31.0, 26.7, 20.0 Spokane, WA: 45.3, 36.2, 33.5 Youngstown, OH: 33.1, 29.4, 18.6	Daily medicare hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Mean CVD counts ranged from 3 to 102/day in the 14 cities. Covariates: SO_2, NO_2, O_3, CO, temperature, relative humidity, barometric pressure. Stats: In first stage, performed city-specific, single-pollutant, generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 14 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	City-specific risk estimates for a 10 $\mu g/m^3$ increase in PM_{10} ranged from -1.2% in Canton to 2.2% in Colorado Springs. Across-city weighted mean risk estimate was largest at lag 0, diminishing rapidly at other lags. Only the mean of lags 0 and 1 was significantly associated with CVD. There was no evidence of statistical heterogeneity in risk estimates across cities for CVD. City-specific risk estimates were not associated with the percent of the population that was non-white, living in poverty, college educated, nor unemployed. No evidence was observed that PM_{10} effects were modified by weather. No multi-pollutant modeling results presented. However, no association was observed between the city-specific PM_{10} risk estimates and the city-specific correlation between PM_{10} and co-pollutants. These results suggest a weak association between PM_{10} and total cardiovascular hospital admissions among the elderly.	Percent Excess CVD Risk (95% CI), combined over cities per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d lag. 5.5% (4.7, 6.2) PM_{10}: 0–1d lag. 6.0% (5.1, 6.8) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d lag. 7.6% (6.0, 9.1)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Schwartz (1999) 8 US metropolitan counties 1988-1990 median, IQR for PM_{10} ($\mu g/m^3$): Chicago, IL: 35, 23 Colorado Springs, CO: 23, 14 Minneapolis, MN: 28, 15 New Haven, CT: 37, 25 St. Paul, MN: 34, 23 Seattle, WA: 29, 20 Spokane, WA: 37, 33 Tacoma, WA: 37, 27	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Median daily hospitalizations: 110, 3, 14, 18, 9, 22, 6, 7, alphabetically by city. Covariates: CO, temperature, dewpoint temp. Stats: robust Poisson regression after removing admission outliers; generalized additive models with LOESS smooths for control of trends, seasons, and weather. Day of week dummy variables. Lag 0 used for all covariates.	In single-pollutant models, similar PM_{10} effect sizes obtained for each county. Five of eight county-specific effects were statistically significant, as was the PM_{10} effect pooled across locations. CO effects significant in six of eight counties. The PM_{10} and CO effects were both significant in a two pollutant model that was run for five counties where the PM_{10}/CO correlation was less than 0.5. Results reinforce those of Schwartz, 1997.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0d. Individual counties: Chicago: 4.7 (2.6, 6.8) CO Spng: 5.6 (−6.8, 19.0) Minneap: 4.1 (−3.6, 12.5) New Hav: 5.8 (2.1, 9.7) St. Paul: 8.6 (2.9, 14.5) Seattle: 3.6 (−0.1, 7.4) Spokane: 6.7 (0.9, 12.8) Tacoma: 5.3 (3.1, 7.6) Pooled: 5.0 (3.7, 6.4) 3.8 (2.0, 5.5) w. CO
Zanobetti et al. (2000b) 10 US cities 1986-1994 PM_{10} ($\mu g/m^3$) median, IQR: Canton, OH: 26, 15 Birmingham, AL: 31, 26 Chicago, Il: 33, 23 Colorado Springs, CO: 23, 13 Detroit, MI: 32, 28 Minneapolis/St. Paul, MN: 24, 18 New Haven, CT: 26, 21 Pittsburgh, PA: 30, 28 Seattle, WA: 27, 21 Spokane, WA: 36, 34	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Median CVD counts ranged from 3 to 103/day in the 10 cities. Covariates: SO_2, O_3, CO, temperature, relative humidity, barommetric pressure. Stats: In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 $\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. Suggests a weak association between PM_{10} and total cardiovascular hospital admissions among the elderly.	Percent Excess Risk (SE) combined over cities: Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d. 5.6 (4.7, 6.4) PM_{10}: 0−1 d. 6.2 (5.4, 7.0) $PM_{10} < 50$ $\mu g/m^3$: 0−1 d. 7.8 (6.2, 9.4)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Linn et al. (2000) Los Angeles 1992-1995 Mean $PM_{10\ est}$ ($\mu g/m^3$): 18	Hospital admissions for total cardiovascular diseases (CVD), congestive heart failure (CHF), myocardial infarction (MI), cardiac arrhythmia (CA) among all persons 30 years and older, and by sex, age, race, and season. ICD9 codes not given. Mean hospital admissions for CVD: 428. Covariates: CO, NO_2, O_3, temperature, rainfall. Daily gravimetric PM_{10} estimated by regression of every sixth day PM_{10} on daily real-time PM_{10} data collected by TEOM. Poisson regression with controls for seasons and day of week. Reported results for lag 0 only. Results reported as Poisson regression coefficients and their standard errors. The number of daily CVD admissions associated with the mean PM_{10} concentration can be computed by multiplying the PM_{10} coefficient by the PM_{10} mean and then exponentiating. Percent effects are calculated by dividing this result by the mean daily admission count for CVD.	In year-round, single-pollutant models, significant effects of CO, NO_2, and PM_{10} on CVD were reported. PM_{10} effects appeared larger in winter and fall than in spring and summer. No consistent differences in PM_{10} effects across sex, age, and race. No multi-pollutant results presented.	% increase with PM_{10} change of 50 $\mu g/m^3$: $PM_{10\ est}$: 0 d. CVD ages 30+ 3.25% (2.04, 4.47) MI ages 30+ 3.04% (0.06, 6.12) CHF ages 30+ 2.02% (–0.94, 5.06) CA ages 30+ 1.01% (–1.93, 4.02)
Morris and Naumova (1998) Chicago, IL 1986-1989 mean, median, IQR, 75th percentile: PM_{10} ($\mu g/m^3$): 41, 38, 23, 51	Daily hospital admissions for congestive heart failure, CHF (ICD9 428), among persons over 65 years. Mean hospitalizations: 34/day. Covariates: O_3, NO_2, SO_2, CO, temperature, relative humidity. Gases measured at up to eight sites; daily PM_{10} measured at one site. Stats: GLM for time series data. Controlled for trends and cycles using dummy variables for day of week, month, and year. Residuals were modeled as negative binomial distribution. Lags of 0-3 days examined.	CO was only pollutant statistically significant in both single- and multi-pollutant models. Exposure misclassification may have been larger for PM_{10} due to single site. Results suggest effects of both CO and PM_{10} on congestive heart failure hospitalizations among elderly, but CO effects appear more robust.	Percent Excess Risk (95% CI) per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d. 3.92% (1.02, 6.90) 1.96% (–1.4, 5.4) with 4 gaseous pollutants
Schwartz (1997) Tucson, AZ 1988-1990 mean, median, IQR: PM_{10} ($\mu g/m^3$): 42, 39, 23	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Mean hospitalizations: 13.4/day. Covariates: O_3, NO_2, CO, SO_2, temperature, dewpoint temperature. Gases measured at multiple sites; daily PM_{10} at one site. Stats: robust Poisson regression; generalized additive model with LOESS smooth for controlling trends and seasons, and regression splines to control weather. Lags of 0-2 days examined.	Both PM_{10} (lag 0) and CO significantly and independently associated with admissions, whereas other gases were not. Sensitivity analyses reinforced these basic results. Results suggest independent effects of both PM_{10} and CO for total cardiovascular hospitalizations among the elderly.	Percent Excess Risk (95% CI) per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d. 6.07% (1.12, 1.27) 5.22% (0.17, 10.54) w. CO

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Gwynn et al (2000) Buffalo, NY	Air pollution health effects associations with total, respiratory, and CVD hospital admissions (HA's) examined using Poisson model controlling for weather, seasonality, long-wave effects, day of week, holidays.	Positive, but non-significant assoc. found between all PM indices and circulatory hospital admissions. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates.	Percent excess CVD HA risks (95% CI) per PM_{10} = 50 $\mu g/m^3$; SO_4 = 15 $\mu g/m^3$; H^+ = 75 nmoles/m^3; COH = 0.5 units/1,000 ft: PM_{10} (lag 3) = 5.7% (−3.3, 15.5) SO_4 (lag 1) = 0.1% (−0.1, 0.4) H^+ (lag 0) = 1.9% (−0.3, 4.2) COH (lag 1) = 2.2% (−1.9, 6.3)
Lippmann et al. (2000) Detroit, MI 1992-1994	Various cardiovascular (CVD)-related, and respiratory (COPD, Pneumonia) hospital admissions (HA's) for persons 65+ yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For heart failure, all PM metrics yielded significant associations. Associations for IHD, dysrhythmia, and stroke were positive but generally non-sig. with all PM indices. Adding gaseous pollutants had negligible effects on various PM metric RR estimates. Most consistent effect of adding co-pollutants was to widen confidence bands on the PM metric RR estimates; a common statistical artifact of correlated predictors. Despite usually low levels, H^+ had strong association with respiratory admissions on the few days it was present. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per $\mu g/m^3$ in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity not usually present.	Percent excess CVD H A risks (95% CI) per 50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$: IHD: $PM_{2.5}$ (lag 2) 4.3 (−1.4, 10.4) PM_{10} (lag 2) 8.9 (0.5, 18.0) $PM_{10-2.5}$ (lag 2) 10.5 (2.7, 18.9) Dysrhythmia: $PM_{2.5}$ (lag 1) 3.2 (−6.5, 14.0) PM_{10} (lag 1) 2.9 (−6.8, 13.7) $PM_{10-2.5}$ (lag 0) 0.2 (−12.2, 14.4) Heart Failure: $PM_{2.5}$ (lag 1) 9.1 (2.4, 16.2) PM_{10} (lag 0) 9.7 (0.2, 20.1) $PM_{10-2.5}$ (lag 0) 5.2 (−3.3, 14.5) Stroke: $PM_{2.5}$ (lag 0) 1.8 (−5.3, 9.4) PM_{10} (lag 1) 4.8 (−5.5, 16.2) $PM_{10-2.5}$ (lag 1) 4.9 (−4.7, 15.5)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Moolgavkar (2000b) Three urban counties: Cook, IL; Los Angeles, CA; Maricopa, AZ. 1987-1995 Pollutant median, IQR: Cook: PM_{10}: 35, 22 LA: PM_{10}: 44, 26 $PM_{2.5}$: 22, 16 Maricopa: PM_{10}: 41, 19	Analysis of daily hospital admissions for total cardiovascular diseases, CVD, (ICD9 codes 390-429) and cerebrovascular diseases, CRD, (ICD9 430-448) among persons aged 65 and over. For Los Angeles, a second age group, 20-64, was also analyzed. Median daily CVD admissions were 110, 172, and 33 in Cook, LA, and Maricopa counties, respectively. PM_{10} available only every sixth day in LA and Maricopa counties. In LA, every-sixth-day $PM_{2.5}$ also was available. Covariates: CO, NO_2, O_3, SO_2, temperature, relative humidity. Stats: generalized additive Poisson regression, with controls for day of week and smooth temporal variability. Single-pollutant models estimated for individual lags from 0 to 5. Two-pollutant models also estimated, with both pollutants at same lag.	In single-pollutant models in Cook and LA counties, PM was significantly associated with CVD admissions at lags 0, 1, and 2, with diminishing effects over lags. $PM_{2.5}$ was also significant in LA for lags 0 and 1. For the 20-64 year old age group in LA, risk estimates were similar to those for 65+. In Maricopa county, no positive PM_{10} associations were observed at any lag. In two-pollutant models in Cook and LA counties, the $PM_{10}/PM_{2.5}$ risk estimates diminished and/or were rendered non-significant. Little evidence observed for associations between CRD admissions and PM. These results suggest that PM is not independently associated with CVD or CRD hospital admissions.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ change in PM_{10} and 25 $\mu g/m^3$ change in $PM_{2.5}$. Cook 65+: PM_{10}, 0 d. 4.2 (3.0, 5.5) PM_{10}, 0 d. w/NO_2. 1.8 (0.4, 3.2) LA 65+: PM_{10}, 0 d. 3.2 (1.2, 5.3) PM_{10}, 0 d. w/CO −1.8 (−4.4, 0.9) $PM_{2.5}$, 0 d. 4.3 (2.5, 6.1) $PM_{2.5}$, 0 d. w/CO 0.8 (−1.3, 2.9) LA 20−64 years old: PM_{10}, 0 d. 4.4 (2.2, 6.7) PM_{10}, 0 d. w/CO 1.4 (−1.3, 4.2) $PM_{2.5}$, 0 d. 3.5 (1.8, 5.3) $PM_{2.5}$, 0 d., w/CO) 2.3 (−0.2, 4.8) Maricopa: PM_{10}, 0 d. −2.4 (−6.9, 2.3)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} ($\mu g/m^3$): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} ($\mu g/m^3$): 29.1, 27.6, 12.0 $PM_{2.5}$ ($\mu g/m^3$): 19.4, 17.5, 9.35 CP ($\mu g/m^3$): 9.39, 8.95, 4.52 10-100 nm PM counts (count/cm^3): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals ($\mu g/m^3$): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates ($\mu g/m^3$): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity ($\mu g/m^3$): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM ($\mu g/m^3$): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon ($\mu g/m^3$): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for dysrhythmias, DYS, (ICD 9 code 427) and all cardiovascular diseases, CVD, (codes 402, 410-414, 427, 428, 433-437, 440, 444, 451-453) for persons aged 16 and older in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all CVD in period 1 were 6.5 and 28.4, respectively. Mean daily ED visits for dysrhythmias and all CVD in period 2 were 11.2 and 45.1, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day of week and hospital entry/exit indicators also included. Pollutants were treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, significant negative association (p=0.02) observed between CVD and 3-day average PM_{10}. There was ca. 2% drop in CVD per 10 $\mu g/m^3$ increase in PM_{10}. CVD was positively associated with NO_2 (p=0.11) and negatively associated with SO_2 (p=0.10). No association observed between dysrhythmias and PM_{10} in period 1. However, dysrhythmias were positively associated with NO_2 (p=0.06). In period 2, i.e., the first year of operation of the superstation, no associations seen with PM_{10} or $PM_{2.5}$. However, significant positive associations observed between CVD and elemental carbon (p=0.005) and organic matter (p=0.02), as well as with CO (p=0.001). For dysrhythmias, significant positive associations observed with elemental carbon (p=0.004), CP (p=0.04), and CO (p=0.005). These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed. Of most concern is the extent to which the data included in the reported analyses from only about half the participating hospitals are representative of the entire set across the study area.	Percent Excess Risk (p-value): Effects computed for 50 $\mu g/m^3$ change in PM_{10}; 25 $\mu g/m^3$ for CP and $PM_{2.5}$; 25,000 counts/cm^3 for 10-100 nm counts. Period 1: PM_{10}, 0-2 d. avg. CVD: −8.2 (0.02) DYS: 4.6 (0.58) Period 2: 0-2 d. avg. in all cases CVD % effect; DYS % effect: PM_{10}: 5.1 (−7.9, 19.9); 13.1 (−14.1, 50.0) $PM_{2.5}$: 6.1 (−3.1, 16.2); 6.1 (−12.6, 28.9) CP: 17.6 (−4.6, 45.0); 53.2 (2.1, 129.6) 10-100 nm counts: −11.0 (0.17); 3.0 (0.87)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada			
Burnett et al. (1995) Ontario, Canada 1983-1988 Sulfate Mean: 4.37 $\mu g/m^3$ Median: 3.07 $\mu g/m^3$ 95th percentile: 13 $\mu g/m^3$	168 Ontario hospitals. Hospitalizations for coronary artery disease, CAD (ICD9 codes 410,413), cardiac dysrhythmias, DYS (code 427), heart failure, HF (code 428), and all three categories combined (total CVD). Mean total CVD rate: 14.4/day. 1986 population of study area: 8.7 million. All ages, <65, >=65. Both sexes, males, females. Daily sulfates from nine monitoring stations. Ozone from 22 stations. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. Day of week effects removed. 0-3 day lags examined. Covariates: ozone, ozone^2, temperature, temperature^2. Linear and quadratic sulfate terms included in model.	Sulfate lagged one day significantly assoc. with total CVD admissions with and without ozone in the model. Larger associations observed for coronary artery disease and heart failure than for cardiac dysrhythmias. Suggestion of larger associations for males and the sub-population 65 years old and greater. Little evidence for seasonal differences in sulfate effects after controlling for covariates.	Effects computed for 95th percentile change in SO_4 SO_4, 1d, no covariates: Total CVD: 2.8 (1.8, 3.8) CAD: 2.3 (0.7, 3.8) DYS: 1.3 (−2.0, 4.6) HF: 3.0 (0.6, 5.3) Males: 3.4 (1.8, 5.0) Females: 2.0 (0.2, 3.7) <65: 2.5 (0.5, 4.5) >=65: 3.5 (1.9, 5.0) SO_4, 1d, w. temp and O_3: Total CVD: 3.3 (1.7,4.8)
Burnett et al. (1997a) Canada's 10 largest cities 1981-1994 COH daily maximum Mean: 0.7 10^3 ln feet Median: 0.6 10^3 ln feet 95th percentile: 1.5 10^3 ln feet	Daily hospitalizations for congestive heart failure (ICD9 code 427) for patients over 65 years at 134 hospitals. Average hospitalizations: 39/day. 1986 population of study area: 12.6 million. Regressions on air quality using generalized estimating equations, controlling for long-term trends, seasonality, day of week, and inter-hospital differences. Models fit monthly and pooled over months. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. 0-3 day lags examined. Covariates: CO, SO_2, NO_2, O_3, temperature, dewpoint temperature.	COH significant in single-pollutant models with and without weather covariates. Only *ln*CO and *ln* NO_2 significant in multi-pollutant models. COH highly colinear with CO and NO_2. Suggests no particle effect independent of gases. However, no gravimetric PM data were included.	Effects computed for 95% change in COH: 0 d lag: 5.5% (2.5, 8.6) 0 d lag w/weather: 4.7% (1.3, 8.2) 0 d lag w/CO, NO_2, SO_2, O_3: −2.26 (−6.5, 2.2)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997b) Metro-Toronto, Canada 1992-1994 Pollutant: mean, median, IQR: COH (10^3 ln ft): 0.8, 0.8, 0.6 H+ (nmol/m^3): 5, 1, 6 SO_4 (nmol/m^3): 57, 33, 57 TP (μg/m^3): 28, 25, 22 FP (μg/m^3): 17, 14, 15 CP (μg/m^3): 12, 10, 7	Daily unscheduled cardiovascular hospitalizations (ICD9 codes 410-414,427, 428) for all ages. Average hospital admissions: 42.6/day. Six cities of metro-Toronto included Toronto, North York, East York, Etobicoke, Scarborough, and York, with combined 1991 population of 2.36 million. Used same stat model as in Burnett et al., 1997c. 0- 4 day lags examined, as well as multi-day averages. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature.	Relative risks > 1 for all pollutants in univariate regressions including weather variables; all but H+ and FP statistically significant. In multivariate models, the gaseous pollutant effects were generally more robust than were particulate effects. However, in contrast to Burnett et al. (1997c), COH remained significant in multivariate models. Of the remaining particle metrics, CP was the most robust to the inclusion of gaseous covariates. Results do not support independent effects of FP, SO_4, or H+ when gases are controlled.	Percent excess risk (95% CI) per 50 μg/m^3 PM_{10}, 25 μg/m^3 $PM_{2.5}$ and $PM_{(10-2.5)}$, and IQR for other indicators. COH: 0–4 d. 6.2 (4.0, 8.4) 5.9 (2.8, 9.1) w. gases H+: 2–4 d. 2.4 (0.4, 4.5) 0.5 (–1.6, 2.7) w. gases SO_4: 2–4 d. 1.7 (–0.4, 3.9) –1.6 (–4.4, 1.3) w. gases TP: 1–4 d. 7.7 (0.9, 14.8) –0.9 (–8.3, 7.1) w. gases FP: 2–4 d. 5.9 (1.8, 10.2) –1.1 (–7.8, 6.0) w. gases CP: 0–4 d. 13.5 (5.5, 22.0) 8.1 (–1.3, 18.3) w. gases

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} ($\mu g/m^3$): 18, 16, 10 CP_{est} ($\mu g/m^3$): 12, 10, 8 $PM_{10\ est}$ ($\mu g/m^3$): 30, 27, 15	Daily hospitalizations for dysrhythmias, DYS (ICD9 code 427; mean 5/day); heart failure, HF (428; 9/d); ischemic heart disease, IHD (410-414; 24/d); cerebral vascular disease, CVD (430-438; 10/d); and diseases of the peripheral circulation, DPC (440-459; 5/d) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were estimated, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models used and non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in cardiac outcome (DVS, HF, IHD). No associations with vascular outcomes, except for CPest with DPC. In multi-pollutant models, PM effects estimates reduced by variable amounts (often >50%) for specific endpoints and no statistically significant (at $p<0.05$) PM associations seen with any cardiac or circulatory outcome (results not shown). Use of estimated PM metrics limits interpretation of pollutant-specific results. However, results suggest that linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when full range of gaseous pollutants also modeled.	Single pollutant models: Percent excess risk (95% CI) per 50 $\mu g/m^3$ PM_{10}; 25 $\mu g/m^3$ $PM_{2.5}$; and 25 $\mu g/m^3$ $PM_{(10-2.5)}$. All cardiac HA (lags 2-5 d): $PM_{2.5}$ 1-poll = 8.1 (2.45, 14.1) $PM_{2.5}$ w/4 gases = −1.6 (−10.4, 8.2); w/CO = 4.60 (−3.39, 13.26) PM_{10} 1-poll = 12.07 (1.43, 23.81) w/4 gases = −1.40 (−12.53, 11.16) w/CO = 10.93 (0.11, 22.92) $PM_{10-2.5}$ 1-poll = 20.46 (8.24, 34.06) w/4 gases = 12.14 (−1.89, 28.2); w/CO = 19.85 (7.19, 34.0) DYS: FP_{est} (0 d): 6.1 (1.9, 10.4) CP_{est} (0 d): 5.2 (−0.21, 1.08) $PM_{10\ est}$: (0 d): 8.41 (2.89, 14.2) HF: FP_{est} (0−2 d): 6.59 (2.50, 10.8) CP_{est} (0−2 d): 7.9 (2.28, 13) $PM_{10\ est}$ (0−2 d): 9.7 (4.2, 15.5) IHD: FP_{est} (0−2 d): 8.1 (5.4, 10.8) CP_{est} (0 d): 3.7 (1.3, 6.3) $PM_{10\ est}$ (0−1 d): 8.4 (5.3, 11.5)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 H+ ($nmol/m^3$): 25.7, 36.8 Sulfate ($nmol/m^3$): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for angina/myocardial infarction (mean 1.8/day), congestive heart failure (1.0/day), dysrhythmia/conduction disturbance (0.8/day), and all cardiac conditions (3.5/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations observed between all cardiac ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations observed with H+, sulfate, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics were significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions. In cause-specific, single-pollutant models, PM tended to be positively associated with dysrhythmia/conductive disturbances but negatively associated with congestive heart failure (no quantitative results presented). The objective decision rule used for selecting lags reduced the risk of data mining; however, the biological plausibility of lag effects beyond 3-5 days is open to question. Some reported associations likely to be spurious.	Percent Excess Risk (p-value) computed for 50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ and mean levels of sulfate and COH. Full year results for all cardiac conditions, single pollutant models: PM_{10}: 3d. 32.5 (10.2, 59.3) $PM_{2.5}$: 3d. 15.1 (−0.3, 32.8) H+: 4−9 d. avg. −1.8 (0.010) Sulfate: 4d. −6.0 (0.001) COH max: 7d. −5.4 (0.027) Full year results for all cardiac conditions, multi-pollutant models: No significant PM associations.

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe			
Atkinson et al. (1999a) Greater London, UK 1992-1994 Pollutant: mean, median, 90-10 percentile range: PM_{10} ($\mu g/m^3$): 28.5, 24.8, 30.7 Black Smoke ($\mu g/m^3$): 12.7, 10.8, 16.1	Daily emergency hospital admissions for total cardiovascular diseases, CVD (ICD9 codes 390-459), and ischemic heart disease, IHD (ICD9 410-414), for all ages, for persons less than 65, and for persons 65 and older. Mean daily admissions for CVD: 172.5 all ages, 54.5 <65, 117.8 ≥65; for IHD: 24.5 <65, 37.6 ≥65. Covariates: NO_2, O_3, SO_2, CO, temperature, relative humidity. Poisson regression using APHEA methodology; sine and cosine functions for seasonal control; day of week dummy variables. Lags of 0-3, as well as corresponding multi-day averages ending on lag 0, were considered.	In single-pollutant models, both PM metrics showed positive associations with both CVD and IHD admissions across age groups. Two-pollutant models were mentioned, but quantitative results were not given.	Effects computed for 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ BS PM_{10} 0 d. All ages: CVD: 3.2 (0.9, 5.5) 0–64 yr: CVD: 5.6 (2.0, 9.4) IHD: 6.8 (1.3, 12.7) 65+ yr: CVD: 2.5 (–0.2, 5.3) IHD: 5.0 (0.8, 9.3) Black Smoke 0 d. All ages: CVD: 2.95 (1.00, 4.94) 0–64 yr: CVD: 3.12 (0.05, 6.29) IHD: 2.78 (–1.88, 7.63) 65+ yr: CVD: 4.24 (1.89, 6.64) IHD (lag 3): 4.57 (0.86, 8.42)

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh, Scotland 1981-1995 (BS and SO_2) 1992-1995 (PM_{10}, NO_2, O_3, CO) Means for long and short series: BS: 12.3, 8.7 PM_{10}: NA, 20.7	Daily emergency hospital admissions for cardiovascular disease (ICD9 codes 410-414, 426-429, 434-440) for persons less than 65 years and for persons 65 or older. Separate analyses presented for long (1981-1995) and short (1992-1995) series. Mean hospital admissions for long and short series: <65, 3.5, 3.4; 65+, 8.0, 8.7. Covariates: SO_2, NO_2, O_3, CO, wind speed, temperature, rainfall. PM_{10} measured by TEOM. Stats: Poisson log-linear regression; trend and seasons controlled by monthly dummy variables over entire series; day of week dummy variables; min daily temperature modeled using octile dummies. Pollutants expressed as cumulative lag 1-3 day moving avg.	In long series, neither BS nor NO_2 were associated with CVD admissions in either age group. In the short series, only 3-day moving average PM_{10} was positively and significantly associated with CVD admissions in single-pollutant models, and only for persons 65 or older. PM_{10} effect remained largely unchanged when all other pollutants were added to the model (quantitative results not given).	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10} and 25 $\mu g/m^3$ change in BS. Long series: BS, 1–3 d. avg. <65: –0.5 (–5.4, 4.6) 65+: –0.5 (–3.8, 2.9) Short series: BS, 1–3 d. avg. <65: –9.5 (–24.6, 8.0) 65+: 5.8 (–4.9, 17.8) PM_{10}, 1–3 d. avg. <65: 2.0 (–12.5, 19.0) 65+: 12.4 (4.6, 20.9)
Wordley et al. (1997) Birmingham, UK 4/1/92-3/31/94 mean, min, max: PM_{10} ($\mu g/m^3$): 26, 3, 131	Daily hospital admissions for acute ischemic heart disease (ICD9 codes 410-429) for all ages. Mean hospitalizations: 25.6/day. Covariates: temperature and relative humidity. Stats: Linear regression with day of week and monthly dummy variables, linear trend term. Lags of 0-3 considered, as well as the mean of lags 0-2.	No statistically significant effects observed for PM_{10} on ischemic heart disease admissions for any lag. Note that PM_{10} was associated with respiratory admissions and with cardiovascular mortality in the same study (results not shown here).	% change (95% CI) per 50 $\mu g/m^3$ change PM_{10} IHD admissions: PM_{10} 0-d lag: 1.4% (–4.4, 7.2) PM_{10} 1-d lag: –1.3% (–7.1, 4.4)
Díaz et al. (1999) Madrid, Spain 1994-1996 TSP by beta attenuation Summary statistics not given.	Daily emergency hospital admissions for all cardiovascular causes (ICD9 codes 390-459) for the Gregorio Maranon University Teaching Hospital. Mean admissions: 9.8/day. Covariates: SO_2, NO_2, O_3, temperature, pressure, relative humidity, excess sunlight. Stats: Box-Jenkins time-series methods used to remove autocorrelations, followed by cross-correlation analysis; sine and cosine terms for seasonality; details unclear.	No significant effects of TSP on CVD reported.	No quantitative results presented for PM.

TABLE 6-16 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Australia			
Morgan et al. (1998) Sydney, Australia 1990-1994 mean, median, IQR, 90-10 percentile range: Daily avg. bscat/10^4m: 0.32, 0.26, 0.23, 0.48 Daily max 1-hr bscat/10^4m: 0.76, 0.57, 60, 1.23	Daily hospital admissions for heart disease (ICD9 codes 410, 413, 427, 428) for all ages, and separately for persons less than 65 and persons 65 or greater. Mean daily admissions: all ages, 47.2; <65, 15.4; 65+, 31.8. PM measured by nephelometry (i.e., light scattering), which is closely associated with $PM_{2.5}$. Authors give conversion for Sydney as $PM_{2.5}$ =30 × bscat. Covariates: O_3, NO_2, temperature, dewpoint temperature. Stats: Poisson regression; trend and seasons controlled with linear time trend and monthly dummies; temperature and dewpoint controlled with dummies for eight levels of each variable; day of week and holiday dummies. Single and cumulative lags from 0-2 considered. Both single and multi-pollutant models were examined.	In single-pollutant models, NO_2 was strongly associated with heart disease admissions in all age groups. PM was more weakly, but still significantly associated with admissions for all ages and for persons 65+. The NO_2 association in the 65+ age group was unchanged in the multi-pollutant model, whereas the PM effect disappeared when NO_2 and O_3 were added to the model.. These results suggest that PM is not robustly associated with heart disease admissions when NO_2 is included, similar to the sensitivity of PM to CO in other studies.	Percent Excess Risk (95% CI): Effects computed for 25 $\mu g/m^3$ $PM_{2.5}$ (converted from bscat). 24-hr avg. $PM_{2.5}$ 0 d. <65: 1.8 (−2.9, 6.7) 65+: 4.9 (1.6, 8.4) All: 3.9 (1.1, 6.8) 24-hr $PM_{2.5}$, 0 d w. NO_2 and O_3. 65+: 0.12 (−1.3, 1.6) 1-hr $PM_{2.5}$, 0 d. <65: 0.19 (−1.6, 2.0) 65+: 1.8 (0.5, 3.2) All: 1.3 (0.3, 2.3)
Asia			
Wong et al. (1999) Hong Kong 1994-1995 median, IQR for PM_{10} ($\mu g/m^3$): 45.0, 34.8	Daily emergency hospital admissions for cardiovascular diseases, CVD (ICD9 codes 410-417, 420-438, 440-444), heart failure, HF (ICD9 428), and ischemic heart disease, IHD (ICD9 410-414) among all ages and in the age categories 5-64, and 65+. Median daily CVD admissions for all ages: 101. Covariates: NO_2, O_3, SO_2, temperature, relative humidity. PM_{10} measured by TEOM. Stats: Poisson regression using the APHEA protocol; linear and quadratic control of trends; sine and cosine control for seasonality; holiday and day of week dummies; autoregressive terms. Single and cumulative lags from 0-5 days considered.	In single-pollutant models, PM_{10}, NO_2, SO_2, and O_3 all significantly associated with CVD admissions for all ages and for those 65+. No multi-pollutant risk coefficients were presented; however, the PM_{10} effect was larger when O_3 was elevated (i.e., above median). A much larger PM_{10} effect was observed for HF than for CVD or IHD. These results confirm the presence of PM_{10} associations with cardiovascular admissions in single-pollutant models, but do not address the independent role of PM_{10}.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}, 0−2 d. avg. CVD: 5−64: 2.5 (−1.5, 6.7) 65+: 4.1 (1.3, 6.9) All: 3.0 (0.8, 5.4) HF (PM_{10}, 0-3 d ave.): All: 26.4 (17.1, 36.4) IHD (PM_{10}, 0-3 d ave.): All: 3.5 (−0.5, 7.7)

For example, Schwartz (1999) extended the analytical approach he had used in Tucson (described below) to eight more U.S. metropolitan areas, limiting analyses to a single county in each location to enhance representativeness of the air pollution data. The locations analyzed were: Chicago, IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN; Seattle, WA; Spokane, WA; and Tacoma, WA. Again, the analyses focused on total cardiovascular (CVD) hospital admissions among persons ≥65 years old. In univariate regressions, remarkably consistent PM_{10} associations with CVD admissions were found across the eight locations, with a 50 $\mu g/m^3$ increase in PM_{10} associated with 3.6 to 8.6% increases in admissions. The univariate eight-county pooled PM_{10} effect was 5.0% (CI 3.7-6.4), similar to the 6.1 % effect per 50 $\mu g/m^3$ observed in the previous Tucson analysis. In a bivariate model that included CO, the pooled PM_{10} effect size diminished somewhat to 3.8% (CI 2.0-5.5) and the CO association with CVD admissions was generally robust to inclusion of PM_{10} in the model.

Additional new results have also recently been published for analyses of daily CVD hospital admissions in persons 65 and older in relation to PM_{10} for a subset of 14 cities from among the 90 cities evaluated in the NMMAPS multi-city study (Samet et al., 2000a,b). Cities included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado Springs, CO; Detroit, MI; Minneapolis/ St. Paul, MN; Nashville, TN; New Haven, CT; Pittsburgh, PA; Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range of years studied encompassed 1985-1994, although this varied by city. Covariates included SO_2, NO_2, O_3, and CO; however these were not analyzed directly as regression covariates. Individual cities were analyzed first by Poisson regression methods on PM_{10} for lags from 0 to 5 days. An overall risk estimate was then computed by taking the inverse-variance weighted mean of the city-specific risk estimates. The city-specific risk estimates for PM_{10} were also examined for correlations with omitted covariates, including other pollutants. No relationship was observed between city-specific risk estimates and measures of socio-economic status, including percent living in poverty, percent non-white, and percent with college educations. The overall weighted mean risk estimate for PM_{10} was greatest for lag 0 and for the mean of lags 0-1. For example, the mean risk estimate for the mean of lags 0-1 was a 6.0% increase in CVD admissions per 50 $\mu g/m^3$ PM_{10} (95% CI: 5.1 - 6.8). The mean risk was larger in a subgroup of data where PM_{10} was less than 50 $\mu g/m^3$, suggesting the lack of a threshold. While no multi-pollutant results were presented,

the authors argued that confounding was not present because the city-specific risk estimates did not correlate with city-mean co-pollutant levels.

Zanobetti et al. (2000b), in an analysis of a subset of 10 cities from among the 14 evaluated by Samet et al. (2000a,b), did include other gaseous co-pollutants in their analyses of CVD hospital admissions for the elderly (≥65 yr) during 1986-1994. After analyzing single cities first, the 10 risk estimates were further analyzed in several second-stage analyses, combining risks across cities and regressing risks on potential risk modifiers and co-pollutant confounders. The same basic pattern of results obtained by Samet et al. (2000a,b) were found, with strongest PM_{10} associations on lag 0 day, smaller effects on lag 1 and 2, and none at longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (95% CI 4.7, 6.4) per 50 $\mu g/m^3$ PM_{10} increment. The 0-1 day lag average excess CVD risk = 6.2% (95% CI 5.4, 7.0) per 50 $\mu g/m^3$ PM_{10} increment. Effect size estimates increased when data were restricted to days with $PM_{10} < 50$ $\mu g/m^3$. No evidence of gaseous (CO, O_3, SO_2) co-pollutant modification of PM effects was seen in the second stage analyses.

Turning to some examples of independent single-city analyses, PM_{10} associations with CVD hospitalizations were also examined in a study by Schwartz (1997), which analyzed three years of daily data for Tucson, AZ linking total CVD hospital admissions for persons ≥ 65 years old with PM_{10}, CO, O_3, and NO_2. As was the above case in Chicago, only one site monitored daily PM_{10} while multiple sites did so for gaseous pollutants. Both PM_{10} and CO were independently (i.e., robustly) associated with CVD-related admissions, whereas O_3 and NO_2 were not. The percent effect of a 50 $\mu g/m^3$ increase in PM_{10} changed only slightly from 6.07 (CI 1.12 - 11.27) to 5.22 (CI 0.17 - 10.54) when CO was included in the model along with PM_{10}.

Morris and Naumova (1998) also found associations with PM_{10} in their analysis of four years of congestive heart failure data among people ≥ 65 years old in Chicago, IL. While the analysis was directed primarily at evaluating modification by temperature of CO effects on congestive heart failure admissions (building on previous results of Morris et al., 1995), results were also presented for PM_{10}, as well as for O_3, NO_2, and SO_2. As many as eight monitoring sites were available for calculating daily gaseous pollutant concentrations; however, only one site in Chicago monitored daily PM_{10}. Only same-day results were presented, based on an initial exploratory analysis showing strongest effects for same-day pollution exposure (i.e., lag 0). Strong and robust associations were seen between congestive heart failure admissions and CO.

Associations between hospitalizations and PM_{10} were also observed in univariate regressions 3.9% (1.0, 6.9) per 50 $\mu g/m^3$ PM_{10} increase), but these diminished somewhat in a multi-pollutant model (2.0%, CI −1.4, 5.4). Although these results may suggest a more robust association with CO than with PM_{10}, the observed differences might be explained by differential exposure misclassification for PM_{10} (monitored at one site) as compared with CO (eight sites).

More recently, Lippmann et al. (2000) reported findings from analyses of relationships between PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ and various categories of CVD hospital admissions among the elderly (65+ yr) in Detroit during 1992-1994. The most striking findings were notable percent excess risk for: (a) ischemic heart disease (IHD) in relation to PM indices, i.e. 8.9% (0.5, 18.0) per 50 μg PM_{10}; 10.5% (2.8, 18.9) per 25 $\mu g/m^3$ $PM_{10-2.5}$; and 4.3% (−1.4, 10.4) per 25 $\mu g/m^3$ $PM_{2.5}$ (all at lag 2d); and (b) heart failure, i.e. 9.7% (0.2, 20.1) per 50 $\mu g/m^3$ PM_{10}; 5.2% (−3.3, 14.5) per 25 $\mu g/m^3$ $PM_{10-2.5}$; and 9.1% (2.4, 6.2) per 25 $\mu g/m^3$ $PM_{2.5}$ (the first two at lag 0 d and the latter at lag 1 d). As discussed earlier with regard to Lippmann et al. (2000) mortality findings, it is difficult to discern whether the observed associations with coarse fraction particles ($PM_{10-2.5}$) are independently due to such particles or may possibly be attributed to the moderately correlated fine particle ($PM_{2.5}$) fraction in Detroit.

Tolbert et al. (2000a) also recently reported preliminary results of analyses of daily hospital emergency department visits for dysrhythmias (DYS) and all CVD categories for persons aged 16 yrs or older, based on analyses of data from 18 of 33 participating hospitals in Atlanta. During Period 1 of the study (1993-1998), PM_{10} from the EPA AIRS database was reported to be negatively associated with CVD visits. During the second period (Aug. 1998 - Aug. 1999) based on use of Atlanta supersite data, however, the effect estimate for CVD excess risk of 5.1% per 50 $\mu g/m^3$ PM_{10} (although not statistically significant) does comport well with those noted above from the Samet and Schwartz studies. Also, although Period 2 CVD estimates (excess risk = 6.1%; CI −3.1, 16.2) per 50 $\mu g/m^3$ $PM_{2.5}$ were not significant at $p \leq 0.05$, positive associations with certain fine particle components, i.e., elemental carbon ($p \leq 0.005$) and organic carbon ($p \leq 0.02$), were significant along with CO ($p \leq 0.005$). Significant positive associations were also found for DYS visits versus elemental carbon ($p = 0.004$), coarse particles ($p \leq 0.04$), and CO ($p \leq 0.005$). However, much caution applies to acceptance of the Tolbert et al. (2000a) findings until more complete analyses from all participating hospitals are carried out and reported.

As for other U.S. studies of cardiovascular morbidity in single cities or urban counties, in an analysis of 1992-1995 Los Angeles data, Linn et al. (2000) also found that PM_{10}, CO, and NO_2 were all significantly associated with increased cardiovascular admission in single-pollutant models among persons aged 30 yr and older, but no multi-pollutant modeling results were presented. Lastly, Moolgavkar (2000b) analyzed PM_{10}, CO, NO_2, O_3, and SO_2 in relation to daily total cardiovascular (CVD) and total cerebrovascular (CrD) admissions for persons aged $\geq$65 from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ). In univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) were associated at some lags with CVD admissions in Cook and LA counties, but not in Maricopa county. In two-pollutant models in Cook and LA counties, the PM risk estimates diminished and/or were rendered non-significant.

The above analyses of daily PM_{10} and CO in U.S. cities, overall, indicate that elevated concentrations of both PM_{10} and CO may enhance risk of CVD-related morbidity leading to acute hospitalizations. The Lippmann results appear to implicate $PM_{2.5}$ and/or $PM_{10-2.5}$ in increased hospital admissions for some categories of CVD among the elderly; and the Tolbert results very preliminarily also hint at both fine and coarse particle components contributing to CVD-related emergency department visits.

Four separate analyses of hospitalization data in Canada have been reported by Burnett and coworkers since 1995 (Burnett et al., 1995, 1997b,c, 1999). A variety of locations, outcomes, PM exposure metrics, and analytical approaches were used in these studies, which hinders somewhat the ability to draw broad, conclusions across the full group. The first (Burnett et al., 1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in Ontario, CN. Cardiovascular and respiratory hospital admissions were analyzed in relation to sulfate and ozone concentrations. Sulfate lagged one day was associated with CVD admissions, with a percent effect of 2.8 (CI 1.8-3.8) per 13 $\mu g/m^3$ without O_3 in the model and 3.3 (CI 1.7-4.8) with O_3 included. When CVD admissions were split out into sub-categories, larger associations were seen between sulfates and coronary artery disease and heart failure than for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the elderly sub-population $\geq$ 65 (3.5% per 13 $\mu g/m^3$) than for those <65 years old (2.5% per 13 $\mu g/m^3$). There was little evidence for seasonal differences in sulfate associations.

Burnett et al. (1997a) analyzed daily congestive heart failure hospitalizations in relation to carbon monoxide and other air pollutants (O_3, NO_2, SO_2, COH) in ten large Canadian cities as a

replication of an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study expanded upon the previous work both by its size (11 years of data for each of 10 large cities) and also by including a measure of PM air pollution (coefficient of haze, COH), whereas no PM data were included in the earlier Morris et al. study. The Burnett study was restricted to the population $\geq$ 65 years old. The authors noted that all pollutants except O_3 were correlated, making it difficult to separate them statistically. COH, CO, and NO_2 measured on the same day as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in univariate models. In multi-pollutant models, CO remained a strong predictor, whereas COH did not (gravimetric PM measures were not evaluated).

The roles played by size-selected gravimetric and chemically speciated particle metrics as predictors of CVD hospitalizations were explored in analysis of data from metropolitan Toronto for the summers of 1992-1994 (Burnett et al., 1997b). The analysis used dichotomous sampler ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$), hydrogen ion, and sulfate data collected at a central site as well as O_3, NO_2, SO_2, CO, and COH data collected at multiple sites in Toronto. Hospital admissions categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac dysrhythmias, and heart failure) and total respiratory. Model specification with respect to pollution lags was completely data-driven, with all lags and averaging times out to 4 days prior to admission evaluated in exploratory analyses and "best" metrics chosen on the basis of maximal t-statistics. The relative risks of CVD admissions were positive and generally statistically significant for all pollutants analyzed in univariate regressions, but especially so for O_3, NO_2, COH, and $PM_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants were generally robust to inclusion of PM covariates, whereas the PM indices (aside from COH) were not robust to inclusion of multiple gaseous pollutants. In particular, $PM_{2.5}$ was not a robust predictor of CVD admissions in multi-pollutant models: whereas an 25 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 5.9% increase (t=1.8) in CVD admissions in a univariate model, the percent effect was reduced to -1.1 (t=0.3) in a model that included O_3, NO_2, and SO_2. COH, like CO and NO_2, is generally thought of as a measure of primary motor-vehicle emissions during the non-heating season. The authors concluded that "particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this study beyond that attributable to climate and gaseous air pollution."

Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease. The analyses also examined several respiratory causes, as well as cerebrovascular and diseases of the peripheral circulation (the latter categories being included because they should show PM associations if one mechanism of PM action is related to increased plasma viscosity, as suggested by Peters et al., 1997a). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ estimated from daily TSP and TSP sulfate data, based on a regression analysis on dichotomous sampling data that were available every sixth day during an eight-year subset of the full study period. This use of estimated rather than measured PM components limits the interpretation of the PM results reported here. In general, use of estimated PM exposure metrics will tend to increase exposure measurement error and thereby tend to decrease effects estimates. Model specification for lags was again data-driven based on maximal t-statistics. Although some statistically significant associations with one or another PM metric were found in univariate models, there were no significant PM associations with any of the three CVD hospitalization outcomes in multi-pollutant models. For example, whereas an 25 $\mu g/m^3$ increase in estimated $PM_{2.5}$ was associated with a 8.05% increase (t-statistic = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$ association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in the model. The gaseous pollutants dominated most regressions. There also were no associations between PM and cerebral or peripheral vascular disease admissions.

The Burnett et al. studies provide some of the most extensive results for PM in conjunction with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the various analyses confuses the picture somewhat. A general finding appears to be lack of robustness of associations between cardiovascular outcomes and PM in multi-pollutant analyses. This was seen for COH in the analysis of 10 Canadian cities (Burnett et al., 1997a), for $PM_{2.5}$ and PM_{10} in the analysis of summer data in Toronto (Burnett et al., 1997b), and for linear combinations of TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in Toronto (Burnett et al., 1999). One exception was the association reported between CVD admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the sulfate association was robust to the inclusion of O_3. Also, although gravimetric PM variables

were not robust predictors in the Toronto summer analysis, COH was (Burnett et al., 1997b), perhaps reflecting the impact of primary motor vehicle emissions. This contrasts, however, with COH's lack of robustness in the 10-city analysis (Burnett et al., 1997a). It is difficult to determine how much weight should be ascribed to the finding of lack of robustness of PM versus gaseous pollutants effects, given the expected large measurement error likely associated with the estimated PM metrics.

Several pertinent new European studies, mainly in the U.K., have also been published since the 1996 PM AQCD. For example, Atkinson et al. (1999b) reported significant associations of both ambient PM_{10} and black smoke (BS) with daily admissions for total cardiovascular disease and ischemic heart disease for 1992-1994 in London, UK, using standard time series regression methods. Associations were observed for persons aged < 65 yr and for persons aged $\geq$ 65 yr. While the authors mention analysis of co-pollutants, no quantitative results were presented for multi-pollutant models. Also, associations with PM_{10}, but not with BS were reported for analyses of daily emergency hospital admissions for cardiovascular diseases from 1992-1995 for Edinburgh, UK (Prescott et al., 1998). Associations were present only in persons 65 and older. The authors reported that the PM_{10} associations were unaffected by inclusion of other pollutants; however, results were not shown. Standard time series regression methods were used. PM_{10} was measured by TEOM. On the other hand, no associations between PM_{10} and daily ischemic heart disease admissions were observed by Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK. However, PM_{10} was associated with respiratory admissions and cardiovascular mortality during the same study period. The inconsistency of results across causes and outcomes is difficult to interpret, but may relate in part to the relatively short time series analyzed. The authors stated that gaseous pollutants did not have significant associations with health outcomes independent of PM, but no results were presented for models involving gaseous pollutants.

Also relevant to the present review of associations between acute cardiovascular morbidity and PM are nine recent studies of acute cardiovascular (CVD) mortality (Borja-Aburto et al., 1997, 1998; Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson et al., 1997; Wordley et al., 1997; Zmirou et al., 1998) reviewed earlier in Section 6.2.2. Acute mortality can be viewed as a more severe manifestation of the same pathophysiologic mechanism responsible for acute hospital admissions following PM exposure.

All nine studies reported significant associations between acute CVD mortality and measures of ambient PM, though the PM metrics utilized and the relative risk estimates varied across studies. PM measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and black smoke (filter reflectance). Where tested, PM associations with acute CVD mortality appeared to be generally more robust to inclusion of gaseous covariates than was the case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998; Wordley et al., 1997; Zmirou et al., 1998). One study which examined multiple alternative PM metrics reported strongest associations with $PM_{2.5}$ and no associations for $PM_{10-2.5}$ and hydrogen ion. These results for acute cardiovascular mortality are qualitatively consistent with those reviewed above for hospital admissions.

One additional recent study of acute PM exposure impacts on CVD mortality is of interest here. Checkoway et al. (2000) studied the possible association between occurrence of out-of-hospital sudden cardiac arrest (SCA) and daily PM levels in the Seattle metropolitan area as measured both by nephelometry and PM_{10} from three monitoring sites. A case-crossover study evaluated 362 SCA cases identified from October 1988 through June 1994. The cases had no prior history of clinically recognized heart disease or other life-threatening conditions. Lag periods for index days of 0 to 5 days were studied. There was no evidence of confounding by ambient daily exposure to CO or SO_2. Relative risk estimates for SCA showed no evidence of an association of 24-h PM levels with increased risks at any lag time studied. The notable strength of this study was the availability of personal risk factor information. The authors provided interpretation of the null results, posing the possibilities that: (1) this case group had a low prevalence of previously detected compromised cardiovascular health (inclusion of persons with prior history of cardiovascular disease should be studied); (2) PM exposures in the Seattle area may be too low to cause an effect; (3) potential for exposure misclassification exists, and (4) the sample size was not large enough to either find or rule out a relative risk less than 1.5. One important comment by the HEI Health Review Committee attached as part of the report was that the induction time for the occurrence of primary arrhythmia may be much shorter than the 24-h time window studied and, as such, other hazard periods (i.e., 1, 2, or 4-h concentrations) might be of more interest for evaluating PM effects on sudden cardiac arrest.

Figure 6-6 illustrates excess risk estimates derived from United States studies of PM_{10} exposure and cardiovascular hospitalizations, standardized to a 50 $\mu g/m^3$ exposure to PM_{10}. Results from available studies show both pooled outcomes for total CVD hospital admissions and studies presenting single U.S. cities. The Samet et al. (2000b) pooled cross-city results for 14 U.S. Cities and Schwartz (1999) results for 8 U.S. cities likely provide the most precise estimates for relationships of U.S. ambient PM_{10} exposure to increased risk for cardiovascular disease hospitalization. Those estimates, and those derived from most other studies depicted in Figure 6-6, generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of 3-10% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$65 yr). Also, other individual-city results from Detroit are indicative of excess risk for ischemic heart disease and heart failure in the range of ca. 4.0 to 10.0% per 25 $\mu g/m^3$ of $PM_{2.5}$ or $PM_{10-2.5}$, as are preliminary individual-city findings from Atlanta suggestive of ca. 4.3% and 10.5% excess risk per 25 $\mu g/m^3$ of $PM_{2.5}$ and $PM_{10-2.5}$, respectively.

6.3.1.3.2 Individual-Level Studies of Cardiovascular Physiology

New studies carried out by various groups have evaluated longitudinal associations between ambient PM and physiologic measures of cardiovascular function. In contrast to the ecologic time-series studies discussed above, these studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions regarding individual risks, as well as to explore mechanistic hypotheses. Heterogeneity of responses across individuals, and across subgroups defined on the basis of age, sex, pre-existing health status, etc., can be assessed. While exposure assessment remains largely ecologic (i.e., the entire population is usually assigned the same exposure value on a given day), exposure is generally well characterized in the small, spatially-clustered study populations. The recent studies fall into two broad classes: those addressing cardiac rhythm, and those addressing blood characteristics. While significant uncertainty still exists regarding the interpretation of results from these new studies, the varied responses that have been reported to be associated with ambient PM and co-pollutants are of much interest in regard to mechanistic hypotheses concerning pathophysiologic processes potentially underlying CVD-related mortality/morbidity effects discussed in preceding sections.

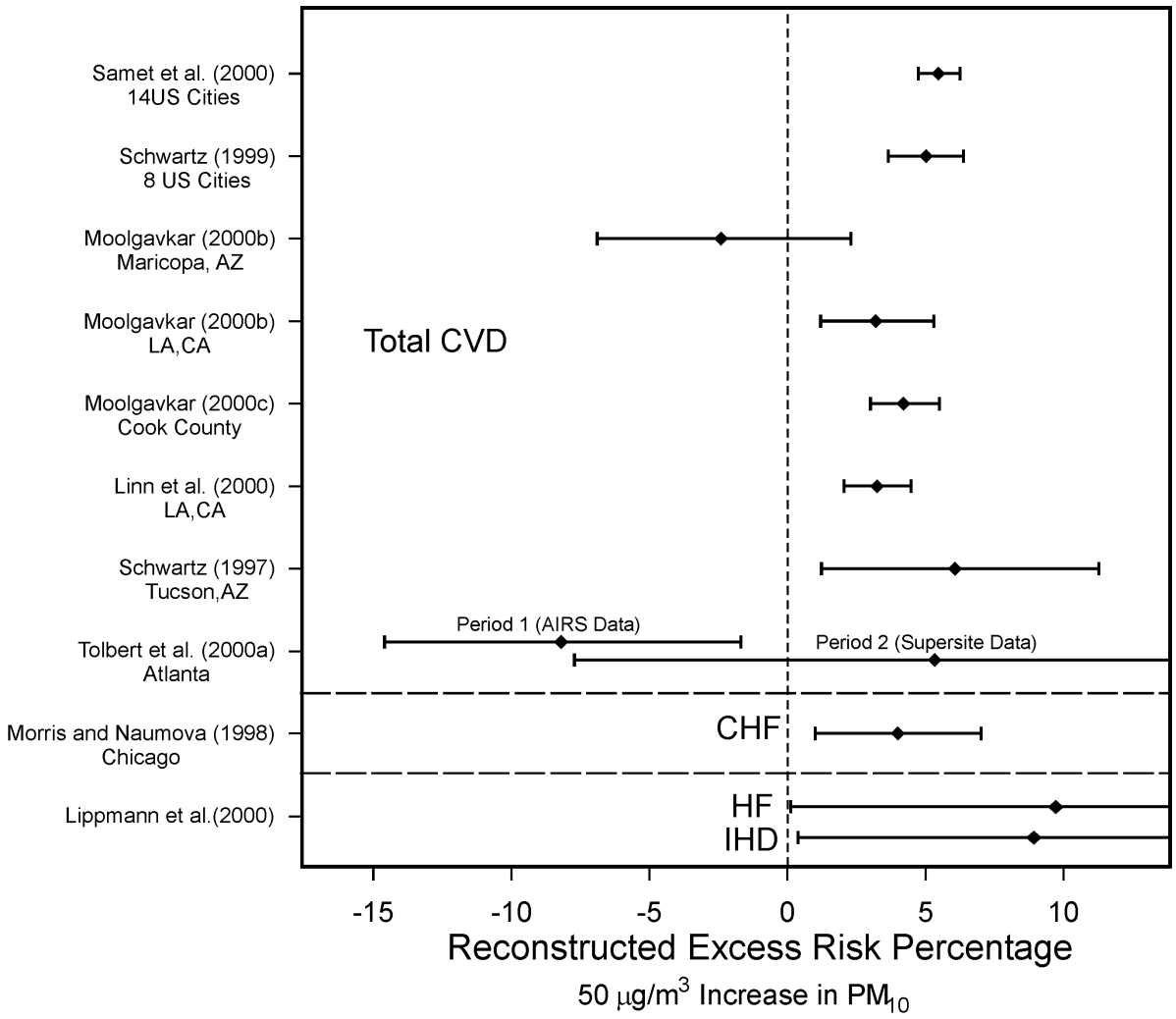

Figure 6-6. Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from selected U.S. PM_{10} studies. CVD = cardiovascular disease. CHF = congestive heart failure.

Heart Rate Rhythm and Variability

Alterations in heart rate and/or rhythm have been hypothesized as possible mechanisms by which ambient PM exposures may exert acute effects on human health. Decreased heart rate variability, in particular, has been identified as a predictor of increased cardiovascular morbidity and mortality (see Appendix 6B). Several independent studies have recently reported temporal associations between PM exposures and various measures of heart beat rhythm in panels of

elderly subjects (Liao et al., 1999; Pope et al., 1999a,b,c; Dockery et al., 1999; Peters et al., 1999a, 2000a; Gold et al., 1998; 2000).

Liao and colleagues (1999) studied 26 elderly subjects (age 65-89 years; 73% female) over three consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were classified as "compromised" based on previous cardiovascular conditions (e.g., hypertension). Daily six-minute resting electrocardiogram (ECG) data were collected, and time intervals between sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval data to separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N–N; also designated R-R) heartbeat intervals (SDNN) was computed for use as a time-domain outcome variable. $PM_{2.5}$ was monitored indoors by TEOM and outdoors by dichotomous sampler. Outdoor $PM_{2.5}$ levels ranged from 8.0 to 32.2 $\mu g/m^3$ (mean = 16.1 $\mu g/m^3$). Regression analyses controlled for inter-subject differences in average variability, allowing each subject to serve as his/her own control. Consistent associations were seen between decreases in all three outcome variables (LF, HF, SDNN) and increases in $PM_{2.5}$ concentrations (both indoors and outdoors), with associations being stronger for the 18 "compromised"subjects. No analyses of heart rate were reported.

Pope and colleagues (1999c) reported similar findings in a panel of six elderly subjects (69-89 years, 5/6 male) with histories of cardiopulmonary disease, and one 23-year old male subject suffering from Crohn's disease and arrhythmias. Subjects carried Holter monitors for up to 48 hours during different weeks that varied in ambient PM_{10} concentrations. N-N heartbeat intervals were recorded and used to calculate several measures of heart rate variability in the time domain: the standard deviation of N-N intervals (SDNN), which is a broad measure of both high and low frequency variations; the standard deviation of the averages of N-N intervals in all five minute segments (SDANN), which is a measure of ultra-low frequency variations; and the root mean squared differences between adjacent N-N intervals (r-MSSD), which is a measure of high frequency variations. Daily gravimetric PM_{10} data obtained from three sites in the study area ranged from circa 10 $\mu g/m^3$ to 130 $\mu g/m^3$ during the study. A simple step function in concentration was observed with high levels occurring only during the first half of the 1.5 month study period. Regression analysis with subject-specific intercepts was performed, with and without control for daily barometric pressure and mean heart rate. Same-day, previous-day, and

the two-day mean of PM_{10} were considered. SDNN and SDANN were negatively associated with both same-day and previous-day ambient PM_{10}, and results were unaffected by inclusion of covariates. Heart rate, as well as r-MSSD, were both positively, but less strongly, associated with PM_{10}. No co-pollutants were studied.

The Pope et al. (1999c) study discussed above was nested within a larger cohort of 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in oxygen saturation might occur as a result of PM exposure, and that this could be a risk factor for adverse cardiac outcomes. The study was carried out in winter months (mid November through mid-March), when frequent inversions lead to fine particle episodes. PM_{10} levels at the three nearest sites averaged from 35 to 43 $\mu g/m^3$ during the study, with daily 24-h levels ranging from 5 to 147 $\mu g/m^3$. Two populations were studied: 52 retired Brigham Young University faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO_2) and heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger. In regression analyses that controlled for inter-individual differences in mean levels, SpO_2 was not associated with PM_{10}, but was highly associated with barometric pressure. In contrast, HR significantly increased in association with PM_{10} and significantly decreased in association with barometric pressure in joint regressions. Including CO in the regressions did not change these basic findings. This was the first study of this type to examine the interrelationships among physiologic measures (i.e., SpO_2 and HR), barometric pressure, and PM_{10}. The profound physiological effects of barometric pressure noted here highlight the importance of carefully controlling for barometric pressure effects in studies of cardiac physiology.

Gold and colleagues (1998, 2000) obtained somewhat different results in a study of heart rate variability among 21 active elderly subjects, aged 53-87 yr, in a Boston residential community. Resting, standing, exercising, and recovering ECG measurements were performed weekly using a standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for definitions). Heart rate also was analyzed as an outcome. Continuous PM_{10} and $PM_{2.5}$ monitoring was conducted by TEOM at a site 6 km from the study site, with PM data corrected for loss of semivolatile mass. Data on CO, O_3, NO_2, SO_2, temperature and relative humidity were available from nearby sites. Outcomes were regressed on $PM_{2.5}$ levels in the

0-24 hour period prior to ECG testing, with and without control for HR and temperature. As for the other studies discussed above, declines in SDNN were associated with $PM_{2.5}$ levels, in this case averaged over 4 hours. These associations reached statistical significance at the 0.05 level only when all testing periods (i.e., resting, standing, exercise) were combined. In contrast to the above studies, both HR and r-MSSD here were negatively associated with $PM_{2.5}$ levels (i.e., lower HR and r-MSSD) when $PM_{2.5}$ was elevated. These associations were statistically significant overall, as well as for several of the individual testing periods, and were unaffected by covariate control.

Peters and colleagues (1999a) reported HR results from a retrospective analysis of data collected as part of the MONICA study (monitoring of trends and determinants in cardiovascular disease) carried out in Augsburg, Germany. Analyses focused on 2,681 men and women aged 25-64 years who had valid ECG measurements taken in winter 1984-1985 and again in winter 1987-1988. Ambient pollution variables included TSP, SO_2, and CO. The earlier winter included a 10-day episode with unusually high levels of SO_2 and TSP, but not of CO. Pollution effects were analyzed in two ways: dichotomously comparing the episode and non-episode periods, and continuously using regression analysis. However, it is unclear from the report to what extent the analyses reflect between-subject vs. within-subject effects. A statistically significant increase in mean heart rate was observed during the episode period versus other periods, controlling for cardiovascular risk factors and meteorology. Larger effects were observed in women. In single-pollutant regression analyses, all three pollutants were associated with increased HR.

In another retrospective study, Peters and colleagues (2000a) examined incidence of cardiac arrhythmias among 100 patients (mean age 62.2 yr.; 79% male) with implanted cardioverter defillibrators followed over a three year period. $PM_{2.5}$ and PM_{10} were measured in South Boston by the TEOM method, along with black carbon, O_3, CO, temperature and relative humidity; SO_2 and NO_2 data were obtained from another site. The 5th percentile, mean, and 95th percentiles of PM_{10} concentrations were 7.8, 19.3, and 37.0 $\mu g/m^3$, respectively. The corresponding values for $PM_{2.5}$ were 4.6, 12.7, and 26.6 $\mu g/m^3$. Logistic regression was used to analyze arrhythmia events in relation to pollution variables, controlling for between-person differences, seasons, day-of-week, and meteorology in two subgroups: 33 subjects with at least one arrhythmia event; and 6 subjects with 10 or more arrhythmia events. In the larger subgroup, only NO_2 on the previous day, and the mean NO_2 over five days, were significantly associated with arrhythmia incidence.

In patients with 10 or more events, the NO_2 associations were stronger. Also, some of the $PM_{2.5}$ and CO lags became significant in this subgroup. These results should be interpreted cautiously given the large number of statistical tests performed.

The above studies present a range of intriguing findings suggesting possible effects of PM on cardiac rhythm. Three independent studies reported decreases in HR variability associated with PM in elderly cohorts, although r-MSSD (a measure of high-frequency HR variability) showed elevations with PM in one study (Pope et al., 1999a). Also, all of the studies which examined HR found an association with PM; most reported positive associations, whereas one (Gold et al., 2000) reported a negative relationship. However, variations in methods and results across the studies argue for caution in drawing strong conclusions regarding PM effects from them, especially in light of the complex intercorrelations which exist among measures of cardiac physiology, meteorology, and air pollution (Dockery et al., 1999).

Viscosity and Other Blood Characteristics

Peters et al. (1997a) state that plasma viscosity is determined by fibrinogen and other large asymmetrical plasma proteins such as immunoglobulin M and $\propto_2$-macroglobulin. They note that in a cohort study of elderly men and women, fibrinogen concentrations were strongly related to inflammatory markers such as neutrophil count and acute-phase proteins, (C-reactive protein and $\propto_1$-antichymotrypsin) and to self-reported infections. Fibrinogen contributes to plasma viscosity, which is a risk factor for ischemic heart disease.

Support for a mechanistic hypothesis, relating to enhanced blood viscosity, is suggested in a recent analysis of plasma viscosity data collected in a population of 3256 German adults in the MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October 1984 to June 1985. An episode of unusually high air pollution concentrations occurred during a 13 day period while these measurements were being collected. The authors reported that, among the 324 persons who provided blood during the episode, there was a statistically significant elevation in plasma viscosity as compared with the 2932 persons studied at other times. The odds ratio for plasma viscosity exceeding the 95th percentile was 3.6 (CI 1.6–8.1) among men and 2.3 (CI 1.0–5.3) among women. Analysis of the distribution of blood viscosity data suggested that these findings were driven by changes in the upper tail of the distribution rather

than by a general shift in mean viscosity, consistent with the likelihood of a susceptible sub-population of individuals.

Peters et al. (2000b) reported on a prospective cohort study of a subset of male participants from the above-described Augsburg, Germany MONICA study. Based on a survey conducted in 1984/85, a sample of 631 randomly selected men/aged 45-64 yr), free of cardiovascular disease at entry, were evaluated in a 3-yr follow-up that examined relationships of air pollution to serum C-reactive protein concentrations. C-reactive protein is a sensitive marker of inflammation, tissue damage, and infections, with acute and chronic infections being related to coronary events, as well as inflammation being related to systemic hypercoagulability and the onset of acute ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and other parts of Germany, the odds of abnormal increases in serum C-reactive protein (i.e., $\geq$90th percentile of pre-episode levels = 5.7 mg/L) tripled and associated increases in TSP levels of 26 $\mu g/m^3$ (5-day averages) were associated with an odds ratio of 1.37 (95% CI 1.08-1.73) for C-reactive protein levels exceeding the 90th percentile levels in two pollutant models also including SO_2 levels. The estimated odds ratio for a 30 $\mu g/m^3$ increase in the 5-day mean for SO_2 was 1.12 (95% CI 0.92 to 1.47; non-significant).

Two other recent studies also examined blood indices in relation to PM pollution (Seaton et al., 1999; Prescott et al., 1999). Seaton and colleagues collected sequential blood samples (up to 12) over an 18 month period in 112 subjects (all over age 60) in Belfast and Edinburgh, UK. Blood samples were analyzed for hemoglobin, packed cell volumes, blood counts, fibrinogen, factor VII, interleuken 6, C-reactive protein. In a subset of 60 subjects, plasma albumin also was measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city. Personal exposure estimates for the three days preceding each blood draw were derived from ambient data adjusted by time-activity patterns and I/O penetration factors. No co-pollutants were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons, temperature, and between-subject differences. Significant changes in several of the blood indices were observed in association with either ambient or estimated personal PM_{10} levels. All changes were negative, except for C reactive protein in relation to ambient PM_{10}, which was positive.

Prescott et al. (1999) also investigated factors that might increase susceptibility to adverse cardiovascular events resulting from PM exposure. Using data from a cohort of 1592 subjects aged 55-74 in Edinburgh, UK, baseline measurements of blood fibrinogen and blood and plasma

viscosity were examined as modifiers of the effects of PM (indexed by BS) on the incidence of fatal and non-fatal myocardial infarction or stroke. All three blood indices were strong predictors of increased cardiac event risk. However, there was no clear evidence of either a main effect of BS, nor interactions between BS and blood indices.

The above findings add support for some intriguing hypotheses regarding possible mechanisms by which PM exposure may be linked with adverse cardiac outcomes. They are especially interesting in terms of implicating both increased blood viscosity and C-reactive protein, a biological marker of inflammatory responses thought to be predictive of increased risk for serious cardiac events.

6.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies

- ***Susceptible subpopulations***. Because they lack data on individual subject characteristics, ecologic time series studies provide only limited information on susceptibility factors based on stratified analyses. The relative impact of PM on cardiovascular (and respiratory) admissions reported in ecologic time series studies are generally somewhat higher than those reported for total admissions. This provides some limited support for hypothesizing that acute effects of PM operate via cardiopulmonary pathways or that persons with pre-existing cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from the ecologic time series studies showing larger relative impacts of PM on cardiovascular admissions in adults aged $\geq$65 yr as compared with younger populations, the differences are neither striking nor consistent. However, the individual-level studies of cardiophysiologic function assessed above generally do suggest that elderly persons with pre-existing cardiopulmonary disease are susceptible to subtle changes in heart rate variability in association with PM exposures. Because younger and healthier populations have not yet been assessed, it is not yet possible to say whether the elderly clearly have especially increased susceptibility, but this does represent a reasonable working hypothesis.
- ***Role of other environmental factors***. The ecologic time series studies published since 1996 all have controlled adequately for weather influences. Thus, it is deemed unlikely that residual confounding by weather accounts for the PM associations observed. With one possible exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac function. Thus, the possibility of

confounding in such studies cannot yet be readily discounted. Co-pollutants have been analyzed rather extensively in many of the recent time-series studies of hospital admissions and PM. In some studies, PM clearly carries an independent association after controlling for gaseous co-pollutants. In others, the "PM effects" are markedly reduced once co-pollutants are added to the model; but this may in part be due to both PM and co-pollutants such as CO and NO_2 being emitted from a common source (motor vehicles) and consequent colinearity between them and/or the gaseous pollutants such as CO having independent effects on cardiovascular function.

- ***Temporal patterns of responses following PM exposure***. The evidence from recent time series studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at lag 0, with some carryover to lag 1, with little evidence for important effects beyond lag 1.
- ***Relation of CVD effects to PM size and chemical composition attributes***. Insufficient data exist from the time series CVD admissions literature or from the emerging individual-level studies to provide clear guidance as to which ambient PM components, defined either on the basis of size or composition, determine ambient PM CVD effect potency. The epidemiologic studies published to date have been constrained by the limited availability of multiple PM metrics. Where multiple metrics exist, they often are of differential quality due to differences in numbers of monitoring sites and in monitoring frequency.
- ***PM effects on blood characteristics related to CVD events***. Interesting, though limited, new evidence has also been derived which is highly suggestive of associations between ambient PM and increased blood viscosity and increased serum C-reactive protein (both related to increased risks of serious cardiac events).

6.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory Hospital Admissions and Medical Visits

6.3.2.1 Introduction

Among the most severe morbidity measures evaluated with regard to PM exposure are hospital admissions. Hospital emergency department (ED) visits represent a somewhat less severe, but related, outcome that has also been studied in relation to air pollution. Also doctors' visits represent a related health measure that, although less studied, is relevant to those who also suffer severe health effects, but captures a different population than ED visits: i.e., those who

choose to visit a private doctor, rather than attend hospital ED. This latter category of pollution-affected persons can represent a large population, yet one largely unevaluated due to the usual lack of centralized data regarding doctors' visits.

This section evaluates present knowledge regarding the epidemiologic associations of hospital admissions and medical visits with ambient PM exposure. It intercompares various studies examining each of the size-related PM mass exposure measures (e.g., for PM_{10}) and study results for various PM chemical components vis-à-vis their relative associations with health effects, and their respective extents of coherence with PM associations exhibited across related health effects measures. In the following discussion, the main focus for quantitative intercomparisons is on studies and results considering PM metrics that quantitatively measure mass or a specific mass constituent, i.e.,: PM_{10}, $PM_{2.5}$, sulfates ($SO_4^{=}$), or acidic aerosols (H^+). Study results for other related PM metrics (e.g., Black Smoke; BS) are also considered, but only qualitatively, primarily with respect to their coherence or lack of coherence with studies using mass or composition metrics measured in North America. In order to consider potentially confounding effects of other co-existing pollutants, study results for various PM metrics are presented both for: (1) when the PM metric is the only pollutant in the model; and, (2) the case where a second pollutant (e.g., ozone) is also included. Results from models with more than two pollutants included simultaneously are not used for quantitative estimates of coefficient size or statistical strength, due to increased likelihood of bias and variance inflation due to multi-collinearity of various pollutants (e.g., see Harris, 1975). The approach taken in this section is first to summarize briefly results and implications of the 1996 PM AQCD document regarding this topic, then to summarize and comment in tabular form on relevant studies newly published since that document, followed by text discussion of key findings most pertinent for present purposes.

6.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document

In the 1996 PM AQCD, it was found that both COPD and pneumonia hospitalization studies showed moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 (or 6 to 25% excess risk increment) per 50 $\mu g/m^3$ PM_{10} increase or its equivalent. While a substantial number of hospitalizations for respiratory illnesses occur in those >65 years of age,

there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals, but did not explicitly examine younger age groups. One exception noted was Pope (1991), who reported an increase in hospitalization for Utah Valley children (aged 0 to 5) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies. Studies examining acute associations between indicators of components of fine particles (e.g., BS; sulfates, $SO_4^{=}$; and acidic aerosols, H^{+}) and hospital admissions were also reported as finding significant relationships. While sulfates were especially predictive of respiratory health effects, it was not clear whether the sulfate-related effects were attributable to their acidity, to the broader effects of associated combustion-related fine particles, or to other factors.

6.3.2.3 New Respiratory-Related Hospital Admissions Studies

Many recent studies have confirmed PM associations with respiratory hospital admissions. These studies have examined various admissions categories, including: total respiratory admissions for all ages and by age; asthma for all ages and by age; chronic obstructive pulmonary disease (COPD) admissions (usually for patients > 64 yrs.), and pneumonia admissions (for patients > 64 yrs.). Table 6-17 summarizes important details regarding the study area, study period, study population, PM indices considered and their concentrations, the methods employed, study results and comments, and the "bottom-line" PM index percent excess risks per standard PM increment (e.g., 50 $\mu g/m^3$ for PM_{10}) from studies published since the 1996 PM AQCD.

The percent excess risk (ER) estimates presented in Table 6-17 are based upon the relative risks (RR's) provided by the authors, but converted into percent increments per standardized increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies. The ER's shown in the table are for the most positively significant pollutant coefficient, which likely overestimates the true health impact of that particular lag (since it may "pick up" some of the effects of intercorrelated adjacent days not included in the model). However, since the ER's usually apply to only a single day of morbidity (e.g., same day, but not following days), the single day results in the table likely underestimate the entire distributed lag effects of a day's pollution on the same and subsequent days (e.g., see Schwartz, 2000b). Thus, in the absence of a

TABLE 6-17. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Samet et al, (2000a,b) Study Period.: 84- 95 14 U.S. Cities: Birmingham, Boulder, Canton, Chicago, Col. Springs, Detroit, Minn./St. Paul, Nashville, New Haven, Pittsburgh, Provo/Orem, Seattle, Spokane, Youngstown. Mean pop. aged 65+ yr per city =143,000 PM_{10} mean = 32.9 $\mu g/m^3$ PM_{10} IQR = NR	Hospital admissions for adults 65+ yrs. for CVD (mean=22.1/day/city), COPD (mean=2.0/day/city), and Pneumonia (mean=5.6/day/city) related to PM_{10}, SO_2, O_3, NO_2, and CO. City-specific Poisson models used with adjustment for season, mean temperature (T) and relative humidity (RH) (but not their interaction), as well as barometric pressure (BP) using LOESS smoothers (span usually 0.5). Indicators for day-of-week and autoregressive terms also included.	PM_{10} positively associated with all three hospital admission categories, but city specific results ranged widely, with less variation for outcomes with higher daily counts. PM_{10} effect estimates not found to vary with co-pollutant correlation, indicating that results appear quite stable when controlling for confounding by gaseous pollutants. Analyses found little evidence that key socioeconomic factors such as poverty or race are modifiers, but it is noted that baseline risks may differ, yielding differing impacts for a given RR.	PM_{10} = 50 $\mu g/m^3$ <u>COPD HA's for Adults 65+ yrs.</u> Lag 0 ER = 7.4% (CI: 5.1, 9.8) Lag 1 ER = 7.5% (CI: 5.3, 9.8) 2 day mean (lag0,lag1) ER = 10.3% (CI: 7.7, 13) <u>Pneumonia HA's for Adults 65+ yrs.</u> Lag 0 ER =8.1% (CI: 6.5, 9.7) Lag 1 ER = 6.7% (CI: 5.3, 8.2) 2 day mean (lag0, lag1) = 10.3% (CI: 8.5, 12.1)
Zanobetti et al. (2000b) 10 U.S. Cities	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular and respiratory disease in persons aged ≥65 yr. Covariates: SO_2, O_3, CO, temperature, relative humidity, barometric pressure. In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 d considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50$\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. Suggests association between PM_{10} and total respiratory hospital admissions among the elderly.	Percent excess respiratory risk (95% CI) per 50 $\mu g/m^3$ PM_{10} increase: COPD (0-1 d lag) = 10.6 (7.9, 13.4) COPD (unconstrained dist. lag) = 13.4 (9.4, 17.4) Pneumonia (0-1 d lag) = 8.1 (6.5, 9.7) Pneumonia (unconstrained dist. lag) = 10.1 (7.7, 12.6)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Chen et al. (2000) Reno-Sparks, NV (90 - 94) Population = 307,000 B-Gauge PM_{10} mean=36.5 $\mu g/m^3$ PM_{10} IQR = 18.3-44.9 $\mu g/m^3$ PM_{10} maximum = 201.3 $\mu g/m^3$	Log of COPD (mean=1.72/day) and gastroenteritis (control) admissions from 3 hospitals analyzed using GAM regression, adjusting for effects of day-of-week, seasons, Weather effects (T, WS), and long-wave effects. No co-pollutants considered.	PM_{10} positively associated with COPD admissions, but no association with gastroenteritis (GE) diseases, indicating biologically plausible specificity of the PM_{10}-health effects association. Association remained even after excluding days with PM_{10} above 150 $\mu g/m^3$.	<u>COPD All age Admissions</u> 50 $\mu g/m^3$ IQR PM_{10} (single pollutant): ER = 9.4% (CI: 2.2, 17.1)
Choudhury et al. (1997) Anchorage, Alaska (90 - 92) Population = 240,000 PM_{10} mean = 41.5 $\mu g/m^3$ PM_{10} (SD) = 40.87 PM_{10} maximum=565 $\mu g/m^3$	Using insurance claims data for state employees and dependents living in Anchorage, Alaska, number of daily medical visits determined for asthma (mean = 2.42/day), bronchitis, and upper respiratory infections. Used linear regression, including a time-trend variable, crude season indicator variables (i.e., spring, summer, fall, winter), and a variable for the month following a volcanic eruption in 1992.	Positive association observed between asthma visits and PM_{10}. Strongest association with concurrent-day PM_{10} levels. No co-pollutants considered. Temperature and RH did not predict visits, but did interact with the PM_{10} association. Morbidity relative risk higher with respect to PM_{10} pollution during warmer days.	<u>Asthma Medical Visits (all ages):</u> For mean = 50 $\mu g/m^3$ PM_{10} (single poll.) Lag = 0 days ER = 20.9% (CI: 11.8, 30.8)
Gwynn et al. (2000) Buffalo, NY (5/88-10/90) PM_{10} mn./max. = 24.1/90.8 $\mu g/m^3$ PM_{10} IQR = 14.8-29.2 $\mu g/m^3$ $SO_4^=$ mn./max. = 2.4/3.9 $\mu g/m^3$ $SO_4^=$ IQR = 23.5 – 7.5 $\mu g/m^3$ H^+ mn/max = 36.4/382 nmol/m^3 H^+ IQR = 15.7-42.2 nmol/m^3 CoH mn/max = 0.2/0.9 $10^{-}3$ ft. CoH IQR = 0.1-0.3	Air pollutant-health effect associations with total, respiratory, and circulatory hospital admissions and mortality examined using Poisson methods controlling for weather, seasonality, long-wave effects, day of week, holidays,	Strongest associations found between $SO_4^=$ and respiratory hospital admissions, while secondary aerosol H^+ and $SO_4^=$ demonstrated the most coherent associations across both respiratory hospital admissions and mortality. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. CoH weakness in associations may reflect higher toxicity by acidic sulfur containing secondary particles versus carbonaceous primary particles.	<u>Respiratory Hospital Admissions(all ages) PM Index (using standardized conc. increment)</u> -Single Pollutant Models For PM_{10} = 50$\mu g/m^3$; SO_4 = 15$\mu g/m^3$; H^+ = 75nmoles/m^3;COH = 0.5 units/1000ft PM_{10}(lag 0) ER = 11% (CI: 4.0, 18) $SO_4^=$(lag 0) ER = 8.2% (CI: 4.1, 12.4) H^+(lag 0) ER = 6% (CI: 2.8, 9.3) CoH(lag0) ER = 3% (CI: –1.2, 7.4)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Jacobs et al. (1997) Butte County, CA (83 - 92) Population = 182,000 PM_{10} mean = 34.3 $\mu g/m^3$ PM_{10} min/max = 6.6 / 636 $\mu g/m^3$ CoH mean = 2.36 per 1000 lin. ft. CoH min/max = 0 / 16.5	Association between daily asthma HA's (mean = 0.65/day) and rice burning using Poisson model with a linear term for temperature, and indicator variables for season and yearly population. Co-pollutants were O_3 and CO. PM_{10} estimated for 5 of every 6 days from CoH.	Increases in rice straw burn acreage found to correlate with asthma HA's over time. All air quality parameters gave small positive elevations in RR. PM_{10} showed the largest increase in admission risk.	Asthma HA's (all ages) For an increase of 50 $\mu g/m^3$ PM_{10}: ER = 6.11% (not statistically significant)
Jamason et al. (1997) New York City, NY (82 - 92) Population = NR PM_{10} mean = 38.6 $\mu g/m^3$	Weather/asthma relationships examined using a synoptic climatological multivariate methodology. Procedure relates homogenous air masses to daily counts of overnight asthma hospital admission.	Air pollution reported to have little role in asthma variations during fall and winter. During spring and summer, however, the high risk categories are associated with high concentration of various pollutants (i.e., PM_{10}, SO_2,NO_2, O_3).	NR
Linn et al. (2000) Los Angeles, CA (92 - 95) Population = NR PM_{10} mean = 45.5 $\mu g/m^3$ PM_{10} Min/Max = 5/132 $\mu g/m^3$	Pulmonary hospital admissions (HA's) (mean=74/day) related to CO, NO_2, PM_{10}, and O_3 in Los Angeles using Poisson model with long-wave, day of week, holidays, and weather controls.	PM_{10} positively associated with pulmonary admissions year-round, especially in winter. No association with cerebro-vascular or abdominal control diseases. However, use of linear temperature, and with no RH interaction, may have biased effect estimates downwards for pollutants here most linearly related to temperature (i.e., O_3 and PM_{10}).	<u>Pulmonary HA's (>29 yrs.)</u> PM_{10} = 50 $\mu g/m^3$ (Lag 0)ER = 3.3% (CI: 1.7, 5)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lipsett et al. (1997) Santa Clara County, CA Population = NR (Winters 88 - 92) PM_{10} mean = 61.2 $\mu g/m^3$ PM_{10} Min/Max = 9/165 $\mu g/m^3$	Asthma emergency department (ER) visits from 3 acute care hospitals (mean=7.6/day) related to CoH, NO_2, PM_{10}, and O_3 using Poisson model with long-wave, day of week, holiday, and weather controls (analysis stratified by minimum T). Every other day PM_{10} estimated from CoH. Residential wood combustion (RWC) reportedly a major source of winter PM. Gastro-enteritis (G-E) ER admissions also analyzed as a control disease.	Consistent relationships found between asthma ER visits and PM_{10}, with greatest effect at lower temperatures. Sensitivity analyses supported these findings. NO_2 also associated, but in simultaneous regressions only PM_{10} stayed associated. ER visits for gastroenteritis not significantly associated with air pollution. Results demonstrate an association between wintertime ambient PM_{10} and asthma exacerbations in an area where RWC is a principal PM source.	<u>Asthma ED Visits (all ages)</u> PM_{10} = 50 $\mu g/m^3$ (2 day lag): At 20° F, ER = 34.7% (CI: 16, 56.5) At 30° F, ER = 22% (CI: 11, 34.2) At 41° F, ER = 9.1% (CI: 2.7, 15.9)
Moolgavkar et al. (1997) Minneapolis-St. Paul 86 - 91 Population.= NR Birmingham, AL '86-'91 Population. = NR PM_{10} mean = 34 $\mu g/m^3$ (M-SP) PM_{10} IQR =22-41 $\mu g/m^3$ (M-SP) PM_{10} mean =43.4 $\mu g/m^3$ (Birm) PM_{10} IQR =26-56 $\mu g/m^3$ (Birm)	Investigated associations between air pollution (PM_{10}, SO_2, NO_2 O_3, and CO) and hospital admissions for COPD (mean/day=2.9 in M-SP; 2.3 in Birm) and pneumonia (mean=7.6 in M-SP; 6.0 in Birm) among older adults (>64 yrs.). Poisson GAM's used, controlling for day-of-week, season, LOESS of temperature (but neither RH effects nor T-RH interaction considered).	In the M-SP area, PM_{10} significantly and positively associated with total daily COPD and pneumonia admissions among elderly, even after simultaneous inclusion of O_3. When four pollutants included in the model (PM_{10}, SO_2, O_3, NO_2), all pollutants remained positively associated. In Birm., neither PM_{10} nor O_3 showed consistent associations across lags. The lower power (fewer counts) and lack of T-RH interaction weather modeling in this Southern city vs. M-SP may have contributed to the differences seen between cities.	<u>COPD + Pneumonia Admissions (>64yrs.)</u> In M-SP, For PM_{10} = 50 $\mu g/m^3$ (max lg) ER(lg 1) = 8.7% (CI: 4.6, 13) With O_3 included simultaneously: ER(lg1)= 6.9% (95 CI: 2.7, 11.3) In Birm, For PM_{10}=50 $\mu g/m^3$ (max lg.) ER(lg 0) = 1.5% (CI: −1.5, 4.6) With O_3 included simultaneously: ER(lg0) = 3.2% (CI: −0.7, 7.2)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Nauenberg and Basu (1999) Los Angeles (91 - 94) Wet Season = 11/1-3/1 Dry Season = 5/1-8/15 Population .= 2.36 Million PM_{10} Mean = 44.81 $\mu g/m^3$ PM_{10} SE = 17.23 $\mu g/m^3$	The effect of insurance status on the association between asthma-related hospital admissions and exposure to PM_{10} and O_3 analyzed, using regression techniques with same day and 8-day weighted moving average levels, after removing trends using Fourier series. Compared results during wet season for all asthma HA's (mean = 8.7/d), for the uninsured (mean=0.77/d), for MediCal (poor) patients (mean = 4.36/d), and for those with other private health or government insurance (mean = 3.62/d).	No associations found between asthma admissions and O_3. No O_3 or PM_{10} associations found in dry season. PM_{10} averaged over eight days associated with increase in asthma admissions, with even stronger increase among MediCal asthma admissions in wet season. The authors conclude that low income is useful predictor of increased asthma exacerbations associated with air pollution. Non-respiratory HA's showed no such association with PM_{10}.	<u>All Age Asthma HA's</u> PM_{10} = 50 $\mu g/m^3$, no co-pollutant, during wet season (Jan. 1 - Mar. 1): <u>All Asthma Hospital Admissions</u> 0-d lag PM_{10} ER = 16.2 (CI: 2.0, 30) 8-d avg. PM_{10} ER = 20.0 (CI: 5.3, 35) <u>MediCal Asthma Hospital Admissions</u> 8-d avg. PM_{10} ER = 13.7 (3.9, 23.4) <u>Other Insurance Asthma HA's</u> 8-d avg. PM_{10} ER = 6.2 (−3.6, 16.1)
Norris et al. (1999) Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 $\mu g/m^3$ PM_{10} IQR = 11.6 $\mu g/m^3$ σ_{sp} mean = 0.4 $m^{-}1/10^{-}4$ ($\approx$12.0 $\mu g/m^3$ $PM_{2.5}$) σ_{sp} IQR = 0.3 $m^{-}1/10^{-}4$ (= 9.5 $\mu g/m^3$ $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) were compared with those from lower hospital utilization areas(1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering (σ_{sp}), CO, SO_2, and NO_2 using a semiparametric Poisson regression model evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. There was no stronger association between ED visits for asthma and air pollution in the higher hospital utilization area than in the lower utilization area in terms of RR's. However, considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city.	Children's (<18 yrs.) Asthma ED Visits Single Pollutant Models: 24h PM_{10} =50 $\mu g/m^3$ Lag1 ER = 75.9% (25.1, 147.4) For 25 $\mu g/m^3$ $PM_{2.5}$ Lag1 ER = 44.5% (CI: 21.7, 71.4) Multiple Pollutant Models: 24h PM_{10} =50 $\mu g/m^3$ Lag1 ER = 75.9% (CI: 16.3, 166) For 25$\mu g/m^3$ $PM_{2.5}$ Lag1 ER = 51.2% (CI: 23.4, 85.2)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Norris et al. (2000) Spokane, WA (1/95 - 3/97) Population = 300,000 PM_{10} mean. = 27.9 $\mu g/m^3$ PM_{10} Min/Max =4.7/186.4 $\mu g/m^3$ PM_{10} IQR = 21.4 $\mu g/m^3$ Seattle, WA (9/95 - 12/96) Pop. Of Children <18 = 107,816 PM_{10} mean. = 21.5 $\mu g/m^3$ PM_{10} Min/Max = 8/69.3 $\mu g/m^3$ PM_{10} IQR = 11.7 $\mu g/m^3$	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yr. (mean=3.2/d) in Spokane and for children <18 yr. (mean=1.8/d) in Seattle. Poisson GAM model applied, controlling for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in both cities. Factor analysis indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with "stagnation" as the "co-pollutant" indicated importance of general air pollution over any single air pollutant index, but not of the importance of various pollutants relative to each other.	<u>Asthma ED Visits</u> Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 50 $\mu g/m^3$ Lag 3 ER = 2.4% (CI: –10.9, 17.6) Persons<18 years (Seattle) For PM_{10} IQR = 50 $\mu g/m^3$ Lag 3 ER = 56.2% (95 CI: 10.4 , 121.1)
Schwartz et al. (1996b) Cleveland (Cayahoga County), Ohio (88 - 90) PM_{10} mean = 43 $\mu g/m^3$ PM_{10} IQR = 26 – 56 $\mu g/m^3$	Review paper including an example drawn from respiratory hospital admissions of adults aged 65 yr and older (mean = 22/day) in Cleveland, OH. Categorical variables for weather and sinusoidal terms for filtering season employed.	Hospital admissions for respiratory illness of persons aged 65 yr and over in Cleveland strongly associated with PM_{10} and O_3, and marginally associated with SO_2 after control for season, weather, and day of the week effects.	<u>Respiratory HA's for persons 65+ years</u> 50 $\mu g/m^3$ PM_{10} ER = 5.8% (CI: 0.5, 11.4)
Tolbert et al. (2000b) Atlanta, GA (92 - 94 Summers) Population = 80% of children in total population of 3 million PM_{10} mn. (SE) = 38.9 (15.5) $\mu g/m^3$ PM_{10} Range = 9, 105 $\mu g/m^3$	Pediatric (<17 yrs. of age) ED visits (mean = 467/day) related to air pollution (PM_{10}, O_3, NO_x, pollen and mold) using GEE and logistic regression and Bayesian models. Autocorrelation, day of week, long-term trend terms, and linear temperature controls included.	Both PM_{10} and O_3 positively associated with asthma ED visits using all three modeling approaches. In models with both O_3 and PM_{10}, both pollutants become non-significant because of high collinearity of the variables (r=0.75).	<u>Pediatric (<17 yrs. of age) ED Visits</u> PM_{10} = 50 $\mu g/m^3$ Lag 1 day ER = 13.2% (CI: 1.2, 26.7) With O_3 8.2 (–7.1, 26.1)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} ($\mu g/m^3$): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} ($\mu g/m^3$): 29.1, 27.6, 12.0 $PM_{2.5}$ ($\mu g/m^3$): 19.4, 17.5, 9.35 CP ($\mu g/m^3$): 9.39, 8.95, 4.52 10-100 nm PM counts ($count/cm^3$): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals ($\mu g/m^3$): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates ($\mu g/m^3$): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity ($\mu g/m^3$): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM ($\mu g/m^3$): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon ($\mu g/m^3$): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for asthma (493), wheezing (786.09) COPD (491, 492, 4966) LRI 466.1, 480, 481, 482, 483, 484, 485, 486), all resp disease (460-466, 477, 480-486, 491, 492, 493, 496, 786.09) for persons ≥16 yr in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all DVD in period 1 were 6.5 and 28.4, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day-of-week and hospital entry/exit indicators also included. Pollutants treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, observed significant COPD association with 3-day average PM_{10}. COPD was also positively associated with NO_2, O_3, CO and SO_2. No statistically significant association observed between asthma and PM_{10} in period 1. However, asthma positively associated with ozone (p=0.03). In period 2, i.e., the first year of operation of the superstation, no statistically significant associations observed with PM_{10} or $PM_{2.5}$. These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	<u>Period 1:</u> PM_{10} (0-2 d): asthma: 5.6% (−8.6, 22.1) COPD: 19.9% (0.1, 43.7) <u>Period 2:</u> (all 0-2 day lag) PM_{10}: asthma 18.8% (−8.7, 54.4) COPD −3.5% (29.9 − 33.0) $PM_{2.5}$: asthma 2.3% (−14.8, 22.7) COPD 12.4% (−7.9, 37.2) $PM_{10-2.5}$ asthma 21.1% (−18.2, 79.3) COPD −23.0% (50.7 − 20.1)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Yang et al (1997) Study Period: 92 - 94 Reno-Sparks, Nevada Population = 298,000 PM_{10} mean = 33.6 $\mu g/m^3$ PM_{10} range = 2.2, 157.3 $\mu g/m^3$	Association between asthma ER visits (mean = 1.75/d, SD=1.53/d) and PM_{10}, CO and O_3 assessed using linear WLS and ARIMA regression, including adjustments for day-of-week, season, and temperature (but not RH or T-RH interaction). Season adjusted only crudely, using month dummy variable.	Only O_3 showed significant associations with asthma ER visits. However, the crude season adjustment and linear model (rather than Poisson) may have adversely affected results. Also, Beta-gauge PM_{10} mass index used, rather than direct gravimetric mass measurements.	NR
Zanobetti, et al. (2000a) Study Period: 86 - 94 Chicago (Cook Count), IL Population = 633,000 aged 65+ PM_{10} mean = 33.6 $\mu g/m^3$ PM_{10} range = 2.2, 157.3 $\mu g/m^3$	Analyzed HA's for older adults (65 + yr) for COPD (mean = 7.8/d), pneumonia (mean = 25.5/d), and CVD, using Poisson regression controlling for temperature, dew point, barometric pressure, day of week, long wave cycles and autocorrelation, to evaluate whether previous admission or secondary diagnosis for associated conditions increased risk from air pollution. Effect modification by race, age, and sex also evaluated.	Air pollution- associated CVD HA's were nearly doubled for those with concurrent respiratory infections (RI) vs. those without concurrent RI. For COPD and pneumonia admissions, diagnosis of conduction disorders or dysrhythmias (Dyshr.) increased PM_{10} RR estimate. The PM_{10} RR effect size did not vary significantly by sex, age, or race, but baseline risks across these groups differ markedly, making such sub-population RR inter-comparisons difficult to interpret.	PM_{10} = 50 $\mu g/m^3$(average of lags 0,1) COPD (adults 65+ yrs.) W/o prior RI. ER = 8.8% (CI: 3.3, 14.6) With prior RI ER = 17.1% (CI: −6.7, 46.9) COPD (adults 65+ yrs.) W/o concurrent Dys. ER = 7.2% (CI: 1.3, 13.5) With concurrent Dys. ER = 16.5%(CI: 3.2, 31.5) Pneumonia (adults 65+ yrs.) W/o pr. Asthma ER = 11% (CI: 7.7, 14.3) With pr. Asthma ER = 22.8% (CI: 5.1, 43.6) Pneumonia (adults 65+ yrs.) W/o pr. Dyshr. ER = 10.4% (CI: 6.9, 14) With pr. Dyshr. ER = 18.8% (CI: 6.3, 32.7)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lippmann et al. (2000) Detroit, MI ('92-'94) Population = 2.1 million PM_{10} Mean = 31 $\mu g/m^3$ (IQR= 19, 38 $\mu g/m^3$; max=105$\mu g/m^3$) $PM_{2.5}$ Mean = 18 $\mu g/m^3$ (IQR= 10, 21 $\mu g/m^3$; max=86 $\mu g/m^3$) $PM_{10-2.5}$ Mean = 12 $\mu g/m^3$ (IQR= 8, 17 $\mu g/m^3$; max=50 $\mu g/m^3$) $SO_4^=$Mean = 5 $\mu g/m^3$ (IQR=1.8, 6.3 $\mu g/m^3$; max=34.5 $\mu g/m^3$) H^+ Mean = 8.8 nmol/m^3 = 0.4 $\mu g/m^3$ (IQR=0, 7nmol/m^3;max=279)	Respiratory (COPD and Pneumonia) HA's for persons 65 + yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For respiratory HA's, all PM metrics yielded RR's estimates >1, and all were significantly associated in single pollutant models for pneumonia. For COPD, all PM metrics gave RR's >1, with H^+ being associated most significantly, even after the addition of O_3 to the regression. Adding gaseous pollutants had negligible effects on the various PM metric RR estimates. The most consistent effect of adding co-pollutants was to widen the confidence bands on the PM metric RR estimates: a common statistical artifact of correlated predictors. Despite usually non-detectable levels, H^+ had strong association with respiratory admissions on the few days it was present. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per $\mu g/m^3$ in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity is usually not present.	**Pneumonia HA's for 65+ yrs.** No co-pollutant: PM_{10} (50 $\mu g/m^3$) 1d lag ER = 22% (CI: 8.3, 36) $PM_{2.5}$ (25 $\mu g/m^3$) 1d lag: ER = 13% (CI: 3.7, 22) $PM_{2.5-10}$ (25 $\mu g/m^3$) 1d lag: ER = 12% (CI: 0.8, 24) H^+ (75 nmol/m^3) 3d lag: ER = 12% (CI: 0.8, 23) O_3 co-pollutant (lag 3) also in model: PM_{10} (50 $\mu g/m^3$) 1d lag, ER = 24% (CI: 8.2, 43) $PM_{2.5}$ (25 $\mu g/m^3$) 1d lag: ER = 12% (CI: 1.7, 23) $PM_{2.5-10}$ (25 $\mu g/m^3$) 1d lag: ER = 14% (CI: 0.0, 29) H^+ (75 nmol/m^3) 3d lag: ER = 11% (CI: –0.9, 24) **COPD Hospital Admissions for 65+ yrs.** No co-pollutant: PM_{10} (50 $\mu g/m^3$) 3d lag ER = 9.6% (CI: –5.1, 27) $PM_{2.5}$ (25 $\mu g/m^3$) 3d lag: ER = 5.5% (CI: –4.7, 17) $PM_{2.5-10}$ (25 $\mu g/m^3$) 3d lag: ER = 9.3% (CI: –4.4, 25) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: 0.0, 28) O_3 co-pollutant (lag 3) also in model: PM_{10} (50 $\mu g/m^3$) 3d lag, ER = 1.0% (-15, 20) $PM_{2.5}$ (25 $\mu g/m^3$) 3d lag: ER = 2.8% (CI: –9.2, 16) $PM_{2.5-10}$ (25 $\mu g/m^3$) 3d lag: ER = 0.3% (CI: –14, 18) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: –0.6, 28)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lumley and Heagerty (1999) Seattle (King Cty.), WA (87-94) Population = NR PM_1 daily mean = NR PM_{1-10} daily mean = NR From Sheppard et al, 1999: PM_{10} mean = 31.5 $\mu g/m^3$ PM_{10} IQR = 19-39 $\mu g/m^3$ $PM_{2.5}$ mean = 16.7 $\mu g/m^3$ $PM_{2.5}$ IQR = 8-21 $\mu g/m^3$	Estimating equations based on marginal generalized linear models applied to respiratory HA's for persons <65 yrs. of age (mean ~ 8/day) using class of variance estimators based upon weighted empirical variance of the estimating functions. Poisson regression used to fit a marginal model for the log of admissions with linear temperature, day of week, time trend, and dummy season variables. No co-pollutants considered.	PM_1 at lag 1 day associated with respiratory HA's in children and younger adults (<65), but not PM_{10-1}, suggesting a dominant role by the submicron particles in $PM_{2.5}$–asthma HA associations reported by Sheppard et al. (1999). 0-day lag PM_1 and 0 and 1 day lag PM_{1-10} had RR near 1 and clearly non-significant. Authors note that model residuals correlated at r=0.2, suggesting the need for further long-wave controls in the model (e.g., inclusion of the LOESS of HA's).	<u>Respiratory HA's for persons <65 yrs. old</u> PM_1 = 25 $\mu g/m^3$, no co-pollutant: 1-d lag ER = 5.9 (1.1, 11.0)
Moolgavkar et al. (2000) King County, WA (87 - 95) Population = NR PM_{10} mean = 30.0 $\mu g/m^3$ PM_{10} IQR =18.9-37.3 $\mu g/m^3$ $PM_{2.5}$ mean =18.1 $\mu g/m^3$ $PM_{2.5}$ IQR =10-23 $\mu g/m^3$	Association between air pollution and hospital admissions (HA's) for COPD (all age mean=7.75/day; 0-19 yrs. mean=2.33/day) investigated using Poisson GAM's controlling for day-of-week, season, and LOESS of temperature. Co-pollutants addressed: O_3, SO_2, CO, and pollens. $PM_{2.5}$ only had one monitoring site versus multiple sites averaged for other pollutants.	Of the PM metrics, PM_{10} showed the most consistent associations across lags (0-4 d). $PM_{2.5}$ yielded the strongest positive PM metric association at lag3 days, but gave a negative association at lag4 days. That $PM_{2.5}$ only had one monitoring site may have contributed to its effect estimate variability. Residual autocorrelations (not reported) may also be a factor. Adding gaseous co-pollutants or pollens decreased the $PM_{2.5}$ effect estimate less than PM_{10}. Analyses indicated that asthma HA's among the young were driving the overall COPD-air pollution associations.	<u>COPD HA's all ages</u> (no co-pollutant) PM_{10} (50 $\mu g/m^3$, lag 2) ER = 5.1% (CI: 0, 10.4) $PM_{2.5}$ (25 $\mu g/m^3$, lag 3) ER = 6.4% (CI: 0.9, 12.1) COPD HA's all ages (CO as co-pollutant) PM_{10} (50 $\mu g/m^3$, lag 2) ER = 2.5% (CI: -2.5, 7.8) $PM_{2.5}$ (25 $\mu g/m^3$, lag 3) ER = 5.6% (CI: 0.2, 11.3)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Moolgavkar (2000a) Study Period: 1987-1995 Chicago (Cook County), IL Population = NR PM_{10} median = 35 $\mu g/m^3$ PM_{10} IQR = 25-47 $\mu g/m^3$ Los Angeles (LA County), CA Population = NR PM_{10} median = 44 $\mu g/m^3$ PM_{10} IQR = 33-59 $\mu g/m^3$ $PM_{2.5}$ median = 22 $\mu g/m^3$ $PM_{2.5}$ IQR = 15-31 $\mu g/m^3$ Phoenix (Maricopa County), AZ Population = NR PM_{10} median = 41 $\mu g/m^3$ PM_{10} IQR = 32-51 $\mu g/m^3$	Investigated associations between air pollution (PM_{10}, O_3, SO_2, NO_2, and CO) and COPD Hospital Admissions (HA's). $PM_{2.5}$ also analyzed in Los Angeles. HA's for adults >65 yr.: median=12/day in Chicago, =4/d in Phoenix; =20/d in LA. In LA, analyses also conducted for children 0-19 yr. (med.=17/d) and adults 20-64 (med.=24/d). Poisson GAM's used controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. PM data available only every 6th day (except for daily PM_{10} in Chicago), vs. every day for gases. Power likely differs across pollutants, but number of sites and monitoring days not presented. Two pollutant models forced to have same lag for both pollutants. Autocorrelations or intercorrelations of pollutant coefficients not presented or discussed.	For >64 adults, CO, NO_2 and O_3 (in summer) most consistently associated with the HA's. PM effects more variable, especially in Phoenix. Both positive and negative significant associations for PM and other pollutants at different lags suggest possible unaddressed negative autocorrelation. In LA, PM associated with admissions in single pollutant models, but not in two pollutant models. The forcing of simultaneous pollutants to have the same lag (rather than maximum lag), which likely maximizes intercorrelations between pollutant coefficients, may have biased the two pollutant coefficients, but information not presented.. Analysis in 3 age groups in LA yielded similar results. Author concluded that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER Single Pollutant Models: COPD HA's (>64 yrs.) (50 $\mu g/m^3$ PM_{10}): Chicago: Lag 0 ER =2% (CI: −0.2, 4.3) LA: Lag 2 ER = 6.1% (CI: 1.1, 11.3) Phoenix: Lag 0 ER = 6.9% (CI: −4.1, 19.3) LA COPD HA's (50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=10.7%(CI: 4.4, 17.3) (0-19 yrs.): $PM_{2.5}$ lg0=4.3%(CI: −0.1, 8.9) (0-19 yrs.): $PM_{(2.5-10)}$ lg2=17.1%(CI: 8.9, 25.8) (20-64 yrs.): PM_{10} lg2=6.5%(CI: 1.7, 11.5) (20-64 yrs.): $PM_{2.5}$ lg2=5.6%(CI: 1.9, 9.4) (20-64 yrs.): $PM_{2.5-10}$ lg2=9%(CI: 3, 15.3) (> 64 yrs): PM_{10} lg2 = 6.1% (1.1, 11.3) (> 64 yrs): $PM_{2.5}$ lg2 = 5.1% (0.9, 9.4) (>64 yrs.): $PM_{2.5-10}$ lg3=5.1% (CI: −0.4, 10.9) (>64 yr) 2 Poll. Models (CO = co-poll.) PM_{10}: Lag 2 ER = 0.6% (CI: −5.1, 6.7) $PM_{2.5}$: Lag 2 ER = 2.0% (−2.9, 7.1)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Sheppard et al. (1999) Seattle, WA, Pop. = NR 1987-1994 PM_{10} mean = 31.5 $\mu g/m^3$ PM_{10} IQR = 19-39 $\mu g/m^3$ $PM_{2.5}$ mean = 16.7 $\mu g/m^3$ $PM_{2.5}$ IQR = 8-21 $\mu g/m^3$ $PM_{2.5-10}$ mean = 16.2 $\mu g/m^3$ $PM_{2.5-10}$ IQR = 9-21 $\mu g/m^3$	Daily asthma hospital admissions (HA's) for residents aged <65 (mean=2.7/day) regressed on PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, SO_2, O_3, and CO in a Poisson regression model with control for time trends, seasonal variations, and temperature-related weather effects. Appendicitis HA's analyzed as a control. Except O_3 in winter, missing pollutant measures estimated in a multiple imputation model. Pollutants varied in number of sites available for analysis, CO the most (4) vs. 2 for PM.	Asthma HA's significantly associated with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ mass lagged 1 day, as well as CO. Authors found PM and CO to be jointly associated with asthma admissions. Highest increase in risk in spring and fall. Results conflict with hypothesis that wood smoke (highest in early study years and winter) would be most toxic. Associations of CO with respiratory HA's taken by authors to be an index of incomplete combustion, rather than direct CO biological effect.	Asthma Admissions (ages 0-64) PM_{10} (lag=1day); 50 $\mu g/m^3$ ER = 13.7% (CI: 5.5%, 22.6) $PM_{2.5}$ (lag=1day); 25 $\mu g/m^3$ ER = 8.7% (CI: 3.3%, 14.3) $PM_{2.5-10}$ (lag=1day); 25 $\mu g/m^3$ ER = 11.1% (CI: 2.8%, 20.1)
Canada			
Burnett et al. (1997b) Toronto, Canada (1992-1994), Pop. = 4 mill. $PM_{2.5}$ mean = 16.8 $\mu g/m^3$ $PM_{2.5}$ IQR = 8-23 $\mu g/m^3$ $PM_{2.5-10}$ mean = 11.6 $\mu g/m^3$ $PM_{2.5-10}$ IQR = 7-14 $\mu g/m^3$ PM_{10} mean = 28.4 $\mu g/m^3$ PM_{10} IQR = 16-38 $\mu g/m^3$ CoH mean = 0.8 (per 10^3 lin. ft.) CoH IQR = 0.5-1.1(per 10^3 lin ft) SO_4 mean = 57.1 nmole/m^3 SO_4 IQR = 14-71 nmole/m^3 H^+ mean = 5 nmole/m^3 H^+ IQR = 0-6 nmole/m^3	Hospital admissions (HA's) for respiratory diseases (tracheobronchitis, chronic obstructive long disease, asthma, pneumonia) analyzed using Poisson regression (adjusting for long-term temporal trends, seasonal variations, effects of short-term epidemics, day-of-week, ambient temperature and dew point). Daily particle measures: $PM_{2.5}$, coarse particulate mass($PM_{10-2.5}$), PM_{10}, SO_4, H^+, and gaseous pollutants (O_3, NO_2, SO_2, and CO) evaluated.	Positive air pollution-HA associations found, with ozone being pollutant least sensitive to adjustment for co-pollutants. However, even after the simultaneous inclusion of O_3 in the model, the association with the respiratory hospital admissions were still significant for PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, CoH,, SO_4, and H^+.	Respiratory HA's all ages(no co-pollutant) PM_{10} (50 $\mu g/m^3$, 4d avg. lag 0) ER = 10.6% (CI: 4.5 - 17.1) $PM_{2.5}$ (25 $\mu g/m^3$, 4d avg. lag 1) ER = 8.5% (CI: 3.4, 13.8) $PM_{2.5-10}$ (25 $\mu g/m^3$, 5d avg. lag 0) ER = 12.5% (CI: 5.2, 20.0) Respiratory HA's all ages(O_3 co-pollutant) PM_{10} (50 $\mu g/m^3$, 4d avg. lag 0) ER = 9.6% (CI: 3.5, 15.9) $PM_{2.5}$ (25 $\mu g/m^3$, 4d avg., lag 1) ER = 6.2% (1.0, 11.8) $PM_{2.5-10}$ (25 $\mu g/m^3$, 5d avg. lag 0) ER = 10.8% (CI: 3.7, 18.1)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} ($\mu g/m^3$): 18, 16, 10 CP_{est} ($\mu g/m^3$): 12, 10, 8 $PM_{10\ est}$ ($\mu g/m^3$): 30, 27, 15	Daily hospitalizations for asthma (493, mean 11/day), obstructive lung disease (490-492, 496, mean 5/day), respiratory infection (464, 466, 480-487, 494, mean 13/day) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were <u>estimated</u>, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models. Non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in respiratory outcome. In multi-pollutant models, there were no significant PM associations with any respiratory outcome (results not shown). Use of estimated PM metrics limits the interpretation of pollutant-specific results reported. However, results suggest that a linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when a full range of gaseous pollutants are also modeled.	Percent excess risk (95% CI) per 50 $\mu g/m^3$ PM_{10}; 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{(10\text{-}2.5)}$: <u>Asthma</u> $PM_{2.5}$ (0-1-2 d): 6.4 (2.5, 10.6) PM_{10} (0-1 d): 8.9 (3.7, 14.4) $PM_{10\text{-}2.5}$ (2-3-4 d): 11.1 (5.8, 16.6) <u>COPD</u> $PM_{2.5}$: 4.8 (−0.2, 10.0) PM_{10}: 6.9 (1.3, 12.8) $PM_{10\text{-}2.5}$ (2-3-4 d): 12.8 (4.9, 21.3) <u>Resp. Infection:</u> $PM_{2.5}$: 10.8 (7.2, 14.5) PM_{10}: 14.2 (9.3, 19.3) $PM_{10\text{-}2.5}$ (0-1-2 d): 9.3 (4.6, 14.2)
Delfino et al. (1997) Montreal, Canada Population= 3 million 6-9/92, 6-9/93 1993 Means (SD): PM_{10}= 21.7 $\mu g/m^3$ (10.2) $PM_{2.5}$= 12.2 $\mu g/m^3$ (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory emergency department (ED) visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using linear regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons aged 2-64 yrs. For patients >64 yr, O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	<u>Respiratory ED Visits</u> Adults >64: (pollutant lags = 1 day) 50 $\mu g/m^3$ PM_{10} ER = 36.6% (10.0, 63.2) 25 $\mu g/m^3$ $PM_{2.5}$ ER = 23.9% (4.9, 42.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Delfino et al. (1998) Montreal, Canada 6-8/89,6-8/90 Mean PM_{10}= 18.6 $\mu g/m^3$ (SD=9.3, 90th% = 30.0 $\mu g/m^3$)	Examined the relationship of daily ED visits for respiratory illnesses by age (mean/day: <2yr.=8.9; 2-34yr.=20.1; 35-64yr.=22.6; >64yr.=20.3) with O_3 and estimated $PM_{2.5}$. Seasonal and day-of-week trends, auto-correlation, relative humidity and temperature were addressed in linear time series regressions.	There was an association between $PM_{2.5}$ and respiratory ED visits for older adults (>64), but this was confounded by both temperature and O_3. The fact that $PM_{2.5}$ was estimated, rather than measured, may have weakened its relationship with ED visits, relative to O_3.	<u>Older Adults(>64 yr) Respiratory ED Visits</u> Estimated $PM_{2.5}$ = 25 $\mu g/m^3$ Single Pollutant: (lag 1 $PM_{2.5}$) ER = 13.2 (–0.2, 26.6) With Ozone (lag 1 $PM_{2.5}$): Est. $PM_{2.5}$ (lag1) ER = 0.8% (CI: –14.4, 15.8)
Stieb et al. (1996) New Brunswick, Canada Population = 75,000 May-Sept. 84 - 92 SO_4^{2-} Mean = 5.5 $\mu g/m^3$ Range: 1-23, 95th% =14 $\mu g/m^3$ TSP Mean = 36.7 $\mu g/m^3$ Range:5-108, 95th% =70 $\mu g/m^3$	Asthma ED visits (mean=1.6/day) related to daily O_3 and other air pollutants (SO_2, NO_2, SO_4^{2-}, and TSP). PM measured only every 6th day. Weather variables included temperature, humidex, dewpoint, and RH. ED visit frequencies were filtered to remove day of week and long wave trends. Filtered values were regressed on pollution and weather variables for the same day and the 3 previous days.	Positive, statistically significant ($p < 0.05$) association observed between O_3 and asthma ED visits 2 days later; strength of the association greater in nonlinear models. Ozone effect not significantly influenced by addition of other pollutants. However, given limited number of sampling days for sulfate and TSP, it was concluded that "a particulate effect could not be ruled out".	<u>Emergency Department Visits (all ages)</u> Single Pollutant Model 100 $\mu g/m^3$ TSP = 10.7% (-66.4, 87.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 H+ ($nmol/m^3$): 25.7, 36.8 Sulfate ($nmol/m^3$): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for asthma (mean 3.5/day), COPD (mean 1.3/day), resp infections (mean 6.2/day), and all respiratory conditions (mean 10.9/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations were observed between all respiratory ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations were observed with H+, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions.	$PM_{2.5}$, (lag 3) 15.1 (−0.2, 32.8) PM_{10}, (lag 3) 32.5 (10.2, 59.3)
Burnett et al. (1997c) 16 Canadian Cities('81-91) Population=12.6 MM CoH mean=0.64(per 10^3 lin. ft) CoH IQR=0.3-0.8(per 10^3 lin ft)	Air pollution data were compared to respiratory hospital admissions (mean=1.46/million people/day) for 16 cities across Canada. Used a random effects regression model, controlling for long-wave trends, day of week, weather, and city-specific effects.	The 1 day lag of 0_3 was positively associated with respiratory admissions in the April to December period, but not in the winter months. Daily maximum 1-hr. CoH from 11 cities and CO also positively associated with HA's, even after controlling for O_3.	Respiratory HA's all ages (with O_3,CO) CoH IQR = 0.5, lag 0: CoH ER = 3.1% (CI: 1.0-4.6%)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe			
Atkinson et al. (1999a) London (92 - 94) Population = NR PM10 Mean = 28.5 $\mu g/m^3$ 10^{th}-90^{th} IQR = 15.8-46.5 $\mu g/m^3$ BS mean =12.7 $\mu g/m^3$ 10^{th}-90^{th} IQR = 5.5-21.6 $\mu g/m^3$	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits from 12 London hospitals considered, but associated population size not reported. Counts for ages 0-14, 15-64, and >64 also examined. Poisson regression used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	PM_{10} positively associated, but not BS, for all-age/all-respiratory category. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship. PM_{10} positively associated for all ages, children, and young adults for asthma ED visits. However, PM_{10}-asthma relationship couldn't be separated from SO_2 in multi-pollutant regressions. Older adult ED visits most strongly associated with CO. No O_3-ED visits relationships found (but no warm season analyses attempted).	PM_{10} (50 $\mu g/m^3$) No co-pollutant: All Respiratory ED visits All age(lag 1d)ER = 4.9% (CI: 1.3, 8.6) <15yrs(lag 2d)ER = 6.4% (CI: 1, 12.2) 15-64yr(lag1d)ER = 8.6% (CI: 3.4, 14) Asthma ED visits All age (lag 1d) ER = 8.9% (CI: 3, 15.2) <15yrs (lag 2d) ER = 12.3% (CI: 3.4, 22) 15-64yr (lg 1d) ER = 13% (CI: 4.6, 22.1) PM_{10} (50 $\mu g/m^3$) 2d lag & co-pollutant: Children's (<15 yrs.) Asthma ED Visits: PM alone: ER = 12.3% (CI: 3.4, 22) &NO_2: ER = 7.8% (CI: −1.2, 17.6) & O_3: ER = 10.5% (CI: 1.6, 20.1) & SO_2: ER = 8.1% (CI: −1.1, 18.2) & CO: ER = 12.1% (CI: 3.2, 21.7)
Atkinson et al. (1999b) London (92 - 94) Population = 7.2 MM PM_{10} Mean = 28.5 10^{th}-90^{th} IQR = 15.8-46.5 $\mu g/m^3$ BS mean = 12.7 $\mu g/m^3$ 10^{th}-90^{th} IQR = 5.5-21.6 $\mu g/m^3$	All-age respiratory (mean=150.6/day), all-age asthma (38.7/day), COPD plus asthma in adults >64 yr. (22.9/day), and lower respiratory (64.1/day) in adults >64 yr (16.7/day) hospital admissions in London hospitals considered. Counts for ages 0-14, 15-64, and >64 yr also examined. Poisson regression used, controlling for season, day-of-week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	Positive associations found between respiratory-related emergency hospital admissions and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} included simultaneously, size and significance of each was reduced. Authors concluded that SO_2 and PM_{10} are both indicators of the same pollutant mix in this city. SO_2 and PM_{10} analyses by temperature tertile suggest that warm season effects dominate. Overall, results consistent with earlier analyses for London, and comparable with those for North America and Europe.	PM_{10} (50 $\mu g/m^3$), no co-pollutant. All Respiratory Admissions: All age (lag 1d) ER = 4.9% (CI: 1.8, 8.1) 0-14 y (lag 1d) ER = 8.1% (CI: 3.5, 12.9) 15-64y (lag 2d) ER = 6.9% (CI: 2.1, 12.9) 65+ y (lag 3d) ER = 4.9% (CI: 0.8, 9.3) Asthma Admissions: All age (lag 3d) ER = 3.4% (CI: −1.8, 8.9) 0-14 y (lag 3d) ER = 5.4% (CI: −1.2, 12.5) 15-64 y(lag 3d) ER = 9.4% (CI: 1.1, 18.5) 65+ y.(lag 0d) ER = 12% (CI: −1.8, 27.7) COPD & Asthma Admissions (65+yrs.) (lag 3d) ER = 8.6% (CI: 2.6, 15) Lower Respiratory Admissions (65+ yrs.) (lag 3d) ER = 7.6% (CI: 0.9, 14.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hajat et al. (1999) London, England (92 - 94) Population = 282,000 PM_{10} mean = 28.2 $\mu g/m^3$ PM_{10} 10^{t}-90^{th}%=16.3-46.4 $\mu g/m^3$ BS mean = 10.1 $\mu g/m^3$ BS 10^{t}-90^{th}%=4.5-15.9 $\mu g/m^3$	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care general practitioner asthma and "other LRD" consultations. Asthma consultation means per day = 35.3 (all ages); 14.(0-14 yrs,); 17.7 (15-64 yrs.); 3.6 (>64 yrs.). LRD means = 155 (all ages); 39.7(0-14 yrs,); 73.8 (15-64 yrs.); 41.1 (>64 yrs.). Time-series analyses of daily numbers of consultations performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children. Authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In adults, the authors concluded that the only consistent association was with PM_{10}. Across all of the various age, cause, and season categories considered, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits:</u> 50 $\mu g/m^3$ PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 5.4% (CI: –0.6, 11.7) 0-14 yrs.(lg 1): ER = 6.4% (–1.5, 14.6) 15-64 yrs.(lg 0): ER = 9.2% (CI: 2.8, 15.9) >64yrs.(lg 2): ER = 11.7% (–1.8, 26.9) -Year-round, 2 Pollutant, Children (0, 14): (PM_{10} lag = 1 day) PM_{10} ER's: W/NO_2: ER = 0.8% (CI: –8.7, 11.4) W/O_3: ER = 5.5% (–2.1, 13.8) W/SO_2: ER = 3.2% (CI: –6.4, 13.7) <u>Other Lower Resp. Dis. Doctor's Visits:</u> 50 $\mu g/m^3$ PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 3.5% (CI: 0, 7.1) 0-14 yrs.(lg 1): ER = 4.2% (CI: –1.2, 9.9) 15-64 yrs.(lg 2): ER= 3.7% (CI: 0.0, 7.6) >64yrs.(lg 2): ER = 6.2% (CI: 0.5, 12.9)
Wordley et al. (1997) Study Period: 4/92 –3/94 Birmingham, UK Population = NR PM_{10} daily values: Mean = 25.6 $\mu g/m^3$ range = 2.8, 130.9 $\mu g/m^3$ PM_{10} 3 day running. mean: Mean = 25.5 $\mu g/m^3$ range = 7.3, 104.7 $\mu g/m^3$	Relation between PM_{10} and total HA's for respiratory (mean = 21.8/d), asthma (mn.=6.2/d), bronchitis (mn.=2.4/d), pneumonia (mn.=3.4/d), and COPD (mn.=3.2/d) analyzed, using linear regression after adjusting for day of week, month, linear trend, RH, and T (but not T-RH interaction). RR's compared for various thresholds vs. mean risk of HA.	PM_{10} positively associated with all HA's for respiratory, asthma, bronchitis, pneumonia, and COPD. Pneumonia, all respiratory, and asthma HA's also significantly positively associated with the mean of PM_{10} over the past three days, which gave 10 to 20% greater RR's per 10 $\mu g/m^3$, as expected given smaller day to day deviations. Other air pollutants examined but not presented, as "these did not have a significant association with health outcomes independent from that of PM_{10}".	50 $\mu g/m^3$ in PM_{10} <u>All Respiratory HA's (all ages)</u> (lag0d) ER = 12.6% (CI: 5.7, 20) <u>Asthma HA's (all ages)</u> (lag2d) ER = 17.6% (CI: 3, 34.4) <u>Bronchitis HA's (all ages)</u> (lag0d) ER= 32.6% (CI: 4.4, 68.3) <u>Pneumonia HA's (all ages)</u> (lag3d) ER = 31.9% (CI: 15, 51.4) <u>COPD HA's (all ages)</u> (lag1d) ER = 11.5% (CI: –3, 28.2)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES\

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh (10/92-6/95) Population = 0.45 MM PM_{10} mean. =20.7 $\mu g/m^3$ PM_{10} min/max=5/72 $\mu g/m^3$ PM_{10} 90^{th}% - 10^{th}% = 20 $\mu g/m^3$	Poisson log linear regression models used to investigate relation of daily HA's with NO_2, O_3, CO, and PM_{10}. Adjustments made for seasonal and weekday variation, daily T (using 8 dummy variables), and wind speed. Separate analyses for age<65 yr. (mean resp HA = 3.4/day) and age >64 yr. (mean resp HA = 8.7/day), and for subjects with multiple HA's.	The two strongest findings were for cardiovascular HA's of people aged >64, which showed a positive association with PM_{10} as a mean of the 3 previous days. PM_{10} was consistently positively associated with Respiratory HA's in both age groups, with the greatest effect size in those >64, especially among those with >4 HA's during '81-'95. Weak significances likely contributed to by low population size.	Single Pollutant Models PM_{10} = 50 $\mu g/m^3$, mean of lags 1-3 Respiratory HA's (age<65) ER = 1.25 (−12.8, 17.5) Respiratory HA's (age>64) ER = 5.33 (−9.3, 22.3) Respiratory HA's (age>64, >4 HA's) ER = 7.93 (−19.0, 43.7)
McGregor et al. (1999) Birmingham, UK. Population = NR Mean PM_{10} = 30.0 $\mu g/m^3$	A synoptic climatological approach used to investigate linkages between air mass types (weather situations), PM_{10}, and all respiratory hospital admissions (mean= 19.2/day) for the Birmingham area.	Study results show distinct differential responses of respiratory admission rates to the six winter air mass types. Two of three types of air masses associated with above- average admission rates also favor high PM_{10} levels. This is suggestive of possible linkage between weather, air quality, and health.	NR
Hagen et al. (2000) Drammen, Sweden(11/94-12/97) Population = 110,000 PM_{10} mean = 16.8 $\mu g/m^3$ PM_{10} IQR = 9.8-20.9 $\mu g/m^3$	Examined PM_{10}, SO_2, NO_2, VOC's, and O_3 associations with respiratory hospital admissions from one hospital (mean = 2.2/day). Used Poisson GAM controlling for temperature and RH (but not their interaction), long-wave and seasonality, day-of-week, holidays, and influenza epidemics.	As a single pollutant, the PM_{10} effect was of same order of magnitude as reported in other studies. The PM_{10} association decreased when other pollutants were added to the model. However, the VOC's showed the strongest associations.	Respiratory Hospital Admissions(all ages) For IQR=50 $\mu g/m^3$ -Single Pollutant Model: PM_{10} (lag 0) ER = 18.3% (CI: −4.2, 46) -Two Pollutant Model (with O_3): PM_{10} (lag 0) ER = 18.3% (CI: −4.2, 45.4) -Two Pollutant Model (with Benzene): PM_{10} (lag 0) ER = 6.5% (CI:-14 , 31.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Dab et al. (1996) Paris, France (87 - 92) Population = 6.1 MM PM_{13} mean = 50.8 $\mu g/m^3$ PM_{13} 5^{th}-95^{th} range = 19.0-137.3 BS mean = 31.9 $\mu g/m^3$ BS 5^{th}-95^{th} Range =11.0-123.3	Daily mortality and general admissions to Paris public hospitals for respiratory causes were considered (means/day: all resp.=79/d, asthma=14/d, COPD=12/d). Time series analysis used linear regression model followed by a Poisson regression. Epidemics of influenza A and B, temperature, RH, holidays, day of week, trend, long-wave variability, and nurses' strike variables included. No two pollutant models considered.	For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association across outcomes. Asthma was significantly correlated with NO_2 levels, but not PM_{13}.	For PM_{13} = 50 $\mu g/m^3$; BS = 25 $\mu g/m^3$; Respiratory HA's (all ages): PM_{13} Lag 0 ER = 2.2% (CI: 0.2, 4.3) BS Lag 0 ER = 1.0% (0.2, 1.8) COPD HA's (all ages): PM_{13} Lag 2 ER = ⁻2.3% (CI: -6.7, 2.2) BS Lag 2 ER = ⁻1.1% (-2.9, 0.6) Asthma HA's (all ages): PM_{13} Lg 2 ER = ⁻1.3% (CI: -4.6, 2.2) BS Lg 0 ER = 1.2% (-0.5, 2.9)
Medina et al. (1997) Greater Paris 91 - 95 Population.= 6.5 MM Mean PM_{13} = 25 $\mu g/m^3$ PM_{13} min/max = 6/95 $\mu g/m^3$ Mean BS = 21 $\mu g/m^3$ BS min/max = 3/130 $\mu g/m^3$	Evaluated short-term relationships between PM_{13} and BS concentrations and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris. Poisson regression used, with non-parametric smoothing functions controlling for time trend, seasonal patterns, pollen counts, influenza epidemics, day-of-week, holidays, and weather.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results also indicate that air pollutant associations noted for hospital ED visits are also applicable to a wider population that visits their doctor.	Doctor's Asthma House Visits: 50 $\mu g/m^3$ PM_{13} Year-round, Single Pollutant: All ages (lg 2): ER = 12.7% (CI: 4.1, 21.9) 0-14 yrs.(lg 0-3): ER = 41.5% (CI: 20, 66.8) 15-64 yrs.(lg 2): ER = 6.3% (CI: -4.6, 18.5)
Anderson et al. (1997) Amsterdam(77 - 89) Barcelona (86- 92) London (87 - 91) Milan (80- 89) Paris (87 - 92) Rotterdam (77 - 89) Populations .= 0.7(A), 1.7(B), 7.2(L),1.5(M),6.5(P),0.6(R)MM BS Means = 6, 41, 13, -, 26, 22 TSP Means = 41,155, -, 105, -,41	All-age daily hospital admissions (HA's) for COPD considered in 6 APHEA cities; Mean/day = 1.1(A), 11(B), 20(L), 5(M), 11(P), 1.1(R). Poisson regression controlling for day of week, holidays, seasonal and other cycles, influenza epidemics, temperature, RH, and autocorrelation. Overall multi-city estimates made using inverse variance wts., allowing for inter-city variance.	Ozone gave the most consistent associations across models. Multi-city meta-estimates also indicated associations for BS and TSP. The warm/cold season RR differences were important only for ozone, having a much stronger effect in the warm season. COPD effect sizes found were much smaller than in U.S. studies, possibly due to inclusion of non-emergency admissions or use of less health-relevant PM indices.	BS (25 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 1.7% (0.5, 2.97) TSP (100 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 4.45% (CI: -0.53, 9.67)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Díaz et al. (1999) Madrid (94 - 96) Population = NR TSP mean ≈ 40 $\mu g/m^3$	ARIMA modeling used to analyze emergency respiratory and circulatory admissions (means/day=7.8,7.6) from one teaching hospital. Annual, weekly, and 3 day periodicities controlled, but no time trend included, and temperature crudely fit with v-shaped linear relationship.	Although TSP correlated at zero lag with admissions in winter and year-round, TSP was never significant in ARIMA models; so effect estimates not reported for TSP. Also, found biologically implausible u-shaped relationship for O_3, possibly indicating unaddressed temperature effects.	N/A
Spix et al. (1998) London (L) (87 - 91) Pop. =7.2 Million (MM) BS Mean = 13 $\mu g/m^3$ Amsterdam (A) (77 - 89) Pop. =0.7 MM BS Mean = 6 μg/m3 TSP mean = 41 $\mu g/m^3$ Rotterdam (R) (77 - 89) Pop. =0.6MM BS Mean = 22 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Paris (P) (87 - 92), Pop.= 6.14 MM BS Mean = 26 $\mu g/m^3$ Milano (M) (80 - 89) Pop. = 1.5 MM TSP Mean =120 ($\mu g/m^3$)	Respiratory (ICD9 460-519) HA's in age groups 15-64 yr and 65 + yrs. related to SO_2, PM (BS or TSP), O_3, and NO_2 in the APHEA study cities using standardized Poisson models with confounder controls for day of week, holidays, seasonal and other cycles, temperature, RH, and autocorrelation. PM lag considered ranged from 0-3 day, but varied from city to city. Quantitative pooling conducted by calculating the weighted means of local regression coefficients using a fixed-effects model when no heterogeneity could be detected; otherwise, a random-effects model employed.	Pollutant associations noted to be stronger in areas where more than one monitoring station was used for assessment of daily exposure. The most consistent finding was an increase of daily HA's for respiratory diseases (adults and elderly) with O_3. The SO_2 daily mean was available in all cities, but SO_2 was not associated consistently with adverse effects. Some significant PM associations were seen, although no conclusion related to an overall particle effect could be drawn. The effect of BS was significantly stronger with high NO_2 levels on the same day, but NO_2 itself was not associated with HA's. Authors concluded that "there was a tendency toward an association of respiratory admissions with BS, but the very limited number of cities prevented final conclusions."	<u>Respiratory Admissions (BS = 25 $\mu g/m^3$)</u> BS (L, A, R, P) 15-64 yrs: 1.4% (0.3, 2.5) 65+ yrs: 1.0% (−0.2, 2.2) TSP (A, R, M) (100 $\mu g/m^3$) 15-64 yrs: 2.0 (−2.1, 6.3) 65+ yrs: 3.2 (−1.2, 7.9) <u>Respiratory HA's</u> BS (L, A, R, P): Warm (25 $\mu g/m^3$) 15-64 yrs: −0.5% (−5.2, 4.4) 65+ yrs: 3.4% (−0.1, 7.1) BS (L, A, R, P): Cold (25 $\mu g/m^3$) 15-64 yrs: 2,0% (0.8, 3.2) 65+ yrs: 0% (−2.2, 2.3) TSP (A, R, M): Warm (100 $\mu g/m^3$) 15-64 yrs: 6.1% (0.1, 12.5) 65+ yrs: 2.0% (−3.9, 8.3) TSP (A, R, M): Cold (100 $\mu g/m^3$) 15-64 yrs: −5.9% (−14.2, 3.2) 65+ yrs: 4.0% (−0.9, 9.2)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Vigotti et al. (1996) Study Period.: 80 - 89 Milan, IT Population = 1.5 MM TSP mean = 139.0 $\mu g/m^3$ TSP IQR = 82.0, 175.7 $\mu g/m^3$	Association between adult respiratory HA's (15-64 yr mean =11.3/day, and 65 + yr mean =8.8/day) and air pollution evaluated, using the APHEA protocol. Poisson regression used with control for weather and long term trend, year, influenza epidemics, and season	Increased risk of respiratory HA was associated with both SO_2 and TSP. The relative risks were similar for both pollutants. There was no modification of the TSP effect by SO_2 level. There was a suggestion of a higher TSP effect on hospital admissions in the cool months.	<u>Young Adult (15-64 yrs.) Resp. HA's</u> 100 $\mu g/m^3$ increase in TSP Lag 2 ER = 5% (CI: 0, 10) <u>Older Adult (65+ yrs.) Resp. HA's</u> 100 $\mu g/m^3$ increase in TSP Lag 1 ER = 5% (CI: –1, 10)
Anderson et al. (1998) London (87 - 92) Population = 7.2 MM BS daily mean = 14.6 $\mu g/m^3$ BS 25-75th IQR = 24-38	Poisson regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 yr. (mean=19.5/d), 15-64 yr. (mean=13.1/d) and 65 + yr. (mean =2.6/d). Analysis controlled for time trends, seasonal factors, calendar effects, influenza epidemics, RH, temperature, and auto-correlation. Interactions with co-pollutants and aeroallergens tested via 2 pollutant models and models with pollen counts (grass, oak and birch).	Daily hospital admissions for asthma found to have associations with O_3, SO_2, NO_2, and particles (BS), but there was lack of consistency across the age groups in the specific pollutant. BS association was strongest in the 65 + group, especially in winter. Pollens not consistently associated with asthma HA's, sometimes being positive, sometimes negative. Air pollution associations with HA's not explained by airborne pollens in simultaneous regressions, and there was no consistent pollen-pollutant interaction.	<u>Asthma Admissions. BS=25 $\mu g/m^3$</u> BS Lag = 0-3 day average concentration All age ER = 5.98% (0.4, 11.9) <15yr. ER = 2.2% (–4.6, 9.5) 15-64yr ER = 1.2% (–5.3, 8.1) 65+ yr. ER = 22.8% (6.1, 42.5) BS=50 $\mu g/m^3$, 2d lag & co-pollutant: <u>Older Adult (>64 yrs.) Asthma Visits:</u> BS alone: ER = 14.6% (2.7, 27.8) &O_3: ER = 20.0% (3.0, 39.8) & NO_2: ER = 7.4% (–8.7, 26.5) SO_2: ER = 11.8% (–2.2, 27.8)
Damiá et al. (1999) Valencia, Spain (3/94-3/95) Population = NR BS mean = 101 $\mu g/m^3$ BS range = 34-213 $\mu g/m^3$	Associations of BS and SO_2 with weekly total ED admissions for asthma patients aged > 12 yrs (mean = 10/week) at one hospital over one year assessed, using linear stepwise regression. Season-specific analyses done for each of 4 seasons, but no other long-wave controls. Linear T, RH, BP, rain, and wind speed included as crude weather controls in ANOVA models.	Both BS and SO_2 correlated with ED admissions for asthma (SO_2: r=0.32; BS: r=0.35), but only BS significant in stepwise multiple regression. No linear relationship found with weather variables. Stratified ANOVA found strongest BS-ED association in the autumn and during above average temperatures. Uncontrolled autocorrelation (e.g., within-season) and weather effects likely remain in models.	<u>Asthma ED Visits (all ages):</u> BS = 40 $\mu g/m^3$ (single pollutant) BS as a lag 0 weekly average: ER = 41.5% (CI = 39.1, 43.9)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Kontos et al. (1999) Piraeus, Athens GR (87 - 92) Population = NR BS mean =46.5 $\mu g/m^3$ BS max =200 $\mu g/m^3$	Relation of respiratory HA's for children (0-14 yrs.) (mean = 4.3/day) to BS, SO_2, NO_2, and O_3 evaluated, using a nonparametric stochastic dynamical system approach and frequency domain analyses. Long wave and effects of weather considered, but non-linearity and interactions of T and RH relation with HA's not addressed.	Pollution found to explain significant portion of the HA variance. Of pollutants considered, BS was consistently among most strongly explanatory pollutants across various reported analyses.	NR
Pantazopoulou et al. (1995) Athens, GR (1988) Population = NR Winter (1/88-3/88,9/88-12/88) BS mean. =75 $\mu g/m^3$ BS 5^{th}-95^{th} %=26 - 161 $\mu g/m^3$ Summer (3/22/88-3/88,9/21/88) BS mean. =55 $\mu g/m^3$ BS 5^{th}-95^{th} %=19 - 90 $\mu g/m^3$	Examined effects of air pollution on daily emergency outpatient visits and admissions for cardiac and respiratory causes. Air pollutants included: BS, CO, and NO_2. Multiple linear regression models used, controlling for linear effects of temperature and RH, day of week, holidays, and dummy variables for month to crudely control for season, separately for winter and summer.	Daily number of emergency visits related positively with each air pollutant, but only reached nominal level of statistical significance for NO_2 in winter. However, the very limited time for each within-season analysis (6 mo.) undoubtably limited the power of this analysis to detect significant effects. Also, possible lagged pollution effects were apparently not investigated, which may have reduced effect estimates.	Single Pollutant Models For Winter (BS = 25 $\mu g/m^3$) Outpatient Hospital Visits ER = 1.1% (−0.7, 2.3) Respiratory HA's ER = 4.3% (0.2, 8.3) For Summer, BS = 25 $\mu g/m^3$) Outpatient Hospital Visits ER = 0.6% (−4.7, 6.0)) Respiratory HA's ER = 5.5% (−3.6, 14.7)
Ponce de Leon et al. (1996) London (4/87-2/92) Population = 7.3 million BS mean. =14.6 $\mu g/m^3$ BS 5^{th}-95^{th} %=6 - 27 $\mu g/m^3$	Poisson regression analysis of daily counts of HA's (means/day: all ages=125.7; Ages 0-14=45.4; Ages 15-64=33.6; Ages 65+=46.7). Effects of trend, season and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity, and autocorrelation addressed. However, temperature modeled as linear, with no RH interaction. Pollution variables were BS, SO_2, O_3, and NO_2, lagged 0-3 days.	O_3 associated with increase in daily HA's, especially in the "warm" season. However, u-shape of the O_3 dose-response suggests that linear temperature control was not adequate. Few significant associations with other pollutants, but these tended to be positive (especially in cold season, Oct-March, and for older individuals for BS).	Respiratory HA's (all ages) Single Pollutant Models For Oct-Mar. BS = 25 $\mu g/m^3$ Lag 1 ER = 0.2% (–1.9, 2.3) For Apr-Sep. BS = 25 $\mu g/m^3$ Lag 1 ER = -2.7% (−6.0, 0.8) Respiratory HA's (>65) Single Pollutant Models For Oct-Mar. BS = 25 $\mu g/m^3$ Lag 2 ER = 1.2% (−2.1, 4.5) For Apr-Sep. BS = 25 $\mu g/m^3$ Lag 2 ER = 4.5% (−1.0, 10.4)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Schouten et al. (1996) Amsterdam/Rotterdam (77 - 89) Amsterdam Pop. = 0.69 Million Rotterdam Pop. = 0.58 Million Amsterdam, NE BS mean. =11 $\mu g/m^3$ BS 5^{th}-95^{th}% = 1 - 37 $\mu g/m^3$ Rotterdam, NE BS mean. =26 $\mu g/m^3$ BS 5^{th}-95^{th} %= 6 -61 $\mu g/m^3$	Daily emergency HA's for respiratory diseases (ICD 460-519), COPD (490-492, 494, 496), and asthma (493). The mean HA/d (range) for these were: 6.70 (0-23), 1.74 (0-9) and 1.13 (0-7) respectively in Amsterdam and 4.79 (0-19), 1.57 (0-9), and 0.53 (0-5) in Rotterdam. HA associations with BS, O_3, NO_2, and SO_2 analyzed, using autoregressive Poisson regression allowing for overdispersion and controlling for season, day of week, meteorological factors, and influenza epidemics.	BS did not show any consistent effects in Amsterdam; but in Rotterdam BS was positively related to HA's. Most consistent BS associations in adults >64 yrs. in winter. Positive O_3 association in summer in people aged >64 in Amsterdam and Rotterdam. SO_2 and NO_2 did not show any clear effects. Results not changed in pollutant interaction analyses. The authors concluded short-term air pollution-emergency HA's association is not always consistent at these individual cities' relatively low counts of daily HA's and low levels of air pollution. Analyses for all ages of all the Netherlands gave a strong BS-HA association in winter.	Single Pollutant Models For BS=25 $\mu g/m^3$, 2 day lag For all of the Netherlands: Respiratory HA's (all ages) Winter: ER = 2.0% (−1.5, 5.7) Summer: ER = 2.4% (0.6, 4.3)
Garty et al. (1998) PM_{10} mean ≈ 45 $\mu g/m^3$ Tel Aviv, Israel (1993)	Seven day running mean of asthma ED visits by children (1-18 yrs.) to a pediatric hospital modeled in relation to PM_{10} in Tel Aviv, Israel.	No PM_{10} associations found with ED visits. The ER visits–pollutant correlation increased significantly when the September peak was excluded. Use of a week-long average and associated uncontrolled long-wave fluctuations (with resultant autocorrelation) likely prevented meaningful analyses of short –term PM associations with ED visits.	N/A

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Sunyer et al. (1997) Barcelona (86 - 92) Population = NR BS Median: 40 $\mu g/m^3$ BS Range: 11-258 (B Helsinki (86 - 92) Population = NR BS Median: - BS Range: - Paris (86 - 92) Population = NR BS Median: 28 $\mu g/m^3$ BS Range: 4-186 $\mu g/m^3$ London (86 - 92) Population = NR BS Median: 13 $\mu g/m^3$ BS Range: 3-95 $\mu g/m^3$	Evaluated relations of BS, SO_2, NO_2, and O_3 to daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)]. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities: ED visits in Barcelona; emergency hospital asthma admissions in London and Helsinki, and total asthma admissions in Paris. Estimates from all cities obtained for entire period and also by warm or cold seasons, using Poisson time-series regression, controlling for temperature and RH, viral epidemics, day of week effects, and seasonal and secular trends. Combined associations were estimated using meta-analysis.	Daily admissions for asthma in adults increased significantly with increasing ambient levels of NO_2, and positively (but non-significantly) with BS. The association between asthma admissions and pollution varied across cities, likely due to differing asthma outcomes considered. In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with BS and NO_2, though the latter only in cold seasons. No association observed in children for O_3. Authors concluded that "In addition to particles, NO_2 and SO_2 (by themselves or as a constituent of a pollution mixture) may be important in asthma exacerbations".	ER per 25 $\mu g/m^3$ BS (24 h Average) Asthma Admissions/Visits: <15 yrs.: London ER = 1.5% (lg 0d) Paris ER = 1.5% (lg 2d) Total ER = 1.5% (−1.1, 4.1) 15-64 yrs: Barcelona ER = 1.8% (lg 3d) London ER = 1.7% (lg 0d) Paris ER = 0.6% (lg 0d) Total ER = 1.0% (−0.8, 2.9) Two Pollutant (per 25 $\mu g/m^3$ BS) Asthma Admissions (24 h Avg) <15 yrs, (BS & NO_2): London ER = 0.6% (lg 0d) Paris ER = 2.9% (lg 2d) Total ER = 1.8% (−0.6, 4.3) <15 yrs, (BS & SO_2): London ER = −1.1% (lg 0d) Paris ER = −1.4% (lg 2d) Total ER = −1.3 (−5.0, 2.5) 15-64 yrs, (BS & NO_2): Barcelona ER = 1.5% (lg 0d) London ER = −4.7% (lg 0d) Paris ER = −0.7% (lg 1d) Total ER = −0.5% (−5.1, 4.4)
Tenías et al (1998) Study Period.: 94 - 95 Valencia, Spain Hosp. Cachment Pop. =200,000 BS mean = 57.7 $\mu g/m^3$ BS IQR = 25.6-47.7 $\mu g/m^3$	Associations between adult (14+ yrs.) emergency asthma ED visits to one city hospital (mean =1.0/day) and BS, NO_2, O_3, SO_2 analyzed, using Poisson auto-regressive modeling, controlling for potential confounding weather and time (e.g., seasonal) and trends using the APHEA protocol.	Association with asthma was positive and more consistent for NO_2 and O_3 than for BS or SO_2. Suggests that secondary oxidative-environment pollutants may be more asthma relevant than primary reduction-environment pollutants (e.g., carbonaceous particles). NO_2 had greatest effect on BS in co-pollutant models, but BS became significant once 1993 was added, showing power to be a limitation of this study.	Adult Asthma HA's, BS = 25 $\mu g/m^3$ For 1993-1995: Lag 0 ER = 10.6% (0.9, 21.1) For 1994-1995: Lag 0 ER = 6.4% (−4.8, 18.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America			
Braga et al. (1999) São Paulo, Brazil (92 - 93) Population = NR PM_{10} mean = 66.3 $\mu g/m^3$ PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) to public hospitals serving 40% of the population were regressed (using both Poisson and maximum likelihood methods) on air pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Air pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". Associations ascribed primarily to auto emissions by the authors.	PM_{10} (50 $\mu g/m^3$), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) (0-5day lg avg.) ER = 8.9% (CI: 4.6, 13.4)
Gouveia and Fletcher (2000) Study Period.:92-94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 $\mu g/m^3$ PM_{10} IQR = 42.9-75.5 $\mu g/m^3$ $PM_{10}10/90^{th}$% =98.1 $\mu g/m^3$ PM_{10} 95^{th}% = 131.6 $\mu g/m^3$	Daily public hospital respiratory disease admissions for children (mean resp. < 5y = 56.1/d; mean pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean pneum.<1y=24.0) and daily levels air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) and were analyzed with Poisson regression. Models adjusted for time trends, seasonal patterns, weekdays, holidays, weather, and serial correlation. PM_{10} measured by Beta-gauge. Private hospitals serving wealthier citizens not in database.	Children's HA's for total respiratory and pneumonia positively associated with O_3, NO_2, and PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with other reports, but smaller RR's. This may be due to higher baseline admission rates in this poor sub-population vs. other studies, but this was not intercompared by the authors.	PM_{10} = 50 $\mu g/m^3$: All Respiratory HA's for children < 5yrs. ER = 2.0% (–0.8, 4.9) Pneumonia HA's for children <5 yrs. ER = 2.5% (–0.8, 6.0) Asthma HA's for children <5 yrs. ER = 2.6% (–4.0, 9.7) Pneumonia HA's for children <1 yrs. ER = 4.7% (0.7, 8.8)
Lin et al. (1999) Sao Paulo, BR (91 - 93) Population = NR PM_{10} mean =65 $\mu g/m^3$ PM_{10} SD = 27 $\mu g/m^3$ PM_{10} range = 15-193 $\mu g/m^3$	Respiratory ED visits by children (0-12 yrs.) to a major pediatric hospital (mean = 56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower respiratory (mean = 8/day) and upper respiratory (mean = 39/day) ED visits, and visits due to wheezing (mean=9/day) all evaluated. Analyses considered effects of season, day of week, and extreme weather (using T, RH dummy variables).	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants all simultaneously added to the model. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models. More than 20% increase in ED visits found on the most polluted days, "indicating that air pollution is a substantial pediatric health concern".	50 $\mu g/m^3$ PM_{10} (0-5 day lag mean) Respiratory ED Visits(<13 yrs.) Single Pollutant Model: PM_{10} ER = 21.7% (CI: 18.2, 25.2) All-Pollutant Model: PM_{10} ER=28.8% (CI: 21.4, 36.7) Lower Respiratory ED Visits (<13 yrs.) Single Pollutant Model: PM_{10} ER = 22.8% (CI: 12.7, 33.9) All-Pollutant Model: PM_{10} ER = 46.9% (CI: 27.9, 68.8)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America (cont'd)			
Ostro et al. (1999b) Santiago, CI (7/92—12/93) <2 yrs. Population ≈ 20,800 3-14 yrs. Population ≈ 128,000 PM_{10} mean. =108.6 $\mu g/m^3$ PM_{10} Min/Max=18.5/380 $\mu g/m^3$ PM_{10} IQR = 70.3 – 135.5 $\mu g/m^3$	Analysis of daily visits to primary health care clinics for upper (URS) or lower respiratory symptoms (LRS) for children 2-14 yr (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2 yr. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 $\mu g/m^3$) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	<u>Lower Resp. Symptoms Clinic Visits</u> PM_{10} = 50 $\mu g/m^3$ Single Pollutant Models: -Children<2 years Lag 3 ER = 2.5% (CI: 0.2, 4.8) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.8, 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (CI: 0, 4.4) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.9, 6.5)
Rosas et al. (1998) SW Mexico City (1991) Population = NR PM_{10} mean. =77 $\mu g/m^3$ PM_{10} min/max= 25/183 $\mu g/m^3$	Log-regression analysis of relations between emergency hospital admissions for asthma for children <15 yrs (mean=2.5/day), adults (mean=3.0/day), and adults >59 yrs (mean=0.65/day) and lag 0-2 d pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	Few statistical associations were found between asthma admissions and air pollutants. Grass pollen was associated with child and adult admissions, and fungal spores with child admissions. Authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Australia			
Smith et al. (1996) Stdy Pd.: 12/92-1/93,12/93-1/94 West Sydney, AU Population = 907,000 -Period 1 (12/92-1/93) B_{scatt} median = 0.25 $10^{-}4$/m B_{scatt} IQR = 0.18-0.39 $10^{-}4$/m B_{scatt} 95th% = 0.86 $10^{-}4$/m -Period 2 (12/93-1/94) B_{scatt} median = 0.19 $10^{-}4$/m B_{scatt} IQR = 0.1-0.38 $10^{-}4$/m B_{scatt} 95th5% = 3.26 $10^{-}4$/m PM_{10} median = 18 $\mu g/m^3$ PM_{10} IQR = 11.5-28.8 $\mu g/m^3$ PM_{10} 95th% = 92.5 $\mu g/m^3$	Study evaluated whether asthma visits to emergency departments (ED) in western Sydney (mean≈10/day) increased as result of bushfire-generated PM (B_{scatt} from nephelometry) in Jan., 1994 (period 2). Air pollution data included nephelometry (B_{scatt}), PM_{10}, SO_2, and NO_2. Data analyzed using two methods: (1) calculation of the difference in proportion of all asthma ED visits between the time periods, and; (2) Poisson regression analyses. Control variables included T, RH, BP, WS, and rainfall.	No difference found in the proportion of all asthma ED visits during a week of bushfire-generated air pollution, compared with the same week 12 months before, after adjusting for baseline changes over the 12-month period. The max. B_{scatt} reading was not a significant predictor of the daily asthma ED visits in Poisson regressions. However, no long-wave controls applied, other than indep. vars., and the power to detect differences was weak (90% for a 50% difference). Thus, the lack of a difference may be due to low statistical strength or to lower toxicity of particles from burning vegetation at ambient conditions vs. fossil fuel combustion.	ED Asthma Visits (all ages) Percent change between bushfire and non bushfire weeks: PM_{10} = 50 $\mu g/m^3$ ER = 2.1% (CI: −0.2, 4.5)
Morgan et al. (1998) Sydney, AU (90 - 94) Population = NR $PM_{2.5}$ 24 h mean = 9.6 $\mu g/m^3$ $PM_{2.5}$ 10th-90th% = 3.6-18 $\mu g/m^3$ $PM_{2.5}$ max-1 h mean = 22.8 $\mu g/m^3$ $PM_{2.5}$ 10th-90th% = 7.5-44.4 $\mu g/m^3$	A Poisson analysis, controlled for overdispersion and autocorrelation via GEE, of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day)), COPD (mean 65+yrs =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM. The authors cited the error introduced by estimating $PM_{2.5}$ and the low PM levels as possible reasons for the weak PM-respiratory HA associations.	Asthma HA's Single Pollutant Model: For 24 hr $PM_{2.5}$ = 25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = −1.5% (CI: −7.8, 5.3) 15-64 yrs.(lag0) ER = 2.3% (CI: −4, 9) For 1h $PM_{2.5}$ =25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = + 0.5% (CI: −1.9, 3.0) 15-64 yrs.(lag0) ER = 1.5% (CI: −0.9, 4) Multiple Pollutant Model: For 24h $PM_{2.5}$ = 25 $\mu g/m^3$ 1-14 yrs.(lag1) ER = −0.6% (CI: −7.4, 6.7) COPD (65+yrs.) Single Pollutant Model: For 24h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER =4.2% (CI: −1.5, 10.3) For 1h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER = 2% (CI: −0.3, 4.4) Multiple Pollutant Model: For 1h $PM_{2.5}$ = 25 $\mu g/m^3$ (lag 0) ER = 1.5% (CI: −0.9, 4)

TABLE 6-17 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS AND HOSPITAL ADMISSIONS STUDIES

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Asia			
Tanaka et al. (1998) Stdy Pd.:1/92-12/93 Kushiro, Japan Pop. = 102 adult asthmatics PM_{10} mean = 24.0 $\mu g/m^3$ PM_{10} IQR = NR	Associations of HA's for asthma (in 44 non-atopic and 58 atopic patients) with weather or air pollutants (NO, NO_2, SO_2,PM_{10}, O_3, and acid fog) evaluated. Odds ratios (OR) and 95% CI's calculated between high and low days for each environmental variable. Poisson regression was performed for the same dichototomized variables.	Only the presence of acid fog had a significant OR >1.0 for both atopics and non-atopics. PM_{10} associated with a reduction in risk (OR<1.0) for both atopics and non-atopics. Poisson regression gave a non-significant effect by PM_{10} on asthma HA's. However, no long-wave or serial auto-correlation controls applied, so the opposing seasonalities of PM vs. HA's indicated in time series data plots are likely confounding these results.	For same-day (lag=0) PM_{10} Adult Asthma HA's OR for <30 vs. >30 $\mu g/m^3$ PM_{10}: Non-atopic OR = 0.77 (CI: 0.61, 0.98) Atopic OR = 0.87 (CI: 0.75, 1.02) Poisson Coefficient for PM_{10} > 30 $\mu g/m^3$ Non-atopic B = -0.01 (SE = 0.15) Atopic B = -0.002 (SE = 0.09)
Wong et al. (1999) Study Period.: 94 - 95 Hong Kong Population = NR PM_{10} mean = 50.1 $\mu g/m^3$ PM_{10} median = 45.0 $\mu g/m^3$ PM_{10} IQR = 30.7, 65.5 $\mu g/m^3$	Poisson regression analyses were applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated. Using the APHEA protocol, models accounted for time trend, season and other cyclical factors, T, RH, autocorrelation and overdispersion. PM_{10} measured by TEOM, which likely underestimates mass.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}. No significant respiratory HA interactions with PM_{10} effect were found for high NO_2, high O_3, or cold season.	PM_{10} = 50 $\mu g/m^3$ (Lags = 0-3 days) Respiratory HA's All age: ER = 8.3% (CI: 5.1, 11.5) 0-4yrs.: ER = 9.9% (CI: 5.4, 14.5) 5-64yrs.: ER = 8.8% (CI: 4.3, 13.4) 65+ yrs.: ER = 9.3% (CI: 5.1, 13.7) Asthma HA's (all ages) ER = 7.7% (1.0, 14.9) COPD HA's (all ages) ER = 10.0% (5.6, 14.3) Pneumonia and Influenza HA's (all ages) ER = 13.1% (7.2, 19.4)
Chew et al. (1999) Singapore (90 - 94) Population = NR TSP mean = 51.2 $\mu g/m^3$ TSP SD = 20.3 $\mu g/m^3$ TSP range = 13-184 $\mu g/m^3$	Child (3-13 yrs.) ED visits (mean = 12.8/day) and HA's (mean = 12.2/day) for asthma related to levels of SO_2, NO_2, TSP, and O_3 using linear regression with weather, day-of-week controls. Auto-correlation effects controlled by including prior day response variable as a regression variable. Separate analyses done for adolescents (13-21 yrs.) (mean ED=12.2, mean HA=3.0/day).	Positive associations found between TSP, SO_2, and NO_2, and daily HA and ED visits for asthma in children, but only with ED visits among adolescents. Lack of power (low counts) for adolescents' HA's appears to have been a factor in the lack of associations. When ED visits stratified by year, SO_2 and TSP remained associated in every year, but not NO_2. Analyses for control diseases (appendicitis and urinary tract infections) found no associations.	TSP(100 $\mu g/m^3$) No co-pollutant: Child (3-13 yrs.)Asthma ED visits Lag 1d ER = 541% (CI: 198.4, 1276.8)

distributed lag model, the maximum lag model is deemed here to provide the closest available estimate of the full pollutant-health effects impact.

Among the numerous epidemiological studies published on PM_{10} morbidity, many evaluated effects of relatively high PM_{10} concentrations. This likely reflects the fact that large populations are required to have enough power for such studies, and large population areas may tend to have higher PM_{10} levels, thus reducing the number of cities available for such evaluations. Despite this, quite a number did evaluate associations at low PM_{10} concentration levels and associations between acute PM_{10} exposures and total respiratory-related hospital admissions have been reported by several investigators for numerous U.S. cities with annual mean ambient concentrations extending to below 50 $\mu g/m^3$.

The recent NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} concentrations and hospital admissions by persons 65 and older in 14 U.S. cities is of particular interest. As noted in Table 6-17 and shown in more detail in Table 6-18, this study indicates PM_{10} effects similar to other cities, but with narrower confidence bands, due to its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each of the 14 cities had mean PM_{10} below 50 $\mu g/m^3$. The cities considered and their respective annual mean/daily maximum. PM_{10} concentrations (in $\mu g/m^3$) are: Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago (36.4/144.7); Colorado Springs (26.9/147.2); Detroit (36.8/133.6);Minneapolis/St Paul (36.8/133.6); Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3); Provo/Orem (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown (33.1/104.0). As seen in Table 6-18, the PM_{10} association remained even when only those days with PM_{10} less than 50 $\mu g/m^3$ were considered.

Other U.S. studies finding associations of respiratory-related hospital admissions or medical visits with PM_{10} levels extending below 50 $\mu g/m^3$ include: Schwartz (1995) in Tacoma; Schwartz (1994b) in Minneapolis; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999) in Seattle; Gwynn et al. (2000) in Buffalo, NY; Linn et al. (2000) in Los Angeles, Nauenberg and Basu (1999) in Los Angeles; and Moolgavkar et al. (1997) in Minneapolis-St. Paul, MN, but not in Birmingham, AL. The excess risk estimates appear to most consistently fall in the range of 5-25% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma visits and hospital admissions usually being higher than for COPD and pneumonia hospital admissions.

TABLE 6-18. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-$\mu g/m^3$ INCREASE IN PM_{10} IN 14 U.S. CITIES

	CVD		COPD		Pneumonia	
	% Increase	(95% CI)	%Increase	(95% CI)	% Increase	(95% CI)
Constratined lag models (Fixed Effect Estimates)						
One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
PM_{10} <50 $\mu g.m^3$ (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Unconstrained distributed Lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.90	(1.46, 2.34)
Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b)

Similar associations between increased respiratory related hospital admissions/medical visits and relatively low short-term PM_{10} levels were also reported by various investigators for several non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant associations between PM_{10} (mean = 25.6 $\mu g/m^3$, max. = 131 $\mu g/m^3$) and respiratory admissions in Birmingham, UK; and Atkinson et al. (1999b) found significant increases in hospital admissions for respiratory disease to be associated with PM_{10} (mean = 28.5 $\mu g/m^3$) in London, UK. Hagen et al. (2000) and Prescott et al. (1998) also found positive but non-significant PM_{10} associations with hospital admissions in Drammen, Sweden (mean = 16.8 $\mu g/m^3$) and Edinburgh, Scotland (mean = 20.7 $\mu g/m^3$), respectively; but both considered relatively small populations, limiting statistical power in these studies.

6.3.2.3.1 Particulate Matter Mass Fractions and Composition Comparisons

While PM_{10} mass is the metric most often employed as the particle pollution index in the U.S. and Canada, some new studies have begun to examine the relative roles of various PM_{10} mass fractions and chemical constituents (such as $SO_4^=$) in the PM-respiratory hospital

admissions association. Several new studies report significant associations of increased respiratory-cause medical visits and/or hospital admissions with ambient $PM_{2.5}$ and/or $PM_{10-2.5}$ ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit, where all PM metrics (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, H^+) were positively related to pneumonia and COPD admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values generally remaining little changed (but with broader confidence intervals) in multipollutant models including one or more gaseous pollutant (e.g., CO, O_3, NO_2, SO_2). Excess risks for pneumonia admissions in the one pollutant model were 13% (3.7, 22) and 12% (0.8, 24) per 25 $\mu g/m^3$ of $PM_{2.5}$ and $PM_{10-2.5}$, respectively; those for COPD admissions were 5.5% (−4.7, 17) and 9.3% (−4.4, 25) per 25 $\mu g/m^3$ $PM_{2.5}$ and $PM_{10-2.5}$, respectively. Also of note, Moolgavkar found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models; but the magnitudes of the risk estimates dropped by more than half to non-statistically significant levels in two-pollutant models including CO. In the same study, similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0−19 yr; 20−64 yr) in Los Angeles, as well. Moolgavkar et al. (2000) also found 5.6% (0.2, 11.3) excess risk for all-ages COPD hospital admissions per 25 $\mu g/m^3$ $PM_{2.5}$ increase in King County, WA.

In contrast to the above Lippmann and Moolgavkar findings, Tolbert reported no significant associations of $PM_{2.5}$ or $PM_{10-2.5}$ with COPD emergency department visits in Atlanta, based on data from less than half of all participating hospitals and ca. 1 yr of supersite air quality data.

Gwynn et al. (2000) considered a 2.5 yr period (May 1988-Oct. 1990) in the Buffalo, NY region in a time-series analysis of daily mortality and hospital admissions for total, respiratory, and circulatory hospital admissions categories. Pollutants considered included: PM_{10}, H^+, $SO_4^=$ COH, O_3, CO, SO_2, and NO_2. The H^+ and $SO_4^=$ concentrations were determined from daily $PM_{2.5}$ samples not analyzed for mass (in order to avoid possible acid neutralization). Various modeling techniques were applied to control for confounding of effect estimates due to seasonality, weather and day-of-week effects. They found multiple significant pollutant-health effect associations, the most significant being between $SO_4^=$ and respiratory hospital admissions. When calculated in terms of increments employed across analyses in this report, various PM RR's were: PM_{10} RR=1.11, 95% C.I.=1.05-1.18(for 50 $\mu g/m^3$); H^+ RR=1.06, 95% C.I.=1.03-1.09 (for

75 nmoles/m^3 = 3.6 $\mu g/m^3$, if as H_2SO_4); and $SO_4^=$ RR=1.08, 95% C.I.=1.04-1.12 (for 155 nmoles/m^3=15 $\mu g/m^3$). As in the Burnett et al. (1997b) study described below, H^+ yielded the highest RR per $\mu g/m^3$ of concentration. These various PM metric associations were not significantly affected by inclusion of gaseous co-pollutants in the regression model. Thus, all PM components considered except COH were found to be associated with increased hospital admissions, but H^+, $SO_4^=$ and O_3 had the most coherent associations with respiratory admissions.

Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data from hospital admissions for respiratory disease on King County, WA for eight years (1987-94), together with air pollution and weather information. However, their weather controls were relatively crude (i.e., seasonal dummy variables and linear temperature terms). This study is notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$ and for finding significant hospital admission associations only with $PM_{1.0}$. This may suggest that the $PM_{2.5}$ vs. PM_{10} separation may not always be sufficient to differentiate submicron fine particle vs. coarse-particle toxicities.

Asthma hospital admission studies conducted in U.S. various communities provide additional important new data. Of particular note is a unique study by Sheppard et al. (1999) which evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3 and CO) and non-elderly adult (<65 years of age) hospital admissions for asthma in Seattle, WA. Both PM and CO were found to be jointly associated with asthma admissions. An estimated 4 to 5% increase in the rate of asthma hospital admissions (lagged 1 day) was reported to be associated with interquartile range changes in PM indices (19 $\mu g/m^3$ for PM_{10}, 11.8 $\mu g/m^3$ for $PM_{2.5}$, and 9.3 $\mu g/m^3$ for $PM_{10-2.5}$), equivalent to excess risk rates as follows: 13% (95% CI 05, 23) per 50 $\mu g/m^3$ for PM_{10}; 9% (95% CI 3, 14) per 25 $\mu g/m^3$ $PM_{2.5}$; 11% (95% CI 3, 20) per 25 $\mu g/m^3$ $PM_{10-2.5}$. Also of note is the Norris et al. (1999) study showing associations of low levels of $PM_{2.5}$ (mean = 12 $\mu g/m^3$) with markedly increased asthma hospital admissions, i.e., excess risk = 44.5% (CI 21.7, 71.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

Turning to non-U.S. studies, Burnett et al. (1997b) evaluated the role that the ambient air pollution mix, comprised of gaseous pollutants and PM indexed by various physical and chemical measures, plays in exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases (tracheobronchitis, chronic obstructive long disease, asthma, and pneumonia). They employed daily measures of fine and coarse particulate mass, aerosol

chemistry (sulfates and acidity), and gaseous pollutants (ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide) collected in Toronto, Ontario, Canada, during the summers of 1992, 1993, and 1994. Positive associations were observed for all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most consistently significant pollutant and least sensitive to adjustment for other gaseous and particulate measures. The PM associations with the respiratory hospital admissions were significant for: PM_{10} (RR=1.11for 50 $\mu g/m^3$; CI=1.05-1.17); $PM_{2.5}$ (fine) mass (RR=1.09 for 25 $\mu g/m^3$; CI=1.03-1.14); $PM_{10-2.5}$ (coarse) mass (RR=1.13 for 25 $\mu g/m^3$; CI=1.05-1.20); sulfate levels (RR=1.11 for 155 nmoles/m^3=15 $\mu g/m^3$; CI=1.06-1.17); and aerosol acidity (RR=1.40 for 75 nmoles/m^3 = 3.6 $\mu g/m^3$, if as H_2SO_4; CI=1.15-1.70). After simultaneous inclusion of ozone in the model, the associations with the respiratory hospital admissions remained significant for: PM_{10} (RR=1.10; CI=1.04-1.16); fine mass (RR=1.06; CI=1.01-1.12); coarse mass (RR=1.11; CI=1.04-1.19); sulfate levels (RR=1.06; CI=1.0-1.12); and aerosol acidity (RR=1.25; CI=1.03-1.53), using the same increments. Of the PM metrics considered here, aerosol acidity yielded the highest RR estimate, despite having the lowest mass concentration increment, suggesting a higher toxicity per μg of exposure to acidic aerosols. Regression models that included all recorded pollutants simultaneously (with high intercorrelations among the pollutants) were also presented.

There have also been numerous new time-series studies examining associations between air pollution and respiratory-related hospital admissions in Europe, as summarized in Table 6-17; but most of these studies relied primarily on black smoke (BS) as their PM metric. BS is a particle reflectance measure that provides an indicator of particulate blackness and is highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton, 1982). In the U.S., Coefficient of Haze (COH) is a metric of particle transmittance that similarly most directly represents a metric of particle blackness and ambient elemental carbon concentration (Wolff et al., 1983) and has been found to be highly correlated with BS (r = 0.9) (Lee et al., 1972). However, the relationship between airborne carbon and total mass of overall aerosol (PM) composition varies over time and from locality to locality, so the BS-mass ratio is less reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-mass relationship is likely to be very different between Europe and the U.S., largely due to differences in local PM source characteristics (e.g., percentages of diesel powered motor vehicles). Therefore, while these European BS-health effects studies are of qualitative use for evaluating

the PM-health effects associations, they are not as useful for quantitative assessment of PM effects relevant to the U.S.

The most recent European air pollution health effects analyses have mainly been conducted as part of the APHEA study, which evaluated 15 European cities from 10 different countries with a total population of over 25 million. All studies used a standardized data collection and analysis approach which included: consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2, and O_3) and the use of time-series regression addressing: seasonal and other long-term patterns; influenza epidemics; day of the week; holidays; weather; and, autocorrelation (Katsouyanni et al., 1996). The general coherence of the APHEA results with other results gained under different conditions strengthens the argument for causality in the air pollution-health effects association. Unfortunately, the general use of the less comparable suspended particle (SPM) measures and BS as PM indicators in some of the APHEA locations and analyses lessens the quantitative usefulness of such analyses in evaluating associations between PM and health effects most pertinent to the U.S. situation.

6.3.2.3.2 Identification of Potential Susceptible Subpopulations

Associations between ambient PM measures and respiratory admissions have been found for all age groups, but older adults and children have been indicated by a number of hospital admissions studies to exhibit the most consistent PM-health effects associations in the literature. As reported in this and previous PM AQCDs, numerous studies of older adults (e.g., those 65+ years of age) have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Anderson et al, 1998). However, only a limited number have specifically studied children as a subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital admissions associations as a function of age in the province of Ontario, reporting that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age).

There are more than a dozen recent respiratory-related hospital admissions studies summarized in Table 6-17 that include children. Looking in detail at these study results reveals that the PM RR's for all children (e.g., 0-18) are not usually noticeably larger than those for adults, but such comparisons of RR's must adjust for differences in the baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double

the rate for adults, then they will have a pollution relative risk (RR) per $\mu g/m^3$ that is half that of the adults given the exact same impact on admissions/100,000/$\mu g/m^3$/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially regarding the population catchment for each age group in each study).

One of the few indications that is notable when comparing children with other age group effect estimates in Table 6-17 is the higher excess risk estimate for infants (i.e., the group <1 yr. of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate roughly twice as large as for other children or adults. This is confirmatory of the excess risk pattern previously found in the above-noted Burnett et al. (1994) study for respiratory-related hospital admissions.

6.3.2.3.3 Evaluation of Pollen as Potential Confounder

Pollen is an atmospheric constituent that has a large effect on asthma incidence and might potentially be a factor that may confound PM-admissions associations, if it is correlated with both PM and hospital admissions. In a London study, airborne pollen did not confound the analysis of air pollution (including black smoke) and daily admissions for asthma during the time period 1987-1992 (Anderson et al., 1998). However, in a study by Moolgavkar et al. (2000) for Seattle, adding pollens to PM time-series regressions of respiratory admissions was found to diminish the PM effect estimates somewhat, but more for PM_{10} than that for $PM_{2.5}$. This latter finding would not be unexpected, given that in general, confounding by bioaerosols is unlikely to account for $PM_{2.5}$-related health impacts due to lack of correlation between daily $PM_{2.5}$ levels and seasonal pollution events and weather-related specification events. Overall, then, pollens do not appear to significantly confound the PM-admissions relationship, despite their large effect on respiratory admissions.

6.3.2.4 Key New Respiratory Medical Visits Studies

As discussed above, medical visits include both hospital emergency department (ED) visits and doctors' office visits. As in the past PM AQCD's, most of the available morbidity studies presented in Table 6-17 are of ED visits and their associations with air pollution. These studies collectively confirm the results provided in the previous AQCD, indicating a positive and

significant association between ambient PM levels and increased respiratory-related hospital visits.

Of the medical visit and hospital admissions studies since the 1996 PM AQCD, the most informative are those that evaluate health effects associations at levels below previously well-implicated PM concentrations. In the case of medical visits, the Norris et al. (1999, 2000) studies of asthma ED visits found significant PM- associated health effects among children in Seattle, even at quite low average PM levels and even after incorporating the effects of other air pollutants (study mean PM_{10} = 21.7 $\mu g/m^3$; estimated mean $PM_{2.5}$ = 12 $\mu g/m^3$). Tolbert et al. (2000b) reported a significant PM_{10} association with pediatric ED visits in Atlanta where the maximum PM_{10} concentration was 105 $\mu g/m^3$. Also, Delfino et al. (1997) found significant PM_{10} and $PM_{2.5}$ associations for respiratory ED visits among older adults in Montreal when mean PM_{10} = 21.7 $\mu g/m^3$ and mean $PM_{2.5}$ = 12.2 $\mu g/m^3$. Medina et al. (1997) reported significant associations between doctor's asthma house visits and PM_{13} (which would have a slightly higher concentration value than PM_{10}) in Paris when mean PM_{13} = 25 $\mu g/m^3$ and maximum daily PM_{13} = 95 $\mu g/m^3$. Hajat et al. (1999) reported significant PM_{10} associations with asthma doctor's visits for children and young adults in London when mean PM_{10} = 28.2 $\mu g/m^3$ and the PM_{10} 90^{th} percentile was only 46.4 $\mu g/m^3$. Overall, then, numerous new medical visits studies indicate PM-health effects associations at lower $PM_{2.5}$ and PM_{10} levels than demonstrated previously for this health outcome.

6.3.2.4.1 Scope of Medical Visit Morbidity Effects

Several of these recent medical visit studies consider a new endpoint for comparison with ED visits: visits in the primary care setting. In particular, key studies showing PM-health effects associations for this health outcome include: the study by Medina et al. (1997) for Paris, France which evaluated doctors' visits to patients in that city; the study by Hajat et al. (1999) that evaluated the relationship between daily General Practice (GP) doctor consultations for asthma and other lower respiratory disease (LRD) and air pollution in London, UK; the study by Choudhury et al. (1997) of private asthma medical visits in Anchorage, Alaska; and the study by Ostro et al. (1999b) of daily visits by young children to primary care health clinics in Santiago, Chile for upper or lower respiratory symptoms.

While limited in number, the above studies collectively provide new insight into the fact that there is a broader scope of severe morbidity associated with PM air pollution exposure than previously documented. As the authors of the London study note: "There is less information about the effects of air pollution in general practice consultations but, if they do exist, the public health impact could be considerable because of their large numbers." Indeed, the Paris doctors' house calls and the London doctors' GP office visits studies both indicate that the effects of air pollution, including PM, can affect many more people than indicated by hospital admissions alone.

These new studies also provide indications as to the quantitative nature of medical visits effects, relative to those for hospital admissions. In the London case, comparing the number of admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study (Hajat et al., 1999) indicates that there are approximately 24 asthma GP visits for every asthma admission in that city. Also, comparing the PM_{10} coefficients indicates that the all-ages asthma effect size for the GP visits (although not statistically different) was about 30% larger than that for hospital admissions. Similarly, the number of doctors' house calls for asthma approximated 45/day in Paris (based on an average 9 asthma house calls in the SOS-Medocina data base, representing 20% of the total; Medina et al., [1997]), versus an average 14 asthma admissions/day (Dab et al., 1996), or a factor of 3 more doctors' house calls than hospital admissions. Moreover, the RR for Paris asthma doctors' house calls was much higher than asthma admissions (RR=1.18 for 25 $\mu g/m^3$ BS for house calls vs. RR=1.01 per 25 $\mu g/m^3$ BS for hospital admissions). Thus, these new studies suggest that looking at only hospital admissions and emergency hospital visit effects may greatly underestimate numbers of respiratory morbidity events in a population due to acute ambient PM exposure.

6.3.2.4.2 Evaluation of Extraneous Factors Potentially Affecting Respiratory Medical Visit Study Outcomes

Some recent studies have examined certain factors that might extraneously affect the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias and random variability in diagnostic classification of air pollution and daily cardiac respiratory emergency department visits such as asthma, COPD, respiratory infection and cardiac. They concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels.

Also, Stieb et al. (1998b) reported that for a population of adults visiting an emergency department with cardiac respiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability in average personal exposure to particulate sulfate, whereas particulate acid exposure was not as well represented by fixed site monitors. Another study investigated possible confounding of respiratory visit effects due to pollens. In London, Atkinson et al. (1999b) studied the association between the number of daily visits to emergency departments for respiratory complaints and measures of outdoor air pollution for PM_{10}, NO_2, SO_2 and CO. They examined different age groups and reported the strongest association for children for visits for asthma, but were unable to separate the effects of PM_{10} and SO_2. Pollen levels did not influence the results, similar to results from the asthma panel studies described below in Section 6.3.3.

6.3.2.5 Summary of Key Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits

The results of new studies discussed above are generally consistent with and supportive of findings presented in the previous PM AQCD (U.S. Environmental Protection Agency, 1996), with regard to ambient PM associations of short-term exposures with respiratory-related hospital admissions/medical visits. Excess risk estimates for specific subcategories of respiratory-related hospital admissions/medical visits for U.S. cities are graphically depicted in Figure 6-7. The excess risk estimates fall most consistently in the range of 5 to 25% per 50 $\mu g/m^3$ PM_{10} increments, with those for asthma visits and hospital admissions tending to be somewhat higher than for COPD and pneumonia hospital admissions.

More limited new evidence substantiates increased risk of respiratory-related hospital admissions due to ambient fine particles ($PM_{2.5}$, $PM_{1.0}$, etc.), and it also points towards associations of such admissions with ambient coarse particles ($PM_{10-2.5}$). Excess risk estimates tend to fall in the range of ca. 5.0 to 15.0% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ for overall respiratory admissions or for COPD admissions, whereas larger estimates are found for asthma admissions (ranging upwards to ca. 40 to 50% for children < 18 yr. old in one study).

Various new medical visits studies (including non-hospital physician visits) indicate that the use of hospital admissions alone can greatly understate the total clinical morbidity effects of air pollution. Thus, these results support the hypothesis that considering only hospital admissions and emergency hospital visit effects may greatly underestimate the numbers of medical visits

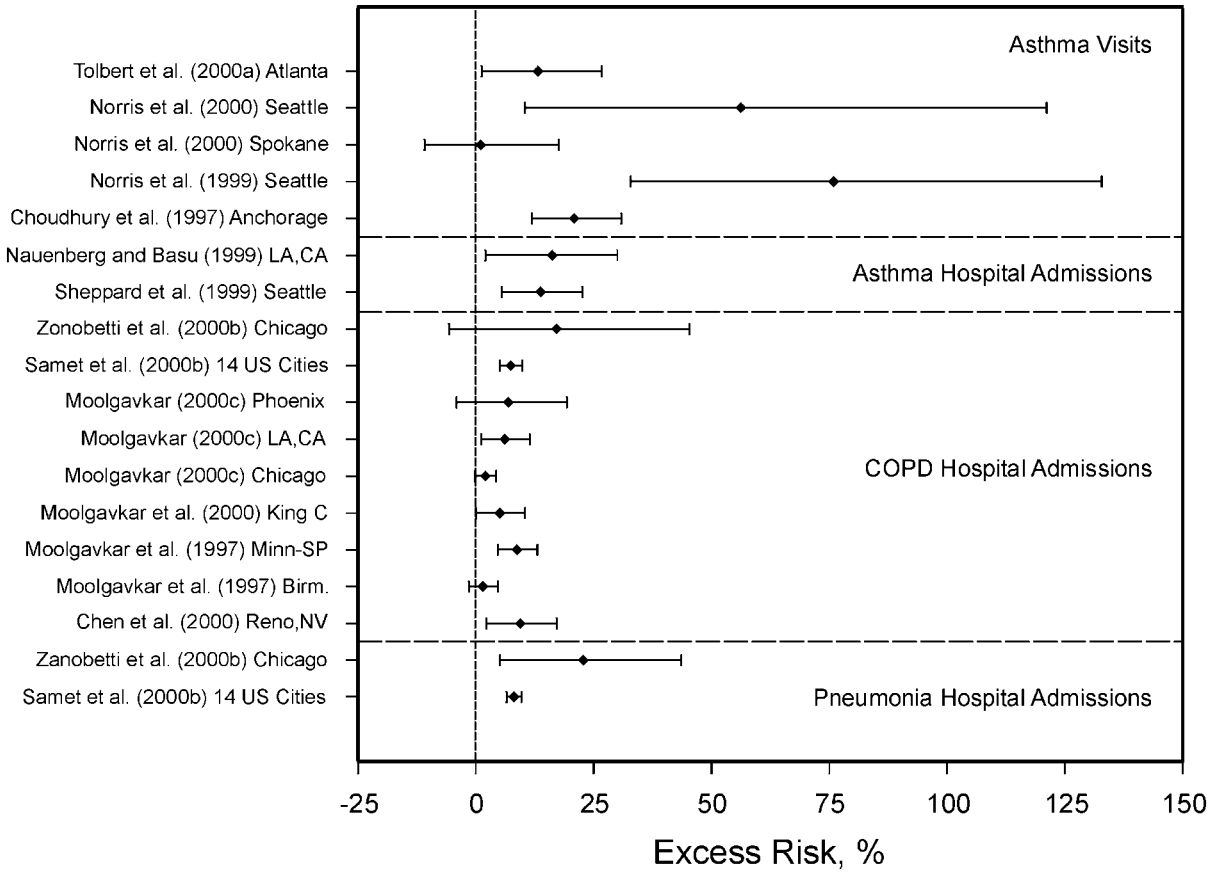

Figure 6-7. Maximum excess risk of respiratory-related hospital admissions and visits per 50-$\mu g/m^3$ PM_{10} increment in selected studies of U.S. cities.

occurring in a population as a result of acute ambient PM exposure. Those groups identified in these morbidity studies as most strongly affected by PM air pollution are older adults and the very young.

6.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory disease studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to PM_{10}. The models for analysis varied and the populations included several different subgroups. Pulmonary function studies were suggestive of short term effects resulting from ambient PM exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min resulting from an increase of

50 $\mu g/m^3$ in 24-h PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups such as asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies were less numerous than the acute studies, and the results were inconclusive.

6.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms

The available acute respiratory symptom studies discussed in the 1996 PM AQCD included several different endpoints, but typically presented results for: (1) upper respiratory symptoms, (2) lower respiratory symptoms, or (3) cough. These respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

The earlier studies of morbidity health outcomes of PM_{10} exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) studied respiratory symptoms in two panels of asthmatics in the Utah Valley. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness (LRI) and the second panel of 21 subjects aged 8 to 72 for LRI of 1.01 (0.81, 1.27) for exposure to PM_{10}. Ostro et al. (1991) reported no association for $PM_{2.5}$ exposure in a panel of 207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 in central Los Angeles, reported a relationship of shortness of breath to O_3 and PM_{10}, but could not separate effects of the two pollutants. These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Numerous new studies of short-term PM exposure effects on lung function and respiratory symptoms have been published since early 1996. Most of these followed a panel of subjects over one or more periods and evaluated daily lung function and/or respiratory symptom associations with changes in ambient PM_{10} and/or $PM_{2.5}$. Lung function was usually measured daily with many studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF). Most analyses included both morning and afternoon measurements. A variety of respiratory symptoms were measured, including cough, phlegm, difficulty breathing,

wheeze, and bronchodilator use. Finally, several measures of airborne particles were used, including: PM_{10}, $PM_{2.5}$, TSP, BS, and sulfate fraction of ambient PM.

These various studies are summarized in several tables presented below. Data on physical and chemical aspects of ambient PM levels (especially for PM_{10} and $PM_{2.5}$ and smaller size fractions) are of particular interest, as are new studies examining health outcome effects and/or exposure measures not studied as much in the past. Each table is organized by study location, PM measure, etc. Where possible, results are presented in terms of the units described earlier. Specific analyses were selected for summarization based on the following criteria:

- Peak flow was used as the primary lung function measurement of interest. While FEV1 would be a good measure, peak flow (PF) is most often measured in these panel studies.
- Cough, phlegm, difficulty breathing, wheeze, and broncho-dilator use were summarized as measures of respiratory symptoms when available.
- Preference was given to results reported for PM_{10} and $PM_{2.5}$ and/or smaller PM.
- The analyses were also restricted to include a short-term lag (zero or one day), a longer-term lag (2- to 5- day), and a moving average analysis, when available. If both 0- and a 1-day lag analyses were presented, the 0-day lag analysis was used for all, but the AM PF results. For longer lags, the measure coming closest to average of 2 to 5 days was selected.

6.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects

Tables 6-19 and 6-20 summarize short-term PM exposure effects on lung function and respiratory symptoms, respectively, in asthmatic subjects. The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. For PM_{10}, 2 of 4 of the newly available point estimates showed decreases, but the majority of the studies were not statistically significant, as shown in Figure 6-8 as an example of PEF outcomes. Lag 1 may be more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies which provided such data. The results were consistent for both AM and PM peak flow analyses. The effects using 2 to five-day lags averaged about the same as did the zero to one-day lags, but the effects had wider confidence limits. Similar results were found for the $PM_{2.5}$ studies, although there were fewer studies. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Gold et al. (1999), Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al. (1997), and Romieu et al. (1996) all found similar results

TABLE 6-19. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Schwartz and Neas (2000) Reanalyses of three recent longitudinal diary studies: Harvard Six Cities, Uniontown, PA; State College, PA.	Analysis of Harvard Six City Study data for 1,844 school children (grades 2-5) from 6 eastern U.S. urban areas only included respiratory symptom diary information. Uniontown and State College analyses also included PEF data.	In both the Harvard Six City and the Uniontown-State College diary studies, fine particle measures were more strongly related to asthma-related responses (i.e., increased lower respiratory symptoms and decreased peak flow).	
Thurston et al. (1997) Summers of 1991-93. Ozone, H+, and sulfates fraction.	Three 5-day summer camps conducted in 1991, 1992, 1993. Symptoms and change in lung function (morning to evening) measured. Linear regression analysis adjusting for pollen and daily maximum temperature was used for analysis of lung function.	No relationship between lung function and pollutants was found.	—
Canada			
Vedal et al. (1998) Port Alberni, BC	Study 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Peak flow measured twice daily. An autoregressive model was fitted to the data using GEE methods. Covariates included temperature, humidity, and precipitation.	PM_{10} was associated with changes in morning peak flow for lags 0, 1, 2, 3, and 4 day average.	—
Europe			
Gielen et al. (1997) Amsterdam, NL Mean PM_{10} level: 30.5 $\mu g/m^3$ (16, 60.3). Mean maximum 8 hr O_3: 67 $\mu g/m^3$.	Study evaluated 61 children aged 7 to 13 years living in Amsterdam, The Netherlands. 77 percent of the children were taking asthma medication and the others were being hospitalized for respiratory problems. Peak flow measurements were taken twice daily. Associations of air pollution were evaluated using time series analyses. The analyses adjusted for pollen counts, time trend, and day of week.	The strongest relationships were found with ozone, although some significant relationships found with PM_{10}.	Lag 0, PM_{10}: Evening PEF = −0.08 (−2.49, 2.42) Lag 1, PM_{10}: Morning PEF = 1.38 (−0.58, 3.35) Lag 2, PM_{10}: Morning PEF = 0.34 (−1.78, 2.46) Evening PEF = −1.46 (−3.23, 0.32)

TABLE 6-19 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Hiltermann et al. (1998) Leiden, NL July-Oct, 1995	270 adult asthmatic patients from an out-patient clinic in Leiden, The Netherlands were studied from July 3 to October 6, 1995. Peak flow measured twice daily. An autoregressive model was fitted to the data. Covariates included temp. and day of week. Individual responses not modeled.	No relationship between ozone and PFT was found	Lag 0, PM_{10}: Average PEF = −0.80 (−3.84, 2.04) 7 day ave., PM_{10}: Average PEF = −1.10 (−5.22, 3.02)
Peters et al. (1996) Erfurt and Weimar, Germany SO_2, TSP, PM_{10}, sulfate fraction, and PSA. Mean PM_{10} level was 112 $\mu g/m^3$.	Panel of 155 asthmatic children in the cities of Erfurt and Weimar, E. Germany studied. Each panelist's mean PEF over the entire period subtracted from the PEF value to obtain a deviation. Mean deviation for all panelists on given day was analyzed using an autoregressive moving average. Regression analyses done separately for adults and children in each city and winter; then combined results calculated.	Five day average SO_2 was associated with decreased PEF. Changes in PEF were not associated with PM levels.	—
Peters et al. (1997b) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Particles measured using size cuts of 0.01 to 0.1, 0.1 to 0.5, and 0.5 to 2.5 μm. Mean PM_{10} level: 55 $\mu g/m^3$ (max 71). Mean SO_2: 100 $\mu g/m^3$ (max 383).	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season of 1991-1992. Morning and evening peak flow readings recorded. An auto-regressive model was used to analyze deviations in individual peak flow values, including terms for time trend, temp., humidity, and wind speed and direction.	Strongest effects on peak flow found with ultrafine particles. The two smallest fractions, 0.01 to 0.1 and 0.1 to 0.5 were associated with a decrease of PEF.	Lag 0, PM_{10}: Evening PEF = −0.38 (−1.83, 1.08) Lag 1, PM_{10}: Morning PEF = −1.30 (−2.36, 0.24) 5 Day Mean, PM_{10}: Morning PEF = −1.51 (−3.20, 0.19) Evening PEF = −2.31 (−4.54, −0.08) Lag 0, $PM_{2.5}$: Evening PEF = −0.75 (−1.66, 0.17) Lag 1, $PM_{2.5}$: Morning PEF = −0.71 (−1.30, 0.12) 5 Day Mean, $PM_{2.5}$: Morning PEF = −1.19 (−1.81, 0.57) Evening PEF = −1.79 (−2.64, −0.95)
Peters et al. (1997c) Sckolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10} level: 47 $\mu g/m^3$ (29, 73). Median SO_2: 46 $\mu g/m^3$ (22, 88).	89 children with asthma in Sokolov, Czech Republic studied. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. The analysis used linear regression for PFT. First order autocorrelations were observed and corrected for using polynomial distributed lag (PDL) structures.	Five day mean SO_2, sulfates, and particle strong acidity were also associated with decreases in PM PFT as well as PM_{10}.	Lag 0, PM_{10}: Morning PEF = −0.71 (−2.14, 0.70) Evening PEF = −0.92 (−1.96, 0.12) 5 Day mean PM_{10}: Evening PEF = −1.72 (−3.64, 0.19) Morning PEF = −0.94 (−2.76, 0.91

TABLE 6-19 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Timonen and Pekkanen (1997) Kupio, Finland PM_{10}, BS, NO_2, and SO_2.	Studied 74 asthmatic children (7 to 12 yr) in Kuoio, Finland. Daily mean PEF deviation calculated for each child. Values were analyzed, then using linear first-order autoregressive model.	Lagged concentrations of NO_2 related to declines in morning PEF as well as PM_{10} and BS.	Lagged concentrations of PM_{10} and BS related to declines in morning PEF.
Pekkanen et al. (1997) Kuopio, Finland PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 18 $\mu g/m^3$ (10, 23). Mean NO_2 level: 28 $\mu g/m^3$.	Studied 39 asthmatic children aged 7-12 years living in Kuopio, Finland. Changes in peak flow measurements were analyzed using a linear first-order autoregressive model.	Changes in peak flow found to be related to all measures of PM, after adjusting for minimum temperature. PN0.032–0.10 ($1/cm^3$) and PN1.0–3.2 ($1/cm^3$) were most strongly associated with morning PEF deviations.	Lag 0, PM_{10}: Evening PEF = –0.35 (–1.14, 0.96) Lag 1, PM_{10}: Morning PEF = –2.70 (–6.65, 1.23) Lag 2, PM_{10}: Morning PEF = –4.35 (–8.02, –0.67) Evening PEF = –1.10 (–4.70, 2.50) Small sized particles had relationships similar to those of PM_{10} for morning and evening PEF.
Segala et al. (1998) Paris, France Nov. 1992 - May 1993. BS, SO_2, NO_2, PM_{13} (instead of PM_{10}), measured. Mean PM_{13} level: 34.2 $\mu g/m^3$ (range 8.8, 95). Mean SO_2 level: 21.7 $\mu g/m^3$ (range 4.4, 83.8). Mean NO_2 level: 56.9 $\mu g/m^3$ (range 23.8, 121.9).	Study of 43 mildly asthmatic children aged 7-15 years living in Paris, France from Nov. 15, 1992 to May 9, 1993. Peak flow measured three times a day. Covariates in the model included temperature and humidity. An autoregressive model was fitted to the data using GEE methods.	Effects found related to PM_{10} were less than those found related to the other pollutants.	Lag 4, PM_{13}: Morning PEF = –0.62 (–1.52, 0.28)
Agócs et al. (1997) Budapest, Hungary	Panel of 60 asthmatic children studied for two months in Budapest, Hungary. Mixed model used relating TSP to morning and evening PEFR measurements, adjusting for SO_2, time trend, day of week, temp., humidity		No significant TSP-PEFR relationships found.
Australia			
Rutherford et al. (1999) Brisbane, Australia PM_{10}, TSP, and particle diameter.	Study examined effects of 11 dust events on peak flow and symptoms of people with asthma in Brisbane, Australia. PEF data for each individual averaged for a period of 7 days prior to the identified event. This mean was compared to the average for several days of PEF after the event, and the difference was tested using a paired t-test.	The paired t-tests were stat. significant for some days, but not others. No general conclusions could be drawn.	—

TABLE 6-19 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Latin America			
Romieu et al. (1996) Mexico City, Mexico During study period, maximum daily 1-h O_3 ranged from 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave, PM_{10} levels ranged from 29 to 363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). For 53 percent of study days, PM_{10} levels exceeded 150 $\mu g/m^3$.	Study of 71 children with mild asthma aged 5-7 years living in the northern area of Mexico City. Morning and evening peak flow measurements recorded by parents. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. Model included terms for minimum temperature.	Ozone strongly related to changes in morning PEF as well as PM_{10}.	Lag 0, PM_{10}: Evening PEF = −4.80 (−8.00, −1.70) Lag 2, PM_{10}: Evening PEF = −3.65 (−7.20, 0.03) Lag 0, $PM_{2.5}$: Evening PEF = −4.27 (−7.12, −0.85) Lag 2, $PM_{2.5}$: Evening PEF = −2.55 (−7.84, 2.74) Lag 1, PM_{10} Morning PEF = −4.70 (−7.65, −1.7) Lag 2, PM_{10} Morning PEF = −4.90 (−8.4, −1.5)
Romieu et al. (1997) Mexico City, Mexico During study period, maximum daily 1-h ozone ranged from 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average ranged from 12 to 126 $\mu g/m^3$.	Study of 65 children with mild asthma aged 5-13 yr in southwest Mexico City. Morning and evening peak flow measurements made by parents. Peak flow measurements standardized for each person and model was fitted using GEE methods. Model included terms for minimum temperature.	Strongest relationships were found between ozone (lag 0 or 1) and both morning and evening PFT.	Lag 0, PM_{10}: Evening PEF = −1.32 (−6.82, 4.17) Lag 2, PM_{10}: Evening PEF = −0.04 (−4.29, 4.21) Morning PEF = 2.47 (−1.75, 6.75) Lag 0, PM_{10}: Morning PEF = 0.65 (−3.97, 5.32)

TABLE 6-20. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Delfino et al. (1996) So. California Summer of 1995. Ozone and PM_{10} measured	Study of 9 adults and 13 children with history of bronchodilator use living in Southern California. An autoregressive logistic model was fitted to symptoms adjusting for temperature and relative humidity	Pollen not associated with asthma symptom scores.	No significant relationships with PM_{10}.
Delfino et al. (1997) San Diego County, CA	A panel of 9 adults and 13 children were followed during late spring 1994 in semi-rural area of San Diego County at the inversion zone elevation of around 1,200 feet. A random effects model was fitted to ordinal symptom scores, bronchodilator use, and PEF in relation to 24-hour PM_{10}. Temp., relative humidity, fugal spores, day of week and O_3 evaluated	Although PM_{10} never exceeded 51 $\mu g/m^3$, bronchodilator use was significantly associated with PM_{10}(0.76 [0.027, 0.27]) puffs per 50 $\mu g/m^3$. Fungal spores were associated with all respiratory outcomes.	—
Delfino et al. (1998) So. California community Aug. - Oct. 1995 Highest 24-hour PM_{10} mean: 54 $\mu g/m^3$	Relationship of asthma symptoms to O_3 and PM_{10} examined in a So. California community with high O_3 and low PM. Panel of 25 asthmatics ages 9 - 17 followed daily, Aug. - Oct., 1995. Longitudinal regression analyses utilized GEE model controlling for autocorrelation, day of week, outdoor fungi and weather.	Asthma symptoms scores significantly associated with both outdoor O_3 and PM_{10} in single pollutant and co-regressions. 1-hr and 8-hr maxi PM_{10} had larger effects than 24-hr mean.	—
Ostro et al. (1995) Los Angeles, CA TSP, sulfates, nitrates, O_3, SO_2, NO_2, and PM_{10} measured.	Study of African-American children, ages 7-12 years with confirmed asthma. 109 children were eligible, most of whom lived central and south-central Los Angeles. Analyses done using "daily reporting of respiratory symptoms including cough, shortness of breath, and wheeze". General logistic regression models used, with GEE corrections for autocorrelation.	relationships found between shortness of breath and PM_{10} or ozone, with symptoms estimated to increase about 9% per each 10 $\mu g/m^3$ increase in PM_{10}.	Lag 0, Symptoms: Short. Breath OR = 1.51 (1.04, 2.17) Others not significant

TABLE 6-20 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate, pollen, daily max temp. measured.	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	Ozone related to respiratory symptoms No relationship between symptoms and other pollutants.	—
Canada			
Vedal et al. (1998) Port Alberni, BC	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	In general, PM_{10} was associated with changes in both peak flow and respiratory symptoms.	Lag 0, Symptoms: Cough OR = 1.40 (1.04, 1.88) Phlegm OR = 1.28 (0.86, 1.89) Lag 2, Symptoms: Cough OR = 1.40 (1.13, 1.73) Phlegm OR = 1.40 (1.03, 1.90)
Europe			
Gielen et al. (1997) Amsterdam, NL	Study of 61 children aged 7 to 13 years living in Amsterdam, NL. 77 percent were taking asthma medication and the others were being hospitalized for respiratory problems. Respiratory symptoms recorded by parents in diary. Associations of air pollution evaluated using time series analyses, adjusted for pollen counts, time trend, and day of week.	Strongest relationships found with O_3, although some significant relationships found with PM_{10}.	Lag 0, Symptoms: Cough OR = 2.19 (0.77, 6.20) Bronch. Dial. OR = 0.94 (0.59, 1.50) Lag 2, Symptoms: Cough OR = 2.19 (0.47, 10.24) Bronch. Dial. OR = 2.90 (1.80, 4.66)
Hiltermann et al. (1998) Leiden, NL July-Oct 1995.	Study of 270 adult asthmatic patients from an out-patient clinic in Leiden, NL from July 3, to October 6, 1995. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data. Covariates included temperature and day of week.	PM_{10}, O_3, and NO_2 were associated with changes in respiratory symptoms.	Lag 0, Symptoms: Cough OR = 0.93 (0.83, 1.04) Short. breath OR = 1.17 (1.03, 1.34) 7 day average, Symptoms: Cough OR = 0.94 (0.82, 1.08) Short. breath OR = 1.01 (0.86, 1.20)

TABLE 6-20 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Hiltermann et al. (1997) The Netherlands	Sixty outpatient asthmatics examined for nasal inflammatory parameters in The Netherlands from July 3 to October 6, 1995. Associations of log transformed inflammatory parameters to 24-h PM_{10} analyzed, using a linear regression model. Mugwort-pollen and O_3 were evaluated.	Inflammatory parameters in nasal lavage of patients with intermittent to severe persistent asthma were associated with ambient O_3 and allergen exposure, but not with PM_{10} exposure.	—
Peters et al. (1997b) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 55 $\mu g/m^3$ (max 71). Mean SO_2: 100 $\mu g/m^3$ (max 383).	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season 1991-1992. Diary used to record presence of cough. Symptom information analyzed using multiple logistic regression analysis.	Weak associations found with 5 day mean sulfates and respiratory symptoms.	Lag 0, PM_{10}: Cough OR = 1.32 (1.16, 1.50) Feeling ill OR = 1.20 (1.01, 1.44) 5 Day Mean, PM_{10}: Cough OR = 1.30 (1.09, 1.55) Feeling ill OR = 1.47 (1.16, 1.86) Lag 0, $PM_{2.5}$: Cough OR = 1.19 (1.07, 1.33) Feeling ill OR = 1.24 (1.09, 1.41) 5 Day Mean, $PM_{2.5}$: Cough OR = 1.02 (0.91, 1.15) Feeling ill OR = 1.21 (1.06, 1.38)
Peters et al. (1997c) Sokolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10}: 47 $\mu g/m^3$ (29, 73). Median SO_2: 46 $\mu g/m^3$ (22, 88).	Study of 89 children with asthma in Sokolov, Czech Republic. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. Logistic regression for binary outcomes used. First order autocorrelations were observed and corrected for using polynomial distributed lag structures.	Significant relationships found between TSP and sulfate with both phlegm and runny nose.	Lag 0, Symptoms: Cough OR = 1.01 (0.97, 1.07) Phlegm OR = 1.13 (1.04, 1.23) 5 Day Mean, Symptoms: Cough OR = 1.10 (1.04, 1.17) Phlegm OR = 1.17 (1.09, 1.27)
Peters et al. (1997c) Sokolov, Czech Republic PM_{10} one central site. SO_4 reported. Mean PM_{10}: 55 $\mu g/m^3$, max 177 $\mu g/m^3$. SO_4 - fine: mean 8.8 $\mu g/m^3$, max 23.8 $\mu g/m^3$	Role of medication use evaluated in panel study of 82 children, mean ages 9.8 yr., with mild asthma in Sokolov, Czech Republic Nov. 1991 - Feb 1992. Linear and logistic regression evaluated PM_{10}, SO_2, temp, RH relationships to respiratory symptoms.	Medicated children, as opposed to those not using asthma medication, increased their beta-agonist use in direct association with increases in 5-day mean of SO_4 particles <2.5 μm, but medication did not prevent decrease in PEF and increase in prevalence of cough attributable to PM air pollution.	Cough 1.16 (1.00, 1.34) 6.5 $\mu g/m^3$ increase 5-day mean SO_4 5-d Mean SO_4/increase of 6.5 $\mu g/m^3$ Beta-Agonist Use 1.46 (1.08, 1.98) Theophylline Use 0.99 (0.77, 1.26) No PM_{10} analysis

TABLE 6-20 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Neukirch et al. (1998) Paris, France SO_2, NO_2, PM_{13} and BS.	Panel of 40 nonsmoking adult asthmatics in Paris studied. GEE models used to associate health outcomes with air pollutants. Models allowed for time-dependent covariates, adjusting for time trends, day of week, temp. and humidity.	Significant relationships found for incidence of respiratory symptoms and three or more day lags of SO_2, and NO_2. Only selected results were given.	Significant relationships found between incidence of respiratory symptoms and three or more day lags of PM_{13}.
Segala et al. (1998) Paris, France SO_2, NO_2, PM_{13} (instead of PM_{10}), and BS.	Study of 43 mildly asthmatic children aged 7-15 yr in Paris. Patients followed Nov. 15, 1992 to May 9, 1993. Respiratory symptoms recorded daily in diary. An autoregressive model fitted to data using GEE methods. Covariates included temp. and humidity.	Effects found related to PM_{13} were less than those found related to the other pollutants.	Lag 2, Symptoms: Short. Breath OR = 1.22 (0.83, 1.81) Resp. Infect. OR = 1.66 (0.84, 3.30)
Güntzel et al. (1996) Switzerland	An asthma reporting system was used in connection with pollutant monitoring in Switzerland from fall of 1988 to fall 1990. A Box-Jenkins ARIMA time series model was used to relate asthma to TSP, O_3, SO_2, and NO_2 after adjusting for temperature.	No significant relationships found.	—
Taggart et al. (1996) Northern England SO_2, NO_2 and BS.	Panel of 38 adult asthmatics studied July 17 to Sept. 22, 1993 in northern England. Used generalized linear model to relate pollutants to bronchial hyper-responsiveness, adjusting for temperature.	Small effects seen in relation to NO_2 and BS.	—
Latin America			
Romieu et al. (1997) Mexico City, Mexico During study period, max daily 1-h O_3 range: 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average range: 12 to 126 $\mu g/m^3$.	Study of 65 children with mild asthma aged 5-13 yr living in southwest Mexico City. Respiratory symptoms recorded by the parents in daily diary. An autoregressive logistic regression model used to analyze presence of respiratory symptoms.	Strongest relationships found between O_3 and respiratory symptoms.	Lag 0, Symptoms: Cough OR = 1.05 (0.92, 1.18) Phlegm OR = 1.05 (0.83, 1.36) Diff. Breath OR = 1.13 (0.95, 1.33) Lag 2, Symptoms: Cough OR = 1.00 (0.92, 1.10) Phlegm OR = 1.00 (0.86, 1.16) Diff. Breath OR = 1.2 (1.1, 1.36)
Romieu et al. (1996) During study period, max daily range: 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave. PM_{10} levels range: 29 to 363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). PM_{10} levels exceeded 150 $\mu g/m^3$ for 53% of study days. 24-h ave. $PM_{2.5}$ levels range 23-177 $\mu g/m^3$ (mean 85.7 $\mu g/m^3$)	Study of 71 children with mild asthma aged 5-7 yr living in northern Mexico City. Respiratory symptoms recorded by parents in daily diary. An autoregressive logistic regression model was used to analyze the presence of respiratory symptoms.	Cough and LRI were associated with increased O_3 and PM_{10} levels.	PM_{10} (lag 0) increase of 50 $\mu g/m^3$ related to: LRI = 1.21 (1.10, 1.42) Cough = 1.27 (1.16, 1.42) Phlegm = 1.21 (1.00, 1.48) $PM_{2.5}$ (lag 0) increase of 25 $\mu g/m^3$ related to: LRI = 1.18 (1.05, 1.36) Cough = 1.21 (1.05, 1.39) Phlegm = 1.21 (1.03, 1.42)

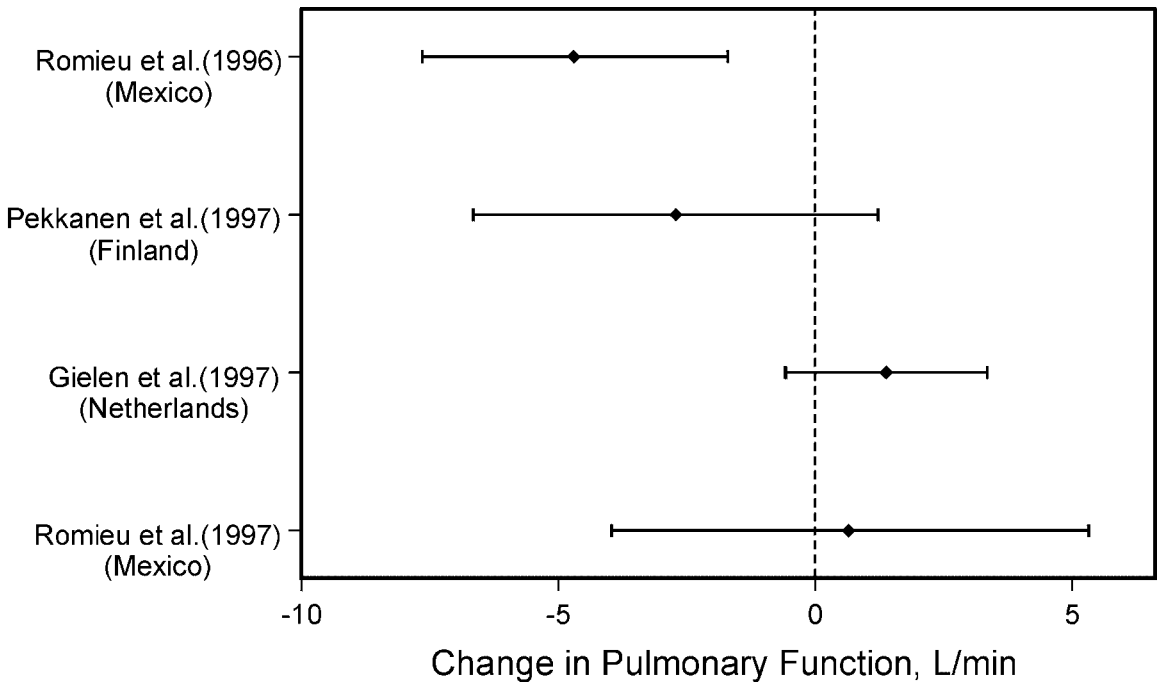

Figure 6-8. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 μg/m^3 PM_{10} on morning Peak flow lagged one-day.

for $PM_{2.5}$ and PM_{10}. The study of Peters et al. (1997b) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas (2000) found larger effects for fine particle measures ($PM_{2.5}$, sulfate, etc.) than for the coarse mode. Naeher et al. (1999) found that H^+ was significantly related to a decrease in morning PEF. Overall, then, PM_{10} and $PM_{2.5}$ both appear to affect lung function in asthmatic, but there is only limited evidence for a stronger effect of fine- versus coarse-mode particles. Also, of the studies provided, few if any analyses were able to separate out the effects of PM_{10} and $PM_{2.5}$ from other pollutants. Gold et al. (1999) attempted to study the interaction of $PM_{2.5}$ and ozone on PEF. The authors found independent effects of the two pollutants, but found that the joint effect was slightly less than the sum of the independent effects.

The effects on respiratory symptoms in asthmatics tended to be positive, although they were much less consistent than the effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant as shown in Figure 6-9 for cough as an example. Cough is a

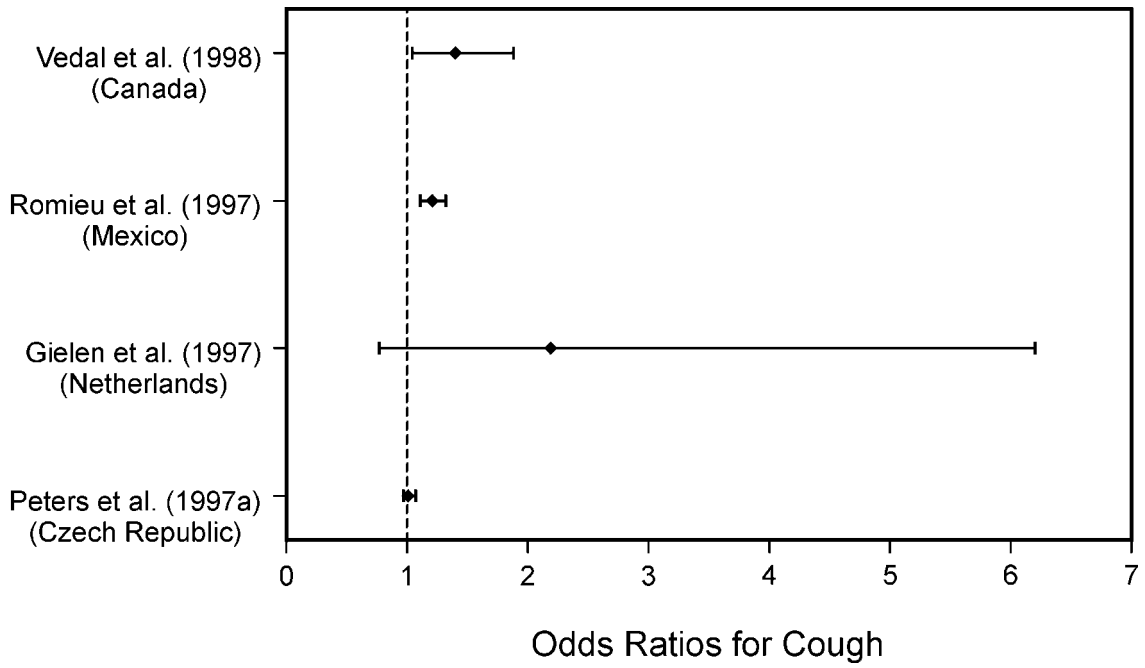

Figure 6-9. Odds ratios with 95% confidence interval for cough per 50-μg/m^3 increase in PM_{10} for selected asthmatic children studies at lag 0.

typical symptom outcome studied. Several studies included both PM_{10} and $PM_{2.5}$ in their analyses. The studies of Peters et al. (1997b) and Tiittanen et al. (1999) found similar effects for the two PM measures, whereas the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$. Also, the Schwartz and Neas (2000) analyses indicated stronger effects of fine particle measures ($PM_{2.5}$, sulfate) than coarse particles on respiratory symptoms in asthmatic school children in eastern United States urban areas.

6.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects

Results of the PM_{10} peak flow analyses in non-asthmatic studies (see Table 6-21) were inconsistent, with fewer studies reporting results in the same manner as for the asthmatic studies. Many of the point estimates showed increases rather than decreases. Similar results were found in the $PM_{2.5}$ studies. The effects on respiratory symptoms in non-asthmatics (see Table 6-22) were similar to those in asthmatics. Most studies showed that PM_{10} increases cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not

TABLE 6-21. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Hoek et al. (1998)	Results summarized from several other studies reported in the literature. These included: asymptomatic children in the Utah Valley (Pope et al., 1991), children in Bennekom, NL (Roemer et al., 1993), children in Uniontown, PA (Neas et al., 1995), and children in State College, PA (Neas et al., 1996). Analyses done using a first-order autoregressive model with adjustments for time trend and ambient temp.	Other pollutants not considered.	Significant decreases in peak flow found to be related to PM_{10} increases.
Lee and Shy (1999) North Carolina Mean 24 h PM_{10} conc. over two years: 25.1 $\mu g/m^3$.	Study of the respiratory health status of residents whose households lived in six communities near an incinerator in southwestern North Carolina. Daily PEFR measured in the afternoon was regressed against 24 hour PM_{10} level lagged by one day. Results were adjusted for gender, age, height, and hypersensitivity.	PM_{10} was not related to variations in respiratory health as measured by PEFR.	—
Korrick et al. (1998) Mt. Washington, NH O_3 levels measured at 2 sites near top of the mountain. $PM_{2.5}$ measured near base of the mountain.	Study of the effects of air pollution on adult hikers on Mt. Washington, NH. Linear and non-linear regressions used to evaluate effects of pollution on lung function.	$PM_{2.5}$ had no effect on the O_3 regression coefficient.	—
Naeher et al. (1999) Virginia PM_{10}, $PM_{2.5}$, sulfate fraction, H+, and ozone	Daily change in PEF studied in 473 non-smoking women in Virginia during summers 1995-1996. Separate regression models run, using normalized morning and evening PEF for each individual.	Ozone was only pollutant related to evening PEF.	Morning PEF decrements were associated with PM_{10}, $PM_{2.5}$, and H+. Estimated effect from $PM_{2.5}$ and PM_{10} was similar. No PM effects found for evening PEF.
Neas et al. (1996) State College, PA $PM_{2.1}$: mean 23.5; max 85.8 $\mu g/m^3$.	Study of 108 children in State College, PA, during summer of 1991 for daily variations in symptoms and PEFRs in relation to $PM_{2.1}$ An autoregressive linear regression model was used. The regression was weighted by reciprocal number of children of each reporting period. Fungus spore conc., temp., O_3 and SO_2 were examined.	Spore concentration associated with deficient in morning PERF.	$PM_{2.1}$ (25 $\mu g/m^3$) related to RR of: PM PFER (lag 0) = −0.05 (−1.73, 0.63) PM PEFR (lag 1) = −0.64 (−1.73, 0.44)

TABLE 6-21 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Neas et al. (1999) Philadelphia, PA Median PM_{10} level: 31.6 in SW camps, 27.8 in NE camps (IQR ranges of about 18). Median $PM_{2.5}$ level: 22.2 in the SW camps, 20.7 in NE camps (IQR ranges about 16.2 and 12.9, respectively). Particle-strong acidity, fine sulfate particle, and O_3 also measured.	Panel study of 156 normal children attending YMCA and YWCA summer camps in greater Philadelphia area in 1993. Children followed for at most 54 days. Morning and evening deviations of each child's PEF were analyzed using a mixed-effects model adjusting for autocorrelation. Covariates included time trend and temp. Lags not used in the analysis.	Analyses that included sulfate fraction and O_3 separately also found relationship to decreased flow. No analyses reported for multiple pollutant models.	Lag 0, PM_{10}: Morning PEF = -8.16 (−14.81, −1.55) Evening PEF = −1.44 (−7.33, 4.44) 5 day ave, PM_{10} Morning PEF = 2.64 (−6.56, 11.83) Evening PEF = 1.47 (−7.31, 10.22) Lag 0, $PM_{2.5}$ Morning PEF = −3.28 (−6.64, 0.07) Evening PEF = −0.91 (−4.04, 2.21) 5 day ave., $PM_{2.5}$ Morning PEF = 3.18 (−2.64, 9.02) Evening PEF = 0.95 (−4.69, 6.57)
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$) measured. Summary levels not given.	Analyses for 1844 school children in grades 2-5 from six urban areas in eastern U.S. and from separate studies from Uniontown and State College, PA. Lower resp. symptoms, cough and PEF used as endpoints. The authors replicated models used in the original analyses. CM and were used individually and jointly in the analyses. Sulfate fractions also used in the analyses. Details of models not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and, not surprisingly, gave similar answers.	Uniontown Lag 0,$PM_{2.5}$: Evening PEF = −1.52 (−2.80, −0.24) State College Lag 0, $PM_{2.5}$: Evening PEF = −0.93 (−1.88, 0.01) Results presented for CM showed no effect. Results for PM_{10} were not given.
Linn et al. (1996) So. California NO_2 ozone, and PM_5 measured.	Study of 269 school children in Southern California twice daily for one week in fall, winter and spring for two years. A repeated measures analysis of covariance was used to fit an autoregressive model, adjusting for year, season, day of week, and temperature.	Morning FVC was significantly decreased as a function of PM_5 and NO_2	—
Europe			
Boezen et al. (1999) Netherlands PM_{10}, BS, SO_2, and NO_2 measured.	Data collected from children during three winters (1992-1995) in rural and urban areas of The Netherlands. Study attempted to investigate whether children with bronchial hyperresponsiveness and high serum Ige levels were more susceptible to air pollution. Prevalence of a 10 percent PEF decrease was related to pollutants for children with bronchial hyperresponsiveness and high serum Ige levels.	No consistent pattern of effects observed with any of the pollutants for 0, 1, and 2 day lags.	—

TABLE 6-21 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Frischer et al. (1999) Austria PM_{10} measured gravimettrically for 14-d periods. Annual mean PM_{10} levels range: 13.6 - 22.9 $\mu g/m^3$. O_3 range: 39.1 ppb - 18.5 pbs between sites.	At nine sites in Austria during 1994, 1995, and 1996, a longitudinal study designed to evaluate O_3 was conducted. During 1994 - 1996, children were measured for FVC, FEV_1 and MEF_{50} six times, twice a year in spring and fall. 1060 children provided valid function tests. Mean age 7.8 ± 0.7 yr. GEE models used. PM_{10}, SO_2, NO_2, and temp. evaluated.	Small but consistent lung function decrements in cohort of school children associated with ambient O_3 exposure.	PM_{10} showed little variation in exposure between study site. For PM_{10}, positive effect seen for winter exposure but was completely confounded by temperature. PM_{10} Summertime β = 0.003 SE 0.012 p=0.77
Grievink et al. (1999) Netherlands PM_{10} and BS.	A panel of adults with chronic respiratory symptoms studied over two winters in The Netherlands starting in 1993/1994. Logistic regression analysis was used to model the prevalence of large PEF decrements. Individual linear regression analysis of PEF on PM was calculated and adjusted for time trends, influenza incidence, and meteorological variables.	Subjects with low levels of serum β-carotene more often had large PEF decrements when PM_{10} levels were higher, compared with subjects with high serum β-carotene. Results suggested serum β-carotene may attenuate the PM effects on decreased PEF.	—
Künzli et al. (2000)	Ackermann-Liebrich et al. (1997) data reanalyzed. Authors showed that a small change in FVC (-3.14 percent) can result in a 60% increase in number of subjects with FVC less than 80 percent of predicted.	The results were for two hypothetical communities, A and B.	—
Roemer et al. (2000) PM_{10} means for 17 panels ranged 11.2 to 98.8 $\mu g/m^3$. SO_2, NO_2, and elemental content of PM also measured.	Combined results from 1208 children divided among 17 panels studied. Separate results reported by endpoints included symptoms as reported in a dairy and PEF. Individual panels were analyzed using multiple linear regression analysis on deviations from mean PEF adjusting for auto-correlation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	PM_{10} analyses not focus of this paper.

TABLE 6-21 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Scarlett et al. (1996) PM_{10}, O_3, and NO_2 measured.	In study of 154 school children, pulmonary function was measured daily for 31 days. Separate autoregressive models for each child were pooled, adjusting for pollen, machine, operator, time of day, and time trend.	PM_{10} was related to changes in FEV and FVC	—
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 $\mu g/m^3$. BS, sulfate fraction, SO_2, and NO_2 also measured.	Panel study of 795 children aged 7 to 11 years, with and without chronic respiratory symptoms living in urban and nonurban areas in the Netherlands. Peak flow measured for three winters starting in 1992/1993. Peak flow dichotomized at 10 and 20% decrements below the individual median. Number of subjects was used as a weight. Minimum temperature day of week, and time trend variables were used as covariates. Lags of 0, 1 and 2 days were used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No multiple pollutant models analyses reported.	Lag 0, PM_{10}, Urban areas Evening PEF OR = 1.15 (1.02, 1.29) Lag 2, PM_{10}, Urban areas Evening PEF OR = 1.07 (0.96, 1.19) 5 day ave, PM_{10}, Urban areas Evening PEF = 1.13 (0.96, 1.32)
van der Zee et al. (2000) Netherlands PM_{10} averages ranged 24 to 53 $\mu g/m^3$. BS, sulfate fraction, SO_2, and NO_2 also measured.	Panel study of 489 adults aged 50-70 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Resp. symptoms and peak flow measured for three winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Peak flow dichotomized at 10 and 20% decrements below the individual median. The number of subjects used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	BS tended to have the most consistent relationship across endpoints. Sulfate fraction also related to increased respiratory effects. No analyses reported for multiple pollutant models. Relationship found between PM_{10} and the presence of 20% decrements in symptomatic subjects from urban areas.	Lag 0, PM_{10}, Urban areas Morning large decrements OR = 1.44 (1.02, 2.03) Lag 2, PM_{10}, Urban areas Morning large decrements OR = 1.14 (0.83, 1.58) 5 day ave, PM_{10}, Urban areas Morning large decrements OR = 1.16 (0.64, 2.10) Results should be viewed with caution because of problems in analysis.

TABLE 6-21 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$ level: 15 (25^{th}, 75^{th} percentiles = 9, 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured.	Six-week panel study of 49 children with chronic respiratory disease followed in the spring of 1995 in Kuopio, Finland. Morning and evening deviations of each child's PEF analyzed, using a general linear model estimated by PROC MIXED. Covariates included a time trend, day of week, temp., and humidity. Lags of 0 through 3 days were used, as well as a 4-day moving average. Various fine particles were examined.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly. Effects varied by lag. Separating effects by size was difficult.	Lag 0, PM_{10}: Morning PEF = 1.21 (−0.43, 2.85) Evening PEF = 0.72 (−0.63, 1.26) 4 day ave, PM_{10} Morning PEF = −1.26 (−5.86, 3.33) Evening PEF = 2.33 (−2.62, 7.28) Lag 0, $PM_{2.5}$ Morning PEF = 1.11 (−0.64, 2.86) Evening PEF = 0.70 (−0.81, 2.20) 4 day ave., $PM_{2.5}$ Morning PEF = −1.93 (−7.00, 3.15) Evening PEF = 1.52 (−3.91, 6.94)
Ward et al. (2000) West Midlands, UK Daily measurements of PM_{10}, $PM_{2.5}$, SO_2, CO, O_3, and oxides of nitrogen.	Panel study of 9 yr old children in West Midlands, UK for two 8-week periods representing winter and summer conditions. Individual PEF values converted to z-values. Mean of the z-values analyzed in a linear regression model, including terms for time trend, day of week, meteorological variables, and pollen count. Lags up to four days also used.	Results on effects of pollution on lung function to be published elsewhere.	—
Cuijpers et al. (1994) Maastricht, NL SO_2, NO_2, BS, ozone, and H+ measured.	Summer episodes in Maastricht, The Netherlands studied. Paired t tests used for pulmonary function tests.	Small decreases in lung function found related to pollutants.	—

TABLE 6-21 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Latin America			
Gold et al. (1999) Mexico City, Mexico Mean 24 h O_3 levels: 52 ppb. Mean $PM_{2.5}$: 30 $\mu g/m^3$. Mean PM_{10}: 49 $\mu g/m^3$.	Peak flow studied in a panel of 40 school-aged children living in southwest Mexico City. Daily deviations from morning and afternoon PEFs calculated for each subject. Changes in PEF regressed on individual pollutants allowing for autocorrelation and including terms for daily temp., season, and time trend.	O_3 significantly contributed to observed decreases in lung function, but there was an independent PM effect.	Both $PM_{2.5}$ and PM_{10} significantly related to decreases in morning and afternoon peak flow. Effects of the two pollutants similar in magnitude when compared on percent change basis.
Australia/New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured.	Study of 40 subjects aged over 55 years with COPD living in Christchurch, New Zealand conducted during winter of 1994. Subjects recorded their peak flow measurements. A log-linear regression model with adjustment for first order auto-correlation was used to analyze peak flow data and a Poisson regression model was used to analyze symptom data.	Few significant associations found between the health endpoints and the pollutants.	Lag 0, PM_{10}: PEF = −0.86 (−2.33, 0.61)
Asia			
Chen et al. (1999) Taiwan Beta-gauge PM_{10} ranged 44.5 to 189.0 $\mu g/m^3$ for peak concentrations.	In 3 Taiwan communities in 1995, PM_{10} by B-gauge measured at selected primary schools in each community. Spirometry tests (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, PEF) obtained in period May 1995 to Jan. 1996 using ATS protocol in study pop. aged 8 to 13 yr. 895 children were analyzed. Study was designed to investigate short-term effect of ambient air pollution in cross-sectional survey. Multivariate linear model analysis used in both one pollutant and multipollutant models, with 1-, 2-, and 7-day lags. SO_2, CO, O_3, NO_2 and PM_{10} examined, as were meteorol. variables.	In the one-pollutant model, daytime peak O_3 conc. with a 1-day lag significantly affected both FVC and FEV_1. NO_2, SO_2, CO affected FVC. PM_{10} showed nonsignificant decrement. No significant result demonstrated in the model for the exposure with 7 days lag. In the multi-pollutant model, only peak O_3 conc. with 1-day lag showed sig. effect on FVC and $FEV_{1.0}$.	One pollutant model daytime average PM_{10} − 2 day lag FVC −0.37 se 0.39

TABLE 6-22. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{2.5}$ to 10) measured . Summary levels not given	Reported on analysis of 1844 school children in grades 2–5 from six urban areas in the eastern U.S., and from separate studies from Uniontown and State College, PA. Lower respiratory symptoms, and cough used as endpoints. The authors replicated the models used in the original analyses. CM and $PM_{2.5}$ were used individually and jointly in the analyses. Sulfates fractions were also used in the analyses. Details of the models were not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and not surprisingly gave similar answers.	$PM_{2.5}$ was found to be significantly related to lower respiratory symptoms even after adjusting for CM, whereas the reverse was not true. However, for cough, CM was found to be significantly related to lower respiratory symptoms even after adjusting for $PM_{2.5}$, whereas the reverse was not true.
Zhang et al. (2000) Vinton, Virginia 24- h PM_{10}, $PM_{2.5}$, sulfate and strong acid measured in 1995.	In southwestern Virginia, 673 mothers were followed June 10 to Aug. 31, 1995 for the daily reports of present or absence of runny or stuffy nose. PM indicator, O_3, NO_2 temp., and random sociodemographic characteristics considered.	Of all pollutants considered, only the level of coarse particles as calculated (PM_{10} - $PM_{2.5}$) independently related to incidence of new episode of runny noses.	—
Canada			
Long et al. (1998) Winnepeg, CN PM_{10}, TSP, and VOC measured.	Study of 428 participants with mild airway obstruction conducted during a Winnepeg pollution episode. Gender specific odds ratios of symptoms were calculated for differing PM_{10} levels using the Breslow-Day test.	Cough, wheezing, chest tightness, and shortness of breath were all increased during the episode	—
Europe			
Boezen et al. (1998) Amsterdam, NL PM_{10}, SO_2, and NO_2 measured.	Study of 75 symptomatic and asymp. adults near Amsterdam for three months during winter 1993-1994. An autoregressive logistic model was used to relate PM_{10} to respiratory symptoms, cough, and phlegm, adjusting for daily min. temp., time trend, day of week.	No relationship found with pulmonary function. Some significant relationships with respiratory disease found in subpopulations	—

TABLE 6-22 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Roemer et al. (1998) Mean PM_{10} levels measured at local sites ranged 11.2 to 98.8 $\mu g/m^3$ over the 28 sites.	Pollution Effects on Asthmatic Children in Europe (PEACE) study was a multi-center study of PM_{10}, BS, SO_2, and NO_2 on respiratory health of children with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Children with chronic respiratory symptoms were selected into the panels. The symptom with one of the larger selection percentages was dry cough (range over sample of study communities 29 to 92% [22/75; 84/91] with most values over 50%). The group as a whole characterized as those with chronic respiratory disease, especially cough.	These studies modeled group rates and are an example of the panel data problem.	—
Roemer et al. (2000) PM_{10} means for the 17 panels ranged 11.2 to 98.8 $\mu g/m^3$. SO_2, NO_2, and PM elemental content also measured.	Combined results from 1208 children divided among 17 panels studied. Endpoints included symptoms as reported in a dairy and PEF. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	The analysis of PM_{10} was not a focus of this paper.
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 $\mu g/m^3$. BS, sulfate fraction, SO_2, and NO_2 also measured.	A panel study of 795 children aged 7 to 11 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Respiratory symptoms measured for 3 winters starting 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. The number of subjects was used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No analyses reported with multiple pollutant models.	Lag 0, PM_{10}, Urban areas Cough OR = 1.04 (0.95, 1.14) Lag 2, PM_{10}, Urban areas Cough OR = 0.94 (0.89, 1.06) 5 day ave, PM_{10}, Urban areas Cough OR = 0.95 (0.80, 1.13)

TABLE 6-22 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Van der Zee et al. (2000) Netherlands Daily measurements of PM_{10}, BS, fine sulfate, nitrate, ammonium and strong acidity.	Panel study of adults aged 50 to 70 yr during 3 consecutive winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. Analysis treated as a time series, adjusting for first order autocorrelation. Number of subjects used as a weight. Min. temp., day of week, time trend variables used as covariates. Lags 0, 1 and 2 days used, as well as 5 day moving average.	BS was associated with upper respiratory symptoms.	Lag 0, Symptoms, Urban areas LRS OR = 0.98 (0.89, 1.08) URS OR = 1.04 (0.96, 1.14) Lag 2, Symptoms, Urban areas LRS OR = 1.01 (0.93, 1.10) URS OR = 1.04 (0.96, 1.13) 5 day ave, Symptoms, Urban areas LRS OR = 0.95 (0.82, 1.11) URS OR = 1.17 (1.00, 1.37)
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$: 15 (25^{th} and 75^{th} percentiles of 9 and 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured.	Six-week panel study of 49 children with chronic respiratory disease followed in spring 1995 in Kuopio, Finland. Cough, phlegm, URS, LRS and medication use analyzed, using a random effects logistic regression model (SAS macro GLIMMIX). Covariates included a time trend, day of week, temp., and humidity. Lags of 0 to 3 days used, as well as 4-day moving average.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly.	Lag 0, PM_{10}: Cough OR = 1.00 (0.87, 1.16) 4 day ave, PM_{10} Cough OR = 1.58 (0.87, 2.83) Lag 0, $PM_{2.5}$ Cough OR = 1.04 (0.88, 1.23) 4 day ave., $PM_{2.5}$ Cough OR = 2.01 (1.04, 3.89)
Keles et al. (1999) Istanbul, Turkey Nov. 1996 to Jan. 1997. TSP levels ranged from annual mean of 22 $\mu g/m^3$ in unpolluted area to 148.8 $\mu g/m^3$ in polluted area.	Symptoms of rhinitis and atopic status were evaluated in 386 students grades 9 and 10 using statistical package for the social sciences, Fisher tests, and multiple regression model as Spearman's coefficient of correlation.	No difference found for atopic status in children living in area with different air pollution levels.	—
Australia/New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured.	Study of 40 subjects aged over 55 yr, with COPD living in Christchurch, New Zealand during winter 1994. Subjects completed diaries twice daily. Poisson regression model used to analyze symptom data.	NO_2 was associated with increased bronchodilator use.	PM_{10} was associated with increased nighttime chest symptoms.
Asia			
Awasthi et al. (1996) India Suspended particulate matter, SO_2, nitrates, coal, wood, PM and kerosene measured.	A cohort of 664 preschool children studied for two weeks each in northern India. Ordinary least squares was used to relate a respiratory symptom complex pollutants.	A significant regression coefficient between PM and symptoms was found	—

statistically significant. Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999), used $PM_{10-2.5}$ as a coarse-mode (CM) particulate measure. Schwartz and Neas (2000) found that CM was significantly related to cough. Tiittanen found that one day lag of CM was related to morning PEF, but there was no effect on evening PEF. Neas et al. found no effects of CM on PEF.

6.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

6.3.3.2.1 Summary of the 1996 Particulate Matter Air Quality Criteria Document Key Findings

In the 1996 PM AQCD, the available respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a similar type of respiratory symptom questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with the highest particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

Interpretation of such studies requires caution in light of the usual difficulties ascribed to cross sectional studies. That is, evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient, but it was impossible to separate out effects of PM and any other factors or pollutants having the same gradient.

Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from airborne particle pollution indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study did find

significant associations of FEV_1 or FVC effects in U.S. and Canadian children with both acidic particles and other fine PM indicators. Overall, the available studies provided only limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.). However, it was noted that cross sectional studies require very large sample sizes to detect differences because they cannot eliminate person to person variation, which is much larger than the within person variation. Thus, lack of statistical significance cannot be taken as proof of no effect.

6.3.3.2.2 New Studies of Long-Term Particulate Matter Exposure Respiratory Effects

Numerous studies have been published since 1996 which evaluate effects of long-term PM exposure on lung function and respiratory illness, as summarized in Table 6-23. The new studies examining PM_{10} and $PM_{2.5}$ in the United States include McConnell et al. (1999), Abbey et al. (1998), Berglund et al. (1999), Peters et al. (1999a,b), and Gauderman et al. (2000), which all examined effects in California cohorts but produced inconsistent results. Probably most notable among these California study results, are those of McConnell et al. (1999) indicating that, as PM_{10} increased across communities, a corresponding increase in bronchitis risk per interquartile range occurred, results consistent with those reported by Dockery et al. (1996), although the high correlation of PM_{10}, acid, and NO_2 precludes clear attribution of the McConnell et al. bronchitis effects specifically to PM alone.

As for other non-U.S. studies, particularly interesting results were obtained by Leonardi et al. (2000) as part of the Central European Air Quality and Respiratory Health (CESAR) study. Blood and serum samples were collected from school children aged 9-11 yrs. in each of 17 communities in Central Europe (N = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations increased across the cities. Regression slopes, adjusted for confounder effects, were largest and statistically significant for $PM_{2.5}$, but small and non-significant for $PM_{10-2.5}$. A similar positive relationship was found between IgG concentration in serum and $PM_{2.5}$ gradient, but not for PM_{10} or $PM_{10-2.5}$. These results tend to suggest a PM effect on immune function more strongly due to ambient fine particle than coarse particle exposure.

Other non-U.S. studies of interest examined other PM measures such as TSP and BS in European countries. In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted twice (with the same 971 children included in both surveys). TSP levels

TABLE 6-23. LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States			
Abbey et al. (1998) California Communities 20 year exposure to respirable particulates, suspended sulfates, ozone, and PM_{10}.	Sex specific multiple linear regressions were used to relate lung function measures to various pollutants in long-running cohort study of Seven Day Adventists (ASHMOG Study).	Sulfates were associated with decreases in FEV.	Frequency of days where PM_{10} > 100 $\mu g/m^3$ associated with FEV decrement in males whose parents had asthma, bronchitis, emphysema, or hay fever. No effects seen in other subgroups.
Berglund et al.. (1999) California communities	Cohort study of Seventh Day Adventists. Multivariate logistic regression analysis of risk factors (e.g., PM) for chronic airway disease in elderly non-smokers, using pulmonary function test and respiratory symptom data.	Significant risk factors identified: childhood respiratory illness, reported ETS exposure, age, sex and parental history.	For $PM_{10} > 100 \mu g/m^3$, 42 d/yr: RR = −1.09 CT (0.92, 1.30) for obstructive disease determined by pulmonary function tests.
Peters et al. (1999a,b) 12 demographically similar communities in So. California. O_3, PM acids, and NO_2 evaluated.	Stepwise logistic regression was used to relate prevalence rates for symptoms to community-specific ambient pollutants after adjustment for race, sex, asthma, body mass, hay fever, and membership in an insurance plan.	Wheeze prevalence was associated with both acid and NO_2.	No significant relationships were found between PM_{10} and symptoms.
Gauderman et al. (2000) 12 So. California communities 1993 to 1997 Pollutants: O_3, NO_2, PM_{10}, and $PM_{2.5}$. PM_{10} levels ranged from 16.1 to 67.6 $\mu g/m^3$ across the communities.	Studies of lung function growth of 3035 children in 12 communities within 200-mile radius of Los Angeles during 1993 to 1997. Cohorts of fourth, seventh, and tenth-graders studied. By grade cohort, a sequence of linear regression models were used to determine over the 4yr of follow-up, if average lung function growth rate of children was associated with average pollutant levels. Adjustment were made for height, weight, body mass index, height by age interaction, report of asthma activity or smoking. Two-pollutant models also used.	Lung growth rate for children in most polluted community, as compared to least polluted, was estimated to result in cumulative reduction of 3.4% in FEV_1 and 5.0% in MMEF over 4-yr study period. Estimated deficits mostly larger for children spending more time outdoors. Due to the high correlation in concentrations across communities, not able to separate effects of each pollutant. No sig. associations seen with O_3.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates were: −0.85% for PM_{10} (p = 0.026); −0.64% for $PM_{2.5}$ (p = 0.052); −0.90% for $PM_{10-2.5}$ (p = 0.030); −0.77% for NO_2 (p = 0.019); and −0.73% for inorganic acid vapor (p = 0.042).

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
McConnell et al. (1999) 12 Southern California communities 1994 air monitoring data. PM_{10} (mean 34.8; range 13.0 - 70.7 $\mu g/m^3$). $PM_{2.5}$ (yearly mean 2 week averaged mean 15.3 $\mu g/m^3$; range 6.7 - 31.5 $\mu g/m^3$).	Cross sectional study of 3,676 school children whose parents completed questionnaires in 1993 that characterized the children's history of respiratory illness. Three groups examined: (1) history of asthma; (2) wheezing but no asthma; and (3) no history of asthma or wheezing. Logistic regression model used to analyze PM, O_3, NO_2, acid vapor effects. This study also described in Peters et al. (1999b,c).	Positive association between air pollution and bronchitis and phlegm observed only among children with asthma. As PM_{10} increased across communities, a corresponding increase in risk of bronchitis per interquartile range occurred. Strongest association with phlegm was for NO_2. Because of high correlation of PM air pollution, NO_2, and acid, not possible to distinguish clearly which most likely responsible for effects.	PM_{10} Asthma Bronchitis 1.4 CI (1.1 – 1.8) Phlegm 2.1 (1.4 – 3.3) Cough 1.1 (10.8 – 1.7) No Asthma / No Wheeze Bronchitis 0.7 (0.4 – 1.0) Phlegm 0.8 (0.6 – 1.3) Cough 0.9 (0.7 – 1.2)
Dockery et al. (1996) 24 communities in the U. S. and Canada.	Respiratory health effects among 13,369 white children aged 8 to 12 yrs analyzed in relation to PM indices. Two-stage logistic regression model used to adjust for gender, history of allergies, parental asthma, parental education, smoking in home.	Although bronchitis endpoint was significantly related to fine PM sulfates, no endpoints were related to PM_{10} levels.	—
Raizenne et al. (1996) 24 communities in the U.S. and Canada Pollutants measured for at least one year prior to lung function tests: PM_{10}, $PM_{2.1}$, particle strong acidity, O_3, NO_2, and SO_2.	Cross-sectional study of lung function. City specific adjusted means for FEV and FVC calculated by regressing the natural logarithm of the measure on sex, ln height, and ln age. These adjusted means were then regressed on the annual pollutant means for each city.	PM measures (e.g., particle strong acidity) associated with FEV and FVC decrement.	—

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe			
Ackermann-Liebrich et al. (1997) Eight Swiss regions Pollutants: SO_2, NO_2, TSP, O_3, and PM_{10}.	Long-term effects of air pollution studied in cross-sectional population-based sample of adults aged 18 to 60 yrs. Random sample of 2,500 adults in each region drawn from registries of local inhabitants. Natural logarithms of FVC and FEV_1 regressed against natural logarithms of height, weight, age, gender, atopic status, and pollutant variables.	Significant and consistent effects on FVC and FEV were found for PM_{10}, NO_2 and SO_2.	Estimated regression coefficient for PM_{10} versus FVC = −0.035 (95% CI −0.041, −0.028). Corresponding value for FEV_1 −0.016 (95% CI −0.023 to −0.01). Thus, 10 $\mu g/m^3$ PM_{10} increase estimated to lead to estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.
Braun-Fahrländer et al. (1997) 10 Swiss communities Pollutants: PM_{10}, NO_2, SO_2, and O_3.	Impacts of long-term air pollution exposure on respiratory symptoms and illnesses were evaluated in cross-sectional study of Swiss school children, (aged 6 to 15 years). Symptoms analyzed using a logistic regression model including covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others.	Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The colinearity of the pollutants prevented any causal separation.	PM_{10} Chronic cough OR 11.4 (2.8, 45.5) Bronchitis OR 23.2 (2.8, 45.5) Wheeze OR 1.41 (0.55, 3.58)
Zemp et al. (1999) 8 study sites in Switzerland. Pollutants: TSP, PM_{10}, SO_2, NO_2, and O_3.	Logistic regression analysis of associations between prevalences of respiratory symptoms in random sample of adults and air pollution. Regressions adjusted for age, BMI, gender, parental asthma, education, and foreign citizenship.	Chronic cough and chronic phlegm and breathlessness were related to TSP, PM_{10} and NO_2.	Chronic cough, chronic phlegm and breathlessness were related to PM_{10}, and TSP.

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Heinrich et al. (1999) Bitterfeld, Zerbstand Hettstedt areas of former East Germany, During Sept. 1992 to July 1993 TSP ranged from 44 to 65 $\mu g/m^3$; PM_{10} measured October 1993 - March 1994 ranged from 33 to 40; and BS ranged from 26 to 42 $\mu g/m^3$	Parents of 2470 school children (5-14 yr) completed respiratory health questionnaire. Children excluded from analysis if had lived < 2 years in their current home, yielding an analysis group of 2,335 children. Outcomes studied: physician diagnosis for asthma, bronchitis, symptom, bronchial reactivity, skin prick test, specific IgE. Multiple logistic regression analyses examined regional effects.	Controlling for medical, socio-demographic, and indoor factors, children in more polluted area had circa 50% increase for bronchitic symptoms and physician-diagnosed allergies compared to control area and circa twice the respiratory symptoms (wheeze, shortness of breath and cough). Pulmonary function tests suggested slightly increased airway reactivity to cold for children in polluted area.	No single pollutant could be separated out as being responsible for poor respiratory health.
Heinrich et al. (2000) Three areas of former E. Germany Pollution measures: SO_2, TSP, and some limited PM_{10} data. TSP decreased from 65, 48, and 44 $\mu g/m^3$ to 43, 39, and 36 $\mu g/m^3$ in the three areas	Cross-sectional study of children (5-14 yr). Survey conducted twice, in 1992-1993 and 1995-1996; 2335 children surveyed in first round, and 2536 in second round. Only 971 children appeared in both surveys. The frequency of bronchitis, otitus media, frequent colds, febrile infections studied. Because changes measured over time in same areas, covariate adjustments not necessary.	PM and SO_2 levels both decreased in the same areas; so results are confounded.	The prevalence of all respiratory symptoms decreased significantly in all three areas over time.
Krämer et al. (1999) Six East and West Germany communities (Leipzig, Halle, Maddeburg, Altmark, Duisburg, Borken) Between 1991 and 1995 TSP levels in six communities ranged from 46 to 102 $\mu g/m^3$. Each East Germany community had decrease in TSP between 1991 and 1995.	The study assessed relationship between TSP and airway disease and allergies by parental questionnaires in yearly surveys of children (5-8 yr) between February and May. The questions included pneumonia, bronchitis ever diagnosed by physician, number of colds, frequent cough, allergic symptoms. In all, 19,090 children participated. Average response was 87%. Analyses were conducted on 14,144 children for whom information on all covariates were available. Variables included gender; parent education, heating fuel, ETS. Logistic regression used, transformed into OR.	TSP and SO_2 simultaneously included in the model. Bronchitis ever diagnosed showed a significant association. A decrease in raw percentage was seen between the start of the study and the end for bronchitis. Bronchitis seemed to be associated only with TSP in spite of huge differences in mean SO_2 levels.	Bronchitis ever diagnosed TSP per 50 $\mu g/m^3$ OR 1.63 CI (1.37 – 1.93) Halle (East) TSP $\mu g/m^3$ / % Bronchitis 1991 102 / 60.5 1992 73 / 54.7 1993 62 / 49.6 1994 52 / 50.4 1995 46 / 51.9

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Baldi et al. (1999) 24 areas of seven French towns 1974-1976 Pollutants: TSP, BS, and SO_2, NO_4 3-year average TSP-mean annual values ranging 45-243 $\mu g/m^3$.	Reanalysis of Pollution Atmospheric of Affection Respiratory Chroniques (PAARC) survey data to search for relationships between mean annual air pollutant levels and prevalence of asthma in 1291 adult (25-59 yrs) and 195 children (5-9 yrs) asthmatics. Random effects logistic regression model used and included age, smoking, and education level in the final model.	Only an association between SO_2 and asthma in adults observed. No other pollutant was associated. Nor was relationship with children seen. Meteorological variables and O_3 not evaluated.	For a 50 $\mu g/m^3$ increase in TSP Adult asthma prevalence OR 1.01 CI 0.92–1.11 SO_2 Adult asthma prevalence OR 1.26 CI 1.04–1.53
Zeghnoun et al. (1999) La Havre, France during 1993 and 1996. Daily mean BS levels measured in three stations ranged 12 - 14 $\mu g/m^3$.	Respiratory drug sales for mucolytic and anticough medications (most prescribed by a physician) were evaluated versus BS, SO_2, and NO_2 levels. An autoregressive Poisson regression model permitting overdispersion control was used in the analysis.	Respiratory drug sales associated with BS, NO_2, and SO_2 levels. Both an early response (0 to 3 day lag) and a longer one (lags of 6 and 9 days) were associated.	—
Leonardi et al. (2000) 17 cities of Central Europe Yearly average concentration (Nov. 1995 - Oct. 1996) across the 17 study areas varied from 41 to 96 $\mu g/m^3$ for PM_{10}, from 29 to 67 $\mu g/m^3$ for $PM_{2.5}$, and from 12 to 38 $\mu g/m^3$ for $PM_{10-2.5}$.	Cross-sectional study collected blood and serum samples from 10-61 school children aged 9 to 11 in each community 11 April to 10 May 1996. Blood and serum samples examined for parameters in relation to PM. Final analysis group of 366 examined for peripheral lymphocyte type and total immunoglobulin classes. Association between PM and each log transformed biomarker studied by linear regression in two-stage model with adjustment for confounding factors (age, gender, number of smokers in house, laboratory, and recent respiratory illness). This survey was conducted within the frame work of the Central European study of Air Quality and Respiratory Health (CEASAR) study.	Number of lymphocytes (B, $CD4^+$, $CD8^d$, and NK) increased with increasing concentration of PM adjusted for confounders. The adjusted regression slopes are largest and statistically significant for $PM_{2.5}$ as compared to PM_{10}, but small and non statistically signif. for $PM_{10-2.5}$. Positive relationship found between concentration of IgG in serum and $PM_{2.5}$ but not for PM_{10} or $PM_{10-2.5}$. Two other models produced similar outcomes: a multi-level linear regression model and an ordinal logistic regression model.	Adjusted Regression slope $PM_{2.5}$ $CD4^+$ 80% 95% CI (34; 143) $p < 0.001$ Total IgG 24% 95% CI (2; 52) p 0.034

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Turnovska and Kostiranev (1999) Dimitrovgrad, Bulgaria, May 1996 Total suspended particulate matter (TSPM) mean levels were 520 ± I 61 $\mu g/m^3$ in 1986 and 187 ± 9 $\mu g/m^3$ in 1996. SO_2, H_2S, and NO_2 also measured.	Respiratory function of 97 schoolchildren (mean age 10.4 ± 0.6 yr) measured in May 1996 as a sample of 12% of all four-graders in Dimitrovgrad. The obtained results were compared with reference values for Bulgarian children aged 7 to 14 yr, calculated in the same laboratory in 1986 and published (Gerginova et al., 1989; Kostiranev et al., 1994). Variation analysis technique were used to treat the data.	Vital capacity and FEV_1 were significantly lower (mean value. = 88.54% and 82.5% respectfully) comparing values between 1986 and 1996. TSPM pollution had decreased by 2.74 times to levels still higher than Bulgarian and WHO standards.	—
Jedrychowski et al. (1999) In Krakow, Poland in 1995 and 1997 Spacial distributions for BS and SO_2 derived from network of 17 air monitoring stations. BS 52.6 $\mu g/m$ ± 53.98 in high area and 33.23 ± 35.99 in low area.	Effects on lung function growth studied in preadolescent children. Lung function growth rate measured by gain in FVC and FEV_1 and occurrence of slow lung function growth (SLFG) over the 2 yr period defined as lowest quintile of the distribution of a given test in gender group. 1129 children age 9 participated in first year and 1001 in follow-up 2 years later. ATS standard questionnaire and PFT methods used. Initially univariate descriptive statistics of pulmonary function indices and SLFG were established, followed by multivariate linear regression analyses including gender, ETS, parental education, home heating system and mold. SO_2 also analyzed.	Statistically significant negative association between air pollution level and lung function growth (FVC and FEV_1) over the follow up in both gender groups. SLFG was significantly higher in the more polluted areas only among boys. In girls there was consistency in the direction of the effect, but not stat. significant. Could not separate BS and SO_2 effects on lung function growth. Excluding asthma subjects subsample (size 917) provided similar results.	Boys SLFG (FVC) OR = 2.15 (CI 1.25 – 3.69) SLFG (FEV_1) OR = 1.90 (CI 1.12 – 3.25) Girls FVC OR = 1.50 (CI 0.84 – 2.68) FEV1 OR = 1.39 (CI 0.78 – 2.44)
Jedrychowski and Flak (1998) In Kracow Poland, in 1991-1995 Daily 24 h concentration of SPM (black smoke) measured at 17 air monitoring stations. High areas had 52.6 $\mu g/m^3$ mean compared to low areas at 33.2 $\mu g/m^3$.	Respiratory health survey of 1,129 school children (aged 9 yr). Respiratory outcomes included chronic cough, chronic phlegm, wheezing, difficulty breathing and asthma. Multi-variable logistic regression used to calculate prevalence OR for symptoms adjusted for potential confounding.	The comparison of adjusted effect estimates revealed chronic phlegm as unique symptom related neither to allergy nor to indoor variable but was associated significantly with outdoor air pollution category (APL). No potential confounding variable had major effect.	It was not possible to assess separately the contribution of the different sources of air pollutants to the occurrence of respiratory symptoms. ETS and household heating (coal vs. gas vs. central heating) appeared to be of minimal importance.

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Latin America			
Calderón-Garcidueñas et al. (2000) Southwest Metropolitan Mexico City (SWMMC) winter of 1997 and summer of 1998.	Study of 59 SWMMC children to evaluate relationship between exposure to ambient pollutants (O_3 and PM_{10}) and chest x-ray abnormalities. Fishers exact test used to determine significance in a 2x2 task between hyperinflation and exposure to SWMMC pollutant atmosphere and to control, low-pollutant city atmosphere.	Bilateral symmetric mild lung hyperinflation was significantly associated with exposure to the SWMMC air pollution mixture ($p>0.0004$). This raises concern for development of chronic disease outcome in developing lungs.	—
Australia			
Lewis et al. (1998) Summary measures of PM_{10} and SO_2 estimated for each of 10 areas in steel cities of New South Wales.	Cross-sectional survey of children's health and home environment between Oct 1993 and Dec 1993 evaluated frequency of respiratory symptoms (night cough, chest colds, wheeze, and diagnosed asthma). Covariates included parental education and smoking, unflued gas heating, indoor cats, age, sex, and maternal allergy. Logistic regression analysis used allowing for clustering by GEE methods.	SO_2 was not related to differences in symptom rates, but adult indoor smoking was.	Night cough OR 1.34 (1.18, 1.53) Chest colds OR 1.43 (1.12, 1.82) Wheeze OR 1.13 (0.93, 1.38)
Asia			
Wong et al. (1999) Hong Kong, 1989 to 1991 Sulfate concentrations in respirable particles fell by 38% after implementing legislation reducing fuel sulfur levels.	3405 nonsmoking, women (mean age 36.5 yr; SD ± 3.0) in a polluted district and a less polluted district were studied for six respiratory symptoms via self-completed questionnaires. Binary latent variable modeling used.	Comparison was by district; no PM measurements reported. Results suggest control regulation may have had some (but not statistically significant) impact.	—

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Wang et al. (1999) Kaohsiung and Panting, Taiwan October 1995 to June 1996 TSP measured at 11 stations, PM_{10} at 16 stations. PM_{10} annual mean ranged from 19.4 to 112.81 $\mu g/m^3$ (median = 91.00 $\mu g/m^3$) TSP ranged from 112.81 to 237.82 $\mu g/m^3$ (median = 181.00). CO, NO_2, SO_2, hydrocarbons and O_3 also measured.	Relationship between asthma and air pollution examined in cross-sectional study among 165,173 high school students (11- 16 yr). Evaluated wheeze, cough and asthma diagnosed by doctor. Video determined if student displayed signs of asthma. Only 155,283 students met all requirements for study analyses and, of these, 117,080 were covered by air monitoring stations. Multiple logistic regression analysis used to determine independent effects of risk factors for asthma after adjusting for age, gender, ETS, parents education, area resident, and home incense use.	Asthma significantly related to high levels of TSP, NO_2, CO, O_3 and airborne dust. However PM_{10} and SO_2 not associated with asthma. The lifetime prevalence of asthma was 18.5% and the 1-year prevalence was 12.5%.	Adjusted OR PM_{10} 1.00 (0.96–1.05) TSP 1.29 (1.24–1.34)
Guo et al. (1999) Taiwan, October 1955 and May 1996 PM_{10} measured by beta-gauge. Also monitoring for SO_2, NO_2, O_3, CO.	Study of asthma prevalence and air pollutants. Survey for respiratory disease and symptoms in middle-school students age < 13 to ≥ 15 yr. Total of 1,018,031 (89.3%) students and their parents responded satisfactorily to the questionnaire. Schools located with 2 km of 55 monitoring sites. Logistic regression analysis conducted, controlling for age, hx eczema, parents education.	Because of close correlation among air pollutants, not possible to separate effects of individual ones. Factor analysis used to group into two classes (traffic-related and stationary fossil fuel-related). No association found between lifetime asthma prevalence and nontraffic related air pollutants (SO_2, PM_{10}).	—
Wang et al. (1999) Chongquing, China April to July 1995 Dichot samplers used to measure $PM_{2.5}$. Mean $PM_{2.5}$ level high in both urban (143 $\mu g/m^3$) and suburban (139 $\mu g/m^3$) area. SO_2 also measured	Study examined relationship between PFT and air pollution. Pulmonary function testing performed on 1,075 adults (35 - 60 yr) who had never smoked and did not use coal stoves for cooking. Generalized additive model used to estimate difference, between two areas for FEV_1, FVC, and FEV_1/FVC% with adjustment for confounding factors (gender; age, height, education, passive smoking, and occupational exposures).	Mean SO_2 concentration in the urban and suburban area highly statistically significant different (213 and 103 $\mu g/m^3$ respectfully). $PM_{2.5}$ difference was small, while levels high in both areas. Estimated effects on FEV1 statistically different between the two areas.	Difference between urban and suburban area excluding occupational exposures: $\underline{FEV_1}$ B – 119.79 SE 28.17 t – 4.25 p < 0.01 $\underline{FVC}$ B – 57.89 SE 30.80 t – 1.88 p < 0.05

TABLE 6-23 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE: RESPIRATORY SYMPTOM, LUNG FUNCTION, AND BIOMARKER EFFECTS

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Zhang et al. (1999) 4 areas of 3 Chinese Cities (1985 - 1988) TSP levels ranged from an annual arithmetic mean 137 $\mu g/m^3$ to 1250 $\mu g/m^3$ using gravimetric methods.	A pilot study of 4 districts of 3 Chinese cities in for the years 1985-1988, TSP levels and respiratory health outcomes studied. 4,108 adults (< 49 yrs) examined by questionnaires for couth, phlegm, wheeze, asthma, and bronchitis. Categorical logistic—regression model used to calculate odds ratio. SO_2 and NO_2 were also examined. Other potential confounding factors (age, education level, indoor ventilation, and occupation) examined in the multiple logistic regression model.	Results suggested that the OR's for cough, phlegm, persistent cough and phlegm and wheeze increased as outdoor TSP concentrations did. .	Wheeze produced largest OR for both mothers and fathers in all locations.
Qian et al. (2000) 4 China cities The 4 year average PM means were 191, 296, 406, and 1067 $\mu g/m^3$. SO_2 and NO_2 measurements were also available.	Pilot cross-sectional survey of 2789 elementary school children in four Chinese communities chosen for their PM gradient. Frequency of respiratory symptoms (cough, phlegm, wheeze, and diagnosed asthma, bronchitis, or pneumonia) assessed by questionnaire. Covariates included parental occupation, education and smoking. The analysis used logistic regression, controlling for age, sex, parental smoking, use of coal in home, and home ventilation.	Results not directly related to pollution levels, but symptom rates were highest in highest pollution area for cough, phlegm, hospitalization for respiratory disease, bronchitis, and pneumonia. No gradient correlating with pollution levels found for the three lower exposure communities.	—

decreased between surveys as did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer et al. (1999) reported a study in six East and West Germany communities, which found yearly decreasing TSP levels to be related to ever-diagnosed bronchitis from 1991-1995. Lastly, Jedrychowski et al. (1999) reported an association between both BS and SO_2 levels in various areas of Krakow, Poland, and slowed lung function growth (FVC and FEV_1).

6.3.3.2.3 Summary of Long-Term Particulate Matter Exposure Respiratory Effects

The methodology used in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to PM) while others reported no significant results. The cross-sectional studies are often confounded, in part, by unexplained differences between geographic regions. The studies that looked for a time trend are also confounded by other conditions that were changing over time. Probably the most credible cross-sectional study remains that described by Dockery et al. (1996) and Raizenne et al. (1996). This study, reported in the previous 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle strong acidity. Whereas most studies included only two to six communities, this study included 24 communities. The effective sample size for a cross sectional analysis is the number of communities, so that six or fewer communities allow many fewer degrees of freedom by which to test hypotheses about various pollutant effects.

Newly available studies since the 1996 PM AQCD, overall, provide evidence consistent with the findings from the above 24-City Study. Most notably several U.S. and European studies report associations between PM measures and bronchitis rates and/or lung function decrements or slowed lung function growth. One also provided evidence of PM effects on immune function in school children, with stronger associations for fine particle indicators than for ambient coarse particles.

6.4 INTERPRETIVE ASSESSMENT OF EPIDEMIOLOGIC DATABASE ON HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER

6.4.1 Introduction

As noted at the outset of this chapter, numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely key contributor to mortality and morbidity effects observed epidemiologically to be associated with ambient air pollution exposures. Since preparation of the last previous PM AQCD in 1996, the epidemiologic evidence concerning ambient PM-related health effects has expanded greatly. The most important types of additions to the database beyond that assessed in the 1996 PM AQCD, as evaluated above are:

- New multi-city studies on a variety of endpoints providing more precise effects estimates than most smaller-scale individual city studies;
- More studies of various health endpoints using ambient PM_{10} and/or closely related mass concentration indices (e.g., PM_{13} and PM_{7}), which substantially lessen the need to rely on non-gravimetric indices (e.g., BS or COH);
- New studies on a variety of endpoints for which information on the ambient PM coarse fraction ($PM_{(10-2.5)}$), the ambient fine-particle fraction ($PM_{2.5}$), and even ambient ultrafine particle mass measures ($PM_{0.1}$ and smaller) were observed and/or estimated from site-specific calibrations;
- A few new studies in which the relationship of some health endpoints to ambient particle number concentrations were evaluated;
- Many new studies which evaluated the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants in the model;
- Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures including PM components, based on empirical combinations (e.g., factor analysis) or source profiles;
- Numerous new studies of cardiovascular endpoints, with particular emphasis on assessment of cardiovascular risk factors as well as symptoms;
- Additional new studies on asthma and other respiratory conditions potentially exacerbated by PM exposure;
- New studies of infants and children as a potentially susceptible population.

The vast majority of the new PM epidemiology studies, both of short-term and long-term PM exposure, continue to show statistically significant excess mortality risk and/or morbidity

endpoints to be associated with ambient PM indexed by a variety of ambient community monitoring methods in many U.S. cities and elsewhere.

Several methodological issues, discussed in the 1996 PM AQCD, are still of much importance in assessing and interpreting the overall PM epidemiology database and its implications for estimating risks associated with exposure to ambient PM concentrations in the United States. The fundamental issue essentially subsuming all of the other modeling issues is the selection of an appropriate statistical model in the absence of any strong prior hypotheses or information about underlying relationships between health outcomes and ambient PM, other copollutants, or other important factors such as seasonal variations and/or demographic characteristics of study populations. These critical methodological issues are: (1) potential confounding of PM effects by co-pollutants (especially major gaseous pollutants such as O_3, CO, NO_2, SO_2); (2) the attribution of PM effects to specific PM components (e.g., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafines, sulfates, metals, etc.) or source-oriented indicators (motor vehicle emissions, vegetative burning, etc.); (3) the temporal relationship between exposure and effect (lags, mortality displacement, etc.); (4) the general shape of exposure-response relationship(s) between PM and/or other pollutants and observed health effects (e.g., potential indications of thresholds for PM effects); and (5) the consequences of measurement error. In addition, the newer multi-city study results, e.g, the NMMAPS analysis of the 90 largest U.S. cities (Samet et al., 2000a,b) show evidence of more geographical heterogeneity in the estimated PM risks across cities and regions than had been seen in the studies assessed in the 1996 PM AQCD. Thus, the issue of geographical heterogeneity in PM effects estimates also warrants further evaluation here.

Assessing the above issue(s) in relation to the PM epidemiology data base remains quite a challenge. The basic issue is that there are an extremely large number of possible models, any of which may turn out to give the best statistical "fit" of a given set of data, and only some of which can be dismissed *a priori* as biologically or physically illogical or impossible, except that putative cause clearly cannot follow effect in time. Most of these models are fitted in a stepwise manner, first by removing effects known almost certainly to be present, including general changes in death rates or hospital admissions rates over long time intervals and across season, by day of week, and attributable to weather and climate. Many of the temporal and weather variable models have been fitted to data using semi-parametric methods such as spline functions or local regression smoothers (loess). The goodness of fit of these base models has been evaluated by

criteria suitable for generalized linear models with Poisson or hyper-Poisson responses (number of events) with a log link function, particularly the Akaike Information Criterion (AIC) and the more conservative Bayes or Schwarz information criterion (BIC), that adjust for the number of parameters estimated from the data. The Poisson over-dispersion index and the auto-correlation of residuals are also often used. Once a best-fitting baseline model is selected, the specification of variables in the base model is often held fixed while a better model is selected using one or more PM indices (e.g., fine and coarse) and/or one or more gaseous co-pollutants. In general, one would expect that the best-fitting models with PM would be models with the largest and most significant PM indices. If PM effects are confounded with those of other pollutants, then a large positive estimated PM effect might be associated with a non-biological estimated negative effect for one or more other criteria pollutants, as found by some analyses for NO_2 in a joint pollutant model (most likely a statistical artifact). Also, if high correlations between PM and one or more gaseous pollutants emitted from a common source (e.g., motor vehicles) exist in a given area, then disentangling their relative individual partial contributions to observed health effects associations becomes very difficult. Unfortunately, there have been very few attempts at broad, systematic investigations of the model selection issue and little reporting in published reports of goodness-of-fit criteria among competing models that provide a better basis by which to better assess or compare models.

Given the now extremely large number of published epidemiologic studies of ambient PM associations with health effects in human populations and the considerably wide diversity in applications of even similar statistical approaches (e.g., "time-series analyses" for short-term PM exposure effects), it is neither feasible nor useful here to try to evaluate the methodological soundness of every individual study. Rather, two feasible approaches are likely to yield useful evaluative information: (1) an overall characterization of evident general commonalities (or notable marked differences) among findings from across the body of studies dealing with particular PM exposure indices and types of health outcomes; and (2) more thorough, critical assessment of key newly published multi-city analyses of PM effects, given that greater scientific weight is likely ascribable to their results than those of smaller sized studies (often of individual cities) yielding presumably less precise effects estimates.

6.4.2 New Assessments of Confounding

As discussed previously, the issue of potential confounding by weather was extensively examined in two studies as reviewed in the 1996 PM AQCD, and was considered essentially resolved. Potential confounding by co-pollutants, however, was nevertheless still suggested by several studies reviewed in the 1996 AQCD. Therefore, discussion of confounding in this section is focused on potential confounding among PM and other major gaseous air pollutants as evaluated in newly available studies.

6.4.2.1 Assessment of Copollutant Confounding

Analyses of one city's data by different researchers may produce conflicting results. For example, Moolgavkar and Luebeck (1996) and Samet et al. (1996) or Kelsall et al. (1997), (which presented essentially the same results) analyzed Philadelphia mortality data for nearly the same period (1973-1988 and 1974-1988, respectively), but produced somewhat different results and interpretations. The notable differences in findings in these studies were: (a) NO_2 in the Samet et al.'s study was mostly negatively associated (except summer) with mortality, while in the Moolgavkar-Luebeck study, NO_2 was mostly positively associated (except winter); and (b) O_3 in Samet et al.'s study was positively associated with mortality across seasons (weakest in the summer), while in the Moolgavkar-Luebeck study, O_3 was positively associated with mortality only in the summer. The differences may have been due to the difference in the optimum lags chosen for pollutants (in Samet et al., concurrent day levels were used for all the pollutants except CO; whereas, in the Moolgavkar-Luebeck study, one-day lag was used for all pollutants except NO_2). Moolgavkar-Luebeck concluded that "..it is not possible with the present evidence to show a convincing correlation between particulate air pollution and mortality", while Samet's group concluded "...These analyses confirm the association between TSP and mortality found in previous studies in Philadelphia and the association is robust to consideration of other pollutants".

Such discrepancies could, in part, result from instability of regression coefficients due to collinearity of co-pollutants, as well as model specification choice. The collinearity problem may be further complicated by different seasonal patterns of concentrations for each pollutant, which also vary from city to city. Thus, evaluation of apparently inconsistent results from one or a few cities analyzed using different model specifications, without quantitative information on city

specific characteristics, is unlikely to yield useful information by which to resolve the issue of confounding. By analyzing multiple cities' data, a more consistent pattern may emerge, although differences in approach may still result in inconsistent multi-city results by different researchers. Several studies have examined the issue of confounding using multi-city analyses. Basic descriptions of these studies were provided in earlier text and in Table 6-1; some of their more salient results regarding confounding by co-pollutants are discussed below.

Samet and co-workers (2000a,b) reported PM_{10} RR estimates for PM_{10}-only and multiple pollutant models that also included O_3 as the only gaseous pollutant or O_3 and another gaseous pollutant, in both 20-cities analysis and 90-cities analysis. The effects of adding gaseous pollutants in the model on PM_{10} coefficients were similar in these two data sets, in that adding O_3 did not change PM_{10} coefficients, but additional inclusions of another gaseous pollutant reduced PM_{10} coefficients somewhat. Figure 6-10 shows the posterior probability results for the 90-cities analysis. It can be seen that the PM_{10} coefficient reduced from about 0.47 to 0.35 when another gaseous pollutant was included in the model besides O_3. Importantly, however, the posterior probabilities that the overall effects are greater than 0 remain 1.0 in all these models. It should also be noted that the results shown in the figure are for PM_{10} at lag 1 day (of the 0-, 1-, and 2-day lags examined, the 1-day lag was most significant). The lags for the gaseous pollutants included in these models were also apparently 1-day lags. This choice of the same lags seems reasonable, as the air pollution variables are generally highly correlated with no lag. However, using the most significant lags for gaseous pollutants might have produced somewhat different results. That is, even though air pollution variables may be highly correlated, or not, at 0 lag, various health effects possibly due to different pollutants may occur with different lag times.

The HEI Health Committee Review Panel commentary on the NMMAPS analyses stated that an important consideration in assessing the validity of the observed PM_{10} effects is whether they are due to PM_{10} itself or due to another air pollutant that is correlated with PM_{10}. That is, do effects of other pollutants confound the observed PM_{10} effect? The NMMAPS investigators took a commonly used approach to address this issue in the mortality analysis: does the addition of other air pollutant concentrations to the PM_{10} regression models result in any substantial change in the estimated PM_{10} effect? If the PM_{10} effect does not change, the other pollutants presumably have not confounded the observed PM_{10} effect. The Panel identified a few issues related to possible confounding effects by co-pollutants, but concluded that the probable impact of any of

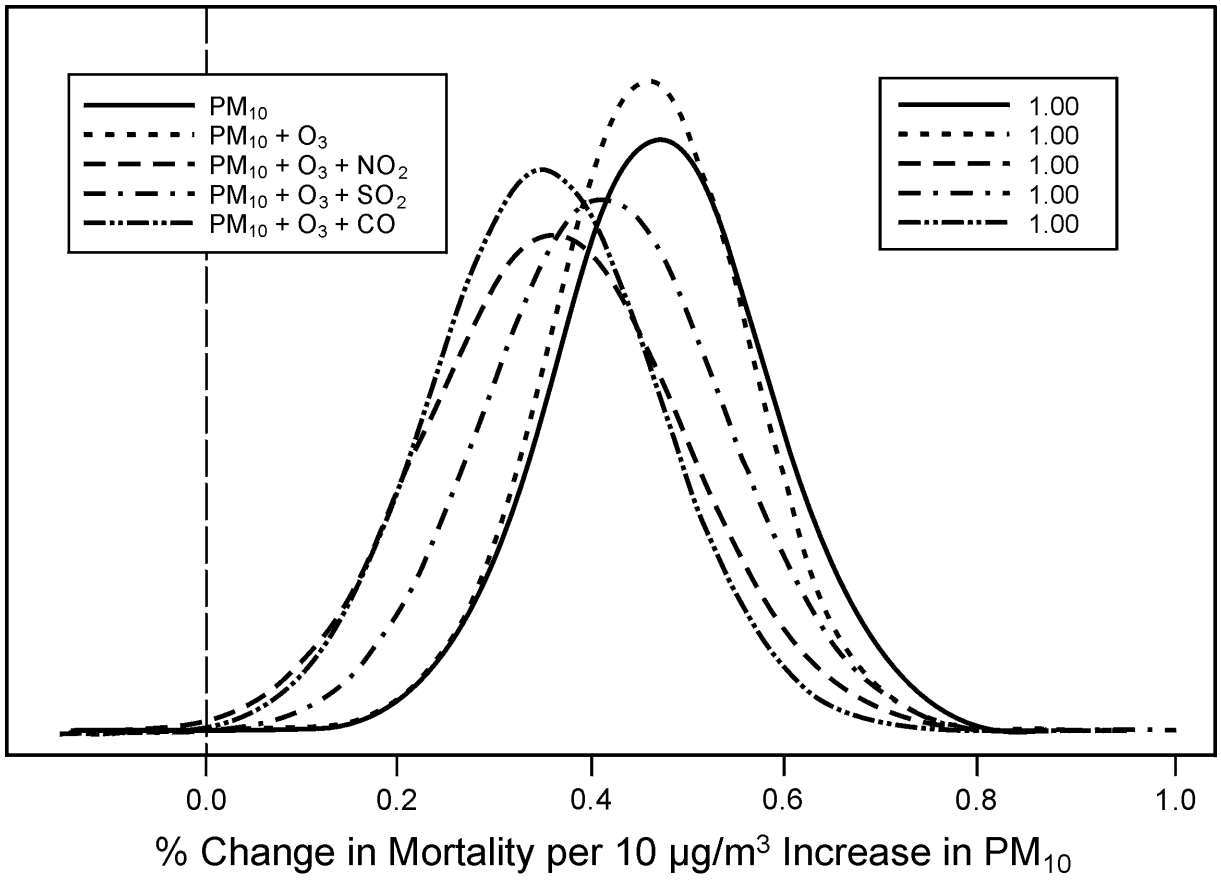

Figure 6-10. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1 with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Samet et al. (2000a,b).

these was not considered to be sufficiently large to alter the observed PM_{10} effect. For example, when the investigators controlled for co-pollutants, they assumed the co-pollutants effect in the model to be linear.

Another consideration is the impact of limiting assessment of the possible confounding effect to the relevant season for pollutants that have seasonal patterns. This assessment is complicated in these data because the seasonal effect of ozone, for example, is assumed to be somewhat different across the cities. Finally, a pollutant (e.g., sulfate or acid aerosols) for which only inadequate data are available in the AIRS database and which, therefore, could not be

analyzed, might be more clearly delineated as responsible for the effects attributed to PM_{10}, per se.

Even given the above considerations, the HEI Review Panel nevertheless agreed that, in the NMMAPS 20 cities analysis of potential copollutant confounding, no convincing evidence was found for PM_{10} effects on mortality being changed by addition of either O_3, SO_2, NO_2, or CO to the models, suggesting that none of the other pollutants is responsible for the observed PM_{10} effects. Subsequent analyses by the investigators, that appear to use similar statistical techniques, controlled for gaseous pollutants in the 90 cities and also did not show a confounding copollutant effects.

In the morbidity analysis, based on assessment of the likelihood of confounding by other pollutants in stage 2 of the modeling for 14 of the NMMAPS cities, there was evidence that the PM_{10} effect on each diagnosis was not confounded, similar to the finding in the mortality analysis (but differences in the approach make it difficult to assess whether morbidity findings are as robust). While the approach used in the morbidity analysis is novel (comparing the PM_{10} regression coefficient with the regression coefficient between PM_{10} and the co-pollutants), the question arises as to the adequacy of statistical power for performing these analyses. Power may be low because the regression is fit to only 14 locations, and in some cases 12 locations, and when the regression coefficients between PM_{10} and the potentially confounding co-pollutants are similar across cities.

The HEI commentary further noted that although NMMAPS focuses on the effects of PM_{10}, examination of the independent effects of other pollutants is also warranted. Effects on daily mortality were found for most of the gaseous pollutants (SO_2 , CO, NO_2) in the 20 cities, although these effects were generally diminished when the model controlled for PM_{10} and other pollutants. In contrast, the PM_{10} effect did not appear to be affected by other pollutants in this model. An effect of each pollutant except ozone on mortality in the 90 cities is shown in the NMMAPS II Report. A relatively strong effect appears to be present for each of those gaseous pollutants in 90 cities in analyses that assess the effect of each pollutant alone. Thus, findings on independent effects of the gaseous pollutants based on the 20 cities should be viewed as preliminary until a 90 city analysis specifically controlling for PM_{10} and other pollutants is available. Evaluation of independent effects of the gaseous pollutants on hospitalizations would also be useful in follow-up analyses.

Schwartz (2000a), in his analysis of 10 U.S. cities' data (see New Multi-City Studies and Table 6-1 for basic study description), took an approach that is different from the usual simultaneous inclusion of co-pollutants in the model to address confounding. He postulated that, if the PM_{10} effect is really due to confounding by another pollutant, one would expect a larger PM_{10} effect in cities or seasons where PM_{10} represents more of that other pollutant (i.e., where the slope of the confounder to PM_{10} is larger). This approach relied on the large variability in the relationship between PM_{10} and possibly confounding gaseous pollutants across the 10 cities. Schwartz first illustrated this idea with a simulated example. In the analysis of the real 10 cities' data, the PM_{10} coefficients obtained from city-specific analyses were regressed on the regression coefficients relating the gaseous pollutant to PM_{10} in each city. If the PM_{10} effects were due to confounding only, according to the model, then such regression would result in zero intercept. To accommodate greater differences in the gaseous pollutants mean level between the indoor heating season and the warm season, the city-specific regressions were conducted by season, producing 20 city-specific coefficients. The results indicated that the resulting intercepts (i.e., PM_{10} effects after controlling for confounders) were not substantially different from that without the gaseous pollutants (0.57, 0.90, and 0.69, for confounding by SO_2, CO, and O_3, respectively, vs. 0.67 percent excess mortality deaths per 10 $\mu g/m^3$ increase in PM_{10}). While this approach appears to be reasonable, it is not certain if the data had sufficient and relevant signals to reflect actual difference in exposures to PM_{10} vs. gaseous co-pollutants across cities and seasons. For example, a high SO_2 to PM_{10} slope in winter may not be as relevant to a high SO_2 to PM_{10} slope in summer, because of the lower air exchange rate in winter. Such air exchange rate would also vary from city to city, possibly further blurring the relevant exposure picture. Also, the gaseous pollutant's slope on PM_{10} can be influenced by error in both PM_{10} and the gaseous pollutants. While such slopes may be more accurately estimated for spatially more uniform pollutants such as O_3 (and fine component of PM in the summer in northeast), for primary pollutants such as CO and SO_2, local source impacts may have contributed to less precision for their slopes on PM_{10}.

In Schwartz's analysis of 10 U.S. cities noted earlier, the new approach was not used to examine the changes in the gaseous pollutants' mortality effects coefficients. Such an analysis would have been useful in providing an overall assessment of possible confounding among the air pollutants. However, such an analysis was conducted in Schwartz's analysis (2000b) of Philadelphia data for 1974-1988. In this analysis, the same approach to test confounding was

applied for both TSP and SO_2. Instead of using the variability in PM_{10} to gaseous pollutants relationships across cities, this Philadelphia data analysis used the changing relationship between TSP and SO_2 over the 15-year period. The mortality data were thus analyzed for warm and cold seasons of each year, yielding 30 regression coefficients for both TSP and SO_2. Regression coefficients for TSP on SO_2, as well as SO_2 on TSP, were also obtained for each period. In the second stage regression, the 30 TSP mortality coefficients were regressed on the regression coefficients of SO_2 on TSP, and vice versa. In addition, visual range-derived extinction coefficient (an indicator of fine particles) was analyzed as a confounder for TSP in the same manner. The results indicated that the RR for SO_2 was substantially reduced (from 1.12 to 1.02 per 50 ppb SO_2 increase) by controlling for TSP, whereas TSP RR was not reduced, but rather increased, by controlling for SO_2 (1.09 to 1.21 per 100 $\mu g/m^3$ TSP increase). However, the TSP RR was reduced (1.09 to 1.01) when the extinction coefficient was included in the model. Therefore, the author concluded that the association between air pollution and daily deaths in Philadelphia was due to fine combustion particles.

A very different approach to co-pollutant modeling was used by Schwartz in the NMMAPS Part II morbidity analyses, and in a recently published paper on mortality (Schwartz, 2000a). The method attempts to identify total or partial confounding of a nominal causal pollutant such as PM_{10} with a co-pollutant or other confounder, based on the relationship between a regression of the health effect on the nominal causal pollutant, as a function of the regression coefficient of the nominal causal pollutant against the designated co-pollutant. If the relationship has zero intercept, then one might infer that the two pollutants are totally confounded, with no direct effect of the causal pollutant on the health endpoint that is not mediated by the co-pollutant. If the relationship has a non-zero intercept, then the causal pollutant and the co-pollutant are partially confounded, with the causal pollutant having a direct effect as well as an effect mediated by the co-pollutant. A non-zero intercept and no relation to the co-pollutant slope implies that only a direct health effect exists with the causal pollutant, with no confounding by the co-pollutant.

Figures 32 and 33 [not shown here] in NMMAPS II (pp. 40-41) appear to show the expected outcome described above. The vertical axes on both of these figures show the risk estimates for cardiovascular disease, COPD, or pneumonia in a single-pollutant model in 12 to 14 cities, with a causal pollutant Z = PM_{10}. There is no statistically significant relationship

between the estimated PM_{10} effect on health, and the slopes between Z = PM_{10} and X = one of the covariables temperature, relative humidity, SO_2, or O_3. Visual examination of these figures suggests that the high-risk estimates for pneumonia vs. the SO_2 or O_3 slopes in Figure 33 occur in Colorado Springs, a relatively small city with very little correlation between co-pollutants and PM. Similarly, the high-risk estimates for COPD vs. the PM-O_3 slope in Figure 33 occur in Boulder, another relatively small Colorado city with very little correlation between co-pollutants and PM. Absent these three points, there is no relationship between the estimated PM_{10} and the regression slopes between PM_{10} and one of temperature, relative humidity, SO_2 or O_3, and certainly not a linear relationship, which implies only a direct relationship with PM_{10}.

The analogous mortality study (Schwartz, 2000a) does not provide as much detail as the morbidity study in NMMAPS II, 2000. Schwartz (p. 566) notes: "For all three cooccurring pollutants, the effect size after controlling for confounding was not substantially (or statistically significantly) different from the baseline result. This is illustrated in Figure 3." Figure 4 [not shown here] plots each of eighteen city-season pairs, showing little or no relationship. The lack of a relationship does not, however, necessarily confirm that there is no confounding. A more complete implementation of this intriguing approach would be of interest. Until that time, however, the potential effects of confounding should be examined by several different approaches, included the estimated correlation matrix among all of the estimated regression coefficients.

In summary, the above results from several multi-city studies using different approaches suggest that possible confounding influences of gaseous pollutants on PM indices are not substantial. However, the interpretation of the relative impact of the gaseous co-pollutants as putative causative agents requires caution and warrants further, more detailed evaluation.

6.4.2.2 Simulation Analysis of Confounding

Since no single model specification can a priori be designated as "correct" in addressing confounding effects of co-pollutants, discrepancies in results among studies, even for the same dataset, are expected. While any assessment of relative "adequacy" of these alternative model specifications is difficult with observational data, the implication of "inadequate" model specifications may be studied through simulations using synthetic data in which the "correct" model is known. Chen et al. (1999) conducted such simulations using a synthetic data set in

which the causal variables are known, and the effects of model misspecification were studied in the presence of two variables (x_1 and x_2), with varying level of correlation, in a Poisson model. They considered three situations: (1) *model underfit,* in which mortality was generated with both x_1 and x_2, but regressed only on x_1; (2) *model overfit,* in which mortality was generated with only x_1, but regressed on both x_1 and x_2; (3) *model misfit,* in which mortality was generated with either x_1 or x_2 but regressed on the other variable. They observed that the confounding of covariates in an overfitted model does not bias the estimated coefficients but does reduce their significance; and that the effect of model underfit or misfit leads to not only erroneous estimated coefficients but also to erroneous significance. Chen et al., based on these observations, suggested that "models which use only one or two air quality variables (such as PM_{10} and SO_2) are probably unreliable, and that models containing several correlated and toxic or potentially toxic air quality variables should also be investigated...". While conceptually useful, this simulation study ignored one factor that is crucial in evaluating the implication of confounding, the relative error. For example, including several correlated pollutants in a regression model may lead to erroneous inferences unless one considers the relative error associated with each of the pollutants. Several simulation studies that considered such relative errors are discussed below.

6.4.2.3 Alternative Approaches to Deal with Confounding

In time-series analyses of the acute effects of PM, the usual approach to deal with gaseous co-pollutants is to treat them as confounders and to simply include them simultaneously in regression models. There has even been a suggestion (as mentioned above) based on a simulation analysis of synthetic data, that "several" correlated pollutants should be included in regression models (Chen et al., 1999). This prevailing approach can not only lead to misleading conclusions in "identifying" a specific "causal" pollutant (e.g., when pollutants have a varying extent of exposure error), but also ignores the potential combined effects of PM and gaseous co-pollutants (e.g., when PM absorbs SO_2 and carries it deeper in the airways, as shown by Amdur and Chen, 1989).

Another potential problem of the simultaneous inclusion of PM and gaseous pollutants is that the gaseous pollutant in question may be coming from the same source, or that the PM constituent may be derived from the gaseous pollutants. For example, SO_2 can be converted to sulfate, which is a PM constituent. Since a *confounder* cannot be an intermediate step in the

causal pathway (Rothman and Greenland, 1998), strictly speaking, SO_2 does not qualify as a confounder of PM, except in a situation where the PM is known to be solely of secondary origin (transported aerosols) and SO_2 is solely from local origin. Furthermore, any reduction in emission of a gaseous pollutant may also affect the level of PM. In such a case, the inference drawn from the results of simultaneous regression may be misleading, because the relative risk for PM is based on the assumption that the covariates could be kept unchanged while the PM level changes.

Alternative approaches are needed to address the above noted weakness in the general practice of effect estimation using simple simultaneous regressions. Several alternative approaches have been tried in recent years to estimate the effects of air pollution. The studies include: (1) Özkaynak et al.'s (1996) analysis of Toronto, CN data; (2) Laden et al.'s (2000) analysis of the Harvard Six Cities $PM_{2.5}$ data; (3) Mar et al.'s (2000) analysis of Phoenix, AZ $PM_{2.5}$ data; and, (4) Tsai et al.'s (2000) analysis of 3 New Jersey cities (Newark, Camden, and Elizabeth) data. These studies, as previously described in this chapter, utilized factor analysis to identify underlying factors that could be characterized in terms of source types. This approach thus greatly lessens or prevents inclusion of correlated individual variables in the regression model (depending on the rotation approach used) and also allows source-oriented evaluation of health impacts of PM components (as discussed more specifically below in Section 6.4.3).

Factor analysis has been routinely used in the air pollution source apportionment field, but its application to evaluation of PM health effects is relatively new. It may be a useful alternative approach for a source-oriented evaluation of the combined effects of fine particles and gaseous co-pollutants. The advantages of the factor analysis approach include: (a) it allows an examination of association between a health outcome and a group(s) of pollutants that vary together (due to the same source type); (b) it reduces multi-collinearity in a regression model; and (c) it may reduce error associated with individual variables. On the other hand, factor analyses can also be vulnerable to several problems: (a) the factors are sometimes quite sensitive to the inclusion or exclusion of variables from the initial correlation matrix; (b) the minor factors are very sensitive to the number of factors considered in the analysis; and (c) the inclusion of variables with other sources of variation (measurement error, other artifacts, or physical properties) can have a major impact on the selection of factors. With respect to the latter problem, there are valid concerns about studies that include both numerous PM elements

determined by XRF and gaseous pollutants (CO, NO_2, O_3) in the initial correlation matrix. There are also additional issues in assessing results from factor analysis studies, including the "interpretability" of resulting factors and technical issues (such as approach used for rotation of factors). Thus, there are still some issues that need to be further investigated.

6.4.3 Role of Particulate Matter Components

In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive associations between ambient PM_{10} concentrations and various health indicators, e.g., mortality, hospital admissions, respiratory symptoms, pulmonary function decrements, etc.. A somewhat more limited number of studies were then available which substantiated mortality and morbidity associations with various fine particle indicators (e.g., $PM_{2.5}$, sulfate, H^+, etc.); and only one, the Harvard Six Cities analysis by Schwartz et al. (1996a), evaluated relative contributions of the fine $PM_{2.5}$ versus coarse ($PM_{10-2.5}$) fraction of PM_{10}, with $PM_{2.5}$ appearing to be associated more strongly with mortality effects than $PM_{10-2.5}$. Lastly, only a very few studies seemed to be indicative of possible coarse particle effects, e.g., increased asthma risks associated with quite high PM_{10} concentrations in a few locations where coarse particles strongly dominated the ambient PM_{10} mix.

6.4.3.1 Fine- and Coarse-Particle Effects on Mortality

A greatly enlarged and still rapidly growing number of new studies published since the 1996 PM AQCD provide much new evidence further substantiating ambient PM associations with increased human mortality and morbidity. As indicated in Table 6-1, most newly reported analyses, with few exceptions, continue to show statistically significant associations between short-term (24-h) PM concentrations and increases in daily mortality in many U.S. and Canadian cities, as well as elsewhere. Also, the reanalyses of Harvard Six City and ACS study data substantiate the original investigator's findings of long-term PM exposure associations with increased mortality as well.

6.4.3.1.1 Effects on Total Mortality

The effects estimates from the newly reported studies generally comport well with those derived from the earlier 1996 PM AQCD assessment, which reported risk estimates for excess

total (nonaccidental) deaths associated with short-term PM exposures as generally falling within the range of ca. 1.5 to 8.5% per 50 $\mu g/m^3$ PM_{10} (24-h) increment and ca. 2.5 to 5.5% increase per 25 $\mu g/m^3$ $PM_{2.5}$ (24-h) increment.

Several new PM epidemiology studies which conducted time-series analyses in multiple cities were noted to be of particular interest, in that they provide evidence of effects across various geographic locations (using standardized methodologies) and more precise pooled effect size estimates with narrow confidence bounds reflecting the typically much stronger power of such multi-city studies over individual-city analyses. Based on pooled analyses across multiple cities, the percent total (non-accidental) excess deaths per 50 $\mu g/m^3$ PM_{10} increment were estimated in different multi-city analyses to be: (1) 2.3% in the 90 largest U.S. cities; (2) 3.4% in 10 U.S. cities; (3) 3.5% in the 8 largest Canadian cities; and (4) 2.0% in Western European cities.

Many new individual-city studies found positive associations (most statistically significant at $p < 0.05$) for the $PM_{2.5}$ fraction, with effect size estimates typically ranging from ca. 2.0 to ca. 8.5% per 25 $\mu g/m^3$ $PM_{2.5}$ for U.S. and Canadian cities. Of the 10 or so new analyses that not only evaluated PM_{10} effects but also made an effort to compare fine versus coarse fraction contributions to total mortality, only two are multi-city analyses yielding pooled effects estimates: (1) the Klemm and Mason (2000) recomputation of Harvard Six Cities data, confirming the original published findings by Schwartz et al. (1996a); and (2) the Burnett et al. (2000) study of the 8 largest Canadian cities. Both of these studies found roughly comparable, statistically significant excess risk estimates for $PM_{2.5}$, i.e., ca. 3% increased total mortality per 25 $\mu g/m^3$ $PM_{2.5}$ increment.

With regard to possible coarse particle short-term exposure effects on mortality, in those new studies which evaluated $PM_{10-2.5}$ effects as well as $PM_{2.5}$ effects, the coarse particle ($PM_{10-2.5}$) fraction was also consistently positively associated with increased total mortality, albeit the coarse effect size estimates were generally less precise than those for $PM_{2.5}$ and statistically significant at $p < 0.05$ in only a few studies. Still, the overall picture tends to suggest that excess total mortality risks may well reflect actual coarse particle effects, in at least some locations. This may be most consistently the case in arid areas (e.g., Southern California, the Phoenix area, Mexico City, and Santiago, Chile) and during summer months (perhaps reflecting, in part, stronger contributions of biogenic materials to coarse fraction $PM_{10-2.5}$ particles during warmer weather). On the other hand, significant (or nearly significant) elevations in coarse PM-related

total mortality risks elsewhere (e.g., eastern U.S. urban areas in the Harvard Six City Study, the 8 largest Canadian cities, and Detroit, MI) may either reflect (a) typically moderate correlations there between $PM_{10-2.5}$ and $PM_{2.5}$ or, possibly, (b) true PM coarse fraction toxic potency. Excess total mortality risks associated with short-term (24-h) exposures to coarse fraction particles capable of depositing in the lower respiratory tract generally fall in the range of 0.5 to 6.0% per 25 $\mu g/m^3$ PM_{10-25} increment for U.S. and Canadian cities.

Three new papers provide particularly interesting new information on relationships between short-term and coarse particle exposures and total elderly mortality (age 65 and older) using exposure TEOM data from the EPA ORD NERL monitoring site in Phoenix, AZ. Each used quite different models but each reported statistically significant relationships between mortality and coarse PM, specifically $PM_{10-2.5}$, an indicator for the thoracic fraction of coarse-mode PM.

Smith et al. (2000) using as the exposure metric a three-day running average performed linear regression of the square root of daily mortality on the long-term trend, meteorological and PM-based variables. Two mortality variables were used, total (non-accidental) deaths for the city of Phoenix and the same for a larger, regional area. Using a linear analysis, effects based on coarse PM were statistically significant for both regions, whereas effects based on fine PM ($PM_{2.5}$) were not. However, when the possibility of a nonlinear response was taken into account, no evidence was found for a nonlinear effect for coarse PM, but fine PM was found to have a statistically significant effect for concentration thresholds of 20 and 25 $\mu g/m^3$. There was no evidence of confounding between fine and coarse PM, suggesting that fine and coarse PM are "essentially separate pollutants having distinct effects". Smith et al. (2000) also observed a seasonal effect for coarse PM, the effect being statistically significant only during spring and summer. Based on a principal component analysis of elemental concentrations, crustal elements are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000) felt that the implication that crustal, rather than anthropogenic elements, were responsible for the PM mortality was counterintuitive.

Clyde et al. (2000) used a more conventional model, a Poisson regression of log deaths on linear PM variables; but they employed Bayesian model averaging to consider a wide variety of variations in the basic model. They considered three regions, the Phoenix metropolitan area, a small subset of zip code to give a region presumably with uniform $PM_{2.5}$, and a still smaller zip code region surrounding the monitoring site, thought to be uniform as to PM_{10} concentrations.

The models considered lags of 0, 1, 2, or 3 days but only for single day PM variables (no running averages as used by Smith et al., 2000). A PM effect with a reasonable probability was found only in the uniform $PM_{2.5}$ region and only for coarse PM.

Mar et al. (2000) used conventional Poisson regression methods and limited their analyses to the smallest area (called Uniform PM_{10} by Clyde et al). They reported modeling data for lag days 0 to 4. Coarse PM was marginally significant on lag day 0. No direct fine particle measures were statistically significant on day 0. A regional sulfate factor determined from source apportionment, however, was statistically significant. No correlations were reported for the source apportionment factors but the correlation coefficient between sulfur (S) in $PM_{2.5}$ (as measured by XRF) with coarse PM was only 0.13, suggesting separate and distinct effects for regional sulfate and coarse PM.

The above three studies of PM- total mortality relationships in Phoenix tend to suggest a statistical association of coarse PM with total elderly mortality in addition to and different from any relationship with fine PM, fine PM components, or source factors for fine PM.

With regard to long-term PM exposure effects on total (non-accidental) mortality, the newly available evidence from the HEI Reanalyses of Harvard Six Cities and ACS data (and extensions, thereof), substantiate well associations attributable to chronic exposures to inhalable thoracic particles (indexed by PM_{15} or PM_{10}) and the fine fraction of such particles (indexed by $PM_{2.5}$ and/or sulfates). Statistically significant excess risk for total mortality was shown by the reanalyses to fall in the range of 4-18% per 20 $\mu g/m^3$ $PM_{15/10}$ increment and 14-28% per 20 $\mu g/m^3$ $PM_{2.5}$ increase, thus suggesting likely stronger associations with fine versus coarse fraction particles. Significant fine PM associations with total mortality were also found in the latest reported AHSMOG results for males, but not in females.

Other recent studies on the relation of mortality to particle composition and source (Laden et al., 2000; Mar et al., 2000; Özkaynak et al., 1996; Tsai et al., 2000) suggest that particles from certain sources may have much higher potential for adverse health effects than others, as delineated by source-oriented evaluations involving factor analyses. Laden et al. (2000) conducted factor analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study data for 1979-1988. In the analysis for all six cities combined, the excess risk for daily mortality was estimated to be 3.4% (CI, 1.7 to 5.2) per 10 $\mu g/m^3$ increment in a mobile source factor; 1.1% (CI, 0.3 to 2.0) per 10 $\mu g/m^3$ for a coal source factor, and −2.3% (CI, −5.8 to 1.2) per 10 $\mu g/m^3$

for a crustal factor. There was large variation among the cities and some suggestion of an association with a fuel oil factor identified by V or Mn, but it was not statistically significant.

Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995-1997 fine particle elemental components and gaseous pollutants (CO, NO_2, SO_2) in an area of Phoenix, AZ, close to the air pollution monitors. The $PM_{2.5}$ constituents included sulfur, Zn, Pb, soil-corrected potassium, organic and elemental carbon, and a soil component estimated from oxides of Al, Si, Ca, Fe, and It. Based on models fitted using one pollutant at a time, statistically significant associations were found between total mortality and PM_{10}, CO (lags 0 and 1), NO_2 (lags 0, 1, 3, 4), S (negative), and soil (negative). Statistically significant associations were also found between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4), $PM_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $PM_{10-2.5}$ (lag 0), and elemental, organic, or total carbon. Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2), and a regional sulfate factor (with a high loading on S). However, total mortality was negatively associated with a soil factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated with the regional sulfate factor.

Tsai et al. (2000) analyzed daily time series of total and cardiorespiratory deaths, using short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to inhalable particle mass (PM_{15}) and fine particle mass ($PM_{2.5}$), the study evaluated data on metals Pb, Mn, Fe, Cd, V, Ni, Zn, Cu, and three fractions of extractable organic matter. Factor analyses were carried out using the metals, CO, and sulfates. The most significant sources or factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO, industrial Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and sulfates were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden oil burning and motor vehicle emissions predicted total mortality, but copper showed a marginal negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn showed marginal negative associations with mortality, as did industrial sources traced by Cu.

The set of results from the above factor analyses studies do not yet allow one to identify with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless, some commonalities across the studies seem to highlight the likely importance of mobile source and other fuel combustion emissions (and apparent lesser importance of crustal particles) as contributing to increased total or cardiorespiratory mortality.

6.4.3.1.2 Effects on Cause-Specific Mortality

Numerous new studies have evaluated PM-related effects on cause-specific mortality. Most all report positive, often statistically significant (at $p < 0.05$), short-term (24-h) PM exposure associations with cardiovascular (CVD)- and respiratory-related deaths. Cause-specific effects estimates appear to mainly fall in the range of 3.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for cardiovascular or combined cardiorespiratory mortality and 2.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for respiratory mortality in U.S. cities. Effect size estimates for the coarse fraction ($PM_{10-2.5}$) for cause-specific mortality generally fall in the range of ca. 3.0 to 8.0% for cardiovascular and ca. 3.0 to 16.0% for respiratory causes per 25 $\mu g/m^3$ increase in $PM_{10-2.5}$.

Also of particular interest, the above noted study by Mar et al. examined the associations of a variety of PM indicators with cardiovascular mortality (for age $\geq$65), again in the zip code area near the Phoenix monitoring site. For this end point, coarse PM was statistically significant on lag day 0 but not on subsequent lag days. $PM_{2.5}$ and a number of fine PM indicators were statistically significant on lag day 1 but not on lag day 0. This suggests a distinct and separate relationship of $PM_{2.5}$ and $PM_{10-2.5}$. As in the case of total mortality, the only fine PM indicator found to be statistically significant on lag day 0 was regional sulfate. However, the low correlation coefficient between S in $PM_{2.5}$ and $PM_{10-2.5}$ ($r = 0.13$) suggests that the two relationships represent different sets of deaths. Thus, there is some evidence suggesting that the risk of cardiovascular mortality , as well as that of total mortality, may be statistically associated with $PM_{10-2.5}$ and that this relationship may be independent of any relationships with fine particle indicators.

6.4.3.2 Fine- and Coarse-Particulate Matter Effects on Morbidity

At the time of the 1996 PM AQCD, fine particle morbidity studies were mostly limited to Schwartz et al. (1994) , Neas et al. (1995, 1994); Koenig et al. (1993); Dockery et al. (1996); and

Raizenne et al. (1996); and discussion of coarse particles morbidity effects was also limited to only a few studies (Gordian et al., 1996; Hefflin et al., 1991) which implicated $PM_{10-2.5}$ a possible important fraction of PM_{10}. Since the 1996 PM AQCD, several new studies have been published in which newly available size-fractionated PM data allowed investigation of the effects of both fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) particles. Fine (FP) and coarse (CP) particle results are presented below for studies by morbidity outcome areas, as follows: cardiovascular disease (CVD) hospital admissions (HA's), respiratory medical visits and hospital admissions, and respiratory symptoms and pulmonary function changes.

As discussed in Section 6.3.1 (on cardiovascular effects associated with acute ambient PM exposure), extensive evidence for significant PM_{10} effects on cardiovascular-related hospital admissions and visits has recently been provided by several new multi-city studies (Schwartz, 1999; Samet et al., 2000a,b; Zanobetti et al., 2000b) that yield pooled estimates of PM-CVD effects across numerous U.S. cities and regions. These studies found not only significant PM associations, but also associations with other gaseous pollutants as well, thus hinting at likely independent effects of certain gases (O_3, CO, NO_2, SO_2) and/or interactive effects with PM. These and other individual-city studies generally appear to confirm likely excess risk of CVD-related hospital admission for U.S. cities in the range of 3-10% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 yr).

In addition to the PM_{10} studies, several new U.S. and Canadian studies evaluated fine-mode PM effects on cardiovascular outcomes. Moolgavkar (2000a) reported $PM_{2.5}$ to be significantly associated with CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997b) reported that fine particles were significantly associated with CVD HA in a single pollutant model, but not when gases were included in multipollutant models for the 8 largest Canadian city data. Stieb et al. (2000) reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED) visits in single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported that $PM_{2.5}$ measured by nepholonetry was associated with CVD HA for all ages and 65+ yr, but not in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao et al., 1999, Pope et al., 1999b,c) reported associations between increases in $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (1998, 2000) reported a negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate

variability measure). Overall, these studies appear to implicate fine particles, as well as possibly some gaseous copollutants, in cardiovascular morbidity, but the relative contributions of fine particles acting alone or in combination with gases such as O_3, CO, NO_2 or SO_2 remain to be more clearly delineated and quantified. The most difficult issue relates to interpretation of reduced PM effect size and /or statistical significance when copollutants derived from the same source(s) as PM are included in multipollutant models.

Section 6.3.1 also discussed U.S. and Canadian studies that present analysis of coarse particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) found significant positive associations of coarse particles ($PM_{10-2.5}$) with ischemic heart disease hospital admissions in Detroit (RR = 1.10, CI 1.026, 1.18). Tolbert et al. (2000a) reported significant positive associations of heart dysrhythmias with CP ($p = 0.04$) as well as for elemental carbon ($p = 0.004$), but these preliminary results must be interpreted with caution until more complete analyses are carried out and reported. Burnett et al. (1997b) noted that CP was the most robust of the particle metrics examined to inclusion of gaseous covariates for cardiovascular hospitalization, but concluded that particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory disease in this study. Based on another Canadian study, Burnett et al. (1999), reported statistically significant associations for CP in univariate models but not in multipollutant models; but the use of estimated rather than measured PM exposures limits the interpretation of the PM results reported.

The collective evidence reviewed above, in general, appears to suggest excess risks for CVD-related hospital admissions of ca. 4.0 to 10% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ increment.

Section 6.3.2 also discussed new studies of effects of short-term PM exposure on the incidence of respiratory hospital admissions and medical visits. Several new U.S. and Canadian studies have yielded particularly interesting results suggestive of roles of both fine and coarse particles respiratory-related hospital admissions. In an analysis of Detroit data, Lippmann et al. (2000) found comparable effect size estimates for $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess risk for pneumonia hospital admissions (in no copollutant model) was 13% (CI 3.7, 22) per 25 $\mu g/m^3$ $PM_{2.5}$ and 12% (CI 0.8, 24) per 25 $\mu g/m^3$ $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not highly correlated, the observed association between coarse particles and health outcomes were possibly not confounded by smaller particles. Despite the greater measurement error associated with $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10}, this indicator of the coarse particles within the thoracic

fraction was associated with some of the outcome measures. The interesting result is that $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics, especially given the effect estimates of $PM_{10-2.5}$ with pneumonia hospital admissions, (lag 1; RR = 1.11, 95% CI: 1.006, 1.233). Burnett et al. (1997b) also reported PM (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) associations with respiratory hospital admissions, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was significant (RR = 1.13 for 25 $\mu g/m^3$; CI = 1.05 - 1.20); and inclusion of ozone still yielded a significant coarse mass RR = 1.11 (CI = 1.04 - 1.19). Moolgavkar et al. (2000) showed the most consistent association for PM_{10} across lags (0-4d), while $PM_{2.5}$ yielded the strongest positive PM metric association at lag 3 days. Also, Moolgavkar (2000a) reported that, in Los Angeles, both PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different lags for single pollutant models but not in two pollutant models. Delfino et al. (1997) reported that both $PM_{2.5}$ and PM_{10} are positively associated with ED visits for respiratory disease. Morgan et al. (1998) reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$ association with COPD HA for 1-hr max PM that was more positive than 24-h average $PM_{2.5}$.

Some new studies appear to substantiate PM associations with asthma-related hospital admissions. For example, Norris et al (1999) reported associations of emergency department visits for asthma in children with both $PM_{2.5}$ and $PM_{10-2.5}$. Two other studies presented uniquely different analyses of hospital admissions in the Seattle, Washington area. Sheppard et al. (1999) studied relationships between PM metrics that included $PM_{10-2.5}$ and non-elderly adult hospital admissions for asthma in the greater Seattle area and reported significant relative rates for PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10.2.5}$, the relative risk was 1.04 (95% CI 1.01, 1.07). In a different analysis, Lumley and Heagerty (1999) examined PM_1 and PM_{10-1} in the King County, WA (Seattle) area during the same time period but for hospital admissions for overall respiratory disease. Since only a significant hospital admission association was found with $PM_{1.0}$ and not PM_{10-1}, a dominant role by sub-micron particles in $PM_{2.5}$ - asthma HA association was suggested, but this may not be an appropriate conclusion based on several differences between the study analysis methods and differences between asthma versus respiratory outcome measures used in the two Seattle studies.

Several other studies (Chen et al. 2000; Choudhury et al., 1997; Moolgavlar 2000a; Lippsett et al., 1997) report results for areas (e.g., Reno-Sparks, NV; Anchorage, AK; Phoenix, AZ; Santa Clara, CA) where coarse particles tend to constituent a large fraction of PM_{10} but no

measures of $PM_{10-2.5}$ were available. These studies showing significant PM_{10} effects on respiratory hospital admissions provide additional data suggestive of likely coarse particle effects on respiratory morbidity.

Thus, although PM_{10} mass has most often been implicated as the PM pollution index affecting respiratory hospital admissions, the overall collection of new studies reviewed in Section 6.3.2 appear to suggest relative roles for both fine and coarse PM mass fractions, such as $PM_{2.5}$ and $PM_{10-2.5}$.

Section 6.3.3 assessed relationships between PM exposure on lung function and respiratory symptoms. While most data examine PM_{10} effects, several studies also examined fine and coarse fraction effects. Schwartz and Neas (2000) report that cough was the only response in which coarse particles appeared to provide an independent contribution to explaining the increased incidence. The correlation between CM and $PM_{2.5}$ was moderate (0.41). Coarse particles had little association with evening peak flow. Tiittanen et al. (1999) also reported a significant effect of $PM_{10-2.5}$ for cough. Thus, cough may be an appropriate outcome related to coarse particle effects. However, the limited data base suggests that further study is appropriate. The report by Zhang, et al. (2000) of an association between coarse particles and the indicator "runny nose" is noted also.

For respiratory symptoms and PFT changes, several new asthma studies report relationships with ambient PM measures. The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Gold et al. (1999), Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al. (1997), and Romieu et al. (1996) all found comparable results for $PM_{2.5}$ and PM_{10}. The study of Peters et al. (1997b) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas (2000) found larger effects for $PM_{2.5}$ than for coarse mode particles. Three studies included both PM_{10} and $PM_{2.5}$ in their analyses of respiratory symptoms. The studies of Peters et al. (1997b) and Tiittanen et al. (1999) found similar effects for the two PM measures. Only the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$.

For non-asthmatics, several studies evaluated $PM_{2.5}$ effects. Naeher et al. (1999) reported similar AM PEF decrements for both $PM_{2.5}$ and PM_{10}. Neas et al. (1996) reported a nonsignificant negative association for PEF and $PM_{2.1}$, and Neas et al. (1999) also reported negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significantly PM

PEF association with $PM_{2.5}$, and Tiittanen et al. (1999) also reported negative but nonsignificant association for PEF and $PM_{2.5}$. Gold et al. (1999) reported significantly PEF results. Schwartz and Neas (2000) reported significant $PM_{2.5}$ effects relative to lower respiratory symptoms. Tiittanen et al. (1999) showed significant effects for cough and $PM_{2.5}$ for a 4-day average.

Another study, Peters et al. (1997b) in Erfurt in 1992 is unique for two reasons: (1) they studied the size distribution in the range 0.01 to 2.5 μm and (2) examined the number of particles. They report that the health effects of 5 day means of the number count (NC) for ultrafine particles were larger than those related to the mass of the fine particles. For NC 0.01 - 0.1, cough was significant for the same day and the five day mean.

In a chronic respiratory disease study of 22-24 North American communities evaluated in the 1996 PM AQCD, Raizenne et al. (1996) found $PM_{2.1}$ to be related to a statistically significant FVC deficit of −3.21% (−4.98, −1.41). Dockery et al. (1996) also reported $PM_{2.1}$ associations with increased bronchitis; odds ratio = 1.50 (95% CI = 0.91, 2.47).

The above new studies offer much more information than was available in 1996. Effects were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory hospital admissions and cough. Still insufficient data exists from these relatively limited studies to allow strong conclusions at this time as to which size-related ambient PM components may be most strongly related to one or another morbidity endpoints. Very preliminarily, however, fine particles appear to be more strongly implicated in cardiovascular outcomes than are coarse ones, whereas both seem to impact respiratory endpoints.

6.4.4 The Question of Lags

In most of the past air pollution health effects time-series studies, after the basic model (the best model with weather and seasonal cycles as covariates) was developed, several pollution lags (usually 0 to 3 or 4 days) were individually introduced and the most significant lag(s) chosen for the RR calculation. While this practice may bias the chance of finding a significant association, without a firm biological reason to establish a fixed pre-determined lag, it appears reasonable. Due to likely individual variability in response to air pollution, the apparent lags of effects observed for aggregated population counts are expected to be “distributed” (i.e., symmetric or skewed bell-shape). The “most significant lag” in such distributed lags is also expected to fluctuate statistically. The “vote-counting” of the most significant lags reported in the past

PM-mortality studies shows that 0 and 1 day lags are, in that order, the most frequently reported "optimal" lags, but such estimates may be biased because these lags are also likely the most frequently examined ones. Thus, a more systematic approach across different data sets was needed to investigate this issue.

The recent Samet et al. (2000b) analysis of the 90 largest U.S. cities provides particularly useful information on this matter. Figure 6-11 depicts Samet et al.'s overall pooled results, showing the posterior distribution of PM_{10} effects for the 90 cities for lag 0, 1, and 2 days. It can be seen that the effect size estimate for lag 1day is about twice that for lag 0 or lag 2 days, though their distributions overlap. However, a careful examination of Figures 6 and 7 in NMMAPS I suggests that the maximum PM_{10} effect may occur in different cities with somewhat different lag relationships. In terms of the magnitude of the estimated PM_{10} effects, Table 6-24, based on NMMAPS I Figure 7 (posterior bivariate distribution for each county; PM_{10} effect adjusted for O_3), suggests that somewhat different patterns may apply in different locations. These data suggest that while lag 1 effects are typically the largest, there may be some situations in which lag 0 or lag 2 effects are larger.

The NMMAPS mortality and morbidity analyses, and another HEI-sponsored study on PM components (Lippmann et al., 2000) illustrate three different ways to deal with temporal structure: (1) assume all sites have the same lag, e.g., 1 day, for a given effect; (2) use the lag or moving average giving the largest or most significant effect; and (3) use a flexible distributed lag model, with parameters adjusted to each site.

The NMMAPS mortality analyses used the first approach. This approach introduces a consistent response model across all locations. However, since the cardiovascular, respiratory, or other causes of acute mortality usually associated with PM are not at all specific, there is little *a priori* reason to believe that they must have the same relation to current or previous PM exposures at different sites. The imposed consistency in lag that maximizes the aggregate effect of lag 1 across all cities, in Figure 15-18 and 24 of NMMAPS II, may obscure important regional or local differences for lags other than 1 day.

The NMMAPS morbidity studies evaluate 0- and 1-day lags, the moving average of 0 and 1-day lags, polynomial distributed lag models, and unrestricted distributed lag models. The first-stage models for each city in the study were fitted for each city, with no restriction as to a consistent model across all cities, and combined across all 14 cities in the second stage as shown

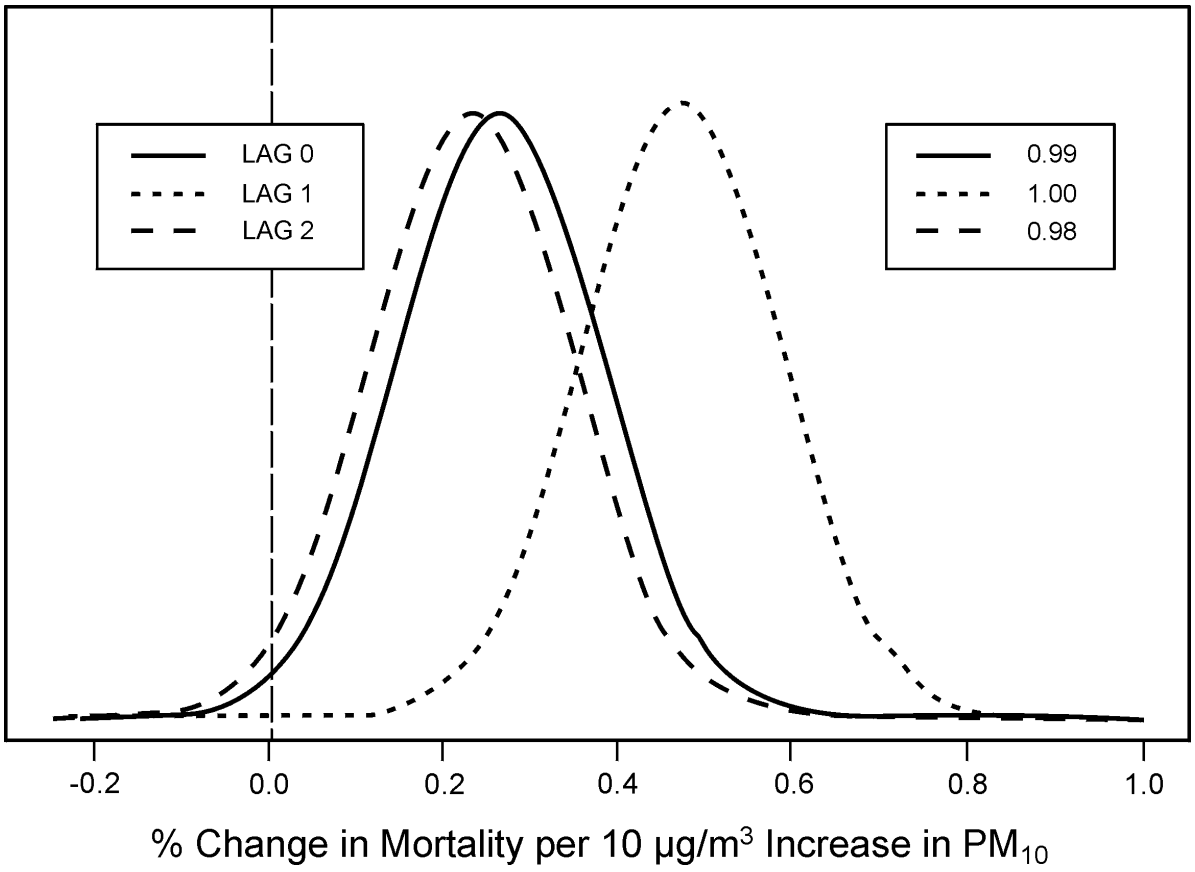

Figure 6-11. Marginal posterior distribution for effects of PM_{10} on all cause mortality at lag 0, 1, and 2 for the 90 cities. From Samet et al. (2000a,b). The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

in Table 14 and Figure 23 of NMMAPS II. A comparison of the data tabulated in the NMMAPS Report Appendices shows large differences across cities in the apparent magnitude of the PM_{10} effect, depending on how the PM concentration data over the preceding few days are used.

The approach used in Lippmann et al. (2000) and many other studies is to use the model that maximizes some global model goodness-of-fit criterion. This leads to selection of different models at different sites, as might be expected. However, the best-fitting model (for lags, for example) is often the model with the largest or most significant PM_{10} coefficient. All models for the pollutant(s) of interest are usually compared among themselves only after a preliminary baseline model has been fitted. The baseline model takes into account most of the other

TABLE 6-24. COMPARISON OF PM_{10} EFFECT SIZES ESTIMATED BY NMMAPS ANALYSES FOR 0, 1, AND 2 DAY LAGS FOR THE 20 LARGEST U.S. CITIES

County	Ordered PM_{10} effect sizes
Los Angeles	Lag 0 < lag 1 << lag 2
New York	Lag 0 = lag 1 >> lag 2
Chicago	Unreadable
Dallas/Fort Worth	Lag 0 > lag 1, lag 1 < lag 2
Houston	Lag 0 < lag 1, lag 1 > lag 2
San Diego	Lag 0 = lag 1 > lag 2
Santa Ana /Anaheim	Lag 0 > lag 1 > lag 2
Phoenix	Lag 0 = lag 1 < lag 2
Detroit	Lag 0 < lag 1, lag 1 > lag 2
Miami	Lag 0 < lag 1 = lag 2
Philadelphia	Lag 0 < lag 1, lag 1 > lag 2
Seattle	Lag 0 < lag 1, lag 1 > lag 2
San Jose	Lag 0 > lag 1 = lag 2
Cleveland	Lag 0 > lag 1, lag 1 < lag 2
San Bernardino	Lag 0 > lag 1 = lag 2
Pittsburgh	Lag 0 < lag 1, lag 1 > lag 2
Oakland	Lag 0 < lag 1 = lag 2
San Antonio	Lag 0 = lag 1 < lag 2
Riverside	Lag 0 < lag 1, lag 1 > lag 2

variables with which PM_{10} could be plausibly associated, so that the remaining variation in morbidity or mortality that can be explained by including PM_{10} indicators with different temporal structures is nearly "orthogonal" or independent of the baseline model. The restriction to the same lag day at all sites certainly increases the precision of that estimate, but possibly at the cost of obscuring different relationships between time of exposure and health effect at other sites.

An additional complication in assessing the shape of a distributed lag is that the apparent spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city and from pollutant to pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and may tend to obscure important nuances of lag structures that may provide important clues to possible different lags between PM exposures and different cause-specific effects.

Thus, it is possible that the extent of lag and its spread may vary depending on the cause of death. For example, Rossi et al. (1999) report that, in their analysis of TSP-cause specific mortality in Milan, Italy, the lags varied for different cause of death (i.e., same day for respiratory infections and heart failure; 3-4 days for myocardial infarction and COPD). Thus, the lag for total mortality may exhibit mixed lags (weighted by the frequency of deaths in each cause). Another example was reported for a recent Mexico City study (Borja-Aburto et al., 1998), in which they found significant $PM_{2.5}$-total mortality associations for same day and 4-day lag, but not for the intervening 2 to 3 days (percent increases per 25 $\mu g/m^3$ were 3.38, −4.00, 1.03, 1.08, 3.43, 2.49, for 0 through 5 day lags, respectively). The authors state: "This phenomenon is consistent with both a harvesting of highly susceptible persons on the day of exposure to high pollution levels and a lagged increase in mortality due to delayed effects of reduction of pulmonary defenses, cardiovascular complications, or other homeostatic changes among less-compromised individuals". It is interesting to note that Wichmann et al. (2000) also reported that the most predictive single day effects on mortality for mass concentrations of 0.01-2.5 μ particles were either immediate (0-1 d lag) or delayed (4-5 d lag) for their data from Erfurt, Germany.

It should also be noted that if one chooses the most significant single lag day only, and if more than one lag day shows positive (significant or otherwise) associations with mortality, then reporting a RR for only one lag would also underestimate the pollution effects. Schwartz (2000b) investigated this issue, using the 10 U.S. cities data where daily PM_{10} values were available for 1986-1993. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were examined using four models: 1-day mean at lag 0 day; 2-day mean at lag 0 and 1 day; second-degree distributed lag model using lags 0 through 5 days; unconstrained distributed lag model

using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results. The results indicated that the effect size estimates for the quadratic distributed model and unconstrained distributed lag model were similar. Both distributed lag models resulted in substantially larger effect size estimates (7.25% and 6.62%, respectively, as percent excess total death per 50 $\mu g/m^3$ increase in PM_{10}) than the single day lag (3.29%) and moderately larger effect size estimates than the two-day average models (5.36%). Samet et al. (2000a,b) also applied 7- and 14-day unconstrained distributed lag models to Chicago, Minneapolis/St. Paul, and Pittsburgh data, and reported that the sum of the 7-day distributed lag coefficients was greater than the estimates based on a single day's value, but the 14-day estimate was substantially lower than the 7-day estimate in Chicago and Minneapolis/ St. Paul. Thus, it is possible that the usual RR estimate using one lag day may underestimate PM effects.

6.4.5 New Assessments of Mortality Displacement

There have been a few studies that investigated the question of "harvesting", a phenomenon in which a deficit in mortality occurs following days with (pollution-caused) elevated mortality, due to depletion of the susceptible population pool. This issue is very important in interpreting the public health implication of the reported short-term PM mortality effects. The 1996 PM AQCD discussed suggestive evidence observed by Spix et al. (1993) during a period when air pollution levels were relatively high. Recent studies, however, generally typically used data from areas with lower, non-episodic pollution levels.

Schwartz (2000c) separated time-series air pollution, weather, and mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) "intermediate" fluctuations; (3) "short-term" fluctuations. By varying the cut-off between the intermediate and short term, evidence of harvesting was sought. The idea is, for example, if the extent of harvesting were a matter of a few days, associations between weekly average values of mortality and air pollution (controlling for seasonal cycles) would not be seen. For COPD, Schwartz (2000c) reported evidence indicating that most of the mortality was only displaced by a few weeks; for pneumonia, heart attacks, and all cause mortality, the effect size increased as longer time scales were included. The percent increase in deaths associated with a 25 $\mu g/m^3$ increase in $PM_{2.5}$ increased from 5.3% (95%CI: 6.8, 9.0) to 9.64% (95%CI: 8.2, 11.1).

Schwartz and Zanobetti (2000) used the same approach described above to analyze a larger data set from Chicago, IL for 1988-1993. Total (non-accidental), in-hospital, out-of-hospital deaths, as well as heart disease, COPD, and pneumonia elderly hospital admissions were analyzed to investigate possible PM_{10}"harvesting" effects. GAM Poisson models adjusting for temperature, relative humidity, day-of-week, and season were applied in baseline models using the average of the same day and previous day's PM_{10}. Seasonal and trend decomposition techniques called STL were applied to the health outcome and exposure data to decompose them into different time-scales (i.e., short-term to long-term), excluding long seasonal cycles (120 day window). The associations were examined with smoothing windows of 15, 30, 45, and 60 days. The effect size estimate for deaths outside hospital was larger than for deaths inside hospital. All cause mortality showed an increase in effect size at longer time scales. The effect size for deaths outside hospital increases more steeply with increasing time scale than that for inside hospital deaths.

Zanobetti et al. (2000a) used GAM distributed lag models to help quantify mortality displacement in Milan, Italy, 1980-1989. Non-accidental total deaths were regressed on smooth functions of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect. TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45^{th} day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.

Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for PM regression coefficients (i.e., mortality relative risk) as observed in frequency domain. Three levels of harvesting, 3 days, 30 days, and 300 days were simulated. As expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the real data from Philadelphia, the regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger suggested that "harvesting-resistant" regression coefficients could be obtained by excluding the

coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of those coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, except perhaps the spectra analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients by frequency (*gain*) may be useful in evaluating the potentially frequency-dependent relationships among multiple time series. A few past examples in air pollution health effects studies include: (1) Shumway et al.'s (1983) analysis of London mortality analysis, in which they observed that significant coherence occurred beyond two week periodicity (they interpreted this as "pollution has to persist to affect mortality"); (2) Shumway et al.'s (1988) analysis of Los Angeles mortality data, in which they also found larger coherence in the lower frequency; (3) Ito's (1990) analysis of London mortality data in which he observed relatively constant gain (regression coefficient) for pollutants across the frequency range, except the annual cycle. These results also suggest that associations and effect size, at least, are not concentrated in the very high frequency range.

Schwartz (2000c), Zanobetti et al. (2000a), and Zeger et al.'s (1999) results all suggest that the extent of harvesting, if any, is not a matter of only a few days. Other past studies that used frequency domain analyses are also at least qualitatively in agreement with the evidence against the short-term only harvesting. Since very long wave cycles (> 6 months) need to be controlled in time-series analyses to avoid seasonal confounding, the extent of harvesting beyond 6 months periodicity is not possible in time-series study design. While these studies suggest that observed short-term associations are not simply due to short-term harvesting, more data are needed to obtain quantitative estimates of the extent of prematurity of deaths.

6.4.6 New Assessment of Threshold in Concentration-Response Relationships

In the 1996 PM AQCD, the limitations of identifying 'threshold' in the concentration-response relationships in observational studies were discussed including the low data density in

the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Also, a threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that need to be noted. For example, Schwartz (1999) discussed that, since individual thresholds would vary from person to person due to individual differences in genetic level susceptibility and pre-existing disease conditions, it would be almost mathematically impossible for a threshold to exist in the population. The person-to-person difference in the relationship between personal exposure and the concentration observed at a monitor would also add to the variability. Because one cannot directly measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed threshold, if any, biologically. Despite these issues, several studies have attempted to address the question of threshold by analyzing large databases, or by conducting simulations.

Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time series studies. Based on the realistic range of error observed from actual Toronto pollution data (average site-to-site correlation: 0.90 for O_3; 0.76 for COH; 0.69 for TSP; 0.59 for SO_2; 0.58 for NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were generated with three PM_{10} threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$). LOESS with a 60% span was used to observe the exposure-response curves for these 18 combinations of exposure-response relationships with error. A parameter threshold model was also fit using non-linear least squares. Graphical presentations indicate that LOESS adequately detects threshold under no error, but the thresholds were "smoothed out" under the extreme error scenario. Use of a parametric threshold model was adequate to give "nearly unbiased" estimates of threshold concentrations even under the conditions of extreme measurement error, but the uncertainty in the threshold estimates increased with the degree of error. They concluded, "if threshold exists, it is highly likely that standard statistical analysis can detect it".

Schwartz and Zanobetti (2000) investigated the presence of threshold by simulation and actual data analysis of 10 U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA, where daily PM_{10} were available for years 1986-1993. First, a simulation was conducted to show that the combining smoothed curves across cities (the authors called this approach "meta-smoothing") could produce unbiased exposure-response curves.

Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were used to generate mortality series in the 10 cities, and GAM Poisson models were used to estimate respective exposure-response curves. Effects of measurement errors were also simulated. In the analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature, dewpoint, and barometric pressure, and day-of-week. Smooth function of PM_{10} with the same span (0.7) was used in each of the cities. The predicted values of the log relative risks were computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the predicted values were combined across cities using inverse-variance weighting. The simulation results indicated that the "meta-smoothing" approach did not bias the underlying relationships for the linear and threshold models, but did result in a slight downward bias for the logarithmic model. Measurement error (additive or multiplicative) in the simulations did not cause upward bias in the relationship below threshold. The threshold detection in the simulation was not very sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.

The Smith et al. (2000) study of associations between daily total mortality and $PM_{2.5}$ and $PM_{10-2.5}$ in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold. In the linear model, the authors found that mortality was significantly associated with $PM_{10-2.5}$, but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model in which several possible thresholds were specified; and (2) a B-spline (spline with cubic polynomials) model with 4 knots. Using the piecewise model, there was no indication that there was a threshold for $PM_{10-2.5}$. However, for $PM_{2.5}$, the piecewise model resulted in suggestive evidence for a threshold, around 20 to 25 $\mu g/m^3$. The B-spline results also showed no evidence of threshold for $PM_{10-2.5}$, but for $PM_{2.5}$, a non-linear curve showed a change in the slope around 20 $\mu g/m^3$. A further Bayesian analysis for threshold selection suggested a clear peak in the posterior density around 22 $\mu g/m^3$. These results, if they in fact reflect reality, make it difficult to evaluate the relative roles of different PM components (in this case, $PM_{2.5}$ vs. $PM_{10-2.5}$). However, the concentration-response curve for $PM_{2.5}$ presented in this publication suggests more of a U- or V-shaped relationship than the usual "hockey stick" relationship. Such a relationship is, unlike temperature-mortality relationship, difficult to interpret biologically. Because the sample size of this data ($\approx$3 years) is relatively small, further investigation of this issue using similar methods but a larger data set is warranted.

Daniels et al. (2000) examined the presence of threshold using the largest 20 U.S. cities for 1987-1994. The authors compared three log-linear GAM regression models: (1) using a linear PM_{10} term; (2) using a cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. The covariates included in these models are similar to those used by the same research group previously (Kelsall et al., 1997; Samet et al., 2000a,b), including the smoothing function of time, temperature and dewpoint, and day-of-week indicators. Total, cardiorespiratory, and other mortality series were analyzed. These models were fit for each city separately, and for model (1) and (2), the combined estimates across cities were obtained by using inverse variance weighting if there was no heterogeneity across cities, or by using a two-level hierarchical model if there was heterogeneity. The best fit among the models, within each city and over all cities, were also determined using the Akaike's Information Criterion (AIC). The results using the spline model showed that, for total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold. For mortality from other causes, however, the curve did not increase until PM_{10} concentrations exceeded 50 $\mu g/m^3$. While the test of heterogeneity indicated that there was considerable heterogeneity in these curves across cities, the shapes of the curves were similar across cities, with no indication of one city unduly influencing the overall estimate of the curves. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models. Thus, these results suggest that linear models without a threshold may well be appropriate for estimating the effects of PM_{10} on the types of mortality of main interest.

6.4.7 New Theoretical Assessments of Consequences of Measurement Error

Since the 1996 PM AQCD, there have been some advances in conceptual framework development to investigate the effects of measurement error on PM health effects estimated in time-series studies. Several new studies evaluated the extent of bias caused by measurement errors under a number of scenarios with varying extent of error variance and covariance structure between co-pollutants.

Zidek et al. (1996) investigated, through simulation, the joint effects of multi-collinearity and measurement error in Poisson regression model, with two covariates with varying extent of

relative errors and correlation. Their error model was of classical error form (W=X+U, where W and X are surrogate and true measurements, respectively, and the error U is normally distributed). The results illustrated the transfer of effects from the "causal" variable to the confounder. However, for the confounder to have larger coefficients than the true predictor, the correlation between the two covariates had to be large ($r = 0.9$), with moderate error ($\sigma > 0.5$) for the true predictor, and no error for the confounder in their scenarios. The transfer-of-causality effect was mitigated when the confounder also became subject to error. Another interesting finding that Zidek et al. reported is the behavior of the standard errors of these coefficients: when the correlation between the covariates was high ($r = 0.9$) and both covariates had no error, the standard errors for both coefficients were inflated by factor of 2; however, this phenomenon disappeared when the confounder had error. Thus, multi-collinearity influences the significance of the coefficient of the causal variable only when the confounder is accurately measured.

Zeger et al. (2000) also conducted a mathematical analysis of PM mortality effects in ordinary least square model (OLS) with the classical error model, under varying extent of error variance and correlation between two predictor variables. The error described here was analytical error (e.g., discrepancy between the co-located monitors). In general, they found that positive regression coefficients are only attenuated, but null predictors (zero coefficient) or weak predictors are only able to appear stronger than true positive predictors under unusual conditions: (1) true predictors must have very large positive or negative correlation (i.e., $|r| > 0.9$); (2) measurement error must be substantial (i.e., error variance $\approx$ signal variance); and (3) measurement errors must have a large negative correlation. They concluded that estimated FP health effects are likely underestimated, although the magnitude of bias due to the analytical measurement error is not very large.

Zeger et al. (1999) illustrated the implication of the classical error model and the Berkson error model (i.e., $X = W + U$) in the context of time-series study design. Their simulation of the classical error model with two predictors, with various combinations of error variance and correlation between the predictors/error terms, showed results similar to those reported by Zidek et al. (1996). Most notably, for the transfer of the effects of one variable to the other (i.e., error-induced confounding) to be large, the two predictors or their errors need to be substantially correlated. Also, for the spurious association of a null predictor to be more significant than the

true predictor, their measurement errors have to be extremely negatively correlated—a condition not yet demonstrated as occurring in actual air pollution data sets.

Zeger et al. also laid out a comprehensive framework for evaluating the effects of exposure measurement error on estimates of air pollution mortality relative risks in time-series studies. The error, the difference between personal exposure and the central station's measurement of ambient concentration was decomposed into three components: (1) the error due to having aggregate rather than individual exposure; (2) the difference between the average personal exposure and the true ambient concentration level; and, (3) the difference between the true and measured ambient concentration level. By aggregating individual risks to obtain expected number of deaths, they showed that the first component of error (the aggregate rather than individual) is a Berkson error, and, therefore is not a significant contributor to bias in the estimated risk. The second error component is a classical error and can introduce bias if there are short-term associations between indoor source contributions and ambient concentration levels. Recent analysis, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000) and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship between the ambient concentration and the nonambient components of personal exposure to PM. However, a bias can arise due to the difference between the personal exposure to ambient PM (indoors plus outdoors) and the ambient concentration. The third error component is the difference between the true and the measured ambient concentration. According to Zeger et al. the final term is largely of the Berkson type if the average of the available monitors is an unbiased estimate of the true spatially averaged ambient level.

Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to estimate the second error component and its influence on estimated risks. The correlation coefficient between the error (the average population PM_{10} total exposure minus the ambient PM_{10} concentration) and the ambient PM_{10} concentration was estimated to be -0.63. Since this correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the regression of mortality on z_t, the daily ambient concentration) will tend to underestimate the coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on $\overline{x}_t$, the daily average total personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then proceed to assess the size of the bias that will result from this exposure misclassification, using daily ambient concentration, z_t. As shown in Equation 9, the daily average total personal exposure, $\overline{x}_t$, can be

separated into a variable component, $\theta_1 z_t$, dependent on the daily ambient concentration, z_t, and a constant component, θ_o, independent of the ambient concentration.

$$\bar{x}_t = \theta_0 + \theta_1 z_t + \varepsilon_t \quad [9]$$

where ε_t is an error term.

If the nonambient component of the total personal exposure is independent of the ambient concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to the ambient concentration. (The ambient component of personal exposure includes exposure to ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated indoors.) In this well-known approach to adjust for exposure measurement error, called regression calibration (Carroll et al., 1995), the estimate of β_x has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$. Thus, for the regression calibration, the value of β_x (based on the total personal exposure) does not depend on the total personal exposure but is given by β_z, based on the ambient concentration, times θ_1, the ratio of the ambient component of personal exposure to the ambient concentration. A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

Zeger et al. (2000) use Equation 9, with $\hat{\theta}_o = 59.95$ and $\theta_1 = 0.60$, estimated from the PTEAM data, to simulate values of daily average personal exposure, x^*_t, from the ambient concentrations, z_t, for PM_{10} in Riverside, CA, 1987-1994. They then compare the mean of the simulated $\hat{\beta}_x$ s, obtained by the series of log-linear regressions of mortality on the simulated x^*_t, with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the log-linear regression of mortality directly on z_t. The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$, is very close to $\theta_1 = 0.60$. Dominici et al. (2000) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical model. Their findings were qualitatively similar in that $\hat{\beta}_x$ was close to $\hat{\beta}_z / \theta_1$. Thus, it appears

that the bias is very close to θ_1 which depends not on the total personal exposure but only on the ratio of the ambient component of personal exposure to the ambient concentration.

Zeger et al. (2000), in the analyses described above, also suggested that the error due to the difference between the average personal exposure and the ambient level (the second error type described above) is likely the largest source of bias in estimated relative risk. This suggestion at least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed relatively high site-to-site correlation ($\approx$0.6-0.9), a similar extent of site-to-site correlation for other pollutants is not necessarily expected. Ito et al. (1998) estimated site-to-site correlations (after adjusted for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint temperature, and relative humidity, using multiple stations' data from seven central and eastern states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles, these variables could be categorized into three groups in terms of the extent of correlation: weather variables ($r > 0.9$); O_3, PM_{10}, NO_2 (r: 0.6 - 0.8); CO and SO_2 ($r < 0.5$). These results suggest that the contribution from the third component of error, as described in Zeger et al. (2000), would vary among pollution and weather variables. Furthermore, the contribution from the second component of error would also vary among pollutants; i.e., the ratio of ambient exposure to ambient concentration, called the attenuation coefficient, is expected to be different for each pollutant. Some of the ongoing studies are expected to shed some light on this issue. However, more information is needed on attenuation coefficients for a variety of pollutants.

With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999), show reasonably good correlation ($r = 0.6$ to 0.9) between ambient PM concentrations and average population PM exposure, lending support for the use of ambient data as a surrogate for personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore, fine particles are expected to show even better site-to-site correlation than PM_{10}. Wilson and Suh (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for $PM_{10-2.5}$ ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger mortality associations for fine particles than coarse particles found in the Schwartz et al. (1996a) study may be due in part to larger measurement error for coarse particles.

However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle association with mortality is a "false positive", but rather, whether the weaker mortality association with coarse particles is a "false negative". Carrothers and Evans (2000) also investigated the joint effects of correlation and relative error, but they specifically addressed the issue of fine (FP) vs. coarse particle (CP) effect, by assuming three levels of relative toxicity of fine vs. coarse particles (β_{FP} / β_{CP} = 1, 3, and 10) and, then, evaluating the bias, ($B = \{E[\beta_{F'}] / E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e., B=1) as long as FP and CP are measured with equal precision, but, if, for example, FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e., B > 1); (2) when FP is more toxic than CP (i.e., β_{FP} / β_{CP} = 3 and 10), however, the equal precision of FP and CP results in downward bias of FP (B < 1), implying a relative overestimation of the less toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more so as the correlation between FP and CP increases. They also applied this model to real data from the Harvard Six Cities Study, in particular, the data from Boston and Knoxville. Estimation of spatial variability for Boston was based on external data and a range of spatial variability for Knoxville (since there was no spatial data available for this city). For Boston, where the estimated FP-CP correlation was low (r = 0.28), estimated error was smaller for FP than for CP (0.85 vs. 0.65, as correlation between true vs. error-added series), and the observed FP to CP coefficient ratio was high (11), the calculated FP to CP coefficient ratio was even larger (26)-thus providing evidence against the hypothesis that FP is absorbing some of the coefficient of CP. For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than for CP (0.9 vs. 0.75), and the observed FP to CP coefficient ratio was 1.4, the calculated true FP to CP coefficient ratio was smaller (0.9) than the observed value, indicating that the coefficient was overestimated for the better-measured FP, while the coefficient was underestimated for the worse-measured CP. Since the amount (and the direction) of bias depended on several variables (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity), the authors concluded "...for instance, it is inadequate to state that differences in measurement error among fine and coarse particles will lead to false negative findings for coarse particles".

Fung and Krewski (1999) conducted a simulation study of measurement error adjustment methods for Poisson models, using scenarios similar to those used in the simulation studies that investigated implication of joint effects of correlated covariates with measurement error. The measurement error adjustment methods employed were the Regression Calibration (RCAL) method (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and Stefanski, 1994). Briefly, RCAL algorithm consists of: (1) estimation of the regression of X on W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its estimate from (1), and conducting the standard analysis (i.e., regression); and (3) adjustment of the resulting standard error of coefficient to account for the calibration modeling. SIMEX algorithm consists of: (1) addition of successively larger amount of error to the original data; (2) obtaining naive regression coefficients for each of the error added data sets; and, (3) back extrapolation of the obtained coefficients to the error-free case using a quadratic or other function. Fung and Krewski examined the cases for: (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$; $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$., all with varying level of correlation (-0.8 to 0.8) with and without classical additive error, and also considering Berkson type error. The behaviors of naive estimates were essentially similar to other simulation studies. In most cases with the classical error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation was small), recovering underlying coefficients. In the presence of Berkson type error, however, even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5). This is the first study to examine the performance of available error adjustment methods that can be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX. Possible reasons why RCAL performed better than SIMEX in these scenarios were not discussed, nor are they clear from the information given in the publication. There has not been a study to apply these error adjustment methods in real time-series health effects studies. These methodologies require either replicate measurements or some knowledge on the nature of error (i.e., distributional properties, correlation, etc.). Since the information regarding the nature of error is still being collected at this time, it may take some time before applications of these methods become practical.

Another issue that measurement error may affect is the detection of threshold in time-series studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape of the exposure-response curve, and that such error could make the exposure-response curve to

appear linear even when a threshold may exist. However, based on a simulation with realistic range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated that the modern smoothing approach, LOESS, can adequately detect threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$) even with the presence of exposure error (see also Section 6.4.6 above).

Other issues related to exposure error that have not been investigated include potential differential error among subpopulations. If the exposure errors are different between susceptible population groups (e.g., people with COPD) and the rest of the population, the estimation of bias may need to take such differences into account. Also, the exposure errors may vary from season to season, due to seasonal differences in the use of indoor emission sources and air exchange rates due to air conditioning and heating. This may possibly explain reported season-specific effects of PM and other pollutants. Such season-specific contributions of errors from indoor and outdoor sources are also expected to be different from pollutant to pollutant.

In summary, the studies that examined joint effects of correlation and error suggest that PM effects are likely underestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of coefficient) due to transferring of effects from other covariates require extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing methods. More data are needed to examine the exposure errors for other pollutants, since their relative error contributions will influence their relative significance in relative risk estimates.

6.4.8 New Assessment of Methodological Issues

6.4.8.1 Time Series Model Specification

Methodological issues in time-series analyses of air pollution-mortality association were discussed extensively in the 1996 PM AQCD. Since then, increasing numbers of researchers have been utilizing essentially the same Poisson regression approach: (1) model seasonal cycles and other temporal trends using smoothing functions of time; (2) model weather effects using smoothing functions of temperature, humidity, and/or their interaction at various lags; (3) after adjustment for these confounding factors, enter various lags (and averaging periods) of air pollutant, and report results for all the lags, and/or report results for the lags that resulted in the highest significance; (4) repeat (3) with other pollutants in the model; (5) conduct sensitivity

analyses using alternative weather model specifications. Seasonal cycles and weather effects are often modeled using Generalized Additive Models (GAM). As the modeling of temporal trends became more efficient using the GAM models, it became clearer that the residual over-dispersion and autocorrelation could be essentially eliminated. Also, more researchers appear to rely on Akaike's Information Criteria (AIC) or on the more conservative Bayes (Schwarz, 1978) Information Criterion (BIC) to choose between models when epidemiological reasoning does not favor one over the other. While these techniques do not necessarily eliminate inadequate model specifications, they do help "standardize" the approaches that researchers can take, reducing the inconsistency in model specification among studies.

A few remaining inconsistencies in approach among studies include: (1) choice of the range of lags and averaging periods of pollution included; (2) smoothing spans used for modeling temporal trends and weather effects; (3) the increment used to calculate relative risks; and, (4) choice to detrend pollution variables. The choice of lag can lead to inconsistent results even for the same data. The choice of the combination of lags multiplies as the number of co-pollutants in the model increases. In the case of temperature effects, it has been repeatedly observed that the heat effects tend to be immediate (0 or 1 day lag), while cold effects tend to lag longer (2 to 4 days). For pollutants, however, reported lags are less consistent. The smoothing span for temporal trends can be determined based on epidemiological reasons (i.e., eliminate influenza epidemics), but the span for weather effects may be determined through data exploration. Using the inter-quartile range for all the co-pollutants may be problematic when co-pollutants have inconsistent distributional characteristics. While these issues may appear rather minor, in practice, they may make substantial differences in reported effects and interpretations.

6.4.8.2 Case-Crossover Study Design

Navidi et al. (1999) proposed the use of "bi-directional" controls in applying the case-crossover design to study acute effects of air pollution. In the original case-crossover studies in which risk factors were behavior-related (e.g., coffee consumption), the control period was chosen prior to the case period (i.e., retrospective uni-directional) because choosing the control period after the event would interfere with behavioral modification associated with the risk factor, possibly resulting in bias. In the case of environmental exposures such as ambient air

pollution, however, the event is unlikely to modify future exposure. Furthermore, in the case of observational air pollution study, the bi-directional control periods would be necessary to avoid confounding due to temporal trends in both events (e.g., influenza-related mortality or morbidity) and exposure (natural seasonal trends). Navidi conducted simulations to illustrate that the relative risk estimates are resistant to confounding by time-trend.

Bateson and Schwartz (1999) also conducted a simulation study to compare five case-crossover control sampling strategies including the matched pair, a symmetric bi-directional, a total history approach, and the two approaches that Navidi proposed. The symmetric bi-directional approach using 1-week lag estimated the true relative risks correctly in the presence of confounding seasonal trends, whereas the other four approaches failed to control for the confounding trends. They concluded that the bi-directional case-crossover design could control for confounding by design, though it is not as efficient as Poisson time-series analysis.

There have been several studies that applied the case-crossover design to analyze air pollution – mortality associations, as described below.

Neas et. al. (1999) analyzed Philadelphia TSP data for 1973-1980. Total, age over 65, cancer, and cardiovascular deaths were analyzed for their association with TSP. A conditional logistic regression analysis with a case-crossover design was conducted using the control periods of 7, 14, and 21 days before and after the case period. Other covariates included temperature on the previous day, dewpoint on the same day, an indicator for hot days (> 80°F), an indicator for humid days (dewpoint > 66°F), and interaction between the same-day temperature and winter season. In each set of the six control periods, TSP was associated with total mortality. A model with four symmetric reference periods 7 and 14 days around the case period produced a similar result. A model with only two symmetric reference periods of 7 days around the case produced a larger estimate. A larger effect was seen for deaths in persons ≥ 65 years of age and for deaths due to pneumonia and to cardiovascular disease. Thus, this study basically confirmed the original findings by Schwartz and Dockery (1992) for this city.

Sunyer et al. (2000) analyzed Barcelona, Spain BS data for 1990-1995. Those who were over age 35 and had sought emergency room services for COPD exacerbation between 1985 and 1989, and had died during 1990-1995 were included in analysis. Total, respiratory, and cardiovascular deaths were analyzed using a conditional logistic regression analysis with a case-crossover design, adjusting for temperature, relative humidity, and influenza epidemics.

Bi-directional control period at 7 days was used. The average of the same and previous 2 days was used for pollution exposure period. Data were also stratified by potential effect modifiers (e.g., age, gender, severity of ER visits, number of ER visits, etc.) and were analyzed. BS levels were associated with all cause deaths. The association was stronger for respiratory causes. Older women, patients admitted to intensive care units, and patients with a higher rate of ER visits were at greater risk of deaths associated with BS.

Lee and Schwartz (1999) analyzed data from Seoul, Korea for 1991-1995. Total deaths were analyzed for their association with TSP, SO_2, and O_3. A conditional logistic regression analysis with a case-crossover design was conducted. Three-day moving average values (current and two past days) of TSP and SO_2, and 1-hr max O_3 were analyzed separately. The control periods are 7 and 14 days before and/or after the case period. Both unidirectional and bi-directional controls (7 or 7 and 14 days) were examined, resulting in six sets of control selection schemes. Other covariates included temperature and relative humidity. Among the six control periods, the two unidirectional retrospective control schemes resulted in odds ratios less than 1; the two unidirectional prospective control schemes resulted in larger odds ratios (e.g., 1.4 for 50 ppb increase in SO_2); and bi-directional control schemes resulted in odds ratios between those for uni-directional schemes. SO_2 was more significantly associated with mortality than TSP. These results suggested that risk estimates were rather sensitive to the choice of the control periods.

These analyses suggest that the overall findings are not very sensitive to these analytic choices; thus we can have more confidence in the mortality results. The sensitivity analyses are not as extensive for examining the PM_{10} effect on morbidity, and the investigators used a different time window across the 14 cities to control for temporal effects. Future analyses of both the mortality and morbidity data might include a seasonally stratified analysis (given the seasonal variability in pollutant concentrations, outcome measures, and potential confounding factors). Loss of statistical power due to the shorter periods of observation in any season should be only a minor issue, at least in the mortality data set.

6.4.9 Heterogeneity of Particulate Matter Effects Estimates

Approximately 35 then-available acute PM exposure community epidemiologic studies were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality

being associated with short-term (24-h) PM exposures indexed by various ambient PM measurement indices (e.g., PM_{10}, $PM_{2.5}$, BS, COH, sulfates, etc.) in many different cities in the United States and internationally. Much homogeneity appeared to exist across various geographic locations, with many studies suggesting, for example, increased relative risk (RR) estimates for total nonaccidental mortality on the order of 1.025 to 1.05 (or 2.5 to 5.0% excess deaths) per 50 $\mu g/m^3$ increase in 24-h PM_{10}, with statistically significant results extending more broadly in the range of 1.5 to 8.0%. The elderly $\geq$65 yrs. old and those with preexisting cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to 1.056 (2.0 to 5.6% excess deaths) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.

Now, more than 70 new time-series PM-mortality studies assessed earlier in this chapter provide extensive additional evidence which, qualitatively, largely substantiates significant ambient PM-mortality relationships, again based on 24-h exposures indexed by a wide variety of PM metrics in many different cities of the United States, in Canada, in Mexico, and elsewhere (in South America, Europe, Asia, etc.). The newly available effect size estimates from such studies are reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996 PM AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increment in 24-h concentration; whereas new $PM_{2.5}$ excess estimates for short-term exposures generally fall in the range of 2 to 8% per 25 $\mu g/m^3$ increment in 24-h $PM_{2.5}$ concentration.

However, somewhat greater spatial heterogeneity appears to exist across newly reported study results, both with regard to PM-mortality and morbidity effects. The newly apparent heterogeneity of findings across locations is perhaps most notable in relation to reports based on multiple-city studies in which investigators used the same analytical strategies and models adjusted for the same or similar co-pollutants and meteorological conditions, raising the possibility of different findings reflecting real location-specific differences in exposure-response relationships rather than potential differences in models used, pollutants measured and included in the models, etc. Some examples of newly reported and well-conducted multiple-city studies include: the NMMAPS analyses of mortality and morbidity in 20 and 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2000); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of eight largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S.

counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several European cities (Katsouyanni et al., 1997; Zmirou et al., 1998). The recently completed large NMMAPS studies of morbidity and mortality in U.S. cities add especially useful and important information about potential U.S. within- and between-region heterogeneity.

6.4.9.1 Evaluation of Heterogeneity of Particulate Matter Mortality Effect Estimates

In all of the U.S. multi-city analyses, the heterogeneity in the PM estimates across cities was not explained by city-specific characteristics in the 2nd stage model. The heterogeneity of effects estimates across cities in the multi-city analyses may be due to chance alone, to mis-specification of covariate effects in small cities, or to real differences from location to location in effects of different location-specific ambient PM mixes, for which no mechanistic explanations are yet known. Or, the apparent heterogeneity may simply reflect imprecise PM effect estimates derived from smaller-sized analyses of less extensive available air pollution data or numbers of deaths in some cities tending to obscure more precise effects estimates from larger-size analyses for other locations, which tend to be consistently more positive and statistically significant.

Some of these possibilities can be evaluated by using data from the NMMAPS study (Samet et al., 2000b). Data in Figure 6-1 were optically scanned and digitized, producing reasonably accurate estimates by comparison with the 20 largest U.S. cities in their Table A-2. The cities were divided among 7 regions, and excess risk with 95% confidence intervals plotted against the total number of effective observations, measured by the number of days of PM_{10} data times the mean number of daily deaths in the community. This provides a useful measure of the weight that might be assigned to the results, since the uncertainty of the RR estimate based on a Poisson mean is roughly inversely proportional to this product. That is, the expected pattern typically shows less spread of estimated excess risk with increasing death-days of data. A more refined weight index would also include the spread in the distribution of PM concentrations. The results are plotted in Figure 6-12 for all cities and Figure 6-13 for each of the 7 regions.

Figure 6-12 for all cities suggests some relationship between precision of the effects estimates and study weight, overall. That is, the more the mortality-days observations, the narrower the 95% confidence intervals and the more precise the effects estimates (with nearly all

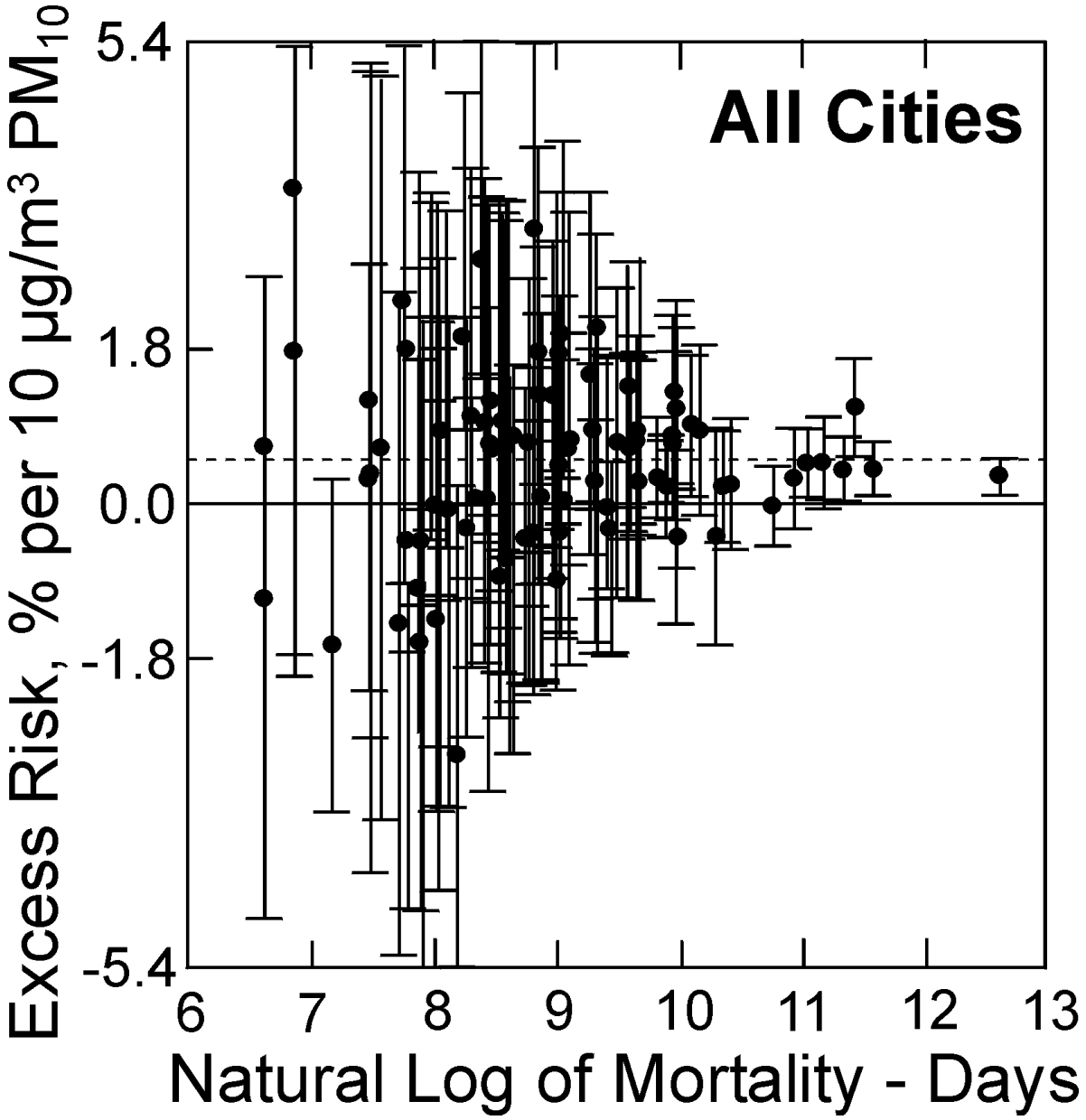

Figure 6-12. The EPA-derived plot showing relationship of PM_{10} total mortality effects estimates and 95% confidence intervals for all cities in the Samet et al. (2000a,b) NMMAPS 90-cities analyses in relation to study size (i.e., the natural logarithm of numbers of deaths times days of PM observations). Note generally narrower confidence intervals for more homogeneously positive effects estimates as study size increases beyond about the log 9 value (i.e., beyond about 8,000 deaths-days of observation). The dashed line depicts the overall nationwide effect estimate (grand mean) of approximately 0.5% per 10 $\mu g/m^3$ PM_{10}.

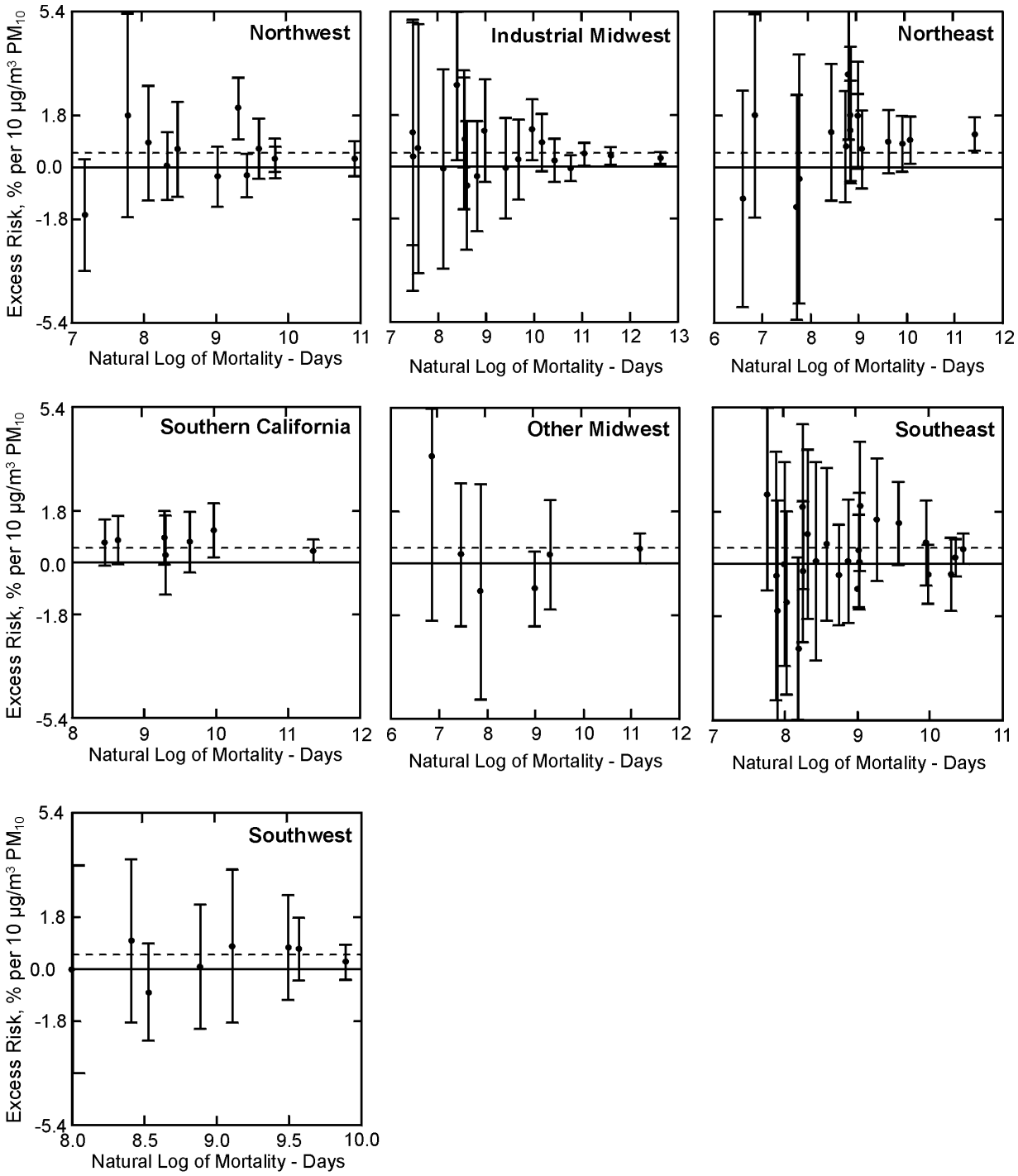

Figure 6-13. The EPA-derived plots showing relationships of PM_{10}-mortality (total, nonaccidental) effects estimates and 95% confidence intervals to study size (defined as in Figure 6-10) for cities broken out by regions as per the NMMAPS regional analyses of Samet et al. (2000a,b). Dashed line on each plate depicts overall nationwide effect estimate (grand mean) of approximately 0.5% per 10 $\mu g/m^3$ PM_{10}.

these for cities with ≥ log 9 mortality-days being positive and many statistically significant at $p \leq 0.05$).

The Figure 6-13 depiction for each of the 7 regions is also informative. In the Northeast, there is considerable homogeneity (not heterogeneity) of effect size for larger study-size cities, even with moderately wide confidence intervals for those with log mortality-days = 8 to 9, and all clearly exceed the overall nationwide grand mean indicated by the dashed line. On the other hand, the smaller study-size Northeast cities (with much wider confidence intervals at log < 8) show much greater heterogeneity of effects estimates and less precision. Also, most of the estimates for larger study-size (log > 9) cities in the industrial midwest are positive and several statistically significant, so that an overall significant regional risk is plausible there as well. There may even be some tendency for relatively large risks for some cities with small study sizes and wide confidence intervals in the industrial midwest, and further investigation of that would be of interest. The plot for Southern California in Figure 6-13 clearly shows a rather consistent estimate of effect size and width of the confidence intervals across cities of varying study-size. All risk estimates are positive and most are significant at $p \leq 0.05$ or nearly so for the Southern California cities. For Northwestern cities plotted in Figure 6-13, the value for Oakland, CA (at ca. log 9.5) is notable (it being very positive and significant), whereas many but not all of the other cities have positive effect estimates not too far off the nationwide grand mean, but with sufficiently wide confidence intervals so as not to be statistically significant at $p \leq 0.05$. The Southwestern cities (except for 2 cities), too, mostly appear to have effect sizes near the nationwide mean, but with confidence intervals too wide to be significant at $p \leq 0.05$. The "Other" (non-industrial or "Upper", as per NMMAPS) Midwest cities and the Southeastern cities in Figure 6-13 show more heterogeneity, although most of the larger study size cities (log ≥ 9.0) tend to be positive and not far off the nationwide mean (even though not significant at $p \leq 0.05$). Given the wide range of effects estimates and confidence intervals seen for Southeastern cities, further splitting of the region might be informative.

In fact, closer reexamination of results for each of the regions may reveal interesting new insights into what factors may account for any apparent disparities among the cities within a given region or across regions. Several possibilities readily come to mind. First, cursory inspection of the mean PM_{10} levels shown for each city in Appendix 6A-2 suggests that many of the cities showing low effects estimates and wide confidence intervals tend to be among those

having the lowest mean PM_{10} levels and, therefore, likely the smallest range of PM_{10} values across which to distinguish any PM-related effect, if present. It may also be possible that those areas with higher $PM_{2.5}$ proportions of PM_{10} mass (i.e., larger percentages of fine particles) may show higher effects estimates (e.g., in Northeastern cities) than those with higher coarse-mode fractions (e.g., as would be more typical of Southwestern cities). Also, more industrialized cities with greater fine-particle emissions from coal combustion (e.g., in the industrial Midwest) and/or those with high fine-particle emissions from heavy motor vehicle emissions (e.g., typical of Southern California cities) may show larger PM_{10} effects estimates than other cities. Lastly, the extent of air-conditioning use may also account for some of the differences, with greater use in many Southeastern and Southwestern cities perhaps decreasing actual human exposure to ambient particles present versus higher personal exposure to ambient PM (including indoors) in those areas where less air-conditioning is used (e.g., the Northeast and industrial Midwest).

6.4.9.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies

Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of U.S. cities to allow considerable resolution of regional PM effects within the "lower 48" states, but an attempt was made to take this approach to a much more detailed level in the Cohort Reanalysis studies than in NMMAPS. There were: 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in the original Pope et al. (1995) ACS analyses and in the HEI reanalyses using the original data; and 63 cities with $PM_{2.5}$ data and 144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis team. The relatively large number of data points utilized in the HEI reanalyses effort and additional analyses allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers.

The patterns for $PM_{2.5}$ and sulfates are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski et al., 2000; Figure 18) has peak levels around Chicago - Gary, in the eastern Kentucky - Cleveland region, and around Birmingham AL, with elevated but lower $PM_{2.5}$ almost everywhere east of the Mississippi, as well as southern California. This is similar to the modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated SO_2

concentrations is the Cleveland - Pittsburgh region. A preliminary evaluation is that secondary sulfates in particles derived from local SO_2 are more likely to be important in the industrial midwest, south from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia, and southwest Pennsylvania, possibly related to combustion of high-sulfur fuels.

The overlay of mortality with air pollution patterns is also of much interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewski et al., 2000; Figure 21) is highest from southern Ohio to northeastern Kentucky/West Virginia, but also includes a significant association over most of the industrial midwest from Illinois to the eastern non-coastal parts of North Carolina, Virginia, Pennsylvania, and New York. This is reflected, in diminished form, by the sulfates and SO_2 maps (Krewski et al., 2000; Figures 19 and 20), where there appears to be a somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that, while SO_2 may be an important precursor of sulfates in this region, there may also be some other (non-sulfur) contributors to associations between $PM_{2.5}$ and long-term mortality, embracing a wide area of the Northcentral Midwest and non-coastal Mid-Atlantic region.

It should be noticed that, while a variety of spatial modeling approaches were discussed in the NMMAPS methodology report (NMMAPS Part I, pp. 66-71 [Samet et al., 2000a]), the primary spatial analyses in the 90-city study (NMMAPS, Part II [Samet et al., 2000b]) were based on a simpler seven-region breakdown of the contiguous 48 states. The 20-city results reported for the spatial model in NMMAPS I show a much smaller posterior probability of a PM_{10} excess risk of short-term mortality, with a spatial posterior probability vs. a non-spatial probability of a PM_{10} effect of 0.89 vs. 0.98 at lag 0, of 0.92 vs. 0.99 at lag 1, and of 0.85 vs. 0.97 at lag 2. The evidence that PM_{10} is associated with an excess short-term mortality risk is still moderately strong with a spatial model, but less strong than with a non-spatial model.

Even so, there is a considerable degree of coherence between the short-term and long-term mortality findings of the two studies, with strong evidence of a modest but significant short-term PM_{10} effect and a large long-term fine particle ($PM_{2.5}$ in general or sulfate) effect in the industrial Midwest. The short-term PM_{10} effects are large in the Northeast and in Southern California (though less certain there), whereas long-term $PM_{2.5}$ effects seem to be moderate to high in these areas as well. This may tend to suggest that at least some of the more notable PM_{10} effects found in the NMMAPS regional analyses may coincide with the presence of higher proportions of fine versus coarse particles in the PM_{10} mix.

The apparently substantial differences in PM_{10} and/or $PM_{2.5}$ effect sizes across different regions should not be attributed merely to possible variations in measurement error or other statistical artifact(s). Some of these differences may reflect: real regional differences in particle composition or co-pollutant mix; differences in relative human exposures to ambient particles or other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in regional population); or other important, as of yet unidentified PM effect modifiers.

6.5 KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES

It is not possible to assign any absolute measure of certainty to conclusions based on the findings of the epidemiology studies discussed in this chapter. However, these observational study findings would be further enhanced by supportive findings of causal studies from other scientific disciplines (dosimetry, toxicology, etc.), as discussed in Chapters 7 to 9. The most salient conclusions derived from the PM epidemiology studies include:

(1) A very large and sufficiently convincing body of epidemiology evidence substantiates strong associations between short- and long-term ambient PM_{10} exposures (inferred from stationary air monitor measures) and mortality/morbidity effects to conclude that PM_{10} (or one or more PM_{10} components) is a probable contributory cause of human health effects.

(2) It is likely that there is meaningful heterogeneity in the city-specific excess risk estimates for the relationships between short-term ambient PM_{10} concentrations and acute health effects. The reasons for such variation in effects estimates are not well understood at this time, but do not negate ambient PM's likely causative contribution to observed PM-mortality and/or morbidity associations in many locations.

(3) A smaller (but growing) body of epidemiology evidence is sufficiently indicative of associations between short- and long-term ambient $PM_{2.5}$ exposures (inferred from stationary air monitor measures) and health effects to conclude that $PM_{2.5}$ (or one or more $PM_{2.5}$ components) is a probable contributing cause of observed PM-associated health effects. Some new epidemiology findings also suggest that health effects are associated with mass or number concentrations of ultrafine (nuclei-mode) particles, but not necessarily more so than for other ambient fine PM components.

(4) An even smaller body of evidence exists which appears to support an association between short-term ambient coarse-fraction ($PM_{10-2.5}$) exposures (inferred from stationary air monitor measures) and short-term health effects in epidemiology studies. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may be a contributory cause of health effects in some locations. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, but several of the locations where significant $PM_{10-2.5}$ effects have been observed (Phoenix, Mexico City, Santiago) tend to be in drier climates and may have contributions to observed effects due to higher levels of organic particles from biogenic processes (endotoxins, molds, etc.) during warm months. Other studies suggest that coarse fraction ($PM_{10-2.5}$) particles of crustal origin are unlikely to exert notable health effects under most ambient exposure conditions.

(5) Long-term PM exposure durations, on the order of months to years, as well as on the order of a few days, are likely associated with serious human health effects (indexed by mortality, hospital admissions/medical visits, etc.). More chronic PM exposures, on the order of years or decades, appear to be associated with life shortening beyond that accounted for by the simple accumulation of the more acute effects of short-term PM exposures (on the order of a few days). While the few studies of this relationship were generally well conducted, notable uncertainties remain regarding the meaning, magnitude, and mechanisms for more chronic health effects of long-term PM exposures. New findings of associations between ambient PM exposures (indexed by various measures) during early pregnancy and/or early post-natally and slowed fetal growth or infant mortality, respectively, suggest potentially much larger life-shortening impacts of PM than previously estimated.

(6) Considerable coherence exists among effect size estimates for ambient PM health effects. For example, results derived from several multi-city studies, based on pooled analyses of data combined across multiple cities (thought to yield the most precise effect size estimates), show the percent excess total (non-accidental) deaths estimated per 50 $\mu g/m^3$ increase in 24-h PM_{10} to be: 2.3% in the 90 largest U.S. cities (4.5% in the Northeast U.S. region); 3.4% in 10 U.S. cities; 3.5% in the 8 largest Canadian cities; and 2.0% in western European cities (using PM_{10} = TSP*0.55). These combined estimates are consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD. These and excess risk estimates from many other individual-city studies, generally falling in the range of ca.

1.5 to 8.0% per 50 $\mu g/m^3$ 24-h PM_{10} increment, also comport well with numerous new studies confirming increased cause-specific cardiovascular- and respiratory-related mortality. They are also coherent with larger effect sizes reported for cardiovascular (in the range of ca. 3.0 to 10.0% per 50 $\mu g/m^3$ 24-h PM_{10} increment) and respiratory (in the range of ca. 5 to 25% per 50 $\mu g/m^3$ 24-h PM_{10}) hospital admissions/visits, as would be expected for these morbidity endpoints versus those for PM_{10}-related mortality.

(7) Several independent panel studies (but not all) that evaluated temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects provide generally consistent indications of decreased heart rate variability (HRV) being associated with ambient PM exposure (decreased HRV being an indicator of increased risk for serious cardiovascular outcomes, e.g., heart attacks). Other studies point toward changes in blood characteristics (e.g., C-reactive protein levels) related to increased risk of ischemic heart disease also being associated with ambient PM exposures. However, these heart rhythm and blood characteristics findings should currently be viewed as providing only limited or preliminary support for PM-related cardiovascular effects.

(8) Notable new evidence now exists which substantiates positive associations between ambient PM concentrations and increased respiratory-related hospital admissions, emergency department, and other medical visits, particularly in relation to PM_{10} levels. Of much interest are new, but limited, findings tending to implicate not only fine particle components but also coarse (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of asthma conditions. Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure.

(9) One major methodological issue affecting epidemiology studies of both short-term and long-term PM exposure effects is that ambient PM of varying size ranges is typically found in association with other air pollutants, including gaseous criteria pollutants (e.g, O_3, NO_2, SO_2, CO), air toxics, and/or bioaerosols. Available statistical methods for assessing potential confounding arising from these associations may not yet be fully adequate. The inclusion of multiple pollutants often produces statistically unstable estimates. Omission of other pollutants may incorrectly attribute their independent effects to PM. Much progress in sorting out relative contributions of ambient PM components versus other copollutants is

nevertheless being made and, overall, tends to substantiate that observed PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants.

(10) It is likely that differences in observed health effects will be found to depend as much on site-specific differences in chemical and physical composition characteristics of ambient particles as on differences in PM mass concentration. For example, the Utah Valley study (Dockery et al., 1999; Pope et al., 1991, 1999b) showed that PM_{10} particles, known to be richer in metals during exposure periods while the steel mill was operating, were more highly associated with adverse health effects than was PM_{10} during the PM exposure reduction while the steel mill was closed. In contrast, PM_{10} or $PM_{2.5}$ was relatively higher in crustal particles during windblown dust episodes in Spokane and in three central Utah sites than at other times, but was not associated with higher total mortality. These differences require more research that may become more feasible as the $PM_{2.5}$ sampling network produces air quality data related to speciated samples.

(11) The above reasons suggest it is inadvisable to pool epidemiology studies at different locations, different time periods, with different population sub-groups, or different health endpoints, without assessing the consequences of these differences. Published multi-city analyses using common data bases, measurement devices, and analytical strategies such as those carried out in the APHEA and NMMAPS studies are likely to be useful after careful evaluation. Pooled analyses of more diverse collections of independent studies of different cities, using varying methodology and/or data quality or representativeness, are likely less credible and should not, in general, be used without careful assessment of their underlying scientific comparability.

(12) It may be possible that different PM components may produce effects which appear at different lags or that different preexisting conditions may lead to different delays between exposure and effect. Thus, although maximum effect sizes for PM effects have often been reported for 0-1 day lags, evidence is also beginning to suggest that more consideration should be given to lags of several days. Also, if it is considered that all health effects occurring at different lag days are all real effects, so that the risks for each lag day should be additive, then higher overall risks may exist than implied by maximum estimates for any particular single or two-day lags.

(13) Certain classes of ambient particles may be distinctly less toxic than others and may not exert human health effects at typical ambient exposure concentrations or only under special circumstances. For example, particles of crustal origin may be relatively non-toxic under most circumstances compared to those of combustion origin. However, crustal particles contaminated with pesticides or herbicides (as may occur in agricultural situations) or with emissions from vehicles, smelters, or other industrial operations may be sufficiently toxic to cause human health effects under some exposure conditions. More research is needed to identify conditions under which one or another class of particles cause little or no adverse health effects, as well as conditions under which particles cause notable effects.

(14) Certain epidemiology evidence suggests that reducing ambient PM_{10} concentrations may reduce a variety of health effects on a time scale from a few days to a few months. This has been found in epidemiology studies of "natural experiments" such as in the Utah Valley, and by supporting toxicology studies using the particles from ambient community sampling filters from the Utah Valley. Recent studies in Germany and in the Czech Republic also support a hypothesis that reductions in air pollution are associated with reductions in the incidence of adverse health effects, but these studies cannot unambiguously attribute improved health to reduced PM alone.

(15) Adverse health effects in children are emerging as a more important area of concern than in the 1996 PM AQCD. Unfortunately, relatively little is known about the relationship of PM to the most serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in older children). Also, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue because childhood illness or death may cost a very large number of productive life-years. Lastly, new epidemiologic studies of ambient PM associations with increased non-hospital medical visits (physician visits) and asthma effects suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed by mortality and/or hospital admissions/visits.

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APPENDIX 6A

Demographic and Pollution Data for 90-City Analysis of NMMAPS Project

TABLE 6A-1. THE 90 CITIES AND THEIR INCLUDED COUNTIES BY POPULATION SIZE WITH MEAN DAILY NUMBER OF DEATHS BY CATEGORY (1987-1994). Evaluated in NMMAPS 90-Cities Analyses, Samet et al. (2000a,b).

City	Abbreviation	County	State	Population	Total	CVD/Respiratory Disease	Other
Los Angeles	la	Los Angeles	CA	8,863,164	148.1	87.0	61.1
New York	ny	Bronx, Kings, New York, Richmond, Queens, Westchester	NY	8,197,430	190.9	108.3	82.6
Chicago	chic	Cook	IL	5,105,067	113.9	62.0	51.9
Dallas/Fort Worth	dlft	Collin, Dallas, Rockwall, Tarrant	TX	3,312,553	47.9	26.0	21.9
Houston	hous	Harris	TX	2,818,199	39.9	20.0	19.8
San Diego	sand	San Diego	CA	2,498,016	41.6	22.6	19.0
Santa Ana/Anaheim	staa	Orange	CA	2,410,556	32.4	18.7	13.6
Phoenix	phoe	Maricopa	AZ	2,122,101	38.4	20.9	17.5
Detroit	det	Wayne	MI	2,111,687	46.9	26.5	20.4
Miami	miam	Dade	FL	1,937,094	43.8	23.6	20.2
Philadelphia	phil	Philadelphia	PA	1,585,577	42.3	21.5	20.8
Minneapolis/St. Paul	minn	Hennepin, Ramsey	MN	1,518,196	26.3	13.9	12.4
Seattle	seat	King	WA	1,507,319	25.6	13.4	12.2
San Jose	sanj	Santa Clara	CA	1,497,577	19.7	10.7	9.0
Cleveland	clev	Cuyahoga	OH	1,412,140	36.5	20.1	16.4
San Bernardino	sanb	San Bernardino	CA	1,418,380	20.6	12.1	8.5
Pittsburgh	pitt	Allegheny	PA	1,336,449	37.6	21.0	16.9
Oakland	oakl	Alameda	CA	1,279,182	22.2	12.2	10.0
Atlanta	atla	Fulton, De Kalb	GA	1,194,788	17.5	8.8	8.7
San Antonio	sana	Bexar	TX	1,185,394	20.1	10.5	9.6
Riverside	rive	Riverside	CA	1,170,413	20.1	12.4	7.7
Denver	denv	Denver, Adams, Arapahoe	CO	1,124,159	9.1	5.0	4.1
Sacramento	sacr	Sacramento	CA	1,041,219	17.2	9.5	7.7
St. Louis	stlo	St. Louis City	MO	993,529	10.7	6.0	4.7
Buffalo	buff	Erie	NY	968,532	25.2	14.8	10.3

TABLE 6A-1 (cont'd). THE 90 CITIES AND THEIR INCLUDED COUNTIES BY POPULATION SIZE WITH MEAN DAILY NUMBER OF DEATHS BY CATEGORY (1987-1994). Evaluated in NMMAPS 90-Cities Analyses, Samet et al. (2000a,b).

City	Abbreviation	County	State	Population	Total	CVD/Respiratory Disease	Other
Columbus	clmo	Franklin	OH	961,437	16.8	8.9	7.9
Cincinnati	cinc	Hamilton	OH	866,228	19.9	11.0	8.9
St. Petersburg	stpe	Pinellas	FL	851,659	29.3	17.7	11.6
Kansas City	kan	Clay, Jackson, Platte	MO	844,510	16.7	9.3	7.5
Honolulu	hono	Honolulu	HI	836,231	11.9	6.4	5.5
Tampa	tamp	Hillsborough	FL	834,054	16.9	9.1	7.8
Memphis	memp	Shelby	TN	826,330	17.5	9.7	7.7
Indianapolis	indi	Marion	IN	797,159	16.9	9.0	8.0
Newark	nwk	Essex	NJ	778,206	18.4	8.7	9.7
Baltimore	balt	Baltimore City	MD	736,014	20.2	9.8	10.4
Salt Lake City	salt	Salt Lake	UT	725,956	9.3	4.9	4.4
Rochester	roch	Monroe	NY	713,968	14.6	7.9	6.7
Worcester	wor	Worcester	MA	709,705	15.2	8.2	6.9
Orlando	orla	Orange	FL	677,491	11.0	5.8	5.2
Jacksonville	jckv	Duval	FL	672,971	13.0	7.0	6.0
Fresno	fres	Fresno	CA	667,490	11.1	6.2	4.9
Louisville	loui	Jefferson	KY	664,937	16.3	8.8	7.5
Boston	bost	Suffolk	MA	663,906	13.2	6.5	6.7
Birmingham	birm	Jefferson	AL	651,525	16.2	8.5	7.7
Washington	dc	Washington DC	DC	606,900	15.5	7.0	8.5
Oklahoma City	okla	Oklahoma	OK	599,611	12.9	7.3	5.6
Providence	prov	Providence	RI	596,270	14.6	7.9	6.7
El Paso	elpa	El Paso	TX	591,610	7.7	3.8	3.9
Tacoma	taco	Pierce	WA	586,203	10.0	5.7	4.3
Austin	aust	Travis	TX	576,407	7.0	3.4	3.6

TABLE 6A-1 (cont'd). THE 90 CITIES AND THEIR INCLUDED COUNTIES BY POPULATION SIZE WITH MEAN DAILY NUMBER OF DEATHS BY CATEGORY (1987-1994). Evaluated in NMMAPS 90-Cities Analyses, Samet et al. (2000a,b).

City	Abbreviation	County	State	Population	Total	CVD/Respiratory Disease	Other
Dayton	dayt	Montgomery	OH	573,809	11.9	6.5	5.4
Jersey City	jers	Hudson	NJ	553,099	11.5	5.9	5.6
Bakersfield	bake	Kern	CA	543,477	8.6	5.0	3.6
Akron	akr	Summit	OH	514,990	10.7	5.8	4.9
Charlotte	char	Mecklenburg	NC	511,433	8.5	4.3	4.2
Nashville	nash	Davidson	TN	510,784	11.0	6.0	5.0
Tulsa	tuls	Tulsa	OK	503,341	10.0	5.8	4.2
Grand Rapids	gdrp	Kent	MI	500,631	8.7	4.9	3.8
New Orleans	no	Orleans	LA	496,938	12.0	5.9	6.1
Stockton	stoc	San Joaquin	CA	480,628	8.5	4.8	3.6
Albuquerque	albu	Bernalillo	NM	480,577	7.6	3.8	3.8
Syracuse	syra	Onondaga	NY	468,973	9.7	5.4	4.3
Toledo	tole	Lucas	OH	462,361	10.8	6.3	4.5
Raleigh	ral	Wake	NC	423,380	5.6	2.9	2.7
Wichita	wich	Sedwick	KS	403,662	7.2	4.0	3.3
Colorado Springs	colo	El Paso	CO	397,014	5.0	2.8	2.3
Baton Rouge	batr	East Baton Rouge	LA	380,105	6.3	3.4	3.0
Modesto	mode	Stanislaus	CA	370,522	6.6	3.8	2.8
Madison	madi	Dane	WI	367,085	5.3	2.9	2.4
Spokane	spok	Spokane	WA	361,364	7.8	4.5	3.3
Little Rock	ltrk	Pulaski	AR	349,660	7.0	3.7	3.3
Greensboro	grnb	Guilford	NC	347,420	6.9	3.8	3.1
Knoxville	knox	Knox	TN	335,749	6.7	3.5	3.1
Shreveport	shr	Bossier, Caddo	LA	334,341	6.8	3.7	3.1
Des Moines	desm	Polk	IA	327,140	6.1	3.4	2.6

TABLE 6A-1 (cont'd). THE 90 CITIES AND THEIR INCLUDED COUNTIES BY POPULATION SIZE WITH MEAN DAILY NUMBER OF DEATHS BY CATEGORY (1987-1994). Evaluated in NMMAPS 90-Cities Analyses, Samet et al. (2000a,b).

City	Abbreviation	County	State	Population	Total	CVD/Respiratory Disease	Other
Fort Wayne	ftwa	Allen	IN	300,836	5.9	3.4	2.5
Corpus Chrisit	corp	Nueces	TX	291,145	4.9	2.5	2.4
Norfolk	nor	Norfolk	VA	261,229	4.8	2.6	2.2
Jackson	jcks	Hinds	MS	254,441	5.3	3.0	2.3
Huntsville	hunt	Madison	AL	238,912	3.9	2.2	1.7
Anchorage	anch	Anchorage	AK	226,338	1.9	0.8	1.1
Lexington	lex	Fayette	KY	225,366	4.1	2.1	2.0
Lubbock	lubb	Lubbock	TX	222,636	3.9	2.3	1.6
Richmond	rich	Richmond City	VA	203,056	5.1	2.7	2.4
Arlington	arlv	Arlington	VA	170,936	2.4	1.3	1.2
Kingston	king	Ulster	NY	165,304	3.0	1.8	1.2
Evansville	evan	Vanderburgh	IN	165,058	4.4	2.5	1.9
Kansas City	kans	Wyandotte	KS	161,993	3.2	1.8	1.4
Olympia	olym	Thurston	WA	161,238	2.8	1.5	1.3
Topeka	tope	Shawnee	KS	160,976	3.6	2.0	1.6

TABLE 6A-2. MEAN DAILY POLLUTION LEVELS BY CITY (1987-1994)
Evaluated in NMMAPS 90-Cities Analyses (Samet et al., 2000a,b)

City	PM_{10} $\mu g/m^3$	O_3 ppb	NO_2 $\mu g/m^3$	SO_2 $\mu g/m^3$	CO ppm
Los Angeles	46.0	22.8	39.4	1.9	15.1
New York	28.8	19.6	38.9	12.8	20.4
Chicago	35.6	18.6	24.3	4.6	7.9
Dallas/Ft. Worth	23.8	25.3	13.8	1.1	7.4
Houston	30.0	20.5	18.8	2.8	8.9
San Diego	33.6	31.6	22.9	1.7	11.0
Santa Ana/Anaheim	37.4	23.0	35.1	1.3	12.3
Phoenix	40.3	22.5	16.6	3.5	12.7
Detroit	40.9	22.6	21.3	6.4	6.6
Miami	25.7	25.9	11.0	NA	10.6
Philadelphia	35.4	20.5	32.2	9.9	11.8
Minneapolis/St. Paul	26.9	NA	17.6	2.6	11.8
Seattle	25.3	19.4	NA	NA	17.8
San Jose	30.4	17.9	25.1	NA	9.4
Cleveland	45.1	27.4	25.2	10.3	8.5
San Bernardino	37.0	35.9	27.9	0.7	10.3
Pittsburgh	31.6	20.7	27.6	14.2	12.2
Oakland	26.3	17.2	21.2	NA	9.1
Atlanta	36.1	25.1	26.0	6.0	8.9
San Antonio	23.8	22.2	NA	NA	10.1
Riverside	52.0	33.4	25.0	0.4	11.2
Denver	29.6	21.4	27.9	5.5	10.3
Sacramento	33.3	26.7	16.3	NA	9.4
St. Louis	30.1	22.8	22.5	11.3	10.5
Buffalo	21.7	22.9	19.0	8.6	7.3
Columbus	29.0	26.0	NA	5.9	7.6
Cincinnati	34.2	25.8	26.7	11.9	10.0
St. Petersburg	23.5	24.6	11.8	NA	7.1
Kansas City	25.9	27.6	9.2	2.4	6.2
Honolulu	15.3	18.9	NA	NA	8.3
Tampa	28.3	23.5	21.2	7.8	7.8
Memphis	30.3	29.0	26.8	6.8	11.9
Indianapolis	32.0	31.9	20.2	7.7	9.0
Newark	32.9	15.2	33.6	9.6	8.7
Baltimore	32.9	21.2	32.9	8.4	9.2

TABLE 6A-2 (cont'd). MEAN DAILY POLLUTION LEVELS BY CITY (1987-1994) Evaluated in NMMAPS 90-Cities Analyses (Samet et al., 2000a,b)

City	PM_{10} $\mu g/m^3$	O_3 ppb	NO_2 $\mu g/m^3$	SO_2 $\mu g/m^3$	CO ppm
Salt Lake City	32.9	23.0	29.6	4.4	13.5
Rochester	21.9	22.7	NA	10.4	6.3
Worcester	22.2	30.0	25.2	6.7	8.9
Orlando	22.7	24.1	11.4	1.5	9.3
Jacksonville	29.9	28.2	14.8	2.2	9.2
Fresno	43.4	29.4	21.7	1.9	6.8
Louisville	30.8	19.8	22.4	8.4	11.2
Boston	26.0	17.9	29.9	10.0	11.3
Birmingham	31.2	22.4	NA	6.6	10.5
Washington DC	28.2	17.5	25.6	11.2	12.3
Oklahoma City	25.0	28.4	13.9	NA	7.1
Providence	30.9	25.4	21.9	9.5	10.0
El Paso	41.2	24.4	23.6	9.1	12.5
Tacoma	28.0	23.8	NA	6.5	16.6
Austin	21.1	25.5	NA	NA	NA
Dayton	27.4	26.6	NA	NA	8.2
Jersey City	30.5	19.7	28.7	10.7	20.1
Bakersfield	53.2	33.3	19.4	3.0	10.5
Akron	22.4	30.5	NA	12.0	7.0
Charlotte	30.7	29.3	16.2	NA	11.1
Nashville	32.4	16.2	NA	11.6	11.2
Tulsa	26.6	31.4	16.6	6.9	6.5
Grand Rapids	22.8	27.7	NA	3.0	5.7
New Orleans	29.0	20.5	21.3	NA	9.4
Stockton	39.0	22.6	24.2	1.7	8.2
Albuquerque	16.9	25.8	NA	NA	7.9
Syracuse	24.5	23.7	NA	3.6	11.7
Toledo	25.6	27.1	NA	5.9	10.3
Raleigh	25.6	35.4	12.7	NA	16.1
Wichita	25.6	24.2	NA	4.8	6.5
Colorado Springs	26.3	24.3	NA	NA	10.9
Baton Rouge	27.3	21.2	16.6	5.2	4.3
Modesto	41.7	26.1	24.2	1.9	9.1
Madison	19.9	29.7	NA	3.3	10.4
Spokane	36.0	32.6	NA	NA	21.9

TABLE 6A-2 (cont'd). MEAN DAILY POLLUTION LEVELS BY CITY (1987-1994) Evaluated in NMMAPS 90-Cities Analyses (Samet et al., 2000a,b)

City	PM_{10} $\mu g/m^3$	O_3 ppb	NO_2 $\mu g/m^3$	SO_2 $\mu g/m^3$	CO ppm
Little Rock	25.8	27.7	9.3	2.6	NA
Greensboro	27.5	NA	NA	4.2	12.2
Knoxville	36.3	29.6	NA	NA	13.6
Shreveport	24.7	28.2	NA	2.3	NA
Des Moines	35.5	11.8	NA	NA	8.6
Fort Wayne	23.2	32.1	NA	4.0	14.4
Corpus Christi	24.7	23.9	NA	1.0	NA
Norfolk	26.0	NA	19.6	6.7	7.3
Jackson	26.4	23.9	NA	NA	7.9
Huntsville	26.0	30.4	12.9	NA	6.3
Anchorage	23.0	NA	NA	NA	16.1
Lexington	24.5	32.8	16.4	6.2	8.8
Lubbock	25.1	NA	NA	NA	NA
Richmond	25.4	NA	23.7	5.8	6.6
Arlington	22.0	29.0	25.5	NA	6.6
Kingston	20.4	NA	NA	NA	NA
Evansville	32.4	NA	NA	NA	NA
Kansas City	43.4	18.5	17.6	4.7	8.2
Olympia	22.7	NA	NA	NA	12.7
Topeka	29.0	NA	NA	NA	NA

TABLE 6A-3. NUMBER OF DAYS FOR WHICH MONITORING WAS AVAILABLE BY POLLUTANT FOR CITIES (1987-1994). Evaluated in 90-Cities NMMAPS Analyses of Samet et al. (2000b)

City	PM_{10}	O_3	NO_2	SO^2	CO
Los Angeles	580	2,922	2,922	2,922	2,922
New York	489	2,922	2,493	2,920	2,920
Chicago	2,683	2,922	2,922	1,409	2,922
Dallas/Fort Worth	624	2,922	2,557	2,908	2,922
Houston	793	2,922	2,557	2,922	2,922
San Diego	521	2,922	2,922	2,922	2,922
Santa Ana/Anaheim	480	2,922	2,922	2,922	2,922
Phoenix	376	2,554	740	1,272	2,554
Detroit	1,348	1,861	2,686	2,922	2,922
Miami	484	2,882	2,863	0	2,919
Philadelphia	495	2,901	2,554	2,919	2,919
Minneapolis/St. Paul	2,764	0	2,725	2,914	2,918
Seattle	2,205	1,820	0	0	2,922
San Jose	945	2,922	1,957	0	2,922
Cleveland	1,298	1,712	2,555	2,922	2,897
San Bernardino	538	2,922	2,922	2,922	2,922
Pittsburgh	2,899	2,883	2,537	2,922	2,920
Oakland	508	2,922	2,921	0	2,922
Atlanta	482	2,200	2,922	2,918	2,839
San Antonio	670	2,918	0	0	2,891
Riverside	545	2,922	2,904	2,908	2,921
Denver	1,645	2,922	2,484	2,860	2,922
Sacramento	488	2,922	2,916	0	2,922
St. Louis	487	1,731	2,919	2,919	2,920
Buffalo	489	2,884	2,522	2,922	2,921
Columbus	1,564	1,494	0	964	2,557
Cincinnati	1,705	1,712	2,554	2,905	2,922
St. Petersburg	367	2,920	2,235	0	2,922
Kansas City	670	2,856	2,922	1,094	2,922
Honolulu	415	1,681	0	0	2,919

TABLE 6A-3 (cont'd). NUMBER OF DAYS FOR WHICH MONITORING WAS AVAILABLE BY POLLUTANT FOR CITIES (1987-1994). Evaluated in 90-Cities NMMAPS Analyses of Samet et al. (2000b)

City	PM_{10}	O_3	NO_2	SO^2	CO
Tampa	508	2,922	941	1,818	2,922
Memphis	480	1,707	2,254	2,823	2,922
Indianapolis	1,269	1,588	2,874	2,922	2,922
Newark	484	2,726	2,882	2,896	2,894
Baltimore	1,220	2,063	2,843	2,912	2,865
Salt Lake City	1,356	2,409	1,903	2,739	2,922
Rochester	486	2,886	0	2,921	2,921
Worcester	450	1,763	2,864	2,452	2,899
Orlando	421	2,920	2,024	2,878	2,921
Jacksonville	555	2,791	2,727	2,738	2,922
Fresno	517	2,922	2,922	2,398	2,922
Louisville	485	2,603	1,604	2,841	2,922
Boston	631	2,882	2,922	2,922	2,922
Birmingham	900	2,200	0	1,916	2,922
Washington	417	2,847	2,842	2,286	2,341
Oklahoma City	563	2,832	2,295	0	2,909
Providence	485	1,634	2,441	2,922	2,921
El Paso	2,587	2,922	2,472	2,906	2,922
Tacoma	482	1,601	0	2,756	2,766
Austin	646	2,909	0	0	0
Dayton	461	1,696	0	0	2,922
Jersey City	1,367	2,843	2,496	2,918	2,883
Bakersfield	550	2,557	2,557	2,557	2,659
Akron	1,495	1,677	0	2,827	2,922
Charlotte	454	1,936	1,593	0	2,922
Nashville	1,989	2,861	0	2,619	2,771
Tulsa	411	2,834	2,462	2,426	2,836
Grand Rapids	777	1,615	0	2,907	2,903
New Orleans	531	2,889	2,879	0	2,922
Stockton	488	2,475	2,379	867	2,906
Albuquerque	1,200	2,922	0	0	2,922
Syracuse	485	2,864	0	2,857	2,908
Toledo	416	1,711	0	2,921	2,897
Raleigh	480	1,267	1,219	0	2,160
Wichita	366	2,913	0	1,423	2,922

TABLE 6A-3 (cont'd). NUMBER OF DAYS FOR WHICH MONITORING WAS AVAILABLE BY POLLUTANT FOR CITIES (1987-1994). Evaluated in 90-Cities NMMAPS Analyses of Samet et al. (2000b)

City	PM_{10}	O_3	NO_2	SO^2	CO
Colorado Springs	481	2,920	0	0	2,922
Baton Rouge	474	2,922	2,880	2,891	2,888
Modesto	199	2,496	2,449	845	2,892
Madison	338	1,698	0	2,432	2,709
Spokane	2,393	974	0	0	2,922
Little Rock	516	2,922	2,921	2,908	0
Greensboro	445	0	0	1,077	1,855
Knoxville	577	1,679	0	0	2,511
Shreveport	349	2,922	0	2,881	0
Des Moines	1,334	2,782	0	0	2,825
Fort Wayne	336	1,587	0	1,219	1,822
Corpus Christi	613	2,919	0	2,920	0
Norfolk	474	0	1,787	2,148	2,921
Jackson	508	2,191	0	0	2,574
Huntsville	1,382	2,173	1,090	0	2,532
Anchorage	2,379	0	0	0	1,488
Lexington	816	1,709	2,871	2,906	2,865
Lubbock	1,306	0	0	0	0
Richmond	474	0	2,537	2,907	2,922
Arlington	313	1,705	2,306	0	2,896
Kingston	323	0	0	0	0
Evansville	404	0	0	0	0
Kansas City	551	2,890	324	2,909	2,775
Olympia	1,135	0	0	0	950
Topeka	269	0	0	0	0

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APPENDIX 6B

Heart Rate Variability as a Predictor of Serious Cardiac Outcomes

As an adjunct to discussion of newly emerging literature evaluating relationships between ambient PM and heart rate variability (HRV), factors affecting HR are reviewed briefly and summarized here. More detail description of HRV, and its measurement and interpretation can be found elsewhere (1996 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology).

Factors Affecting Heart Rate. The heart has a spontaneous rhythm of approximately 100 beats/min in the absence of extrinsic influences, because the electrical signal triggering heartbeat originates in and spreads throughout the heart via a specialized conduction system. The tissue structures that comprise the conduction system of the heart include the sinoatrial (SA) node, the internodal pathways, the atrioventricular (AV) node, the bundle of His and its branches, and the Purkinje system. Although all parts of the conduction system are capable of spontaneous electrical discharge and heartbeat initiation, it is the SA node (with its higher rate of discharge) that is the normal cardiac pacemaker in the healthy heart. The spontaneous discharge rate of the SA node, and therefore heartbeat, is modulated by nervous impulses and by circulating substances, such as epinephrine that originate outside the heart. One category of modulating input to the heart is through the sympathetic and parasympathetic divisions of the autonomic nervous system via numerous nerve fibers that innervate the heart.

Stimulation of the heart via parasympathetic nerve fibers decreases the rate of discharge of the SA node, thereby decreasing HR (bradycardia), and decreases the excitability of the AV junctional fibers between the atrial musculature and the AV node, thereby slowing transmission of the impulse into the ventricles. Stimulation of the heart via sympathetic fibers increases the rate of discharge of the SA node, thereby increasing HR (tachycardia) and increasing the excitability of the AV node and increasing transmission of the cardiac impulse into the ventricle. During the resting state parasympathetic input to the heart predominates, so the normal resting HR is well below the inherent rate of 100 beats/min. The HR along with stroke volume determines cardiac output, which interacts with peripheral resistance to determine blood pressure.

The autonomic control of HR is modulated by the vasomotor center located in the brain in the reticular substance of the medulla and lower third of the pons. Impulses sent forth from the vasomotor center through the parasympathetic and sympathetic neurons regulate HR and vasomotor tone. The medial portion of the vasomotor center transmits inhibitory impulses that

decrease HR through the parasympathetic nerve fibers (vagus nerve). The lateral portions of the vasomotor center transmit excitatory impulses that increase both HR and contractility through sympathetic nerve fibers to the heart. In this way, the vasomotor center can either increase or decrease HR, as well as vasomotor tone. The vasomotor center, in turn, is influenced by impulses arising in higher centers of the brain.

Thus, HR is the resultant of the intrinsic rate of the heart modified by various internal and external factors. Most important of these is the output of the vasomotor center delivered via the autonomic nervous system. Other factors affecting HRV include exercise and changes in ambient temperature and oxygen tension.

Measures of Heart Rate Variability. Heart rate variability is being used increasingly in applications from basic research to clinical practice (Berntson et al., 1997). Meaningful analysis of HRV is dependent on fidelity of the basic cardiac input signal that is derived from the electrocardiogram (ECG). This signal is digitized and a series of intervals between successive R (R-R) waves are determined. The population of R-R intervals or pairs of R-R intervals are treated as if they were a set of temporarily unordered data. The variability of these measures is expressed either by conventional statistical measures (Malik, 1995) or other analytical methods, whereby specific patterns of HRV may be related to specific physiological processes and mechanisms.

A wide variety of estimates of HRV have been described. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) has recommended standard time domain measures that index overall heart rate variability, short-term heart rate variability, and long-term heart rate variability (Table 9-9). A measure recommended for HRV is the standard deviation of all normal-to-normal (N-N), also designated as R-R, heart beat intervals (SDNN). The recommended estimate of short-term variability is the root mean square of the successive beat differences (rMSSD) and that for longer-term variability is the standard deviation of the mean N-N interval for each 5-min segment of recording (SDANN).

Periodic components of HRV tend to aggregate within several frequency domains (see Table 6B-1). In young healthy individuals at rest, the most conspicuous frequency band is at the normal respiratory frequency of 0.15 to 0.4 Hz and is termed high-frequency (HF) domain. The

TABLE 6B-1. TERMS USED IN EXPRESSING HEART RATE VARIABILITY

Abbreviation	Definition	Domain
HR	Heart rate (beats/min)	—
HRV	Heart rate variability	—
SDNN	Standard deviation of all normal to normal heart beat intervals	Time
rMSSD	Root mean square of successive beat differences	Time
SPANN	Standard deviation of the mean normal to normal (N-N) interval for each 5 min	Time
HF Domain	0.15 - 0.4 HZ	Frequency
LF Domain	0.05 - 0.15 HZ	Frequency
VLF Domain	0.003 - 0.05 HZ	Frequency

band from 0.05 to 0.15 Hz is termed low-frequency (LF) domain. Other domains have been described including very low frequencies (VLF), 0.003 to 0.05 Hz, and ultra-low frequencies (ULF) that include circadian rhythms. Thus, HRV is quantitated by both time domain metrics (NN, SDNN, rMSSD, and SDANN) and frequency domain metrics (HF, LF, and ULF).

Factors Affecting Heart Rate Variability. Heart rate variability after a myocardial infarction is associated with increased mortality (Kleiger et al., 1987). Aging and gender also are associated with depressed HRV (Umetani et al., 1998). Reardon and Malik (1996) examined the affect of aging in healthy subjects (age range 40 to 102 years; 39 women) with normal resting ECGs. In all subjects, 24-h Holter recordings were performed and used to measure HRV. The HRV triangular index decreased significantly with age, whereas rMSSD did not change. There was a significant difference in HRV index in subjects >70 years compared with those <70 years. There was no significant difference in rMSSD between the two age groups. The authors conclude that aging reduces HRV and decreased HRV may reflect reduced responsiveness of autonomic activity to external environmental stimuli with age.

Umetani et al. (1998) studied the effects of age and gender on 24-h HR and HRV in healthy subjects (10 to 99 years old; 112 male and 148 female). The authors conclude that (1) HRV in healthy subjects declines with aging; (2) HRV of healthy subjects, particularly those >65 years old, may decrease to below levels associated with increased risk of mortality; (3) gender influences HRV (gender differences in HRV are age and measure dependent); and (4) age and gender also affect HRV.

Tsuji et al. (1994) studied HRV in the original subjects of the Framingham Heart Study. Subjects with transient or persistent nonsinus rhythm, 50% of recorded time, and those taking antiarrhythmic medications were excluded. The associations between HRV measures and all-cause mortality during 4 years of follow-up were assessed. A 1-SD decrement in low-frequency power was associated with 1.70 times greater hazard for all-cause mortality (95% confidence interval of 1.37 to 2.09). The authors concluded that estimation of HRV offers prognostic information beyond that provided by the evaluation of traditional risk factors.

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7. DOSIMETRY OF PARTICULATE MATTER

7.1 INTRODUCTION

A basic principle in health effects evaluation is that the dose delivered to the target site of concern, rather than the external exposure, is the proximal cause of any biological response. Characterization of the exposure-dose-response continuum for particulate matter (PM), a fundamental objective of any dose-response assessment for evaluation of health effects, requires the elucidation and understanding of the mechanistic determinants of inhaled particle dose, which is dependent initially on the deposition of particles within the respiratory tract. Particle deposition refers to the removal of particles from their airborne state because of their aerodynamic or thermodynamic behavior in air. Once particles have deposited onto the surfaces of the respiratory tract, they subsequently will be subjected to either absorptive or nonabsorptive particulate removal processes. This may result in their removal from airway surfaces, as well as their removal to various degrees from the respiratory tract. Particulate matter translocated from initial deposition sites is said to have undergone clearance. Clearance of deposited particles depends upon the initial site of deposition and upon the physicochemical properties of the particles, both of which impact upon specific translocation mechanisms. Retained particle burdens are determined by the dynamic relationship between deposition and clearance mechanisms.

This chapter is concerned with particle dosimetry, the study of the deposition, translocation, clearance and retention of particles within the respiratory tract and extrapulmonary tissues. It summarizes basic concepts as presented in the 1996 EPA document, Air Quality Criteria for Particulate Matter or "PM AQCD" (U.S. Environmental Protection Agency, 1996), specifically in Chapter 10; and it updates the state of the science based upon new literature on particle deposition, clearance and retention appearing since publication of the 1996 PM AQCD. Although the basic mechanisms governing deposition and clearance of inhaled particles have not changed, there has been significant additional information on the role of certain biological determinants of the deposition/clearance process, such as gender and age. Also, the

understanding of regional dosimetry and the particle size range over which this has been evaluated has been expanded.

The dose from inhaled particles deposited and retained in the respiratory tract is governed by a number of factors. These include exposure concentration and exposure duration, respiratory tract anatomy and ventilatory parameters, and by physicochemical properties of the particles themselves (e.g., particle size, hygroscopicity, solubility). The basic characteristics of particles as they relate to deposition and retention, as well as anatomical and physiological factors influencing particle deposition and retention, were discussed in depth in the 1996 PM AQCD. Thus, in this current chapter, only an overview of basic information related to one critical factor in deposition, namely particle size, is provided (Section 7.1.1), so as to allow the reader to understand the different terms used in the remainder of this chapter and subsequent ones dealing with health effects. This is followed, in Section 7.1.2, by a basic overview of respiratory tract structure as it relates to deposition evaluation. The ensuing major sections of this chapter then provide updated information on particle deposition, clearance, and retention in the respiratory tract of humans, as well as laboratory animals, which are useful in the evaluation of PM health effects. Issues related to the phenomenon of particle overload as it may apply to human exposure and the use of instillation as an exposure technique to evaluate PM health effects also are discussed. The final sections of the chapter deal with mathematical models of particle disposition in the respiratory tract.

It must be emphasized that any dissection into discrete topics of factors that control dose from inhaled particles tends to mask the dynamic and interdependent nature of the intact respiratory system. For example, although deposition is discussed separately from clearance mechanisms, retention (i.e., the actual amount of particles found in the respiratory tract at any point in time) is determined by the relative rates of both deposition and clearance. Thus, assessment of overall dosimetry requires integration of these various components of the overall process.

7.1.1 Size Characterization of Inhaled Particles

Information about particle size distribution is important in the evaluation of effective inhaled dose. This section summarizes particle attributes requiring characterization and provides general definitions important in understanding particle fate within the respiratory tract.

Particles exist in the atmosphere as aerosols, which are airborne suspensions of finely dispersed solid or liquid particles. Because aerosols can consist of almost any material, their description in simple geometric terms can be misleading unless important factors relating to constituent particle size, shape, and density are considered. Although the size of particles within aerosols can be described based on actual physical measurements (such as those obtained with a microscope), in many cases it is better to use some equivalent diameter in place of the physical diameter. The most commonly used metric is aerodynamic equivalent diameter (AED), whereby particles of differing geometric size, shape and density are compared in terms of aerodynamic behavior (i.e., terminal setting velocity) of particles that are unit density (1 gm/cm^3) spheres. The aerodynamic behavior of unit density spherical particles constitutes a useful standard by which many types of particles can be compared in terms of certain deposition mechanisms.

It is important to note that aerosols present in natural and work environments have polydisperse size distributions. This means that the constituent particles within an aerosol have a range of sizes and are more appropriately described in terms of a size distribution parameter. The lognormal distribution (i.e., the situation whereby the logarithms of particle diameter are distributed normally) can be used for describing size distributions of most aerosols. In linear form, the logarithmic mean is the median of the distribution, and the metric of variability around this central tendency is the geometric standard deviation (σg). The σg, a dimensionless term, is the ratio of the 84th (or 16th) percentile particle size to the 50th percentile size. Thus, the only two parameters needed to describe a log normal distribution of aerosol particle sizes are the median diameter and the geometric standard deviation. However, the actual size distribution may be obtained in various ways. For example, when a distribution is described by counting particles, the median is called the count median diameter (CMD). On the other hand, the median of a distribution based on particle mass in an aerosol is the mass median diameter (MMD). When using aerodynamic diameters, a term that is encountered frequently is mass median aerodynamic diameter (MMAD), which refers to the median of the distribution of mass with respect to aerodynamic equivalent diameter. Most of the present discussion will focus on MMAD because it is the most commonly used measure of aerosol distribution. However, alternative distributions should be used for particles with actual physical size below about 0.5 μm, because, for these, aerodynamic properties become less important. One such metric is

thermodynamic-equivalent size, which is the diameter of a spherical particle that has the same diffusion coefficient in air as the particle of interest.

7.1.2 Structure of the Respiratory Tract

Detailed discussion of respiratory tract structure was provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996), and only a brief synopsis is presented here. For dosimetry purposes, the respiratory tract can be divided into three regions: (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists of head airways (i.e., nasal or oral passages) through the larynx and represents the areas through which inhaled air first passes. In humans, inhalation can occur through the nose or mouth (or both, known as oronasal breathing). However, most laboratory animals commonly used in respiratory toxicological studies are obligate nose breathers.

From the ET region, inspired air enters the TB region at the trachea. From the level of the trachea, the conducting airways then undergo branching for a number of generations. The terminal bronchiole is the most peripheral of the distal conducting airways and these lead, in humans, to the respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli (all of which comprise the A region). All of the conducting airways, except the trachea and portions of the mainstem bronchi, are surrounded by parenchymal tissue. This is composed primarily of the alveolated structures of the A region and associated blood and lymphatic vessels. It should be noted that these respiratory tract regions are comprised of various cell types, and that there are distinct differences in the cellular composition of the ET, TB, and A regions. Although a discussion of cellular structure of the respiratory tract is beyond the scope of this section, details may be found in a number of sources (e.g., Crystal et al., 1997).

7.2 PARTICLE DEPOSITION

This section discusses the deposition of particles in the respiratory tract. It begins with an overview of the basic physical mechanisms that govern deposition. This is followed by an update on both total respiratory tract and regional deposition patterns in humans. Some critical

biological factors that may modulate deposition are then presented. The section ends with a discussion of new information related to interspecies patterns of particle deposition.

7.2.1 Mechanisms of Deposition

Particles may deposit within the respiratory tract by five mechanisms: (1) inertial impaction, (2) sedimentation, (3) diffusion, (4) electrostatic precipitation, and (5) interception.

Sudden changes in airstream direction and velocity cause particles to fail to follow the streamlines of airflow. As a consequence, the particles contact, or impact, onto airway surfaces. The ET and upper TB airways are characterized by high air velocities and sharp directional changes and, thus, dominate as sites of inertial impaction. Impaction is a significant deposition mechanism for particles larger than 1 μm AED.

All aerosol particles are continuously influenced by gravity, but particles with an AED >0.5 μm are affected to the greatest extent. A particle will acquire a terminal settling velocity when a balance is achieved between the acceleration of gravity acting on the particle and the viscous resistance of the air, and it is this settling out of the airstream that takes it into contact with airway surfaces. Both sedimentation and inertial impaction can influence the deposition of particles within the same size range. These deposition processes act together in the ET and TB regions, with inertial impaction dominating in the upper airways and gravitational settling becoming increasingly dominant in the lower conducting airways, especially for the largest particles, which can penetrate into the smaller bronchi.

Particles having actual physical diameters <1 μm are subjected increasingly to diffusive deposition because of random bombardment by air molecules, which results in contact with airway surfaces. The root mean square displacement that a particle experiences in a unit of time along a given cartesian coordinate is a measure of its diffusivity. The density of a particle is unimportant in determining particle diffusivity. Thus, instead of having an aerodynamic equivalent size, diffusive particles of different shapes can be related to the diffusivity of a thermodynamic equivalent size based on spherical particles.

The particle size region around 0.3 to 0.5 μm frequently is described as consisting of particles that are small enough to be minimally influenced by impaction or sedimentation and large enough to be minimally influenced by diffusion. Such particles are the most persistent in inhaled air and undergo the lowest extent of deposition in the respiratory tract.

Interception is deposition by physical contact with airway surfaces. The interception potential of any particle depends on its physical size, and fibers are the chief concern in relation to the interception process. Their aerodynamic size is determined predominantly by their diameter, rather than their length.

Electrostatic precipitation is deposition related to particle charge. The minimum charge an aerosol particle can have is zero when it is electrically neutral. This condition rarely is achieved because of the random charging of aerosol particles by air ions. Aerosol particles will acquire charges from these ions by collisions with them because of their random thermal motion. Furthermore, many laboratory generated aerosols are charged. Such aerosols will lose their charge slowly as they attract oppositely charged ions. An equilibrium state of these competing processes eventually is achieved. This Boltzmann equilibrium represents the charge distribution of an aerosol in charge equilibrium with bipolar ions. The minimum amount of charge is very small, with a statistical probability that some particles within the aerosol will have no charge, and others will have one or more charges.

The electrical charge on some particles may result in an enhanced deposition over what would be expected from size alone. This results from image charges induced on the surface of the airway by these particles or to space-charge effects, whereby repulsion of particles containing like charges results in increased migration toward the airway wall. The effect of charge on deposition is inversely proportional to particle size and airflow rate. This type of deposition is probably small compared to the effects of turbulence and other deposition mechanisms, and generally has been considered to be a minor contributor to overall particle deposition. However, a recent study (Cohen et al., 1998) employing hollow airway casts of the human tracheobronchial tree assessed deposition of ultrafine (0.02 μm) and fine (0.125 μm) particles; the deposition of singly charged particles was found to be 5 to 6 times that of particles having no charge and 2 to 3 times that of particles at Boltzmann equilibrium. This suggests that electrostatic precipitation may, in fact, be a significant deposition mechanism for ultrafine, and some fine, particles within the TB region.

7.2.2 Deposition Patterns in the Human Respiratory Tract

Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition is necessary for understanding and interpreting the health effects associated

with exposure to particles. Particles deposited in the various respiratory tract regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times. This section summarizes concepts of particle deposition in humans and laboratory animals as reported in U.S. Environmental Protection Agency (1996), and provides additional information based on studies published since the release of that earlier document.

The ambient air often contains particles that are too massive to be inhaled. The descriptor "inhalability" is used to denote the overall spectrum of particle sizes that potentially are capable of entering the respiratory tract. Inhalability is defined as the ratio of the number concentration of particles of a certain aerodynamic diameter that are inspired through the nose or mouth to the number concentration of the same diameter particle present in an inspired volume of ambient air (International Commission on Radiological Protection, 1994). In general, for humans, unit density particles >100-μm diameter have a low probability of entering the mouth or nose in still air. However, there is no sharp cutoff to zero probability. Furthermore, there is no lower limit to inhalability as long as the particle exceeds a critical size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties, in contrast to those of free ions or gas molecules.

7.2.2.1 Total Respiratory Tract Deposition

Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 7-1. These data were obtained by various investigators using different sizes of spherical test particles in healthy male adults under different ventilation conditions; the large standard deviations reflect interindividual and breathing pattern-related variability of deposition efficiencies. Deposition with nose breathing is generally higher than that with mouth breathing because of the superior filtration capabilities of the nasal passages. For particles with aerodynamic diameters greater than 1 μm, deposition is governed by impaction and sedimentation, and it increases with increasing AED. When AED is >10 μm, almost all inhaled particles are deposited. As the particle size decreases from $\approx$0.5 μm, diffusional deposition becomes dominant and total deposition depends more on the actual physical diameter of the particle, with decreasing particle diameter leading to an increase in total deposition. Total deposition shows a minimum for particle diameters in the range of 0.3 to 0.5 μm where, as noted above, neither sedimentation, impaction or diffusion deposition are very effective.

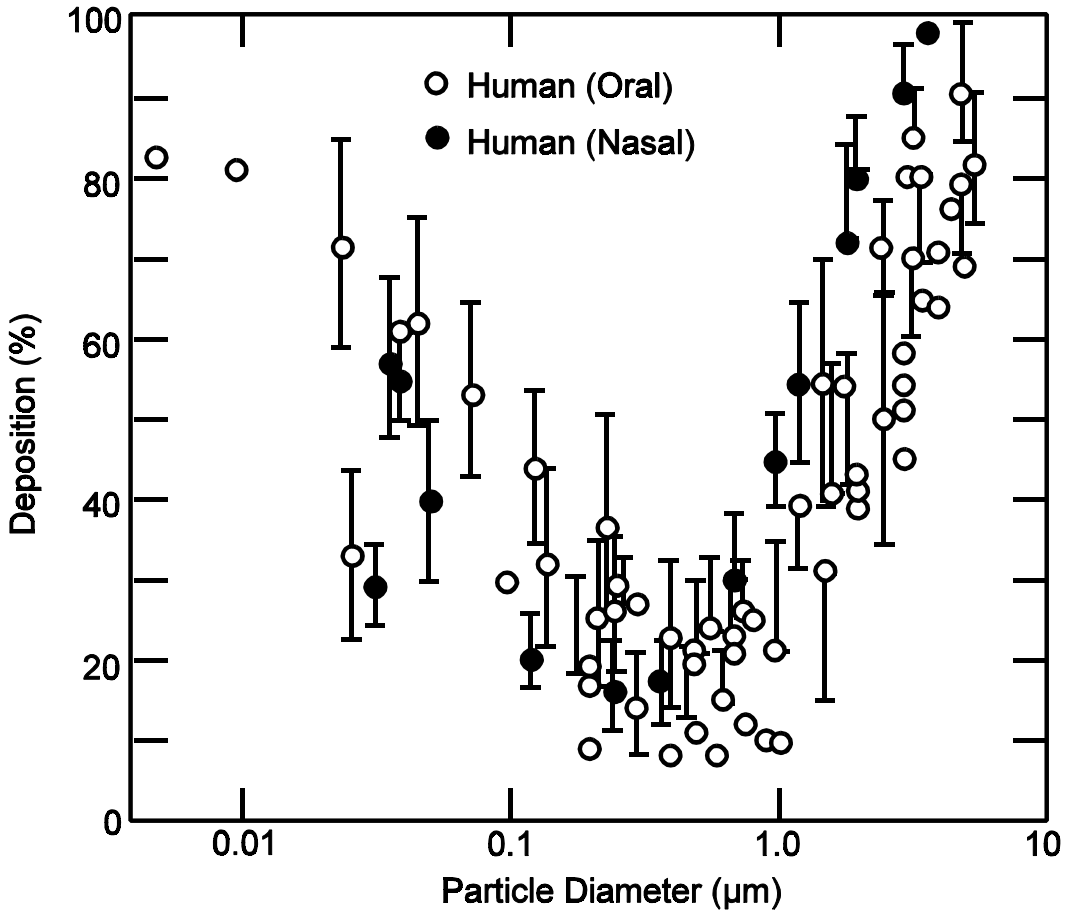

Figure 7-1. Total deposition data (percentage deposition of amount inhaled) in humans as a function of particle size. All values are means with standard deviations when available. Particle diameters are aerodynamic (MMAD) for those ≥0.5 μm.

Source: Modified from Schlesinger (1988).

Besides particle size, breathing pattern is the most important factor affecting lung deposition. Recently, Kim (2000) reported total lung deposition values in healthy adults for a wide range of breathing patterns; tidal volume 375 to 1500 mL, flow rate 150 to 1000 mL/s, and respiratory time 2 to 12 s. Total lung deposition increased with increasing tidal volume at a given flow rate and increased with increasing flow rate at a given respiratory time. Various deposition values were correlated with a single composite parameter consisting of particle size, flow rate, and tidal volume.

One of the specific size modes of the ambient aerosol that is being evaluated in terms of potential toxicity is the ultrafine mode (i.e., particles having diameters <0.1 μm [CMD]). There is little information on total respiratory tract deposition of such particles. Frampton et al. (2000) exposed healthy adult females to 26.7-nm diameter carbon particles (at 10 $\mu g/m^3$) for 2 h. The inspired and expired particle number concentration and size distributions were evaluated. Total respiratory tract deposition fraction was determined for six particle size fractions, ranging from 7.5 to 133.4 nm. They found an overall total lung deposition fraction of 0.66 (by particle number) or 0.58 (by particle mass), indicating that exhaled mean particle diameter was slightly larger than inhaled diameter. The deposition fraction decreased with increasing particle size within the ultrafine range, from 0.76 at the smallest size to 0. 47 at the largest. Jaques and Kim (2000) found the greatest deposition fraction for smaller particles and for breathing patterns with longer residence times (i.e., low flow and higher tidal volume) consistent with deposition by diffusion.

A property of some ambient particulate species that affects deposition is hygroscopicity, the propensity of a material for taking up and retaining moisture under certain conditions of humidity and temperature. Such particles can increase in size in the humid air within the respiratory tract and, when inhaled, will deposit according to their hydrated size rather than their initial size. The implications of hygroscopic growth on deposition has been reviewed extensively by Morrow (1986) and Hiller (1991), whereas the complications of studying lung deposition of hygroscopic aerosols have been reviewed recently by Kim (2000). In general, compared to nonhygroscopic particles of the same initial size, the deposition of hygroscopic aerosols in different regions of the lung may be higher or lower, depending on the initial size. Thus, for particles with initial sizes larger than $\approx$0.5 μm, the influence of hygroscopicity is to increase total deposition, whereas for smaller ones total deposition is decreased.

7.2.2.2 Deposition in the Extrathoracic Region

The fraction of inhaled particles depositing in the ET region is quite variable, depending on particle size, flow rate, breathing frequency and whether breathing is through the nose or the mouth. Mouth breathing bypasses much of the filtration capabilities of the nasal airways, leading to increased deposition in the lungs (TB and A regions). The ET region is clearly the site of first contact with particles in the inhaled air, and essentially acts as a “prefilter” for the lungs.

Since release of the 1996 PM AQCD, a number of studies have explored ET deposition with in vivo studies, as well as in both physical and mathematical model systems. In one study, the relative distribution of particle deposition between the oral and nasal passages was assessed during "inhalation" by use of a physical model (silicone rubber) of the human upper respiratory system, extending from the nostrils and mouth through the main bronchi (Lennon et al., 1998). Monodisperse particles ranging in size from 0.3 to 2.5 μm were used at various flow rates ranging from 15 to 50 L/min. Total deposition was assessed, as was regional deposition in the oral passages, lower oropharynx-trachea, nasal passages, and nasopharynx-trachea. Deposition within the nasal passages was found to agree with available data obtained from a human inhalation study (Heyder and Rudolf, 1977), being proportional to particle size, density, and inspiratory flow rate. It also was found that for oral inhalation, the relative distribution between the oral cavity and the oropharynx-trachea was similar, whereas for nasal inhalation, the nasal passages contained most of the particles deposited in the model, with only about 10% depositing in the nasopharynx-trachea section. Furthermore, the deposition efficiency of the nasopharynx-trachea region was greater than that of the oropharynx-trachea region.

For simulated oronasal breathing, deposition in the ET region depended primarily on particle size rather than flow rate. For all flows and for all breathing modes, total deposition in the ET region increased as particle diameter increased. Such information on deposition patterns in the ET region is useful in refining empirical deposition models.

Deposition within the nasal passages was further evaluated by Kesavanathan and Swift (1998), who examined the deposition of 1- to 10-μm particles in the nasal passages of normal adults under an inhalation regime in which the particles were drawn through the nose and out through the mouth at flow rates ranging from 15 to 35 L/min. At any particle size, deposition increased with increasing flow rate; whereas, at any flow rate, deposition increased with increasing particle size. In addition, as was shown experimentally by Lennon et al. (1998) under oronasal breathing conditions, deposition of 0.3- to 2.5-μm particles within the nasal passages was significantly greater than within the oral passages, and nasal inhalation resulted in greater total deposition in the model than did oral inhalation. These results are consistent with other studies discussed in the 1996 PM AQCD and with the known dominance of impaction deposition within the ET region.

For ultrafine particles (d < 0.1 μm), deposition in the ET region is controlled by diffusion, which depends only on the particle's geometric diameter. Prior to 1996, ET deposition for this particle size range had not been studied extensively in humans, and this remains the case. In the earlier document, the only data available for ET deposition of ultrafine particles were from cast studies. More recently, deposition in the ET region was examined using mathematical modeling. Three dimensional numerical simulations of flow and particle diffusion in the human upper respiratory tract, which included the nasal region, oral region, larynx, and first two generations of bronchi, were performed by Yu et al. (1998). Deposition of particles ranging from 0.001 to 0.1 μm in these different regions was calculated under inspiratory and expiratory flow conditions. Deposition efficiencies in the total model were lower on expiration than inspiration, although the former were quite high. Nasal deposition of ultrafine particles can also be quite high. For example, nasal deposition accounted for up to 54% of total deposition in the model system for 0.001-μm particles. The total deposition efficiency in the model was 75% (of the amount entering), for this size particle. With oral breathing, deposition efficiency was estimated at 48% (of amount entering) (Yu et al., 1998).

Swift and Strong (1996) examined the deposition of ultrafine particles, ranging in size from 0.053 to 0.062 μm, in the nasal passages of normal adults during constant inspiratory flows of 6 to 22 L/min. The results are consistent with results noted in studies above, namely that the nasal passages are highly efficient collectors for ultrafine particles. In this case, fractional deposition ranged from 94 to 99% (of amount inhaled). There was found to be only a weak dependence of deposition on flow rate, which contrasts with results noted above (i.e., Lennon et al., 1998) for particles >0.3 μm, but is consistent with diffusion as the deposition mechanism.

Cheng et al. (1997) examined oral airway deposition in a replicate cast of the human nasal cavity, oral cavity, and laryngeal-tracheal sections. Particle sizes ranged from 0.005 to 0.150 μm, and constant inspiratory and expiratory flow rates of 7.5 to 30 L/min were used. They noted that the deposition fractions within the oral cavity were essentially the same as that in the laryngeal-tracheal sections for all particle sizes and flowrates. They ascribed this to the balance between flow turbulence and residence time in these two regions. Svartengren et al. (1995) examined the effect of changes in external resistance on oropharyngeal deposition of 3.6-μm particles in asthmatics. Under control mouthpiece breathing conditions (flow rate 0.5 L/s), the median deposition as a percentage of inhaled particles in the mouth and throat was 20%

(mean = 33%; range 12 to 84%). Although the mean deposition fell to 22% with added resistance, the median value remained at 20% (range 13 to 47%). Fiberoptic examination of the larynx revealed that there was a trend for increased mouth and throat deposition associated with laryngeal narrowing. Katz et al. (1999) indicate, on the basis of mathematical model calculations, that turbulence plays a key role in enhancing particle deposition in the larynx and trachea.

The results of all of the above studies support the previously known ability of the ET region, and especially the nasal passages, to act as an efficient filter for inhaled particles. Even ultrafine particles have significant deposition within the ET region, and this region, therefore, serves as an important filter for such particles as well as for larger ones, potentially reducing the amount of particles within a wide range that are available for deposition in the TB and A regions.

7.2.2.3 Deposition in the Tracheobronchial and Alveolar Regions

Particles that do not deposit in the ET region enter the lung, but their regional deposition in the lung cannot be precisely measured. Much of the available regional deposition data have been obtained from experiments with radioactive labeled poorly soluble particles. These have been described previously (U.S. Environmental Protection Agency, 1996). Although there are no new regional data obtained by means of the radioactive aerosol method since the publication of that document, a novel serial bolus delivery method has been introduced. Using this bolus technique, regional deposition has been measured for fine and coarse aerosols (Kim et al., 1996) and for ultrafine aerosols (Kim and Jacques, 2000). The serial bolus method uses nonradioactive aerosols and can measure regional deposition in virtually an unlimited number of lung compartments. The Kim and Jaques studies cited above measured regional deposition in 10 serial compartments of the lung, and obtained tracheobronchial and alveolar deposition for particles ranging from 0.04 to 5.0 μm in diameter. TB and alveolar deposition also have been measured in men and women using this method (Kim and Hu, 1998).

7.2.2.4 Local Distribution of Deposition

Airway structure and its associated air flow patterns are exceedingly complex and ventilation distribution of air in different parts of the lung is uneven. Thus, it is expected that particle deposition patterns within the ET, TB, and A regions would be highly nonuniform, with

some sites exhibiting deposition that is much greater than average levels within these regions. This was discussed in detail previously in the 1996 PM AQCD. Basically, using deposition data from living subjects as well as from mathematical and physical models, enhanced deposition has been shown to occur in the nasal passages and trachea and at branching points in the TB and A regions. Recently, Churg and Vedal (1996) examined retention of particles on carinal ridges and tubular sections of airways from lungs obtained at necropsy. Results indicated significant enhancement of particle retention on carinal ridges through the segmental bronchi; the ratios were similar in all airway generations examined.

Deposition "hot spots" at airway bifurcations have undergone additional analyses using mathematical modeling techniques. Using calculated deposition sites, a number of studies showed a strong correlation between secondary flow patterns and deposition sites and density for large (10 μm) particles, as well as for ultrafine particles (0.01 μm) (Heistracher and Hofmann, 1997; Hofmann et al., 1996). This supports experimental work, noted in U.S. Environmental Protection Agency (1996), indicating that, like larger particles, ultrafine particles also show enhanced deposition at airway branch points, even in the upper tracheobronchial tree.

The pattern of particle distribution on a more regional scale was evaluated by Kim et al. (1996). Deposition patterns were measured in situ in healthy nonsmoking young adult males, using an aerosol bolus technique that delivered 1-, 3-, or 5-μm particles into specific volumetric depths within the lungs. The distribution of particle deposition was uneven, and it was noted that sites of peak deposition shifted from distal to proximal regions of the lungs with increasing particle size. Furthermore, the surface dose was found to be greater in the conducting airways than in the alveolar region for all of the particle sizes evaluated. Within the conducting airways, the largest airway regions (i.e., 50 to 100 mL volume) received the greatest surface doses.

Kim and Fisher (1999) studied local deposition efficiencies and deposition patterns of aerosol particles (2.9 to 6.7 μm) in sequential double bifurcation tube models with two different branching geometries: one with in-plane (A) and another with out of plane (B) bifurcation. The deposition efficiencies (DE) in each bifurcation increased with increasing Stokes number (Stk). With symmetric flow conditions, DE was somewhat smaller in the second than the first bifurcation in both models. DE was greater in the second bifurcation in model B than in model A. With asymmetric flows, DE was greater in the low-flow side compared to the high-flow side and this was consistent in both models. Deposition pattern analysis showed highly localized

deposition on and in the immediate vicinity of each bifurcation ridge, regardless of branching pattern and flow pattern.

Comer et al. (2000) used the same three-dimensional computer simulation technique to measure local deposition patterns in sequentially bifurcating, airway models. The simulation was for 3-, 5-, and 7-μm particles and assumed steady, laminar, constant property air flow with symmetry about the first bifurcation. The overall trend of the particle deposition efficiency (i.e., an exponential increase with Stokes number) was similar for all bifurcations. Local deposition patterns consistently showed that the majority of the deposition occurred in the carinal region.

Kim and Jaques (2000) used the respiratory bolus technique to measure the respiratory dose of fine particles (0.04, 0.06, 0.08, and 0.1 μm) in young adults. Under normal breathing conditions (tidal volume 500 mL, respiratory flow rate 250 mL/s), bolus aerosols were delivered sequentially to a lung depth ranging from 50 to 500 mL in 50-mL increments. The results indicate that regional deposition varies widely along the depth of the lung regardless of the particle sizes used. Peak deposition occurred in the lung regions situated between 150 and 200 mL from the mouth and sites of peak deposition shifted proximally with a decrease in particle size. Deposition dose per unit surface area was greatest in the proximal lung regions and decreased rapidly with increased lung depth. Peak surface dose was 5 to 7 times greater than the average lung dose. These results indicate that local enhancement of dose occurs in healthy lungs, and dose enhancement could be an important factor in eliciting pathophysiological effects.

7.2.2.5 Deposition of Specific Size Modes of Ambient Aerosol

The studies described in previous sections generally evaluated deposition using individual particle sizes within certain ranges, without consideration of specific relevant ambient size ranges. Some recent studies, however, have considered the deposition profiles of particle modes that exist in ambient air, so as to provide information on dosimetry of these "real world" particle size fractions. One such study (Venkataraman and Kao, 1999) examined the contribution of two specific size modes of the PM_{10} ambient aerosol, namely the fine mode (defined as particles with diameters up to 2.5 μm) and the coarse mode (defined as particles with diameters 2.5 to 10 μm), to total lung and regional lung doses (i.e., a daily dose expressed as μg/day, and a surface dose expressed a $\mu g/cm^2$/day) resulting from a 24-h exposure to a particle concentration of 150 $\mu g/m^3$. The study also evaluated deposition in terms of two metrics, namely mass dose and number dose.

Deposition was calculated using a mathematical model for a healthy human lung under both moderate exertion and vigorous exertion. Regional deposition values were obtained for the nasopharyngeal region (NP), the tracheobronchial tree (TB), and the pulmonary airways (A).

The daily mass dose from exposure to PM_{10} for three breathing cycles resulted in 36% of the inhaled coarse particle mass deposited in the lung and 30% in the NP, 4% in TB, and 2% in A. About 9% of the fine particle mass was deposited in the lungs, 1.5% in NP and TB and 6% in A. The daily mass dose peaked in the A airways (generation 20) for all breathing patterns, whereas that for the coarse fractions was comparable in the TB and A regions. The mass per unit surface area of various airways from the fine and coarse fractions was larger in the trachea and first few generations of bronchi (gen 3 to 5). It was suggested that these large surface doses may be related to aggravation of upper respiratory tract illness in geographical areas where coarse particles were present.

The daily number dose from exposure to PM_{10} resulted in 18% of the inhaled coarse particles being deposited in the lungs, 13% in the NP, 2% in the TB, and 3% in A. About 11% of inhaled fine particle number was deposited in the lungs, 0.06% in NP, 2% in TB, and 9% in A. Daily number dose was different for fine and coarse fractions in all lung airways, with the dose from the fine fraction higher by about 100 times in the NP and about 10^5 times in internal lung airways. The surface number dose (particles/cm^2/day) was 10^3 to 10^5 times higher for fine than for coarse particles in all lung airways, indicating the larger number of fine particles depositing. Particle number doses did not follow trends in mass doses and are much higher for fine than coarse particles and are higher for different breathing patterns. It also was concluded that the fine fraction contributes 10,000 times greater particle number per alveolar macrophage than the coarse fraction particles. These results must be viewed with caution because they were obtained using a pure mathematical model that must be validated.

Another evaluation of deposition that included consideration of size mode of the ambient aerosol was that of Broday and Georgopoulos (2000). In this case, a mathematical model was used to account for particle hygroscopic growth, transport, and deposition in tracking the changes in the size distribution of inhaled aerosols. It was concluded that different rates of particle growth in the inspired air resulted in a change in the size distribution of the aerosol, such that increased mass and number fractions of inspired fine particles are found in the size range between 0.1 to 1 μm and, therefore, deposit to a lesser extent due to a decrease in diffusion

deposition. On the other hand, particles that were originally in the 0.1- to 1-μm size range when inhaled will undergo enhanced deposition because of their increase in size resulting from hygroscopic growth. Thus, the speciation of the inhaled polydisperse aerosol and its initial size distribution affect the evolution of size distribution once inhaled and, thus, its deposition profile in the respiratory tract. Hygroscopicity of respirable particles must be considered for accurate predictions of deposition. Because different fractions likely have different chemical composition, such changes in deposition patterns will affect dosimetry and biological responses.

7.2.3 Biological Factors Modulating Deposition

Experimental deposition data in humans are commonly derived using healthy adult Caucasian males. Various factors can act to alter deposition patterns from those obtained in this group. Evaluation of these factors is important to help understand potentially susceptible subpopulations, because differences in biological response following pollutant exposure may be caused by dosimetry differences as well as by differences in innate sensitivity. The effects of different biological factors on deposition were discussed in U.S. Environmental Protection Agency (1996) and are summarized below, with additional information obtained from more recent studies.

7.2.3.1 Gender

Males and females differ in body size and ventilatory parameters; so, it is expected that there would be gender differences in deposition. Using particles in the 2.5- to 7.5-μm size range Pritchard et al. (1986) indicated that, for comparable particle sizes and inspiratory flow rates, females had higher ET and TB deposition and smaller A deposition than did males. The ratio of A deposition to total thoracic deposition in females also was found to be smaller. These differences were attributed to gender differences in airway size.

In a recent study (Bennett et al., 1996), the total respiratory tract deposition of 2-μm particles was examined in adult males and females aged 18 to 80 years who breathed with a normal resting pattern. Deposition was assessed in terms of a deposition fraction, which was the difference between the amount of particles inhaled and exhaled during oral breathing. Although there was a tendency for a greater deposition fraction in females compared to males, because

males had greater minute ventilation, the deposition rate (i.e., deposition per unit time) was greater in males than in females.

Kim and Hu (1998) assessed regional deposition patterns in healthy adult males and females using aerosols with median aerodynamic sizes of 1, 3, and 5 μm and a bolus delivery technique, which involved controlled breathing. The total deposition in the lungs was similar for both genders with the smaller particle, but was greater in women for the 3- and 5-μm particles, regardless of the inhalation flow rate used; this difference ranged from 9 to 31%, with higher values associated with higher flow rates. The pattern of deposition was similar for both genders, although females showed enhanced deposition peaks for all three particle sizes. The volumetric depth location of these peaks was found to shift from peripheral (increased volumetric depth) to proximal (shallow volumetric depth) regions of the lung with increasing particle size, but the shift was greater in females than in males. Thus, deposition appeared to be more localized in the lungs of females compared to those of males. These differences were attributed to a smaller size of the upper airways in females than in males (particularly of the laryngeal structure). Local deposition of 1-μm particles was somewhat flow dependent, but for larger (5-μm) particles was largely independent of flow (flows did not include those that would be typical of exercise).

In a related study, Kim et al. (2000) evaluated differences in deposition between males and females related to exercise levels of ventilation and breathing patterns. Using particles at the same size noted above and a number of breathing conditions, total lung deposition was comparable between men and women for l-μm particles but was greater in women than men for 3- and 5-μm particles with all breathing patterns. The gender difference was about 15% at rest, and variable during exercise, depending on particle size. However, total lung deposition rate (deposition per unit time) was found to be 3 to 4 times greater during moderate exercise than during rest for all particle sizes. Thus, it was concluded that exercise may increase the health risk from particles because of increased deposition, and that women may be more susceptible to this exercise-induced change.

Jaques and Kim (2000) and Kim and Jaques (2000) expanded the evaluation of deposition in males and females to particles <1 μm. They measured total lung deposition in healthy adults using sizes in the ultrafine mode (0.04 to 0.1 μm), in addition to those having diameters of 1 and 5 μm. Total lung deposition was greater in females than in males for 0.04- and 0.06-μm particles. The difference was negligible for 0.08- and 0.1-μm particles. Therefore, the gender

effect was particle-size dependent, showing a greater deposition in females for very small ultrafine and large coarse particles, but not for fine particles ranging from 0.08 to 1 μm. A local deposition fraction was determined in each volumetric compartment of the lung to which particles are injected based on the inhalation procedure (Kim and Jaques, 2000). The deposition fraction was found to increase with increasing lung depth from the mouth, reach a peak value and then decrease with further increase in lung volumetric depth. The height of the peak and its depth did vary with particle size and breathing pattern. Peak deposition for the 5-μm particles was more proximal than that for the 1-μm particles, whereas that for the ultrafine particles occurred between these two peaks. For the ultrafine particles, the peak deposition became more proximal as particle size decreased. Although this pattern of deposition distribution was similar for both men and women, the region of peak deposition was shifted closer to the mouth and peak height was slightly greater for women than for men for all exposure conditions.

7.2.3.2 Age

Airway structure and respiratory conditions vary with age, and these variations may alter the deposition pattern of inhaled particles. The limited experimental studies reported in the earlier PM AQCD (U. S. Environmental Protection Agency, 1996) indicated results ranging from no clear dependence of total deposition on age to slightly higher deposition in children than adults. Potential regional deposition differences between children and adults were assessed to a greater extent using mathematical models. These indicated that if the entire respiratory tract and a complete breathing cycle at normal rate are considered, that ET deposition in children generally would be higher than that in adults, but that TB and A regional deposition in children may be either higher or lower than the adult, depending on particle size (Xu and Yu, 1986). Enhanced deposition in the TB region would occur for particles <5 μm in children (Xu and Yu, 1986; Hofmann et al., 1989a).

An age dependent theoretical model to predict regional particle deposition in childrens' lungs, and that incorporates breathing parameters and morphology of the growing lung, was developed by Musante and Martonen (1999). The model was used to compare deposition, at rest, of monodisperse aerosols, ranging from 0.25 to 5 μm, in the lungs of children (aged 7, 22, 48, and 98 mo) to that in adults (aged 30 years). Compared to adults, A deposition was highest in the 48- and 98-mo subjects for all particle sizes, TB deposition was found to be a monotonically

decreasing function of age for all sizes; and total lung deposition (i.e., TB+A) was generally higher in children than adults, with children of all ages showing similar total deposition fractions.

This model was used by Musante and Martonen (2000a) to evaluate the deposition of a polydisperse aerosol that has been extensively used in toxicological studies, namely residual oil fly ash (ROFA) having an MMAD of 1.95 μm. Deposition was evaluated under resting breathing conditions. The mass based deposition fraction of the particles was found to decrease with age from 7 mo to adulthood, but the mass deposition per unit surface area in the lungs of children could be significantly greater than that in the adult.

Cheng et al. (1995) examined deposition of ultrafine particles in replica casts of the nasal airways of children aged 1.5 to 4 years. Particle sizes ranged from 0.0046 to 0.2 μm, and both inspiratory and expiratory flowrates were used (3 to 16 L/min). Deposition efficiency was found to decrease with increasing age for a given particle size and flowrate.

Oldham et al. (1997) examined the deposition of monodisperse particles, having diameters of 1, 5, 10, and 15 μm, in hollow airway models that were designed to represent the trachea and the first few bronchial airway generations of an adult, a 7-year-old child, and a 4-year-old child. They noted that in most cases, the total deposition efficiency was greater in the child-size models than in the adult model.

Bennett et al. (1997a) analyzed the regional deposition of 4.5 μm, poorly soluble particles in children and in adults with mild cystic fibrosis (CF), but who likely had normal upper airway anatomy, such that intra- and extrathoracic deposition would be similar to that in healthy adults. The mean age of the children was 13.8 years and adults were 29.1 years. ET deposition, as a percentage of total respiratory tract deposition, was higher by about 50% in children compared to CF and healthy adults (30.7%, 20.1%, and 16.0%, respectively). There was an age dependence of ET deposition in the children, in that the percentage ET deposition tended to be higher at a younger age; the younger group (<14 years) had almost twice the percentage ET deposition of the older group (>14 years). Additional analyses showed an inverse correlation of extrathoracic deposition with body height. There was no significant difference in lung or total respiratory tract deposition between the children and adults. Because ET deposition was age dependent and total deposition was not, this suggests that the ET region does a more effective job in children of filtering out the particles that would otherwise reach the TB region. However, because the lungs

of children are smaller than those of adults, children may still have comparable deposition per unit surface area as would adults.

Bennett and Zeman (1998) measured the deposition of monodisperse 2 μm (MMAD) particles in children aged 7 to 14 years and adolescents aged 14 to 18 years for comparison to that in adults (19 to 35 years). Each subject inhaled the particles by following their previously determined individual spontaneous resting breathing pattern. Deposition was assessed by measuring the amount of particles inhaled and exhaled. There was no age-related difference in deposition within the children group. There was also no significant difference in deposition between the children and adolescents, between the children and adults, or between the adolescents and adults. However, the investigators noted that, because the children had smaller lungs and higher minute volumes relative to lung size, they likely would receive greater doses of particles per lung surface area compared to adults. Furthermore, deposition in children did vary with tidal volume, increasing with increasing volume to a greater extent than was seen in adults. These additional studies still do not provide unequivocal evidence for significant differences in deposition between adults and children, even when considering differences in lung surface area. However, it should be noted that differences in levels of activity between adults and children are likely to play a fairly large role in age-related differences in deposition patterns of ambient particles. Children generally have higher activity levels during the day, and higher associated minute ventilation per lung size, which can contribute to a greater size-specific dose of particles. Activity levels in relationship to exposure are discussed more fully in Chapter 5.

Another subpopulation of potential concern related to susceptibility to inhaled particles is the elderly. In the study of Bennett et al. (1996), in which the total respiratory tract deposition of 2-μm particles was examined in people aged 18 to 80 years, the deposition fraction in the lungs of people with normal lung function was found to be independent of age, depending solely on breathing pattern and airway resistance.

7.2.3.3 Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that in healthy individuals. The effect of airway diseases on deposition has been studied extensively, as described in the earlier PM AQCD (U.S. Environmental Protection Agency, 1996). Studies described therein had shown that people with

chronic obstructive pulmonary disease (COPD) had very heterogeneous deposition patterns, with differences in regional deposition compared to normals. People with asthma and obstructive pulmonary disease tended to have greater TB deposition than did healthy people. Furthermore, there tended to be an inverse relationship between bronchconstriction and the extent of deposition in the A region, whereas total respiratory tract deposition generally increased with increasing level of airway obstruction. The described studies were performed during controlled breathing, where all subjects breathed with the same tidal volume and respiratory rate. However, although resting tidal volume is similar or elevated in people with COPD compared to normals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, some of the reported differences in the deposition of particles could have been caused by increased fractional deposition with each breath. Although the extent to which lung deposition may change with respect to particle size, breathing pattern, and disease status in people with COPD is still unclear, some recent studies have attempted to provide additional insight into this issue.

Bennett et al. (1997b) measured the fractional deposition of insoluble 2-μm particles in people with severe to moderate COPD (mix of emphysema and chronic bronchitis, mean age 62 years) and compared this to healthy older adults (mean age 67 years) under conditions where the subjects breathed using their individual resting breathing pattern, as well as a controlled breathing pattern. People with COPD tended to breathe with elevated tidal volume and at a faster rate than people with healthy lungs, resulting in about 50% higher resting minute ventilation. Total respiratory tract deposition was assessed in terms of deposition fraction, a measure of the amount deposited based on measures of aerosol inhaled and amount exhaled, and deposition rate, the particles deposited per unit time. Under typical breathing conditions, people with COPD had about 50% greater deposition fraction than did age-matched healthy adults. Because of the elevation in minute ventilation, people with COPD had average deposition rates about 2.5 times that of healthy adults. Similar to previously reviewed studies (U.S. Environmental Protection Agency, 1996), these investigators observed an increase in deposition with an increase in airway resistance, suggesting that, at rest, COPD resulted in increased deposition of fine particles in proportion to the severity of airway disease. The investigators also reported a decrease in deposition with increasing mean effective airspace diameter; this suggested that the enhanced deposition was associated more with the chronic bronchitic

component of COPD than with the emphysematous component of the disease. Greater deposition was noted with natural breathing compared to the fixed pattern.

Kim and Kang (1997) measured lung deposition of 1-μm particles inhaled via the mouth by healthy adults (mean age 27 years) and by those with various degrees of airway obstruction, namely smokers (mean age 27 years), smokers with small airway disease (SAD; mean age 37 years), asthmatics (mean age 48 years), and patients with COPD (mean age 61 years) breathing under the same controlled pattern. Deposition fraction was obtained by measuring the number of particles inhaled and exhaled, breath by breath. There was a marked increase in deposition in people with COPD. Deposition was 16%, 49%, 59%, and 103% greater in smokers, smokers with SAD, asthmatics and people with COPD, respectively, than healthy adults. Deposition in COPD patients was significantly greater than that associated with either SAD or asthma; there was no significant difference in deposition between people with SAD and asthma. Deposition fraction was found to be correlated with percent predicted forced expiratory volume (FEV_1) and forced expiratory flow (FEF25-75%). Airway resistance was not correlated strongly with total lung deposition. Kohlhäufl et al. (1999) also showed increased deposition of fine particles (0.9 μm) in women with bronchial hyperresponsiveness.

Segal et al. (2000a) developed a mathematical model for airflow and particle motion in the lungs that was used to evaluate how lung cancer affects deposition patterns in the lungs of children. It was noted that the presence of airway tumors could affect deposition, by increasing probability of inertial deposition and diffusion. The former would occur on the upstream surfaces of tumors, whereas the latter would occur on downstream surfaces. It was concluded that particle deposition is affected by the presence of airway disease, but that effects may be systematic and could be predicted and incorporated into dosimetry models.

Thus, the database related to particle deposition and lung disease suggests that total lung deposition generally is increased with obstructed airways, regardless of deposition distribution between the TB and A regions. Airflow distribution is very uneven in COPD because of the irregular pattern of obstruction, and there can be closure of small airways. In this situation, a part of the lung is inaccessible, and particles can penetrate deeper into other better ventilated regions. Thus, deposition can be enhanced locally in regions of active ventilation, particularly in the A region. The relationships between lung deposition and airway obstruction or ventilation distribution were previously studied in vivo in animal models (Kim, 1989; Kim et al., 1989).

7.2.3.4 Anatomical Variability

As indicated above, variations in anatomical parameters between genders and between healthy people and those with obstructive lung disease can affect deposition patterns. However, previous analyses generally have overlooked the effect on deposition of normal interindividual variability in airway structure in healthy individuals. This is an important consideration in dosimetry modeling, which often is based on a single idealized structure. Studies available since 1996 have attempted to assess the influence of such variation in respiratory tract structure on deposition patterns.

The ET region is the first to contact inhaled particles and, therefore, deposition within this region would reduce the amount of particles available for deposition in the lungs. Variations in relative deposition within the ET region will, therefore, propagate through the rest of the respiratory tract, creating differences in calculated doses from individual to individual.
A number of studies have examined the influence of variations in airway geometry on deposition in the ET region.

Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size from 0.004 to 0.15 μm at two constant inspiratory flow rates, 167 and 33 mL/s. Deposition was evaluated in relation to measures of nasal geometry as determined by magnetic resonance imaging and acoustic rhinometry. They noted that interindividual variability in deposition was correlated with the wide variation of nasal dimensions, in that greater surface area, smaller cross-sectional area and increasing complexity of airway shape were all associated with enhanced deposition.

Using a regression analysis of data on nasal airway deposition derived from Cheng et al. (1996), Guilmette et al. (1997) noted that the deposition efficiency within this region was highly correlated with both nasal airway surface area and volume; this indicated that airway size and shape factors were important in explaining intraindividual variability noted in experimental studies of human nasal airway aerosol deposition. Thus, much of the variability in measured deposition among people resulted from differences in the size and shape of airway regions.

Kesavanathan and Swift (1998) also evaluated the influence of geometry in affecting deposition in the nasal passages of normal adults from two ethnic groups. Mathematical modeling of the results indicated that the shape of the nostril affected particle deposition in the nasal passages, but that there still remained large intersubject variations in deposition when this

was accounted for, and that likely was caused by geometric variability in the mid and posterior regions of the nasal passages.

Bennett et al. (1998) studied the role of anatomic dead space (ADS) in particle deposition and retention in bronchial airways using an aerosol bolus technique. They found that the fractional deposition was dependant on the subject's ADS, and that a significant number of particles were retained beyond 24 h. This finding of prolonged retention of insoluble particles in the airways is consistent with the findings of Scheuch et al. (1995) and Stahlhofen et al. (1986a). Bennett et al. (1999) also found a lung volume-dependent asymmetric distribution of particles between the left and right lung; the left:right ratio was increased at increased percentage of total lung capacity (e.g., at 70% TLC, L:R was 1.60).

From the analysis of detailed deposition patterns measured by a serial bolus delivery method, Kim and Hu (1998) and Kim and Jaques (2000) found a marked enhancement in deposition in the very shallow region of the lungs in females. The enhanced local deposition for both ultrafine and coarse particles was attributed to a smaller size of the upper airways, particularly of the laryngeal structure.

Hofmann et al. (2000) examined the role of heterogeneity of airway structure in the rat acinar region in affecting deposition patterns within this area of the lungs. By the use of different morphometric models, they showed that substantial variability in predicted particle deposition would result.

7.2.4 Interspecies Patterns of Deposition

The primary purpose of this document is to assess the health effects of particles in humans. As such, human dosimetry studies have been stressed. Such studies avoid uncertainties associated with extrapolation of dosimetry from laboratory animals to humans. Nevertheless, animal models have been and are currently being used in evaluations of health effects from particulate matter, because there are ethical limits to the types of studies that can be performed on human subjects. Because of this, there is considerable need to understand dosimetry in animals, and to understand dosimetric differences between animals and humans. In this regard, there has been a number of new studies that were designed to assess particle dosimetry in commonly used animals and to relate this to dosimetry in humans.

The various species used in inhalation toxicology studies that serve as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, or A) when exposed to the same aerosol at the same inhaled concentration. Such interspecies differences are important, because any adverse toxic effect is often related to the quantitative pattern of deposition within the respiratory tract as well as to the exposure concentration; this pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which deposited material is cleared and redistributed (Schlesinger, 1985). Differences in patterns of deposition between humans and animals were summarized previously in the earlier PM AQCD (U.S. Environmental Protection Agency, 1996; Schlesinger et al., 1997). Such differences in initial deposition must be considered when relating biological responses obtained in laboratory animal studies to effects in humans.

One of the issues that must be considered in interspecies comparisons of hazards from inhaled particles is inhalability of the aerosol in the atmosphere of concern. Although this may not be an issue for humans per se as far as exposure to ambient particles are concerned, it can be an important issue when attempting to relate results of studies using animal species employed in inhalation toxicological studies (Miller et al., 1995). For example, differences in inhalability between rat and human become very pronounced for particles >5 μm, and some differences are also evident for particles as small as l μm.

Several recent studies have addressed various aspects of interspecies differences in deposition using mathematical modeling approaches. Hofmann et al. (1996) compared deposition between rat and human lungs using three-dimensional asymmetric bifurcation models and mathematical procedures for obtaining air flow and particle trajectories. Deposition in segmental bronchi and terminal bronchioles was evaluated under both inspiration and expiration, at particle sizes of 0.01, 1, and 10 μm (which covered the range of deposition mechanisms from diffusion to impaction). Total deposition efficiencies of all particles in the upper and lower airway bifurcations were comparable in magnitude for both rat and human. However, the investigators noted that penetration probabilities from preceding airways must be considered. When considering the higher penetration probability in the human lung, the resulting bronchial deposition fractions were generally higher in human than rat. For all particle sizes, deposition at rat bronchial bifurcations was less enhanced on the carinas compared to that found in human airways.

Hofmann et al. (1996) attempted to account for interspecies differences in branching patterns in deposition analyses. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that morphologic asymmetry was a major determinant of the heterogeneity of local deposition patterns. They noted that many interspecies deposition calculations used morphometry that was described by deterministic lung models (i.e., the number of airways in each airway generation adopts a constant value, and all airways in a given generation have identical lengths and diameters). Such models cannot account for variability and branching asymmetry of airways in the lungs. Thus, their study employed computations that used stochastic morphometric models of human and rat lungs (Koblinger and Hofmann, 1985, 1988; Hofmann et al., 1989b) and evaluated regional and local particle deposition. Stochastic models of lung structure describe, in mathematical terms, the inherent asymmetry and variability of the airway system, including diameter, length and angle. They are based on statistical analyses of actual morphometric analyses of lungs. The model also incorporated breathing patterns for humans and rats. The dependence of deposition on particle size was found to be similar in both rats and humans, with deposition minima in the size range of 0.1 to 1 μm for both total deposition and deposition within the TB region. This was not found to occur in the A region, where a deposition maximum occurred at about 0.02 to 0.03 μm in both species followed by a decline, and then another maximum between 3 and 5 μm. The deposition decrease in the A region at the smallest and largest sizes resulted from the filtering efficiency of upstream airways. Although deposition patterns were qualitatively similar in rat and human, total respiratory tract and TB deposition in the human lung appeared to be consistently higher than in the rat. Alveolar region deposition fraction in humans was lower than in the rat over the size range of 0.001 to 10 μm. Furthermore, both species showed a similar pattern of dependence of deposition on flow rate.

The above model also assessed local deposition. In both human and rat, deposition of 0.001- and 10-μm particles was highest in the upper bronchial airways, whereas 0.1- and 1-μm particles showed higher deposition in more peripheral airways, namely the bronchiolar airways in rat and the respiratory bronchioles in humans. Deposition was variable within any branching generation because of differences in airway dimensions, and regional and total deposition also exhibited intrasubject variations. Airway geometric differences between rats and humans were reflected in deposition. Because of the greater branching asymmetry in rats, prior to about

generation 12, each generation showed deposition maxima at two particle sizes, reflecting deposition in major and minor daughters. These geometric differences became reduced with depth into the lung; beyond generation 12, these two maxima were no longer seen. A later analysis (Hofmann and Bergmann, 1998), using a stochastic morphometric model of human and rat lungs to compare regional and local particle deposition in the human and rat lungs over a wide range of particle sizes (1 to 10 μm) and flow rates, noted that, although there were quantitative differences in the deposition patterns within the lungs of these two species, the dependence of deposition on particle size and flow rate was qualitatively similar. This indicates that the dependence of deposition on physical factors is similar for all species.

Another comparison of deposition in lungs of humans and rats was performed by Musante and Martonen (2000b). An interspecies mathematical dosimetry model was used to determine the deposition of residual oil fly ash (ROFA) in the lungs under sedentary and light activity breathing patterns. This latter was mimicked in the rat by increasing the CO_2 level in the exposure system. The MMAD of the aerosol was 1.95 μm. They noted that physiologically comparable respiratory intensity levels did not necessarily correspond to comparable dose distribution in the lungs. Because of this, the resting rat may not be a good model for the resting human. The ratio of aerosol mass deposited in the TB region to that in the A region for the human at rest was 0.961, indicating fairly uniform deposition throughout the lungs. On the other hand, in the resting rat, the ratio was 2.24, indicating greater deposition in the TB region than in the A region. However, by mimicking light activity in the rat, the ratio was reduced to 0.97, similar to the human. This suggests that ventilatory characteristics in animal models may have to be adjusted to provide for comparable regional deposition to that in humans.

The relative distribution of particles deposited in the bronchial and alveolar region airways may differ in the lungs of animals and humans, for the same total amount of deposited matter, because of structural differences. The effect of such structural difference between rat and human airways on particle deposition patterns was examined by Hofmann et al. (1999) in an attempt to find the most appropriate morphometric parameter to characterize local particle deposition for extrapolation modeling purposes. Particle deposition patterns were evaluated as functions of three morphometric parameters, namely (1) airway generation, (2) airway diameter, and (3) cumulative path length. It was noted that airway diameter was a more appropriate

morphometric parameter for comparison of particle deposition patterns in human and rat lungs than was airway generation.

The influence of exposure concentration on the pattern of particle retention in rats (exposed to diesel soot) and humans (exposed to coal dust) was examined by Nikula et al. (2000) using histological lung sections obtained from both species. The exposure concentrations for diesel soot were 0.35, 3.5, or 7.0 mg/m^3, and exposure duration was 7 h/day, 5 days/week for 24 mo. The human lung sections were obtained from nonsmoking nonminers, nonsmoking coal miners exposed to levels $\leq$2 mg dust/m^3 for 3 to 20 years, or nonsmoking miners exposed to <10 mg/m^3 for 33 to 50 years. In both species, the volume density of deposition increased with increasing dose (which is related to exposure duration and concentration). In rats, the diesel exhaust particles were found to be primarily in the lumens of the alveolar duct and alveoli, whereas, in humans, retained dust was found primarily in the interstitial tissue. Thus, different lung cells contact retained particles in the two species and may result in different biological responses with chronic dust exposure.

The manner in which particle dose is expressed, that is, the specific dose metric, may impact on relative differences in deposition between humans and other animal species. For example, although deposition when expressed on a mass per unit alveolar surface area basis may not be different between rats and humans, dose metrics based on particle number per various anatomical parameters (e.g., per alveolus or alveolar macrophage) can differ between rats and humans, especially for particles around 0.1 to 0.3 μm (Miller et al., 1995). Furthermore, in humans with lung disease such as asthma or COPD, differences between rat and human can be even more pronounced.

The probability of any biological effect in humans or animals depends on deposition and retention of particles, as well as the underlying dose-response relationship. Interspecies dosimetric extrapolation must consider differences in deposition, clearance, and dose response. Thus, even similar deposition patterns may not result in similar effects in different species because dose also is affected by clearance mechanisms and species sensitivity. In addition, the total number of particles deposited in the lung may not be the most relevant dose metric to compare species. For example, it may be the number of deposited particles per unit surface area that determines response. More specifically, even if deposition is similar in rat and human, there would be a higher deposition density in the rat because of the smaller surface area of rat lung.

Thus, species-specific differences in deposition density should be considered when health effects observed in laboratory animals are being evaluated in terms of the human situation.

7.3 PARTICLE CLEARANCE AND TRANSLOCATION

This section discusses the clearance and translocation of particles that have deposited in the respiratory tract. A basic overview of biological mechanisms and pathways of clearance in the various region of the respiratory tract is presented first. This is followed by an update on regional kinetics of particle clearance. Interspecies patterns of clearance are then addressed, followed by new information on biological factors that may modulate clearance.

7.3.1 Mechanisms and Pathways of Clearance

Particles that deposit on airway surfaces may be cleared from the respiratory tract completely, or may be translocated to other sites within this system, by various regionally distinct processes. These clearance mechanisms, which are outlined in Table 7-1, can be categorized as either absorptive (i.e., dissolution) or nonabsorptive (i.e., transport of intact particles) and may occur simultaneously or with temporal variations. It should be mentioned that particle solubility in terms of clearance refers to solubility within the respiratory tract fluids and cells. Thus, a poorly soluble particle is considered to be one whose rate of clearance by dissolution is insignificant compared to its rate of clearance as an intact particle. For the most part, all deposited particles are subject to clearance by the same mechanisms, with their ultimate fate a function of deposition site, physicochemical properties (including solubility and any toxicity), and sometimes deposited mass or number concentration. Clearance routes from the various regions of the respiratory tract have been discussed previously in detail (U.S. Environmental Protection Agency, 1996; Schlesinger et al., 1997). They are schematically shown in Figure 7-2 (for extrathoracic and tracheobronchial regions) and in Figure 7-3 (for poorly soluble particle clearance from the alveolar region) and are reviewed only briefly below.

TABLE 7-1. OVERVIEW OF RESPIRATORY TRACT PARTICLE CLEARANCE AND TRANSLOCATION MECHANISMS

Extrathoracic region (ET)
Mucociliary transport
Sneezing
Nose wiping and blowing
Dissolution and absorption into blood
Tracheobronchial region (TB)
Mucociliary transport
Endocytosis by macrophages/epithelial cells
Coughing
Dissolution and absorption into blood/lymph
Alveolar region (A)
Macrophages, epithelial cells
Interstitial
Dissolution and absorption into blood/lymph

Source: Schlesinger (1995).

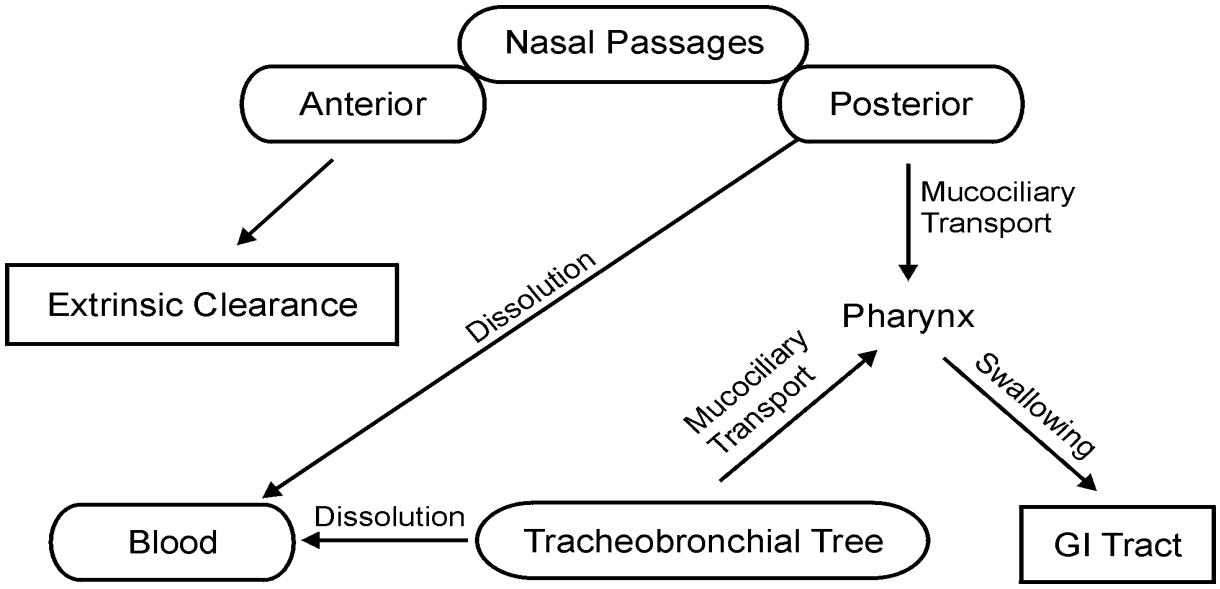

Figure 7-2. Major clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree.

Source: Adapted from Schlesinger et al. (1997).

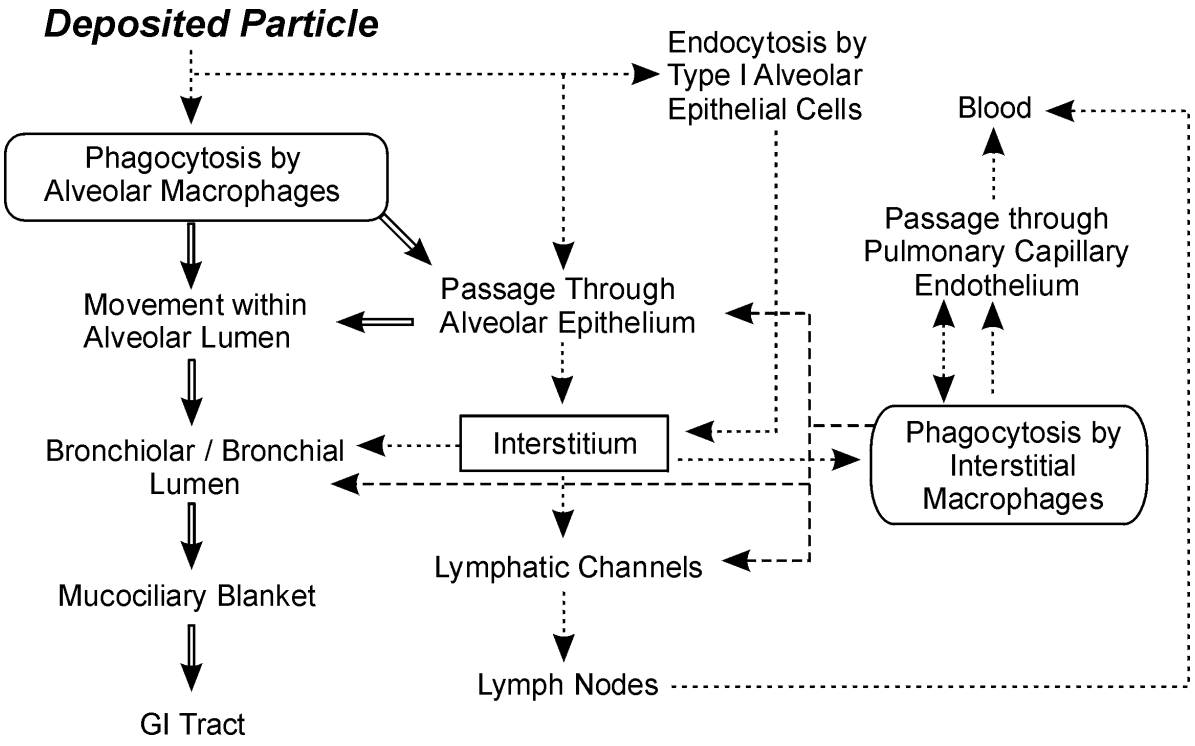

Figure 7-3. Diagram of known and suspected clearance pathways for poorly soluble particles depositing in the alveolar region.

Source: Modified from Schlesinger et al. (1997).

7.3.1.1 Extrathoracic Region

The clearance of poorly soluble particles deposited in the posterior portions of the nasal passages occurs via mucociliary transport, with the general flow of mucus towards the nasopharynx. Mucus flow in the most anterior portion of the nasal passages is forward, clearing deposited particles to the vestibular region where removal is by sneezing, wiping, or blowing.

Soluble material deposited on the nasal epithelium is accessible to underlying cells via diffusion through the mucus. Dissolved substances may be translocated subsequently into the bloodstream. The nasal passages have a rich vasculature, and uptake into the blood from this region may occur rapidly.

Clearance of poorly soluble particles deposited in the oral passages is by coughing and expectoration or by swallowing into the gastrointestinal tract. Soluble particles are likely to be rapidly absorbed after deposition.

7.3.1.2 Tracheobronchial Region

Poorly soluble particles deposited within the TB region are cleared by mucociliary transport towards the oropharynx, followed by swallowing. Poorly soluble particles also may traverse the epithelium by endocytotic processes, entering the peribronchial region, be engulfed via phagocytosis by airway macrophages, which can then move cephalad on the mucociliary blanket, or enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles may be absorbed through the epithelium into the blood. There is, however, evidence that even some soluble particles may be cleared by mucociliary transport (Bennett and Ilowite, 1989; Matsui et al., 1998).

7.3.1.3 Alveolar Region

Clearance from the A region occurs via a number of mechanisms and pathways. Particle removal by macrophages comprises the main nonabsorptive clearance process in this region. These cells, which reside on the epithelium, phagocytize and transport deposited material that they contact by random motion or via directed migration under the influence of chemotactic factors.

Although alveolar macrophages normally comprise up to about 5% of the total alveolar cells in healthy, nonsmoking humans and other mammals, the actual cell count may be altered by particle loading. The magnitude of any increase in cell number is related to the number of deposited particles rather than to total deposition by weight. Thus, equivalent masses of an identically deposited substance would not produce the same response if particle sizes differed, and the deposition of smaller particles would tend to result in a greater elevation in macrophage number than would deposition of larger particles.

Particle-laden macrophages may be cleared from the A region along a number of pathways. As noted in Figure 7-3, this includes cephalad transport via the mucociliary system after the cells reach the distal terminus of the mucus blanket; movement within the interstitium to a lymphatic channel; or perhaps traversing of the alveolar-capillary endothelium, directly entering the

bloodstream. Particles within the lymphatic system may be translocated to tracheobronchial lymph nodes, which can become reservoirs of retained material. Particles subsequently reaching the postnodal lymphatic circulation will enter the blood. Once in the systemic circulation, these particles, or transmigrated macrophages, can travel to extrapulmonary organs. Deposited particles that are not ingested by alveolar macrophages may enter the interstitium, where they are subject to phagocytosis by resident interstitial macrophages, and may travel to perivenous, peribronchiolar or subpleural sites, where they become trapped, increasing particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the redistribution of initially diffuse deposits into focal aggregates. Some particles or components can bind to epithelial cell membranes or macromolecules, or other cell components, delaying clearance from the lungs.

Churg and Brauer (1997) examined lung autopsy tissue from 10 never-smokers from Vancouver, Canada. They noted that the geometric mean particle diameter (GMPD) in lung parenchymal tissue was 0.38 μm (σg = 2.4). Ultrafines were less than 5% of the total retained particulate matter. Metal particles had a GMPD of 0.17 μm and silicates 0.49 μm. Ninety-six percent of retained PM was less than 2.5 μm.

Clearance by the absorptive mechanism involves dissolution in the alveolar surface fluid, followed by transport through the epithelium and into the interstitium, and diffusion into the lymph or blood. Although factors affecting the dissolution of deposited particles are poorly understood, solubility is influenced by the particle's surface to volume ratio and other properties, such as hydrophilicity and lipophilicity (Mercer, 1967; Morrow, 1973; Patten, 1996). Thus, as noted, materials generally considered to be relatively insoluble still may have high dissolution rates and short dissolution half-times if the particle size is small.

Some deposited particles may undergo dissolution in the acidic milieu of the phagolysosomes after ingestion by macrophages. Intracellular dissolution may be the initial step in translocation from the lungs for these particles and for material associated with these particles (Kreyling, 1992; Lundborg et al., 1985). Following dissolution, the material can be absorbed into the blood. Dissolved materials may then leave the lungs at rates that are more rapid than would be expected based on an "expected" normal dissolution rate in lung fluid.

7.3.2 Clearance Kinetics

The kinetics of clearance has been reviewed in U.S. Environmental Protection Agency (1996) and in a number of monographs (e.g., Schlesinger et al., 1997) and is discussed only briefly here. The actual time frame over which clearance occurs affects the cumulative dose delivered to the respiratory tract, as well as that delivered to extrapulmonary organs.

7.3.2.1 Extrathoracic Region

Mucus flow rates in the posterior nasal passages are highly nonuniform, but the median rate in a healthy adult human is about 5 mm/min, resulting in a mean anterior to posterior transport time of about 10 to 20 min for poorly soluble particles (Rutland and Cole, 1981; Stanley et al., 1985). Particles deposited in the anterior portion of the nasal passages are cleared more slowly by mucus transport, and are usually more effectively removed by sneezing, wiping, or nose blowing (Fry and Black, 1973; Morrow, 1977).

7.3.2.2 Tracheobronchial Region

Mucus transport in the tracheobronchial tree occurs at different rates in different local regions; the velocity of movement is fastest in the trachea, and it becomes progressively slower in more distal airways. In healthy nonsmoking humans, using noninvasive procedures and no anesthesia, average tracheal mucus transport rates have been measured at 4.3 to 5.7 mm/min (Yeates et al., 1975, 1981; Foster et al., 1980; Leikauf et al., 1981, 1984), whereas that in the main bronchi has been measured at ≈2.4 mm/min (Foster et al., 1980). Estimates for human medium bronchi range between 0.2 to 1.3 mm/min, whereas those in the most distal ciliated airways range down to 0.001 mm/min (Morrow et al., 1967; Cuddihy and Yeh, 1988; Yeates and Aspin, 1978).

The total duration of bronchial clearance, or some other time parameter, often is used as an index of mucociliary kinetics. Although clearance from the TB region is generally rapid, there is experimental evidence, discussed in U.S. Environmental Protection Agency (1996), that a fraction of material deposited in the TB region is retained much longer than the 24 h commonly used as the outer range of clearance time for particles within this region (Stahlhofen et al., 1986a,b; Scheuch and Stahlhofen, 1988; Smaldone et al., 1988). Some recent studies described

below continue to support the concept that TB regional clearance consists of both a fast and a slow component.

Falk et al. (1997) studied clearance in healthy adults using monodisperse Teflon particles (6.2 μm) inhaled at two flow rates. A considerable fraction (about 50%) of particles deposited in small airways had not cleared within 24 h following exposure. These particles cleared with a half time of 50 days. Although the deposition sites of the particles were not confirmed experimentally, calculations suggested these to be in the smaller ciliated airways. Camner et al. (1997) also noted that clearance from the TB region was incomplete by 24 h postexposure, and suggested that this may be caused by incomplete clearance from bronchioles. Healthy adults inhaled teflon particles (6, 8, and 10 μm) under low flow rates to maximize deposition in the small ciliated airways. The investigators noted a decrease in 24-h retention with increasing particle size, indicating a shift with increasing size toward either a smaller retained fraction, deposition more proximally in the respiratory tract, or both. They calculated that a large fraction, perhaps as high as 75%, of particles depositing in generations 12 through 16 was still retained at 24 h postexposure.

In a study to examine retention kinetics in the tracheobronchial tree (Falk et al., 1999), normal nonsmoking adults inhaled radioactively tagged 6.1-μm particles at both a normal flow rate and slow flow rate designed to deposit particles preferentially in the small ciliated airways. Lung retention was measured from 24 h to 6 mo after exposure. Following the normal inhalation, 14% of the particles retained at 24 h cleared with a half time of 3.7 days, and 86% with a half time of 217 days. Following the slow inhalation, 35% of the particles retained at 24 h cleared with a half time of 3.6 days, and 65% with a half time of 170 days. Deposition calculated using a number of mathematical models indicated higher deposition in the bronchiolar region (generations 9 through 15) with the slow rate inhalation compared to the normal rate. The experimental data and predictions of the deposition modeling indicated that 40% of the particles deposited in the conducting airways during the slow inhalation were retained after 24 h. The particles that cleared with the shorter half time were mainly deposited in the bronchiolar region, but only about 25% of the particles deposited in this region cleared in this phase. This study provided additional confirmation for a phase of slow clearance from the bronchial tree.

The underlying sites and mechanisms of long-term TB retention in the smaller airways are not known. Some proposals were presented in the earlier PM AQCD (U.S. Environmental

Protection Agency, 1996). This slow clearing tracheobronchial compartment likely is associated with bronchioles <1 mm in diameter (Lay et al., 1995; Kreyling et al., 1999; Falk et al., 1999). Based on a study in which an adrenergic agonist was used to stimulate mucus flow, so as to examine the role of mucociliary transport in the bronchioles, it was found that clearance from the smaller airways was not influenced by the drug, suggesting to the investigators that mucociliary transport was not as an effective clearance mechanism from this region as in larger airways (Svartengren et al., 1998, 1999). Although slower or less effective mucus transport may result in longer retention times in these small airways, other factors may account for long-term TB retention. One such proposal is the movement of particles into the gel phase because of surface tension forces in the liquid lining of the small airways (Gehr et al., 1990, 1991). The issue of particle retention in the tracheobronchial tree certainly is not resolved.

Long-term TB retention patterns are not uniform. There is an enhancement at bifurcation regions (Radford and Martell, 1977; Henshaw and Fews, 1984; Cohen et al., 1988), the likely result of both greater deposition and less effective mucus clearance within these areas. Thus, doses calculated based on uniform surface retention density may be misleading, especially if the material is, toxicologically, slow acting.

7.3.2.3 Alveolar Region

Particles deposited in the A region generally are retained longer than those deposited in airways cleared by mucociliary transport. There are limited data on alveolar clearance rates in humans. Within any species, reported clearance rates vary widely because, in part, of different properties of the particles used in the various studies. Furthermore, some chronic experimental studies have employed high concentrations of poorly soluble particles, which may have interfered with normal clearance mechanisms, resulting in clearance rates different from those that would typically occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle “overload”. This is discussed later in greater detail in Section 7.4.

There are numerous pathways of A region clearance, and the utilization of these may depend on the nature of the particles being cleared. Little is known concerning relative rates along specific pathways. Thus, generalizations about clearance kinetics are difficult to make. Nevertheless, A region clearance is usually described as a multiphasic process, each phase

considered to represent removal by a different mechanism or pathway, and often characterized by increased retention half times following exposure.

The initial uptake of deposited particles by alveolar macrophages is very rapid and generally occurs within 24 h of deposition (Lehnert and Morrow, 1985; Naumann and Schlesinger, 1986; Lay et al., 1998). The time for clearance of particle-laden alveolar macrophages via the mucociliary system depends on the site of uptake relative to the distal terminus of the mucus blanket at the bronchiolar level. Furthermore, clearance pathways, and subsequent kinetics, may depend to some extent on particle size. For example, some smaller ultrafine particles (perhaps <0.02 μm) may be less effectively phagocytosed than larger ones (Oberdörster, 1993).

Uningested particles may penetrate into the interstitium within a few hours following deposition. This transepithelial passage seems to increase as particle loading increases, especially to that level above which macrophage numbers increase (Ferin, 1977; Ferin et al., 1992; Adamson and Bowden, 1981). It also may be particle size dependent, because insoluble ultrafine particles (<0.1 μm diameter) of low intrinsic toxicity show increased access to the interstitum and greater lymphatic uptake than do larger particles of the same material (Oberdörster et al., 1992; Ferin et al., 1992). However, ultrafine particles of different materials may not enter the interstitium to the same extent. Similarly, a depression of phagocytic activity, a reduction in macrophage ability to migrate to sites of deposition (Madl et al., 1998), or the deposition of large numbers of ultrafine particles may increase the number of free particles in the alveoli, perhaps enhancing removal by other routes. In any case, free particles may reach the lymph nodes, perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985), although this route is not certain and may be species dependent.

The extent of lymphatic uptake of particles may depend on the effectiveness of other clearance pathways, in that lymphatic translocation probably increases when phagocytic activity of alveolar macrophages is decreased. This may be a factor in lung overload. However, it seems that the deposited mass or number of particles must exceed some threshold below which increases in loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle and Brieger, 1961). In addition, the rate of translocation to the lymphatic system may be somewhat particle size dependent. Although no human data are available, translocation of latex particles to the lymph nodes of rats was greater for 0.5- to 2-μm particles than for 5- and

9-μm particles (Takahashi et al., 1992), and smaller particles within the 3- to 15-μm size range were found to be translocated at faster rates than were larger sizes (Snipes and Clem, 1981). On the other hand, translocation to the lymph nodes was similar for both 0.4-μm barium sulfate or 0.02-μm gold colloid particles (Takahashi et al., 1987). It seems that particles $\leq$2 μm clear to the lymphatic system at a rate independent of size, and it is particles of this size, rather than those $\geq$5 μm, that would have significant deposition within the A region following inhalation. In any case, the normal rate of translocation to the lymphatic system is quite slow, and elimination from the lymph nodes is even slower, with half times estimated in tens of years (Roy, 1989).

Soluble particles depositing in the A region may be cleared rapidly via absorption through the epithelial surface into the blood. Actual rates depend on the size of the particle (i.e., solute size), with smaller molecular weight solutes clearing faster than larger ones. Absorption may be considered as a two stage process, with the first stage being dissociation of the deposited particles into material that can be absorbed into the circulation (i.e., dissolution), and the second stage being uptake of this material. Each of these stages may be time dependent. The rate of dissolution depends on a number of factors, including particle surface area and chemical structure. A portion of the dissolved material may be absorbed more slowly because of binding to respiratory tract components. Accordingly, there is a very wide range for absorption rates, depending on the physicochemical properties of the material deposited.

7.3.3 Interspecies Patterns of Clearance

The inability to study the retention of certain materials in humans for direct risk assessment requires use of laboratory animals. Because dosimetry depends on clearance rates and routes, adequate toxicologic assessment necessitates that clearance kinetics in these animals be related to those in humans. The basic mechanisms and overall patterns of clearance from the respiratory tract are similar in humans and most other mammals. However, regional clearance rates can show substantial variation between species, even for similar particles deposited under comparable exposure conditions, as extensively reviewed elsewhere (U.S. Environmental Protection Agency, 1996; Schlesinger et al., 1997; Snipes et al., 1989).

In general, there are species-dependent rate constants for various clearance pathways. Differences in regional and total clearance rates between some species are a reflection of differences in mechanical clearance processes. For example, the relative proportion of particles

cleared from the A region in the short and longer term phases differs between laboratory rodents and larger mammals, with a greater percentage cleared in the faster phase in rodents. A recent study (Oberdörster et al., 1997) showed interstrain differences in mice and rats in the handling of particles by alveolar macrophages. Macrophages of B6C3F1 mice could not phagocytize 10-μm particles, but those of C57 black/6Jmice did. In addition, the nonphagocytized 10-μm particles were efficiently eliminated from the alveolar region, whereas previous work in rats found that these large particles, after uptake by macrophages, were retained persistently (Snipes and Clem, 1981; Oberdörster et al., 1992). The end result of interspecies differences in clearance for consideration in assessing particle dosimetry is that the retention of deposited particles can differ between species, and this may result in differences in response to similar particulate exposure atmospheres.

Hsieh and Yu (1998) summarized the existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and human. Clearance at different initial lung burdens, ranging from 0.001 to 10 mg particles/g lung, was analyzed using a two-phase exponential decay function. Two clearance phases in the alveolar region, namely fast and slow, were associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with the lymph nodes. Rats and mice were noted to be fast clearers compared to the other species. Increasing the initial lung burden resulted in an increasing mass fraction of particles cleared by the slower phase. As lung burden increased beyond 1 mg particles/g lung, the fraction cleared by the slow phase increased to almost 100% for all species. However, the rate for the fast phase was similar in all species and did not change with increasing lung burden of particles, while the rate for the slow phase decreased with increasing lung burden. At elevated burdens, the “overload” effect on clearance rate was greater in rats than in humans, an observation consistent with previous findings (Snipes, 1989).

7.3.4 Biological Factors Modulating Clearance

A number of factors have been assessed in terms of modulation of normal clearance patterns. These include aging, gender, workload, disease, and irritant inhalation, and have been discussed in detail previously (U.S. Environmental Protection Agency, 1996).

7.3.4.1 Age

Studies previously described (U.S. Environmental Protection Agency, 1996) indicated that there appeared to be no clear evidence for any age-related differences in clearance from the respiratory tract, either from child to adult, or young adult to elderly. Studies of mucociliary function have shown either no changes or some slowing in mucous clearance function with age after maturity, but at a rate that would be unlikely to significantly affect overall clearance kinetics.

7.3.4.2 Gender

Previous studies (U.S. Environmental Protection Agency, 1996) indicated no gender related differences in nasal mucociliary clearance rates in children (Passali and Bianchini Ciampoli, 1985) nor in tracheal transport rates in adults (Yeates et al., 1975).

7.3.4.3 Physical Activity

The effect of increased physical activity on mucociliary clearance is unresolved, with previously discussed studies (U.S. Environmental Protection Agency, 1996) indicating either no effect or an increased clearance rate with exercise. However, it is possible to have an enhanced mucus transport by nonmucociliary mechanisms such as a two-phase gas-liquid interaction. During exercise, breathing patterns become similar to “huffing”, fast expiration compared to inspiration. With this breathing mode, effective mucus transport has been demonstrated in simulated airway models (Kim et al., 1987). There are no data concerning changes in A region clearance with increased activity levels. Breathing with an increased tidal volume was noted to increase the rate of particle clearance from the A region, and this was suggested to result from distension-related evacuation of surfactant into proximal airways, resulting in a facilitated movement of particle-laden macrophages or uningested particles because of the accelerated motion of the alveolar fluid film (John et al., 1994).

7.3.4.4 Respiratory Tract Disease

Various respiratory tract diseases are associated with clearance alterations. The examination of clearance in individuals with lung disease requires careful interpretation of results because differences in deposition of particles used to assess clearance function may occur

between normal individuals and those with respiratory disease; this would impact directly on the measured clearance rates, especially in the tracheobronchial tree. Earlier studies reported in U.S. Environmental Protection Agency (1996) noted findings of slower nasal mucociliary clearance in humans with chronic sinusitis, bronchiectasis, rhinitis, or cystic fibrosis and slowed bronchial mucus transport associated with bronchial carcinoma, chronic bronchitis, asthma, and various acute respiratory infections. However, a recent study by Svartengren et al. (1996a) concluded, based on deposition and clearance patterns, that particles cleared equally effectively from the small ciliated airways of healthy humans and those with mild to moderate asthma. However, this similarity was ascribed to effective therapy for the asthmatics.

In another study, Svartengren et al. (1996b) examined clearance from the TB region in adults with chronic bronchitis who inhaled 6-μm Teflon particles. Based on calculations, particle deposition was assumed to be in small ciliated airways at low flow and in larger airways at higher flow. The results were compared to that obtained in healthy subjects from other studies. At low flow, a larger fraction of particles was retained over 72 h in people with chronic bronchitis compared to healthy subjects, indicating that clearance resulting from spontaneous cough could not fully compensate for impaired mucociliary transport in small airways. For larger airways, patients with chronic bronchitis cleared a larger fraction of the deposited particles over 72 h than did healthy subjects, but this was reportedly because of differences in deposition resulting from airway obstruction.

An important mechanism of clearance from the tracheobronchial region, under some circumstances, is cough. Although cough is generally a reaction to an inhaled stimulus, in some individuals with respiratory disease, spontaneous coughing also serves to clear the upper bronchial airways of deposited substances by dislodging mucus from the airway surface. Recent studies confirm that this mechanism likely plays a significant role in clearance for people with mucus hypersecretion, at least for the upper bronchial tree, and for a wide range of deposited particle sizes (0.5 to 5 μm) (Toms et al., 1997; Groth et al., 1997). There appears to be a general trend towards an association between the extent (i.e., number) of spontaneous coughs and the rate of particle clearance, with faster clearance associated with a greater number of coughs (Groth et al., 1997). Thus, recent evidence continues to support cough as an adjunct to mucociliary movement in the removal of particles from the lungs of individuals with COPD. However, some recent evidence suggests that, like mucociliary function, cough-induced clearance may become

depressed with worsening airway disease. Noone et al. (1999) found that the efficacy of clearance via cough in patients with primary ciliary dyskinesia, who rely on coughing for clearance because of immotile cilia, correlated with lung function (FEV1), in that decreased cough clearance was associated with decreased percentage of predicted FEV1.

Earlier reported studies (U.S. Environmental Protection Agency, 1996) indicated that rates of A region particle clearance were reduced in humans with chronic obstructive lung disease and in laboratory animals with viral infections, whereas the viability and functional activity of macrophages was impaired in human asthmatics and in animals with viral induced lung infections. However, any modification of functional properties of macrophages appears to be injury specific, in that they reflect the nature and anatomic pattern of disease.

A factor that may affect clearance of particles is the integrity of the epithelial surface lining of the lungs. Damage or injury to the epithelium may result from disease or from the inhalation of chemical irritants. Earlier studies performed with particle instillation had shown that alveolar epithelial damage at the time of deposition in mice resulted in increased translocation of inert carbon to pulmonary interstitial macrophages (Adamson and Hedgecock, 1995). A similar response was observed in a more recent assessment (Adamson and Prieditis, 1998), whereby silica (<0.3 μm) was instilled into a lung having alveolar epithelial damage, as evidenced by increased permeability, and particles were noted to reach the interstitium and lymph nodes.

7.4 PARTICLE OVERLOAD

Experimental studies using some laboratory rodents have employed high exposure concentrations of relatively nontoxic, poorly soluble particles. These particle loads interfered with normal clearance mechanisms, producing clearance rates different from those that would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with a phenomenon that has been termed particle “overload”, defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate that exceeds the capacity of that clearance pathway. It has been hypothesized that in the rat, overload will begin when deposition approaches 1 mg particles/g lung tissue (Morrow, 1988). Overload is a nonspecific effect noted in experimental studies using many different kinds of poorly soluble particles and results in A region clearance slowing or stasis, with an associated chronic inflammation and

aggregation of macrophages in the lungs and increased translocation of particles into the interstitium.

The relevance of lung overload to humans exposed to poorly soluble, nonfibrous particles remains unclear. Although it is likely to be of little relevance for most "real world" ambient exposures, it may be of concern in interpreting some long-term experimental exposure data and, perhaps, also for occupational exposures. For example, it has been suggested that a condition called progressive massive fibrosis, which is unique to humans, has features indicating that dust overload is a factor in its pathogenesis (Green, 2000). This condition is associated with cumulative dust exposure and impaired clearance, and can occur following high exposure concentrations associated with occupational situations. In addition, the relevance to humans is clouded by the suggestion that macrophage-mediated clearance is normally slower and perhaps of less relative importance in overall clearance in humans than in rats (Morrow, 1994), and that there can be significant differences in macrophage loading between species. On the other hand, overload may be a factor in individuals with compromised lungs under normal exposure conditions. Thus, it has been hypothesized (Miller et al., 1995) that localized overload of particle clearance mechanisms in people with compromised lung status may occur, whereby these mechanisms are overwhelmed, resulting in morbidity or mortality from particle exposure.

7.5 COMPARISON OF DEPOSITION AND CLEARANCE PATTERNS OF PARTICLES ADMINISTERED BY INHALATION AND INTRATRACHEAL INSTILLATION

The most relevant exposure route to evaluate the toxicity of particulate matter is inhalation. However, many studies delivered particles by intratracheal instillation. This latter technique has been used because it is easy to perform; requires significantly less effort, cost, and amount of test material than does inhalation; and can deliver a known, exact dose of a toxicant to the lungs. Because particle disposition is a determinant of dose, it is important to compare deposition and clearance of particles delivered by these two routes. However, in most instillation studies, the effect of this route of administration on particle deposition and clearance per se was not examined. Although these parameters were evaluated in some studies, it has been very difficult to compare particle deposition/clearance between different inhalation and instillation studies

because of differences in experimental procedures and in the manner by which particle deposition/clearance was quantitated. A recent paper provided a detailed evaluation of the role of instillation in respiratory tract dosimetry and toxicology studies (Driscoll et al., 2000), and a short summary derived from this paper is provided in this section.

The pattern of initial regional deposition is strongly influenced by the exposure technique used. Furthermore, the patterns within specific respiratory tract regions also are influenced in this regard. Depending on particle size, inhalation results in varying degrees of deposition within the ET airways, a region that is completely bypassed by instillation. Thus, differences in amount of particles deposited in the lower airways will occur between the two procedures.

The exposure technique also influences the intrapulmonary distribution of particles, which potentially would affect routes and rates of ultimate clearance from the lungs and dose delivered to specific sites within the respiratory tract or to extrapulmonary organs. Intratracheal instillation tends to disperse particles fairly evenly within the tracheobronchial tree, but can result in heterogeneous distribution in the alveolar region, whereas inhalation tends to produce a more homogeneous distribution throughout the major conducting airways as well as the alveolar region for the same particles. Thus, inhalation results in a randomized distribution of particles within the lungs, whereas intratracheal instillation produces an heterogeneous distribution in that the periphery of the lung receives little particle load and most of the instilled particles are found in regions that have a short path length from the major airways. Furthermore, inhalation results in greater deposition in apical areas of the lungs and less in basal areas, whereas intratracheal instillation results in less apical than basal deposition.

Comparison of the kinetics of clearance of particles administered by instillation or inhalation have shown similarities, as well as differences, in rates for different clearance phases, dependent on the exposure technique used. However, some of the differences in kinetics may be explained by differences in the initial sites of deposition.

One of the major pathways of clearance involves particle uptake and removal via pulmonary macrophages. Dorries and Valberg (1992) noted that inhalation resulted in a lower percentage of particles recovered in lavaged cells and a more even distribution of particles among macrophages. More individual cells received measurable amounts of particles via inhalation than via intratracheal instillation, whereas with the latter, many cells received little or no particles, although others received very high burdens. Furthermore, with intratracheal instillation,

macrophages at the lung periphery contained few, if any, particles, whereas cells in the regions of highest deposition were overloaded, reflecting the heterogeneity of particle distribution when particles are administered via instillation. Thus, the route of exposure influences the particle distribution in the macrophage population and could, by assumption, influence clearance pathways and clearance kinetics.

In conclusion, inhalation may result in deposition within the ET region, the extent of which depends on the size of the particles used. Of course, intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly to the tracheobronchial tree. Although some studies indicate that short (0 to 2 days) and long (100 to 300 days postexposure) phases of clearance of insoluble particles delivered either by inhalation or intratracheal instillation are similar, other studies indicate that the percentage retention of particles delivered by instillation is greater than that for inhalation, at least up to 30 days postexposure. Thus, there is some inconsistency. Perhaps the most consistent conclusion regarding differences between inhalation and intratracheal instillation is related to the intrapulmonary distribution of particles. Inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs. On the other hand, instillation results in a heterogeneous distribution, especially within the alveolar region, and focally high concentrations of particles. The bulk of instilled material penetrates beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of particles. This difference is reflected in particle burdens within macrophages, with those from animals inhaling particles being burdened more homogeneously and those from animals with instilled particles showing some populations of cells with no particles and others with heavy burdens. This difference reflects on clearance pathways, dose to cells and tissues, and systemic absorption. Exposure method, thus, clearly influences dose distribution.

7.6 MODELING THE DISPOSITION OF PARTICLES IN THE RESPIRATORY TRACT

7.6.1 Modeling Deposition and Clearance

The biologic effects of inhaled particles are a function of their disposition. This, in turn, depends on their patterns of both deposition and clearance. Removal of deposited materials involves the competing processes of macrophage-mediated clearance and dissolution-absorption.

Over the years, mathematical models for predicting deposition, clearance and, ultimately, retention of particles in the respiratory tract have been developed. Such models help interpret experimental data and can be used to make predictions of deposition for cases where data are not available.

A review of various mathematical deposition models was given by Morrow and Yu (1993) and in U.S. Environmental Protection Agency (1996). There are three major elements involved in mathematical modeling. First, a structural model of the airways must be specified in mathematical terms. Second, deposition efficiency in each airway must be derived for each of the various deposition mechanisms. Finally, a computational procedure must be developed to account for the transport and deposition of the particles in the airways. As noted earlier, most models are deterministic, in that particle deposition probabilities are calculated using anatomical and airflow information on an airway generation by airway generation basis. Other models are stochastic, whereby modeling is performed using individual particle trajectories and finite element simulations of airflow.

Recent reports involve modeling the deposition of ultrafine particles and deposition at airway bifurcations. Zhang and Martonen (1997) used a mathematical model to simulate diffusion deposition of ultrafine particles in the human upper tracheobronchial tree and compared the results to those in a hollow cast obtained by Cohen et al. (1990). The model was in good agreement with experimental data. Zhang and Martonen (1997) studied the inertial deposition of particles in symmetric three-dimensional models of airway bifurcations, mathematically examining effects of geometry and flow. They developed equations for use in predicting deposition based on Stokes numbers, Reynolds numbers, and bifurcation angles for specific inflows.

Models for deposition, clearance, and dosimetry of the respiratory tract of humans have been available for the past four decades. The International Commission on Radiological Protection (ICRP) has recommended three different mathematical models during this time period (International Commission on Radiological Protection, 1960, 1979, 1994). These models make it possible to calculate the mass deposition and retention in different parts of the respiratory tract and provide, if needed, mathematical descriptions of the translocation of portions of the deposited material to other organs and tissues beyond the respiratory tract.

A morphological model based on laboratory data from planar gamma camera and single-photon emission tomography images has been developed (Martonen et al., 2000; Segal et al., 2000b). This model defines the parenchymal wall in mathematical terms, divides the lung into distinct left and right components, derives a set of branching angles from experimental measurements, and confines the branching network within the left and right components (so there is no overlapping of airways). The authors conclude that this more physiologically realistic model can be used to calculate PM deposition patterns for risk assessment.

Musante and Martonen (2000c) developed an age-dependent theoretical model to predict dosimetry in the lungs of children. The model comprises dimensions of individual airways and geometry of branching airway networks within developing lungs and breathing parameters as a function of age. The model suggests that particle size, age, and activity level markedly affect deposition patterns of inhaled particles. Simulations thus far predict a lung deposition fraction of 38% in an adult and 73%, nearly twice as high, in a 7-mo-old for 2μ-particles inhaled during heavy breathing. The authors conclude that use of this model will be useful for estimating dose delivered to sensitive subpopulations, such as children.

Segal et al. (2000a) developed a computer model for airflow and particle motion in the lungs of children to study how airway disease, specifically cancer, affects inhaled PM deposition. The model considers how tumor characteristics (size and location) and ventilatory parameters (breathing rates and tidal volumes) influence particle trajectories and deposition patterns. The findings indicate that PM may be deposited on the upstream surfaces of tumors because of enhanced efficiency of inertial impaction. Also, submicron particles and larger particles, respectively, may be deposited on the downstream surfaces of tumors because of enhanced efficiency of diffusion and sedimentation. The mechanisms of diffusion and sedimentation are functions of the particle residence times in airways. Eddies downstream of tumors would trap particles and allow more time for deposition to occur by diffusion and sedimentation. The authors conclude that particle deposition is complicated by the presence of airway disease but that the effects are systematic and predictable.

Broday and Georgopoulos (2000) recently have presented a model that solves a variant of the general dynamic equation for size evolution of respirable particles within human tracheobronchial airways. The model considers polydisperse aerosols with respect to size and heterosperse with respect to thermodynamic state and chemical composition. The aerosols have

an initial bimodal lognormal size distribution that evolves with time in response to condensation-evaporation and deposition processes. Simulations reveal that submicron size particles grow rapidly and cause increased number and mass fractions of the particle population to be found in the intermediate size range. Because deposition by diffusion decreases with increasing size, fine hygroscopic particles persist longer in the inspired air than nonhygroscopic particles of comparable initial size distribution. In contrast, the enhanced deposition fraction of hygroscopic particles, initially from the intermediate size range, increases their deposition fraction in the airways. The model demonstrates that the combined effect of growth and deposition tends to decrease the size nonuniformity of persistent particles in the airways and form an aerosol that is characterized by a smaller variance; these factors also alter the deposition profile along airways.

Another respiratory tract dosimetry model was developed, concurrently with the new ICRP model, by the National Council on Radiation Protection and Measurements (NCRP) (1997). As with the ICRP model (International Commission on Radiological Protection, 1994), the new NCRP model addresses inhalability of particles, revised subregions of the respiratory tract, dissolution-absorption as an important aspect of the model, and body size and age. The NCRP model defines the respiratory tract in terms of a naso-oro-pharyngo-laryngeal (NOPL) region, a tracheobronchial (TB) region, a pulmonary (P) region, and lung-associated lymph nodes (LN). Deposition and clearance are calculated separately for each of these regions. As with the 1994 ICRP model, inhalability of aerosol particles is considered, and deposition in the various regions of the respiratory tract is modeled using methods that relate to mechanisms of inertial impaction, sedimentation, and diffusion.

Fractional deposition in the NOPL region was developed from empirical relationships between particle diameter and air flow rate. Deposition in the TB and P regions were projected from model calculations based on geometric or aerodynamic particle diameter and physical deposition mechanisms such as impaction, sedimentation, diffusion, and interception. Deposition in the TB and P regions used the lung model of Yeh and Schum (1980), with a method of calculation similar to that of Findeisen (1935) and Landahl (1950). This method was modified to accomodate an adjustment of lung volume and substitution of realistic deposition equations. These calculations were based on air flow information and idealized morphometry, using a typical pathway model. Comparison of regional deposition fraction predictions between the NCRP and ICRP models was provided in U.S. Environmental Protection Agency (1996).

Inhalability was defined as per the American Conference of Governmental Industrial Hygenists (1985) definition. Breathing frequency, tidal volume, and functional residual capacity are the ventilatory factors used to model deposition. These were related to body weight and to three levels of physical activity, namely low activity, light exertion and heavy exertion.

Clearance from all regions of the respiratory tract was considered to result from competitive mechanical and absorptive mechanisms. Mechanical clearance in the NOPL and TB regions was considered to result from mucociliary transport. This was represented in the model as a series of escalators moving towards the glottis and where each airway had an effective clearance velocity. Clearance from the P region was represented by fractional daily clearance rates to the TB region, the pulmonary LN region, and the blood. A fundamental assumption in the model was that the rates for absorption into blood were the same in all regions of the respiratory tract; the rates of dissolution-absorption of particles and their constituents were derived from clearance data primarily from laboratory animals. The effect of body growth on particle deposition also was considered in the model, but particle clearance rates were assumed to be independent of age. Some consideration for compromised individuals was incorporated into the model by altering rates (compared to normal) for the NOPL and TB regions.

Mathematical deposition models for deposition in a number of nonhuman species have been developed and discussed previously (U.S. Environmental Protection Agency, 1996). Despite difficulties, modeling studies in laboratory animals remain a useful step in extrapolating exposure-dose-response relationships from laboratory animals to human. Some additional work on modeling deposition in animals has been reported, but it merely expands on work and approaches already noted in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996).

Respiratory-tract clearance begins immediately on deposition of inhaled particles. Given sufficient time, the deposited particles may be removed completely by these clearance processes. However, single inhalation exposures may be the exception rather than the rule. It generally is accepted that repeated or chronic exposures are common for environmental aerosols. As a result of such exposures, accumulation of particles may occur. Chronic exposures produce respiratory tract burdens of inhaled particles that continue to increase with time until the rate of deposition is balanced by the rate of clearance. This is defined as the “equilibrium respiratory tract burden”.

It is important to evaluate these accumulation patterns, especially when assessing ambient chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled

particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined as "species-dependent concentrations of airborne particles which, when chronically inhaled, produce equal lung deposits of inhaled particles per gram of lung during a specified exposure period" (Schlesinger et al., 1997). Available data and approaches to evaluate exposure atmospheres that produce similar respiratory tract burdens in laboratory animals and humans have been discussed in detail in the previous criteria document.

Several laboratory animal models have been developed to help interpret results from specific studies that involved chronic inhalation exposures to nonradioactive particles (Wolff et al., 1987; Strom et al., 1988; Stöber et al., 1994). These models were adapted to data from studies involving high level chronic inhalation exposures in which massive lung burdens of low toxicity, poorly soluble particles were accumulated, but the models have not been adapted to chronic exposures to low concentrations of aerosols in which particle overload does not occur.

Asgharian et al. (2000) described a method for calculating a deposited fraction for a specific size distribution based on a summary of published data on regional deposition of different size particles. The method is based on constructing nomograms that are used to estimate alveolar deposition fractions for three species (human, monkey, and rat). The data is then incorporated into a regression model that calculates more exact deposition fractions. The model is somewhat constrained at present because of limitations in the underlying deposition database.

Hofmann et al. (2000) used three different morphometric models of the rat lung to compute particle deposition in the acinar airways: the multipath lung model (MPL), with a fixed airway geometry; the stochastic lung (SL) model, with a randomly selected branching structure; and a hybrid of the MPL and SL models. They calculated total and regional deposition for a range of particle sizes during quiet and heavy breathing. Although the total bronchial and acinar deposition fractions were similar for the three models, the SL and the hybrid models predicted a substantial variation in particle deposition among different acini. Acinar deposition variances in the MPL model were consistently smaller than in the SL and the hybrid lung models. The authors conclude that the similarity of acinar deposition variations in the latter two models and their independence of the breathing pattern suggest the heterogeneity of the acinar airway structure is primarily responsible for the heterogeneity of acinar particle deposition.

7.6.2 Models To Estimate Retained Dose

Models have been used routinely to express retained dose in terms of temporal patterns for alveolar retention of acutely inhaled materials. Available information for a variety of mammalian species and humans can be used to predict deposition patterns in the respiratory tract for inhalable aerosols with reasonable degrees of accuracy. Additionally, alveolar clearance data for mammalian species commonly used in inhalation studies are available from numerous experiments that involved small amounts of inhaled radioactive particles.

An important factor in using models to predict retention patterns in laboratory animals or humans is the dissolution-absorption rate of the inhaled material. Factors that affect the dissolution of materials or the leaching of their constituents in physiological fluids, and the subsequent absorption of these constituents, are not fully understood. Solubility is known to be influenced by the surface-to-volume ratio and other surface properties of particles (Mercer, 1967; Morrow, 1973). The rates at which dissolution and absorption processes occur are influenced by factors that include the chemical composition of the material. Temperature history of materials is an important consideration for some metal oxides. For example, in controlled laboratory environments, the solubility of oxides usually decreases when the oxides are produced at high temperatures, which generally results in compact particles having small surface-to-volume ratios. It is sometimes possible to accurately predict dissolution-absorption characteristics of materials based on physical/chemical considerations; but, predictions for in vivo dissolution-absorption rates for most materials, especially if they contain multivalent cations or anions, should be confirmed experimentally.

Phagocytic cells, primarily macrophages, clearly play a role in dissolution-absorption of particles retained in the respiratory tract (Kreyling, 1992). Some particles dissolve within the phagosomes because of the acidic milieu in those organelles (Lundborg et al., 1984, 1985), but the dissolved material may remain associated with the phagosomes or other organelles in the macrophage rather than diffuse out of the macrophage to be absorbed and transported elsewhere (Cuddihy, 1984). This same phenomenon has been reported for organic materials. For example, covalent binding of benzo[*a*]pyrene or metabolites to cellular macromolecules resulted in an increased alveolar retention time for that compound after inhalation exposures of rats (Medinsky and Kampcik, 1985). Understanding these phenomena and recognizing species similarities and

differences are important for evaluating alveolar retention and clearance processes and interpreting results of inhalation studies.

Dissolution-absorption of materials in the respiratory tract is clearly dependent on the chemical and physical attributes of the material. Although it is possible to predict rates of dissolution-absorption, it is prudent to experimentally determine this important clearance parameter. It is important to understand the impact of this clearance process for the lung, TLNs, and other body organs that might receive particles, or their constituents that enter the circulatory system from the lung.

Insufficient data were available to adequately model long-term retention of particles deposited in the conducting airways of any mammalian species at the time of the previous document, and this remains the case. Additional research must be done to provide the information needed to properly evaluate retention of particles in conducting airways.

However, a number of earlier studies discussed in the previous document and in Section 7.2.2.2 herein noted that some particles were retained for relatively long times in the upper respiratory tract and tracheobronchial regions, effectively contradicting the general conclusion that almost all inhaled particles that deposit in the TB region clear within hours or days. These studies have demonstrated that variable portions of the particles that deposit in, or are cleared through, the TB region are retained with half times on the order of weeks or months. Long-term retention and clearance patterns for particles that deposit in the head airways and TB region must continue to be thoroughly evaluated because of the implications of this information for respiratory tract dosimetry and risk assessment.

Model projections are possible for the A region using the cumulative information in the scientific literature relevant to deposition, retention, and clearance of inhaled particles. Clearance parameters for six laboratory animal species were summarized in U.S. Environmental Protection Agency (1996). Recently, Nikula et al. (1997) evaluated results in rats exposed to high levels of either diesel soot or coal dust. Although the amount of retained material was similar in both species, the rats retained a greater portion in the lumens of the alveolar ducts and alveoli than did monkeys, whereas the monkeys retained a greater portion of the material in the interstitium than did rats. The investigators concluded that intrapulmonary retention patterns in one species may not be predictive of those in another species at high levels of exposure, but this may not be the case at lower levels.

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8. TOXICOLOGY OF PARTICULATE MATTER

8.1 INTRODUCTION

Toxicological research on ambient particulate matter (PM) is used to address several related questions, including (1) what causal mechanisms may be involved in the toxicological response to PM exposures, (2) what factors affect individual or subpopulation susceptibility to the effects of PM exposures, (3) what characteristics of PM (e.g., size, composition) are producing observed toxicity, and (4) what are the combined effects of PM and gaseous co-pollutants in producing toxic responses? A variety of research approaches are used to address these questions, including in vivo studies of human volunteers to controlled exposures; in vivo studies of animals such as nonhuman primates, dogs and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. Similarly, a variety of exposure conditions are employed, including whole body and nose-only inhalation exposures to artificially generated PM or concentrated ambient air, pulmonary instillation, and in vitro exposure to test materials in solution. The various research designs are targeted to test hypotheses and, ultimately, provide a scientific basis for an improved understanding of the role of PM in producing health effects identified by epidemiological studies.

Because of the sparsity of toxicological data on ambient PM at the time the previous PM Air Quality Criteria Document or "PM AQCD" (U.S. Environmental Protection Agency, 1996a) was completed, the discussion of respiratory effects of PM were organized into specific chemical components of ambient PM or model "surrogate" particles (e.g., acid aerosols, metals, ultrafine particles, bioaerosols, "other particle matter"). In this chapter, the conclusions of the 1996 PM AQCD are summarized for each of these components. Since completion of the previous document, there are many new studies demonstrating the potentially adverse effects of combustion-related particles. The main reason for this increased interest in combustion particles is that these particles are typically the dominant sources represented in the fine fraction of ambient PM.

This chapter is organized as follows. The respiratory effects of specific components of ambient PM or surrogate particles delivered by in vivo exposures of both humans and laboratory

animals are discussed first (Section 8.2), followed by systemic and cardiovascular effects of particles (Section 8.3) and effects in laboratory animal models that mimic human disease (Section 8.4). The in vitro exposure studies are discussed next (Section 8.5) because they provide valuable information on potential hazardous constituents and mechanisms of PM injury. The remaining section on exposure studies examines the health effects of mixtures of ambient PM or PM surrogates with gaseous pollutants (Section 8.6). This organization provides the underlying data for evaluation in the final section of this chapter (Section 8.7), but it may fail to adequately convey the extensive and intricate linkages among the pulmonary, cardiac, and nervous systems, all of which may be involved individually and in concert to represent the effects of exposure to PM.

8.2 RESPIRATORY EFFECTS OF PARTICULATE MATTER IN HEALTHY HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES

The following sections assess the results of human exposure to various types of PM and also discuss controlled animal toxicology studies, as well as in vitro studies using animal or human respiratory cells. The discussion focuses on those studies published since the previous 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a).

The biological responses occurring in the respiratory tract following controlled PM inhalation encompass a continuum of changes, including changes in pulmonary inflammation, pulmonary function, and systemic effects. The observed responses are dependent on the physicochemical characteristics of the PM, the total exposure, and the health status of the host. Many of the responses are usually seen only at higher level exposures characteristic of occupational and laboratory animal studies and not at (typically much lower) ambient particle concentrations; however, there are substantial differences in the inhalability and deposition profiles of PM in humans and rodents (see Chapter 7 for details). Observed responses and dose-response relationships also are very dependant on the variable being measured.

Particulate matter is a broad term that encompasses thousands of chemical species, many of which have not been investigated in controlled laboratory animal or human studies. However, a full discussion of all types of particles that have been studied is beyond the scope of this

chapter. Thus, specific criteria were used to select topics for presentation. High priority was placed on studies that may (1) elucidate health effects of major common constituents of ambient PM or (2) contribute to enhanced understanding of the epidemiological studies (e.g., use of ambient particles, "surrogate" particles, or particles with low inherent toxicity that may cause effects because of their physicochemical characteristics, such as their size and composition). Most studies, therefore, have been designed to address the question of biologic plausibility, rather than providing dose-response or risk assessment quantitation.

Diesel exhaust particles (DPM) generally fit the criteria; but, because they are described elsewhere in great detail (U. S. Environmental Protection Agency, 1999; Health Effects Institute, 1995), they are not covered extensively in this chapter except in the discussions of their immunological effects. Particles with high inherent toxicity, such as silica and asbestos, that are of concern primarily because of occupational exposure, also are excluded from this chapter and are discussed in detail elsewhere (U.S. Environmental Protection Agency, 1996b; Gift and Faust, 1997). Most of the laboratory animal studies summarized here have used high particulate mass concentrations administered by inhalation, compared to ambient levels, even when laboratory animal-to-human dosimetric differences or high doses by intratracheal instillation are considered. More research on particle dose extrapolation is needed, therefore, to determine species differences and the importance of exercise and other factors influencing particle deposition in humans that together can account for a 50-fold or more difference in dose.

As mentioned earlier, the data available in the previous 1996 PM AQCD were from studies that investigated the respiratory effects of specific components of ambient PM or surrogate particles. More recently, pulmonary effects of controlled exposures to ambient PM have been investigated by the use of aerosol concentrators (Sioutas et al., 1995; Gordon et al., 1998). These concentrators are capable of exposing animals or humans to PM concentrations that are up to 90-fold higher than ambient PM levels and have been used to investigate the effects of ambient PM in normal and compromised animals and humans.

8.2.1 Acid Aerosols

There have been extensive studies of the effects of controlled exposures to aqueous acid aerosols on various aspects of lung function in humans and laboratory animals. Many of these studies were reviewed in the previous criteria document (U.S. Environmental Protection Agency

1996a) and in the Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989); more recent studies are summarized in the present document (see Table 8-1). Methodology and measurement methods for controlled human exposure studies have been reviewed elsewhere (Folinsbee et al., 1997).

These studies illustrate that aqueous acidic aerosols have minimal effects on symptoms and mechanical lung function in young healthy adult volunteers at concentrations as high as 2000 $\mu g/m^3$. The findings include minimal changes in lung function accompanied by only mild lower respiratory symptoms. However at concentrations as low as 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. Brief exposures ($\leq$1 h) to low concentrations ($\approx$100 $\mu g/m^3$) may accelerate clearance while longer (multihour) exposures to higher concentrations (>100 $\mu g/m^3$) can depress clearance. Asthmatic subjects appear to be more sensitive to the effects of acidic aerosols on mechanical lung function. Responses have been reported in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$ and modest bronchoconstriction has been seen in adult asthmatics exposed to concentrations $\geq$400 $\mu g/m^3$, but the available data are not consistent.

A previously described acid aerosol exposure in humans (1000 $\mu g/m^3$) did not result in airway inflammation (Frampton et al., 1992), and there was no evidence of altered macrophage host defenses. More recently, Zelikoff et al. (1997) compared the responses of rabbits and humans exposed to similar concentrations of acid aerosol. For both rabbits and humans, there was no evidence of PMN infiltration into the lung and no change in BAL protein level, although there was an increase in LDH in rabbits but not in humans. Macrophages showed less antimicrobial activity in rabbits; insufficient data were available for humans. Macrophage phagocytic activity was slightly reduced in rabbits but not in humans. Superoxide production by macrophages was somewhat depressed in both species. No respiratory effects of long-term exposure to acid aerosol were found in dogs (Heyder et al., 1999).

8.2.2 Metal Particles, Fumes, and Smoke

Data from occupational and laboratory animal studies reviewed in the previous criteria document (U. S. Environmental Protection Agency, 1996a) indicated that acute exposures to very high levels (hundreds of $\mu g/m^3$ or more) or chronic exposures to lower levels (up to 15 $\mu g/m^3$, albeit high compared to ambient levels) of metallic particles could have an effect on the respiratory tract. However, it was concluded on the basis of available data that the metals at

TABLE 8-1. RESPIRATORY EFFECTS OF ACID AEROSOLS IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effects of Particles	Reference
Healthy beagle dogs; n = 16	Neutral sulfite aerosol	Inhalation	1.5 mg/m^3	1.0 μm MMAD δg = 2.2	16.5 h/day for 13 mo	Long-term exposure to particle-associated sulfur and hydrogen ions at concentrations close to ambient levels caused only subtle respiratory responses and no change in lung pathology.	Heyder et al. (1999)
	Acidic sulfate aerosol	Inhalation	5.7 mg/m^3	1.1 μm MMAD δg = 2.0	6 h/day for 13 mo		
Asthmatic subjects; 13 M, 11 F	H_2SO_4 aerosol NH_4^+/SO_4^{-2} aerosol	Inhalation by face mask	500 μg/m^3	9 μm MMAD 7 μm MMAD	1 h	Exposure to simulated natural acid fog did not induce bronchoconstriction and did not change bronchial responsiveness in asthmatics.	Leduc et al. (1995)
Female Fischer 344 rats Female Hartley Guinea Pigs	H_2SO_4 aerosol	Inhalation	94 mg/m^3 43 mg/m^3	0.80 ± 1.89 δg 0.93 ± 2.11 δg	4h	Acid aerosol increased surfactant film compressibility in guinea pigs.	Lee et al. (1999)
Healthy nonsmokers; 10 M, 2 F; 21-37 years old	H_2SO_4 aerosol	Inhalation	1,000 μg/m^3	0.8-0.9 μm MMAD	3 h	No inflammatory responses; LDH activity in BAL was elevated. Effect on bacterial killing by macrophages was inconclusive; latex particle phagocytosis was reduced 28%.	Zelikoff et al. (1997)

BAL - Bronchoalveolar lavage
LDH - Lactate dehydrogenase
MMAD - Mass median aerodynamic diameter
MMD - Mass median diameter
δg - Geometric standard deviation

concentrations present in the ambient atmosphere (1 to 14 $\mu g/m^3$) were not likely to have a significant acute effect in healthy individuals. These metals include arsenic, cadmium, copper, vanadium, iron, and zinc. Other metals found at concentrations less than 0.5 $\mu g/m^3$ were not reviewed in the previous criteria document. However, published data added to the existing PM data base demonstrate that particle-associated metals are plausible causal components of PM.

Only limited controlled human exposure studies have been performed with particles other than acid aerosols (see Table 8-2). Controlled inhalation exposure studies to high concentrations of two different metal fumes, MgO and ZnO, demonstrate the differences in response based on particle metal composition (Kuschner et al., 1997). Up to 6400 mg/m^3• min cumulative dose of MgO had no effect on lung function (spirometry, $D_{L_{CO}}$), symptoms of metal fume fever, or changes in inflammatory mediators or cells recovered by BAL. However, lower concentrations of ZnO fume (165 to 1110 mg/m^3• min) induced a neutrophilic inflammatory response in the airways 20 h postexposure. Lavage fluid PMNs, TNF-α, and IL-8 were increased by ZnO exposure. However, the concentrations used in these exposure studies exceed ambient levels by more than 1000-fold. The absence of a response to an almost 10-fold higher concentration of MgO compared with ZnO indicates that metal composition may be more important than particle size (ultrafine/fine) when considering observed health responses to inhaled PM. Fine et al. (1997) have shown elevated body temperature (metal fume fever) and increased levels of plasma IL-6 (from 2.9 to 6.4 pg/mL) in naive subjects exposed to the 8-h TLV concentration of ZnO of 5 mg/m^3 for 2 h.

Several metals have been shown to stimulate cytokine release in cultured human pulmonary cells including zinc, chromium, cobalt, and vanadium. Boiler makers, exposed occupationally to approximately 400 to 500 $\mu g/m^3$ of fuel oil ash, showed acute nasal inflammatory responses characterized by increased PMNs and elevated IL-8 that were associated with vanadium levels (increased about ninefold) in the upper airway (Woodin et al., 1998). Irsigler et al. (1999) reported that V_2O_5 can induce asthma and bronchial hyperreactivity in exposed workers.
A comparison of autopsy cases in Mexico City from the 1950s versus the 1980s indicated substantially higher levels of (5- to 20-fold) Cd, Co, Cu, Ni, and Pb in lung tissue from the1980s (Fortoul et al., 1996). Similar studies have examined metal content in human blood and lung tissue (Tsuchiyama et al., 1997; Osman et al., 1998). The autopsy data suggest that chronic exposures to urban air pollution leads to an increased deposition of metals in human tissues.

TABLE 8-2. RESPIRATORY EFFECTS OF METAL PARTICLES, FUMES, AND SMOKE IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Naive subjects; 8 M, 5 F; 30.8± 7.7 years old	ZnO	Inhalation by face mask	2.5 mg/m^3 5 mg/m^3	0.3 μm MMD	2h	Increased oral temperature after 2.5- and 5.0-mg/m^3 exposure. Elevated IL-6 after exposure to 5 mg/m^3. Symptoms (myalgia, cough, fatigue) peaked 9 h after 5 mg/m^3 exposure.	Fine et al. (1997)
Healthy nonsmokers; 12 M, 4 F; 18-35 years old	Colloidal iron oxide	Bronchial instillation	5 mg in 10 mL	2.6 μm	1, 2, and 4 days after instillation	L-ferritin increased after iron oxide particle exposure; transferrin was decreased. Both lactoferrin and transferrin receptors were increased.	Ghio et al. (1998a)
Vanadium plant workers; 40 M; 19-60 years old	V_2O_5	Ambient air	<0.05-1.53 mg/m^3	N/A	Variable	12/40 workers had bronchial hyperreactivity that persisted in some for up to 23 mo.	Irsigler et al. (1999)
Healthy nonsmokers; 4 M, 2 F; 21-43 years old	MgO ZnO	Inhalation	100-200 mg/m^3	99% < 1.8 μm 29% < 0.1 μm	45 min	No significant differences in BAL inflammatory cell concentrations, BAL interleukins (IL-1, IL-6, IL-8), tumor necrosis factor, pulmonary function, or peripheral blood neutrophils.	Kuschner et al. (1997)
Healthy nonsmokers; 27 M, 7 F; 20-36 years old	Fe_2O_3	Intrapulmonary instillation	3×10^8 microspheres in 10 mL saline.	2.6 μm	N/A	Transient inflammation induced initially (neutrophils, protein, LDH, IL-8) was resolved by 4 days postinstillation.	Lay et al. (1998)
Fischer 344 rats. (250 g)	Fe_2O_3	Intratracheal instillation	7.7×10^7 microspheres in 5 mL saline	2.6 μm	N/A	Transient inflammation at 1 day postinstillation.	Lay et al. (1998)
NMRI mice; Mouse peritoneal macrophage	MnO_2	Intratracheal instillation; in vitro	0.037, 0.12, 0.75, 2.5 mg/animal	surface area of 0.16, 0.5; 17, 62 m^2/g	Sacrificed at 5 days	LDH, protein and cellular recruitment increased with increasing surface area; freshly ground particles had enhanced cytotoxicity.	Lison et al. (1997)
7-week-old WISTAR Furth rats; C57BL6 and DBA3NCR mice	CdO Fume	Nose-only Inhalation	1.04 mg/m^3 Rats dose = 18.72 μg Mouse dose = 4.59 μg	CMD = 0.008 μm δg = 1.1	1 × 3 h	Mice created more metallothionein than rats, which may be protective of tumor formation.	McKenna et al. (1998)
Rat, M, F344, 175-225 g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 μg/m^3 Instillation at 500 μg for fine, 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	Inflammation produced by intratracheal inhalation (both severity and persistence) was less than that produced by instillation; ultrafine particles produced greater inflammatory response than fine particles for both dosing methods.	Osier and Oberdörster (1997)

TABLE 8-2 (cont'd). RESPIRATORY EFFECTS OF METAL PARTICLES, FUMES, AND SMOKE IN HUMANS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat, M. F344, 175-225 g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 $\mu g/m^3$ Instillation at 500 μg for fine, 750 μg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	MIP-2 increased in lavage cells but not in supernatant in those groups with increased PMN (more in instillation than in inhalation; more in ultrafine than in fine); TNF-α levels had no correlation with either particle size or dosing methods.	Osier et al. (1997)
Rats	$NaVO_3$ $VOSO_4$ V_2O_5	Intratracheal instillation	21 or 210 μg V/kg ($NaVO_3$, $VOSO_4$ soluble) 42 or 420 μg V/kg (V_2O_5) less soluble	N/A	1 h or 10 days following instillation	PMN influx was greatest following $VOSO_4$, lowest for V_2O_5; $VOSO_4$ induced inflammation persisted longest; MIP-2 and KC (CXC chemokines) were rapidly induced as early as 1 h postinstillation and persisted for 48 h; Soluble V induced greater chemokine mRNA expression than insoluble V; AMs have the highest expression level.	Pierce et al. (1996)
Boilermakers (18 M), 26-61 years old, and utility worker controls (11 M), 30-55 years old	V_2O_5	Inhalation of fuel-oil ash	0.4-0.47 mg/m^3 0.1-0.13 mg/m^3	10 μm	6 weeks	Exposure to fuel-oil ash resulted in acute upper airway inflammation, possibly mediated by increased IL-8 and PMNs.	Woodin et al. (1998)

BAL - Bronchoalveolar lavage
CMD - Count median diameter
IL - Interleukin
LDH - Lactate dehydrogenase
MIP-2 - Macrophage inflammatory protein-2
mRNA - Messenger RNA (ribonucleic acid)
N/A - Data not available.

Iron is the most abundant of the elements that are capable of catalyzing oxidant generation and also present in ambient urban particles. Lay et al. (1998) and Ghio et al. (1998a) tested the hypothesis that the human respiratory tract will attempt to diminish the added, iron-generated oxidative stress. They examined the cellular and biochemical response of human subjects instilled with iron (III) oxide via the intrapulmonary route. Saline alone and iron-containing particles suspended in saline were instilled into separate lung segments of human subjects. Subjects underwent bronchoalveolar lavage at 1 to 91 days after instillation of 2.6-μm diameter iron oxide agglomerates. Lay and colleagues found the greatest iron oxide-induced inflammatory response in the alveolar fraction of the lavage fluid, although a significant increase in macrophages also was observed in the bronchial fraction. The peak response for all cellular and biochemical changes occurred at 1 day postinstillation. Lung lavage within 1 day of exposure revealed decreased transferrin concentrations and increased ferritin and lactoferrin concentrations, consistent with a host-generated decrease in the availability of catalytically reactive iron (Ghio et al., 1998a). Normal iron homeostasis returned within 4 days of the iron particle instillation. The same iron oxide preparation, which contained a small amount of soluble iron, produced similar pulmonary changes in rats. Instillation of rats with two iron oxide preparations that contained no soluble iron did not produce injury or inflammation (see Section 8.2.2), thus suggesting that soluble iron was responsible for the observed intrapulmonary changes. Although only a small amount of the iron instilled in human subjects was "active", it is not clear if the total dose of iron oxide delivered acutely to the lung segments (approximately 5 mg or 2.1×10^8 particles) would be relevant to deposition of iron oxide particles at the concentrations of iron present in ambient urban air (generally less than 1 $\mu g/m^3$).

8.2.3 Ambient Combustion-Related and Surrogate Particulate Matter

The majority of the in vivo exposures to ambient particles have utilized intratracheal instillation techniques in laboratory animals. Discussions on the pros and cons of this technique are covered in Chapter 7 (Section 7.5), and these issues have also been reviewed elsewhere (Driscoll et al., 2000; Oberdörster et al., 1997; Osier and Oberdörster, 1997). In most of these studies, PM samples were collected on filters, resuspended in a vehicle (usually saline), and a small volume of the suspension was instilled intratracheally into the animals. The physiochemcial characteristics of PM are altered by deposition on a filter and resuspension in an

aqueous medium. In addition, the doses used in these instillation studies are generally high compared to ambient concentrations, even when laboratory animal-to-human dosimetric differences are considered. Therefore, in terms of direct extrapolation to humans in ambient exposure scenarios, greater importance should be place on inhalation studies. However, delivery of PM by instillation has the advantage that much less material is needed and the delivered dose can be determined directly without extrapolating from estimates of lung deposition. Instillation studies have proven valuable in comparing the effects of different types of PM and for investigating the mechanisms by which particulates cause lung injury and inflammation. Tables 8-3, 8-4, and 8-5 outline studies in which various biological endpoints were measured following exposures to ambient PM, complex combustion-related PM, or laboratory-derived surrogate PM, respectively.

There were only limited data available from human studies or laboratory animal studies on ultrafine aerosols at the time of the release of the previous criteria document (U.S. Environmental Protection Agency, 1996a). In vitro studies have shown that ultrafine particles have the capacity to cause injury to cells of the respiratory tract. High levels of ultrafine particles, as metal or polymer "fume," are associated with toxic respiratory responses in humans and other mammals. Such exposures are associated with cough, dyspnea, pulmonary edema, and acute inflammation. At concentrations less than 50 $\mu g/m^3$, freshly generated insoluble ultrafine teflon polymer fume particles can be severely toxic to the lung. However, it was not clear what role in the observed effects was played by fume gases which adhered to the particles. Thus, it was not clear at the time of the previous review what role, if any, ambient ultrafine particles may play in PM-induced mortality and morbidity. Newer data from clinical exposures have demonstrated that composition and not particle size was responsible for the adverse health effects associated with exposures to metal fumes containing both ultrafine and fine particles (Kuschner et al., 1997).

Toxicologic studies of other particulate matter species also were discussed in the previous criteria document. These studies included exposures to fly ash, volcanic ash, coal dust, carbon black, TiO_2, and miscellaneous other particles, either alone or in mixture. Some of the particles discussed were considered to be models of "nuisance" or "inert" dusts (i.e., those having low intrinsic toxicity) and were used in instillation studies to delineate nonspecific particle effects from effects of known toxicants. A number of studies on "other PM" examined effects of up to 50,000 $\mu g/m^3$ of respirable particles with inherently low toxicity. Although there was no

TABLE 8-3. RESPIRATORY EFFECTS OF AMBIENT PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Male S-D rats 200-225 g, control and SO_2-treated	Concentrated ambient particles (Boston) (CAP)	Harvard/EPA fine particle concentrator animals restrained in chamber	206,733, 607 $\mu g/m^3$ for Days 1-3; 29 °C, 59% RH	0.18 μm $\delta g = 2.9$	5 h/day for 3 days	PEF and TV increased in CAPS exposed animals. Increased protein and % neutrophils and lymphocytes in lavage fluid after CAPS exposure. Responses were greater in SO_2-bronchitis animals. No changes in LDH. No deaths occurred.	Clarke et al. (1999)
S-D rats 60 days	Provo, UT, TSP filters (10 years old), soluble and insoluble extracts	Intratracheal instillation	100-1000 μg of PM extract in 0.5 mL saline	N/A	24 h	Inflammation (PMN) and lavage fluid protein was greater with the soluble fraction containing more metal (Zn, Fe, Cu).	Ghio et al. (1999a)
Healthy nonsmokers; 18 to 40 yr old	CAP	Inhalation	23.1 to 311.1 $\mu g/m^3$	0.65 μm $\delta g = 2.35$	2 h; analysis at 18 h	Increased BAL neutrophils in both bronchial and alveolar fractions	Ghio et al. (2000a)
Mongral dogs, some with balloon occluded LAD coronary artery n = 14	CAP	Inhalation via tracheostomy	69-828 $\mu g/m^3$	0.23 to 0.34 μm $\delta g = 0.2$ to 2.9	6 h/day × 3 days	Decreased respiratory rate and increased lavage fluid neutrophils in normal dogs.	Godleski et al. (2000)
Male F 344 rats, monocrotaline treated	CAP	Inhalation	132 to 919 $\mu g/m^3$	0.2 to 1.2 μm $\delta g = 0.2$ to 3.9	1 × 3 h or 3 × 6 h	No inflammatory responses, no cell damage responses, no PFT changes.	Gordon et al. (2000)
8-mo-old Bi TO-2 male hamsters							
Rats	CAP	Nose-only inhalation	110-350 $\mu g/m^3$	N/A	3 h	Increased peripheral blood neutrophils and decreased lymphocytes.	Gordon et al. (1998)
S-D rats Human Bronchial Epithelial (BEAS-2B) cells	TSP collected in Provo	Intratracheal instillation	TSP filter samples (36.5 mg/mL) agitated in deionized H_2O_2 for 96 h, centrifuged at 1200g for 30 min, lyophylized and resuspended in deionized H_2O_2 or saline	N/A (TSP samples, comprised 50 to 60% PM_{10})	Sacrificed at 24 h	Provo particles caused cytokine-induced neutrophil-chemoattractant-dependent inflammation of rat lungs; Provo particles stimulated IL-6 and IL-8 production, increased IL-8 mRNA and ICAM-1 in BEAS-2B cells, and stimulated IL-8 secretion in primary cultures of BEAS-2B cells; cytokine secretion was preceded by activation of NF-κB and was reduced by SOD, DEF, or NAC; quantities of Cu^{2+} found in Provo particles replicated the effects	Kennedy et al. (1998)

TABLE 8-3 (cont'd). RESPIRATORY EFFECTS OF AMBIENT PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
90 to 100-day-old male S-D rats with or without SO_2-induced bronchitis	CAP	Instillation	650 $\mu g/m^3$		6 h/day × 2-3 days	Increased BALF protein and neutrophil influx in bronchitic rats; responses were variable between exposure regimens.	Kodavanti et al. (2000a)
Rats Wis (HAN strain)	Ambient PM Edinburgh, CB, CB Ultrafine (UCB)	Intratracheal instillation	50-125 μg in 0.2 mL	PM_{10} CB = (200-500 nm) UCB = 20 nm	Sacrificed at 6 h	Increased PMN, protein, and LDH following PM_{10}; greater response with ultrafine CB but not CB; decreased GSH level in BAL; free radical activity (deplete supercoil DNA); leukocytes from treated animals produced greater NO and TNF.	Li et al. (1996, 1997)

TABLE 8-4. RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
M Syrian golden hamsters 90-125g	Kuwaiti oil fire particles Urban particles from St. Louis, MO	Intratracheal instillation	0.15, 0.75, and 3.75 mg/100g	Oil fire particles: <3.5 μm, 10 days of 24-h samples (April 30 to May 9, 1991), in Ahmadi, Kuwait	Sacrificed 1 and 7 days post instillation	Increases in PMN, AM, albumin, LDH, myeloperoxidase, and β-N-acetylglucosaminidase; acute toxicity of the particles found in the smoke from the Kuwaiti oil fires is comparable to that of urban particles.	Brain et al. (1998)
NMRI mouse	CFA CMP WC	Intratracheal instillation	CMP: 20 μg arsenic/kg, or CMP: 100 mg particles/kg, WC alone (100 mg/kg), CFA alone (100 mg/kg [i.e., 20 μg arsenic/kg]), CMP mixed with WC (CMP, 13.6 mg/kg [(i.e., 20 μg arsenic/kg]), WC (86.4 mg/kg) and $Ca_3(AsO_4)_2$ mixed with WC (20 μg arsenic/kg), WC (100 mg/kg)	N/A	1, 5, 30 days posttreatment, lavage for total protein content, inflammatory cell number and type, and TNF-α production particle retention	Mild inflammation for WC; $Ca_3(AsO_4)_2$ caused significant inflammation; CMP caused severe but transient inflammation; CFA caused persistent alveolitis; cytokine production was upregulated in WC- and $Ca_3(AsO_4)$ treated animals after 6 and 30 days, respectively; a 90% inhibition of TNF-α production still was still observed at Day 30 after administration of CMP and CFA; a significant fraction persisted (10-15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at Day 30. Suppression of TNF-α production is dependent on the slow elimination of the particles and their metal content from the lung	Broeckaert et al. (1997)
Rats, male, S-D, 60 days old MCT (60 mg/kg), ip	Emission source PM Ambient airshed PM ROFA	Intratracheal instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 and 96 h following instillation	Increases in PMNs, albumin, LDH, PMN, and eosinophils following exposure to emission and ambient particles; induction of injury by emission and ambient PM samples is determined primarily by constituent metals and their bioavailability; MCT-ROFA show enhanced neutrophilic inflammation and an increase in mortality.	Costa and Dreher (1997)
WISTAR male rats Bor: WISW strain	Coal oil fly ash	Inhalation (chamber)	0, 11, 32, and 103 mg/m^3	1.9-2.6 μm δg = 1.6-1.8	6 h/day, 5days/week, 4 weeks	At the highest concentration, type II cell proliferation and mild fibrosis occurred and increased perivascular lymphocytes were seen. The main changes at the lowest concentration were particle accumulation in AM and mediastinal lymph nodes. Lymphoid hyperplasia observed at all concentrations. Effects increased with exposure duration.	Dormans et al. (1999)

TABLE 8-4 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat, male, S-D, 60 days old	ROFA	Intratracheal instillation	8.33 mg/mL 0.3 mL/rat	1.95 μm MMAD	Analysis at 24 and 96 h	Increased PMNs, protein, LDH at both time points.	Dreher et al. (1997)
Male S-D rats 60 days old	#6 ROFA, volcanic ash	Instillation in NaCl solution	0.3, 1.7 8.3 mg/mL 8.3 mg/mL	1.95 μm δg = 2.19 1.4 μm	24 h	Plasma fibrinogen elevated after ROFA instillation but not volcanic ash	Gardner et al. (2000)
5-day-old male S-D rats	Low S #6 ROFA, volcanic ash saline	Intratracheal	0.3, 1.7, 8.3 mg/mL in saline 8.3 mg/kg BW 1 mL/kg BW	1.95 μm δg = 1.95 1.4 μm	24 h	Increased WBC count in ROFA-exposed rats plasma fibrinogen increased 86% in ROFA rats at highest concentration.	Gardner et al. (2000)
Rat, male, S-D, 60 days old	Two ROFA samples R1 had 2× saline-leachable sulfate, Ni, and V and 40× Fe as R2; R2 had 31× higher Zn	Intratracheal instillation	2.5 mg in 0.3 mL	R1: 1.88 μm, MMAD R2: 2.03 μm, MMAD	Analysis at 4 days	Four of the 24 animals treated with R2 or R2s (supernatant) died; none in R1s treated animals; more AM, PMN, eosinophils protein, and LDH in R2 and R2s animals; more focal alveolar lesions, thickened alveolar septae, hyperplasia of type II cells, alveolar fibrosis in R2 and R2s animals; baseline pulmonary function and airway hyperreactivity were worse in R2 and R2s groups.	Gavett et al. (1997)
Female Balb/cJ mice 7-15 weeks	ROFA	Intratracheal instillation	60 μg in 50 μL (dose 3mg/kg)	< 2.5	N/A	ROFA caused increases in eosinophils, IL-4 and IL-5 and airway responsiveness in ovalbumin-sensitized and challenged mice.	Gavett et al. (1999)
7-week-old Female Balb/cJ mice (16-21 g)	ROFA lo-S residual oil	Inhalation and instillation challenge with OVA	158 ± 3 mg/m^3	$PM_{2.5}$ sample	1, 3, 8, 15 days after instillation	Increased BAL protein and LDH at 1 and 3 days but not at 15 days postexposure. Combined OVA and ROFA challenge increased all damage markers and enhanced allergen sensitization. Increased methacholine response after ROFA.	Gavett et al. (1999)
Rat, male, S-D	ROFA	Intratracheal instillation	500 μg/animal	3.6 μm	Analyzed 4 and 96 h postexposure	Ferritin and transferrin were elevated; greatest increase in ferritin, lactoferrin, transferrin occurred 24 h postexposure.	Ghio et al. (1998b)
Mice, normal and Hp, 105 days old	ROFA	Intratracheal instillation	50 μg	1.95 μm	Analysis at 24 h	Diminished lung injury (e.g., decreased lavage fluid ascorbate, protein, lactate dehydrogenase, inflammatory cells, cytokines) in Hp mice lacking transferrin; associated with increased metal storage and transport proteins.	Ghio et al. (2000b)
2-day-old BALB/C mice sensitized to ovalbumin (OVA)	Aerosolized ROFA leachate	Nose-only inhalation	50 mg/mL		30 min	Increased airway response to methylcholine and to OVA in ROFA exposed mice; increased airway inflammation also.	Hamada et al. (1999)

TABLE 8-4 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat, male, S-D, 60 days old	ROFA	Intratracheal instillation	1.0 mg in 0.5 mL saline	1.95 μm	Analysis at 24 h	Increased PMNs, protein.	Kadiiska et al. (1997)
Rats MCT	FOFA	Inhalation	580 ± 110 $\mu g/m^3$	2.06 μm MMAD $\delta g = 1.57$	6 h/day for 3 days	Death occurred only in MCT rats exposed to ROFA. Neutrophils in lavage fluid were increased significantly in MCT rats exposed to ROFA versus filtered air. MIP-2 mRNA expression in lavage cells was induced in normal animals exposed to fly ash.	Killingsworth et al. (1997)
Male S-D and F-344 rats (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm $\delta g = 2.14$	Sacrificed at 24 h	Increase in neutrophils in both S-D and F-344 rats; a time-dependent increase in eosinophils occurred in S-D rats but not in F-344 rats.	Kodavanti et al. (1996)
Male S-D, WIS, and F-344 rats (60 days old)	ROFA	Intratracheal instillation	8.3 mg/kg	1.95 μm $\delta g = 2.14$	Sacrificed at 6, 24, 48, and 72 h; 1, 3, and 12 weeks	Inflammatory cell infiltration, as well as alveolar, airway, and interstitial thickening in all three rat strains; a sporadic incidence of focal alveolar fibrosis in S-D rats, but not in WIS and F-344 rats; cellular fibronectin (cF_n) mRNA isoforms EIIIA(+) were up-regulated in S-D and WIS rats but not in F-344 rats. Fn mRNA expression by macrophage and alveolar and airway epithelium and within fibrotic areas in S-D rats; increased presence of Fn EIIIA(+) protein in the areas of fibrotic injury and basally to the airway epithelium.	Kodavanti et al. (1997a)
Male S-D Rats, 60 days old	ROFA $Fe_2(SO_4)_3$, VSO_4, $NiSO_4$	Intratracheal instillation	8.33 mg/kg ROFA-equivalent dose of metals	1.95 μm $\delta g = 2.14$	Analysis at 3, 24, and 96 h, postinstillation	ROFA-induced pathology lesions were as severe as those caused by Ni. Metal mixture caused less injury than ROFA or Ni alone; Fe was less pathogenic. Cytokine and adhesion molecule gene expression occurred as early as 3 h after exposure. V-induced gene expression was transient but Ni caused persistent expression and injury.	Kodavanti et al. (1997b)
Male S-D rats, 60 days old	10 ROFA compositionally different particles from a Boston power plant	Intratracheal instillation	0.833, 3.33, 8.3 mg/kg	1.99–2.59 μm MMAD	Sacrificed at 24 h	ROFA-induced increases in BAL protein and LDH, but not PMN, were associated with water-leachable total metal, Ni, Fe, and S; BALF neutrophilic inflammation was correlated with V but not Ni or S. Chemiluminescence signals in vitro (AM) were greatest with ROFA containing soluble V and less with Ni plus V.	Kodavanti et al. (1998a)

TABLE 8-4 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
60-day-old male S-D rats treated with MCT (60 mg/kg)	ROFA	Intratracheal instillation; Nose-only inhalation	0, 0.83, 3.3 mg/kg 15 mg/m^3	1.95 μm δg = 2.14	24-96 h 6 h/day for 3 days analysis at 0 or 18 h	Both IT and IN rats showed inflammatory responses (IL-6, MIP-2, inflammatory cells, etc.). 58% of IT rats exposed to ROFA died within 96 h. No mortality occurred in the IN rats. ROFA exacerbated lung lesions (edema, inflammatory cells, alveolar thickening) in MCT rats.	Kodavanti et al. (1999)
Male WKY and SH rats, 11-13 weeks old	ROFA VSO_4, $NiSO_4$, or saline	Intratracheal Instillation	0.83-3.33 mg/mL/kg 1.5 μmol kg	1.95 μm δg = 2.14	1-4 days, analysis at 6 or 24 h	Increased BALF protein and LDH alveotis with macrophage accumulation in alveoli; increased neutrophils in BAL. Increased pulmonary protein leakage and inflammation in SH rats. Effects of metal constituents of ROFA were strain specific; vanadium caused pulmonary injury only in SH rats; nickel was toxic in both SH and WKY rats.	Kodavanti et al. (2000b)
Male WKY and SH rats, 11-13 weeks old	ROFA	Nose-only Inhalation	15 mg/m^3	1.95 μm δg = 2.14	6 h/day × 3 day, analysis at 0 or 18 h	More pulmonary injury in SH rats. Increased RBCs in BALF of SH rats. ROFA increased airway reactivity to Ach in both SH and WKY rats. Increased protein, albumin, and LDH in BALF after ROFA exposure (SH>WKY). Increased oxidative stress in SH rats. SH rats failed to increase glutathione.	Kodavanti et al. (2001)
Brown Norway rat	ROFA	Intratracheal instillation	200 μg 100 μg	N/A	N/A	ROFA enhanced the response to house dust mite (HDM) antigen challenge. Eosinophil numbers, LDH, BAL protein, and IL-10 were increased with ROFA + HDM versus HDM alone.	Lambert et al. (1999)
60-day-old male S-D rats	#6 ROFA from Florida	Intratracheal instillation	0.9% in saline (9 mg/100 mg) total dose 1000 μg	1.95 ± 0.18 μm	15 min to 24 h	Production of acetaldehyde increased at 2 h postinstillation.	Madden et al. (1999)
60-day-old S-D rats, male	Florida ROFA; Domestic oil fly ash	Intratracheal instillation	1000 μ in 0.5 mL		15 min to 24 h	ROFA induced production of acetaldehyde with a peak at about 2 h. No acetaldehyde was seen in plasma at any time. DOFA increased acetaldehyde, as did V and Fe.	Madden et al. (1999)
60-day-old male S-D rats	ROFA	Intratracheal instillation	400-1000 μg/mL	N/A	12 h post-IT	ROFA increased PGE_2 via cycloxygenase expression.	Samet et al. (2000)
60-day-old male S-D rats	LoS, #6 ROFA	Intratracheal instillation	1000 μg/mL in saline	3.6 μm	1, 4, or 24 h	No inflammation until 24 h.	Silbajoris et al. (2000)

TABLE 8-4 (cont'd). RESPIRATORY EFFECTS OF COMPLEX COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
60-day-old male S-D rats and 60-day male Wistar-Kyoto rats, 60-day-old male SH rats, some cold-stressed, some ozone-exposed, some MCT-treated	Ottawa dust, ROFA, and volcanic ash	Intratracheal instillation, nose-only inhalation	Dose: 0, 0.25, 1.0, and 2.5 mg/rat	1.95 μm	6 h/day for 3-day inhalation; instillation - 96 h post-IT	IT ROFA caused acute and dose-related increase in pulmonary inflammation; no effect of volcanic ash.	Watkinson et al. (2000)

TABLE 8-5. RESPIRATORY EFFECTS OF SURROGATE PARTICULATE MATTER

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Syrian golden hamsters 900 M 900 F	Toner TiO_2 Silica	Nose-only inhalation	1.5, 6.0, or 24 mg/m^3 40 mg/m^3 3 mg/m^3	4.0 μm 1.1 μm 1.4 μm	3, 9, 15 mo 6 h/day 5days/week	Retention increased with increased exposure.	Creutzenberg et al. (1998)
C57Bl/6J mice	PTFE TiO_2	Inhalation	PTFE: 1.25, 2.5, or 5 x 10^5 particles/cc TiO_2-F: 10 mg/m^3 NiO: 5 mg/m^3 Ni_3S_2: 0.5 mg/m^3	PTFE: 18 nm TiO_2-F: 200 nm TiO_2-D: 10 nm	30 min or 6 h/day, 5days/week, 6 mo	Effects on the epithelium caused by direct interactions with particles, not a result of macrophage-derived mediators, and suggest a more significant role in the overall pulmonary response than previously suspected; type II cell growth factor production may be significant in the pathogenesis of pulmonary fibrosis.	Finkelstein et al. (1997)
Rat	PTFE Fumes	Whole body inhalation	1, 2.5, or 5 × 10^5 particles/cm3	18 nm	15 min, analysis 4 h postexposure	Increased PMN, mRNA of MnSOD and MT, IL-1α, IL-1β, IL-6, MIP-2, TNF-α mRNA of MT and IL-6 expressed around all airways and interstitial regions; PMN expressed IL-6, MT, and TNF-α; AM and epithelial cells were actively involved.	Johnston et al. (1996)
Mice,C57BL/6J, 8 weeks and 8 mo old	PTFE Fumes	Whole body inhalation	1, 2.5, or 5 × 10^5 particles/cm3	18 nm	30-min exposure, analysis 6 h following exposure	Increased PMN, lymphocytes, and protein levels in old mice over young mice; increased TNF-α mRNA in old mice over young mice; no difference in LDH and β-Glucuronidase.	Johnston et al. (1998)
MCT-treated S-D rats	Fluorescent microspheres	Inhalation	3.85 ± 0.81 $\mu g/m^3$	1.0 μm 1.38 ± 0.10 μm	3 h/day × 3 days	Monocrotaline-treated animals contained fewer microspheres in their macrophages, probably because of impaired chemotaxis.	Madl et al. (1998)
Male S-D rat (200g)	Diesel, SiO_2, carbon black	Intratracheal instillation	1 mg in 0.4 mL.	DEP Collected as TSP - disaggregated in solution by sonication (20 nm); SiO_2 (7 nm); carbon black	Sacrificed at 2, 7, 21, 42, and 84 days postinstillation	Amorphous SiO_2 increased permeability, and neutrophillic inflammation. Carbon black and DEP translocated to interstitum and lymph nodes by 12 weeks.	Murphy et al. (1998)
Male mice, 6-8 weeks old (AJ, AKRJ, Sulfate, B6C3F1), BALBcJ strains raised in a pathogen free laboratory Swiss-Webster mice	Carbon black Regal 660 $SO_4^=$	Nose only inhalation	10 $\mu g/m^3$ 285 $\mu g/m^3$	0.29 μm ± 2.7 μm	4 h	Differences in inflammatory responses (PMN) across strains. Appears to be genetic component to the susceptibility.	Ohtsuka et al. 2000

mortality, some mild pulmonary function changes after exposure to 5,000 to 10,000 $\mu g/m^3$ of inert particles were observed in rats and guinea pigs. Lung morphology studies revealed focal inflammatory responses, some epithelial hyperplasia, and fibrotic responses after exposure to >5,000 $\mu g/m^3$. Changes in macrophage clearance after exposure to >10,000 $\mu g/m^3$ were equivocal (no infectivity effects). In studies of mixtures of particles and other pollutants, effects were variable depending on the toxicity of the associated pollutant. In humans, co-exposure to carbon particles appeared to increase responses to formaldehyde but not to acid aerosol. None of the "other" particles mentioned above are present in ambient air in more than trace quantities. Thus, it was concluded that the relevance of any of these studies to standard setting for ambient PM may be extremely limited.

Recent studies that examined the acute effects of intratracheal instillation of ambient PM have shown clearly that PM obtained from various sources can cause lung inflammation and injury. Costa and Dreher (1997) showed that instillation of PM samples from three emission sources (two oil and one coal fly ash) and four ambient airsheds (St Louis, MO; Washington, DC; Dusseldorf, Germany; and Ottawa, Canada) resulted in increases in lung PMN and eosinophils in rats 24 h after instillation. Biomarkers of permeability (total protein and albumin) and cellular injury (LDH) also were increased. This study demonstrated that the lung dose of bioavailable transition metal, not instilled PM mass, was the primary determinant of the acute inflammatory response. Kennedy et al. (1998) reported a similar dose-dependent inflammation (i.e., increase in protein and PMN in lavage fluid, proliferation of bronchiolar epithelium, and intraalveolar hemorrhage) in rats instilled with water-extracted particles (TSP) collected in Provo, UT. This study also indicated that the metal constituent, in this case PM-associated Cu, was a plausible cause of the outcome. Likewise, instillation of ambient PM_{10} collected in Edinburgh, Scotland, also caused pulmonary injury and inflammation in rats (Li et al., 1996, 1997). Brain et al. (1998) examined the effects of instillation of particles that resulted from the Kuwaiti oil fires in 1991 compared to urban particulate matter collected in St. Louis (NITS SRM 1648, collected in a bag house in early 1980s) and showed that on an equal mass basis, the acute toxicity of the Kuwaiti oil fire particles was similar to that of urban particles collected in the United States.

The fact that instillation of ambient PM collected from different geographical areas and from a variety of emission sources consistently caused pulmonary inflammation and injury tends

to corroborate epidemiological studies that report increased respiratory morbidity and mortality associated with PM in many different geographical areas and climates. However, high-dose instillation studies may produce different effects on the lung than inhalation exposures done at more relevant concentrations. This concern is somewhat diminished by the results of an inhalation study of concentrated PM in healthy nonsmokers. Ghio et al. (2000a) exposed 38 volunteers exercising intermittently at moderate levels of exertion for 2 h to either filtered air or particles concentrated from the air in Chapel Hill, NC (23 to 311 $\mu g/m^2$). Analysis of cells and fluid obtained 18 h after exposure showed a mild increase in neutrophils in the bronchial and alveolar fractions. No respiratory symptoms or decrements in pulmonary function were found after exposure to CAP.

Because emission sources contribute to the overall ambient air particulate burden (Spengler and Thurston, 1983), many studies investigating the response of laboratory animals to particle exposures have used fly ash as a useful source of particle for exposure (see Table 8-3). The residual oil fly ash (ROFA) samples used in toxicological studies have been collected from a variety of sources such as boilers, bag houses used to control emissions from power plants, and from the fine particles that are emitted downstream of the collection devices.

ROFA has a high content of water soluble sulfate and metals, accounting for 82 to 92% of water-soluble mass, while the water-soluble mass fraction in ambient air varies from low teens to more than 60% (Costa and Dreher, 1997; Prahalad et al., 1999). More than 90% of the metals in ROFA are transition metals, whereas these metals are only a small subfraction of the total ambient PM mass. Thus, the dose of bioavailable metal that is delivered to the lung when ROFA is instilled into a laboratory animal can be orders of magnitude greater than a ambient PM dose, even under a worst-case scenario.

Intratracheal instillation of various doses of ROFA suspension has been shown to produce severe inflammation, an indicator of pulmonary injury that includes recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA in rats have been shown to depend on aqueous leachable chemical constituents of the particles (Dreher et al., 1997; Kodavanti et al., 1997b). A leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension (Dreher et al., 1997). Depletion of Fe, Ni, and V from the ROFA leachate eliminated its pulmonary toxicity. Correspondingly, minimal lung injury was observed in animals exposed

to saline-washed ROFA particles. A surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA. Interestingly, ferric sulfate and vanadium sulfate antogonized the pulmonary toxicity of nickel sulfate. Interactions between different metals and the acidity of PM were found to influence the severity and kinetics of lung injury induced by ROFA and its soluble transition metals.

To further investigate the response to ROFA with differing metal and sulfate composition, male Sprague Dawley rats (60 days old) were exposed to ROFA or metal sulfates (iron, vanadium, and nickel, individually or in combination) (Kodavanti et al., 1997b). Transition metal sulfate mixtures caused less injury than ROFA or Ni alone, suggesting metal interactions. In addition, this study showed that V-induced effects were less severe than that of Ni and were transient. Ferric sulfate was least pathogenic. Cytokine gene expression was induced prior to the pathology changes in the lung and the kinetics of gene expression suggested persistent injury by nickel sulfate. Another study by the same investigators was performed using 10 different ROFA samples collected at various sites within a power plant burning residual oil firing chamber (Kodavanti et al., 1998a). Animals received intratracheal instillations of either saline, or a saline suspension of whole ROFA (<3.0 μm MMAD) at three concentrations (0.833, 3.33, or 8.33 mg/kg). This study showed that ROFA-induced PMN influx appeared to be associated with its water-leachable V content; however, protein leakage appeared to be associated with water-leachable Ni content. ROFA-induced in vitro activation of AM was highest with ROFA containing leachable V but not with Ni plus V, suggesting that the potency and the mechanism of pulmonary injury may differ between emissions containing bioavailable V and Ni.

Other studies have shown that soluble metal components play an important role in the toxicity of emission source particles. Gavett et al. (1997) investigated the effects of two ROFA samples of equivalent diameters, but having different metal and sulfate content, on pulmonary responses in Sprague-Dawley rats. ROFA sample 1 (R1) (the same emission particles used by Dreher et al. [1997]) had approximately twice as much saline-leachable sulfate, nickel, and vanadium, and 40 times as much iron as ROFA sample 2 (R2); whereas R2 had a 31-fold higher zinc content. Rats were instilled with suspensions of 2.5 mg R2 in 0.3 mL saline, the supernatant of R2 (R2s), the supernatant of 2.5 mg R1 (R1s), or saline only. By 4 days after instillation, 4 of 24 rats treated with R2s or R2 had died. None of those treated with R1s or saline died. Pathological indices, such as alveolitis, early fibrotic changes and perivascular edema, were

greater in both R2 groups. In surviving rats, baseline pulmonary function parameters and airway hyperreactivity to acetylcholine were significantly worse in R2 and R2s groups than in the R1s groups. Other than BAL neutrophils, which were significantly higher in the R2 and R2s groups, no other inflammatory cells (macrophages, eosinophils, or lymphocytes) or biochemical parameters of lung injury were significantly different between the R2 and R2s groups and the R1s group. Although soluble forms of zinc had been found in guinea pigs to produce a greater pulmonary response than other sulfated metals (Amdur et al., 1978), and, although the level of zinc was 30-fold greater in R2 than R1, the precise mechanisms by which zinc may induce such responses are unknown. Nevertheless, these results show that the composition of soluble metals and sulfate leached from ROFA, a type of emission source particle, is critical in the development of airway hyperractivity and lung injury.

It has been shown that reactive oxygen species play an important role in the in vivo toxicity of ROFA, Dye et al. (1997) pretreated rats with an intraperitoneal injection of saline or dimethylthiourea (DMTU) (500 mg/kg), followed 30 min later by intratracheal instillation of either acidic saline (pH = 3.3) or an acidified suspension of ROFA (500 μg). The systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. In a subsequent study, these investigators determined that oxidant generation, possibly induced by soluble vanadium compounds in ROFA, are responsible for the subsequent rat tracheal epithelial cells gene expression, inflammatory cytokine productions (MIP-2 and IL-6), and cytotoxicity (Dye et al., 1999).

In addition to transition metals, other components in fly ash also may cause lung injury. The effects of arsenic compound in coal fly ash or copper smelter dust on the lung integrity and on the ex vivo release of TNFα by alveolar phagocytes were investigated by Broeckaert et al. (1997). Female Naval Medical Research Institute (NMRI) mice were instilled with different particles normalized for the arsenic content (20 μg/kg body weight [i.e., 600 ng arsenic/mouse]) and the particle load (100 mg/kg body weight [i.e., 3 mg/mouse]). Mice received tungsten carbide (WC) alone, coal fly ash (CFA) alone, copper smelter dust (CMP) mixed with WC, and $Ca_3(AsO_4)_2$ mixed with WC (see Table 8-2 for concentration details). Copper smelter dust caused a severe but transient inflammatory reaction, whereas a persisting alveolitis (30 days postexposure) was observed after treatment with coal fly ash. In addition, TNFα production in

response to LPS by alveolar phagocytes were significantly inhibited at Day 1 and still was observed at 30 days after administration of CMP and CFA. Although arsenic was cleared from the lung tissue 6 days after $Ca_3(AsO_4)_2$ administration, a significant fraction persisted (10 to 15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at Day 30. It is possible that suppression of TNF-α production is dependent upon the slow elimination of the particles and their metal content from the lung.

In summary, intratracheally injected ROFA produced acute lung injury and inflammation. The water soluble metals in ROFA appear to play a key role in the acute effects of instilled ROFA. Although studies done with ROFA clearly show that combustion generated particles with a high metal content can cause substantial lung injury, there is still insufficient data to extrapolate these effects to the low levels of particle associated transition metals in ambient PM.

8.2.4 Ambient Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxins, and plant and animal debris. Such biological aerosols can produce various health effects including: infections, hypersensitivity, and toxicoses. Bioaerosols present in the ambient environment have the potential to cause disease in humans under certain conditions. However, it was concluded in the previous criteria document (U.S. Environmental Protection Agency, 1996a) that bioaerosols, at the concentrations present in the ambient environment, would not account for the observed effects of particulate matter on human mortality and morbidity reported in PM epidemiological studies. Moreover, bioaerosols generally represent a rather small fraction of the measured urban ambient PM mass and are typically present even at lower concentrations during the winter months when notable ambient PM effects have been demonstrated. Bioaerosols tend to be in the coarse fraction of PM, but some bioaerosols are found in the fine fraction.

More recent studies on ambient bioaerosols are summarized in Table 8-6. Endotoxin exposure in pig farmers is associated with a large annual decline in FEV_1 (mean of 73 ml/year), which is about 2 to 3 times more rapid than in healthy adults (Vogelzang et al., 1998). Michel et al. (1997) examined the dose-response relationship to inhaled lipopolysaccharide (LPS: the purified derivative of endotoxin) in normal healthy volunteers exposed to 0, 0.5, 5, and 50 μg of LPS. Inhalation of 5 or 50 μg of LPS resulted in increased PMNs in blood and sputum samples. At the higher concentration, a slight (3%) but not significant decrease in FEV_1 was observed.

TABLE 8-6. RESPIRATORY EFFECTS OF AMBIENT BIOAEROSOLS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Healthy nonsmokers, 9 M; 23 to 37 years of age	Swine building	Inhalation, with and without mouth and nose occlusion	N/A	N/A	5 h	Significantly reduced FEV_1, increased methacholine broncho-responsiveness, and increased BAL inflammatory cells for all exposures. Effects were not modified by the route of exposure.	Cormier et al. (1998)
Fischer 344 rats, 8 weeks to 20 months old, N = 3/group	LPS (endotoxin) UF carbon ozone	Inhalation	100 $\mu g/m^3$	0.72 μm 25 nm $\delta g = 1.6$	12 min 6 h	Significant interaction of LPS and O_3 on inflammatory responses in young rats. O_3 and UF-C interacted with "priming" by LPS to produce greater PMN response. LPS has a priming effect on lung inflammatory response to O_3 and UF-C.	Elder et al. (2000)
Healthy subjects; 5 M, 4 F, 24 to 50 years of age	LPS (endotoxin)	Inhalation	0.5 $\mu g/m^3$ 5.0 $\mu g/m^3$ 50 $\mu g/m^3$	1 - 4 μm MMAD	30 min	Significant decrease in PMN luminol-enhanced chemiluminescence with 0.5 μg LPS; increase in blood CRP and PMNs, and increase in sputum PMNs, monocytes, and MPO with 5.0 μg LPS; increase in temperature, blood PMNs, blood and urine CRP, sputum PMNs, monocytes, lymphocytes, TNFα, and ECP with 50 μg LPS.	Michel et al. (1997)
Healthy subjects; 32 M, 32 F, 16 to 50 years of age	Indoor pool water spray	Inhalation	N/A	0.1 - 7.5 μm	N/A	Recurring outbreaks of pool-associated granulomatous pneumonitis (n = 33); case patients had higher cumulative work hours. Analysis indicated increased levels of endotoxin in pool air and water.	Rose et al. (1998)
Pig farmers, n = 171, 82symptomatic and 89 asymptomatic	Dust Endotoxin	Inhalation	2.63 mg/m^3 $\delta g = 1.3$ 105 ng/m^3 $\delta g = 1.5$	N/A	5 h/day average lifetime exposure	Large decline in FEV_1 (73 ml/year) and FVC (55 ml/year) associated with long-term average exposure to endotoxin.	Vogelzang et al. (1998)
Potato plant workers, low exposures (37 M), high exposures (20 M)	Endotoxin	Inhalation	21.2 EU/m^3 low $\delta g = 1.6$ 55.7 EU/m^3 high $\delta g = 2.1$	N/A	8 h	Decreased FEV_1, FVC, and MMEF over the work shift that was concentration related; endotoxin effects on lung function can be expected above 53 EU/m^3 ($\approx$4.5 ng/m^3) over 8 h.	Zock et al. (1998)

Cormier et al. (1998) reported an approximate 10% decline in FEV_1 and an increase in methacholine airway responsiveness after a 5-h exposure inside a swine containment building. This exposure induced significant neutrophilic inflammation in both the nose and the lung. Although these exposures are massive compared to endotoxin levels in ambient PM in U.S. cities, these studies serve to illustrate the effects of endotoxin and associated bioaerosol material in healthy nonsensitized individuals.

Some health effects have been observed after occupational exposure to complex aerosols containing endotoxin at concentrations relevant to ambient levels. Zock et al. (1998) reported a decline in FEV_1 ($\approx$3%) across a shift in a potato processing plant with up to 56 endotoxin units (EU)/m^3 in the air. Rose et al. (1998) reported a high incidence (65%) of BAL lymphocytes in lifeguards working at a swimming pool where endotoxin levels in the air were on the order of 28 EU/m^3. Although these latter two studies may point towards pulmonary changes at low concentrations of airborne endotoxin, it is not possible to rule out the contribution of other agents in these complex organic aerosols.

8.3 SYSTEMIC EFFECTS OF PARTICULATE MATTER IN HEALTHY HUMANS AND LABORATORY ANIMALS: IN VIVO EXPOSURES

A small number of epidemiology studies have demonstrated that increases in cardiac-related deaths are associated with exposure to PM (U.S. Environmental Protection Agency, 1996a), and that PM-related cardiac deaths appear to be as great or greater than those attributed to respiratory causes (see Chapter 6). The toxicological consequences of inhaled particles on the cardiovascular system had not been extensively investigated prior to 1996. Since then (see Table 8-7), Costa and colleagues (Costa and Dreher, 1997) have demonstrated that intratracheal instillation of high levels of ambient particles can increase or accelerate death related to monocrotaline administration in rats. These deaths did not occur with all types of ambient particles tested. Some dusts, such as volcanic ash from Mount Saint Helens, were relatively inert, whereas other ambient dusts, including those from urban sites, were toxic. These early observations suggested that particle composition plays an important role in the adverse health effects associated with episodic exposure to ambient PM, despite the "general particle" effect attributed to the epidemiological associations of ambient PM exposure and increased mortality in

TABLE 8-7. CARDIOVASCULAR EFFECTS AND OTHER SYSTEMIC EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
Fischer 344 rats, male; 200-250 g	OTT	Nose-only Inhalation	40 mg/m^3	4 to 5 μm MMAD	4 h	Increased plasma levels of endothelin-1. No acute lung injury; however, lung NO production decreased and macrophage inflammatory protein-2 from lung lavage cells increased after exposure.	Bouthillier et al. (1998)
Rats, S-D, male, 60 days old, MCT and healthy, n = 64	ROFA	Instillation	0.0, 0.25, 1.0, and 2.5 mg/rat	1.95 μm	Analysis at 96 h	Dose-related hypothermia and bradycardia in healthy rats, potentiated by compromised models.	Campen et al. (2000)
Female mongrel dogs, 14 to 17 kg	CAP	Inhalation via tracheostomy	3-360 μg/m^3	0.2 to 0.3 μm	6 h/day for 3 days	Peripheral blood parameters were related to specific particle constituents. Factor analysis from paired and crossover experiments showed that hematologic changes were not associated with increases in total CAP mass concentration.	Clarke et al. (2000)
Rats, male, S-D, 60 days old, MCT (60 mg/kg), ip and healthy	Emission source PM Ambient airshed PM ROFA	Instillation	Total mass: 2.5 mg/rat Total transition metal: 46 μg/rat	Emission PM: 1.78-4.17 μm Ambient PM: 3.27-4.09 μm	Analysis at 24 and 96 h following instillation	ROFA alone induced some mild arrhythumas; MCT-ROFA showed enhanced neutrophilic inflammation; MCT-ROFA animals showed more numerous arrhythmias including S-T segment inversions and A-V block.	Costa and Dreher (1997)
Rats, S-D; male; 60 days old	ROFA	Instillation	0.3, 1.7, or 8.3 mg/kg	1.95 μm δg = 2.19	Analysis at 24 h	Increased plasma fibrinogen at 8.3 mg/kg only.	Gardner et al. (2000)
Healthy nonsmokers, 18 to 40 years old	CAP	Inhalation	23.1 to 311.1 μg/m^3	0.65 μm δg = 2.35	2 h, analysis at 18 h	Increased blood fibrinogen.	Ghio et al. (2000a)
Mongrel dogs, some with balloon occluded LAD coronary artery, n = 14	CAP	Inhalation via tracheostomy	69-828 μg/m^3	0.23 to 0.34 μm δg = 0.2 to 2.9	6 h/day for 3 days	Decreased time to ST segment elevation and increased magnitude in compromised dogs. Decreased heart and respiratory rate and increased lavage fluid neutrophils in normal dogs.	Godleski et al. (2000)
F-344 rat, male, MCT-treated Hamster, 6-8 mo old; Bio TO-2	CAP	Inhalation	132-919 μg/m^3	0.2-1.2 μm δg = 0.2-3.9	3 h, evaluated at 3 and 24 h	No increase in cardiac arrhythmias; PM associated increases in HR and blood cell differential counts, and atrial conduction time of rats were inconsistent. No adverse cardiac or pulmonary effects in hamsters.	Gordon et al. (2000)

TABLE 8-7 (cont'd). CARDIOVASCULAR EFFECTS AND OTHER SYSTEMIC EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
Rats, S-D, MCT (50 mg/kg SC), 250 g	FOFA	Inhalation	580 ± 110 $\mu g/m^3$	2.06 μm MMAD $\delta g = 1.57$	6 h/day for 3 days	Increased expression of the proinflammatory chemokine MP-2 in the lung and heart of MCT-treated rats; less in healthy rats. Significant mortality only in MCT-treated rats.	Killingsworth et al. (1997)
12 to 13-week-old male WKY and SH rats	ROFA	Nose-only inhalation	15 mg/m^3	N/A	6 h/day for 3 days	Cardiomyopathy and monocytic cell infiltration, along with increased cytokine expression, was found in left ventricle of SH rats because of underlying cardiovascular disease. ECG showed exacerbated ST segment depression caused by ROFA.	Kodavanti et al. (2000b)
Hartley guinea pig, male, 890 g	DEP	Intravenous	500 mg/mL solution	0.34 μm	10% solution every 5 min	DMSO extract of DEP solution induced arrhythmias and deaths by AV block; thus, water-soluble fractions of DEP may be responsible for cardiotoxicity.	Minami et al. (1999)
Healthy 10.5-year-old beagles, n = 4	ROFA	Oral inhalation	3 mg/m^3	2.22 μm MMAD $\delta g = 2.71$	3 h/day for 3 days	No consistent changes in ST segment, the form or amplitude of the T wave, or arrhythmias; slight bradycardia during exposure.	Muggenberg et al. (2000)
Rabbit, New Zealand White, female, 1.8 to 2.4 kg	Colloidal carbon	Instillation	2 mL of 1% colloidal carbon (20 mg)	<1 μm	Examined for 24 to 192 h after instillation	Colloidal carbon stimulated the release of BRDU-labeled PMNs from the bone marrow. The supernatant of alveolar macrophages treated with colloidal carbon in vitro also stimulated the release of PMNs from bone marrow, likely via cytokines.	Terashima et al. (1997)
Rat, S-D male, MCT	ROFA	Instillation	0, 250, 1000, or 2500 μg in 0.3 mL saline	1.95 μm MMAD $\delta g = 2.19$	Monitored for 96 h after instillation of ROFA particles	Dose-related increases in the incidence and duration of serious arrhythmic events in normal rats. Incidence and severity of arrythmias were increased greatly in the MCT rats. Deaths were seen at each instillation level in MCT rats only (6/12 died after MCT + ROFA).	Watkinson et al. (1998)

TABLE 8-7 (cont'd). CARDIOVASCULAR EFFECTS AND OTHER SYSTEMIC EFFECTS OF PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Cardiovascular Effects	Reference
(1) Healthy S-D rats and cold-stressed, ozone-treated, and MCT-treated rats	ROFA	Intratracheal instillation	0.0, 0.25, 1.0, or 2.5 mg/rat	1.95 μm	Monitored for 96 h after instillation	(1) Healthy rats exposed IT to ROFA demonstrated dose-related hypothermia, bradycardia, and increased arrhythmias. Compromised rats demonstrated exaggerated hypothermia and cardiac responses to IT ROFA. Mortality was seen only in the MCT-treated rats exposed to ROFA by IT. (2) Pulmonary hypertensive (MCT-treated S-D) and systemically hypertensive (SH) rats exposed to ROFA by inhalation demonstrated similar effects, but of diminished amplitude. There were no lethalities by the inhalation route. (3) Older rats exposed IT to OTT showed a pronounced biphasic hypothermia and a severe drop in HR accompanied by increased arrhythmias; exposure to ROFA caused less pronounced, but similar effects. No cardiac effects were seen with exposure to MSH. (4) Ni and V showed the greatest toxicity; Fe-exposed rats did not differ from controls.	Watkinson et al. (2000)
(2) Heathy and MCT-treated S-D rats, SH rats, WKY rats	ROFA	Inhalation	15 mg/m^3	1.95 μm	6 h/day for 3 days		
(3) 15-mo-old SH rats	OTT ROFA MSH	Intratracheal instillation	2.5 mg 0.5 mg 2.5 mg	1.95 μm	Monitored for 96 h after instillation		
(4) MCT-treated S-D rats	$Fe_2(SO_4)_3$ VSO_4 $NiSO_2$	Intratracheal instillation	105 μg 245 μg 262.5 μg	1.95 μm	Monitored for 96 h after instillation		

many regions of the United States (i.e., regions with varying particle composition). Work that examines the role of inherent susceptibility to the adverse effects of PM in compromised animal models provides a potentially important link to epidemiological observations.

To date, studies examining the systemic and cardiovascular effects of particles have used a number of compromised animal models, largely rodents, to mimic human disease. Two studies in normal or compromised dogs (Godleski et al., 2000; Muggenberg et al., 2000) also have been published as well as the preliminary results from human exposure studies (see Section 8.4.1). The following discussion of the systemic effects of PM first describes studies performed using metal-laden ROFA as a source particle and then compares these findings with studies using concentrated ambient PM.

Killingsworth and colleagues (1997) used a fuel oil fly ash to examine the adverse effects of a model urban particle in an animal model (monocrotaline-MCT) of cardiorespiratory disease; MCT causes pulmonary vascular inflammation and hypertension. They observed 42% mortality in MCT rats exposed to approximately 580 $\mu g/m^3$ fly ash for 6 h/day for 3 consecutive days. Deaths did not occur in MCT rats exposed to filtered air or in saline-treated rats exposed to fly ash. The increase in deaths in the MCT/fly ash group was accompanied by an increase in neutrophils in lavage fluid and an increased immunostaining of MIP-2 in the heart and lungs of the MCT/fly ash animals. Cardiac immunohistochemical analysis indicated increased MIP-2 in cardiac macrophages. The fly ash-induced deaths did not result from a change in pulmonary arterial pressure; the cause of death was not identified.

In a similar experimental model, Watkinson et al. (1998) examined the effects of intratracheally instilled ROFA (0.0, 0.25, 1.0, 2.5 mg in 3 mL saline) on ECG measurements in control and MCT rats. They observed a dose-related increase in the incidence and duration of serious arrhythmic events in control animals exposed to ROFA particles and these effects were clearly exacerbated in the MCT animals. Similar to the results of Killingsworth et al. (1997), health animals treated with ROFA suffered no deaths, but MCT rats had 1, 2, and 3 deaths in the low-, medium-, and high-dose groups, respectively. This study suggests that ROFA PM may be implicated in conductive and hypoxemic arrhythmias associated with the cardiac-related deaths.

Kodavanti et al. (1999) exposed MCT rats to ROFA by either intratracheal instillation (0.83 or 3.33 mg/kg) or nose-only inhalation (15 mg/m^3, 6 h/day for 3 consecutive days). Similar to Watkinson et al. (1998), intratracheal instillation of ROFA in MCT rats resulted in 58%

mortality, whereas no mortality occurred in MCT rats exposed to ROFA by inhalation exposure. No mortality occurred in healthy rats exposed to ROFA or in MCT rats exposed to clean air. Despite the fact that mortality was not associated with ROFA inhalation exposure of MCT rats, exacerbation of lung lesions and pulmonary inflammatory cytokine gene expression, as well as ECG abnormalities, clearly were evident.

Watkinson and colleagues further examined the effect of instilled ROFA in two additional rodent models of compromised health (Watkinson et al., 2000; Campen et al., 2000). The effect of ozone-induced pulmonary inflammation (preexposure to 1 ppm ozone for 6 h) or housing in the cold (10 °C) on the response to ROFA in rats was similar to that produced by MCT. Bradycardia, arrhythmias, and hypothermic changes were consistently observed in the ozone and hypothermic animals treated with ROFA, although, unlike in the MCT animals, no deaths occurred. Thus, in three rodent models of cardiopulmonary disease/stress, instillation of 0.25 mg or more of ROFA can produce systemic changes that can be considered adverse health effects and address potential mechanisms of toxicity consistent with the epidemiology and panel studies showing cardiac effects in humans.

Watkinson and colleagues (2000) also sought to examine the relative toxicity of different particles on the cardiovascular system of spontaneously hypertensive rats. They instilled 2.5 mg of representative particles from ambient (Ottawa) or natural (Mount Saint Helens volcanic ash) sources and compared the response to 0.5 mg ROFA. Instilled particles were either mass equivalent dose or adjusted to produce equivalent metal dose. They observed adverse changes in ECG, heart rate, and arrhythmia incidence that were much greater in the Ottawa- and ROFA-treated rats than in the Mount Saint Helens-treated rats. The cardiovascular changes observed with the Ottawa particles were actually greater than with the ROFA particles. These series of experiments by Watkinson and colleagues clearly demonstrate that instillation of particles, albeit at a very high concentration, can produce cardiovascular effects. They also demonstrate that PM exposures of equal mass dose did not produce the same cardiovascular effects, suggesting that PM composition was responsible for the observed effects and that PM metal content was a better indicator than PM mass.

Because of concerns regarding the relevance of particles administered by intratracheal instillation, investigators also have examined the cardiovascular effects of ROFA particles using more realistic inhalation exposure protocols. Kodavanti et al. (2000b) found that exposure to a

high concentration of ROFA (15 mg/m^3 for 6 h/day for 3 days) produced alterations in the ECG waveform of spontaneously hypertensive (SH) but not normotensive rats. Although the ST segment area of the ECG was depressed in the SH rats exposed to air, further depressions in the ST segment were observed at the end of the 6-h exposure to ROFA on Days 1 and 2. The enhanced ST segment depression was not observed on the third day of exposure, suggesting that adaptation to the response had occurred. Thus, exposure to a high concentration of ROFA exacerbated a defect in the electroconductivity pattern of the heart in an animal model of hypertension. This ROFA-induced alteration in the ECG waveform was not accompanied by an enhancement in the monocytic cell infiltration and cardiomyopathy that also develop in SH rats. Further work is necessary to determine the relevance of this ROFA study to PM at concentrations relevant to ambient exposures.

Godleski and colleagues (2000) have performed a series of important experiments examining the cardiopulmonary effects of inhaled concentrated ambient PM on normal mongrel dogs and on dogs undergoing coronary artery occlusion. Dogs were exposed to concentrated ambient PM for 6 h/day for 3 consecutive days. The investigators found little evidence of pulmonary inflammation or injury in normal dogs exposed to PM (daily range of mean concentrations was approximately 100 to 1000 μg/m^3). A greater than twofold increase in percent neutrophils ($p < 0.05$) was the only lavage parameter that was significantly different from sham-exposed animals. Despite the absence of major pulmonary effects, a significant increase in heart rate variability (an indice of cardiac autonomic activity), a decrease in heart rate, and an increase in T alternans (an indice of vulnerability to ventricular fibrillation) were observed. The significance of these effects is not yet clear as the effects did not occur on all exposure days. For example, the change in heart rate variability was observed on 10 of the 23 exposure days. In support of the "general particle" theory, exposure assessment of particle composition produced no specific components of the particles that were correlated with the day-to-day variability in response. Moreover, whereas the heart rate variability change suggests a proarrhythmic response, the increase in T alternans suggests an anti-arrhythmic effect of inhaled concentrated ambient PM.

The most important finding in the experiments of Godleski and colleagues (2000) was the observation of a potential increase in ischemic stress of the cardiac tissue from repeated exposure to concentrated ambient PM. During coronary occlusion in four dogs exposed to PM, they

observed a significantly more rapid development of ST elevation of the ECG waveform. In addition, the peak ST-segment elevation was greater after PM exposure. Together, these changes suggest that concentrated ambient PM can augment the ischemia associated with coronary artery occlusion in this dog model. Additional work in more dogs as well as other species is necessary to determine the significance of these findings to the human response to ambient PM.

Contrary to the adverse effects of inhaled concentrated ambient PM reported by Godleski and colleagues in a peer-reviewed publication on ambient PM (Godleski et al., 2000). Muggenberg and colleagues (2000) have found that exposure to high concentrations of ROFA produces no consistent changes in amplitude of the ST-segment, form of the T wave, or arrhythmias in dogs. In their studies, four beagle dogs were exposed to 3 mg/m^3 ROFA particles generated for 3 h/day for 3 consecutive days with a Wright dust feeder. They did note that there was a slight but variable decrease in heart rate, but the changes were not statistically or biologically significant. The ROFA was collected from the same power plant as the Godleski study but at a later time point. The transition metal content of the ROFA used by Muggenberg was approximately 15% by mass, a value that is on the order of a magnitude higher than that found in ambient urban PM samples. Although the study did not specifically address the effect of metals, it suggests that inhalation of high concentrations of metals may have little effect on the cardiovascular system of a healthy individual. Therefore, the different findings between the dog studies illustrate the difficulties in extrapolating animal toxicology data to human health effects.

In a series of studies, Gordon, Nadziejko, and colleagues examined the response of the rodent cardiovascular system to concentrated ambient PM derived from New York city air (Gordon et al., 2000). Particles of 0.2 to 2.5 μm in diameter were concentrated up to 10 times their levels in ambient air ($\approx$150 to 900 $\mu g/m^3$) to maximize possible differences in effects between normal and cardiopulmonary-compromised laboratory animals. ECG changes were not detected in normal Fischer 344 rats or hamsters exposed to concentrated ambient PM for 1 to 3 days. Similarly, no deaths or ECG changes were observed in MCT rats or cardiomyopathic hamsters exposed to PM. Contrary to the decrease in heart rate observed in dogs exposed to concentrated ambient PM (Godleski et al., 2000), heart rate was increased in both normal and MCT rats exposed to PM. The increase was approximately 5% and was not observed on all exposure days. Thus, extrapolation of the heart rate changes in these animal studies to human

health effects is difficult, although the increase in heart rate in rats is similar to that observed in human population studies (see Chapter 6).

Gordon and colleagues (1998) have reported other cardiovascular effects in animals exposed to inhaled CAP. Increases in peripheral blood platelets and neutrophils were observed in control and MCT rats at 3 h, but not 24 h, after exposure to 150 to 400 $\mu g/m^3$ concentrated ambient PM (CAP). This neutrophil effect, likely a result of vascular demargination, did not appear to be dose related and did not occur on all exposure days, thus, suggesting that day-to-day changes in particle composition may play an important role in the systemic effects of inhaled particles. Terashima et al. (1997) also examined the effect of particles on circulating neutrophils. They instilled rabbits with 20 mg colloidal carbon, a relatively inert particle (<1 μm), and observed a stimulation of the release of 5'-bromo-2'deoxyuridine (BrdU)-labeled PMNs from the bone marrow at 2 to 3 days after instillation. Because the instilled supernatant from rabbit AMs treated in vitro with colloidal carbon also stimulated the release of PMNs from the bone marrow, they hypothesized that cytokines released from activated macrophages could be responsible for this systemic effect.

The results of epidemiology studies have suggested that homeostatic changes in the vascular system can occur after episodic exposure to ambient PM. Ghio et al. (2000a) have shown that inhalation of concentrated PM in healthy nonsmokers causes increased levels of blood fibrinogen. They exposed 38 volunteers exercising intermittently at moderate levels of exertion for 2 h to either filtered air or particles concentrated from the air in Chapel Hill, NC (23 to 311 $\mu g/m^2$). Blood obtained 18 h after exposure contained significantly more fibrinogen than blood obtained before exposure. The observed effects in blood may associated with the mild inflammation also found 18 h after exposure to CAP (see Section 8.2.3).

Gardner et al. (2000) examined whether the instillation of particles would alter blood coagulability factors in laboratory animals. Sprague-Dawley rats were instilled with 0.3, 1.7, or 8.3 mg/kg of ROFA or 8.3 mg/kg Mount Saint Helens volcanic ash. They observed an increase in plasma fibrinogen in healthy rats. Because fibrinogen is a known risk factor for ischemic heart disease and stroke, the authors suggested that this alteration in the coagulation pathway could take part in the triggering of cardiovascular events in susceptible individuals. Elevations in plasma fibrinogen, however, were observed in healthy rats only at the highest treatment dose, and no other changes in clotting function were noted. Because the lower treatment doses are known

to cause pulmonary injury and inflammation, albeit to a lower extent, the absence of plasma fibrinogen changes at these lower doses suggests that only high levels of pulmonary injury are able to produce an effect in healthy test animals.

In summary, controlled animal studies have provided initial evidence that high concentrations of inhaled or instilled particles can have systemic, especially cardiovascular, effects. In the case of MCT rats, these effects can be lethal. Understanding the pathways by which very small concentrations of inhaled ambient PM can produce systemic, life-threatening changes, however, is far from clear. Among the hypotheses that have been proposed to account for the nonpulmonary effects of PM are activation of neural reflexes, cytokine effects on heart tissue (Killingsworth et al., 1997), alterations in coagulability (Seaton et al., 1995; Sjögren, 1997), and perturbations in homeostatic processes such as heart rate or heart rate variability (Watkinson et al., 1998). A great deal of research using controlled exposures of animal and human subjects to PM will be necessary to test mechanistic hypotheses generated to date, as well as those that are likely to be proposed in the future.

8.4 SUSCEPTIBILITY TO THE EFFECTS OF PARTICULATE MATTER EXPOSURE

Susceptibility of an individual to adverse health effects of PM can vary depending on a variety of host factors such as age, nutritional status, physiological activity profile, genetic predisposition, or preexistent disease. The potential for preexistent disease to alter adverse response to toxicant exposure is widely acknowledged but poorly understood. Because of inherent variability (necessitating large numbers of subjects) and ethical concerns associated with using diseased subjects in clinical research studies, a solid database on human susceptibilities is lacking. For more control over both host and environmental variables, animal models often are used. However, care must be taken in extrapolation from animal models of human disease to humans. Rodent models of human disease, their use in toxicology and the criteria for judging their appropriateness as well as their limitations must be considered (Kodavanti et al., 1998b; Kodavanti and Costa, 1999).

8.4.1 Effects of Particulate Matter on Cardiopulmonary Compromised Hosts

Epidemiological studies suggest there may be subsegments of the population that are especially susceptible to effects from inhaled particles (see Chapter 6). The elderly with chronic cardiopulmonary disease, those with pneumonia and possibly other lung infections, and those with asthma (at any age) appear to be at higher risk than healthy people of similar age. Unfortunately, most toxicology studies have used healthy adult animals. An increasing number of newer studies have examined effects of ambient particles in compromised host models. Costa and Dreher (1997) used a rat model of cardiopulmonary disease to explore the question of susceptibility and the possible mechanisms by which PM effects are potentiated. Rats with advanced monocrotaline (MCT)-induced pulmonary vasculitis/hypertension were given intratracheal instillations of ROFA (0, 0.25, 1.0, and 2.5 mg/rat). The MCT animals had a marked neutrophilic inflammation. In the context of this inflammation, ROFA induced a four- to fivefold increase in BAL PMNs. There was increased mortality at 96 h that was ROFA-dose dependent. The results of this study indicate that particles, albeit at a high concentration, enhanced the neutrophilic inflammation and mortality in MCT animals.

Kodavanti et al. (1999) also studied PM effects in the MCT rat model of pulmonary disease. Rats treated with 60 mg/kg MCT were exposed to 0, 0.83. or 3.3 mg/kg ROFA by intratracheal instillation and to 15 mg/kg ROFA by inhalation. Both methods of exposure caused inflammatory lung responses and ROFA exacerbated the lung lesions, as shown by increased lung edema, inflammatory cells, and alveolar thickening.

The manner in which MCT can alter the response of rats to inhaled particles was examined by Madl and colleagues (1998). Rats were exposed to fluorescent colored microspheres (1 μm) 2 weeks after treatment with MCT. In vivo phagocytosis of the microspheres was altered in the MCT rats in comparison with control animals. Fewer microspheres were phagocytized in vivo by alveolar macrophages and there was a concomitant increase in free microspheres overlaying the epithelium at airway bifurcations. The decrease in in vivo phagocytosis was not accompanied by a similar decrease in vitro. Macrophage chemotaxis, however, was impaired significantly in MCT rats compared with control rats. Thus, MCT appeared to impair particle clearance from the lungs via inhibition of macrophage chemotaxis.

The sulfur dioxide (SO_2)-induced model of chronic bronchitis has also been used to examine the potential interaction of PM with preexisting lung disease. Clarke and colleagues

pretreated Sprague Dawley rats for 6 weeks with air or 170 ppm SO_2 for 5 h/day and 5 days/week (Clarke et al., 1999). Exposure to concentrated air particles for 5 h/day for 3 days at an average concentration of 515 $\mu g/m^3$ produced changes in pulmonary function as evidenced by significant increases in tidal volume in both air- and SO_2-pretreated rats. Exposure to concentrated ambient PM also produced significant changes in both cellular and biochemical markers in lavage fluid. In comparison to control animal values, protein was increased approximately threefold in SO_2-pretreated animals exposed to concentrated ambient PM. Lavage fluid neutrophils and lymphocytes were increased significantly in both pretreatment groups of rats exposed to concentrated ambient PM, with greater increases in both cell types in the SO_2-pretreated rats. Thus, exposure to concentrated ambient PM produced adverse changes in the respiratory system, but no deaths, in both normal rats and in a rat model of chronic bronchitis.

Clarke et al. (2000) next examined the effect of concentrated ambient PM in normal rats of different ages. Unlike the earlier study that used Sprague-Dawley rats, 4- and 20-mo-old Fischer 344 were examined after 3 days of exposure to concentrated ambient PM. They found that exposure to daily mean concentrations of 80, 170, and 50 $\mu g/m^3$ PM produced statistically significant increases in total neutrophil counts (up over 10-fold) in lavage fluid of the young, but not the old, rats. Thus, repeated exposure to relatively low concentrations of ambient PM produced an inflammatory response, although the actual percent neutrophils in the concentrated ambient PM-exposed young rats was low (approximately 3%). On the other hand, Gordon and colleagues found no evidence of neutrophil influx in the lungs of normal and monocrotaline-treated Fischer 344 rats exposed in nine separate experiments to concentrated ambient PM (Gordon et al., 2000) as high as 400 $\mu g/m^3$ for a 6-h exposure or 192 $\mu g/m^3$ for three daily 6-h exposures. Similarly, normal and cardiomyopathic hamsters showed no evidence of pulmonary inflammation or injury after a single exposure to concentrated ambient PM. Gordon and colleagues did report a statistically significant doubling in protein concentration in lavage fluid in monocrotaline-treated rats exposed for 6 h to 400 $\mu g/m^3$ concentrated ambient PM. Because of the disparity in findings in the response of normal Fischer 344 rats to concentrated ambient PM between these two labs, it is important that the reproducibility of these experiments be examined.

Kodavanti and colleagues (1998b) also have examined the effect of concentrated ambient PM in normal rats and rats with sulfur dioxide-induced chronic bronchitis. In four separate exposures to PM, there was a significant increase in lavage fluid protein in bronchitic rats from

only one exposure protocol in which the rats were exposed to 444 and 843 $\mu g/m^3$ PM on 2 consecutive days (6 h/day). Neutrophil counts were increased in bronchitic rats exposed to concentrated ambient PM in three of the four exposure protocols, but was decreased in the fourth protocol. No other changes in normal or bronchitic rats were observed, even in the exposure protocols with higher PM concentrations. Thus, rodent studies have demonstrated that inflammatory changes can be produced in normal and compromised animals exposed to concentrated ambient PM. These findings are important because only a limited number of studies have used real-time inhalation exposures to actual ambient urban PM.

Pulmonary function measurements are often less invasive than other means to assess the effects of inhaled air pollutants on the mammalian lung. Although the publication of the 1996 PM AQCD, a number of investigators have examined the response of rodents and dogs to inhaled ambient particles. In general, these investigators have demonstrated that ambient PM has minimal effects on pulmonary function tests. Gordon et al. (2000) exposed normal and monocrotaline-treated rats to filtered air or 181 $\mu g/m^3$ concentrated ambient PM for 3 h. For both normal and monocrotaline-treated rats, no differences in lung volume measurements or diffusion capacity for carbon monoxide were observed between the air or PM exposed animals at 3 or 24 h after exposure. Similarly, in cardiomyopathic hamsters, concentrated ambient PM had no effect on these same pulmonary function measurements.

In an examination of the effect of concentrated ambient PM on airway responsiveness in mice, Goldsmith and colleagues (1999) exposed control and ovalbumin-sensitized mice to an average concentration of 787 $\mu g/m^3$ PM for 6 h/day for 3 days. Although ovalbumin sensitization itself produced an increase in the nonspecific airway responsiveness to inhaled methylcholine, concentrated ambient PM did not change the response to methylcholine in ovalbumin-sensitized or control mice. For comparison, these investigators examined the effect of inhalation of an aerosol of the active soluble fraction of ROFA on control and ovalbumin-sensitized mice and demonstrated that ROFA could produce nonspecific airway hyperresponsiveness to methylcholine in both control and ovalbumin-sensitized mice. Similar increases in airway responsiveness have been observed after exposure to ROFA in normal and ovalbumin-sensitized rodents (Gavett et al., 1997, 1999; Hamada et al., 1999, 2000). Other pulmonary function endpoints have been studied in animals exposed to concentrated ambient PM. Clarke et al. (1999) observed that tidal volume was increased slightly in both control rats

and rats with sulfur dioxide-induced chronic bronchitis exposed to 206 to 733 $\mu g/m^3$ PM on 3 consecutive days. No changes in peak expiratory flow, respiratory frequency, or minute volume were observed after exposure to concentrated ambient PM. In the series of dog studies by Godleski et al. (2000) (also see Section 8.3), no signficant changes in pulmonary functions were observed in normal mongrel dogs exposed to concentrated ambient PM, although a 20% decrease in respiratory frequency was observed in dogs that underwent coronary artery occlusion and were exposed to PM. Thus, studies using normal and compromised animal models exposed to concentrated ambient PM have found minimal biological effects of ambient PM on pulmonary function.

In studying the influence of age on susceptibility to PM, Johnston et al. (1998) exposed 8-week-old mice (young) and 18-mo-old mice (old) to polytetrafluoroethylene fumes (PTFE) (0, 10, 25, and 50 $\mu g/m^3$) for 30 min. Lung lavage endpoints (PMN, protein, LDH, and β-glucuronidase) as well as lung tissue mRNA levels for various cytokines, metallothionein and for Mn superoxide dismutase were measured 6 h following exposure. Protein, lymphocyte, PMN, and TNF-α mRNA levels were increased in older mice when compared to younger mice. These findings suggest that the inflammatory response to PTFE fumes is altered with age, being greater in the older animals. Although Teflon particles are not a valid surrogate for ambient ultrafine particles (Oberdörster et al., 1992), this study did provide evidence to support the hypothesis that particle-induced pulmonary inflammation is different between young and old organisms.

Kodavanti et al. (2000b; 2001) used genetically predisposed spontaneously hypertensive (SH) rats as a model of cardiovascular disease to study PM-related susceptibility. The SH rats were found to be more susceptible to acute pulmonary injury from intratracheal ROFA exposure than normotensive control Wistar Kyoto (WKY) rats (Kodavanti et al., 2001). The primary metal constituents of ROFA, V and Ni, caused differential species-specific effects. Vanadium, which was less toxic than Ni in both strains, caused inflammatory responses only in WKY rats, whereas Ni was injurious to both WKY and SH rats (SH > WKY). This differential responsiveness of V and Ni was correlated with their specificity for airway and parenchymal injury, discussed in another study (Kodavanti et al., 1998b). When exposed to the same ROFA by inhalation, SH rats were more sensitive than WKY rats in regards to vascular leakage (Kodavanti et al., 2000b). The SH rats exhibited a hemorrhagic response to ROFA. Oxidative

stress was much higher in ROFA exposed SH rats than matching WKY rats. Also, SH rats, unlike WKY rats, showed a compromised ability to increase BALF glutathione in response to ROFA, suggesting a potential link to increased susceptibility. Cardiovascular effects were characterized by ST-segment area depression of the ECG in ROFA-exposed SH but not WKY rats. These studies demonstrate the potential utility of cardiovascular disease models for the study of PM health effects and show that genetic predisposition to oxidative stress and cardiovascular disease may play a role in sensitivity to increased PM-related cardiopulmonary injury.

In summary, although these studies are just emerging and are only now being replicated or followed more thoroughly to investigate the mechanisms, they do provide evidence of enhanced susceptibility to inhaled PM in "compromised" hosts.

8.4.2 Genetic Susceptibility to Inhaled Particles

A key question in understanding the adverse health effects of inhaled PM is which individuals are susceptible to PM. Although factors such as age and health status have been studied in both epidemiology and toxicology studies, a number of investigators have begun to examine the importance of genetic susceptibility in the response to inhaled particles because of considerable evidence that genetic factors play a role in the response to inhaled pollutant gases. To accomplish this goal, investigators typically have studied the interstrain response to particles in rodents. The response to ROFA instillation in different strains of rats has been investigated by Kodavanti et al. (1996, 1997a). In the first study, male Sprague Dawley (SD) and Fischer-344 (F-344) rats were instilled intratracheally with saline or ROFA particles. ROFA instillation produced an increase in lavage fluid neutrophils in both SD and F-344 rats, whereas a time-dependent increase in eosinophils occurred only in SD rats. In a subsequent study (Kodavanti et al., 1997a), SD, Wistar (WIS), and F-344 rats (60 days old) were exposed to saline or ROFA (8.3 mg/kg) by intratracheal instillation and examined for up to 12 weeks. Histology indicated focal areas of lung damage showing inflammatory cell infiltration as well as alveolar, airway, and interstitial thickening in all three rat strains during the week following exposure. Trichrome staining for fibrotic changes indicated a sporadic incidence of focal alveolar fibrosis at 1, 3, and 12 weeks in SD rats, whereas WIS and F-344 rats showed only a modest increase in trichrome staining in the septal areas. One of the isoforms of fibronectin mRNA was upregulated in

ROFA-exposed SD and WIS rats, but not in F-344 rats. Thus, there appeared to be a rat strain-dependent variability in the fibrotic response to instilled ROFA.

Kleeberger and colleagues have examined closely the role that genetic susceptibility plays in the effect of inhaled acid-coated particles on macrophage function. Nine inbred strains of mice were exposed nose-only to acid-coated particles (10 mg/m^3 with 285 μg/m^3 sulfate) for 4 h (Yoshinori et al., 2000). Significant inter-strain differences in Fc-receptor-mediated macrophage phagocytosis were observed, with C57BL/6J mice being the most sensitive. Although neutrophil counts were increased more in C3H/HeOuJ and C3H/HeJ strains of mice than in the other strains, the overall magnitude of change was small and not correlated with the changes in macrophage phagocytosis. In follow-up studies, Ohtsuka et al. (2000a,b) performed a genome-wide scan with a intercross cohort derived from C57BL/6J and C3H/HeJ mice. Analyses of macrophage dysfunction phenotypes of segregant and nonsegregant populations derived from these two strains indicate that two unlinked genes control susceptibility. They identified a 3-centiMorgan segment on mouse chromosome 17 that contains an acid-coated particle susceptibility loci. Interestingly, this quantitative trait loci overlaps with those described for ozone-induced inflammation (Kleeberger et al., 1997) and acute lung injury (Prows et al., 1997) and contains several promising candidate genes that may be responsible for the observed genetic susceptibility for macrophage dysfunction in mice exposed to acid-coated particles.

Only one study has examined the interstrain susceptibility to ambient particles. C57BL/6J and C3H/HeJ mice were exposed to 250 μg/m^3 concentrated ambient PM for 6 h and examined at 0 and 24 h after exposure for changes in lavage fluid parameters and cytokine mRNA expression in lung tissue (Shukla et al., 2000). No interstrain differences in response were observed. Surprisingly, although no indices of pulmonary inflammation or injury were increased over control values in the lavage fluid, increases in cytokine mRNA expression were observed in both murine strains exposed to PM. Although the increase in cytokine mRNA expression was generally small (approximately twofold), the effect on IL-6, TNF-α, TGF-β2, and γ-interferon was consistent and replication of this study is necessary.

Thus, a handful of studies have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled particles. Similar strain differences in response to inhaled metal particles have been observed by other investigators (McKenna et al., 1998; Wesselkamper et al., 2000), although the concentration of metals used in these studies is more relevant to occupational

rather than environmental exposure levels. It remains to be determined whether genetic susceptibility plays as significant a role in the adverse effects of ambient PM as does age or health status.

8.4.3 Effect of Particulate Matter on Allergic Hosts

Relatively little is known about the effects of inhaled particles on humoral (antibody) or cell-mediated immunity. Alterations in the response to a specific antigenic challenge have been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 $\mu g/m^3$) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to nonspecific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This nonspecific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although, its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized to either specific or nonspecific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Jacobs et al., 1997; Lipsett et al., 1997).

Nel et al. (1998) have suggested that the rise in the U.S. prevalence rate for allergic rhinitis (5% in the 1950s to about 20% in the 1980s) may be related to increased diesel particulate matter (DPM), in addition to other combustion related PM. Combustion particles also may serve as carrier particles for allergens (Knox et al., 1997).

A number of in vivo and in vitro studies have demonstrated that DPM can alter the immune response to challenge with specific antigens and suggest that DPM may act as an adjuvant. These studies have shown that treatment with DPM enhances the secretion of antigen-specific IgE in mice (Takano et al., 1997) and in the nasal cavity of human subjects (Diaz-Sanchez et al., 1996, 1997; Ohtoshi et al., 1998). Because IgE levels play a major role in allergic asthma (Wheatley and Platts-Mills, 1996), upregulation of its production could lead to an increased response to inhaled antigen in particle-exposed individuals.

Only a small number of studies have examined the mechanisms underlying the enhancement of allergic asthma by ambient urban particles. Ohtoshi et al. (1998) reported that a coarse size-fraction of resuspended ambient PM, collected in Tokyo, induced the production of

granulocyte macrophage colony stimulating factor (GMCSF), an upregulator of dendritic cell maturation and lymphocyte function, in human airway epithelial cells in vitro. In addition to increased GMCSF, epithelial cell supernatants contained increased IL-8 levels when incubated with DPM, a principal component of ambient particles collected in Tokyo. Although the sizes of the two types of particles used in this study were not comparable, the results suggest that ambient PM, or at least the DPM component of ambient PM, can upregulate the immune response to inhaled antigen through GMCSF production. Similarly, Takano et al. (1998) has reported airway inflammation, airway hyperresponsiveness, and increased GM-GSF and IL-5 in mice exposed to diesel exhaust.

Gavett et al. (1999) have investigated the effects of ROFA (intratracheal instillation) in ovalbumin (OVA) sensitized and challenged mice. Instillation of 3 mg/kg (approximately 60 μg) ROFA induced inflammatory and physiological responses in the OVA mice that were related to increases in Th2 cytokines (IL-4, IL-5). ROFA induced greater than additive increases in eosinophil numbers and in airway responsiveness to methylcholine.

Hamada et al. (1999, 2000) have examined the effect of a ROFA leachate aerosol in a neonatal mouse model of allergic asthma. In the first study, neonatal mice sensitized by ip injection with OVA developed airway hyperresponsiveness, eosinophilia, and elevated serum anti-ovalbumin IgE after a challenge with inhaled OVA. Exposure to the ROFA leachate aerosol had no marked effect on the airway responsiveness to inhaled methacholine in nonsensitized mice, but did enhance the airway hyperresponsiveness to methylcholine produced in OVA-sensitized mice. No other interactive effects of ROFA exposure with OVA were observed. In a subsequent study, Hamada et al. clearly demonstrated that, whereas inhaled OVA alone was not sufficient to sensitize mice to a subsequent inhaled OVA challenge, pretreatment with a ROFA leachate aerosol prior to the initial exposure to aerosolized OVA resulted in an allergic response to the inhaled OVA challenge. Thus, exposure to a ROFA leachate aerosol can alter the immune response to inhaled OVA both at the sensitization stage at an early age and at the challenge stage.

Lambert et al. (1999) also examined the effect of ROFA on a rodent model of pulmonary allergy. Rats were instilled intratracheally with 200 or 1,000 μg ROFA 3 days prior to sensitization with house dust mite antigen. HDM sensitization after 1000 μg ROFA produced increased eosinophils, LDH, BAL protein, and IL-10 relative to HDM alone. The immediate

bronchoconstrictive and associated antigen-specific IgE response to a subsequent antigen challenge was increased in the ROFA-treated group in comparison with the control group. Together, these studies suggest the components of ROFA can augment the immune response to antigen. Evidence that metals are responsible for the ROFA-enhancement of an allergic sensitization was demonstrated by Lambert et al. (2000). In this follow-up study, Brown Norway rats were instilled with 1 mg ROFA or the three main metal components of ROFA (iron, vanadium, or nickel) prior to sensitization with instilled house dust mite. The three individual metals were found to augment different aspects of the immune response to house dust mite. Nickel and vanadium produced an enhanced immune response to the antigen as seen by higher house dust mite-specific IgE serum levels after an antigen challenge at 14 days after sensitization. Nickel and vanadium also produced an increase in the lymphocyte proliferative response to antigen in vitro. In addition, the antigen-induced bronchoconstrictive response was greater only in nickel-treated rats. Thus, instillation of metals at concentrations equivalent to those present in the ROFA leachate mimicked the response to ROFA, suggesting that the metal components of ROFA are responsible for the increased allergic sensitization observed in ROFA-treated animals.

Goldsmith et al. (1999) have compared the effect of inhalation of concentrated ambient PM for 6 h/day for 3 days versus the effect of a single exposure to a ROFA leachate aerosol on the airway responsiveness to methylcholine in OVA-sensitized mice. Daily exposure to ROFA leachate aerosols significantly enhanced the airway hyperresponsiveness in OVA-sensitized mice. Importantly, exposure to concentrated ambient PM (average concentration of 787 $\mu g/m^3$) had no effect on airway responsiveness in six separate experiments. Thus, the effect of the ROFA leachate aerosols on the induction of airway hyperresponsiveness in allergic mice was significantly different than that of a high concentration of concentrated ambient PM. Although airway responsiveness was examined at only one postexposure time point, these findings do suggest that a great deal of caution should be used in interpreting the results of studies using ROFA particles or leachates in the attempt to investigate the biologic plausibility of the adverse health effects of PM.

Several other studies have examined in greater detail the contribution to allergic asthma of the particle component and the organic fraction of DPM. Tsien et al. (1997) treated transformed IgE-producing human B lymphocytes in vitro with the organic extract of DPM. The organic phase extraction had no effect on cytokine production but did increase IgE production.

Moreover, these experiments determined that DPM appeared to be acting on cells already committed to IgE production, thus suggesting a mechanism by which the organic fraction of combustion particles can directly affect B cells and influence human allergic asthma.

Cultured epithelial cells from atopic asthmatics show a greater response to DPM exposure when compared with cells from nonatopic nonasthmatics. IL-8, GM-CSF, and soluble ICAM-1 increased in response to DPM at a concentration of 10 μg/mL DPM (Bayram et al., 1998a,b). This study suggests that particles could modulate airway disease through their actions on airway epithelial cells. This study also suggests that bronchial epithelial cells from asthmatics are different from those of nonasthmatics in regard to their mediator release in response to DPM.

Sagai and colleagues (1996) repeatedly instilled mice with DPM for up to 16 weeks and found increased numbers of eosinophils, goblet cell hyperplasia, and nonspecific airway hyperresponsiveness, changes which are central features of chronic asthma (National Institutes of Health, 1997). Takano et al. (1997) extended this line of research and examined the effect of repeated instillation of DPM on the specific response to antigen (OVA) in mice. They observed that antigen-specific IgE and IgG levels were significantly greater in mice repeatedly instilled with both DPM and OVA. Because this upregulation in antigen-specific immunoglobulin production was not accompanied by an increase in inflammatory cells or cytokines in lavage fluid, it would suggest that, in vivo, DPM may act directly on immune system cells, as described in the work by Tsien et al. (1997). Animal studies have confirmed that the adjuvant activity of DPM also applies to the sensitization of Brown Norway rats to timothy grass pollen (Steerenberg et al., 1999).

Diaz-Sanchez and colleagues (1996) have continued to study the mechanism of DPM-induced upregulation of allergic response in the nasal cavity of human subjects. In one study, a 200 μL aerosol bolus containing 0.15 mg of DPM was delivered into each naris of subjects with or without seasonal allergies. In addition to increases in IgE in nasal lavage fluid (NAL), they found an enhanced production of IL-4, IL-6, and IL-13, cytokines known to be B cell proliferation factors. The levels of several other cytokines also were increased, suggesting a general inflammatory response to a nasal challenge with DPM. In a following study, these investigators delivered ragweed antigen, alone or in combination with DPM, on two occasions, to human subjects with both allergic rhinitis and positive skin tests to ragweed (Diaz-Sanchez et al. 1997). They found that the combined challenge with ragweed antigen and DPM produced

significantly greater antigen-specific IgE and IgG4 in NAL. A peak response was seen at 96 h postexposure. The combined treatment also induced expression of IL-4, IL-5, IL-10, and IL-13, with a concomitant decrease in expression of Th1-type cytokines. Although the treatments were not randomized (antigen alone was given first to each subject), the investigators reported that pilot work showed no interactive effect of repeated antigen challenge on cellular and biochemical markers in NAL. DPM also resulted in the nasal influx of eosinophils, granulocytes, monocytes, and lymphocytes, as well as the production of various inflammatory mediators. The combined DPM plus ragweed exposure did not increase the rhinitis symptoms beyond those of ragweed alone.

Blomberg et al. (1998) observed a 10-fold increase in NAL fluid ascorbate concentration after a 1-h exposure to diluted diesel exhaust (300 $\mu g/m^3$ particles and 1.6 ppm NO_2). However, there were no effects on BAL ascorbate levels. Rudell et al. (1990) had previously shown increased BAL neutrophils in nonsmoking subjects exposed to 100 $\mu g/m^3$ of DPM in diesel exhaust (gases were present). Thus, diesel exhaust (particles and gases) can produce an enhanced response to antigenic material in the nasal cavity. Extrapolation of these findings, of enhanced allergic response in the nose, to the lung, would suggest that ambient combustion particles containing DPM may have significant effects on allergic asthma. These studies provide biological plausibility for the exacerbation of allergic asthma associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities and countries that rely heavily on diesel-powered vehicles. It must be noted that the potential contribution of DPM to the rising prevalence in asthma is complicated by the fact that DPM levels have been decreasing over the last decade (CALEPA report). The reported decrease in DPM levels is a result of the increased combustion efficiency of diesel engines. This improvement in diesel engine design also has brought about a significant decrease in the particle size of diesel emissions. Thus, the balance between a decrease in diesel emissions and the production of a potentially more toxic particle size needs further exploration.

8.4.4 Resistance to Infectious Disease

The development of an infectious disease requires both the presence of the appropriate pathogen, as well as host susceptibility to the pathogen. There are numerous specific and

nonspecific anti-microbial host defenses against microbes, and the ability of inhaled particles to modify resistance to bacterial infection could result from a decreased ability to clear or kill microbes. Rodent infectivity models frequently have been used to examine the effect of inhaled particles on host defense and infectivity. Mice or rats are challenged with a bacterial or viral load either before or after exposure to the particles (or gas) of interest; mortality rate, survival time, or bacterial clearance are then examined. A number of studies that have used the infectivity model to assess the effect of inhaled PM were discussed previously (U.S. Environmental Protection Agency, 1982, 1989, 1996a). In general, acute exposure to sulfuric acid aerosols at concentrations up to 5,000 $\mu g/m^3$ were not very effective in enhancing mortality in a bacterially mediated murine model. In rabbits, however, sulfuric acid aerosols altered anti-microbial defenses after exposure for 2 h/day for 4 days to 750 $\mu g/m^3$ (Zelikoff et al., 1994). Acute or short-term repeated exposures to high concentrations of relatively inert particles have produced conflicting results. Carbon black (10,000 $\mu g/m^3$) was found to have no effect on susceptibility to bacterial infection (Jakab, 1993), whereas a very high concentration of TiO_2 decreased the clearance of microbes and the bacterial response of lymphocytes isolated from mediastinal lymph nodes (Gilmour et al., 1989a,b). In addition, exposure to DPM has been shown to enhance the susceptibility of mice to the lethal effects of some, but not all, microbial agents (Hatch et al., 1985; Hahon et al., 1985). Thus, the pulmonary response to microbial agents has been shown to be altered at relatively high particle concentrations in animal models. Moreover, these effects appear to be highly dependent on the microbial challenge and the test animal studied. Pritchard et al. (1996) observed in rats exposed to particles with a high concentration of metals (e.g., ROFA), that the increased mortality rate after streptococcus infection was associated with the amount of metal in the PM.

Despite the reported association between ambient PM and deaths caused by pneumonia (Schwartz, 1994), there are few recent studies that have examined the mechanisms that may be responsible for the effect of PM on infectivity. In one study, Cohen and colleagues (1997) examined the effect of inhaled vanadium (V) on immunocompetence. Healthy rats were repeatedly exposed to 2 mg/m^3 V, as ammonium metavanadate, and then instilled with polyinosinic-polycytidilic acid (poly I:C), a double-stranded polyribonucleotide that acts as a potent immunomodulator. Induction of increases in lavage fluid protein and neutrophils was greater in animals preexposed to V. Similarly, IL-6 and interferon-gamma were increased in

V-exposed animals. Alveolar macrophage function, as determined by zymosan-stimulated superoxide anion production and by phagocytosis of latex particles, was depressed to a greater degree after poly I:C instillation in V-exposed rats as compared to filtered air-exposed rats. These findings provide evidence that inhaled V, a trace metal found in combustion particles and shown to be toxic in vivo in studies using instilled or inhaled ROFA (Dreher et al., 1997; Kodavanti et al., 1997b, 1999), has the potential to inhibit the pulmonary response to microbial agents. It must be taken into consideration that these effects were found at very high occupational exposure concentrations of V, and as with many studies, care must be taken in extrapolating the results to the ambient exposure of healthy individuals or those with preexisting cardiopulmonary disease to trace concentrations (approximately 3 orders of magnitude lower concentration) of metals in ambient PM.

8.5 MECHANISMS OF PARTICULATE MATTER TOXICITY AND PATHOPHYSIOLOGY: IN VITRO EXPOSURES

8.5.1 Introduction

The mechanisms that underlie injury from PM exposure are unclear. Section 8.5.2 discusses the more recently published in vitro studies that provide an approach toward identifying potential mechanisms by which PM mediates health effects. The remaining sections discuss potential mechanisms in relation to PM characteristics based on these available data.

8.5.2 Experimental Exposure Data

In vitro exposure is a useful technique to provide information on potential hazardous PM constituents and mechanisms of PM injury, especially when only limited quantities of the test material are available. Exposing respiratory cells to particles in vitro not only reduces the amount of material needed for the experiments but also provides an opportunity to investigate the mechanisms of particle toxicity. In addition, in vitro exposure allows the examination of the response to particles in only one or two cell types. Limitations of in vitro studies include difficulty in extrapolating dose-response relationships and from in vitro to in vivo biological response and mechanistic extrapolations. In addition to alterations in physiochemcial characteristics of PM because of the collection and resuspension processes, these exposure

conditions do not simulate the air-cell interface that actually exists within the lungs, and, thus, the exact dosage delivered to target cells is not known. Furthermore, unless an in vitro exposure system that is capable of delivering particles uniformly to monolayers of airway epithelial cells cultured in an air-liquid interface system is used (Chen et al., 1993), the conventional incubation system alters the microenvironment surrounding the cells and may alter the mechanisms of cellular injury induced by these agents.

Even with these limitations, in vitro studies do provide an approach to identify potential cellular and molecular mechanisms by which PM mediates health effects. These mechanisms can then be evaluated in vivo. In vitro studies are summarized in Table 8-8.

8.5.2.1 Ambient Particles

Several studies have exposed airway epithelial cells, alveolar macrophages, or blood monocytes to ambient PM to investigate cellular processes such as oxidant generation and cytokine production that may contribute to the pathophysiological response seen in vivo. Among the ambient PM being examined were samples collected from Boston (Goldsmith et al., 1998), North Provo, UT (Ghio et al., 1999a,b), St. Louis, MO (SRM 1648, Dong et al., 1996; Becker and Soukup, 1998), Washington, DC (SRM 1649, Becker and Soukup, 1998), Ottawa, Canada (EHC-93, Becker and Soukup, 1998), Dusseldorf and Duisburg, Germany (Hitzfeld et al., 1997), Mexico City (Bonner et al., 1998), and Terni, Italy (Fabiani et al., 1997).

Because soluble metals of ROFA have been shown to be associated with biological effect and toxicity, several studies have investigated whether the soluble components in ambient PM may have the same biological activities. Ambient PM samples collected from North Provo, UT, (during 1981 and 1982) were used to test whether the soluble components or ionizable metals, which accounted for approximately 0.1% of the mass, are responsible for the biological activity of ambient PM. The oxidant generation (thiobarbituric acid reactive products), release of IL-8 from BEAS-2B cells, and PMN influx in rats exposed to these samples correlated with sulfate content and the ionizable fraction of these PM samples (Ghio et al., 1999a,b). In addition, these particles stimulated IL-6 and IL-8 production as well as increased IL-8 mRNA and enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in BEAS-2B cells (Kennedy et al., 1998). Cytokine secretion was preceded by activation of nuclear factor kappa B (NF-κB) and was reduced by treatment with superoxide dismutase (SOD), Deferoxamine (DEF), or

TABLE 8-8. IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human bronchial epithelial cells, asthmatic (ASTH) nonasthmatic (NONA)	DPM	In vitro	10-100 μg/mL	0.4 μm	2, 4, 6, 24 h	DPM caused no gross cellular damage. Ciliary beat frequency was attentuated at all doses. DPM caused IL-8 release at lower dose in ASTH than NONA. Higher concentrations of DPM suppressed IL-8, GM-CSF, and RANTES in ASTH cells.	Bayram et al. (1998a)
Human bronchial epithelial cells (smokers)	DPM	In vitro	10-100 μg/mL	0.4 μm	24 h	DPM attenuated ciliary beating. Release of IL-8, protein, GM-CSF, and SICAM-1 increased after DPM exposure.	Bayram et al. (1998b)
Human and rat alveolar macrophages	Four Urban air particles: ROFA DPM Volcanic ash Silica	In vitro exposure, 2×10^5 cells exposed for 2 h	Urban and DPM: 12, 27, 111, 333, or 1000 μg/mL SiO_2 and TiO_2: 4, 12, 35, or 167 μg/mL Fe_2O_3: 1:1, 3:1; 10:1 particles/cell ratio	Urban particles: 0.3-0.4 μm DPM: 0.3 μm ROFA: 0.5 μm Volcanic ash: 1.8 μm Silica: 05-10 μm TiO_2: <5 μm Latex: 3.8 μm	2 h for cytotoxicity, 16-18 h for cytokine assay; chemiluminescence at 30 minutes	UAP-induced cytokine production (TNF, IL-6) in AM of both species that is not related to respiratory burst or transition metals but may be related to LPS (blocked by polymyxin B but not DEF) ROFA induced strong chemiluminescence but had weak effects on TNF production.	Becker et al. (1996)
Human AM and blood monocytes	Urban air particles; St. Louis SRM 1648; Washington, DC, SRM 1649; Ottawa, Canada, EHC-93	In vitro	33 or 100 μg/mL	0.2 to 0.7 μm	3, 6, or 18-20 h	Phagocytosis was inhibited by UAP at 18 h. UAP caused decreased expression of β_2-integrins involved in antigen presentation and phagocytosis.	Becker and Soukup (1998)
Rat alveolar macrophages	PM_{10} Mexico City 1993; volcanic ash (MSHA)	In vitro	1-100 μg/mL	<10 μm	24 h	PM_{10} stimulated alveolar macrophages to induce up-regulation of PDGF $\propto$ receptor on myofiboroblasts. Endotoxin and metal components of PM_{10} stimulate release of IL-β. This is a possible mechanism for PM_{10}-induced airway remodeling.	Bonner et al. (1998)
NHBE cells	ROFA	In vitro	0, 50, or 200 μg/mL		Analysis at 2 and 24 h postexposure	Increase in expression of the cytokines IL-6, IL-8, and TNF-α; inhibition by DMTU or deferoxamine.	Carter et al. (1997)

TABLE 8-8 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Supercoiled DNA	PM_{10} from Edinburgh, Scotland	In vitro	996.2 ± 181.8 μg/filter in 100 μL	PM_{10}	8 h	PM_{10} caused damage to DNA; mediated by hydroxyl radicals (inhibited by mannitol) and iron (DEF). Clear supernatant has all of the suspension activity. Free radical activity is derived either from a fraction that is not centrifugeable on a bench centrifuge or that the radical generating system is released into solution.	Donaldson et al. (1997)
Rat AM	UAP DPM	In vitro	50 to 200 μg/mL	DPM: 1.1 – 1.3 μm UAP: St Louis, between 1974 and 1976 in a baghouse, sieved through 200-mesh (125 μm)	2 h exposure; supernatant collected 18 h postexposure	Dose dependent increase in TNF-α, IL-6, CINC, MIP-2 gene expression by urban particles but not with DPM; cytokine production were not related to ROS; cytokine production can be inhibited by polymyxin B; LPS was detected on UAP but not DPM; endotoxin is responsible for the cytokine gene expression induced by UAP in AM..	Dong et al. (1996)
Primary cultures of RTE	ROFA	In vitro	5, 10, or 20 $\mu g/cm^2$	Same as Dreher et al. (1997)	Analysis at 6 and 24 h	Particle induced epithelial-cell detachment and lytic cell injury; alterations in the permeability of the cultured RTE cell layer; increase in LDH, G-6-PDH, gluathione reductase, glutathione S-transferase; mechanism of ROFA-induced RTE cytotoxicity and pulmonary cellular inflammation involves the development of an oxidative burden.	Dye et al. (1997)
Peripheral blood monocytes	Organic extract of TSP, Italy	In vitro	42.5 μg extract/m^3 (acetone)	N/A, collected from high-volume sampler (60 m^3/h)	2 h	Superoxide anion generation was inhibited at a particulate concentration of 0.17 mg/mL when stimulated with PMA; 50% increase in LDH; disintegration of plasma membrane.	Fabiani et al. (1997)
Rat AM	ROFA, iron sulfate, nickel sulfate, vanadyl sulfate Latex particles with metal complexed on the surface	In vitro (0.7×10^6 cells/mL)	0.01–1.0 mg/mL	3.6 μm MMAD	Up to 400 min	Increase chemiluminescence, inhibited by DEF and hydroxyl radical scavengers; solutions of metal sulfates and metal-complexed latex particles similarly elevated chemiluminescence in a dose-and time-dependent manner.	Ghio et al. (1997a)

TABLE 8-8 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
NHBE BEAS-2B	ROFA	In vitro	5–200 μg/mL	3.6 μm	2 and 24 h	mRNA for ferritin did not change; ferritin protein increase; mRNA for transferrin receptor decreased, mRNA for lactoferrin increased; transferrin decreased whereas lactoferrin increased; deferoxamine alone increased lactoferrin mRNA.	Ghio et al. (1998c)
BEAS-2B respiratory epithelial cells	Oil fly ash	In vitro	100 μg/mL	N/A	≈1h	Lactoferrin binding with PM metal occurred within 5 min. V and Fe $^{(III)}$, but not Ni, bound to the lactoferrin receptor.	Ghio et al. (1999b)
BEAS-2B	Provo TSP soluble and insoluble extract	In vitro	500 μg/mL	TSP	24 h	Water soluble fraction caused greater release of IL-8 than insoluble fraction. The effect was blocked by deferoxamine and presumably because of metals (Fe, Cu, Zn, Pb).	Ghio et al. (1999a)
ØX174 RF1 DNA	PM_{10} from Edinburgh, Scotland	In vitro	3.7 or 7.5 μg/mL	PM_{10}	8 h	Significant free radical activity on degrading supercoiled DNA; mainly because of hydroxyl radicals (inhibited by mannitol); Fe involvement (DEF-B conferred protection); more Fe^{3+} was released compared to Fe^{2+}, especially at pH 4.6 than at 7.2.	Gilmour et al. (1996)
Hamster AM	ROFA or CAP	In vitro	0, 25, 50, 100, or 200 μg/mL	CAP: 0.1–2.5 μm (from Harvard concentrator) TiO_2: 1 μm	30 min incubation, analysis immediately following	Dose-dependent increase in AM oxidant stress with both ROFA and CAP. Increase in particle uptake; Mac-type SR mediate a substantial proportion of AM binding; particle-associated components (e.g., transition metals) are likely to mediate intracellular oxidant stress and proinflammatory activation.	Goldsmith et al. (1997)
Hamster AM	CAP, ROFA, and their water-soluble and particulate fractions	In vitro	0-200 mg/mL	CAP = 0.125 μm ROFA = 1.0 μm	30 min	ROFA and CAPs (water soluble components) caused increases in DCFH oxidation; CAPs samples and components showed substantial day-to-day variability in their oxidant effects; ROFA increased MIP-2 and TNF-α production in AM and can be inhibitable by NAC.	Goldsmith et al. (1998)
AMs from female CD rats	Vanadyl chloride sodium metavanadate	In vitro	10-1000 μm metavanadate	N/A	30 min	Metavanadate caused increased production of ROS. The LOEL was 50 μM.	Grabowski et al. (1999)

TABLE 8-8 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human PMN	Aqueous and organic extracts of TSP in Dusseldorf and Duisburg, Germany	In vitro	0.42–0.78 mg dust/mL	Collected by high volume sampler, 90% <5 μm, 50% <1μm, maximum at 0.3–0.45 μm Extracted using water and then dichloromethane to yield aqueous and organic extracts	Up to 35 min	PM extract alone significantly stimulated the production and release of ROS in resting but not in zymosan-stimulated PMN. The effects of the PM extracts were inhibited by SOD, catalase and sodium azide (NaN_3); Zymosan-induced LCL is inhibited by both types of extracts, but aqueous extracts have a stronger inhibitory effect.	Hitzfeld et al. (1997)
Human AM	UAP (#1648, 1649) Volcanic ash ROFA	In vitro	0, 25, 100, or 200 μg/mL	Volume median diameter: ROFA 1.1 μm #1648: 1.4 μm #1649: 1.1 μm volcanic ash 2.3 μm	24 h	ROFA highly toxic; urban PM toxic at 200μg/mL; ROFA produced significant apoptosis as low as 25 μg/mL; UAP produced apoptosis at 100 μg/mL; UAP and ROFA also affect AM phenotype: increased immune stimulatory, whereas decreased immune suppressor phenotype.	Holian et al. (1998)
Rat AM	ROFA, 10 samples with differing metal composition	In vitro	0 or 50 μg/mL	1.99 - 2.55 μm MMAD	1-6 h	Macrophage activation, as determined by chemiluminescence was maximal with the V-rich particles as opposed to V plus Ni-rich particles.	Kodavanti et al (1998a)
BEAS-2B, airway epithelial cells	ROFA	In vitro	0, 0.5, or 2.0 mg in 10 mL	N/A	1 h	ROFA induced production of acetaldehyde in dose-dependant fashion.	Madden et al. (1999)
Male (Wistar) rat lung macrophages	Urban dust SRM 1649, TiO_2, quartz	In vitro	0-100 μg in 1 mL	N/A	18 h	Cytotoxicity ranking was quartz > SRM 1649 > TiO_2, based on cellular ATP decrease and LDH, acid phosphatase, and β-glucuronidase release.	Nadeau et al. (1996)
Human blood monocytes and neutrophils (PMN)	Ambient air particles, carbon black, oil fly ash, coal fly ash	In vitro	100 μg in 0.2 mL	N/A	40 min.	ROS generation, measured by LCL increased in PMN, was correlated with Si, Fe, Mn, Ti, and Co content but not V, Cr, Ni, and Cu. Deferoxamine, a metal ion-chelator, and did not affect LCL in PMN, suggesting that metal ions are not related to the induction of LCL.	Prahalad et al. (1999)
Human airway epithelium-derived cell lines BEAS-2B (S6-subclone)	ROFA	In vitro	0, 6, 12, 25, or 50 μg/mL	1.96 μm	1 and 24 h	Activation of IL-6 gene by NF-κB activation and binding to specific sequences in promoter of IL-6 gene; inhibition of NF-κB activation by DEF and NAC; increase in PGE_2, IL-6, TNF, and IL-8; activation NF-κB may be a critical first step in the inflammatory cascade following exposure to ROFA particles.	Quay et al. (1998)
Human airway epithelium-derived cell line BEAS 2B	ROFA	In vitro	2, 20, or 60 $\mu g/cm^2$	1.96 μm	24-h exposure	Epithelial cells exposed to ROFA for 24 h secreted substantially increased amounts of the PHS products prostaglandins E_2 and $F_{2\alpha}$; ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in PHS activity.	Samet et al. (1996)

TABLE 8-8 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human airway epithelium-derived cell line BEAS	ROFA Synthetic ROFA (soluble Ni, Fe, and V)	In vitro	ROFA: 0–200 μg/mL Synthetic ROFA (100μg/mL): Ni, 64 μM Fe, 63 μM V, 370 mM	ROFA: 1.96 μm Synthetic ROFA: N/A (soluble)	Up to 24 h	Tyrosine phosphatase activity, which was known to be inhibited by vanadium ions, was markedly diminished after ROFA treatment; ROFA exposure induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in BEAS cells.	Samet et al. (1997)
Human airway epithelium-derived cell lines BEAS-2B	Particle components As, Cr, Cu, Fe, Ni, V, and Zn	In vitro	500 μM of As, F, Cr (III), Cu, V, Zn	N/A (soluble)	20 min and 6 and 24 h	Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells; activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK under these conditions; the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn; acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells.	Samet et al. (1998)
A549 ØX174 RFI DNA	Urban particles: SRM 1648, St. Louis SRM 1649, Washington, DC	In vitro	1 mg/mL for Fe mobilization assay	SRM 1648: 50% < 10 μm SRM 1649: 30% < 10 μm	Up to 25 h	Single-strand breaks in DNA were induced by PM only in the presence of ascorbate, and correlated with amount of Fe that can be mobilized; ferritin in A549 cells was increased with treatment of PM suggesting mobilization of Fe in the cultured cells.	Smith and Aust (1997)
Rat (Wistar) AM RAM cells (a rat AM cell line)	TiO_2	In vitro	20, 50, or 80 μg/mL	N/A	4 h	Opsonization of TiO_2 with surfactant components resulted in a modest increase in AM uptake compared with that of unopsonized TiO_2; surfactant components increase AM phagocytosis of particles.	Stringer and Kobzik (1996)
A549	ROFA, α-quartz, TiO_2	In vitro	1 mg/mL	N/A	60 min	Exposure of A549 cells to ROFA, α-quartz, but not TiO_2, caused increased IL-8 production in TNF-α primed cells in a concentration-dependent manner.	Stringer and Kobzik (1998)

TABLE 8-8 (cont'd). IN VITRO EFFECTS OF PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc.	Particle or Constituent	Exposure Technique	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
A549	TiO_2, Fe_2O_3, CAP, and the fibrogenic particle α-quartz	In vitro	TiO_2 [40 μg/mL], Fe_2O_3 [100 μg/mL], α-quartz [200 μg/mL], or CAP [40 μg/mL]	N/A	24 h	TiO_2 > Fe_2O_3 > α-quartz > CAP in particle binding; binding of particle was found to be calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was calcium-independent; scavenger receptor, mediate particulate binding; α-quartz, but not TiO_2 or CAP, caused a dose-dependent production of IL-8.	Stringer et al. (1996)
RLE-6TN cells (type II like cell line)	$PM_{2.5}$, Burlington, VT; Fine/ultrafine TiO_2	In vitro	1, 2.5, 5, or 10 μg/mL	$PM_{2.5}$: 39 nm Fine TiO_2: 159 nm UF TiO_2: 37 nm	24 and 48 h exposure	Increases in c-Jun kinase activity, levels of phosphorylated c-Jun immunoreactive protein, and transcriptional activation of activator protein-1-dependent gene expression; elevation in number of cells incorporating 5'-bromodeoxyuridine.	Timblin et al. (1998)
rat, Long Evans epithelial cells	CFA PFA α-quartz.			2.6 μm 17.7 μm 2.5 μm	3 h	CFA produced highest level of hydroxyl radicals; iron content is more important than quartz content.	Van Maanen et al. (1999)
BEAS-2B human bronchial epithelial cells	ROFA Birmingham, AL. 188 mg/g of VO	In vitro	100 μg/mL	N/A	2-6 h	ROFA caused increased intracellular Ca^{++}, IL-6, IL-8, and TNF-α through activation of capsicin- and pH-sensitive receptors.	Veronesi et al. (1999)

N-acetylcysteine. The addition of similar quantities of Cu^{2+} as found in the Provo extract replicated the biological effects observed with particles alone. When normal constituents of airway lining fluid (mucin or ceruloplasmin) were added to BEAS cells, particulate-induced secretion of IL-8 was modified. Mucin reduced IL-8 secretion, whereas ceruloplasmin significantly increased IL-8 secretion and activation of NF-κB. The authors suggest that copper ions may cause some of the biologic effects of inhaled PM in the Provo region and may provide an explanation for the sensitivity of asthmatics to Provo PM seen in epidemiologic studies.

There are regional as well as daily variations in the composition of ambient PM and, hence, its biological activities. For example, concentrated ambient PM (CAP, from Boston urban air) has substantial day-to-day variability in its composition and oxidant effects (Goldsmith et al., 1998). Similar to Utah PM, the water-soluble component of Boston CAPs significantly increased AM oxidant production and inflammatory cytokine (MIP2 and TNFα) production over negative control values. These effects can be blocked by metal chelators or antioxidants. The regional difference in biological activity of ambient PM has been shown by Becker and Soukup (1998). The oxidant generation, phagocytosis, as well as the expressions of receptors important for phagocytosis in human alveolar macrophage and blood monocyte were reduced significantly by PM exposure.

Becker and Soukup (1998) and others (Dong et al., 1996, Becker et al., 1996) have suggested that the biological activity of the ambient PM may result from the presence of endotoxin on the particles rather than metal-associated oxidant generation. Using the same urban particles (SRM 1648), cytokine production (TNF-α, IL-1, Il-6, CINC, and MIP-2) was increased in macrophages following treatment with 50 to 200 μg/mL of urban PM (Dong et al., 1996). The urban particle-induced TNF-α secretion was abrogated completely by treatment with polymyxin B, an antibiotic that blocks LPS-associated activities, but not with antioxidants. Although it is possible that LPS may be responsible for ambient PM induced cytokine gene expression, extrapolation of these in vitro results to a potential role for endotoxin in the adverse effects of ambient PM must be done with caution because the investigators could not exclude the possibility that the presence of endotoxin with the PM was caused by inadvertent contamination during the year-long collection process or from the handling of the particles.

The involvement of endotoxin, at least partially, in PM induced biological effects was supported more recently by Bonner et al. (1998). Urban PM_{10} collected from north, south, and

central regions of Mexico City was used with SD rat AM to examine PM effects on platelet derived growth factor (PDGF) receptors on lung myofibroblasts (Bonner et al., 1998). Mexico City PM_{10} (but not volcanic ash) stimulated secretion of upregulatory factors for the PDGF α receptor, possibly via IL-1β. In the presence of an endotoxin-neutralizing protein, the Mexico City PM_{10} effect on PDGF was blocked partially, suggesting that LPS was responsible partially for the effect of the PM_{10} on macrophages. In addition, both LPS and vanadium (both present in the PM_{10}) acted directly on lung myofibroblasts. However, the V levels in Mexico City PM_{10} were probably not high enough to exert an independent effect. The authors concluded that PM_{10} exposure could lead to airway remodeling by enhancing myofibroblast replication and chemotaxis.

The effects of water soluble as well as organic components (extracted in dichloromethane) of ambient PM were investigated by exposing human PMN to PM extracts (Hitzfeld et al., 1997). PM was collected with high-volume samplers in two German cities, Dusseldorf and Duisburg; these sites have high traffic and high industrial emissions, respectively. Organic, but not aqueous, extracts of PM alone significantly stimulated the production and release of ROS in resting human PMN. The effects of the PM extracts were inhibited by SOD, catalase, and sodium azide (NaN_3). Similarly, the organic fraction (extractable by acetone) of ambient PM from Terni, Italy, had been shown to produce cytotoxicity, superoxide release in response to PMA and zymosan in peripheral monocytes (Fabiani et al., 1997).

8.5.2.2 Residual Oil Fly Ash

In a series of studies using the same ROFA samples, several experiments have investigated the biochemical and molecular mechanisms involved in ROFA induced cellular injury. Prostaglandin metabolism in cultured human airway epithelial cells (BEAS-2B and NHBE) exposed to ROFA was investigated by Samet et al. (1996). Epithelial cells exposed to ROFA for 24 h secreted substantially increased amounts of prostaglandins E2 and F2 α. The ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in activity of the PHS-2 form of prostaglandin H synthase as well as mRNA coded for this enzyme. In contrast, expression of the PHS1 form of the enzyme was not affected by ROFA treatment of airway epithelial cells. These investigators further demonstrated that noncytotoxic levels of ROFA induced a significant dose- and time-dependent increase in protein tyrosine phosphate, an

important regulator of signal transduction leading to cell growth and proliferation. ROFA-induced increases in protein phosphotyrosines were associated with its soluble fraction and were mimicked by V-containing solutions but not iron or nickel solutions (Samet et al., 1997).

ROFA also stimulates respiratory cells to secret inflammatory cytokines such as IL-6, IL-8, and TNF. Normal human bronchial epithelial (NHBE) cells exposed to ROFA produced significant amounts of IL-8, IL-6, and TNF, as well as mRNAs coding for these cytokines (Carter et al., 1997). Increases in cytokine production, but not m-RNA expression, were dose-dependent. The cytokine production was inhibited by the addition of metal chelator, DEF, or the free radical scavenger, DMTU. Similar to the data of Samet et al. (1997), V but not Fe or Ni compounds were responsible for these effects. Cytotoxicity, decreased cellular glutathione levels in primary cultures of rat tracheal epithelial (RTE) cells exposed to suspensions of ROFA indicated that respiratory cells exposed to ROFA were under oxidative stress. Treatment with buthionine sulfoxamine (an inhibitor of γ-glutamyl cysteine synthetase) augmented ROFA-induced cytotoxicity, whereas treatment with DMTU inhibited ROFA-induced cytoxicity further suggested that ROFA-induced cell injury may be mediated by hydroxyl-radical-like ROS (Dye et al., 1997). Using BEAS-2B cells, a time- and dose-dependent increase in IL-6 mRNA induced by ROFA was shown to precede by the activation of nuclear proteins NF-kB (Quay et al., 1998). Taking together, ROFA exposure increases oxidative stress, perturbs protein tyrosine phosphate homeostasis, activates NF-kB, and up-regulates inflammatory cytokine and prostaglandin synthesis and secretion to produce lung injury.

Stringer and Kobzik (1998) observed that "primed" lung epithelial cells exhibited enhanced cytokine responses to PM. Compared to normal cells, exposure of TNF-α-primed A549 cells to ROFA or α -quartz caused increased IL-8 production in a concentration-dependent manner for particle concentrations ranging from 0-200 μg/mL. Addition of the antioxidant NAC (1.0 mM) decreased ROFA and α -quartz-mediated IL-8 production by approximately 50% in both normal and TNF- α -primed A549 cells. Exposure of A549 cells to ROFA caused an increase in oxidant levels that could be inhibited by NAC. These data suggest that (1) lung epithelial cells primed by inflammatory mediators show increased cytokine production after exposure to PM, and (2) oxidant stress is an important mechanism for this response.

In summary, exposure of lung cells to ambient PM or ROFA leads to increased production of cytokines and the effects may be mediated, at least in part, through production of ROS.

Day-to-day variations in the components of PM, such as soluble transition metals, which may be critical to eliciting the response, are suggested. The involvement of organic components in ambient PM also was suggested in some studies.

8.5.3 Potential Cellular and Molecular Mechanisms

8.5.3.1 Reactive Oxygen Species

Ambient particulate matter contains transition metals, such as iron (most abundant), copper, nickel, vanadium, and cobalt. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen species (ROS). These reactions can be demonstrated by the iron-catalyzed Haber-Weiss reactions that follow.

$$\text{Reductant}^{n} + \text{Fe(III)} \rightarrow \text{Reductant}^{n+1} + \text{Fe(II)} \quad (1)$$

$$\text{Fe(II)} + O_2^- \rightarrow \text{Fe(III)} + O_2^- \quad (2)$$

$$HO_2^- + O_2^- + H^+ \rightarrow O_2 + H_2O_2 \quad (3)$$

$$\text{Fe(II)} + H_2O_2 \rightarrow \text{Fe(III)} + {}^{\bullet}OH + HO^- \text{ (Fenton Reaction)} \quad (4)$$

Iron will continue to participate in the redox cycle in the above reactions as long as there is sufficient O_2 or H_2O_2 and reductants.

Soluble metals from inhaled PM dissolved into the fluid lining of the airway lumen can react directly with biological molecules (acting as a reductant in the above reactions) to produce ROS. For example, ascorbic acid in the human lung epithelial lining fluid can react with Fe(III) from inhaled PM to cause single strand breaks in supercoiled plasmid DNA, ϕX174 RFI (Smith and Aust, 1997). The DNA damage caused by a PM_{10} suspension can be inhibited by mannitol, an hydroxyl radical scavenger, further confirming the involvement of free radicals in these reactions (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997). Because the clear supernatant of the centrifuged PM_{10} suspension contained all of the suspension activity, the free radical activity is derived either from a fraction that is not centrifugable (10 min at 13,000 rpm

on a bench centrifuge) or the radical generating system is released into solution (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997).

In addition to measuring the interactions of ROS and biomolecules directly, the role of ROS in PM-induced lung injury also can be assessed by measuring the electron spin resonance (ESR) spectrum of radical adducts or fluorescent intensity of dichlorofluorescin (DCFH), an intracellular dye that fluoresces on oxidation by ROS. Alternatively, ROS can be inhibited using free radical scavengers, such as dimethylthiourea (DMTU); antioxidants, such as glutathione or N-acetylcysteine (NAC); or antioxidant enzymes, such as superoxide dismutase (SOD). The diminished response to PM after treatment with these antioxidants indicates the involvement of ROS.

As described earlier, Kadiiska et al. (1997) used the ESR spectra of 4-POBN [α-(4-pyridyl 1-oxide)-N-tert-butylnitrone] adducts to measure ROS in rats instilled with ROFA and demonstrated the association between ROS production within the lung and soluble metals in ROFA. Using DMTU to inhibit ROS production, Dye et al. (1997) had shown that systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. Goldsmith et al. (1998), as described earlier, showed that ROFA and CAPs caused increases in ROS production in AMs. The water-soluble component of both CAPs and ROFA significantly increased AM oxidant production over negative control values. In addition, increased PM-induced cytokine production was inhibited by NAC. Li et al. (1996, 1997) instilled rats with PM_{10} particles (collected on filters from an Edinburgh, Scotland, monitoring station). Six hours after intratracheal instillation of PM_{10}, they observed a decrease in glutathione (GSH) levels in the BAL fluid. Although this study does not describe the composition of the PM_{10}, the authors suggest that changes in GSH, an important lung antioxidant, support the contention that the free radical activity of PM_{10} is responsible for its biological activity in vivo.

In addition to ROS generated directly by PM, resident or newly recruited AMs or PMNs also are capable of producing these reactive species on stimulation. The ROS produced during the oxidative burst can be measured using a chemiluminescence (CL) assay. With this assay, AM CL signals in vitro have been shown to be greatest with ROFA containing primarily soluble V and were less with ROFA containing Ni plus V (Kodavanti et al., 1998a). As described earlier, exposures to Dusseldorf and Duisburg PM increased the resting ROS production in

PMNs, which could be inhibited by SOD, catalase, and sodium azide (Hitzfeld et al., 1997). Stringer and Kobzik (1998) showed that addition of NAC (1.0 mM) decreased ROFA-mediated IL-8 production by approximately 50% in normal and TNF-α-primed A549 cells. In addition, exposures of A549 cells to ROFA caused a substantial (and NAC inhibitable) increase in oxidant levels as measured by DCFH oxidation. In human AMs, Becker et al. (1996) found a CL response for ROFA, but not urban air particles (Ottawa and Dusseldorf) or volcanic ash.

Metal compounds of PM are the most probable species capable of catalyzing ROS generation on exposure to PM. To determine elemental content and solubility in relation to their ability to generate ROS, PMN or monocytes were exposed to a wide range of ambient air particles from divergent sources (one natural dust, two types of oil fly ash, two types of coal fly ash, five different ambient air samples, and one carbon black sample) (Prahalad et al., 1999), and CL production was measured over a 20-min period postexposure. Percent of sample mass accounted for by XRF detectable elements was 1.2% (carbon black); 22 to 29% (natural dust and ambient air particles); 13 to 22% (oil fly ash particles); and 28 to 49% (coal fly ash particles). The major proportion of elements in most of these particles were aluminosilicates and insoluble iron, except oil derived fly ash particles in which soluble vanadium and nickel were in highest concentration, consistent with particle acidity as measured in the supernatants. All particles induced CL response in cells, except carbon black. The CL response of PMNs in general increased with all washed particles, with oil fly ash and one urban air particle showing statistical differences between deionized water washed and unwashed particles. These CL activities were significantly correlated with the insoluble Si, Fe, Mn, Ti, and Co content of the particles. No relationship was found between CL and soluble transition metals such as V, Cr, Ni, and Cu. Pretreatment of the particles with a metal ion chelator, deferoxamine, did not affect CL activities. Particle sulfate content and acidity of the particle suspension did not correlated with CL activity.

Soluble metals can be mobilized into the epithelial cells or AMs to produce ROS intracellularly. Size fractionated coal fly ash particles (2.5, 2.5 to 10, and <10 μm) of bituminous b (Utah coal), c (Illinois coal), and lignite (Dakota coal) were used to compare the amount of iron mobilization in A549 cells and by citrate (I mM) in cell-free suspensions (Smith et al., 1998). Iron was mobilized by citrate from all three size fractions of all three coal types. More iron, in Fe(III) form, was mobilized by citrate from the <2.5-μm fraction than from the >2.5-μm fractions. In addition, the amount of iron mobilized was dependent on the type of coal used to

generate the fly ash (Utah coal > Illinois coal = Dakota coal) but not related to the total amount of iron present in the particles. Ferritin (an iron storage protein) levels in A549 cells increased by as much as 11.9-fold in cells treated with coal fly ash (Utah coal > Illinois coal > Dakota coal). More ferritin was induced in cells treated with the <2.5-μm fraction than with the >2.5-μm fractions. Mossbauer spectroscopy of a fly ash sample showed that the bioavailable iron was assocated with the glassy aluminosilicate fraction of the particles (Ball et al., 2000). As with the bioavailability of iron, there was an inverse correlation between the production of IL-8 and fly ash particle size with the Utah coal fly ash being the most potent.

Using ROFA and colloidal iron oxide, Ghio et al. (1997b; 1998a,b,c; 1999c; 2000b) have shown that exposures to these particles disrupted iron homeostasis and induced the production of ROS in vivo and in vitro. Treatment of animals or cells with metal-chelating agents such as DEF with an associated decrease in response has been used to infer the involvement of metal in PM-induced lung injury. Metal chelation by DEF (1 mM) caused significant inhibition of particulate-induced AM oxidant production, as measured using DCFH (Goldsmith et al., 1998). DEF treatment also reduced NF-κB activation and cytokine secretion in BEAS-2B cells exposed to Provo PM (Kennedy et al., 1998). However, treatment of ROFA suspension with DEF was not effective in blocking leachable metal induced acute lung injury (Dreher et al., 1997). Dreher et al. (1997) indicated that DEF could chelate $Fe^{(III)}$ and $V^{(II)}$, but not $Ni^{(II)}$, suggesting that metal interactions played a significant role in ROFA-induced lung injury.

Other than Fe, several V compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of V, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5. However, metal components of fly ash have not been shown to consistently increase ROS production from bovine AM treated with combustion particles (Schluter et al., 1995). For example, As(III), Ni(II), and Ce(III), which are major components of fly ash, had been shown to inhibit the secretion of superoxide anions (O_2^-) and hydrogen peroxide. In the same study, O_2^- were lowered by Mn(II) and Fe(II), whereas V(IV) increased O_2^- and H_2O_2. In contrast, Fe(III) increase O_2^- productions, demonstrating that the oxidation state of

metal may influence its oxidant generating properties. Other components of fly ash, such as Cd(II), Cr(III), and V(V), had no effects on ROS.

It is likely that a combination of several components rather than a single metal in PM is responsible for the PM induced cellular response. For example, V and Ni+V but not Fe or Ni alone (in saline with the final pH at 3.0) resulted in increased epithelial permeability, decreased cellular glutathione, cell detachment, and lytic cell injury in rat tracheal epithelial cells exposed to soluble salts of these metals at equivalent concentrations found in ROFA (Dye et al., 1999). Treatment of V-exposed cells with buthionine sulfoximine further increased cytotoxicity. Conversely, treatment with radical scavenger dimethyl thiourea inhibited the effects in a dose-dependent manner. These results showed that soluble metal or combinations of several metals in ROFA are responsible for these effects.

Similar to combustion particles such as ROFA, the biological response to exposure to ambient PM also appear to depend on the metal content of the particles. Human subject were instilled with 500 μg (in 20 mL sterile saline) of Utah Valley dust (UVD1, 2, 3, collected during 3 successive years) on the left segmental bronchus and on the right side with sterile saline as control. Twenty-four-hour postinstillation, a second bronchoscopy was performed and phagocytic cells were obtained on both side of the segmental bronchus. AM from subjects instilled with UVD, obtained by bronchoaveolar lavage 24 h postinstillation, were incubated with fluoresceinated yeast (Saccharomyces cerevisiae) to assess their phagocytic ability. Although the same proportion of AMs were exposed to UVD phagocytized yeast, AMs exposed to UVD1, which were collected while a local steel mill was open, took up significantly less particles than AMs exposed to other extracts (UVD2 when the steel mill was closed and UVD3 when the plant reopened). AMs exposed to UVD1 also exhibited a small decrease in oxidant activity (using dihydrorhodamine-123, DHR). AMs from healthy volunteers were incubated in vitro with the various UVD extracts to assess whether similar effects on human AMs function could be observed to those seen following in vivo exposure. The percentage of AMs that engulfed yeast particles was significantly decreased by exposure to UVD1 at 100 μg/mL, but not at 25 μg/mL. However, the amount of particles engulfed was the same following exposure to all three UVD extracts. AMs also demonstrated increased oxidant stress (using chemiluminescence) after in vitro exposure to UVD1 and this effect was not abolished with pretreatment of the extract with the metal chelator deferoxamine. As with the AMs exposed to UVD in vivo, AM exposed to

UVD in vitro had a decreased oxidant activity (DHR assay). UVD1 contains 61 times and 2 times the amount of Zn compared to UVD 2 and UVD3, respectively, whereas UVD3 contained 5 times more Fe than UVD1. Ni and V were present only in trace amounts. Using the same particles, Frampton et al. (1999) exposed BEAS-2B cells for 2 and 24 h. Similar results were observed for oxidant generation in these cells (i.e., UVD 2, which contains the lowest concentrations of soluble iron, copper, and zinc, produced the least response). Only UVD 3 produced cytotoxicity at a dose of 500 μg/mL. UVD 1 and 3, but not 2, induced expression of IL-6 and 8 in a dose-dependent fashion. Taken together, these data showed that biological response to ambient particles exposure is heavily dependent on the source and, hence, the chemical composition of PM.

8.5.3.2 Intracellular Signaling Mechanisms

In has been shown that the intracellular redox state of the cell modulates the activity of several transcription factors, including NF-κB, a critical step in the induction of a variety of proinflammatory cytokine and adhesion-molecule genes. NF-κB is a heterodimeric protein complex that in most cells resides in an inactive state in the cell cytoplasm by binding to inhibitory kappa B alpha (IkBα). On appropriate stimulation by cytokines or ROS, IκBα is phosphorylated and subsequently degraded by proteolysis. The dissociation of IκBα from NF-κB allows the latter to translocate into the nucleus and bind to appropriate sites in the DNA to initiate transcription of various genes. Two studies in vitro have shown the involvement of NF-κB in particulate-induced cytokine and intercellular adhesion molecule-1 (ICAM-1) production in human airway epithelial cells (BEAS-2B) (Quay et al., 1998; Kennedy et al., 1998). Cytokine secretion was preceded by activation of NF-κB and was reduced by treatment with antioxidants or metal chelators. These results suggest that metal-induced oxidative stress may play a significant role in the initiation phase of the inflammatory cascade following particulate exposure.

A second well-characterized human transcription factor, AP-1, also responds to the intracellular ROS concentration. AP-1 exists in two forms, either in a homodimer of c-jun protein or a heterodimer consisting of c-jun and c-fos. Small amounts of AP-1 already exist in the cytoplasm in an inactive form, mainly as phosphorylated c-jun homodimer. Many different oxidative stress-inducing stimuli, such as UV light and IL-1, can activate AP-1. Exposure of rat

lung epithelial cells to ambient PM in vitro resulted in increases in c-jun kinase activity, levels of phosphroylated c-jun immunoreactive protein, and transcriptional activation of AP-1-dependent gene expression (Timblin et al., 1998). This study demonstrated that interaction of ambient particles with lung epithelial cells initiates a cell signaling cascade related to aberrant cell proliferation.

Early response gene transactivation has been linked to the development of apoptosis, a unique type of programmed cell injury and a potential mechanism to account for PM-induced changes in cellular response. Apoptosis of human AMs exposed to ROFA (25 μg/mL) or urban PM was observed by Holian et al. (1998). In addition, both ROFA and urban PM upregulated the expression of the $RFD1^+$ AM phenotype, whereas only ROFA decreased the $RFD1^+7^+$ phenotype. It has been suggested that an increase in the AM phenotype ratio of $RFD1^+/RFD1^+7^+$ may be related to disease progression in patients with inflammatory diseases. These data showed that ROFA and urban PM can induce apoptosis of human AMs and increase the ratio of AM phenotypes toward a higher immune active state and may contribute to or exacerbate lung inflammation.

Another intracellular signaling pathway that can lead to diverse cellular responses such as cell growth, differentiation, proliferation, apoptosis, and stress responses to environmental stimuli, is the phosphorylation-dependent, mitogen-activated protein kinase (MAPK). Noncytotoxic levels of ROFA have been shown to induce significant dose- and time-dependent increases in protein tyrosine phosphate levels in BEAS cells (Samet et al., 1997). In a subsequent study, the effects of As, Cr, Cu, Fe, Ni, V, and Zn on the MAPK, extracellular receptor kinase (ERK), c-jun N-terminal kinase (JNK), and P38 in BEAS cells were investigated (Samet et al., 1998). Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells. Activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK. Similarly, the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn. The same acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells. These data suggest that MAPK may mediate metal-induced expression of inflammatory proteins in human bronchial epithelial cells. The ability of ROFA to

induce activation of MAPKs in vitro was demonstrated by Silbajoris et al. (2000). In addition, Gerchen et al. (1996) showed that the ROS production induced by PM was markedly decreased by the inhibition of protein kinase C as well as phospholipase A_2.

The major cellular response downstream of ROS and the cell signaling pathways described above is the production of inflammatory cytokines or other reactive mediators. In an effort to determine the contribution of cyclooxygenase to the pulmonary responses to ROFA exposure in vivo, Samet et al. (2000) intratracheally instilled Sprague Dawley rats with ROFA (200 or 500 μg in 0.5 mL saline). These animals were pretreated, intraperitoneally, with 1 mg/kg ROFA (in 20% ethanol in saline) 30 min prior to the intratracheal exposure. At 12 h after intratracheal instillations, intraperitoneal injections (1 mL) were repeated. ROFA treatment induced a marked increase in the level of PGE_2 recovered in the BALF, which was effectively decreased by pretreating the animals with specific prostaglandin H synthase 2 (COX2) inhibitor NS398. Immunohistochemical analyses of rat airway showed concomitant expression of COX2 in the proximal airway epithelium of rats treated with soluble fraction of ROFA. This study further showed that, although COX2 products participated in ROFA induced lung inflammation, the COX metabolites are not involved in IL-6 expression nor the influx of PMN influx into the airway. However, the rationale for the use of intraperitoneal challenge was not elaborated.

The production of cytokines and mediators also has been shown to depend on the type of PM used in the experiments. A549 cells (a human airway epithelial cell line) were exposed to several PM, carbon black (CB, Elftex-12, Cabot Corp.), diesel soot (ND from NIST, LD produced from General Motors LH 6.2 V8 engine at light duty cycle), ROFA (from the heat exchange section of the Boston Edison), OAA (Ottowa ambient air PM, EHC-93), SiO_2, and Ni_3S_2 at 1mg/cm^2 (Seagrave and Nikula, 2000). Results indicated that (1) SiO_2 and Ni_3S_2 caused dose dependent acute toxicity and apototic changes; (2) ROFA and LD, ND were significant only at the highest concentrations, (3) SiO_2 and Ni_3S_2 increased IL-8 (three and eight times over the control, respectively) at low concentrations but suppressed IL-8 at high concentrations, (4) OAA and ROFA also induced IL-8 but lower than SiO_2 and Ni_3S_2, and (5) both diesel soots suppressed IL-8 production. The order of potency in alkaline phasphatase production is OAA > LD = ND > ROFA >> SiO_2 = Ni_3S_2. These results demonstrated that not only the type of particle used but also the exposure-dose influence the biological response.

Expression of MIP-2 and IL-6 genes was significantly upregulated as early as 6 h post-ROFA-exposure in rat tracheal epithelial cells, whereas gene expression of iNOS was maximally increased 24 h postexposure. V but not Ni appeared to be mediating the effects of ROFA on gene expression. Treatment with dimethylthiourea inhibited both ROFA and V induced gene expression in a dose-dependent manner (Dye et al., 1999).

It appears that many biological responses are produced by PM whether it is composed of a single component or a complex mixture. A technical approach is to use the newly developed gene array to monitor the expressions of many mediator genes, which regulate complex and coordinated cellular events involved in tissue injury and repair, in a single assay. Using an array consisting of 27 rat genes representing inflammatory and anti-inflammatory cytokines, growth factors, adhesion molecules, stress proteins, transcription factors, and antioxidant enzymes, Nadadur et al. (2000) measured the expressions of these genes in rats intratracheally instilled with ROFA (3.3 mg/kg), $NiSO_4$ (1.3 μmol/kg), and VSO_4 (2.2 μmol/kg). Their data revealed a twofold induction of IL-6 and TIMP-1 at 24 h post-ROFA or Ni exposure. The expression of cellular fibronectin (cFn-EIIIA), ICAM-1, IL-1b, and iNOS gene also were increased 24 h post-ROFA, V, or Ni exposure. This study demonstrated that gene array may provide a tool for screening the expression profile of tissue specific markers following exposure to PM.

To investigate the interaction between respiratory cells and PM, Kobzik (1995) showed that scavenger receptors are responsible for AM binding of unopsonized PM and that different mechanisms mediate binding of carbonaceous dusts such as DPM. In addition, surfactant components can increase AM phagocytosis of environmental particulates in vitro, but only slightly relative to the already avid AM uptake of unopsonized particles (Stringer and Kobzik, 1996). Respiratory tract epithelial cells are also capable of binding with PM to secrete cytokine IL-8. Using a respiratory epithelial cell line (A549), Stringer et al. (1996) found that binding of particles to epithelial cells was calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was not calcium dependent. In addition, as observed in AMs, PM binding by A549 cells also was mediated by scavenger receptors, albeit those distinct from the heparin-insensitive acetylated-LDL receptor. Furthermore, α-quartz, but not TiO_2 or CAPs, caused a dose-dependent production of IL-8 (range 1 to 6 ng/mL), demonstrating a particle-specific spectrum of epithelial cell cytokine (IL-8) response.

8.5.3.3 Other Potential Cellular and Molecular Mechanisms

In addition to inducing cytokine mediated inflammation, PM also may affect the alveolar surfactant's ability to reduce both the tendency of alveoli to collapse at the end of expiration and the transudation of fluid from the capillaries to the airspace. Lee et al. (1999) exposed guinea pigs and rats to high concentrations of sulfuric acid aerosol (43 and 94 mg/m^3, 0.9 μm MMAD) and investigated the effects of this aerosol on the surface properties of reconstituted phospholipid using a captive bubble surfactometer. The acid exposure significantly increased the surface tension of guinea pig but not rat BAL. The most sensitive index of surfactant inhibition was found to be the maximum film compressibility of the compression isotherm. The index was 119 times greater for the acid exposed guinea pigs compared to control animals. These results were associated with an increase in protein and PMN in the BAL. Although unusually high concentrations of acid aerosols were used in this study, the results may explain the lack of response in the rat to acid aerosol exposures.

The potential mechanism involving in the alteration of surface tension may be related to changes in the expression of matrix metalloproteinases (MMPs), such as pulmonary matrilysin and gelatinase A and B, and tissue inhibitor of metalloproteinase (TIMP) (Su et al., 2000a,b). Sprague Dawley rats exposed to ROFA by intratracheal injection (2.5 mg/rat) had increased mRNA levels of matrilysin, gelatinase A, and TIMP-1. Gelatinase B, not expressed in control animals, was increased significantly from 6 to 24 h following ROFA exposure. Alveolar macrophages, epithelial cells, and inflammatory cells were major cellular sources for the pulmonary MMP expression. The expression of Gelatinase B in rats exposed to the same dose of ambient PM (<1.7 μm and 1.7 to 3.7 μm) collected from Washington, DC, was significantly increased as compared to saline control, whereas the expression of TIMP-2 was suppressed. Ambient PM between 3.7 and 20 μm also increased the Gelatinase B expression. Increases in MMPs, which degrade most of the extracellular matrix, suggest that ROFA and ambient PM can similarly increase the total pool of proteolytic activity to the lung and contribute in the pathogenesis of PM-induced lung injury.

Sensory nerves originating from trigeminal, nodos, and dorsal root ganglion neurons (DRGs) extend their terminals into the nasal and/or pulmonary epithelium. These nerve terminals together with sensory irritant receptors (capsaicin and acid sensitive receptors) found on the cell bodies can be triggered by irritants such as ambient PM or its components. The

activation of these receptors and nerve terminals can result in the release of inflammatory cytokines leading to airway disorders. Intracellular calcium levels increased immediately in BEAS-2B cells exposed to ROFA, which is followed by increased in IL-6, IL-8, and TNFα gene expressions (Veronesi et al., 1999). Furthermore, acidic media alone or soluble components of ROFA produced similar effects. These responses were reduced by pretreating cells with neuropeptide antagonists. However, treating cells with capsaicin antagonist, a pH receptor antagonist, or exposing cells to ROFA in Ca^{2+} free media inhibited both intracellular Ca^{2+} as well as cytokine release. Using synthetic polymer microspheres (SPMs) resembling ROFA particles in size (2 and 6 μm in diameter) and surface potential (zeta potential $\approx$29 mV) but lacking confounding factors such as metals or biologics, Oortgiesen et al. (2000) demonstrated that BEAS-2B and DRGs responded to both ROFA and charged SPMs with an increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) concentration and the release of IL-6, whereas neutral SPMs bound with polyethylene glycol (0 mV zeta potential) were relatively ineffective. In DRGs, the SPM-induced increases in $[Ca^{2+}]_i$ were correlated with the presence of acid- or capsaicin-sensitive pathways. By this pathway, soluble components of ROFA, which is acidic, and other acidic PM may initiate or exacerbate symptoms of airway inflammation. These data not only demonstrated that the surface chemistry of the particles determines whether cells are activated but also that direct contact of the particle with the target cells and their receptors is necessary for particles to evoke a response.

8.5.4 Specific Particle Size and Surface Area Effects

Most particles used in laboratory animal toxicology and occupational studies are greater than 0.1 μm in size. However, the enormous number and huge surface area of the ultrafine particles demonstrate the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5-μm diameter particle; particle surface area is also greatly increased (Table 8-9).

Many studies summarized in U.S. Environmental Protection Agency (1996a), as well as in this document, suggest that the surface of particles or substances that are released from the surface (e.g., transition metals) interact with the biological system, and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine

TABLE 8-9. NUMBERS AND SURFACE AREAS OF MONODISPERSE PARTICLES OF UNIT DENSITY OF DIFFERENT SIZES AT A MASS CONCENTRATION OF 10 $\mu g/m^3$

Particle Diameter (μm)	Particle Number (per cm^3 air)	Particle Surface Area (μm^2 per cm^3 air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24

Source: Oberdörster et al. (1995).

particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean high concentrations of transition metals being available to cause oxidative stress to cells.

Two groups have examined the toxic differences between fine and ultrafine particles, with the general finding that the ultrafine particles show a significantly greater response at similar mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). However, only a few studies have investigated the ability of ultrafine particles to generate a greater oxidative stress when compared to fine particles of the same material. Studies by Gilmour et al. (1996) have shown that at equal mass, ultrafine TiO_2 caused more plasmid DNA strand breaks than fine TiO_2. This effect could be inhibited with mannitol. Osier and Oberdörster (1997) compared the response of rats (F344) exposed by intratracheal inhalation to "fine" (approximately 250 nm) and "ultrafine" (approximately 21 nm) TiO_2 particles with rats exposed to similar doses by intratracheal instillation. Animals receiving particles through inhalation showed a smaller pulmonary response, measured by BAL parameters, in both severity and persistence, when compared with those animals receiving particles through instillation. These results demonstrate a difference in pulmonary response to an inhaled versus an instilled dose, which may result from differences in dose rate, particle distribution, or altered clearance between the two methods. Consistent with these in vivo studies, Finkelstein et al. (1997) has shown that exposing primary cultures of rat Type II cells to 10 μg/mL ultrafine TiO_2 (20 nm) causes increased TNF and IL-1 release

throughout the entire 48-h incubation period. In contrast, fine TiO_2 (200 nm) had no effect. In addition, ultrafine polystyrene carboxylate-modified microspheres (UFP, fluorospheres, molecular probes 44 ± 5 nm) have been shown induce a significant enhancement of both substance P and histamine release after administration of capsaicin (10^{-4} M), to stimulate C-fiber, and carbachol (10^{-4} M), a cholinergic agonist in rabbit intratracheally instilled with UFP (Nemmar et al., 1999). A significant increase in histamine release also was recorded in the UFP-instilled group following the administration of both Substance P (10^{-6} M) plus thiorpan (10^{-5} M) and compound 48/80 (C48/80, 10^{-3} M) to stimulate mast cells. BAL analysis showed an influx of PMN, an increase in total protein concentration, and an increase in lung wet weight/dry weight ratio. Electron microscopy showed that both epithelial and endothelial injuries were observed. The pretreatment of rabbits in vivo with a mixture of either SR 140333 and SR 48368, a tachykinin NK_1 and NK_2 receptor antagonist, or a mixture of terfenadine and cimetidine, a histamine H_1 and H_2 receptor antagonist, prevented UFP-induced PMN influx and increased protein and lung WW/DW ratio.

As discussed earlier, it is believed that ultrafine particles caused greater cellular injury because of the relatively large surface area for a given mass. However, in a study that compared the response to carbon black particles of two different sizes, Li et al. (1999) demonstrated that in the instillation model, a localized dose of particle over a certain level causes the particle mass to dominate the response, rather than the surface area. Ultrafine carbon black (ufCB, Printex 90), 14 nm in diameter, and fine carbon black (CB, Huber 990), 260 nm in diameter, were instilled intratracheally in rats and BAL profile at 6 h was assessed. At mass of 125 μg or below, ufCB generated a greater response (increase LDH, epithelial permeability, decrease in GSH, TNF, and NO productions) than fine CB at various time postexposure. However, higher dose of CB caused more PMN influx than the ufCB. In contrast to the effect of CB, which showed dose-related increasing inflammatory response, ufCB at the highest dose caused less of a neutrophil influx than at the lower dose. Moreover, when the PMN influx was expressed as a function of surface area, CB produced greater response than ufCB at all doses used in this study. Although particle insterstitialization with a consequent change in the chemotatic gradient for PMN was offered as an explanation, these results need further scrutinization.

Oberdörster et al. (2000) recently completed a series of studies in rats and mice using ultrafine particles of various chemical compositions (PTFE, TiO_2, C, Fe, Fe_2O_3, Pt, V, and V_2O_5).

In old rats sensitized with endotoxin and exposed to ozone plus ultrafine carbon particles, they found a ninefold greater release of reactive oxygen species in old rats than in similarly treated young rats. Exposure to ultrafine PM alone in sensitized old rats also caused an inflammatory response.

Although the exact mechanism of ultrafine-induced lung injury remains unclear, it is likely that ultrafine particles, because of their small size, can easily penetrate the airway epithelium and cause cellular damage. Using electron microscopy to examine rat tracheal explants treated with fine (0.12 μm) and ultrafine (0.021 μm) TiO_2 partilces for 3 or 7 days, Churg et al. (1998) found both size particles in the epithelium at both time points, but in the subepithelial tissues, they were found only at Day 7. The volume proportion (the volume of TiO_2 over the entire volume of epithelium or subepithelium area) of both fine and ultrafine particles in the epithelium increased from 3 to 7 days. It was greater for ultrafine at 3 days but was greater for fine at 7 days. The volume proportion of particles in the subepithelium at day 7 was equal for both particles, but the ratio of epithelial to subepithelial volume proportion was 2:1 for fine and 1:1 for ultrafine. Ultrafine particles persist in the tissue as relatively large aggregates, whereas the size of fine particle aggregates becomes smaller over time. Ultrafine particles appear to enter the epithelium faster and, once in the epithelium, a greater proportion of them is translocated to the subepithelial space compared to fine particles. However, if it is assumed that the volume proportion is representative of particle number, the number of particles reaching the interstitial space is directly proportional to the number applied (i.e., there is no preferential transport from lumen to interstitium by size). These data are in direct contrast to the results of instillation or inhalation of fine and ultrafine TIO_2 particles reported earlier (Ferin et al., 1990, 1992). Free of inflammatory cells, possibility of overloading of the explants with dust, and the use of liquid suspension for exposure were among the possible reasons cited for the observed effects.

Only two studies examined the influence of specific surface area on biological activity (Lison et al., 1997; Oettinger et al., 1999). The biological responses to various MnO_2 dusts with different specific surface area (0.16, 0.5, 17, and 62 m^2/g) were compared in vitro and in vivo (Lison et al., 1997). In both systems, the results show that the amplitude of the response is dependent on the total surface area that is in contact with the biological system, indicating that surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles with a specific surface area of 5 m^2/g also were examined in vitro. These particles exhibited an

enhanced cytotoxic activity, which was almost equivalent to that of particles with a specific surface area of 62 m^2/g, indicating that undefined reactive sites produced at the particle surface by mechanical cleavage also may contribute to the toxicity of insoluble particles. In another study, two types of carbon black particles, Printex 90 (P90, Degussa, Germany, formed by controlled combustion, consists of defined granules with specific surface area of 300 m^2/g and particle size of 14 nm) and FR 101 (Degussa, Germany, with specific surface area of 20 m^2/g and particle size of <95 nm, has a coarse structure, and the ability to adsorb polycyclic and other carbons) were used in the study (Oettinger et al., 1999). Exposure of AMs to 100 $\mu g/10^6$ cells of FR 101 and P90 resulted in a 1.4- and 2.1-fold increase in ROS release. These exposures also caused a fourfold up-regulation of NF-kB gene expression. These studies indicated that PM of single component with larger surface properties produce greater biological response than similar particles with smaller surface area. By exposing bovine AMs to metal oxide coated silica particles, Schluter et al. (1995) showed that most of the metal coatings (Li, Cr, Fe, Mn, Ni, Ph, and V) had no effect on ROS production by these cells. However, coating with CuO markedly lowered the O_2^- and H_2O_2, whereas V(IV) increases both ROI. This study demonstrated that, in addition to specific area, chemical composition of the particle surface also influence its cellular response.

8.5.5 Pathophysiological Mechanisms for the Effects of Low Concentrations of Particulate Air Pollution

The pathophysiological mechanisms involved in PM-associated cardiovascular and respiratory health effects still are not elucidated fully, but progress has been made since the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a) was prepared. This section summarizes current hypotheses and reviews the toxicological evidence for these potential pathophysiological mechanisms.

8.5.5.1 Direct Pulmonary Effects

When the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a) was written, the lung was thought to be the primary organ to affected by particulate air pollution. There is growing toxicological and epidemiological evidence that the cardiovascular system is affected as well. Nonetheless, understanding how particulate air pollution causes or exacerbates respiratory

disease remains an important goal. There is some toxicological evidence for the following three mechanisms for direct pulmonary effects.

Particulate Air Pollution Causes Lung Injury and Inflammation

In the last few years, numerous studies have shown that instilled and inhaled ROFA, a product of fossil fuel combustion, can cause substantial lung injury and inflammation. The toxic effects of ROFA are largely caused by its high content of soluble metals, and the pulmonary effects of ROFA can be reproduced by equivalent exposures to soluble metal salts. In contrast, controlled exposures of animals to sulfuric acid aerosols, acid coated carbon, and sulfate salts cause little lung injury or inflammation, even at high concentrations. Inhalation of concentrated ambient PM (which contains only small amounts of metals) by laboratory animals at concentrations in the range of 100 to 1000 $\mu g/m^3$ have been shown in some (but not all) studies to cause mild pulmonary injury and inflammation. Rats with SO_2-induced bronchitis and monocrotaline-treated rats have been reported to have a greater inflammatory response to concentrated ambient PM than normal rats. These studies suggest that exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

Particulate Air Pollution Causes Increased Susceptibility to Respiratory Infections

At this time there are no newly published studies on the effects of inhaled concentrated ambient PM on host susceptibility to infectious agents. Ohtsuka et al. (2000a,b) have shown that in vivo exposure of mice to acid-coated carbon particles at a mass concentration of 10,000 $\mu g/m^3$ causes decreased phagocytic activity of alveolar macrophages, even in the absence of lung injury.

Particulate Air Pollution Increases Airway Reactivity and Exacerbates Asthma

The strongest evidence supporting this hypothesis is from studies on diesel particulate matter (DPM). DPM has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 8.2.4.2). In vitro studies have suggested that the organic fraction of DPM is involved in the increased IgE production. ROFA leachate also has been shown to enhance antigen-specific airway reactivity in mice (Goldsmith et al., 1999) indicating that soluble metals can also enhance an allergic response. However, in this same study, exposure of mice to concentrated ambient PM did not affect antigen-specific airway reactivity. It is

premature to conclude from this one experiment that concentrated ambient PM does not exacerbate allergic airways disease because the chemical composition of the PM (as indicated by studies with DPM and ROFA) may be more important than the mass concentration.

8.5.5.2 Systemic Effects Secondary to Lung Injury

When the 1996 PM AQCD was written, it was thought that cardiovascular-related morbidity and mortality most likely would be secondary to impairment of oxygenation or some other consequence of lung injury and inflammation. Newly available toxicologic studies provide some additional evidence regarding such possibilities.

Lung Injury from Inhaled Particulate Matter Causes Impairment of Oxygenation and Increased Work of Breathing That Adversely Affects the Heart

Instillation of ROFA has been shown to cause a 50% mortality rate in monocrotaline-treated rats (Watkinson et al., 2000). Although blood oxygen levels were not measured in this study, there were ECG abnormalities consistent with severe hypoxemia in about half of the rats that subsequently died. Given the severe inflammatory effects of instilled ROFA and the fact that monocrotaline-treated rats have increased lung permeability as well as pulmonary hypertension, it is plausible that instilled ROFA can cause severe hypoxemia leading to death in this rat model. Results from studies in which animals (normal and compromised) were exposed to concentrated ambient PM (at concentrations many times higher than would be encountered in the United States) indicate that ambient PM is unlikely to cause severe disturbances in oxygenation or pulmonary function. However, even a modest decrease in oxygenation can have serious consequences in individuals with ischemic heart disease. Kleinman et al. (1998) has shown that a reduction in arterial blood saturation from 98 to 94% by either mild hypoxia or by exposure to 100 ppm CO significantly reduced the time to onset of angina in exercising volunteers. Thus, information is needed on the effects of PM on arterial blood gases and pulmonary function to fully address the above hypothesis.

Lung Inflammation and Cytokine Production Cause Adverse Systemic Hemodynamic Effects

It has been suggested that systemic effects of particulate air pollution may result from activation of cytokine production in the lung (Li et al., 1997). In support of this idea,

monocrotaline-treated rats exposed to inhaled ROFA (15,000 $\mu g/m^3$, 6 h/day for 3 days) showed increased pulmonary cytokine gene expression, bradycardia, hypothermia, and increased arrhythmias (Watkinson et al., 2000). However, spontaneously hypertensive rats had a similar cardiovascular response to inhaled ROFA (except that they also developed ST segment depression) with no increase in pulmonary cytokine gene expression. Studies in dogs exposed to concentrated ambient PM showed minimal pulmonary inflammation and no positive staining for IL-8, IL-1, or TNF in airway biopsies. However, there was a significant decrease in the time of onset of ischemic ECG changes following coronary artery occlusion in PM-exposed dogs compared to controls (Godleski et al., 2000). Thus, there is not a clear-cut link between changes in cardiovascular function and production of cytokines in the lung. Because human and animal exposure studies of ambient PM are using increasingly sophisticated and sensitive measures of cardiac function, basic information on the effects of mild pulmonary injury on these cardiac endpoints is needed to understand the mechanisms of how inhaled PM affects the heart.

Lung Inflammation from Inhaled Particulate Matter Causes Increased Blood Coagulability That Increases the Risk of Heart Attacks and Strokes

There is abundant evidence linking risk of heart attacks and strokes to small prothrombotic changes in the blood coagulation system. However, the published toxicological evidence that moderate lung inflammation causes increased blood coagulability is inconsistent. Ghio et al. (2000) have shown that inhalation of concentrated ambient PM in healthy nonsmokers causes increased levels of blood fibrinogen. Gardner et al. (2000) have shown that a high dose (8,300 $\mu g/kg$) of instilled ROFA in rats causes increased levels of fibrinogen, but no effect was seen at lower doses. Exposure of dogs to concentrated ambient PM had no effect on fibrinogen levels (Godleski et al., 2000). The coagulation system is as multifaceted and complex as the immune system, and there are many other sensitive and clinically significant parameters that should be examined in addition to fibrinogen. Thus, it is premature to draw any conclusions on the relationship between PM and blood coagulation.

Interaction of Particulate Matter with the Lung Affects Hematopoiesis

Terashima et al. (1997) found that instillation of fine carbon particles (20,000 μg/rabbit) stimulated release of PMNs from the bone marrow. In further support of this hypothesis, Gordon

and colleagues reported that the percentage of PMNs in the peripheral blood increased in rats exposed to ambient PM in some but not all exposures. On the other hand, Godleski et al. (2000) found no changes in peripheral blood counts of dogs exposed to concentrated ambient PM. Thus, direct evidence that PM ambient concentrations can affect hematopoiesis remains to be demonstrated.

8.5.5.3 Direct Effects on the Heart

Changes in heart rate, heart rate variability, and conductance associated with ambient PM exposure have been reported in animal studies (Godleski et al., 2000; Gordon et al., 2000; Watkinson et al., 2000), in several human panel studies (described in Chapter 6), and in a reanalysis of data from the MONICA study (Peters et al., 1997). Some of these studies included endpoints related to respiratory effects but few significant adverse respiratory changes were detected. This raises the possibility that ambient PM may have effects on the heart that are independent of adverse changes in the lung. There is certainly precedent for this idea. For example, tobacco smoke (which is a mixture of combustion-generated gases and PM) causes cardiovascular disease by mechanisms that are independent of its effect on the lung. Two types of hypothesized direct effects of PM on the heart are noted below.

Inhaled Particulate Matter Affects the Heart by Uptake of Particles into the Circulation or Release of a Soluble Substances into the Circulation.

Drugs can be rapidly and efficiently delivered to the systemic circulation by inhalation. This implies that the pulmonary vasculature absorbs inhaled materials, including charged substances such as small proteins and peptides. Cigarettes are a widely used method for delivering nicotine to the blood stream. It is likely that soluble materials absorbed onto airborne particles find their way into the blood stream, but it is not clear whether the particles themselves enter the blood. It is anticipated that more information will be available on this important question in the next few years.

Inhaled Particulate Matter Affects Autonomic Control of the Heart and Cardiovascular System

There is growing evidence for this idea as described above. This raises the question of how inhaled particles could affect the autonomic nervous system. Activation of neural receptors in

the lung is a logical area to investigate. Studies in conscious rats have shown that inhalation of wood smoke causes marked changes in sympathetic and parasympathetic input to the cardiovascular system that are mediated by neural reflexes (Nakamura and Hayashida, 1992). Although research on airway neural receptors and neural-mediated reflexes is a well established discipline, the cardiovascular effects of stimulating airway receptors continue to receive less attention than the pulmonary effects. Previous studies of airway reflex-mediated cardiac effects usually employed very high doses of chemical irritants, and the results may not be applicable to air pollutants. There is a need for basic physiological studies to examine effects on cardiovascular system when airway and alveolar neural receptors are stimulated in a manner relevant to air pollutants.

8.6 RESPONSES TO PARTICULATE MATTER AND GASEOUS POLLUTANT MIXTURES

Ambient PM itself is a mixture of particles of varying size and composition. The following discussion examines effects of mixtures of ambient PM, or PM surrogates, with gaseous pollutants. Ambient PM co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide. Toxicological interactions between PM and gaseous co-pollutants may be antagonistic, additive, or synergistic (Mauderly, 1993). The presence and nature of any interaction appears to depend on the size and concentration of pollutants in the mixture, exposure duration, and the endpoint being examined. It is not possible to predict a priori from the presence of certain pollutants whether any interaction will occur and, if there is interaction, whether it will be synergistic, additive, or antagonistic (Table 8-10).

Mechanisms responsible for the various forms of interaction are speculative. In terms of potential health effects, the greatest hazard from pollutant interaction is the possibility of synergy between particles and gases, especially if effects occur at concentrations at which no effects occur when individual constituents are inhaled. Various physical and chemical mechanisms may underlie synergism. For example, physical adsorption or absorption of some material on a particle could result in transport to more sensitive sites, or sites where this material would not normally be deposited in toxic amounts. This physical process may explain the interaction found

TABLE 8-10. RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and Particles	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Respiratory Effects of Inhaled Particles on Markers in Lavage Fluid	Reference
Rats, Fischer NNia, male, 22 to 24 mo old	Carbon, ammonium bisulfate, and O_3	Inhalation	50 $\mu g/m^3$ carbon + 70 $\mu g/m^3$ ammonium bisulfate + 0.2 ppm O_3 or 100 $\mu g/m^3$ carbon +140 $\mu g/m^3$ ammonium bisulfate + 0.2 ppm O_3	0.4 μm MMAD δg = 2.0	4 h/day, 3 days/week for 4 weeks	No changes in protein concentration in lavage fluid or in prolyl 4-hydroxylase activity in blood. Slight, but statistically significant decreases in plasma fibronectin in animals exposed to the combined atmospheres compared to animals exposed to O_3 alone.	Bolarin et al. (1997)
Rats	O_3 and Ottawa urban dust	Inhalation	40,000 $\mu g/m^3$ and 0.8 ppm O_3	4.5 μm MMAD	Single 4-h exposure followed by 20 h clean air	CO-exposure to particles potentiated O_3-induced septal cellurity. Enhanced septal thickening associated with elevated production of macrophage inflammatory protein-2 and endothelin 1 by lung lavage cells.	Bouthillier et al. (1998)
Lambs	Ambient NOx, SO_2, CO, and PM	Natural 24-h exposure in urban and rural areas			3 mo	Irritation characterized by mucus hypersecretion and morphological changes in the epithelium in the nasopharyngeal mucosa in lambs exposed in urban area.	Gulisano et al. (1997)
Mice, Swiss, female, 5 weeks old	SO_2 and carbon	Inhalation, flow-past, nose-only	10,000 $\mu g/m^3$ carbon with or without 5 to 20 ppm SO_2 at 10% or 85% RH	0.3 μm MMAD δg = 2.7	Single 4-h exposure	Macrophage phagocytosis was depressed only in animals exposed to the combination of SO_2 and carbon at 85% humidity. This inhibition in macrophage function lasted at least 7 days after exposure.	Jakab et al. (1996)
Rats, S-D, male, 250-300 g	H_2SO_4 and O_3	Inhalation, nose-only	500 $\mu g/m^3$ H_2SO_4 aerosol (two different particle sizes), with or without 0.6 ppm O_3	Fine (0.3 μm MMD, δg = 1.7) and ultrafine (0.06 μm, δg = 1.4)	4 h/day for 2 days	The volume percentage of injured alveolar septae was increased only in the combined ultrafine acid/O_3 animals. BrdU labeling in the periacinar region was increased in a synergistic manner in the combined fine acid/O_3 animals.	Kimmel et al. (1997)
S-D rats 300 g	O_3 and H_2SO_4-coated carbon	Inhalation nose-only	0.2 ppm O_3 + 50 $\mu g/m^3$ C + 100 $\mu g/m^3$ H_2SO_4 0.4 ppm O_3 +250 $\mu g/m^3$ C +500 $\mu g/m^3$ H_2SO_4	0.26 μm δg = 2.2	4 h/day for 1 day or 5 days	No airway inflammation at low dose. Greater inflammatory response at high dose; greater response at 5 days than 1 day. Contrasts with O_3 alone where inflammation was greatest at 0.40 ppm on Day 1.	Kleinman et al. (1999)

TABLE 8-10 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and Particles	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration	Respiratory Effects of Inhaled Particles on Markers in Lavage Fluid	Reference
Rats	H_2SO_4 and O_3	Inhalation, whole body	20 to 150 $\mu g/m^3$ H_2SO_4 and 0.12 or 0.2 ppm O_3	0.4 to 0.8 μm	Intermittent (12 h/day) or continuous exposure for up to 90 days	No interactive effect of H_2SO_4 and O_3 on biochemical and morphometric endpoints.	Last and Pinkerton (1997)
Healthy and asthmatic children	H_2SO_4, SO_2, and O_3	Inhalation	60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3	0.6 μm H_2SO_4	Single 4-h exposure with intermittent exercise	A positive association between acid concentration and symptoms, but not spirometry, in asthmatic children. No changes in healthy children.	Linn et al. (1997)
Pigeons (Columba livia)	Ambient gases and particles	Natural 24-h exposure in urban and rural areas			Continuous ambient exposure	Increased number of AMs and decreased number of lamellar bodies in type II epithelial cells in urban pigeons.	Lorz and López (1997)
Canine	Ambient gases and particles	Natural 24-h exposure in four urban areas of Mexico City and one rural area			Continuous ambient exposure	No significant differences in AMs or total cell counts in lavage from dogs studied among the five regions. A significant increase in lavage fluid neutrophils and lymphocytes in the southwest region, where the highest O_3 levels were recorded, compared to the two industrial regions with the highest PM levels.	Vanda et al. (1998)
Rats	O_3 and resuspended urban PM	Inhalation, whole-body	0.8 ppm O_3 and 5,000 or 50,000 $\mu g/m^3$ PM		Single 4-h exposure	PM alone caused no change in cell proliferation in bronchioles or parenchyma. Co-exposure with O_3 greatly potentiated the proliferative changes induced by O_3 alone. These changes were greatest in the epithelium of the terminal bronchioles and alveolar ducts.	Vincent et al. (1997)

in studies of mixtures of carbon black and formaldehyde or of carbon black and acrolein (Jakab, 1992, 1993).

Chemical interactions between particles and gases can occur on particle surfaces, thus, forming secondary products that may be more active toxicologically than the primary materials and that can then be carried to a sensitive site. The hypothesis of such chemical interactions has been examined in the gas and particle exposure studies by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992) and Jakab and colleagues (Jakab and Hemenway, 1993; Jakab et al., 1996). These investigators have demonstrated that synergism occurs as secondary chemical species are produced, especially under conditions of increased temperature and relative humidity.

Another potential mechanism of gas-particle interaction may involve a pollutant-induced change in the local microenvironment of the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) suggested that the observed synergism between ozone and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of ozone by producing a change in the reactivity or residence time of reactants, such as radicals, involved in ozone-induced tissue injury.

As noted in U.S. Environmental Protection Agency (1996a), the toxicology database for mixtures containing PM other than acid sulfates is still quite sparse. Vincent et al. (1997) exposed rats to 0.8 ppm ozone in combination with 5 or 50 mg/m^3 of resuspended urban particles for 4 h. Although PM alone caused no change in cell proliferation (^{3}H-thymidine labeling), co-exposure to either concentration of resuspended PM with ozone greatly potentiated the proliferative effects of exposure to ozone alone. These interactive changes occurred in epithelial cells of the terminal bronchioles and the alveolar ducts. These findings using resuspended dusts, although at high concentrations, are consistent with studies demonstrating interaction between sulfuric acid (H_2SO_4) aerosols and ozone. Kimmel and colleagues (1997) examined the effect of acute co-exposure to ozone and fine or ultrafine H_2SO_4 aerosols on rat lung morphology. They determined morphometrically that alveolar septal volume was increased in animals co-exposed to ozone and ultrafine, but not fine, H_2SO_4. Interestingly, cell labeling, an index of proliferative cell changes, was increased only in animals co-exposed to fine H_2SO_4 and ozone, as compared to animals exposed to ozone alone. Importantly, Last and Pinkerton (1997) extended their previous work and found that subchronic exposure to acid aerosols (20 to 150 μg/m^3 H_2SO_4) had no

interactive effect on the biochemical and morphometric changes produced by either intermittent or continuous ozone exposure (0.12 to 0.2 ppm). Thus, the interactive effects of ozone and acid aerosol co-exposure in the lung disappeared during the long-term exposure.

Kleinman et al. (1999) examined the effects of ozone plus fine, H_2SO_4-coated, carbon particles (MMAD = 0.26 μm) for 1 or 5 days. They found the inflammatory response with the ozone-particle mixture was greater after 5 days (4 h/day) than after Day 1. This contrasted with ozone exposure alone (0.4 ppm), which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure.

Studies have examined interaction between carbon particles and gaseous co-pollutants. Jakab et al. (1996) challenged mice with a single 4-h exposure to a high concentration of carbon (10 mg/m^3) in the presence of SO_2 at low and high relative humidities. Macrophage phagocytosis was depressed significantly only in mice exposed to the combined pollutants under high relative humidity conditions. This study demonstrates that fine carbon particles can serve as an effective carrier for acidic sulfates where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days postexposure. Bolarin et al. (1997) exposed rats to only 50 or 100 μg/m^3 carbon particles in combination with ammonium bisulfate and ozone. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus ozone alone. Thus as, previously noted, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors, including the gaseous co-pollutant, concentration, and time.

In a complex series of exposures, Oberdörster and colleagues examined the interaction of ultrafine carbon particles (100 μg/m^3) and ozone (1 ppm) in young and old Fischer 344 rats that were pretreated with aerosolized endotoxin (Elder et al., 2000). In old rats, exposure to carbon and ozone produced an interaction that resulted in a greater influx in neutrophils than that produced by either agent alone. This interaction was not seen in young rats. Oxidant release from lavage fluid cells was also assessed and the combination of endotoxin, carbon particles, and ozone produced an increase in oxidant release in old rats. This combination produced the opposite response in the cells recovered from the lungs of the young rats, indicating that the

lungs of the aged animals underwent greater oxidative stress in response to this complex pollutant mix of particles, ozone, and a biogenic agent.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm ozone in healthy and asthmatic children. The children performed intermittent exercise during the 4-h exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children, and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to ozone exposure (Linn et al., 1994; Frampton et al., 1995); the timing and sequence of the exposures may be important.

Three unique animal field studies have examined the adverse respiratory effects of complex mixtures in urban and rural environments. These studies have taken advantage of the differences in pollutant makeup of urban and rural environments and studied animals under natural, continuous exposure conditions. Gulisano et al. (1997) examined the morphologic changes produced by continuous ambient exposure to air pollutants in lambs raised for 3 mo in rural (n = 2) or urban (n = 10) environments. Compared to the lungs of the rural lambs, irritation, as characterized by mucus hypersecretion and morphological changes in the epithelial cells lining the nasopharyngeal region, was present in the lambs exposed to urban air pollution. Lorz and López (1997) performed a similar study using pigeons as the test animal. They observed an increase in the number of AMs and a decrease in the number of lamellar bodies in Type II epithelial cells in the lungs of urban pigeons. Extrapolation of these studies is hampered by an incomplete characterization of the exposure atmospheres. A more thorough examination of the ambient level of pollutants was performed in the study by Vanda et al. (1998), who studied the effect of pollutant exposure in dogs raised in four urban regions of Mexico City and one nearby rural area. They found no significant differences in AM number or total cell counts in lavage fluid from the dogs among the five regions. A significant increase in lavage fluid neutrophils and

lymphocytes was found in dogs from the urban region with the highest ozone levels in comparison to the regions with the highest PM levels. Thus, the effect of ozone on cellular parameters in lavage fluid appeared to be greater than that for PM. In summary, each of these three animal field studies provides evidence that urban air pollutants can produce greater lung changes than would occur from exposure to rural pollution. However, extrapolation of these results is severely hampered by the uncontrolled exposure conditions, small sample size, behavior patterns, and nutritional factors. Thus, in these field studies, it is difficult to assign a role to PM in the observed adverse pulmonary effects.

8.7 SUMMARY

8.7.1 Biological Plausibility

Toxicological studies can play an integral role in answering the following two key questions regarding biological plausibility of PM health effects.

(1) What component (or components) of ambient PM cause health effects?

(2) Are the statistical associations between PM and health effects biologically plausible?

This summary focuses on the progress that toxicological studies have made towards answering these questions.

8.7.1.1 Link Between Specific Particulate Matter Components and Health Effects

Key to the validity of the biological plausibility is the need to identify the components of airborne PM responsible for the adverse effects and the individuals at risk. The plausibility of the association between PM and increases in morbidity and mortality has been questioned because the adverse cardiopulmonary effects have been observed at very low PM concentrations, often below the current NAAQS for PM_{10}. To date, toxicology studies on PM have provided only very limited evidence for specific PM components being responsible for observed cardiopulmonary effects of ambient PM. Studies have shown that some components of particles are more toxic than others. For example, high concentrations of ROFA and associated soluble metals have produced clinically significant effects (including death) in compromised animals. The relevance of these findings to understanding the adverse effects of PM components is

tempered, however, by the large difference between metal concentrations delivered to the test animals and metal concentrations present in the ambient urban environment. Such comparisons must be applied to the interpretation of all studies that examine the individual components of ambient urban PM. A summary of potential contributions of individual physical/chemical factors of particles to cardiopulmonary effects is given below.

Acid Aerosols

There is relatively little new information on the effects of acid aerosols, and the conclusions of the 1996 PM AQCD are unchanged. It was previously concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects, but asthmatics may develop small changes in pulmonary function. This conclusion is supported by the recent study of Linn and colleagues (1997) in which children (26 children with allergy or asthma and 15 healthy children) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 h. There were no significant effects on symptoms or pulmonary function when data from the entire group was analyzed, but the allergy group had a significant increase in symptoms after the acid aerosol exposure.

Although pulmonary effects of acid aerosols have been the subject of extensive research in past decades, the cardiovascular effects of acid aerosols have received little attention. Zhang et al. (1997) reported that inhalation of acetic acid fumes caused reflex mediated increases in blood pressure in normal and spontaneously hypertensive rats. Thus, acid components should not be ruled out totally as possible mediators of PM health effects. In particular, the cardiovascular effects of acid aerosols at realistic concentrations need further investigation.

Metals

The previous PM AQCD (U.S. Environmental Protection Agency, 1996a) mainly relied on data related to occupational exposures to evaluate the potential toxicity of metals in particulate air pollution. Since that time, in vivo and in vitro studies using ROFA or soluble transition metals have contributed substantial new information on the health effects of particle-associated soluble metals. Although there are some uncertainties about differential effects of one transition metal versus another, water soluble metals leached from ROFA have been shown consistently (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro and in vivo.

Even though it is clear that combustion particles that have a high content of soluble metals can cause lung injury and even death in compromised animals, it has not been established that the small quantities of metals associated with ambient PM are sufficient to cause health effects. Moreover, it cannot be assumed that metals are the primary toxic component of ambient PM. In studies in which various ambient and emission source particulates were instilled into rats, the soluble metal content did appear to be the primary determinant of lung injury (Costa and Dreher, 1997). However, one published study has compared the effects of inhaled ROFA (at 1 mg/m^3) to concentrated ambient PM (four experiments, at mean concentrations of 475 to 900 $\mu g/m^3$) in normal and SO_2- induced bronchitic rats. A statistically significant increase in at least one lung injury marker was seen in bronchitic rats with only one out of four of the concentrated ambient exposures, whereas inhaled ROFA had no effect even though the content of soluble iron, vanadium, and nickel was much higher in the ROFA sample than in the concentrated ambient PM. Although the role of metals in contributing to health effects of ambient PM is not established, the recent studies based on ROFA have important implications.

Ultrafine Particles

When this subject was reviewed in the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a), it was not known whether the pulmonary toxicity of freshly generated ultrafine teflon particles was due to particle size or a result of absorbed fumes. Subsequent studies with other types of ultrafine particles have shown that the chemical constituents of ultrafines substantially modulate their toxicity. For example, Kuschner et al. (1997) have established that inhalation of MgO particles produces far fewer respiratory effects than does ZnO. Also, inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge (100 $\mu g/m^3$ for 6 h) caused minimal lung inflammation (Elder et al., 2000), compared to ultrafine Teflon or metal particles. On the other hand, instillation of 125 μg of ultrafine carbon black (20 nm) caused substantially more inflammation than did the same dose of fine particles of carbon black (200 to 250 nm), suggesting that ultrafine particles may cause more inflammation than larger particles (Li et al., 1997). However, the chemical constituents of the two sizes of carbon black used in this study were not analyzed, and it cannot be assumed that the chemical composition was the same for the two sizes. Thus, there is still insufficient toxicological evidence to conclude that ambient concentrations of ultrafine particles contribute to the health

effects of particulate air pollution. However, with acid aerosols, studies of ultrafine particles have focused largely on effects in the lung, and it is possible that inhaled ultrafine particles may have systemic effects that are independent of effects on the lung.

Bioaerosols

Recent studies support the conclusion of the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a), which stated that bioaerosols, at concentrations present in the ambient environment, would not account for the reported health effects of ambient PM. Dose-response studies in healthy volunteers exposed to 0.55 and 50 μg endotoxin, by the inhalation route, showed a threshold for pulmonary and systemic effects for endotoxin between 0.5 and 5.0 μg (Michel et al., 1997). Monn and Becker (1999) examined effects of size fractionated outdoor PM on human monocytes and found cytokine induction characteristic of endotoxin activity in the coarse-size fraction but not in the fine fraction. Available information suggests that ambient concentrations of endotoxin are very low and do not exceed 0.5 ng/m^3.

Diesel Exhaust Particles

As described in Section 8.2.4.2, there is growing toxicological evidence that diesel PM exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has been linked to eosinophil degranulation and induction of cytokine production, suggesting that the organic constituents of diesel PM is responsible part for the immune effects. It is not known whether the adjuvant-like activity of diesel PM is unique or whether other combustion particles have similar effects. It is important to compare the immune effects of other source-specific emissions, as well as concentrated ambient PM, to diesel PM to determine the extent to which exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and asthma.

Organic Compounds

Published research on the acute effects of particle-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles. Like metals, organics are common constituents of combustion-generated particles and have been found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial

portion of the mass of ambient PM (10 to 60% of the total dry mass [Turpin, 1999]). The organic fraction of ambient PM has been evaluated for its mutagenic effects. Although the organic fraction of ambient PM is a poorly characterized heterogeneous mixture of an unknown number of different compounds, strategies have been proposed for examining the health effects of this potentially important constituent (Turpin, 1999).

Ambient Particle Studies

Ambient particle studies should be the most relevant in understanding the susceptibility of individuals to PM and the underlying mechanisms. Studies have used collected urban PM for intratracheal administration to healthy and compromised animals. Despite the difficulties in extrapolating from the bolus delivery used in such studies, they have provided strong evidence that the chemical composition of ambient particles has a major influence on toxicity. More recent work with inhaled concentrated ambient PM has observed cardiopulmonary changes in rodents and dogs at high concentrations of fine PM. No comparative studies to examine the effects of ultrafine and coarse ambient PM have been done, although a new ambient particle concentrator developed by Sioutas and colleagues should permit the direct toxicological comparison of various ambient particle sizes. Importantly, it has become evident that, although the concentrated ambient PM studies can provide important dose-response information, identify susceptibility factors in animal models, and permit examination of mechanisms related to PM toxicity, they are not particularly well suited, however, for the identification of toxic components in urban PM. Because only a limited number of exposures using concentrated ambient PM can be reasonably conducted by a given laboratory in a particular urban environment, there may be insufficient information to conduct a factor analysis on an exposure/response matrix. This may also hinder principal component analysis techniques that are useful in identifying particle components responsible for adverse outcomes.

8.7.1.2 Susceptibility

Progress has been made in understanding the role of individual susceptibility to ambient PM effects. Studies have consistently shown that animals with compromised health, either genetic or induced, are more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models has created problems. Moreover, because PM

seems to affect broad categories of disease states, ranging from cardiac arrhythmias to pulmonary infection, it can be difficult to know what disease models to use in understanding the biological plausibility of the adverse health effects of PM. Thus, the identification of susceptible animal models has been somewhat slow, but overall it represents solid progress when one considers that data from millions of people are necessary in epidemiology studies to develop the statistical power to detect small increases in PM-related morbidity and mortality.

8.7.2 Mechanisms of Action

The mechanisms that underlie the biological responses to ambient PM are not clear. Various toxicologic studies using particulate matter having diverse physicochemical characteristics have shown that these characteristics have a great impact on the specific response that is observed. Thus, there may, in fact, be multiple biological mechanisms that may be responsible for observed morbidity/mortality because of exposure to ambient PM, and these mechanisms may be highly dependent on the type of particle in the exposure atmosphere. However, it should be noted that many controlled exposure studies used particle concentrations much higher than those typically occurring in ambient air. Thus, some of the mechanisms elicited may not occur with exposure to lower levels. Clearly, controlled exposure studies have not as yet been able to unequivocally determine the particle characteristics and the toxicological mechanisms by which ambient PM may affect biological systems.

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CHAPTER 9. INTEGRATIVE SYNTHESIS: PARTICULATE MATTER ATMOSPHERIC SCIENCE, AIR QUALITY, HUMAN EXPOSURE, DOSIMETRY, AND HEALTH RISKS

9.1 INTRODUCTION

This chapter focuses on integration of key information on exposure-dose-response risk assessment components drawn from the preceding detailed chapters, to provide a coherent framework for assessment of human health risks posed by ambient particulate matter (PM) in the United States. As such, the chapter updates the integrated assessment provided in the 1996 Particulate Matter Air Quality Criteria Document (1996 PM AQCD; U.S. Environmental Protection Agency, 1996) of available scientific information regarding ambient PM sources, exposures, and health risks as they pertain to the United States. This assessment must be considered provisional at this time, pending public comment and Clean Air Scientific Advisory Committee (CASAC) review of other earlier, more detailed chapters from which key findings were extracted for discussion and preliminary integration here. More complete integration and conclusions will be incorporated in chapter revisions to be made subsequent to the CASAC review.

This chapter first provides background information on key features of atmospheric particles, highlighting important distinctions between fine- and coarse-mode particles with regard to their size, chemical composition, sources, atmospheric behavior, and potential human exposure relationships—distinctions that collectively continue to suggest that fine- and coarse-mode particles should be treated as two distinct subclasses of air pollutants. Information on recent trends in U.S. concentrations of different ambient PM size and composition fractions (e.g., PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) and ranges of variability seen in U.S. regions and urban air sheds also is summarized to place the ensuing health effects discussions in perspective.

The chapter next summarizes key points regarding respiratory tract dosimetry, followed by discussion of the extensive PM epidemiologic database that has expanded greatly during recent years. The latter includes numerous new studies of populations throughout the world published

since the 1996 PM AQCD that contain further evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM found in contemporary U.S. urban air sheds. Evaluations of other possible explanations for the reported PM epidemiology results (e.g., effects of weather, other co-pollutants, choice of models, etc.) also are discussed, ultimately leading to the conclusion that the reported associations of PM exposure and effects are valid. The newer evidence is then discussed that (a) further substantiates associations of such serious health effects with U.S. ambient PM_{10} levels, (b) also more strongly establishes fine particles (as indexed by various indicators, e.g., $PM_{2.5}$) as likely being important contributors to the observed human health effects, and (c) now provides additional information on associations between coarse-fraction ($PM_{10-2.5}$) particles and adverse health impacts. The overall coherence of the newer epidemiologic database also is discussed, which strengthens the 1996 PM AQCD evaluation suggesting a likely causal role of ambient PM in contributing to the reported effects.

The nature of the observed effects and the biological mechanisms that might underlie such effects then are discussed. The discussion of potential mechanisms of injury examines ways in which PM could induce health effects. The increased, but still limited, availability of new experimental evidence necessary to evaluate or directly substantiate the viability of hypothesized mechanisms is noted. Information concerning possible contributions of particular classes of specific ambient PM constituents also is summarized.

The chapter also provides information on the identification of population groups at special risk for ambient PM effects and factors placing them at increased risk, which need to be considered in generating risk estimates for the possible occurrence of PM-related health events in the United States.

9.2 ATMOSPHERIC SCIENCE CONSIDERATIONS

As discussed in Chapter 2 of this document, airborne PM is not a single pollutant but many classes of pollutants; each class consists of several to many individual chemical species. One classification is based on the natural division of the atmospheric aerosol into fine- and coarse-mode particles. Fine-mode particles, in general, are smaller than coarse-mode particles; they also differ in many other aspects such as formation mechanisms, chemical composition, sources,

physical behavior, human exposure relationships, and control approaches required for risk reduction. Such differences alone are sufficient to justify consideration of fine- and coarse-mode particles as separate pollutants, regardless of the extent or lack of evidence regarding differences in respiratory tract dosimetry or associated health effects in laboratory animals or humans. The various physical and chemical differences between fine- and coarse-mode particles, their sources, ambient concentrations, factors affecting human exposure, and their respiratory tract deposition are summarized concisely below as a prelude to discussion of key health effects associated with ambient PM exposures and other information useful in assessing PM-related public health risks in the United States.

Atmospheric particles originate from a variety of sources and possess a range of morphological, chemical, physical, and thermodynamic properties. The composition and behavior of airborne particles are linked with those of surrounding gases. Aerosol may be defined as a suspension of solid or liquid particles in air and includes both the particles and all vapor or gas phase components of air. However, the term aerosol often is used, as is PM, to refer to the suspended particles only. A complete description of the atmospheric aerosol would include an accounting of the size, morphology, and chemical composition of each particle and the relative abundance of each particle type as a function of particle size.

9.2.1 Ambient Particulate Matter Size Distinctions

Atmospheric particles differ in density and are not always spherical. Therefore, their diameters often are described by an "equivalent" diameter. The aerodynamic equivalent diameter (AED), defined as the diameter of a spherical particle with a density of 1 g/cm^3 that would have a settling velocity equal to the particle in question, is important for particle transport, collection, and respiratory tract deposition.

The distribution of particles with respect to size is an important physical parameter governing their behavior. Because atmospheric particles cover several orders of magnitude in particle size, size distributions often are expressed in terms of the logarithm of the particle diameter (D), on the X-axis, and the differential concentration on the Y-axis. If the differential concentration is plotted on a linear scale, the surface, volume, mass, or number of particles between D and $D + \Delta D$ is proportional to the area under the curve. Atmospheric aerosol size distributions frequently are approximated by a sum of log-normal distributions.

The aerosol community uses various approaches or conventions in the classification of particles by size, including modes, based on the observed size distributions in the atmosphere and formation mechanisms and cut point, usually based on the 50% cut point of the specific sampling device i.e., the particle size at which 50% of the particles enter and 50% of the particles are excluded, as summarized below.

Atmospheric size distributions show that most atmospheric particles are quite small, below 0.1 μm, whereas most of the particle volume (and therefore most of the mass) and much of the surface area is found in particles greater than 0.1 μm. The surface area peaks around ca. 0.2 μm. An important feature of the mass or volume size distributions of atmospheric aerosols is their multimodal nature. Volume-size distributions, measured in ambient air in the United States, almost always are found to be bimodal, with a minimum between 1.0 and 3.0 μm (see Figure 9-1). The distribution of particles that are mostly larger than the minimum is termed the coarse mode, whereas the distribution of particles that are mostly smaller than the minimum is termed the fine mode. In the ambient atmosphere, fine-mode particles include both the nuclei mode and the accumulation mode. The nuclei mode, that portion of the fine-particle fraction with diameters below about 0.1 μm, can be observed as a separate mode in mass or volume distributions only in clean or remote areas or near sources of new particle formation by nucleation. Accumulation-mode particles are that portion of the fine-particle fraction with diameters above about 0.1 μm. Toxicologists use the term “ultrafine” to refer to particles in the nuclei-mode size range. Aerosol physicists and material scientists tend to use “nanoparticles” to refer to particles in this size range generated in the laboratory.

Another set of definitions of particle size fractions arises from considerations related to size-selective sampling (see Figure 9-2). Size-selective sampling refers to the collection of particles below or within a specified aerodynamic size range, usually defined by the upper 50% cut point size, and has arisen in an effort to measure particle size fractions with some special significance (e.g., health, visibility, source apportionment). Dichotomous samplers split the particles into smaller and larger fractions, which may be collected on separate filters. However, a fraction ($\approx$10%) of the fine particles are collected with the coarse particle fraction. Cascade impactors use multiple size cuts to obtain a distribution of size cuts for mass or chemical composition measurements.

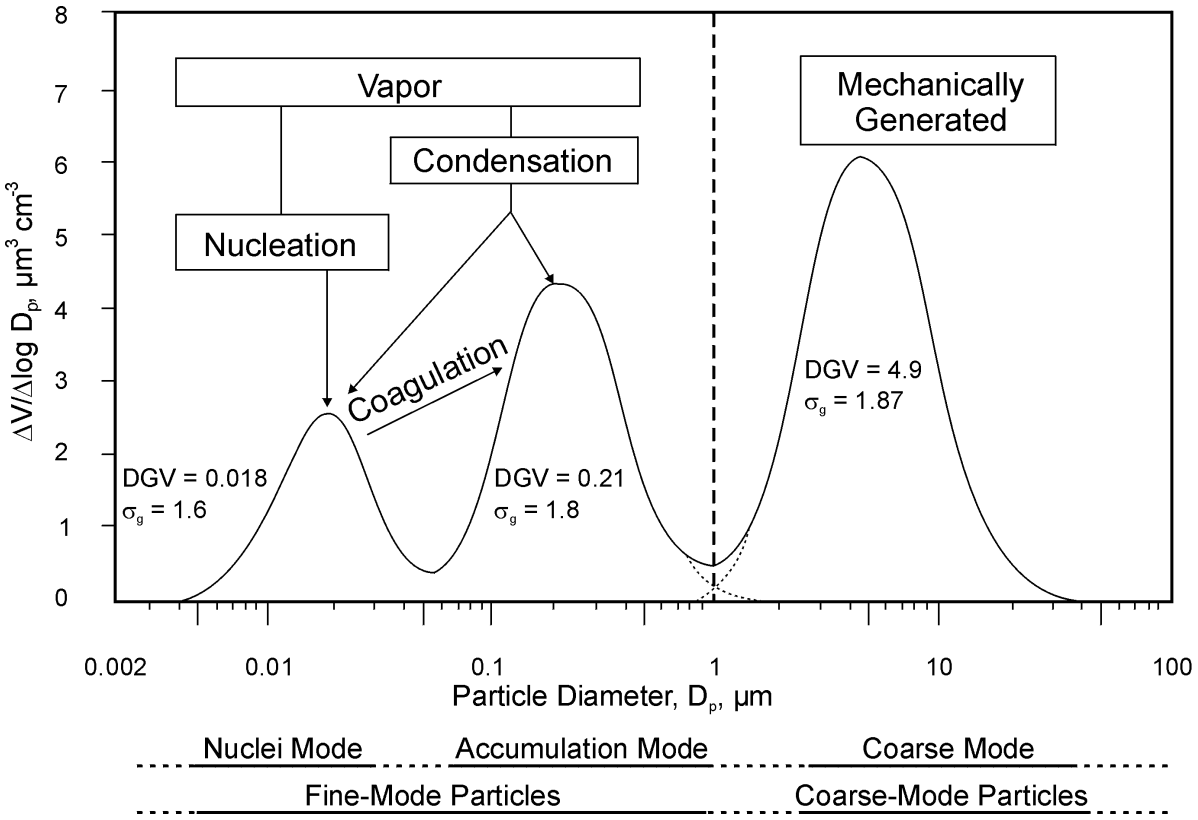

Figure 9-1. Volume-size distribution, measured in traffic, showing fine- and coarse-mode particles and the nuclei and accumulation modes within the fine-particle mode. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and σ_g (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, coagulation).

Source: Adapted from Wilson and Suh (1997).

Prior to 1987, the indicator for the National Ambient Air Quality Standards (NAAQS) for PM was total suspended particulate matter (TSP). TSP is defined by the design of the High Volume Sampler (hivol), which collects all of the fine particles but only part of the coarse particles. The upper cut off size of the hivol depends on the wind speed and direction and may vary from 25 to 40 μm. In 1987, the NAAQS for PM were revised to use PM_{10}, rather than TSP, as the indicator for the PM NAAQS (Federal Register, 1987). The use of PM_{10} as an indicator is an example of size-selective sampling. The selection of PM_{10} as an indicator was based on

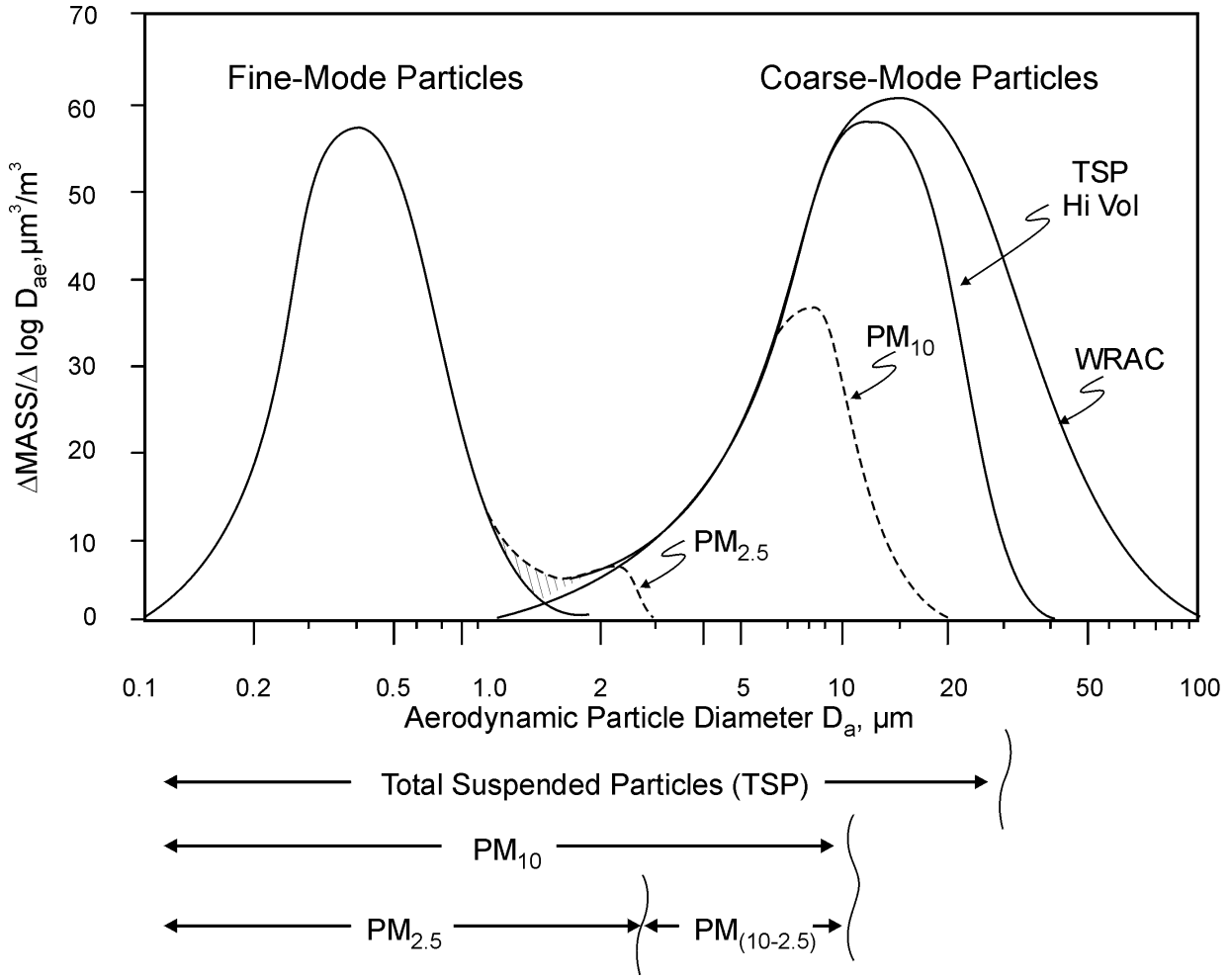

Figure 9-2. An idealized distribution of ambient particulate matter showing fine- and coarse-mode particles and the fractions collected by size-selective samplers. WRAC is the Wide Range Aerosol Classifier, which collects the entire coarse mode (Lundgren and Burton, 1995).

Source: Adapted from Wilson and Suh (1997).

dosimetric considerations and was intended to focus regulatory concern on those particles small enough to enter the thoracic region of the human respiratory tract. The $PM_{2.5}$ indicator promulgated by U. S. Environmental Protection Agency (EPA) in 1997 is also an example of size-selective sampling.

An idealized distribution showing the typically observed division of ambient aerosols into fine- and coarse-mode particles and size fractions collected by the WRAC, TSP, PM_{10}, $PM_{2.5}$, and

$PM_{(10-2.5)}$ samplers, is shown in Figure 9-2. PM_{10} samplers, as defined in Appendix J to 40 Code of Federal Regulations (CFR) Part 50 (Code of Federal Regulations, 1991a; Federal Register, 1987), collect all of the fine particles and part of the coarse particles. The upper cut point is defined as having a 50% collection efficiency at 10 ± 0.5 μm AED. The slope of the collection efficiency curve is defined in amendments to 40 CFR, Part 53, (Code of Federal Regulations, 1991b).

Over the years, the terms "fine" and "coarse", as applied to particle sizes, have lost the original precise meaning of fine and coarse mode. In any given article, therefore, the meaning of fine and coarse, unless defined, must be inferred from the author's usage. In particular, $PM_{2.5}$ and fine-mode particles are not equivalent. In this chapter and document, the term "mode" is used with fine and coarse when it is desired to specify the distribution of fine- or coarse-mode particles as shown in Figures 9-1 and 9-2.

9.2.2 Fine- and Coarse-Mode Particle Distinctions vis-a-vis Sources, Formation Mechanisms, and Atmospheric Behavior

Table 9-1 summarizes important physical and chemical properties, sources, and atmospheric behavior that distinguish between nuclei-mode (ultrafine) and accumulation-mode components of fine particles, as well as coarse-mode particles.

Several processes influence the formation and growth of particles. New particles may be formed by nucleation from gas-phase material. Particles may grow by condensation as gas-phase material condenses onto existing particles. Particles also may grow by coagulation as two particles combine to form one. Gas-phase material condenses preferentially on smaller particles and the rate constant for coagulation of two particles decreases as the particle size increases. Therefore, nuclei-mode particles grow into the accumulation mode, but accumulation mode particles do not grow into the coarse mode under normal atmospheric conditions.

As discussed in Chapter 2 of this document, the major constituents of atmospheric PM are sulfate, nitrate, ammonium, and hydrogen ions; particle-bound water; elemental carbon; a great variety of organic compounds; and crustal material. Atmospheric PM contains a large number of elements in various compounds and concentrations and hundreds to thousands of specific organic compounds. Particulate matter can be primary or secondary. Particulate matter is called primary if it is in the same chemical form in which it was emitted into the atmosphere. Particulate matter

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

	Fine		
	Nuclei	Accumulation	Coarse
Formed from:	Combustion, high-temperature processes, and atmospheric reactions		Break-up of large solids/droplets
Formed by:	Nucleation Condensation Coagulation	Condensation Coagulation Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding, and abrasion of surfaces) Evaporation of sprays Suspension of dusts Reactions of gases in or on particles
Composed of:	Sulfates Elemental carbon Metal compounds Organic compounds with very low, saturation vapor pressure at ambient temperature	Sulfate, SO_4^- Nitrate, NO_3^- Ammonium, NH_4^+ Hydrogen ion, H^+ Elemental carbon Large variety of organic compounds Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc. Particle-bound water	Suspended soil or street dust Fly ash from uncontrolled combustion of coal, oil, and wood Nitrates and chlorides from HNO_3 and HCl Oxides of crustal elements (Si, Al, Ti, and Fe) $CaCO_3$, NaCl, and sea salt Pollen, mold, and fungal spores Plant and animal fragments Tire, brake pad, and road wear debris
Solubility:	Probably less soluble than accumulation mode	Largely soluble, hygroscopic, and deliquescent	Largely insoluble and nonhygroscopic
Sources:	Combustion Atmospheric transformation of SO_2 and some organic compounds High temperature processes	Combustion of coal, oil, gasoline, diesel fuel, and wood Atmospheric transformation products of NO_x, SO_2, and organic compounds, including biogenic organic species (e.g., terpenes) High-temperature processes, smelters, steel mills, etc.	Resuspension of industrial dust and soil tracked onto roads and streets Suspension from disturbed soil (e.g., farming, mining, unpaved roads) Construction and demolition Uncontrolled coal and oil combustion Ocean spray Biological sources
Atmospheric half-life:	Minutes to hours	Days to weeks	Minutes to hours
Removal processes:	Grows into accumulation mode	Forms cloud droplets and rains out Dry deposition	Dry deposition by fallout Scavenging by falling rain drops
Travel distance:	<1 to 10s of km	100s to 1000s of km	<1 to 10s of km (100s to 1000s in dust storms)

Source: Adapted from Wilson and Suh (1997).

is called secondary if it is formed by chemical reactions in the atmosphere. Primary coarse particles usually are formed by mechanical processes. Primary fine particles are emitted from sources either directly as particles or as vapors that rapidly condense to form particles.

Most of the sulfate and nitrate and a portion of the organic compounds in atmospheric particles are secondary (i.e., they are formed by chemical reactions in the atmosphere). Secondary aerosol formation depends on numerous factors, including the concentrations of precursors; the concentrations of other gaseous reactive species such as ozone (O_3), hydroxyl radical, peroxy radicals, or hydrogen peroxide; atmospheric conditions, including solar radiation and relative humidity; and the interactions of precursors and preexisting particles within cloud or fog droplets or on or in the liquid film on solid particles. As a result of such transformations, it is considerably more difficult to relate ambient concentrations of secondary species to individual sources of precursor emissions than it is to identify the sources of primary particles.

The atmospheric lifetimes of particles vary with the aerodynamic diameter of the particle. Coarse particles can settle rapidly from the atmosphere within minutes or hours and normally travel only short distances. However, when mixed high into the atmosphere, as in dust storms, the smaller-sized, coarse-mode particles may have longer atmospheric residence times and travel greater distances. Nuclei-mode particles rapidly grow into accumulation-mode fine particles, which are kept suspended by normal air motions and have very low deposition rates to surfaces. They can be transported thousands of kilometers and remain in the atmosphere for a number of days. Particulate matter can be removed from the atmosphere by wet and dry deposition. Dry deposition rates are expressed in terms of a deposition velocity, which varies with particle size, reaching a minimum between 0.1 and 1.0 μm AED. For small particles, dry deposition is accomplished by impaction on surfaces by turbulent motion. For larger particles (i.e., coarse mode), buoyancy forces are not large enough to overcome the force of gravity, and gravitational settling becomes important. Soluble particles are removed from the atmosphere primarily by incorporation into cloud droplets, which then rain out. Coarse-mode and ultrafine, but not accumulation-mode, particles are removed by impaction with falling rain drops.

9.2.3 Particle Size-Related Distinctions vis-a-vis Number, Surface Area, and Mass

The distribution of particles in terms of numbers, surface area, and mass in relation to size is gaining more attention as efforts focus on trying to identify specific toxic components of the ambient PM mix that may contribute to observed human health and environmental effects. Examples of averaged atmospheric size distributions are shown in Figures 9-3 and 9-4. Figure 9-3 describes the number of particles as a function of particle diameter for rural, urban-influenced rural, urban, and freeway-influenced urban aerosols. For the urban data, the particle volume distribution is shown in Figure 9-4. The particle diameter is always shown on a logarithmic scale. The particle number frequently is shown on a logarithmic scale to display the wide range in number concentration for different particle sizes and different sites. When shown on an arithmetic scale the volume, surface area, or number of particles in any specified size range is proportional to the corresponding area under the curve (see Figure 9-5). These distributions show that most of the particles are very small (<0.1 μm), whereas most of the particle volume (and therefore most of the mass) and the surface area is found in particles >0.1 μm. Also, particle surface area peaks around 0.2 μm.

The number concentrations of coarse particles are usually too small to be seen in arithmetic plots (Figure 9-3b) but can be seen in a logarithmic plot (Figure 9-3a). Whitby and Sverdrup (1980) observed that rural aerosols, not much influenced by nearby sources, have a small accumulation mode and no observable nuclei mode. For urban aerosols, the accumulation- and coarse-particle modes are comparable in volume. However, in urban aerosols, the nuclei-mode can be observed only in volume distributions that are influenced by nearby traffic or other sources of nuclei-mode particles. Still, the nuclei-mode dominates the number distributions of urban aerosols. Whitby's conclusions were based on extensive studies of size distributions in a number of western and midwestern locations during the 1970s (Whitby, 1978; Whitby and Sverdrup, 1980). No size-distribution studies of similar scope have been published since then. Newer data from particle counting techniques and size-segregation impactor studies, including data from Europe (U.S. Environmental Protection Agency, 1996) and Australia (Keywood et al., 1999), show similar results.

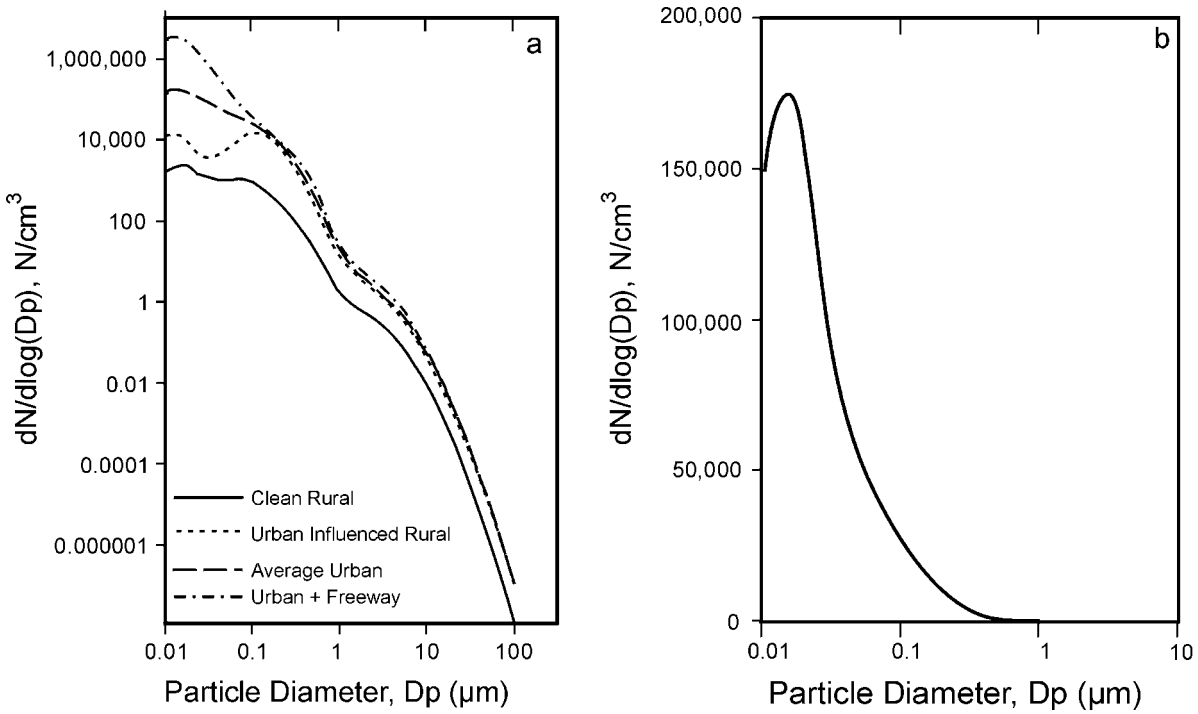

Figure 9-3. Number of particles as a function of particle diameter: (a) number concentrations are shown on a logarithmic scale to display the wide range by site and size, and (b) number concentrations for the average urban distribution are shown on a linear scale for which the area under any part of the curve is proportional to particle number in that size range.

Source: Whitby and Sverdrup (1980).

9.2.4 Nuclei-Mode Particles (Ultrafine Particles)

The 1996 PM AQCD extensively discussed information on distinctions between coarse- and fine-mode particles, in general, with regard to human exposures, lung dosimetry, and health impacts. During recent years, increasing attention has focused on nuclei-mode particles or "ultrafine particles" (as a subclass of fine particles) as they may exhibit potentially enhanced toxicity in comparison to larger sized particles, even of similar chemical composition. Nuclei-mode particles are the result of nucleation of gas-phase species to form condensed-phase species with very low equilibrium vapor pressure. In the atmosphere there are four major classes of sources that yield substances with equilibrium vapor pressures low enough to form nuclei-mode particles; these are described below.

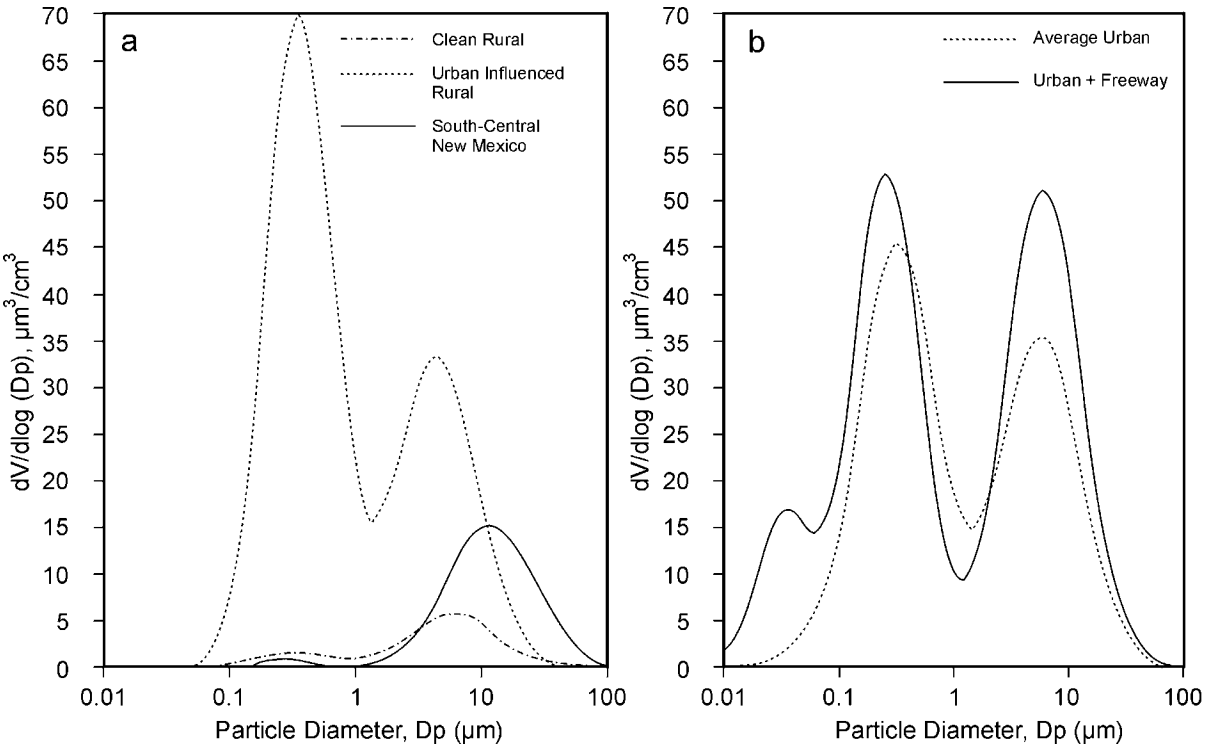

Figure 9-4. Particle volume distribution as a function of particle diameter: (a) for the averaged rural and urban-influenced rural number distributions shown in Figure 9-3 and a distribution from south central New Mexico, and (b) for the averaged urban and freeway-influenced urban number distributions shown in Figure 9-3.

Source: Whitby and Sverdrup (1980) and Kim et al. (1993).

(1) *Particles containing heavy metals.* Nuclei-mode particles of metal oxides or other metal compounds are generated during metal smelting processes or, more widely, when metallic impurities in coal or oil are vaporized during combustion and the vapor undergoes nucleation. Metallic ultrafine particles also may be formed from metals in lubricating oil or fuel additives that are vaporized during combustion of gasoline or diesel fuels.

(2) *Elemental carbon (EC) or soot.* Elemental carbon particles are formed primarily by condensation of C_2 molecules generated during combustion processes. Because EC has a very low equilibrium vapor pressure, ultrafine EC particles can nucleate even at high

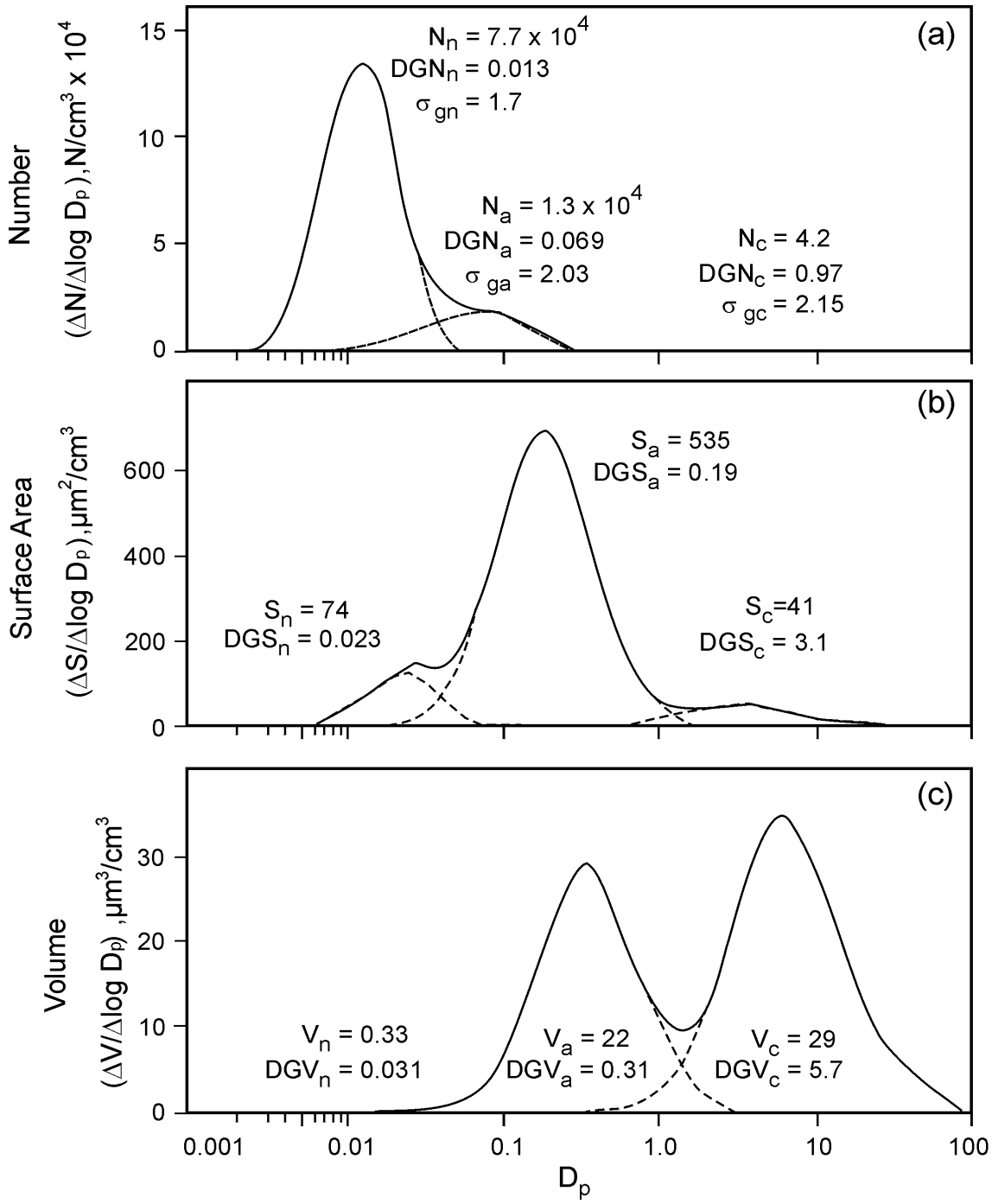

Figure 9-5. Distribution of coarse (c), accumulation (a), and nuclei- or ultrafine (n) -mode particles by three characteristics, (1) number (N), (2) surface area (S), and (3) volume (V) for the grand average continental size distribution. DGV = geometric mean diameter by volume; DGS = geometric mean diameter by surface area; DGN = geometric mean diameter by number; D_p = geometric diameter.

Source: Whitby (1978).

temperatures (Kittelson, 1998; Morawska et al., 1998). Thus, substantial amounts of EC can be released into the air as the result of biomass burning (because of agricultural clearing, forest fires, etc.) or combustion of fossil fuels (e.g., gasoline or diesel fuel derived from oil or coal used for power generation, industrial boilers, etc.).

(3) *Sulfates and nitrates.* Sulfuric acid (H_2SO_4), or its neutralization products with ammonia (NH_3) (i.e., ammonium sulfate [$(NH_4)_2SO_4$] or ammonium acid sulfate [NH_4HSO_4]), are generated in the atmosphere by conversion of sulfur dioxide (SO_2) to H_2SO_4. As H_2SO_4 is formed, it can either nucleate to form new ultrafine particles, or it can condense onto existing nuclei-mode or accumulation-mode particles (Clark and Whitby, 1975; Whitby, 1978). However, the possible formation of ultrafine ammonium nitrate (NH_4NO_3) by reaction of NH_3 and nitric acid (HNO_3) apparently has not been investigated.

(4) *Organic carbon (OC).* Recent smog chamber studies and indoor experiments show that atmospheric oxidation of certain organic compounds found in the atmosphere can produce highly oxidized organic compounds with an equilibrium vapor pressure low enough to result in nucleation (Kamens et al., 1999; Weschler and Shields, 1999). Organic carbon compounds originate from a wide variety of processes, including biomass burning, fossil fuel combustion, use of various dry cleaning or industrial solvents, and release of naturally occurring substances (e.g., terpenes) from certain terrestrial plant species.

Ambient concentrations of nuclei-mode particles importantly reflect a balance between formation and removal processes. Nuclei-mode particles are removed mainly by growth into the accumulation mode but also may be removed by dry deposition. Such growth takes place as other low-vapor-pressure material condenses onto the particles or as nuclei-mode particles coagulate with themselves or with accumulation-mode particles. Because the rate of coagulation will vary with the concentration of accumulation-mode particles, it might be expected that atmospheric concentrations of nuclei-mode particles would increase with decreases in accumulation-mode mass. On the other hand, the concentration of particles would be expected to decrease with a decrease in the rate of generation of particles by reduction in emissions of metal and carbon particles or a decrease in the rate of generation of H_2SO_4 or condensable organic

vapor. The rate of generation of H_2SO_4 depends on the concentration of SO_2 and OH radicals. OH is generated primarily by the photolysis of ozone at wavelengths <320 nm, followed by the reaction of electronically excited oxygen atoms with water vapor.

Exposure to ultrafine particles may occur near sources of primary ultrafine particles (e.g., in traffic). Secondary ultrafine particles are generated by photochemistry throughout the boundary layer; so exposure to ultrafine particles is not limited to locations near primary sources. Models exist to predict formation and coagulation rates, but no careful analyses of how rapidly various ultrafine (nuclei-mode) particles may agglomerate or adhere to larger particles as they "age" in the ambient air or how this may impact lung deposition of such particles has been published. Thus, it may be important to monitor particle number and surface area, as well as mass, to further delineate PM exposure-response relationships and to determine the relative effectiveness of strategies for reducing particle mass, surface area, and number to ameliorate PM-related health risks.

9.3 CHARACTERIZATION OF U.S. AMBIENT PARTICULATE MATTER CONCENTRATIONS AND CONTRIBUTING SOURCES AND EMISSIONS

9.3.1 Ambient Particulate Matter Measurement Methods

The EPA decision to revise the PM standards by adding daily and annual $PM_{2.5}$ NAAQS has led to renewed interest in the measurement of atmospheric particles and better understanding of problems in obtaining precise and accurate airborne particle measurements.

The U.S. Federal Reference Methods (FRM) for $PM_{2.5}$ and PM_{10} provide relatively precise (±10%) methods for determining the mass of material remaining on a Teflon filter after equilibration at 25 °C and 40% relative humidity. However, many uncertainties exist as to relationships between the mass and composition of material remaining on the filter, as measured by the FRM, and the mass and composition of material that exists in the atmosphere as suspended PM. It is currently not possible to characterize accurately the material that exists as a particle in the atmosphere, in part because of difficulties in creating a reference standard for particles suspended in the atmosphere. As a result, EPA defines accuracy for PM measurements in terms of agreement of a candidate sampler with a reference sampler under standardized

conditions for sample collection, storage, and analysis. Therefore, intercomparisons of samplers become very important in determining how well various samplers agree and how various design choices influence what is actually measured. Data from ambient PM monitoring is needed to guide implementation of a standard; to determine whether or not a standard has been attained; and to determine effects on health, ecosystems, visibility, and the transfer of solar ultraviolet and visible radiation.

Current filtration-based mass measurements lead to significant evaporative losses, during and possibly after collection, of a variety of semivolatile components (i.e., species that exist in the atmosphere in dynamic equilibrium between the condensed phase and gas phase). Important examples include ammonium nitrate, semivolatile organic compounds, and particle-bound water. In designing an aerosol indicator, choices must be made regarding the treatment of the semivolatile components. Other areas where choices must be made include selection of an upper cut point; separation of fine- and coarse-mode PM; and treatment of pressure, temperature, and relative humidity.

It is becoming increasingly apparent that the semivolatile component of PM impacts significantly the quality of the measurement, and leads to both positive and negative sampling artifacts. Negative artifacts, because of the loss of ammonium nitrate and semivolatile organic compounds, occur during sampling, because of temperature, relative humidity, composition of the aerosol, or because of pressure drop across the filter. Negative artifacts also occur during handling and storage because of evaporation. Positive artifacts occur when volatile species adsorb onto, or react with, filter media or collected PM.

The loss of particulate nitrate may be determined by comparing nitrate collected on a Teflon filter to that collected on a nylon filter (which absorbs nitrate), preceded by a denuder to remove nitric acid. In two studies, the $PM_{2.5}$ mass lost because of volatilization of ammonium nitrate was found to represent 10 to 20% of the total $PM_{2.5}$ mass and almost a third of the nitrate. Semivolatile organic compounds (SVOC) can similarly be lost from Teflon filters because of volatilization during or after collection. Such losses can cause the $PM_{2.5}$ mass to be underestimated significantly. The FRM for $PM_{2.5}$ will suffer loss of particulate nitrates and SVOC, similar to the losses experienced with other single-filter collection systems.

It is generally desirable to collect and measure ammonium nitrate and SVOC. However, it is also desirable to remove the particle-bound water before determining the mass. Calculations

and measurements indicate that aerosol water content is strongly dependent on composition, but that liquid water could represent a significant mass fraction of aerosol concentration at relative humidities above 60%.

Federal Reference Methods for equilibrated mass have been specified for PM_{10} and $PM_{2.5}$. In addition to FRM sampling to determine compliance with PM standards, EPA requires states to conduct speciation sampling to determine contributions from different source categories and to evaluate exposure to trace elements. The current speciation samplers include three filters: (1) a Teflon filter for equilibrated mass and elemental analysis; (2) a nylon filter, preceded by a nitric acid denuder, to collect nitrate; and (3) a quartz fiber filter for elemental and organic carbon (but without any correction for positive or negative artifacts caused by adsorption of volatile organic compounds on the quartz filters or evaporation of semivolatile organic compounds from the collected particles).

The EPA expects that more than 200 local agency monitoring sites throughout the United States will operate continuous PM monitors. However, EPA has not yet provided any guidance regarding appropriate continuous monitoring techniques. All currently available continuous measurements of suspended particle mass share the problem of dealing with semivolatile PM components (i.e., so as not to include particle-bound water as part of the mass, the particle-bound water must be removed by heating or dehumidification). However, heating also causes loss of ammonium nitrate and semivolatile organic components. Several candidates for continuous PM mass measurements, which use dehumidification instead of heating to remove particle-bound water, currently are being field tested. In addition to continuous mass measurement, a number of techniques for continuous measurement of sulfate, nitrate, or elements are being tested. Aerosol time-of-flight mass spectroscopy provides a new technique for real-time measurement of correlated size and composition profiles of individual atmospheric aerosol particles.

For measurement of the chemical composition of PM collected on a filter, adequate techniques exist for measurement of the heavier elements (Na and higher); sulfate, nitrate, ammonium, and hydrogen ions; and total carbon. The split between elemental carbon and organic carbon is defined operationally and depends on the measurement technique used. The definition of elemental carbon (measured by oxidation to CO_2 and quantification of the CO_2 formed) and black carbon (measured by optical absorption or transmission) is also operational and determined by the methods used. Determination of the mass of organic material (carbon plus

molecularly bound hydrogen and oxygen) remains a problem, as does the identification of the many individual organic compounds. However, measurement techniques for polynuclear aromatic hydrocarbons (PAH) and some other toxic compounds in PM are well developed.

9.3.2 Patterns and Trends in U.S. Particulate Matter Concentrations

Since the 1987 setting of the PM_{10} NAAQS, extensive PM_{10} monitoring has been carried out throughout the United States, allowing for confident characterization of PM_{10} patterns and trends during the past decade or so. However, only very recently, with the deployment of a nationwide $PM_{2.5}$ monitoring network during 1998, has it became possible to begin, in a systematic fashion, to characterize $PM_{2.5}$ patterns and trends, starting with data for 1999.

9.3.2.1 PM_{10} Trends and Concentrations

Annual average PM_{10} mass concentrations throughout the United States, for different regions within the United States, and for most subregions or cities, have generally decreased over the past decade. Nationwide average PM_{10} concentrations decreased from 31.7 $\mu g/m^3$ in 1989 to 23.7 $\mu g/m^3$ in 1998. Decreases were largest (38%) in the Pacific Northwest and smallest in the Southeast (18%).

Annual mean PM_{10} concentrations in urban areas, found in EPA's Air Information Retrieval System database (Fitz-Simons et al., 2000), generally were greater than about 20 $\mu g/m^3$ for 1999. Annual average concentrations above 50 $\mu g/m^3$ are found in several locations in southern and central California, Nevada, Arizona, Texas, South Carolina, and Puerto Rico. At rural sites in national parks, wilderness areas, and national monuments in the western United States, the annual average PM_{10} concentrations were in the range of 5 to 10 $\mu g/m^3$. Higher PM_{10} concentrations have been reported at some rural sites in the eastern United States. The corresponding $PM_{2.5}$ concentrations in western rural or remote sites were approximately 3 $\mu g/m^3$ and, in eastern rural or remote sites, were in the range of 5 to 10 $\mu g/m^3$.

A few attempts to infer various types of "background" levels of $PM_{2.5}$ and PM_{10} have been made. The background levels most relevant to the present criteria document include: (1) an uncontrollable"background" (which includes the "natural background" defined below and anthropogenic sources outside of North America), and (2) a "natural background" (which includes all natural sources but excludes all anthropogenic sources anywhere in the world).

Annual average background levels of PM_{10} (according to the first definition) have been estimated to range from 4 to 8 $\mu g/m^3$ in the western United States and 5 to 11 $\mu g/m^3$ in the eastern United States. Corresponding $PM_{2.5}$ background levels have been estimated to range from 1 to 4 $\mu g/m^3$ in the western United States and from 2 to 5 $\mu g/m^3$ in the eastern United States.

9.3.2.2 $PM_{2.5}$ Trends and Concentrations

The recently deployed $PM_{2.5}$ FRM network has returned data for a large number of sites across the United States beginning in January of 1999. As of the end of 1999, the network consisted of 1025 monitors. Annual mean $PM_{2.5}$ concentrations for 1999 ranged from about 5 $\mu g/m^3$ to more than 20 $\mu g/m^3$. As might be expected, annual average $PM_{2.5}$ concentrations towards the low end of the range were found in relatively small, nonindustrialized cities such as Bangor, ME; Fargo, ND; Cheyenne, WY; and Albuquerque, NM. Higher annual averages were found in larger urban areas such as Atlanta, GA, and Los Angeles, CA, as well as in a number of urban areas in the eastern United States. Because FRM measurements of $PM_{2.5}$ only began in January 1999, data tend to be limited in many areas, especially for the first quarter. However, a number of observations can be made regarding $PM_{2.5}$ concentrations and the patterns of seasonal variability in urban areas across the United States. Generally, similar patterns of seasonal variability were found at all sites within Metropolitan Statistical Areas (MSAs) sampled nationwide, although there were exceptions at individual sites, which may have been related to contributions from local sources as opposed to contributions from regional background sources. At sites in the eastern United States, highest quarterly mean values and maximum values occurred during the third quarter (summer) of 1999, with exceptions occurring at several locations. For example, at monitoring sites in Miami and Puerto Rico, maximum concentrations occurred during the second quarter and may have been related to the transport of dust from the Sahara Desert. At sites west of the Mississippi River, highest mean values occurred during the first or fourth quarter (winter or autumn) of 1999, and, again, there were exceptions. Because of the limited nature of these data, definitive conclusions regarding long-term patterns of seasonal variability cannot be drawn from these data alone. These findings are generally consistent with those based on longer term data sets such as the Metropolitan Acid Aerosol Characterization Study (MAACS) in the eastern United States and the California Air Resources Board (CARB) network of dichotomous samplers in California. Very limited data sets are available for obtaining

trends in $PM_{2.5}$ concentrations in urban areas. Data obtained by the CARB indicate that annual average $PM_{2.5}$ concentrations decreased from 35 to 50% in large urban areas in California from 1990 to 1995. Smaller decreases ranging from 2 to 34% were observed as part of the children's health study in southern California. In contrast, the urban IMPROVE site in Washington, DC measured only a 5% decline in $PM_{2.5}$ concentrations from 1989-1997.

9.3.2.3 Spatial Variability in $PM_{2.5}$ Concentrations

The 1999 FRM $PM_{2.5}$ data indicate that, in general, $PM_{2.5}$ concentrations are highly correlated among sites within several MSAs (Atlanta, GA; Detroit, MI; Phoenix-Mesa, AZ; and Seattle-Bellevue-Everett, WA), although there are some exceptions to this rule. These findings are consistent with those of earlier studies in Philadelphia, PA; and Los Angeles, CA. Concentrations of $PM_{2.5}$ also tended to be highly correlated on much larger spatial scales in many areas in the United States, supporting the inference that $PM_{2.5}$ is a regionally distributed pollutant.

9.3.2.4 Relationships Among Particulate Matter in Different Size Fractions

$PM_{2.5}$ to PM_{10} ratios from the FRM network were generally higher in the eastern ($\approx$0.7) than in the central or western ($\approx$0.5) United States during 1999. These values are consistent with those found in numerous earlier studies presented in the 1996 PM AQCD.

The results of ambient monitoring studies and receptor modeling studies in the eastern United States indicate that $PM_{2.5}$ is dominated by secondary components. Depending on the origin of OC in ambient samples, $PM_{2.5}$, on average, also may be dominated by secondary components throughout the rest of the United States. Primary constituents represent smaller but still important components of $PM_{2.5}$, on average. Crustal materials constitute the largest fraction of $PM_{(10-2.5)}$ throughout the United States. Crustal materials in the lower tail of the coarse-mode particles also may be present in the $PM_{2.5}$-size fraction. Data collected in several airsheds, including the Los Angeles Basin, Bakersfield and Fresno, CA; and Philadelphia, PA, suggest that secondary PM components are more uniformly distributed than are primary components. Compositional data obtained at multiple sites in other urban areas are sparse.

9.3.2.5 Short-Term Temporal Variability of Particulate Matter Concentrations

Hour-to-hour changes in $PM_{2.5}$ concentrations have been obtained at 31 sites by various continuous monitors. The 1999 nationwide composite circadian variability in $PM_{2.5}$ concentrations obtained by these monitors indicate two typical intra-day peaks. The first peak occurs from about 6 to 9 a.m. and the second peak occurs from about 5 to 10 p.m. The amplitude of these peaks is much smaller than the daily mean concentration. It also should be noted that this pattern may not be apparent in the data obtained by any given monitor on any given day. Although the 98th percentile values for positive and negative excursions in 24-h $PM_{2.5}$ concentrations are typically less than 20 $\mu g/m^3$, maximum hour-to-hour excursions may be over 200 $\mu g/m^3$ in some locations.

The only data sets from which the long-term, day-to-day variability in $PM_{2.5}$ and PM_{10} concentrations could be assessed, based on daily filter measurements, were obtained in Philadelphia, PA, from 1992 to 1995 and in Phoenix, AZ, from 1995 through 1997. In the Philadelphia data set, average day-to-day concentration differences obtained were 6.8 ± 6.5 $\mu g/m^3$ for $PM_{2.5}$ and 8.6 ± 7.5 $\mu g/m^3$ for PM_{10}, whereas maximum day-to-day differences obtained were 54.7 $\mu g/m^3$ for $PM_{2.5}$ and 50.4 $\mu g/m^3$ for PM_{10}. In the Phoenix, AZ, data set, average day-to-day $PM_{2.5}$ concentration differences were 2.9 ± 3.0 $\mu g/m^3$, and the maximum day-to-day concentration difference was 23 $\mu g/m^3$.

9.3.3 Sources of Particulate Matter

As shown in Table 9-1, fine and coarse particles have different types of sources. The major sources of fine and coarse PM are summarized in Table 9-2. Because of the complexity of the composition of ambient $PM_{2.5}$ and $PM_{(10-2.5)}$, sources are best discussed in terms of individual constituents of both primary and secondary $PM_{2.5}$ and $PM_{(10-2.5)}$. Each of these constituents can have anthropogenic and natural sources, as shown in Table 9-2. The distinction between natural and anthropogenic sources is not always obvious. For example, although windblown dust might seem to be the result of natural processes, highest emission rates are associated with agricultural activities in areas that are susceptible to periodic drought, such as in the dust bowl region of the mid-western United States. Also, most forest fires in the United States could be classified as human in origin, either through prescribed burning, by accident, or through forest management practices, which allow the buildup of combustible material, thereby increasing the likelihood of

TABLE 9-2. CONSTITUENTS OF ATMOSPHERIC PARTICLES AND THEIR MAJOR SOURCES

	Sources					
	Primary (PM < 2.5 μm)		Primary (PM > 2.5 μm)		Secondary PM Precursors (PM < 2.5 μm)	
Aerosol species	Natural	Anthropogenic	Natural	Anthropogenic	Natural	Anthropogenic
$SO_4^=$ Sulfate	Sea spray	Fossil fuel combustion	Sea spray	—[a]	Oxidation of reduced sulfur gases emitted by the oceans and wetlands and SO_2 and H_2S emitted by volcanism and forest fires	**Oxidation of SO_2 emitted from fossil fuel combustion[b]**
NO_3^- Nitrate	—	—	—	—	Oxidation of NO_x produced by soils, forest fires, and lighting	**Oxidation of NO_x emitted from fossil fuel combustion and in motor vehicle exhaust**
Minerals	Erosion and reentrainment	Fugitive dust, paved and unpaved roads, and agriculture and forestry	Erosion and reentrainment	**Fugitive dust, paved and unpaved road dust, and agriculture and forestry**	—	—
NH_4^+ Ammonium	—	—	—	—	Emissions of NH_3 from wild animals and undisturbed soil	**Emissions of NH_3 from animal husbandry, sewage, and fertilized land**
Organic Carbon (OC)	Wildfires	**Prescribed burning, wood burning, motor vehicle exhaust,** and cooking	—	Tire and asphalt wear and paved road dust	Oxidation of hydrocarbons emitted by vegetation, (terpenes, waxes) and wildfires	Oxidation of hydrocarbons emitted by motor vehicles, prescribed burning, and wood burning
Elemental Carbon (EC)	Wildfires	**Motor vehicle exhaust, wood burning,** and cooking	—	—	—	—
Metals	Volcanic activity	**Fossil fuel combustion, smelting**, and brake wear	Erosion, reentrainment, and organic debris	—	—	—
Bioaerosols	Viruses and bacteria	—	Plant, insect fragments, pollen, fungal spores, and bacterial agglomerates	—	—	—

[a]Dash (—) indicates either very minor source or no known source of component.
[b]Major source of each component shown in boldface type.

fire from whatever cause. As seen in Table 9-2, emissions of crustal material (mineral dust), organic debris, and sea spray are concentrated mainly in the coarse fraction of PM_{10} (>2.5 μm AED). A small fraction of this material is in the $PM_{2.5}$ size range (<2.5 μm AED). Nevertheless, the concentrations of crustal material can be appreciable, especially during dust events. Emissions from combustion sources (mobile and stationary sources, biomass burning, etc.) are predominantly in the $PM_{2.5}$ size range.

The results of receptor modeling studies throughout the United States indicate that the combustion of fossil and biomass fuels is a major source of $PM_{2.5}$. Fugitive dust, found mainly in the $PM_{(10-2.5)}$ range size, represents the largest source of PM_{10} in many locations in the western United States. Quoted uncertainties in source apportionments of constituents in ambient aerosol samples typically range from 10 to 50%. It is apparent that a relatively small number of source categories, compared to the total number of chemical species that are typically measured in ambient monitoring-source receptor model studies, are needed to account for most of the observed mass of PM in these studies.

Although most emphasis in this discussion has been on sources within the United States, it should be remembered that sources outside the United States also contribute to ambient PM levels in the United States that can, at times, exceed the ambient NAAQS level for PM. Perry et al. (1997) have found that the highest concentrations of mineral dust in the $PM_{2.5}$ fraction are found in the eastern United States during the summer and not in arid areas of the western United States. This dust originates from the Sahara Desert and is then transported across the Atlantic Ocean. Much of the Saharan dust that reaches the United States is in the $PM_{2.5}$ size range. Large-scale dust storms in the deserts of central Asia also have contributed to PM levels in the Northwest on an episodic basis. In addition, uncontrolled biomass burning in Central America and Mexico occasionally contributes to elevated U.S. ambient PM levels, having led at times to brief exceedances of daily PM NAAQS level in Texas. Wildfires throughout the United States, Canada, Mexico, and Central America all contribute to background concentrations of PM in the United States.

9.4 HUMAN EXPOSURES TO AMBIENT PARTICULATE MATTER

The concentration of PM in the air inhaled by a person is not necessarily the same as that measured at a community ambient-air monitoring station. Personal exposure is defined as the concentration, integrated over a time period, of PM near the breathing zone but not influenced by exhaled breath. Total personal exposure, including ambient and nonambient PM, may be measured by a personal exposure monitor (PEM) carried by the person. There are several reasons why an individual's personal exposure may be different from the ambient concentration. First, the concentration of PM outside a person's home may be different from the concentration measured at a monitoring station. However, for cities where sufficient information is available (e.g., see Section 9.3.2), PM concentrations measured at different pairs of stations (sited to measure community-wide pollution levels rather than individual source contributions) have been found to be highly correlated for $PM_{2.5}$ and PM_{10}, but not so highly correlated for $PM_{10\text{-}2.5}$. Although it would be desirable to check the spatial variability of PM indicators in each city where epidemiologic studies are conducted, it seems likely that $PM_{2.5}$ and PM_{10} concentrations are distributed evenly enough so that one site, or the average of several sites, provides an adequate measure of the community average concentration for $PM_{2.5}$ and PM_{10}. This may not be the case for $PM_{10\text{-}2.5}$, for specific chemical components, for source contributions, or for sites located near sources.

Second, the concentration of ambient PM found indoors is generally less than the concentration of ambient PM outdoors. Ambient air, and the ambient PM it contains, penetrates indoors through open doors and windows and through small openings in the building structure. An equal volume of indoor air moves out of the indoor microenvironment. Unless the air exchange rate is very high, the ambient PM that penetrates indoors will be removed by deposition more rapidly than it can be replaced. The ratio of ambient PM indoors to ambient PM outdoors, called the infiltration factor, depends on the air exchange rate and, also, on the penetration efficiency and deposition or removal rate, both of which vary with particle aerodynamic size. The infiltration factor is a maximum for particles within the accumulation mode ($\approx$0.3 to 0.7 μm AED) and decreases for smaller (ultrafine) or larger (coarse-mode) particles. For a given size particle, the relationship between the indoor and outdoor PM concentration, given by the infiltration factor, will vary with the air exchange rate. For a home closed for heating or air-conditioning, the air exchange rate depends on the temperature difference between the indoor and

outdoor air; the greater the difference, the greater the air exchange rate. If windows are opened for ventilation or doors are opened frequently, the air exchange rate will be higher.

The relationship between ambient concentration of PM and personal exposure to ambient PM also is modulated by the time spent outdoors, because, while outdoors, a person is exposed to the ambient concentration. The ratio of personal exposure to ambient PM to the ambient PM concentration is called the attenuation factor and is given the symbol α. Both the infiltration factor and the attenuation factor, α, may be estimated by several techniques. The most direct method is to measure the personal exposure and ambient concentration of a chemical species that has no indoor sources and is in the same size range as the PM component of interest. Candidates are sulfate and, in homes with no open combustion, elemental carbon. The ratio of the personal exposure to the tracer to the ambient concentration of the tracer gives α. In turn, α times the ambient concentration of the appropriate PM indicator gives the personal exposure to that component of ambient PM.

Personal exposure also contains a component resulting from indoor sources of PM, which tend to produce ultrafine and coarse-mode particles rather than accumulation-mode particles. Important indoor sources are tobacco smoke and other open combustion (ultrafine); cleaning, sweeping, dusting, vacuuming (coarse); oven cooking (ultrafine); and resuspension caused by walking on rugs (coarse). Stove-top cooking produces both ultrafine and coarse-mode particles. Vacuum cleaners may produce ultrafine carbon or copper particles from motor brushes. Another recently identified indoor source involves PM generated by the reaction of ozone (which infiltrates with ambient air) with terpenes from air fresheners or cleaning agents. Indoor-generated ultrafine particles will grow into the accumulation mode unless they are removed first by deposition or air exchange. Indoor-generated PM would be expected to have a lower proportion of transition and toxic metals and highly oxidized and nitrated organic compounds than ambient air.

Community time-series epidemiology studies evaluate the daily totals of deaths (or other health outcomes) in the community in relation to concentrations of one or more air pollutants measured at stationary community ambient air monitoring sites (assumed to be representative of the community average). There has been some controversy over whether the ambient concentration should be considered to be a surrogate for total human personal exposure or only for exposure to the ambient-generated component of total personal exposure. Some exposure

analysts feel that ambient concentrations represent a surrogate for total personal exposure (the sum of exposure to ambient-generated pollution plus exposure to nonambient exposure). This view is difficult to reconcile with epidemiologic studies that find statistically significant relationships between ambient concentrations and health outcomes, even though correlations of ambient concentrations with total personal exposures are found to be near zero. On the other hand, certain other scientists have argued that the ambient concentration represents a surrogate only for exposure to the ambient-generated component of total PM exposure.

Recent studies of exposure error suggest that, provided ambient-generated and nonambient PM have equal toxicity, the increase in health outcomes per unit increase in concentration, compared to β_E, the increase in health outcome per unit increase in exposure, will not be biased by the nonambient component of exposure if the nonambient component is independent of the ambient concentration. Both logic and experiment suggest that nonambient PM exposures are independent of daily ambient concentrations. However, the increase in health outcomes per unit increase in ambient concentration will be biased low compared to the increase in health outcomes per unit increase in exposure. For a constant average ratio of exposure to ambient-generated PM to PM concentration (the attenuation factor, α, discussed earlier), the bias will be given by this ratio which might be expected to vary from a few tenths (0.1s) to nearly 1.0 depending on air exchange and indoor removal rates. Thus, it seems reasonable to conclude that community time-series epidemiology studies provide information on the statistical association of exposure to ambient-generated pollutants with health outcomes, but do not provide any information on the relationship of nonambient exposure with health outcomes. It is likely that the nonambient component of total personal exposure also has health effects. However, techniques other than community time-series epidemiology must be used to identify relationships between nonambient exposure and health outcomes.

9.5 DOSIMETRY CONSIDERATIONS

A basic health effects assessment principle is that dose delivered to the target site, rather than external exposure, is the proximal cause of biological responses. Characterization of an exposure-dose-response continuum for PM (key objective of any dose-response assessment for evaluation of health effects) requires elucidation of mechanistic determinants of inhaled particle

dose, which depend initially on deposition of particles in the respiratory tract. Once deposited on respiratory tract surfaces, particles undergo absorptive or nonabsorptive removal (clearance) processes that may result in their removal from airway surfaces and translocation from the respiratory tract. Clearance depends on initial site of deposition and physicochemical properties of the particles; both impact translocation mechanisms. Retained particle burdens are determined by dynamic relationships between deposition and clearance mechanisms. The dose from inhaled particles deposited and retained in the respiratory tract is governed by many factors (e.g., exposure concentration and duration, respiratory tract anatomy and ventilatory parameters, and physicochemical properties of the particles (e.g., particle size, hygroscopicity, solubility).

Particles exist in the atmosphere as aerosols (i.e., airborne suspensions of finely dispersed solid or liquid particles). As noted in Chapter 2 and Section 9.2.1, the most commonly used metric AED, whereby particles of differing geometric size, shape, and density are compared aerodynamically with the instability behavior (i.e., terminal setting velocity) of particles that are unit density (1 gm/cm^3) spheres. Importantly, aerosols present in natural and work environments have polydisperse size distributions (i.e., particles within an aerosol have a range of sizes most appropriately described by a size distribution). Aerosol size distributions are frequently modeled by a sum of lognormal distributions, one for each mode (nuclei, accumulation, and coarse). Two parameters needed to describe a log normal distribution of aerosol particle sizes are the median diameter and the geometric standard deviation. When using aerodynamic diameters, the mass median aerodynamic diameter (MMAD) refers to the median of the distribution of mass with respect to the AED, the most commonly used measure of aerosol distribution.

As Chapter 7 notes, for dosimetry purposes, the respiratory tract can be divided into three main regions: (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists of head airways (i.e., nasal or oral passages) through the larynx, the areas through which inhaled air first passes. In humans, inhalation can occur via the nose or mouth or both (i.e., oronasal breathing). From the ET region, inspired air enters the TB region at the trachea. From the trachea, the conducting airways then undergo branching for several generations. The terminal bronchioles are the most peripheral of the distal conducting airways and these lead, in humans, to respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli, all comprising the A region.

9.5.1 Particle Deposition in the Respiratory Tract

Knowledge of respiratory tract regional deposition patterns for particles of different sizes is important for understanding possible health effects associated with exposure to ambient PM and for extrapolating and interpreting data obtained from studies of laboratory animals. Particles deposited in various respiratory tract regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times.

Particles deposit in the respiratory tract by five mechanisms: (1) inertial impaction, (2) sedimentation, (3) diffusion, (4) electrostatic precipitation, and (5) interception. Sudden changes in airstream direction and velocity cause inhaled particles to impact onto airway surfaces. The ET and upper TB airways are dominant sites of inertial impaction, a key mechanism for particles with AED >1 μm. Particles with AED > 0.5 μm mostly are affected by sedimentation out of the airstream. Both sedimentation and inertial impaction influence deposition of particles in the same size range and occur in the ET and TB regions, with inertial impaction dominating in the upper airways and gravitational settling (sedimentation) increasingly more dominant in lower conducting airways. Particles with actual physical diameters <1 μm are increasingly subjected to diffusive deposition due to random bombardment by air molecules, resulting in contact with airway surfaces. Particles circa 0.3 to 0.5 μm in size are small enough to be little influenced by impaction or sedimentation and large enough to be minimally influenced by diffusion, and so, they undergo the least respiratory tract deposition. The interception potential of any particle depends on its physical size; fibers are of chief concern for interception, their aerodynamic size being determined mainly by their diameter. Electrostatic precipitation is deposition related to particle charge; effects of charge on deposition are inversely proportional to particle size and airflow rate. This type of deposition is likely small compared to effects of other deposition mechanisms and is generally a minor contributor to overall particle deposition, but one recent study found it to be a significant TB region deposition mechanism for ultrafine, and some fine, particles.

Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 9-6 for healthy male adults under different ventilation conditions. The ET region acts as an efficient filter that reduces penetration of inhaled particles to the TB and A regions of the lower respiratory tract. Total respiratory tract deposition increases with particle size for particles >1.0 μm AED, is at a minimum for particles 0.3 to 0.5 μm, and increases as particle size

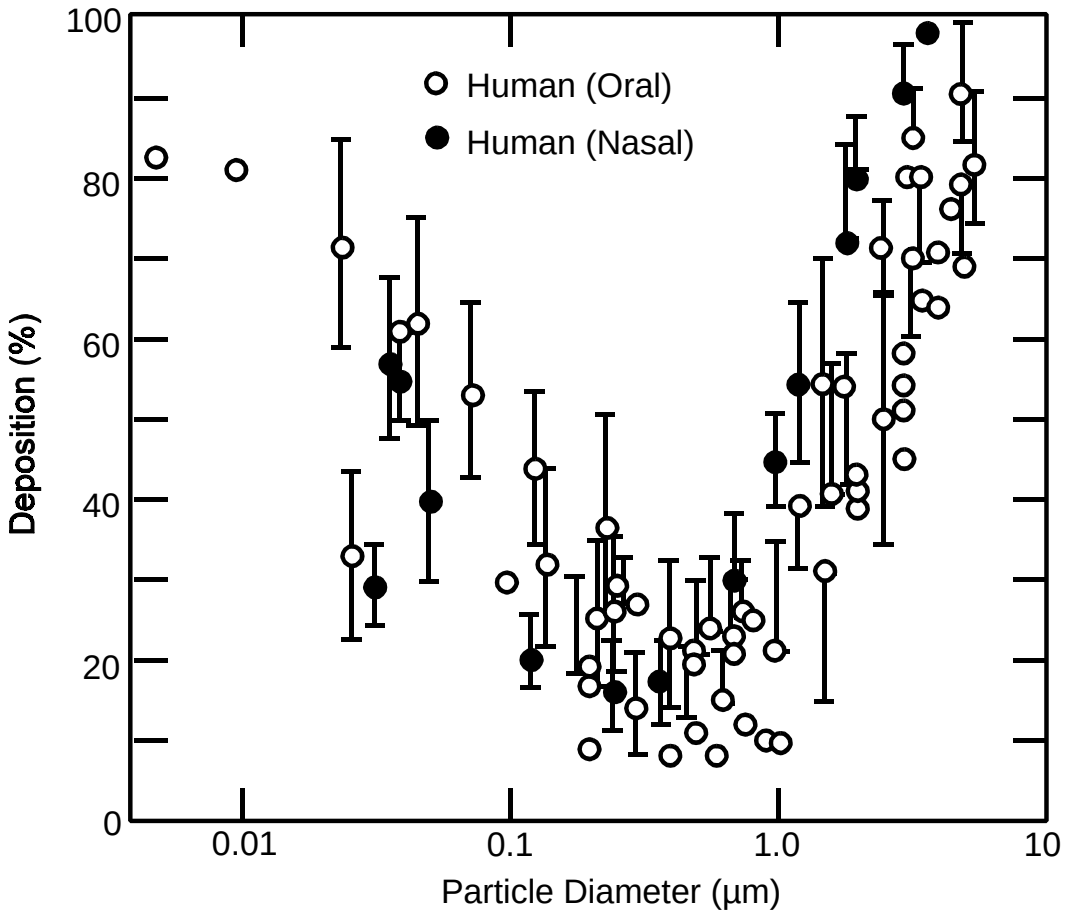

Figure 9-6. Total human respiratory tract deposition (percent deposition of amount inhaled) as a function of particle size. All values are means with standard deviations as available. Particle diameters are aerodynamic (MMAD) for those ≥0.5 μm.

Source: Modified from Schlesinger (1988).

decreases below that range. The ET deposition is higher with nose breathing than for mouth breathing, with increased ventilation rates associated with increasing levels of physical activity or exercise leading to more oronasal breathing and increased delivery of inhaled particles to TB and A regions in the lung.

Hygroscopicity, the propensity of a material for taking up and retaining moisture, is a property of some ambient particle species and affects respiratory tract deposition. Such particles can increase in size in humid air in the respiratory tract and, when inhaled, deposit according to

their hydrated size rather than their initial size. Compared to nonhygroscopic particles of the same initial size, deposition of hygroscopic aerosols in different regions varies, depending on initial size: hygroscopicity generally increases total deposition for particles with initial sizes larger than $\approx$0.5 μm, but decreases deposition for smaller ones.

Enhanced particle retention occurs on carinal ridges in the trachea and through segmental bronchi; and deposition "hot spots" occur at airway bifurcations or branching points. Peak deposition sites shift from distal to proximal sites as a function of particle size, with greater surface dose in conducting airways than in the A region for all particle sizes. Whereas both fine ($\leq$2.5 μm) and coarse (2.5 to 10 μm) inhalable particles deposit to about the same extent on a percent particle mass basis in the trachea and upper bronchi, a distinctly higher percent of fine particles deposit in the A region. However, surface number dose (particles/cm^2/day) is much higher for fine particles than for coarse, indicating much higher numbers of fine particles depositing, with the fine fraction contributing upwards of 10,000 times greater particle number per alveolar macrophage.

Ventilation rate, gender, age, and respiratory disease status are all factors that affect total and regional respiratory tract particle deposition. In general, because of somewhat faster breathing rates and likely smaller airway size, women have somewhat greater deposition of inhaled particles than men in upper TB airways, but somewhat lower A region deposition than for men. Children appear to show four effects: (1) greater total respiratory tract deposition than adults (possibly as much as 50% greater for those <14 years old than for adults >14 years), (2) distinctly enhanced ET region deposition (decreasing with age from 1 year), (3) enhanced TB deposition for particles <5 μm, and (4) enhanced A region deposition (also decreasing with age). Overall, given that children have smaller lungs and higher minute volumes relative to lung size, they likely receive greater doses of particles per lung surface area than adults for comparable ambient PM exposures. This and the propensity for young children to generally exhibit higher activity levels and associated higher breathing rates than adults likely contribute to enhanced susceptibility to ambient particle effects resulting from particle dosimetry factors. In contrast, limited available data on respiratory tract deposition across adult age groups (18 to 80 years) with normal lung function do not indicate age-dependent effects (e.g., enhanced deposition in healthy elderly adults). Altered PM deposition patterns resulting from respiratory disease status may put

certain groups of adults (including some elderly), as well as certain groups of children, at greater risk for PM effects.

Both information noted in the 1996 PM AQCD and newly published findings indicate that respiratory disease status is an especially important determinant of respiratory tract particle deposition. Of particular importance is the finding that chronic obstructive disease states contribute to more heterogenous deposition patterns and differences in regional deposition. One new study indicates that people with COPD tend to breath faster and deeper than those with normal lungs (i.e., about 50% higher resting ventilation), and had ca. 50% greater deposition than age-matched healthy adults under typical breathing conditions and average deposition rates 2.5 times higher under elevated ventilation rates. Enhanced deposition appears to be associated more with the chronic bronchitic than the emphysematous component of COPD. In this and other new studies, fine-particle deposition increased markedly with increased degree of airway obstruction (ranging up to ca. 100% greater with severe COPD). With increasing airway obstruction and uneven airflow because of irregular obstruction patterns, particles tend to penetrate more into remaining better ventilated lung areas, leading to enhanced focal deposition at airway bifurcations and alveoli in those A region areas. In contrast, TB deposition increases with increasingly more severe bronchoconstrictive states, as occur with asthmatic conditions.

Differences between humans and animals in deposition patterns were summarized in the 1996 PM AQCD and by Schlesinger et al. (1997) and should be considered when relating biological responses obtained in laboratory animal studies to effects in humans. Various species used in inhalation toxicology studies serving as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, A) when exposed to the same aerosol at the same inhaled concentration.

New mathematical modeling studies evaluate interspecies differences in respiratory tract deposition. For example, Hofmann et al. (1996) found total deposition efficiencies for all particles (0.01, 1, and 10 μm) at upper and lower airway bifurcations to be comparable for rats and humans, but when higher penetration probabilities from preceding airways in the human lung were considered, bronchial deposition fractions were mostly higher for humans. For all particle sizes, deposition at rat bronchial bifurcations was less enhanced on the carinas than in human airways. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that interspecies differences in morphologic

asymmetry is a major determinant of local deposition patterns. The dependence of deposition on particle size is similar in rats and humans, with deposition minima in the 0.1- to 1-μm size range for both total deposition and deposition in the TB and A regions, but total respiratory tract and TB deposition was consistently higher in the human lung. Alveoli region deposition in humans was lower than in rat for 0.001- to 10-μm particles (deposition of such particles being highest in the upper bronchial airways), whereas it was higher for 0.1- and 1-μm particles in more peripheral airways (i.e., bronchiolar airways in rat, respiratory bronchioles in humans). In a new histology study, Nikula et al. (2000) examined particle retention in rats (exposed to diesel soot) and humans (exposed to coal dust). In both, the volume density of deposition increased with increasing dose. In rats, diesel exhaust particles were found mainly in lumens of the alveolar duct and alveoli, whereas in humans, retained dust was mainly in interstitial tissue. Thus, in the two species, different lung cells appear to contact retained particles and may result in different biological responses with chronic exposure.

The probability of any biological effect of PM in humans or animals depends on particle deposition and retention, as well as underlying dose-response relationships. Interspecies dosimetric extrapolation must consider differences in deposition, clearance, and dose-response. Even similar deposition patterns may not result in similar effects in different species, because dose also is affected by clearance mechanisms and species sensitivity. Total number of particles deposited in the lung may not be the most relevant dose metric by which to compare species; rather, the number of deposited particles per unit surface area may determine response. Even if deposition is similar in rats and humans, there would be a higher deposition density in the rat because of the smaller surface area of rat lung. Thus, species-specific differences in deposition density are important when attempting to extrapolate health effects observed in laboratory animals to humans.

9.5.2 Particle Clearance and Translocation

Particles depositing on airway surfaces may be cleared from the respiratory tract completely or translocated to other sites within this system by regionally specific clearance mechanisms, as follow: *ET region*—mucociliary transport, sneezing, nose wiping and blowing, and dissolution and absorption into blood; *TB region*—mucociliary transport, endocytosis by macrophages and epithelial cells, coughing, and dissolution and absorption into blood and lymph;

A region—macrophages, epithelial cells, interstitial, and dissolution and absorption into blood and lymph. Clearance routes from various respiratory tract regions are depicted in Chapter 7 (Figures 7-2 and 7-3).

Regionally specific clearance defense mechanisms operate to clear deposited particles of varying particle characteristics (size, solubility, etc.) from the ET, TB, and A regions and are variously affected by different disease states. For example, particles are cleared from the ET region by mucociliary transport to the nasopharynx area, dissolution and absorption into the blood, or sneezing, wiping or blowing of the nose, but such clearance is slowed by chronic sinusitis, bronchiectasis, rhinitis, and cystic fibrosis. Also, in the TB region, poorly soluble particles are cleared mainly by upward mucociliary transport or by phagocytosis by airway macrophages that move upward on the mucociliary blanket, followed by swallowing. Soluble particles in the TB region are absorbed mostly into the blood and some by mucociliary transport. Although TB clearance is generally fast and much material is cleared in <24 h, the slow component of TB clearance (likely associated with bronchides <1-mm diameter) results in upwards of 40 to 50% of deposited 6- to 10-μm particles being retained for >24 h and clearance half-times of about 50 days. Bronchial mucous transport is slowed by bronchial carcinoma, chronic bronchitis, asthma, and various acute respiratory infections; these are disease conditions that logically would be expected to increase retention of deposited particle material and, thereby, increase the probability of toxic effects from inhaled ambient PM components reaching the TB region. Also, spontaneous coughing, an important TB region clearance mechanism, does not appear to fully compensate for impaired mucociliary clearance in small airways and may become depressed with worsening airway disease, as seen in COPD.

Clearance of particles from the A region via alveolar macrophages and their mucociliary transport is usually rapid (<24 h). However, penetration of uningested particles into the interstitium increases with increasing particle load and results in increased translocation to lymph nodes. Soluble particles not absorbed quickly into the blood stream and translocated to extrapulmonary organs (e.g., the heart) within minutes also may enter the lymphatic system, with lymphatic translocation probably being increased as other clearance mechanisms (e.g., removal by macrophages) are taxed or overwhelmed under "particle overload" conditions. Particles <2 μm clear to the lymphatic system at a rate independent of size; particles of this size, more so than those >5.0 μm, are deposited significantly in the A region. Translocation into the lymphatic

system is quite slow, and elimination from lymph nodes even slower (half-times estimated in decades). Focal accumulations of reservoirs of potentially toxic materials and their slow release for years after initial ambient PM exposure may account partially for the higher relative risks observed in epidemiologic studies to be associated with long-term ambient PM exposure beyond additive effects of acute PM exposures. Alveolar region clearance rates are decreased in human COPD sufferers and slowed by acute respiratory infections, and the viability and functioning of alveolar macrophages are reduced in human asthmatics and in animals with viral lung infections, this suggests that persons with asthma or acute lung infections are likely at increased risk for ambient PM exposure effects.

Differences in regional and total clearance rates between some species reflect differences in mechanical clearance processes. The importance of interspecies clearance differences is that retention of deposited particles can differ between species and may result in differences in response to similar PM exposures. Hsieh and Yu (1998) summarize existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and human. Two clearance phases "fast" and "slow" in the A region are associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with lymph nodes. Rats and mice are fast clearers, compared to other species. Increasing initial lung burden results in an increasing mass fraction of particles cleared by the slower phase. As lung burden increases beyond 1 mg particle/g lung, the fraction cleared by the slow phase increases to almost 100% for all species. The rate for the fast phase is similar in all species, not changing with increasing lung burden, whereas the slow phase rate decreases with increasing lung burden. At elevated burdens, the "overload" effect on clearance rate is greater in rats than in humans.

9.5.3 Deposition and Clearance Patterns of Particles Administered by Inhalation Versus Intratracheal Instillation

Inhalation is the most directly relevant exposure route for evaluating PM toxicity, but many studies deliver particles by intratracheal instillation. Because particle disposition is a determinant of dose, it is important to compare deposition and clearance of particles delivered by instillation versus inhalation. It is difficult to compare particle deposition and clearance among different inhalation and instillation studies because of differences in experimental methods and in quantification of particle deposition and clearance. Key points from a recent detailed evaluation

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

9.5.4 Inhaled Particles as Potential Carriers of Toxic Agents

It has been proposed that particles also may act as carriers to transport toxic gases into the deep lung. Water-soluble gases, which would be removed by deposition to wet surfaces in the upper respiratory system during inhalation, could dissolve in particle-bound water and be carried with the particles into the deep lung. Equilibrium calculations indicate that particles do not increase vapor deposition in human airways. However, these calculations do show that soluble gases are carried to higher generation airways (deeper into the lung) in the presence of particles than in the absence of particles. In addition, species such as SO_2 and formaldehyde react in water, reducing the concentration of the dissolved gas-phase species and providing a kinetic resistence to evaporation of the dissolved gas. Thus, the concentration of the dissolved species may be greater than that predicted by the equilibrium calculations. Also, certain other toxic species (e.g., nitric oxide [NO], nitrogen dioxide [NO_2], benzene, polycyclic aromatic hydrocarbons [PAH], nitro-PAH, a variety of allergens) may be absorbed onto solid particles and

carried into the lungs. Thus, ambient particles may play important roles not only in inducing direct health impacts of their constituent components but also in facilitating delivery of toxic gaseous pollutants or bioagents into the lung and may, thereby, serve as key mediators of health effects caused by the overall air pollutant mix.

9.6 HEALTH EFFECTS OF AMBIENT PARTICULATE MATTER

9.6.1 Introduction

This section evaluates available scientific evidence regarding the physiologic and health effects of exposure to ambient PM. The three main objectives of this evaluation are (1) to summarize and evaluate strengths and limitations of available epidemiologic findings; (2) to assess the biomedical coherence of findings across studied endpoints; and (3) to evaluate the biologic plausibility of available evidence in light of (a) linkages between specific PM components and health effects and (b) various dosimetric, mechanistic, and pathophysiologic considerations.

Epidemiologic findings are emphasized first because they provide the strongest body of evidence directly relating ambient PM concentrations to biomedical outcomes. Numerous epidemiologic studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints, including mortality, hospital admissions, emergency department visits, other medical visits, respiratory illness and symptoms measured in community surveys, and physiologic changes in pulmonary function. Associations have been consistently observed between both short- and long-term PM exposure and these endpoints. The general internal consistency of the epidemiologic database and available findings demonstrate well that notable human health effects are associated with exposures to ambient PM at concentrations currently found in many geographic locations across the United States. However, many difficulties still exist with regard to delineating the magnitudes and variabilities of risk estimates for ambient PM, the ability to attribute observed health effects to specific PM constituents, the time intervals over which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations, and the nature and magnitude of the overall public health risk imposed by ambient PM exposure.

The etiology of most air-pollution-related health outcomes is highly multifactorial, and the impact of ambient air pollution exposure on these outcomes is often small in comparison to that of other etiologic factors (e.g., smoking). Also, ambient PM exposure usually is accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical/chemical components. Assessment of the health effects attributable to PM and its constituents within an already-subtle total air pollution effect is difficult even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects may not characterize fully the etiology of effects that actually depend on simultaneous exposure to multiple air pollutants. In this regard, several viewpoints existed at the time of the 1996 PM AQCD regarding how best to interpret the epidemiology data: one saw the PM exposure indicators as surrogate measures of complex ambient air pollution mixtures, and the reported PM-related effects as representative of those of the overall mixture; another held that reported PM-related effects are attributable to PM components (per se) of the air pollution mixture and reflect independent PM effects, and a third viewpoint holds that PM can be viewed both as a surrogate indicator, as well as a specific cause of health effects.

Several other key issues and problems also must be considered when attempting to interpret the data reviewed in this document. For example, although the epidemiology data provide strong support for the associations mentioned above, questions remain regarding potential underlying mechanisms. Although much progress has been made toward identification of anatomic sites at which particles trigger specific health effects and elucidation of biological mechanisms underlying induction of such effects, this area of scientific inquiry is still at an early stage. Nevertheless, compared to the lack of much solid evidence available in the 1996 PM AQCD, there now is a stronger basis for assessing biologic plausibility of the epidemiologic observations given notable improvement in conceptual formulation of reasonable mechanistic hypotheses and evidence bearing on such hypotheses. Several hypotheses are discussed later with regard to possible mechanisms by which ambient PM may exert human health effects, and new evidence is discussed that tends to support a causal relationship between low ambient concentrations of PM and observed increased mortality or morbidity risks. At the same time, much still remains to be done to identify more confidently specific causal agents among typical ambient PM constituents.

9.6.2 Community-Health Epidemiologic Evidence for Ambient Particulate Matter Effects

In recent years, epidemiologic studies showing associations of ambient air pollution exposure with mortality, exacerbation of preexisting illness, and pathophysiologic changes have increased concern about the extent to which exposure to ambient air pollution exacerbates or causes harmful health outcomes at pollutant concentrations now experienced in the United States. The PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely key contributor to mortality and morbidity effects observed epidemiologically to be associated with ambient air pollution exposures. New studies appearing since the 1996 PM AQCD are important in extending results of earlier studies to many more cities and in confirming earlier findings.

In epidemiologic studies of ambient air pollution, small positive estimates of air pollutant health effects have been observed quite consistently, frequently being statistically significant at $p \leq 0.05$. If ambient air pollution promotes or produces harmful health effects, relatively small effect estimates from current PM concentrations in the United States and many other countries would generally be expected on biological and epidemiologic grounds. Also, magnitudes and significance levels of observed air pollution-related effects estimates would be expected to vary somewhat from place to place, if the observed epidemiologic associations denote actual effects, because (a) not only would the complex mixture of PM vary from place to place, but also (b) affected populations may differ in characteristics that could affect susceptibility to air pollution health effects. Such characteristics include sociodemographic factors, underlying health status, indoor-outdoor activities, diet, medical care access, exposure to risk factors other than ambient air pollution (such as extreme weather conditions), and variations in factors (e.g., air-conditioning) affecting human exposures to ambient-generated PM.

Although it has been argued by some that the observed effects estimates for ambient air pollution are not sufficiently constant across epidemiologic studies and that epidemiologic studies are trustworthy only if they show relatively large effects estimates (e.g., large relative risks), these arguments have only limited weight in relation to ambient air pollution studies. Also, in any large population exposed to ambient air pollution, even a small relative risk for a widely prevalent health disorder could result in a substantial public health burden attributable to air pollution exposure.

As noted above, small health effects estimates generally have been observed for ambient air pollutants, as would be expected on biological and epidemiologic grounds. In contrast to effects estimates derived for the 1952 London smog episode with relative risk (RR) exceeding 4.0 (i.e., 400% increase over baseline) for extremely high ($\geq$2 mg/m^3) ambient PM concentrations, effects estimates in most current epidemiology studies at distinctly lower PM concentrations (often $\leq$100 μg/m^3) are relatively small. The statistical estimates (1) are more often subject to small (but proportionately large) differences in estimated effects of PM and other pollutants; (2) may be sensitive to a variety of methodological choices; and (3) sometimes may not be statistically significant, reflecting low statistical power of the study design to detect a small but real effect.

The ambient atmosphere contains numerous air pollutants, and it is important to continue to recognize that health effects associated statistically with any single pollutant may actually be mediated by multiple components of the complex ambient mix. Specific attribution of effects to any single pollutant may therefore be overly simplistic. Particulate matter is one of many air pollutants derived from combustion sources, including mobile sources. These pollutants include PM, carbon monoxide (CO), sulfur oxides, nitrogen oxides, and ozone, all of which have been considered in various epidemiologic studies to date. Many volatile organic compounds (VOCs) or semivolatile compounds (SVOCs) also emitted by combustion sources or formed in the atmosphere have not yet been systematically considered in relation to noncancer health outcomes usually associated with exposure to criteria air pollutants. In many newly available epidemiologic studies, harmful health outcomes are often associated with multiple combustion-related or mobile-source-related air pollutants, and some investigators have raised the possibility that PM may be a key surrogate or marker for a larger subset of the overall ambient air pollution mix. This possibility takes on added potential significance to the extent that ambient aerosols indeed may not only exert health effects directly attributable to their constituent components, per se, but also serve as carriers for more efficient delivery of water soluble toxic gases (e.g., O_3, NO_2, SO_2) deeper into lung tissue, as noted earlier in Section 9.5.5. This suggests that airborne particle effects may be enhanced by the presence of other toxic agents or mistakenly attributed to them if their respective concentrations are highly correlated temporally. Thus, although associations of PM with harmful effects continue to be observed consistently across most new studies, the newer findings do not fully resolve issues concerning relative contributions to the observed epidemiologic associations of (1) PM acting alone, (2) PM acting in combination with

gaseous co-pollutants, (3) the gaseous pollutants per se, and (4) the overall ambient pollutant mix.

It seems likely that, for pollutants whose concentrations are not highly correlated, effects estimates in multipollutant models would be more biologically and epidemiologically sound than those in single-pollutant models, although it is conceivable that single-pollutant models also might be credible if independent biological plausibility evidence supported designation of PM or some other single pollutant as likely being the key toxicant in the ambient pollutant mix evaluated. However, neither of these possibilities have been demonstrated convincingly, and scientific consensus as to optimal interpretation of modeling outcomes for time series air pollution studies has not yet been achieved. Therefore, the choice of appropriate effects estimates to employ in risk assessments for ambient PM effects remains a difficult issue. Issues related to confounding by co-pollutants, along with issues related to time scales of exposure and response and concentration-response function, importantly apply to new epidemiologic studies relating concentrations of PM or correlated ambient air pollutants to hospital admissions, exacerbation of respiratory symptoms, and asthma in children, to reduced pulmonary function in children and adults, and to changes in heart rate, and heart rate variability in adults.

With considerable new experimental evidence also in hand, it is now possible to hypothesize various ways in which ambient exposure to multiple air pollutants (including not only PM acting alone but also in combination with others) could plausibly be involved in the complex chain of biological events leading to harmful health effects in the human population. The newer experimental evidence, therefore, adds considerable support for interpreting the epidemiologic findings discussed below as being indicative of causal relationships between exposures to ambient PM and consequent associated increased morbidity and mortality risks.

9.6.2.1 Short-Term Particulate Matter Exposure Effects on Mortality

This section focuses primarily on discussion of short-term PM exposure effects on mortality, but also highlights some morbidity effects in relation to the mortality findings. Morbidity effects are discussed more fully after discussion of long-term mortality effects in the section following this one.

9.6.2.1.1 Summary of Previous Findings on Short-Term Particulate Matter Exposure-Mortality Effects

Time series mortality studies reviewed in the 1996 PM AQCD provided strong evidence that ambient PM air pollution is associated with increased daily mortality. The 1996 PM AQCD summarized about 35 PM-mortality time series studies published between 1988 and 1996. Available information from those studies was consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. The PM_{10} relative risk estimates derived from the PM_{10} studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is associated with an increased risk of premature total mortality (total deaths minus accidents and injuries) mainly on of the order of relative risk (RR) = 1.025 to 1.05 (i.e., 2.5 to 5.0% excess risk) in the general population, with statistically significant increases being reported more broadly across the range of 1.5 to 8.5% per 50 $\mu g/m^3$ PM_{10}. Higher relative risks were indicated for the elderly and for those with preexisting respiratory conditions. Also, based on the then recently published Schwartz et al. (1996a) analysis of Harvard Six City data, the 1996 PM AQCD found the relative risk for excess total mortality in relation to 24-h fine-particle concentrations to be in the range of RR = 1.026 to 1.055 per 25 $\mu g/m^3$ $PM_{2.5}$ (i.e., 2.6 to 5.5% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$). Relative risk estimates for morbidity and mortality effects associated with standard increments in ambient PM_{10} concentrations and for fine-particle indicators (e.g., $PM_{2.5}$, sulfates, etc.) were presented in Chapters 12 and 13 of the 1996 PM AQCD (see Appendix 9A), and those effect estimates are updated below in light of the extensive newly available evidence discussed in Chapter 6 of this document.

Although numerous studies reported PM-mortality associations, several important issues needed to be addressed in interpreting those relative risks. The 1996 PM AQCD extensively discussed the following critical issues: (1) seasonal confounding and effect modification, (2) confounding by weather, (3) confounding by co-pollutants, (4) measurement error, (5) functional form and threshold, (6) harvesting and life shortening; and (7) the roles of specific PM components.

Season-specific analyses are often not feasible because of small magnitudes of expected effect size or small sample sizes (low power) available for some studies. Some studies had earlier suggested possible season-specific variations in PM coefficients, but it was not clear if these were caused by peak variations in PM effects from season to season, varying extent of PM

correlations with other co-pollutants, or weather factors during different seasons. The likelihood of PM effects being accounted for mainly by weather factors was addressed by various methods that controlled for weather variables in most studies (including some involving sophisticated synoptic weather pattern evaluations), and that possibility was found to be very unlikely.

Many early PM studies considered at least one co-pollutant in the mortality regression, and an increasing number have examined multiple pollutants. Usually, when PM indices were significant in single-pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate PM associations. In multiple-pollutant models performed by season, the PM coefficients became less stable, again possibly because of varying correlations of PM with co-pollutants among seasonal or smaller sample sizes. However, in many studies, PM indices showed the highest significance in both single- and multiple-pollutant models. Thus, PM-mortality associations did not appear to be seriously distorted by co-pollutants.

Interpretation of the relative significance of each pollutant in mortality regression in relation to its relative causal strength was difficult, however, because of lack of quantitative information on pertinent exposure measurement errors among the air pollutants. Measurement errors can influence the size and significance of air pollution coefficients in time series regression analyses, an issue also important in assessing confounding among multiple pollutants, because the varying extent of such errors among pollutants may influence corresponding relative significance. The 1996 PM AQCD discussed several types of exposure measurement and characterization errors, including site-to-site variability and site-to-person variability. These errors are thought to bias the estimated PM coefficients downward in most cases, but there was insufficient quantitative information available at the time to allow estimation of such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Some studies indicated that associations were seen monotonically to even below the PM standards. It was considered difficult, however, to statistically identify a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, use of relative risk (rate ratio) derived from log-linear Poisson models was deemed adequate.

The extent of prematurity of death (i.e., mortality displacement [or harvesting]) in observed PM-mortality associations has important public health policy implications. At the time of the

1996 PM AQCD review, only a few studies had investigated this issue. Although one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalized because this estimate was obtained for identifiable PM episodes. Insufficient evidence then existed to suggest the extent of prematurity for nonepisodic periods, from which most of the recent PM relative risks were derived.

Only a few PM-mortality studies had analyzed fine particles and chemically specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+). The results suggested that $PM_{2.5}$ was associated most significantly with mortality among the PM components. Although H^+ was not significantly associated with mortality in this and earlier analyses, the smaller sample size for H^+ than for other PM components made direct comparison difficult. Also, certain respiratory morbidity studies showed associations between hospital admissions and visits with components of PM in the fine-particle range. Thus, the 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Overall, then, the outcome of assessment of the above key issues in the 1996 PM AQCD can be thusly summarized: (1) observed PM effects are not likely seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) observed PM effects are not likely significantly confounded by weather; (3) observed PM effects may be confounded or modified to some extent by co-pollutants, and such extent may vary from season to season; (4) determining the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement/characterization error among pollutants (there was not sufficient information on this); (5) no clear evidence for any threshold for PM-mortality associations was reported (statistically identifying a threshold from existing data also was considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was conducted to investigate harvesting in nonepisodic U.S. data); and (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in light of historical data, biological plausibility, and results from morbidity studies, a greater role for fine particles than coarse particles was suggested as being likely.

9.6.2.1.2 Updated Epidemiologic Findings for Short-Term Ambient Particulate Matter Exposure Effects on Mortality

With regard to updating the assessment of PM effects in light of new epidemiologic information published since the 1996 PM AQCD, the most salient key points on relationships between short-term PM exposure and mortality (drawn from Chapter 6 discussions in this document) can be summarized as follows.

Since the 1996 PM AQCD, there have been more than 70 new time-series PM-mortality analyses, several of which investigated multiple cities using consistent data analytical approaches. With only few exceptions, the estimated mortality relative risks in these studies are generally positive, many are statistically significant, and they generally comport well with previously reported PM-mortality effects estimates delineated in the 1996 PM AQCD. There are also now numerous additional studies demonstrating associations between short-term (24-h) PM exposures and various morbidity endpoints.

Several new studies conducted time series analyses in multiple cities. The major advantage of these studies over meta-analyses for multiple "independent" studies is the consistency in data handling and model specifications, thus eliminating variation in results attributable to study design. Also, many of the cities included in these studies were ones for which no earlier time series analyses had been conducted. Therefore, unlike regular meta-analysis, they likely do not suffer from omission of negative studies caused by publication bias. Furthermore, any spatial or geographic variability of air pollution effects can be systematically evaluated in such multi-city analyses.

PM_{10} Effect Size Estimates. In the NMMAPS (Samet et al., 2000a,b) analysis of the 90 largest U.S. cities, the combined nationwide relative risk estimate was about a 2.3% increase in total mortality per 50-$\mu g/m^3$ increase in PM_{10}. The NMMAPS effect size estimates did vary somewhat by U.S. region (see Figures 6-2 and 6-3), with the largest estimate being for the Northeast (4.5% for a 1-day lag, the lag typically showing maximum effect size for most U.S. regions). Various other U.S. multi-city analyses, as well as single-city analyses, obtained PM_{10} effect sizes mainly in the range of 2.5 to 5.0% per 50-$\mu g/m^3$ increase in PM_{10}. There is some evidence that, if the effects over multiple days are considered, the effect size may be larger. What heterogeneity existed for the estimated PM_{10} risks across NMMAPS cities could not be explained with the city-specific explanatory variables (e.g., as the mean levels of pollution and

weather), mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error.

Also, the multi-city APHEA study showed generally consistent associations between mortality and both SO_2 and PM indices in western European cities, but not for central and eastern European cities. The pooled estimate of PM_{10}-mortality relative risks for western European cities comport well with estimates derived from U.S. data. The contrast between western and central/eastern Europe results might result from possible differences in representativeness of exposure measures, air pollution mix or resultant toxicity, proportions of sensitive subpopulations, climate, etc.

Certain other individual-city studies using similar methodology in analyses for each city (but not generating combined overall pooled effect estimates) also report variations in PM effect size estimates between cities and in their robustness to inclusion of gaseous copollutants in multi-pollutant models. Thus, one cannot entirely rule out that real differences may exist in excess risk levels associated with varying size distributions, number, or mass of the chemical constituents of ambient PM; the combined influences of varying co-pollutants present in the ambient air pollution mix from location to location or season to season; or to variations in the relationship between exposure and ambient PM concentration.

Nevertheless, there still appears to be reasonably good consistency among the results derived from those several new multi-city studies providing pooled analyses of data combined across multiple cities (thought to yield the most precise effect size estimates). Such analyses indicate the percent excess total (nonaccidental) deaths estimated per 50 $\mu g/m^3$ increase in 24-h PM_{10} to be 2.3% in the 90 largest U.S. cities (4.5% in the Northeast region); 3.4% in 10 U.S. cities; 3.5% in the eight largest Canadian cities; and about 2.0% in western European cities (using PM_{10} = TSP*0.55). These combined estimates are reasonably consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD (i.e., 1.5 to 8.5% per 50 $\mu g/m^3$ PM_{10}). These and other excess risk estimates from many other individual-city studies comport well with a number of new studies confirming increased cause-specific cardiovascular- and respiratory-related mortality, and those noted below as showing ambient PM associations with increased cardiovascular and respiratory hospital admissions and medical visits.

Fine and Coarse Particle Effect Size Estimates. Table 9-3 summarizes effects estimates (RR values) for increased mortality and/or morbidity associated with variable increments in short-term (24-h) exposures to ambient fine particles indexed by various fine PM indicators ($PM_{2.5}$, sulfates, H^+, etc.) in U.S. and Canadian cities. Table 9-4 shows analogous effect size estimates for inhalable thoracic fraction coarse particles (i.e., $PM_{10-2.5}$). In both tables, studies that were highlighted in comparable tables in the 1996 PM AQCD are indicated by italics.

The effect size estimates derived for $PM_{2.5}$ as an ambient fine particle indicator (especially those based on directly measured versus estimated $PM_{2.5}$ levels) generally appear to fall in the range of 2.0 to 8.5% increase in total (nonaccidental) deaths per 25-$\mu g/m^3$ increment in 24-h $PM_{2.5}$ for U.S. and Canadian cities. Cause-specific effects estimates appear to fall mainly in the range of 3.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for cardiovascular or combined cardiorespiratory mortality and 2.0 to 7.0% per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ for respiratory mortality in U.S. cities.

In the 1996 PM AQCD, there was only one study, the Harvard Six Cities study, in which the relative importance of fine and coarse particles was examined. That study suggested that fine particles, but not coarse particles, were associated with daily mortality. Now, more than 10 studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality (see Figure 9-7). Although some of these studies (e.g., the Santa Clara County, CA, analysis and the eight largest Canadian cities analysis) suggest that $PM_{2.5}$ is more important than $PM_{10-2.5}$ in predicting mortality fluctuations, several others (e.g., the Mexico City and Santiago, Chile studies) seem to suggest that $PM_{10-2.5}$ may be as important as $PM_{2.5}$ in certain locations (some shown to date being drier, more arid areas). Seasonal dependence of PM components' associations observed in some of the locations (e.g., higher coarse [$PM_{10-2.5}$] fraction estimates for summer than winter in Santiago, Chile) hint at possible contributions of biogenic materials (e.g., molds, endotoxins, etc.) to the observed coarse particle effects in at least some locations. Overall, for U.S. and Canadian cities, effect size estimates for the coarse fraction ($PM_{10-2.5}$) of those inhalable thoracic particles capable of depositing in TB and A regions of the respiratory tract generally appear to fall in the range of 0.5 to 6.0% excess total (nonaccidental) deaths per 25 $\mu g/m^3$ of 24-h $PM_{10-2.5}$. Respective increases for cause-specific mortality are 3.0 to 8.0% for cardiovascular and 3.0 to 16.0% for respiratory causes per 25-$\mu g/m^3$ increase in 24-h $PM_{10-2.5}$.

Chemical Components of Particulate Matter. Several new studies examined the role of specific chemical components of PM. Studies of U.S. and Canadian cities showed mortality

TABLE 9-3. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
Acute Total Mortality			
Six City:[A]			
Portage, WI	*$PM_{2.5}$*	*1.030 (0.993, 1.071)*	*11.2 (±7.8)*
Topeka, KS	*$PM_{2.5}$*	*1.020 (0.951, 1.092)*	*12.2 (±7.4)*
Boston, MA	*$PM_{2.5}$*	*1.056 (1.038, 1.0711)*	*15.7 (±9.2)*
St. Louis, MO	*$PM_{2.5}$*	*1.028 (1.010, 1.043)*	*18.7 (±10.5)*
Kingston/Knoxville, TN	*$PM_{2.5}$*	*1.035 (1.005, 1.066)*	*20.8 (±9.6)*
Steubenville, OH	*$PM_{2.5}$*	*1.025 (0.998, 1.053)*	*29.6 (±21.9)*
Overall Six-City Results	*$PM_{2.5}$*	*1.015 (1.011, 1.019)*	*Median 14.7*
Six U.S. Cities[B]	$PM_{2.5}$	Overall 1.010 (1.028, 1.053) Mobile 1.087 (1.042, 1.134) Coal 1.028 (1.006, 1.050) Crustal 0.944 (0.863, 1.032)	Means 11.3-30.5
Santa Clara County, CA[C]	$PM_{2.5}$	1.08 ($p < 0.01$)	13 (2, 105)
Buffalo, NY[D]	$SO_4^=$	1.034 (1.009, 1.062)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[E]	$PM_{2.5}$	1.042 ($p < 0.055$)	17.28 (-0.6, 72.6)
Detroit, MI[F]	$PM_{2.5}$	1.031 (0.994, 1.069)	18 (6, 86)
Phoenix, AZ[G]	$PM_{2.5}$	1.030 (1.000, 1.076)	13.0 (0, 42)
Phoenix, AZ[H]	$PM_{2.5}$	(>25 $\mu g/m^3$) 2.868 (1.126, 7.250) (<25 $\mu g/m^3$) 0.779 (0.610, 0.995)	NR
Los Angeles, CA[I]	$PM_{2.5}$	1.06 (NS, from figure)	22 (4, 86)
San Bernadino and Riverside Counties, CA[J]	Est. $PM_{2.5}$	1.003 (0.992, 1.015)	32.5 (9.3, 190.1)
Coachella Valley, CA[K]	$PM_{2.5}$	1.118 (1.013, 1.233)	16.8 (5, 48)
Boston, MA[L]	$PM_{2.5}$	1.053 (1.018, 1.090)	15.6 (±9.2)
Three New Jersey Cities:[M]			
Newark, NJ	$PM_{2.5}$	1.043 (1.028, 1.059)	42.1 (±22.0)
Camden, NJ	$PM_{2.5}$	1.057 (1.001, 1.115)	39.9 (±18.0)
Elizabeth, NJ	$PM_{2.5}$	1.018 (0.946, 1.095)	37.1 (±19.8)
Eight Canadian Cities[N]	$PM_{2.5}$	1.030 (1.011, 1.050)	13.3 (max 86)

TABLE 9-3 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
Toronto, Canada[O]	Est. $PM_{2.5}$	1.048 (1.033, 1.064)	18.0 (8, 90)
Montreal, Canada[P]	$PM_{2.5}$	1.044 (1.025, 1.063)	17.4 (2.2, 72.0)
Cause-Specific Mortality			
Cardiorespiratory:			
Three New Jersey Cities:[M]			
Newark, NJ	$PM_{2.5}$	1.051 (1.031, 1.072)	42.1 (±22.0)
Camden, NJ	$PM_{2.5}$	1.062 (1.006, 1.121)	39.9 (±18.0)
Elizabeth, NJ	$PM_{2.5}$	1.023 (0.950, 1.101)	37.1 (±19.8)
Total Cardiovascular:			
Santa Clara County, CA[C]	$PM_{2.5}$	1.07 ($p > 0.05$)	13 (2, 105)
Buffalo, NY)[D]	$SO_4^=$	1.040 (0.995, 1.088)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[F] (seven-county area)	$PM_{2.5}$	1.028 ($p < 0.055$)	17.28 (-0.6, 72.6)
Detroit, MI[G]	$PM_{2.5}$	1.032 (0.977, 1.089)	18 (6, 86)
Phoenix, AZ[H]	$PM_{2.5}$	1.187 (1.057, 1.332)	13.0 (0, 42)
Los Angeles, CA[I]	$PM_{2.5}$	1.266 (1.003, 1.048)	22 (4, 86)
San Bernadino and Riverside Counties, CA[J]	Est. $PM_{2.5}$	1.007 (0.997, 1.017)	32.5 (9.3, 190.1)
Coachella Valley, CA[K]	$PM_{2.5}$	1.086 (0.937, 1.258)	16.8 (5, 48)
Cerebrovascular:			
Los Angeles, CA[I]	$PM_{2.5}$	1.036 (0.994, 1.080)	22 (4, 86)
Total Respiratory:			
Santa Clara County, CA[C]	$PM_{2.5}$	1.13 ($p > 0.05$)	13 (2, 105)
Buffalo, NY[D]	$SO_4^=$	1.108 (1.007, 1.219)	61.7 (0.78, 390.5) nmol/m^3
Philadelphia, PA[F] (seven-county area)	$PM_{2.5}$	1.014 ($p > 0.055$)	17.28 (-0.6, 72.6)
Detroit, MI[G]	$PM_{2.5}$	1.023 (0.897, 1.166)	18 (6, 86)
San Bernadino and Riverside Counties, CA[J]	Est. $PM_{2.5}$	1.021 (0.997, 1.045)	32.5 (9.3, 190.1)

TABLE 9-3 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
COPD:			
Los Angeles, CA[I]	$PM_{2.5}$	1.027 (0.966, 1.091)	22 (4, 86)
Increased Hospitalization			
Ontario, Canada[Q]	*$SO_4^=$*	*1.03 (1.02, 1.04)*	*R = 3.1-8.2*
Ontario, Canada[R]	*$SO_4^=$* *O_3*	*1.03 (1.02, 1.04)* *1.03 (1.02, 1.05)*	*R = 2.0-7.7*
NYC/Buffalo, NY[S]	*$SO_4^=$*	*1.05 (1.01, 1.10)*	*NR*
Toronto, Canada[S]	*H^+ (Nmol/m^3)* *$SO_4^=$* *$PM_{2.5}$*	*1.16 (1.03, 1.30)** *1.12 (1.00, 1.24)* *1.15 (1.02, 1.78)*	*28.8 (NR/391)* *7.6 (NR, 48.7)* *18.6 (NR, 66.0)*
Total Respiratory:			
King County, WA[T]	PM_1	1.058 (1.011, 1.110)	NR
Toronto, Canada[U]	$PM_{2.5}$	1.085 (1.034, 1.138)	16.8 (1, 66)
Buffalo, NY[D]	$SO_4^=$	1.082 (1.042, 1.128)	61.7 (0.78, 390.5) nmol/m^3
Montreal, Canada[V]	$PM_{2.5}$	1.261 (1.059, 1.503)	Summer 93 12.2 (max 31)
Montreal, Canada[W]	$PM_{2.5}$	1.137 (0.998, 1.266)	18.6 (SD 9.3)
St. John, Canada[X]	$PM_{2.5}$	1.057 (1.006, 1.110)	Summer 93 8.5 (max 53.2)
Pneumonia:			
Detroit, MI[F]	$PM_{2.5}$	1.125 (1.037, 1.220)	18 (6, 86)
Respiratory infections:			
Toronto, Canada[U]	$PM_{2.5}$	1.108 (1.072, 1.145)	18.0 (max 90)
COPD:			
Atlanta, GA[Z]	$PM_{2.5}$	1.124 (0.921, 1.372)	19.4 (±9.35)
Detroit, MI[F]	$PM_{2.5}$	1.055 (0.953, 1.168)	18 (6, 86)
King County WA[AA]	$PM_{2.5}$	1.064 (1.009, 1.121)	18.1 (3, 96)
Los Angeles, CA[BB]	$PM_{2.5}$	1.051 (1.009, 1.094)	Median 22 (4, 86)
Toronto, Canada[Y]	$PM_{2.5}$	1.048 (0.998, 1.100)	18.0 (max 90)

TABLE 9-3 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
Asthma:			
Atlanta, GA[Z]	$PM_{2.5}$	1.023 (0.852, 1.227)	19.4 (±9.35)
Seattle, WA[CC]	$PM_{2.5}$	1.087 (1.033, 1.143)	16.7 (6, 32)
Seattle, WA[DD]	Est. $PM_{2.5}$	1.445 (1.217, 1.714)	4.8 (1.2, 32.4)
Toronto, Canada[Y]	$PM_{2.5}$	1.064 (1.025, 1.106)	18.0 (max 90)
Total Cardiovascular:			
Atlanta, GA[Y]	$PM_{2.5}$	1.061 (0.969, 1.162)	19.4 (±9.35)
Buffalo, NY[D]	$SO_4^=$	1.015 (0.987, 1.043)	61.7 (0.78, 390.5) nmol/m^3
Los Angeles, CA[EE]	$PM_{2.5}$	(65+) 1.043 (1.025, 1.061) (<65) 1.035 (1.018, 1.053)	Median 22 (4, 86)
St. John, Canada[X]	$PM_{2.5}$	1.151 (1.006, 1.110))	Summer 93 8.5 (max 53.2)
Toronto, Canada[U]	$PM_{2.5}$	1.059 (1.018, 1.102)	16.8 (1, 66)
Ischemic Heart Disease:			
Detroit, MI[F]	$PM_{2.5}$	1.043 (0.986, 1.104)	18 (6, 86)
Toronto, Canada[Y]	$PM_{2.5}$	1.080 (1.054, 1.108)	18.0 (max 90)
Dysrhythmias:			
Atlanta, GA[Z]	$PM_{2.5}$	1.061 (0.874, 1.289)	19.4 (±9.35)
Detroit, MI[F]	$PM_{2.5}$	1.032 (0.934, 1.140)	18 (6, 86)
Toronto, Canada[Y]	$PM_{2.5}$	1.061 (1.019, 1.104)	18.0 (max 90)
Heart Failure:			
Detroit, MI[F]	$PM_{2.5}$	1.091 (1.023, 1.162)	18 (6, 86)
Toronto, Canada[Y]	$PM_{2.5}$	1.066 (1.025, 1.108)	18.0 (max 90)
Cerebrovascular:			
Los Angeles, CA[EE]	$PM_{2.5}$	1.015 (0.992, 1.038)	Median 22 (4, 86)
Toronto, Canada[Y]	$PM_{2.5}$	"NEG" reported	18.0 (max 90)
Peripheral circulation diseases:			
Toronto, Canada[Y]	$PM_{2.5}$	"NEG" reported	18.0 (max 90)

TABLE 9-3 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
Stroke:			
Detroit, MI[F]	$PM_{2.5}$	1.018 (0.947, 1.095)	18 (6, 86)
Increased Respiratory Symptoms		Odd Ratio (95% CI) per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	
Southern California[FF]	*$SO_4^=$*	*1.48 (1.14, 1.91)*	*R = 2-37*
Six Cities[GG] (Cough)	*$PM_{2.5}$* *$SO_4^=$* *H^+*	*1.24 (1.00, 1.54)* *1.86 (0.86, 4.03)* *1.19 (0.66, 2.15)*	*18.0 (max 86.0)* *2.5 (max 15.1)* *18.1 (max 371.1) nmol/m^3*
Six Cities[GG] (Lower Resp. Symp.)	*$PM_{2.5}$* *$SO_4^=$* *H^+*	*1.58 (1.18, 2.10)* *6.82 (2.09, 17.35)* *1.16 (0.10, 13.73)*	*18.0 (max 86.0)* *2.5 (max 15.1)* *18.1 (max 371.1) nmol/m^3*
Uniontown, PA[HH] (Evening Cough)	*$PM_{2.5}$*	*1.45 (1.07, 1.97)*	*24.5 (max 88.1)*
Connecticut summer camp[II]	$SO_4^=$	1.71 (1.30, 2.25)	7.0 (1.1, 26.7)
State College, PA[JJ] (Wheeze)	$PM_{2.1}$	1.59 (0.94, 2.71)	23.5 (max 85.8)
State College, PA[JJ] (Cough)	$PM_{2.1}$	1.61 (1.21, 2.17)	23.5 (max 85.8)
State College, PA[JJ] (Cold)	$PM_{2.1}$	1.2.45 (1.29, 4.64)	23.5 (max 85.8)
Decreased Lung Function		PEFR change (L/min) per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	
Uniontown, PA[HH]	*$PM_{2.5}$*	*PEFR -1.38 (-2.77, 0.02)*	*24.5 (max 88.1)*
Uniontown, PA[KK] (Reanalysis)	$PM_{2.5}$	pm PEFR -1.52, (-2.80, -0.24)	24.5 (max 88.1)
State College, PA[KK] (Reanalysis)	$PM_{2.5}$	pm PEFR -0.93 (-1.88, 0.01)	23.5 (max 85.8)
Connecticut summer camp[II]	$SO_4^=$	PEFR -5.4 (-12.3, 1.52)	7.0 (1.1, 26.7)
Southwest, VA[LL]	$PM_{2.5}$	am PEFR -1.825 (-3.45, -0.21)	21.62 (3.48, 59.65)
State College, PA[JJ]	$PM_{2.1}$	pm PEFR -0.63 (-1.73, 0.44)	23.5 (max 85.8)

TABLE 9-3 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (± CI)** per 25-$\mu g/m^3$ PM Increase or 15-$\mu g/m^3$ $SO_4^=$ Increase or 75-nmol/m^3 H^+ increase	Reported PM Levels Mean (Min, Max)***
Philadelphia, PA[MM]	$PM_{2.5}$	am PEFR -3.18 (-6.64, 0.07) pm PEFR -0.91 (-4.04, 2.21)	22.2 (IQR 16.2)

* Studies highlighted in the 1996 CD are in italics; new studies in plain text.
** Relative Risk (95% Confidence Interval), except for Fairley (1999) and Lipfert et al. (2000), where insufficient data were available to calculate confidence intervals so p-value is given in parentheses.
*** Min, Max 24-h PM indicator level shown in parentheses unless otherwise noted as (±S.D.), NR = not reported, or R = range of values from min-max, no mean value reported.

References:

[A]Schwartz et al. (1996a)
[B]Laden et al. (2000)
[C]Fairley (1999)
[D]Gwynn et al. (2000)
[E]Lipfert et al. (2000a)
[F]Lippmann et al. (2000)
[G]Mar et al. (2000)
[H]Smith et al. (2000)
[I]Moolgavkar (2000a)
[J]Ostro (1995)
[K]Ostro et al. (2000)
[L]Schwartz (2000a)
[M]Tsai et al. (2000)
[N]Burnett et al. (2000)
[O]Burnett et al. (1998a)
[P]Goldberg et al. (2000)
[Q]Burnett et al. (1994)
[R]Burnett et al. (1995)
[S]Thurston et al. (1992, 1994)
[T]Lumley and Heagerty (1999)
[U]Burnett et al. (1997)
[V]Delfino et al. (1997)
[W]Delfino et al. (1998)
[X]Stieb et al. (2000)
[Y]Burnett et al. (1999)
[Z]Tolbert et al. (2000)
[AA]Moolgavkar et al. (2000)
[BB]Moolgavkar (2000b)
[CC]Sheppard et al. (1999)
[DD]Norris et al. (1999)
[EE]Moolgavkar (2000c)
[FF]Ostro et al. (1993)
[GG]Schwartz et al. (1994)
[HH]Neas et al. (1995)
[II]Thurston et al. (1997)
[JJ]Neas et al. (1996)
[KK]Schwartz and Neas (2000)
[LL]Naeher et al. (1999)
[MM]Neas et al. (1999)

TABLE 9-4. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES ($PM_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-$\mu g/m^3$ Increase	Reported PM Levels Mean (Min, Max)***
Acute Mortality			
Six Cities:[A]			
Portage, WI	*$PM_{10-2.5}$*	*1.013 (0.970, 1.058)*	*6.6 (±6.8)*
Topeka, KS	*$PM_{10-2.5}$*	*0.968 (0.920, 1.015)*	*14.5 (±12.2)*
Boston, MA	*$PM_{10-2.5}$*	*1.005 (0.985, 1.030)*	*8.8 (±7.0)*
St. Louis, MO	*$PM_{10-2.5}$*	*1.005 (0.983, 1.028)*	*11.9 (±8.5)*
Kingston/Knoxville, TN	*$PM_{10-2.5}$*	*1.025 (0.985, 1.066)*	*11.2 (±7.4)*
Steubenville, OH	*$PM_{10-2.5}$*	*1.061 (1.013, 1.111)*	*16.1 (±13.0)*
Overall Six-City Results	*$PM_{10-2.5}$*	*1.004 (0.999, 1.010)*	*Median 9.0*
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.013 (0.994, 1.032)	17.9 (0, 149)
Detroit, MI[C]	$PM_{10-2.5}$	1.040 (0.988, 1.094)	13 (4, 50)
Philadelphia, PA[D]	$PM_{10-2.5}$	1.052 ($p > 0.055$)	6.80 (-20.0, 28.3)
Phoenix, AZ[E]	$PM_{10-2.5}$	1.030 (0.995, 1.066)	33.5 (5, 187)
Phoenix, AZ[F]	$PM_{2.5}$	(>25 $\mu g/m^3$) 1.185 (1.069, 1.314) (<25 $\mu g/m^3$) 1.020 (1.005, 1.035)	NR
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.02 ($p > 0.05$))	11 (0, 45)
Eight Canadian Cities[H]	$PM_{10-2.5}$	1.018 (0.992, 1.044)	12.9 (max 99)
Cause-Specific Mortality			
Total Cardiovascular:			
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.026 (1.006, 1.045)	17.9 (0, 149)
Detroit, MI[C]	$PM_{10-2.5}$	1.078 (1.000, 1.162)	13 (4, 50)
Philadelphia, PA[D] (seven-county area)	$PM_{10-2.5}$	1.034 ($p > 0.055$)	6.80 (-20.0, 28.3)
Phoenix, AZ[E]	$PM_{10-2.5}$	1.064 (1.014, 1.117)	33.5 (5, 187)
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.03 ($p > 0.05$)	11 (0, 45)
Total Respiratory:			
Coachella Valley, CA[B]	$PM_{10-2.5}$	1.026 (1.006, 1.045)	17.9 (0, 149)
Detroit, MI[D]	$PM_{10-2.5}$	1.074 (0.910, 1.269)	13 (4, 50)
Philadelphia, PA[D] (seven-county area)	$PM_{10-2.5}$	1.030 ($p > 0.055$)	6.80 (-20.0, 28.3)
Santa Clara County, CA[G]	$PM_{10-2.5}$	1.16 ($p > 0.05$)	11 (0, 45)

TABLE 9-4 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES ($PM_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-$\mu g/m^3$ Increase	Reported PM Levels Mean (Min, Max)***
Increased Hospitalization			
Total Respiratory:			
Toronto, Canada[I]	$PM_{10-2.5}$	1.125 (1.052, 1.20)	11.6 (1, 56)
Pneumonia:			
Detroit, MI[C]	$PM_{10-2.5}$	1.119 (1.006, 1.244)	13 (4, 50)
Respiratory infections:			
Toronto, Canada[J]	$PM_{10-2.5}$	1.093 (1.046, 1.142)	12.2 (max 68)
COPD:			
Atlanta, GA[K]	$PM_{10-2.5}$	0.770 (0.493, 1.202)	9.39 (±4.52)
Detroit, MI[C]	$PM_{10-2.5}$	1.093 (0.958, 1.247)	13 (4, 50)
Toronto, Canada[J]	$PM_{10-2.5}$	1.128 (1.049, 1.213)	12.2 (max 68)
Total Cardiovascular:			
Atlanta, GA[K]	$PM_{10-2.5}$	1.176 (0.954, 1.450)	9.39 (±4.52)
Toronto, Canada[I]	$PM_{10-2.5}$	1.205 (1.082, 1.341)	11.6 (1, 56)
Ischemic Heart Disease:			
Detroit, MI[C]	$PM_{10-2.5}$	1.105 (1.027, 1.189	13 (4, 50)
Toronto, Canada[J]	$PM_{10-2.5}$	1.037 (1.013, 1.062))	12.2 (max 68)
Dysrhythmias:			
Detroit, MI[C]	$PM_{10-2.5}$	1.002 (0.877, 1.144)	13 (4, 50)
Atlanta, GA[K]	$PM_{10-2.5}$	1.532 (1.021, 2.30)	9.39 (±4.52)
Toronto, Canada[J]	$PM_{10-2.5}$	1.051 (0.998, 1.108)	12.2 (max 68)
Heart Failure:			
Detroit, MI[C]	$PM_{10-2.5}$	1.052 (0.967, 1.144)	13 (4, 50)
Toronto, Canada[J]	$PM_{10-2.5}$	1.079 (1.023, 1.138)	12.2 (max 68)
Stroke:			
Detroit, MI[C]	$PM_{10-2.5}$	1.049 (0.953, 1.155)	13 (4, 50)
Cerebrovascular:			
Toronto, Canada[J]	$PM_{10-2.5}$	"NEG" reported	12.2 (max 68)
Peripheral Circulation Diseases:			
Toronto, Canada[J]	$PM_{10-2.5}$	1.056 (1.003, 1.112)	12.2 (max 68)

TABLE 9-4 (cont'd). EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF COARSE-FRACTION PARTICLES ($PM_{10-2.5}$) FROM U.S. AND CANADIAN STUDIES*

Study Location	Indicator	RR (±CI)** per 25-$\mu g/m^3$ Increase	Reported PM Levels Mean (Min, Max)***
Asthma:			
Seattle, WA[L]	$PM_{10-2.5}$	1.111 (1.028, 1.201)	16.2 (6, 29)
Toronto, Canada[J]	$PM_{10-2.5}$	1.111 (1.058, 1.166)	12.2 (max 68)
Increased Respiratory Symptoms		Odds Ratio (95% CI) per 25-$\mu g/m^3$ PM Increase	
Six U.S. Cities[M] (Lower Respiratory Symptoms)	$PM_{10-2.5}$	1.51 (0.94, 4.87)	NR
Six U.S. Cities[M] (Cough)	$PM_{10-2.5}$	1.77 (1.24, 2.55)	NR
Southwest Virginia[N] (Runny or Stuffy Nose)	$PM_{10-2.5}$	2.62 (1.16, 5.87)	NR
Decreased Lung Function		PEFR change (L/min) per 25-$\mu g/m^3$ PM Increase	
Southwest Virginia[O]	$PM_{10-2.5}$	am PEFR 5.3 (2.6, 8.0)	27.07 (4.89, 69.07)
Uniontown, PA[M] (Reanalysis)	$PM_{10-2.5}$	pm PEFR +1.73 (5.67, -2.2)	NR
State College, PA[M] (Reanalysis)	$PM_{10-2.5}$	pm PEFR -0.28 (2.86, -3.45)	NR
Philadelphia, PA[P]	$PM_{10-2.5}$	am PEFR -4.31 (-11.44, 2.75)	9.5 (IQR 5.1)

* Studies highlighted in the 1996 CD are in italics; new studies in plain text.
** Relative Risk (95% Confidence Interval), except for Fairley (1999) and Lipfert et al. (2000), where insufficient data were available to calculate confidence intervals so p-value is given in parentheses.
*** Min, Max 24-h PM indicator level shown in parentheses unless otherwise noted as (±S.D.), NR = not reported, or R = range of values from min-max, no mean value reported.

References:

[A]Schwartz et al., (1996a)
[B]Ostro et al. (2000)
[C]Lippmann et al (2000)
[D]Lipfert et al (2000)
[E]Mar et al. (2000)
[F]Smith et al. (2000)
[G]Fairley (1999)
[H]Burnett et al. (2000)
[I]Burnett et al. (1997)
[J]Burnett et al. (1999)
[K]Tolbert et al. (2000)
[L]Sheppard et al. (1999)
[M]Schwartz and Neas (2000)
[N]Naeher et al. (1999)
[O]Zhang et al. (2000)
[P]Neas et al. (1999)

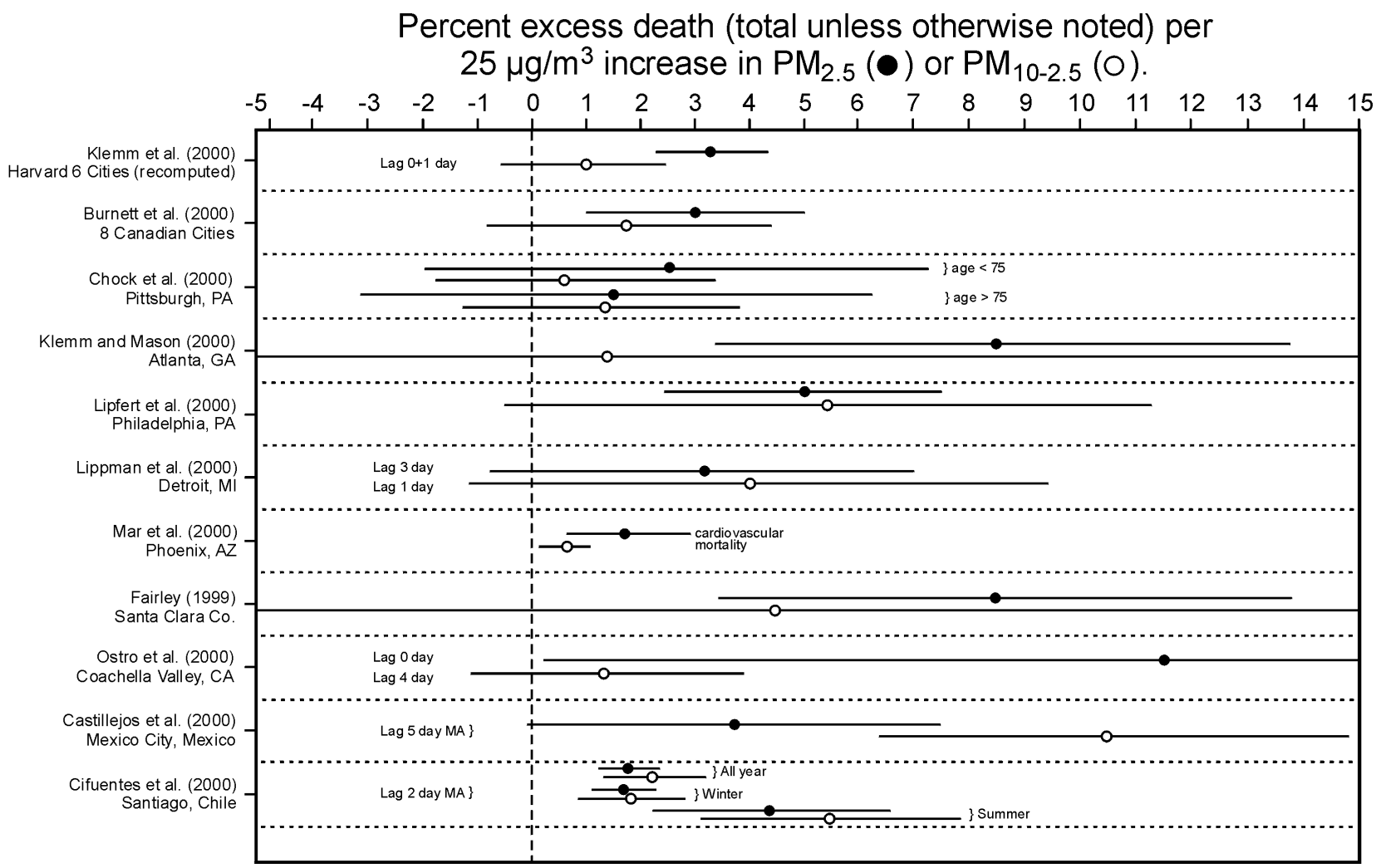

Figure 9-7. Percent excess risks estimated per 25-μg/m^3 increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10-2.5}$ data for multiple years. All lags = 1 day, unless indicated otherwise.

associations with one or more of several specific fine particle components of PM, including H^+, sulfate, nitrate, as well as COH; but their relative importance varied from city to city, likely depending, in part, on their concentrations (e.g., no clear associations in those cities where H^+ and sulfate levels were very low [i.e., circa nondetection limits]). Figure 9-8 depicts relatively consistent estimates of total mortality excess risk resulting from a 5-$\mu g/m^3$ increase in sulfate, possibly reflecting impacts of sulfate per se or perhaps sulfate serving as a surrogate for fine particles in general. Sulfate effect size estimates generally fall in the range of 1 to 4% excess total mortality per 5-$\mu g/m^3$ increase for U.S. and Canadian cities.

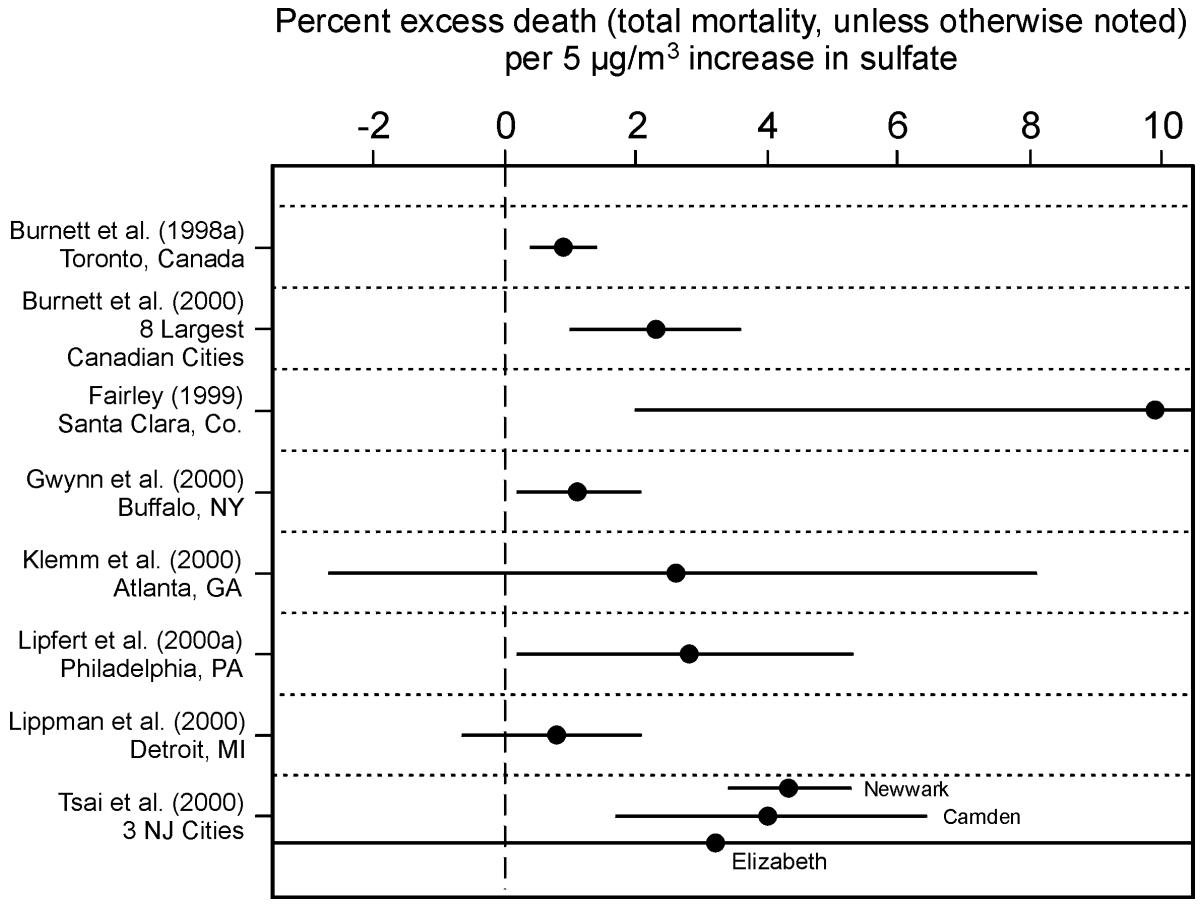

Figure 9-8. Relative risks estimated per 5-$\mu g/m^3$ increase in sulfate from U.S. and Canadian studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

A significant factor in some western cities is the occasional occurrence of high levels of windblown crustal particles that constitute the major part of the coarse PM fraction and a substantial fraction of intermodal fine particles ($PM_{2.5-1}$). The small-size tail of the windblown crustal particles extends into the $PM_{2.5-1}$ size range (intermodal), at times contributing significantly to $PM_{2.5}$. Claiborn et al. (2000) report that in Spokane, WA, $PM_{2.5}$ constitutes about 30% of PM_{10} on dust event days, but 48% on days preceding the dust event. The intermodal fraction represents about 51% of $PM_{2.5}$ during windblown dust events, about 28% on preceding days. However, PM_1 in Spokane often shows little change during dust events, when coarse particles (presumably crustal particles) are transported into the region. The lack of increased mortality during periods of time with high wind speeds and presumably high crustal material concentrations was shown by Schwartz et al. (1999) for Spokane, and by Pope et al. (1999a) for three cities in the Wasatch front region of Utah. Other recent studies suggest that coarse particles also may be associated with excess mortality as well as fine particles in certain U.S. locations e.g., in Phoenix, AZ (Smith et al., 2000; Clyde et al., 2000; Mar et al., 2000) the Coachella Valley of California (Ostro et al., 2000), Mexico City (Castillejos et al., 2000) or Santiago, Chile (Cifuentes et al., 2000). However, the coarse particle association with mortality may not be caused by the crustal components. An important advantage of using source profiles for $PM_{2.5}$ in western cities is that it allows separation of crustal PM from accumulation-mode PM derived from anthropogenic origins.

Several new studies highlighted in Chapter 6 conducted source-oriented evaluations of PM components using factor analysis (see Table 9-5). The results of these studies (Laden et al., 2000; Mar et al., 2000; Tsai et al., 2000; Özkaynak et al., 1996) generally suggest that a number of combustion-related source-types are associated with excess mortality risk, including: regional sulfate; automobile emissions; coal combustion; oil burning; and vegetative (biomass) burning. In contrast, the crustal factor from fine particles was generally not positively associated with total mortality, with Mar et al. (2000) reporting a negative association between the crustal component of $PM_{2.5}$ and cardiovascular mortality.

However, these source-oriented evaluation results are derived from relatively limited underlying analytic bases and must be viewed with caution at this time. For example, whereas Laden et al. (2000) had 6211 days of every-other-day data from the Harvard Six City Study of eastern/midwest U.S. cities, they had only elements in $PM_{2.5}$ analyzed by X-ray fluorescence

TABLE 9-5. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PARTICULATE MATTER COMPONENTS IN RECENT STUDIES

Author, City	Source Types Identified (or Suggested) and Associated Tracers	Source Types Associated with Mortality. Comments.
Laden et. al., (2000) Harvard Six Cities 1979-1988	Soil and crustal material: Si Motor vehicle emissions: Pb Coal combustion: Se Fuel oil combustion: V Salt: Cl Note: the trace elements are from $PM_{2.5}$ samples	The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000). Phoenix, AZ 1995-1997	*$PM_{2.5}$ (from DFPSS) trace elements:* Motor vehicle emissions and resuspended road dust: Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 Soil: Al, Si, and Fe Vegetative burning: OC and K_S (soil-corrected potassium) Local SO_2 sources: SO_2 Regional sulfate: S ---------- *$PM_{10-2.5}$ (from dichot) trace elements:* Soil: Al, Si, K, Ca, Mn, Fe, Sr, and Rb A source of coarse fraction metals: Zn, Pb, and Cu A marine influence: Cl	$PM_{2.5}$ factors results: Soil factor and local SO_2 factor were negatively associated with total mortality. Regional sulfate was positively associated with total mortality on the same day, but negatively associated on the lag 3 day. Motor vehicle factor, vegetative burning factor, and regional sulfate factor were significantly positively associated with cardiovascular mortality. Factors from dichot $PM_{10-2.5}$ trace elements were not analyzed for their associations with mortality because of the small sample size (every-third-day samples from June 1996).
Özkaynak et al. (1996). Toronto, Canada.	Motor vehicle emissions: CO, COH, and NO_2	Motor vehicle factor was a significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	Motor vehicle emissions: Pb and CO Geological (Soil): Mn and Fe Oil burning: V and Ni Industrial: Zn, Cu, and Cd (separately) Sulfate/secondary aerosol: Sulfate Note: The trace elements are from PM_{15} samples.	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.

(XRF) spectroscopy (no organic PM or gases) and they used Pb as a tracer to identify a motor vehicle source, Se to identify a coal combustion source, and Si as a tracer for soil. The "motor vehicle" and "coal combustion" sources were statistically significant for total mortality as well as

mortality resulting from ischemic heart disease and respiratory diseases (COPD plus pneumonia). The crustal component had a negative association with total mortality.

The Mar et al. (2000) study had 3 years of pollutant data for Phoenix, AZ. In addition to elements determined by XRF, they had pollutant gases (CO, NO_2, SO_2, and O_3) and total, organic, and elemental carbon. They were able to identify five sources. Motor vehicles (plus resuspended road dust), vegetative burning, and regional sulfate all had statistically significant associations with cardiovascular mortality, but soil (indexed by Si and Al, as crustal markers) had a statistically significant negative association.

Tsai et al. (2000) had only 156 days of data and used measurements of CO, sulfate, and some elements; and they did not have Si, Ca, Al, or Mg as soil tracers nor Se as a tracer of coal combustion, although much of the sulfate probably came from coal combustion. They had three fractions of extractable organic matter, but these did not appear to be useful in determining source factors. Nevertheless, they were still able to identify motor vehicles, oil burning, and sulfate as statistically significant ($p > 0.05$) factors for both total daily deaths and combined cardiovascular and respiratory daily deaths in at least one or another of the three New Jersey cities studied (Newark, Camden, and Elizabeth). Also, an industrial source containing Zn and Cd was statistically significant for total deaths in Newark; and an industrial source containing Cd was marginally statistically significant for cardiorespiratory disease in Elizabeth.

Özkaynak et al. (1996) had only TSP, coefficient of haze (COH), and gases; however, they reported that a factor with COH, CO, and NO_2 (considered to be representative of motor vehicle emissions) was associated with mortality in Toronto, Canada.

None of these studies had measurements of nitrate or semivolatile organic compounds nor did they use the newest, and most effective, techniques for source apportionment. For example, using positive matrix factorization, Ramadan et al. (2000) were able to determine eight factors using the same data set as Mar et al. (2000). In spite of these deficiencies, all four studies were able to associate one or more types of morality with motor vehicles, several with coal combustion, and three with sulfate.

Factor analyses also were described briefly in a report by Lippmann et al. (2000). In that study, neither sulfate nor acid aerosols were related significantly to morbidity or mortality, but the concentrations were extremely low (with about 70% of the acid measurements below detection limit).

It is difficult to compare these source-related assessments. They are based on different regions of the country over different periods of time when the sources of particles and other urban air pollutants were changing greatly. Furthermore, each of these studies constructed factors based on city-specific data. Thus, the factors in each study are based on the idiosyncrasies of the specific data set for each city in the study, so the factors may indeed represent different sources in different locations. Nevertheless, although somewhat limited at this time, the new factor analysis results appear to implicate ambient PM derived from fossil fuel (oil, coal) combustion and vegetative burning, and secondarily formed sulfates as important contributors to observed mortality effects, but not crustal particles.

In summary, there is evidence that exposure to particles from several different source categories and, of different composition and size may have independent associations with health outcomes. The excess risks from different types of combustion sources (coal, oil, gasoline, wood, and vegetation) may vary from place to place and from time to time, so that substantial intra-regional and inter-regional heterogeneity would be expected. Likewise, although earlier evaluations in the 1996 PM AQCD seemed to indicate coarse particles and intermodal particles of crustal composition as not likely being associated with adverse health effects, there are now some reasonably credible studies suggesting that coarse particles (although not necessarily those of crustal composition) may sometimes be as associated with excess mortality in at least some locations.

9.6.2.2 Updated Epidemiologic Findings for Long-Term Particulate Matter Exposure Effects on Mortality

The 1996 PM AQCD indicated that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins (see appendix Table 9A-3). The PM effect size estimates for total mortality from these studies also indicated that a substantial portion of these deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events. Table 9-6 shows long-term exposure effects estimates (RR values) per variable increments in ambient PM indicators in U.S. and Canadian cities, including results from newer analyses since the 1996 PM AQCD.

TABLE 9-6. EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Increased Total Mortality in Adults		Relative Risk (95% CI)	
Six City[B]	*$PM_{15/10}$ (20 $\mu g/m^3$)*	*1.18 (1.06-1.32)*	*18-47*
	$PM_{2.5}$ (20 $\mu g/m^3$)	*1.28 (1.09-1.51)*	*11-30*
	$SO_4^=$ (15 $\mu g/m^3$)	*1.46 (1.16-2.16)*	*5-13*
ACS Study[C] *(151 U.S. SMSA)*	*$PM_{2.5}$ (20 $\mu g/m^3$)*	*1.14 (1.07-1.21)*	*9-34*
	$SO_4^=$ (15 $\mu g/m^3$)	*1.10 (1.06-1.16)*	*4-24*
Six City Reanalysis[D]	$PM_{15/10}$ (20 $\mu g/m^3$)	1.19 (1.06-1.34)	18.2-46.5
	$PM_{2.5}$ (20 $\mu g/m^3$)	1.28 (1.09-1.51)	11.0-29.6
ACS Study Reanalysis[D]	$PM_{15/10}$ (20 $\mu g/m^3$) (SSI)	1.02 (0.99-1.04)	58.7 (34-101)
	$PM_{2.5}$ (20 $\mu g/m^3$)	1.14 (1.08-1.21)	9.0-33.4
Southern California[E]	PM_{10} (50 $\mu g/m^3$)	1.242 (0.955-1.616) (males)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	1.082 (1.008-1.162) (males)	
	PM_{10} (50 $\mu g/m^3$)	0.879 (0.713-1.085) (females)	51 (±17)
	PM_{10} (cutoff = 30 days/year >100 $\mu g/m^3$)	0.958 (0.899-1.021) (females)	
Increased Bronchitis in Children		Odds Ratio (95% CI)	
Six City[F]	*$PM_{15/10}$ (50 $\mu g/m^3$)*	*3.26 (1.13, 10.28)*	*20-59*
Six City[G]	*TSP (100 $\mu g/m^3$)*	*2.80 (1.17, 7.03)*	*39-114*
24 City[H]	*H^+ (100 nmol/m^3)*	*2.65 (1.22, 5.74)*	*6.2-41.0*
24 City[H]	*$SO_4^=$ (15 $\mu g/m^3$)*	*3.02 (1.28, 7.03)*	*18.1-67.3*
24 City[H]	*$PM_{2.1}$ (25 $\mu g/m^3$)*	*1.97 (0.85, 4.51)*	*9.1-17.3*
24 City[H]	*PM_{10} (50 $\mu g/m^3$)*	*3.29 (0.81, 13.62)*	*22.0-28.6*
Southern California[I]	*$SO_4^=$ (15 $\mu g/m^3$)*	*1.39 (0.99, 1.92)*	—
12 Southern California communities[J] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	0.94 (0.74, 1.19) 1.16 (0.79, 1.68)	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[K] (children with asthma)	PM_{10} (19 $\mu g/m^3$) PM_{25} (15 $\mu g/m^3$) Acid vapor (1.8 ppb)	1.4 (1.1, 1.8) 1.4 (0.9, 2.3) 1.1 (0.7, 1.6)	13.0-70.7 6.7-31.5 1.0-5.0 ppb

TABLE 9-6 (cont'd). EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Increased Cough in Children		Odds Ratio (95% CI)	
12 Southern California communities[J] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	1.06 (0.93, 1.21) 1.13 (0.92, 1.38)	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[K] (children with asthma)	PM_{10} (19 $\mu g/m^3$) PM_{25} (15 $\mu g/m^3$) Acid vapor (1.8 ppb)	1.1 (0.0.8, 1.7) 1.3 (0.7, 2.4) 1.4 (0.9, 2.1)	13.0-70.7 6.7-31.5 1.0-5.0 ppb
Increased Obstruction in Adults			
Southern California[L]	PM_{10} (cutoff of 42 days/year >100 $\mu g/m^3$)	1.09 (0.92, 1.30)	NR
Decreased Lung Function in Children			
Six City[F]	*$PM_{15/10}$ (50 $\mu g/m^3$)*	*NS Changes*	*20-59*
Six City[G]	*TSP (100 $\mu g/m^3$)*	*NS Changes*	*39-114*
24 City[M]	*H^+ (52 nmoles/m^3)*	*–3.45% (-4.87, -2.01) FVC*	*6.2-41.0*
24 City[M]	*$PM_{2.1}$ (15 $\mu g/m^3$)*	*–3.21% (-4.98, -1.41) FVC*	*18.1-67.3*
24 City[M]	*$SO_4^=$ (7 $\mu g/m^3$)*	*–3.06% (-4.50, -1.60) FVC*	*9.1-17.3*
24 City[M]	*PM_{10} (17 $\mu g/m^3$)*	*–2.42% (-4.30, -.0.51) FVC*	*22.0-28.6*
12 Southern California communities[N] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	-24.9 (-47.2, -2.6) FVC -24.9 (-65.08, 15.28) FVC	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[N] (all children)	PM_{10} (25 $\mu g/m^3$) Acid vapor (1.7 ppb)	-32.0 (-58.9, -5.1) MMEF -7.9 (-60.43, 44.63) MMEF	28.0-84.9 0.9-3.2 ppb
12 Southern California communities[O] (4^{th} grade cohort)	PM_{10} (51.5 $\mu g/m^3$) $PM_{2.5}$ (25.9 $\mu g/m^3$) $PM_{10-2.5}$ (25.6 $\mu g/m^3$) Acid vapor (4.3 ppb)	-0.58 (-1.14, -0.02) FVC growth -0.47 (-0.94, 0.01) FVC growth -0.57 (-1.20, 0.06) FVC growth -0.57 (-1.06, -0.07) FVC growth	NR
12 Southern California communities[O] (4^{th} grade cohort)	PM_{10} (51.5 $\mu g/m^3$) $PM_{2.5}$ (25.9 $\mu g/m^3$) $PM_{10-2.5}$ (25.6 $\mu g/m^3$) Acid vapor (4.3 ppb)	-1.32 (-2.43, -0.20) MMEF growth -1.03 (-1.95, -0.09) MMEF growth -1.37 (-2.57, -0.15) MMEF growth -1.03 (-2.09, 0.05) MMEF growth	NR

TABLE 9-6 (cont'd). EFFECT ESTIMATES PER INCREMENTS[A] IN LONG-TERM MEAN LEVELS OF FINE AND INHALABLE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels * Means ($\mu g/m^3$)
Decreased Lung Function in Adults			
Southern California[P] (% predicted FEV_1, females)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	+0.9 % (-0.8, 2.5) FEV_1	52.7 (21.3, 80.6)
Southern California[P] (% predicted FEV_1, males)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	+0.3 % (-2.2, 2.8) FEV_1	54.1 (20.0, 80.6)
Southern California[P] (% predicted FEV_1, males whose parents had asthma, bronchitis, emphysema)	PM_{10} (cutoff of 54.2 days/year >100 $\mu g/m^3$)	-7.2 % (-11.5, -2.7) FEV_1	54.1 (20.0, 80.6)
Southern California[P] (% predicted FEV_1, females)	$SO_4^=$ (1.6 $\mu g/m^3$)	Not reported	7.4 (2.7, 10.1)
Southern California[P] (% predicted FEV_1, males)	$SO_4^=$ (1.6 $\mu g/m^3$)	-1.5 % (-2.9, -0.1) FEV_1	7.3 (2.0, 10.1)

*Range of mean PM levels given unless, as indicated, studies reported overall study mean (min, max), or mean (±SD); NR=not reported.
[A]Results calculated using PM increment between the high and low levels in cities, or other PM increments given in parentheses; NS Changes = No significant changes.

References:
[B]Dockery et al. (1993)
[C]Pope et al. (1995)
[D]Krewski et al. (2000)
[E]Abbey et al. (1999)
[F]Dockery et al. (1989a)
[G]Ware et al. (1986)
[H]Dockery et al. (1996)
[I]Abbey et al. (1995a,b,c)
[J]Peters et al. (1999b)
[K]McConnell et al. (1999)
[L]Berglund et al. (1999)
[M]Raizenne et al. (1996)
[N]Peters et al. (1999a)
[O]Gauderman et al. (2000)
[P]Abbey et al. (1998)

One of the most important advances since the 1996 PM AQCD is the substantial verification and extension of the findings of the Six City prospective cohort study (Dockery et al., 1993) and the cohort study relating American Cancer Society (ACS) health data to fine-particle data from 50 cities and sulfate data from 151 cities (Pope et al., 1995). The reanalyses, sponsored by the Health Effects Institute (HEI), included a data audit, replication of

the original investigators' findings, and additional analyses to explore the sensitivity of the original findings to other model specifications. The investigators of the HEI Reanalysis Project (Krewski et al., 2000) first performed a data audit, using random samples to verify the accuracy of the data sets used in the original Six City analyses, including death certificate data, air pollution data, and socioeconomic data. In general, the air pollution data were reproducible and correlated highly with the original aerometric data in Pope et al. (1995).

The reanalyses substantially verified the findings of the original investigators, with $PM_{2.5}$ or sulfate relative risk (RR) estimates for total mortality and for cardiopulmonary mortality differing at most by ±0.02 (±2% excess risk) from the least polluted to the most polluted cities in the study. A larger difference was noted for the $PM_{2.5}$ lung cancer relative risk in the Six Cities study, 1.37 originally and 1.43 in the reanalysis, neither estimate being statistically significant. The sensitivity analyses for the Six Cities study found generally similar results with other individual covariates included. The time-dependent covariate model for total mortality (taking into account higher postexposures in early years of the study and changes over time to the last years of the study) had a substantially lower RR than the model without time-dependent covariates. Educational level made a large difference, with individuals having less than a high school education at much greater risk for mortality than those with any postsecondary education.

Among the ecological covariates, sulfates adjusted for artifact had little effect on the risk estimates for total mortality compared to that without adjustment, but, in the ACS study, the filter adjustment actually increased the relative risk for all causes and cardiopulmonary mortality, while substantially reducing the estimated sulfate effect on lung cancer. Inclusion of SO_2 as an additional ecological covariate greatly reduced the estimated $PM_{2.5}$ and sulfate effects in the ACS study, whereas a spatial model including SO_2 effects caused only a modest reduction of the estimated $PM_{2.5}$ and sulfate effects. However, the SO_2 effects were reduced greatly when sulfates were included in the model. Sulfur dioxide and sulfates often are highly correlated, because of the formation of secondary sulfates.

Many model selection issues in the prospective cohort studies are analogous to those in the time series analyses. One issue of particular concern is whether the exposure indices used in the analyses adequately characterize the exposure of the participants in the study during the months or years preceding death. This question is particularly conspicuous in regard to the Pope et al. (1995) study, in which $PM_{2.5}$ and sulfate data were collected in the 1979 to 1982 period from the

EPA AIRS database and the Inhalable Particle Network, largely preceding the collection of the ACS cohort data by only a few years, and so possibly not adequately reflecting exposure to presumably much higher PM concentrations occurring long before the cohort was recruited, nor exposure to presumably lower concentrations during the study. This issue was raised in the 1996 PM AQCD. However, the Six Cities Study did have air pollution data and repeated survey data over time, with $PM_{2.5}$ and sulfate data measured every other day and sometimes daily, and so the new investigators were able to use the information about time-dependent cumulative PM concentrations during the course of the study. Changes in smoking status and body mass index over the 10 to12 years of the study had little effect on risk estimates, but taking into account the decrease in particle concentrations from the earlier years to the later years reduced the effect size estimate substantially, although it remained statistically significant. Nevertheless, overall, the reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) "replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

The shape of the relationship of concentration to mortality also was explored. Preliminary findings suggest some possible nonlinearity, but further study is needed. Among the most important new findings of the study are spatial relationships between mortality and air pollution, discussed later below.

With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies generally have found that the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, was the PM constituent most consistently associated with chronic PM exposure-mortality. Although the relative measurement errors of the various PM constituents must be further evaluated as a possible source of bias in these estimate comparisons, the Harvard Six-Cities study and the latest reported AHSMOG prospective semi-individual study results (Abbey, et al., 1999a,b,c; McConnell et al., 2000) studies are both indicative of the fine mass components of PM likely being associated more strongly with the mortality effects of PM than coarse PM components; and the ACS study, which only evaluated fine particle indicators, further substantiates ambient fine particle effects.

Several other new studies report epidemiologic evidence indicating that: (a) PM exposure early in pregnancy (during the first month) may be associated with slowed intrauterine growth

leading to low birth weight events (Dejmek et al., 1999); and (b) early postnatal PM exposures may lead to increased infant mortality (Woodruff et al., 1997; Boback and Leon, 1999; Loomis et al., 1999; Lipfert et al., 2000b).

Recent investigations of the public health implications of effect estimates for long-term PM exposures also were reviewed in Chapter 6. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne PM of ambient origin can have substantial effects on life expectancy. For example, a calculation for the 1969 to 71 life table for U.S. white males indicated that a chronic exposure increase of 10 $\mu g/m^3$ PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25. The new evidence noted above of infant mortality associations with PM exposure suggests that life shortening in the entire population from long-term PM exposure could well be significantly larger than estimated by Brunekreef (1997).

9.6.2.3 Relationships of Ambient Particulate Matter Concentrations to Morbidity Outcomes

New epidemiology studies add greatly to the overall database relating morbidity outcomes to ambient PM levels. These include much additional evidence for cardiovascular and respiratory diseases being related to ambient PM. The newer epidemiology studies expand the evidence on cardiovascular (CVD) disease and are discussed first below, followed by discussion of respiratory disease effects with particular emphasis on newly enhanced evidence for PM-asthma relationships.

9.6.2.3.1 Cardiovascular Effects of Ambient Particulate Matter Exposures

About 75% of all U.S. deaths occur in persons at least 65 years old, and, of these, nearly 40% are for cardiac causes (nearly 45%, if deaths from cerebrovascular causes are also included). Thus, if ambient PM exposure indeed produces increased total mortality in the elderly, it would seem possible that cardiovascular (CVD) deaths may be involved.

Cardiovascular Hospital Admissions. Just two studies were available for review in the 1996 PM AQCD that provided data on acute cardiovascular morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time series design using

standard statistical methods. Analyzing 4 years of data on the ≥65-year-old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett and colleagues (1995) reported significant associations between particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk because of sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that, "There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints." The PM AQCD went on to state that acute impacts on CVD admissions had been demonstrated for elderly populations (i.e., ≥65), but that insufficient data existed to assess relative impacts on younger populations.

Although the literature still remains relatively sparse, an important new body of data now exists that both extends the available quantitative information on relationships between ambient PM pollution and hospital CVD admissions, and that, more intriguingly, illuminates some of the physiological changes that may occur on the mechanistic pathway leading from PM exposure to adverse cardiac outcomes. Figure 9-9 depicts excess risk estimates derived from 10 studies of acute PM_{10} exposure effects on CVD admissions in U.S. cities. Although new studies depicted in Figure 9-9 have reported generally consistent associations between daily hospitalizations for cardiovascular disease and measures of PM, the data not only implicate PM, but also CO and NO_2 as well, possibly because of covarying of PM and these other gaseous pollutants derived from common emission sources (e.g., motor vehicles). Taken as a whole, this body of evidence suggests that PM is likely an important risk factor for cardiovascular hospitalizations in the United States.

For example, in the recently published NMMAPS 14-city analysis of daily CVD hospital admissions in persons 65 and older in relation to PM_{10} (Samet et al., 2000a,b). The mean risk estimate (for average 0-1 day lag) was a 8.5% increase in CVD admissions per 50 $\mu g/m^3$ PM_{10} (95% CI: 1.0 to 33.0%). No relationship was observed between city-specific risk estimates and measures of socioeconomic status, including percent living in poverty, percent non-white, and percent with college educations. In another study, remarkably consistent PM_{10} associations with cardiovascular admissions were observed across eight U.S. metropolitan areas, with a 25 $\mu g/m^3$

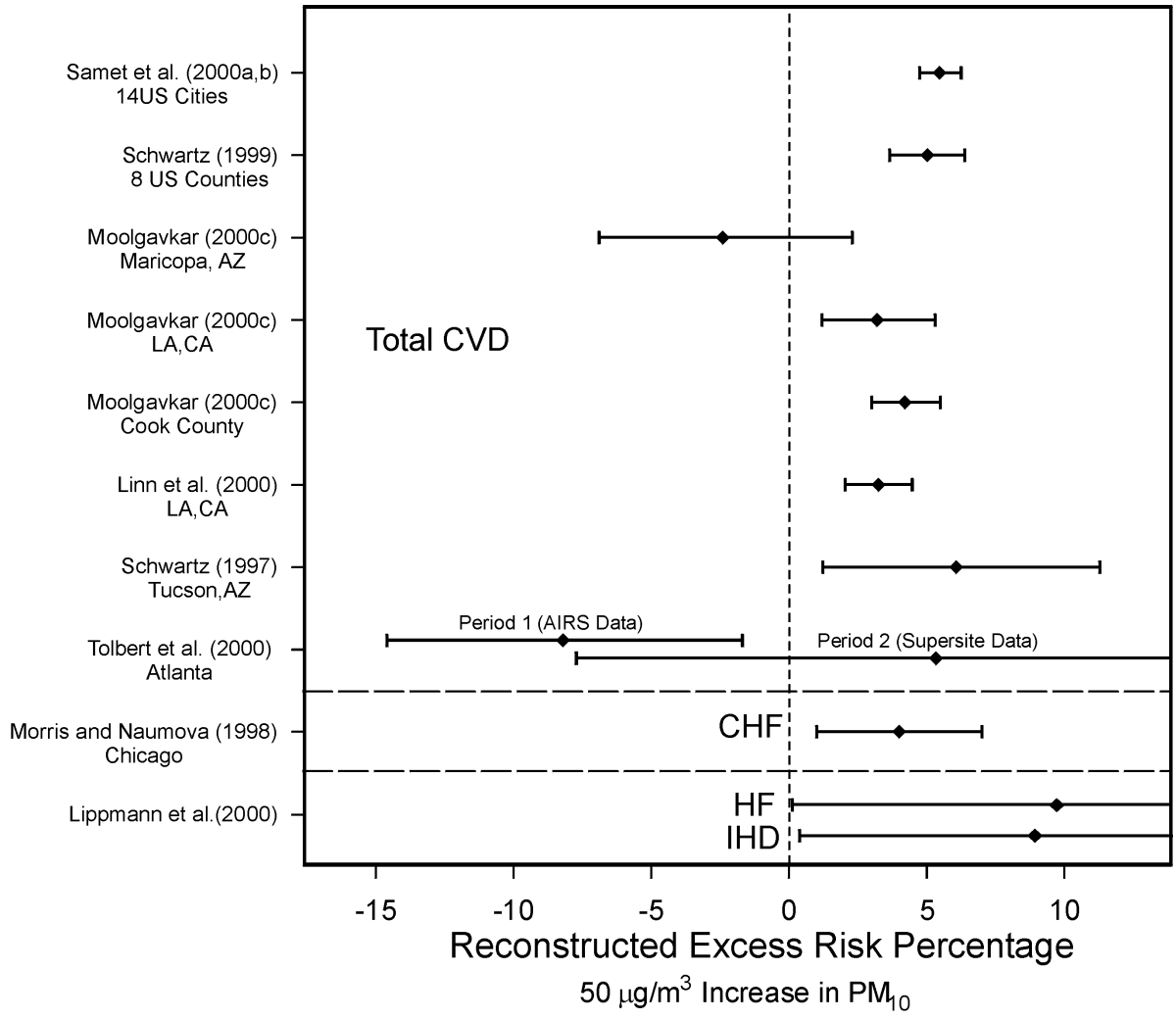

Figure 9-9. Acute cardiovascular hospitalizations and PM exposure excess risk estimates derived from selected U.S. PM_{10} studies. CVD = cardiovascular disease and CHF = congestive heart failure.

increase in PM_{10} associated with between 1.8 and 4.2 percent increases in admissions (Schwartz, 1999). Also, in a study of Los Angeles data from 1992-1995, PM_{10}, CO, and NO_2 were all significantly associated with increased cardiovascular admission in single-pollutant models among persons 30 and older (Linn et al., 2000). Moolgavkar (2000c) analyzed PM_{10}, CO, NO_2, O_3, and SO_2 in relation to daily total cardiovascular (CVD) and total cerebrovascular admissions for persons 65 and older from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ), and found that, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) was associated with CVD

admissions in Cook and LA counties but not in Maricopa county. On the other hand, in two-pollutant models in Cook and LA counties, the PM risk estimates diminished and/or were rendered nonsignificant.

The recent NMMAPS study of PM_{10} concentrations and hospital admissions by persons 65 and older in 14 U.S. cities provides particularly important findings of positive and significant associations, even when concentrations are below 50 $\mu g/m^3$ (Samet et al., 2000a,b). As noted in Table 9-7, this study indicates PM_{10} effects similar to other cities, but with narrower confidence bands, because of its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each of the 14 cities had mean PM_{10} below 50 $\mu g/m^3$.

TABLE 9-7. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-$\mu g/m^3$ INCREASE IN 24-HOUR PM_{10} IN 14 U.S. CITIES

	CVD		COPD		Pneumonia	
	% Increase	(95% CI)	% Increase	(95% CI)	% Increase	(95% CI)
Constrained Lag Models (Fixed Effect Estimates)						
One-day mean[a]	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Previous-day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Two-day mean[b]	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
PM_{10} <50 $\mu g.m^3$ (2-day mean)[b]	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Unconstrained Distributed Lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.90	(1.46, 2.34)
Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)

[a]Lag.
[b]Mean of lag 0 and lag 1.

Source: Samet et al., 2000a,b.

Physiologic Measures of Cardiac Function. Several very recent studies by independent groups of investigators have also reported longitudinal associations between ambient PM concentrations and physiologic measures of cardiovascular function. These studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions regarding individual risks, as well as to explore mechanistic hypotheses. For example, several studies recently have reported temporal associations between PM exposures and various electrocardiogram (ECG) measures of heart beat or rhythm in panels of elderly subjects. Reduced HR variability is a predictor of increased cardiovascular morbidity and mortality risks. Three independent studies reported decreases in HR variability associated with PM in elderly cohorts, although r-MSSD (one measure of high-frequency HR variability) showed elevations with PM in one study. Differences in methods used and results obtained across the studies argue for caution in drawing any strong conclusions yet regarding PM effects from them, especially in light of the complex intercorrelations that exist among measures of cardiac physiology, meteorology, and air pollution (Dockery et al., 1999). Still, the new heart rhythm results, in general, comport well with other findings of cardiovascular mortality and morbidity endpoints being associated with ambient PM. Chapter 5 discusses available exposure studies of elderly subjects with CVD, such as the Sarnat et al. (2000) Baltimore study. Less active groups tend to have lower exposure to nonambient PM because of reduced personal activity. However, Williams et al. (2000a,b,c) report a very high pooled correlation coefficient between $PM_{2.5}$ personal exposure and outdoor concentrations. These exposure studies tend to enhance the plausibility of panel study findings of impacts on HR variability being caused by exposure to ambient-generated PM.

Changes in Blood Characteristics. Additional epidemiologic findings (Peters et al., 1997a) also provide new evidence for ambient PM exposure effects on blood characteristics (e.g., increased c-reactive protein in blood) thought to be associated with increased risk of serious cardiac outcomes (e.g., heart attacks).

- **Key Conclusions Regarding PM-CVD Morbidity**. Overall, the newly available studies of PM-CVD relationships appear to support the following conclusions regarding several key issues:

- **Temporal Patterns of Response.** The evidence from recent time series studies of CVD admissions suggests rather strongly that PM effects are likely maximal at lag 0, with some carryover to lag 1.

- **Physical and Chemical Attributes Related to Particulate Matter Health Effects.** The characterization of ambient PM attributes associated with acute CVD is incomplete. Insufficient data exist from the time series CVD hospital admissions literature or from the emerging individual-level studies to provide clear guidance as to which PM attributes, defined either on the basis of size or composition, determine potency. The epidemiologic studies published to date have been constrained by the limited availability of multiple PM metrics. Where multiple PM metrics exist, they often are of differential quality because of differences in numbers of monitoring sites and in monitoring frequency. Until more extensive and consistent data become available for epidemiologic research, the question of PM size and composition, as they relate to acute CVD impacts, will remain open.

- **Susceptible Subpopulations.** Because they lack data on individual subject characteristics, ecologic time series studies provide only limited information on susceptibility factors based on stratified analyses. The relative impact of PM on cardiovascular (and respiratory) admissions reported in ecologic time series studies is generally somewhat higher than those reported for total admissions. This provides some limited support for the hypothesis that acute effects of PM operate via cardiopulmonary pathways or that persons with preexisting cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from the ecologic time series studies showing larger relative impacts of PM on cardiovascular admissions in adults 65 and over as compared with younger populations, the differences are neither striking nor consistent. Some individual-level studies of cardiophysiologic function suggest that elderly persons with preexisting cardiopulmonary disease are susceptible to subtle changes in heart rate variability (HRV) in association with PM exposures. However, because younger and healthier populations have not yet been assessed, it is not possible to say at present whether the elderly have clearly increased susceptibility compared to other groups, as indexed by cardiac pathophysiological indices such as HRV.

- **Role of Other Environmental Factors.** The ecologic time series morbidity studies published since 1996 generally have controlled adequately for weather influences. Thus, it is unlikely that residual confounding by weather accounts for the PM associations observed. With one possible exception (Pope et al., 1999b), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac physiologic function. Thus, the possibility of confounding in such studies as yet cannot be discounted totally or readily. Co-pollutants have been analyzed rather extensively in many of the recent time series studies of hospital admissions and PM. In some studies, PM clearly carries an independent association after controlling for gaseous co-pollutants. In others, the "PM effects" are reduced markedly once co-pollutants are added to the model. Among the gaseous criteria pollutants, CO has emerged as the most consistently associated with cardiovascular (CVD) hospitalizations. The CO effects are generally robust in the multi-pollutant model, sometimes as much so as PM effects. However, the typically low levels of ambient CO concentrations in most such studies and minimal expected impacts on carboxyhemoglobin levels and consequent associated hypoxic effects thought to underlie CO CVD effects complicate interpretation of the CO findings and argue for the possibility that CO may be serving as a general surrogate for combustion products (e.g., PM) in the ambient pollution mix. See the recently completed EPA CO criteria document (U.S. Environmental Protection Agency, 2000a).

9.6.2.3.2 Respiratory Effects of Ambient Particulate Matter Exposures

The number of studies examining hospitalization and emergency department visits for respiratory-related causes and other respiratory morbidity endpoints has increased markedly since the 1996 PM AQCD. In addition to evaluating statistical relationships for PM_{10}, quite a few new studies also evaluated other PM metrics. Those providing estimates of increased risk in U.S. and Canadian cities for respiratory-related morbidity measures (hospitalizations, respiratory symptoms, etc.) in relation to 24-h increments in ambient fine particles ($PM_{2.5}$) or coarse fraction ($PM_{10-2.5}$) of inhalable thoracic particles are included in Tables 9-3 and 9-4, respectively.

Respiratory-Related Hospital Admission/Visits. PM hospital admissions/ visit studies that evaluated excess risks in relation to PM_{10} measures are still quite informative. Maximum excess risk estimates for PM_{10} associations with respiratory-related hospital admissions and visits in

U.S. cities are shown in Figure 9-10. Nearly all the studies showed positive, statistically significant relationships between ambient PM_{10} and increased risk for respiratory-related doctors' visits and hospital admissions. Overall, the results substantiate well ambient PM_{10} impacts on respiratory-related hospital admissions/visits. The excess risk estimates fall most consistently in the range of 5 to 25.0% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma hospital admissions and doctor's visits being higher than for COPD and pneumonia hospitalization. Other, more limited, new evidence (not depicted in Figure 9-10) shows excess risk estimates for overall respiratory-related or COPD hospital admissions falling in the range of 5 to 15.0% per 24-h 25 $\mu g/m^3$ increment in $PM_{2.5}$ or $PM_{10-2.5}$. Larger estimates are found for asthma admissions or physician visits, ranging up to ca. 40 to 50% for children <18 yr old in one study.

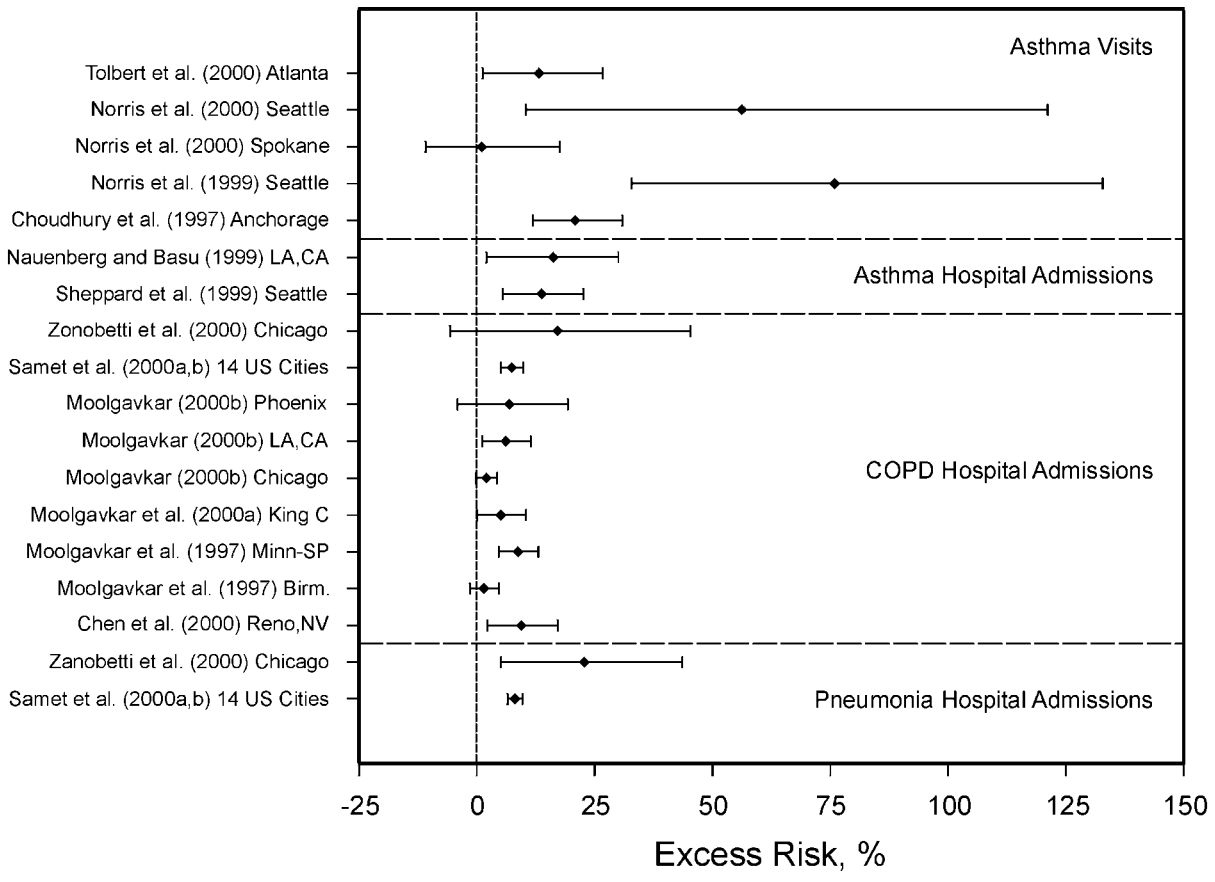

Figure 9-10. Maximum excess risk in selected studies of U.S. cities relating PM_{10} estimate of exposure (50 $\mu g/m^3$) to respiratory-related hospital admissions and visits.

Of particular note in Figure 9-10, are the large effect size estimates now being reported for asthma hospitalizations and visits. Very importantly, these hospital admission/visit studies and other new studies on respiratory symptoms and lung function decrements in asthmatics are emerging as possibly indicative of ambient PM likely being a notable contributor to exacerbation of asthma. Additional evidence for PM-asthma effects is also emerging from panel studies of lung function and respiratory symptoms, and these are discussed in more detail below.

New panel studies of lung function and respiratory symptoms in asthmatic subjects have been conducted by more than 10 research teams in various locations world-wide. As a group, the studies examine health outcome effects that are similar, such as pulmonary peak flow rate (PEFR); and the studies typically characterize the clinical-symptomatic aspects in a sample of mild to moderate asthmatics (mainly children aged 5 to 16 yrs) observed in their natural setting. Their asthma typically is being treated to keep them symptom free (with "normal" pulmonary function rates, and activity levels) and to prevent recurrent exacerbations of asthma. Severity of their asthma is characterized by symptom, pulmonary function, and medication use and would be classified to include mild intermittent to mild persistent asthma suffers (National Institutes of Health, 1997). As a group, they may thusly differ from asthmatics examined in studies of hospitalization or doctor visits for acute asthmatic episodes, who may have more severe asthma.

Most studies reported ambient PM_{10} results, but $PM_{2.5}$ was examined in two studies. Other ambient PM measures (BS and SO_4) also were used. For these studies, mean PM_{10} levels range from a low of 13 $\mu g/m^3$ in Finland to a high of 167 $\mu g/m^3$ in Mexico City. The Mexico City level is over three times more than each of the other levels and is unique compared to the others. Related 95% CI for these means or ranges show 1-day maximums above 100 $\mu g/m^3$ in four studies, with two of these above 150 $\mu g/m^3$. Hence, these studies mainly evaluated different PM metrics indexing PM concentrations in the range found in U.S. cities (see Chapter 3). All the studies controlled for temperature, and several controlled for relative humidity.

Many panel studies are analyzed using a design that takes advantage of the repeated measures on the same subject. Study subject number (N) varied from 12 to 164, with most having N >50; and all gathered adequate subject-day data to provide sufficient power for their analyses. Linear models often are used for lung function and logistic models for dichotomous outcomes. Meteorological variables are used as covariates; and medication use is also sometimes evaluated as a dependent variable or treated as an important potential confounder. However,

perhaps the most critical choice in the model is selection of the lag for the pollution variable. Presenting lag periods with only the strongest associations introduces potential bias, because the biological basis for lag structure may be related to effect. No biological bases for pertinent lag periods are known, but some hypotheses can be proposed. Acute asthmatic reactions can occur 4 to 6 h after exposure and, thus, 0-day lag may be more appropriate than 1-day lags for that acute reaction. Lag 1 may be more relevant for morning measurement of asthma outcome from PM exposure the day before, and longer term lags (i.e., 2 to 5 days) may represent the outcome of a more prolonged inflammatory mechanism; but too little information is now available to predetermine appropriate lag(s).

Chapter 7 noted that people with asthma tend to have greater TB deposition then do healthy people, but this data was not derived from the younger age group studied in most asthma panel studies. The Peters et al. (1997b) study is unique for two reasons: (1) they studied the size distribution of the particles in the range 0.01 to 2.5 μm and (2) examined the number of particles. They reported that asthma-related health effects of 5-day means of the number of ultrafine particles were larger than those of the mass of the fine particles. In contrast, Pekkanen et al. (1997) also examined a range of PM sizes, but PM_{10} was more consistently associated with PEF. Delfino et al. (1998) is unique in that they report larger effects for 1- and 8-h maximum PM_{10} than for the 24-h mean.

The results for the asthma panels of the peak flow analysis consistently show small decrements for both PM_{10} and $PM_{2.5}$. The effects using 2- to 5-day lags averaged about the same as did the 0 to 1 day lags. Stronger relationships often were found with ozone. The analyses were not able to clearly separate co-pollutant effects. The effects on respiratory symptoms in asthmatics also tended to be positive. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use. The only endpoint more strongly related to longer lag times was bronchodilator use, which was observed in three studies. The peak flow decrements and respiratory symptoms are indicators for asthma episodes.

For PM_{10}, nearly all of the point estimates showed decreases, but most were not statistically significant, as shown in Figure 9-11 as an example of PEF outcomes. Lag 1 may be more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies that provided this data. The results were consistent for both AM and PM peak flow analyses. Similar results were found for the $PM_{2.5}$ studies, although there were fewer

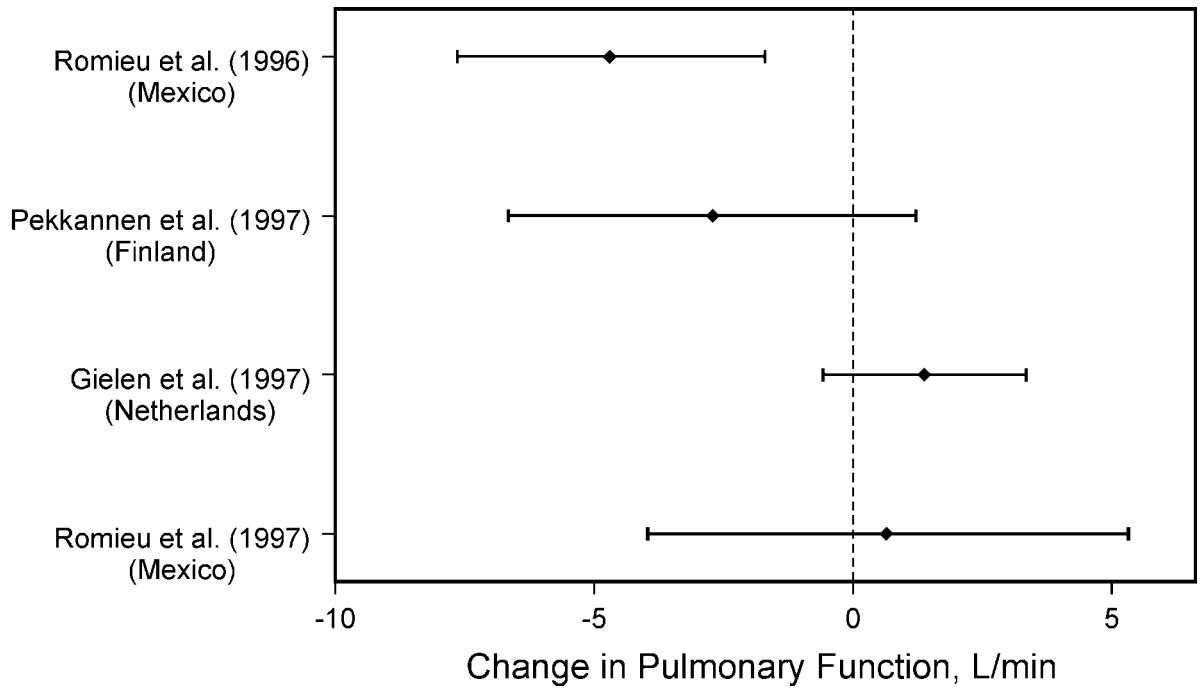

Figure 9-11. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 $\mu g/m^3$ PM_{10} on morning Peak flow lagged 1 day.

studies. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Gold et al. (1999), Naeher et al. (1999), Tiittanen et al. (1999), Pekkanen et al. (1997), and Romieu et al. (1996) all found similar results for $PM_{2.5}$ and PM_{10}. The study of Peters et al. (1997b) found slightly larger effects for $PM_{2.5}$. The study of Schwartz and Neas (2000) found larger effects for $PM_{2.5}$ than for the coarse mode. Naeher et al. (1999) found that H^+ was related significantly to a decrease in morning PEF. Thus, there is no evidence here for a stronger effect of $PM_{2.5}$ when compared to PM_{10}. Also, of studies that provided analyses that attempted to separate out effects of PM_{10} and $PM_{2.5}$ from other pollutants, Gold et al. (1999) studied possible interactive effects of $PM_{2.5}$ and ozone on PEF; they found independent effects of the two pollutants, but the joint effect was slightly less than the sum of the independent effects.

The effects on respiratory symptoms in asthmatics also tended to be positive, although much less consistent than the lung function effects. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use (although generally not statistically

significant), as shown in Figure 9-12 for cough as an example. Three studies included both PM_{10} and $PM_{2.5}$ in their analyses. The studies of Peters et al. (1997c) and Tiittanen et al. (1999) found comparable effects for the two measures. Only the Romieu et al. (1996) found slightly larger effects for $PM_{2.5}$. These studies also give no good evidence for a stronger effect of $PM_{2.5}$ when compared to PM_{10}.

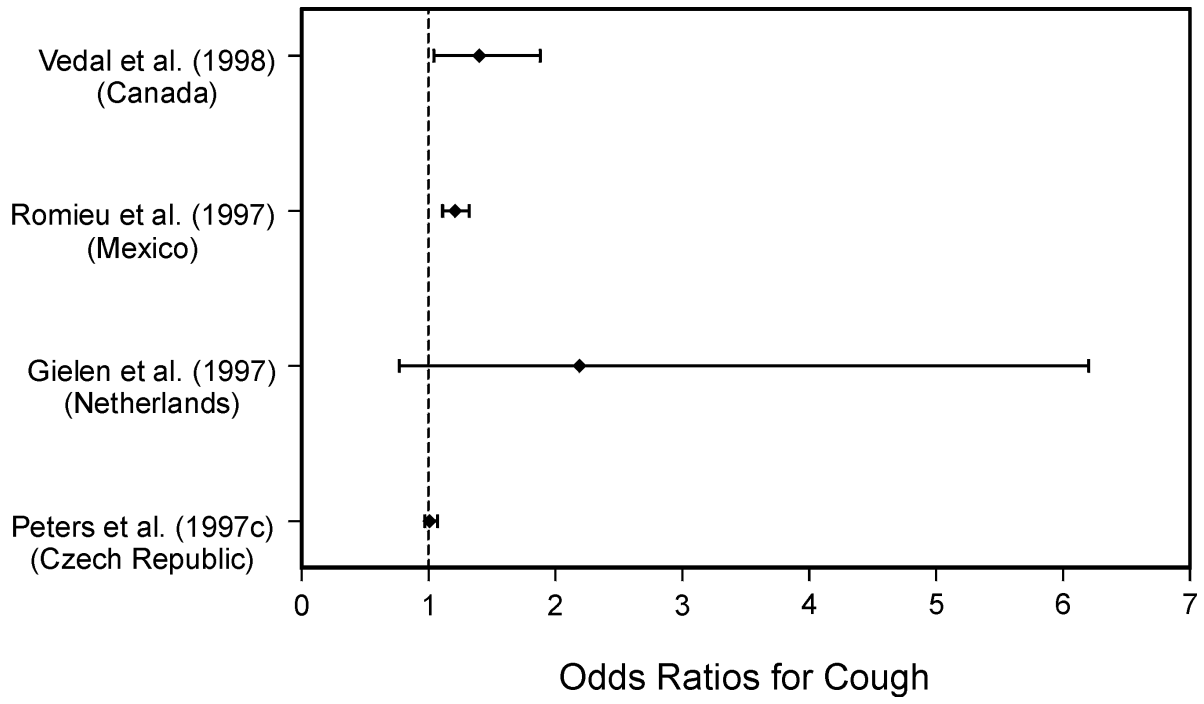

Figure 9-12. Odds ratios for cough for a 50-$\mu g/m^3$ increase in PM_{10} for selected asthmatic children studies, with lag 0 with 95% CI.

The results of PM_{10} peak flow analyses for nonasthmatic populations were inconsistent. Fewer studies reported results in the same manner as the asthmatic studies. Many of the point estimates showed increases rather than decreases. $PM_{2.5}$ studies found similar results. The effects on respiratory symptoms in nonasthmatics were similar to those in asthmatics: most studies showed that PM_{10} increases cough, phlegm, and difficulty breathing, but these increases were generally not statistically significant. Schwartz and Neas (2000) found that $PM_{10\text{-}2.5}$ coarse

particles were significantly related to cough. Tiittanen et al. (1999) found that 1-day lag of $PM_{10-2.5}$ was related to morning PEF, but not evening PEF. Neas et al. (1999) found no coarse mode effects of PEF in non-asthmatic subjects.

9.6.2.3.3 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a similar type of questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a chronic PM exposure effect on respiratory disease. The analysis of chronic cough, chest illness, and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with highest exposure of strongly acidic particles when compared with the least polluted community. Fine PM sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

The studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) all had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect on children of PM pollution indexed by TSP, PM_{15}, $PM_{2.5}$, or sulfates. In contrast, the latest 24-city analyses reported by Raizenne et al. (1996) found significant associations of effects on FEV_1 or FVC in U.S. and Canadian children with both acidic particles and other PM indicators. Overall, the available studies provided limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.).

A number of studies have been published since 1996, which evaluate the effects of long-term PM exposure on lung function and respiratory symptoms, as presented in Chapter 6. The methodology in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to PM), whereas others reported no significant results. Of particular note are several studies reporting associations

between long-term PM exposures (indexed by various measures) or changes in such exposures over time and chronic bronchitis rates, consistent with bronchitis results from the Dockery et al. (1996) study noted above.

Unfortunately, the cross-sectional studies often are potentially confounded, in part, by unexplained differences in geographic regions; and it is difficult to separate out results consistent with a PM gradient from any other pollutants or factors having the same gradient. The studies that looked for a time trend also are confounded by other conditions that changed over time. The most credible cross-sectional study remains that described by Dockery et al. (1996) and Raizenne et al. (1996). Whereas most studies include two to six communities, this study included 24 communities and is considered to provide the most credible estimates of long-term PM exposure effects on lung function and respiratory symptoms.

9.6.2.4 Methodological Issues

Chapter 6 discussed several still important methodological issues related to assessment of the overall PM epidemiologic database. These include, especially, issues related to model specifications and consequent adequacy of control for potentially confounding of PM effects by co-pollutants, evaluations of possible source relationships to pollutant effects that may be useful in sorting out better effects attributable to PM versus other co-pollutants or both, and other issues such as lag structure. Key points are discussed concisely below.

9.6.2.4.2 Time Series Studies: Confounding by Co-Pollutants in Individual Cities

The co-pollutant issue was discussed at length in the 1996 document and still remains an important issue. It must be recognized that there are large differences in concentrations of measured gaseous co-pollutants (and presumably unmeasured pollutants as well) in different parts of the United States, as well as the rest of the world; and the concentrations are often correlated with concentrations of PM and its components because of commonality in source emissions, wind speed and direction, atmospheric processes, and other human activities and meteorological conditions. Large sources in the United States include motor vehicle emissions (gasoline combustion, diesel fuel combustion, evaporation, particles generated by tire wear, etc.), coal combustion, fuel oil combustion, industrial processes, residential wood burning, solid waste combustion, and so on. Thus, one might reasonably expect some large correlations among PM

and co-pollutants, but possibly with substantial differences in relation by season in different cities or regions. Statistical theory suggests that PM and co-pollutant effect size estimates will be highly unstable and often insignificant in multi-pollutant models when collinearity exists. Many recent studies demonstrate this effect, for both hospital admissions (Moolgavkar, 2000b) and mortality (Moolgavkar, 2000a; Chock et al., 2000). Because the problem seems largely insoluble in studies in single cities, the new multi-city studies (Samet et al., 2000a,b; Schwartz, 1999; Schwartz and Zanobetti, 2000) have provided important new insights. See discussions of NMMAPS analysis in Chapter 6 and below for discussion of issues related to control for co-pollutant effects. Overall, although such issues may warrant further evaluation, it now appears unlikely that such confounding accounts for the vast array of effects attributed to ambient PM based on the rapidly expanding PM epidemiology database.

Numerous new studies have reported associations not only between PM, but also gaseous pollutants (O_3, SO_2, NO_2, and CO), and mortality. In many of these studies, simultaneous inclusion of one or more gaseous pollutants in regression models did not markedly affect PM effect size estimates, as was generally the case in the NMMAPS analyses for 90 cities (see Figure 9-13). On the other hand, some studies reporting positive and statistically significant effects for gaseous copollutants (e.g., O_3, NO_2, SO_2, CO) found varying degrees of robustness of their effects estimates or those of PM in multipollutant models. Thus, although it is likely that there are independent health effects of PM and gaseous pollutants, there is not yet sufficient evidence by which to confidently separate out fully the relative contributions of PM versus those of other gaseous pollutants or by which to quantitate modifications of PM effects by other co-pollutants, including possible synergistic interactions that may vary seasonally or from location to location. Overall, it appears, however, that ambient PM and O_3 can be most clearly separated out as likely having independent effects, their concentrations often not being highly correlated. More difficulty is encountered, at times, in sorting out whether NO_2, CO, or SO_2 are exerting independent effects in cities where they tend to be highly correlated with ambient PM concentrations, possibly because of derivation of important PM constituents from the same source (e.g., NO_2, CO, PM from mobile sources) or a gaseous pollutant (e.g., SO_2) serving as a precursor for a significant PM component (e.g., sulfate).

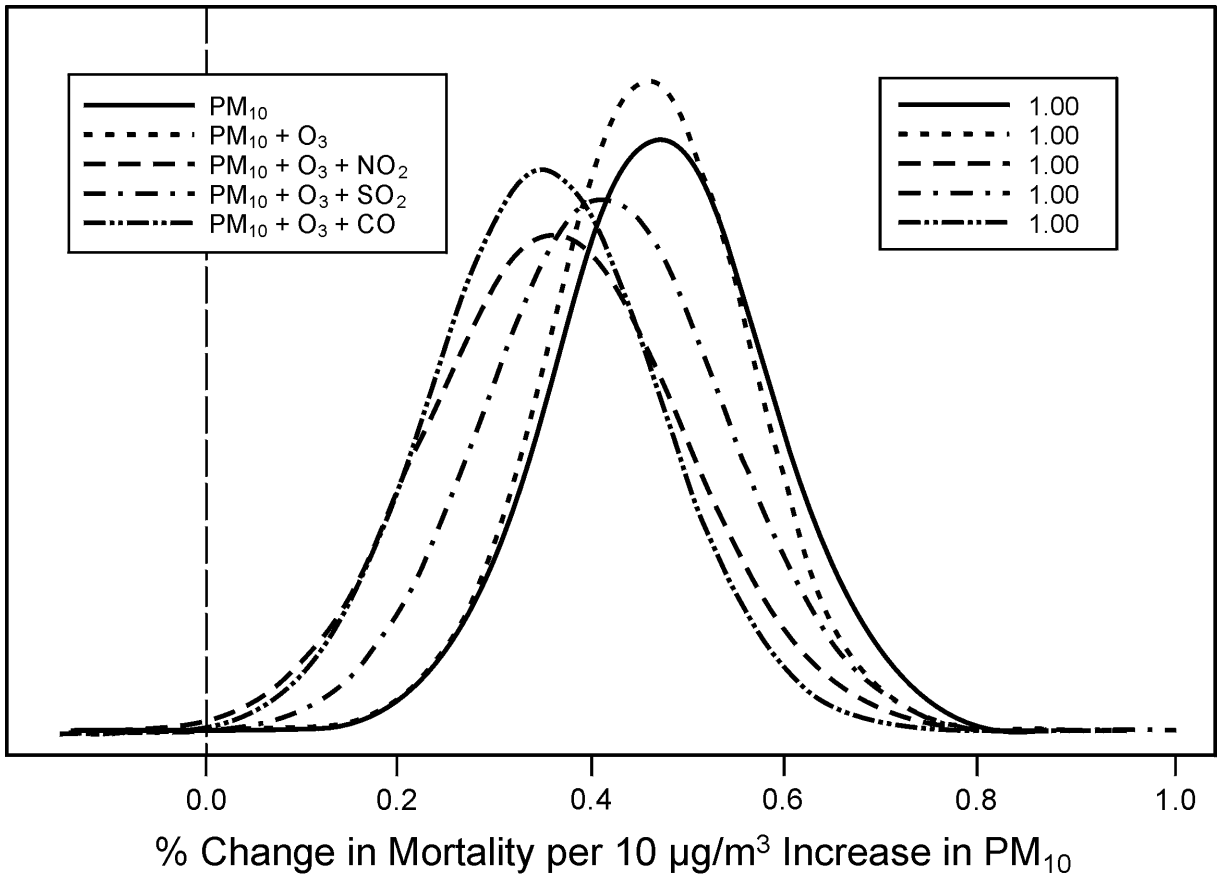

Figure 9-13. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1, with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Samet et al. (2000a,b).

9.6.2.4.3 Time Series Studies: Model Selection for Lags, Moving Averages, and Distributed Lags

A number of different approaches have been used to evaluate the temporal dependence of mortality or morbidity on time-lagged PM concentrations, including unweighted moving averages of PM concentrations over one or more days, general weighted moving averages, and polynomial distributed moving averages. Unless there are nearly complete daily data, each different lag will be using a different set of mortality data corresponding to spaced PM measurement; for example, for lag 0 with every-sixth-day PM measurements, the mortality data

are on the same day as the PM data, for lag 1 the mortality data are on the next day after the PM data, and so on. Although this effect is likely to be small, it should nonetheless be kept in mind.

The issue of dealing with lag structure, which may not necessarily be the same for all cities or for all regions, can be illustrated by NMMAPS findings. As shown in Table 9-8, the rank ordering of effects by lag days differs somewhat among NMMAPS regions. The combined data set suggests that lag 1 provides the best fit, but with some regional differences. This raises the question as to whether a single lag model should be assumed to characterize a diverse set of regional findings. Because the particle constituents, co-pollutants, susceptible subpopulations, and meteorological covariates are likely to differ substantially from one region to another, the timing of the largest mortality effects also may be presumed to differ in at least some cases. This undoubtedly contributes to the variance of the estimated effects.

TABLE 9-8. PERCENT INCREASE IN MORTALITY PER 10 $\mu g/m^3$ PM_{10} IN SEVEN U.S. REGIONS (from Figure 23 in NMMAPS II)

Region	Rank Order of Effects by Lags
Northwest	lag 0 < lag 1 = lag 2
Southwest	lag 0 < lag 1 < lag 2
Southern California	lag 0 < lag 1, lag 1 > lag 2, lag 0 < lag 2
Upper Midwest	lag 0 > lag 1, lag 0 > lag 2, lag 1 < lag 2
Industrial Midwest	lag 0 < lag 1, lag 1 > lag 2
Northeast	lag 0 < lag 1, lag 1 >> lag 2
Southeast	lag 0 << lag 1, lag 1 > lag 2
Combined	lag 0 < lag 1, lag 1 > lag 2

The distributed lag models used in the NMMAPS II morbidity studies are a noteworthy methodological advance. The fitted distributed lag models showed significant heterogeneity across cities for COPD and pneumonia, however (see Table 15 therein), again raising the

question of how heterogeneous effects can best be combined so as not to obscure potentially real city-specific or region-specific differences.

Only three cities with nearly complete daily PM_{10} data were used to evaluate more general multi-day lag models (Chicago, Minneapolis/St. Paul, Pittsburgh), and these show somewhat different patterns of effect, with lag 0 < lag 1 and lag 1 >> lag 2 for Chicago, lag 0 = lag 1 > lag 2 for Minneapolis, and lag 0 < lag 1 = lag 2 for Pittsburgh. The 7-day distributed lag model is significant for Pittsburgh, but less so in the other cities. The remaining data are limited intrinsically in what they can reveal about temporal structure.

9.6.2.4.4 Time Series Studies: Model Selection for Concentration-Response Functions

Given the number of analyses that needed to be performed, it is not surprising that most of the NMMAPS studies focused on linear concentration-response models. More recent studies (Daniels et al., 2000) for the 20 largest U.S. cities have found posterior mean effects of 2 to 2.7% excess risk of total daily mortality per 50 $\mu g/m^3$ 24-h PM_{10} at lags 0, 1, 0+1 days; 2.4 to 3.5% excess risk of cardiovascular and respiratory mortality; and 1.2 to 1.7% for other causes of mortality. The posterior 95% credible regions are all significantly greater than 0. However, the threshold models gave distinctly different estimates of 95% credible regions for the threshold for total mortality (15 $\mu g/m^3$ at lag 1, range 10 to 20), cardiovascular and respiratory mortality (15 $\mu g/m^3$ at lag 0+1, range 0 to 20), and other causes of mortality (65 $\mu g/m^3$ at lag 0+1, range 50 to 75 $\mu g/m^3$).

Another problem is that the shape of the relationship between mortality and PM_{10} may depend, to some extent, on the associations of PM_{10} with gaseous co-pollutants. The association is not necessarily linear, and is indeed likely to have both seasonal and secular components that depend on the city location. Thus, further elaborations of these models may be desirable.

9.6.2.4.5 Effects of Exposure Error in Daily Time Series Epidemiology

There has been considerable controversy over how to deal with the nonambient component of personal exposure. Recent biostatistical analyses of exposure error have indicated that the nonambient component will not bias the statistically calculated risk in community time-series epidemiology, provided that the nonambient component of personal exposure is independent of

the ambient concentration. Consideration of the random nature of nonambient sources and recent studies, in which estimates of α, ambient-generated PM divided by ambient PM concentrations, have been used to estimate separately the ambient-generated and nonambient components of personal exposure, support the assumption that the nonambient exposure is independent of the ambient concentration. Therefore, it is reasonable to conclude that community time series epidemiology describes statistical associations between health effects and exposure to ambient-generated PM, but does not provide any information on possible health effects resulting from exposure to nonambient PM (e.g., indoor-generated PM).

From the point of view of exposure error, it is also significant to note that, although ambient concentrations of a number of gaseous pollutants (O_3, NO_2, SO_2) often are found to be highly correlated with various PM parameters, personal exposures to these gases are not correlated highly with personal exposure to PM indicators. The correlations of the ambient concentrations of these gases also are not correlated highly with the personal exposure to these gases. Therefore, when significant statistical associations are found between these gases and health effects, it could be that these gases may, at times, be serving as surrogates for PM rather than being causal themselves. Pertinent information on CO has not been reported.

The attenuation factor, α, is a useful variable. For relatively constant α, the risk because of a personal exposure to 10 $\mu g/m^3$ of ambient PM is equal 1/α times the risk from a concentration of 10 $\mu g/m^3$ of ambient PM, where α varies from a low of 0.1 to 0.2 to a maximum of 1.0. (The health risk for an interquartile change in ambient concentration of PM is the same as that for an interquartile change in exposure to ambient PM). Differences in α among cities, reflecting differences in air-exchange rates (e.g., because of variation in seasonal temperatures and in extent of use of air conditioners) and differences in indoor/outdoor time ratios, may, in part, account for any differences in risk estimates based on statical associations between ambient concentrations and health effects for different cities or regions. If α were 0.3 in city A, but 0.6 in city B, and the risks for an increase in personal exposure of 10 $\mu g/m^3$ were identical, then a regression of health effects on ambient concentrations would yield a health risk for city B that would be twice that obtained for city A.

A number of exposure analysts have discussed the PM exposure paradox (i.e., that epidemiology yields statistically significant associations between ambient concentrations and health effects even though there is a near zero correlation between ambient concentrations and

personal exposure in many studies). Several explanations have been advanced to resolve this paradox. First, personal exposure contains both an ambient-generated and a nonambient component. Community time series epidemiology yields information only on the ambient-generated component of exposure. Therefore, the appropriate correlation to investigate is the correlation between ambient concentration and personal exposure to ambient-generated PM, not between ambient concentrations and total personal exposure (i.e., the sum of ambient-generated and nonambient PM). Second, biostatistical analysis of exposure error indicates that if the risk function is linear in the PM indicator, the average of the sum of the individual risks (risk function times individual exposure) may be replaced by the risk function times the community average exposure. Thus, the appropriate correlation (of ambient concentrations and ambient-generated exposure) is not the pooled correlation of different days and different people but the correlation between the daily ambient concentrations and the community average daily personal exposure to ambient-generated PM. Because the nonambient component is not a function of the ambient concentration, its average will tend to be similar each day. Therefore, the correlation coefficient will depend on α but not on the nonambient exposure. These types of correlation yield high correlation coefficients.

A few studies have conducted simulation analyses of effects of measurement errors on the estimated PM mortality effects. These studies suggest that ambient PM excess risk effects are more likely underestimated than overestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of the coefficient) because of transferring of effects from other covariates require extreme conditions and are therefore very unlikely. The error because the difference between the average personal exposure and the ambient concentration is likely the major source of bias in the estimated relative risk. One study also suggested that apparent linear exposure-response curves are unlikely to be artifacts of measurement error.

In conclusion, for time-series epidemiology, ambient concentration is a useful surrogate for personal exposure to ambient-generated PM, although the risk per unit ambient PM concentration is biased low by the factor α compared to the risk per unit exposure to ambient-generated PM. Epidemiologic studies of statistical associations between long-term effects and long term ambient concentrations compare health outcome rates across cities with different ambient concentrations. Ordinarily, PM exposure measurement errors are not expected to influence the interpretation of findings from either the community time-series or long-term

epidemiologic studies that have used ambient concentration data if they include sufficient adjustments for seasonality and key personal and geographic confounders. When individual level health outcomes are measured in small cohorts, to reduce exposure misclassification errors, it is essential that better real-time exposure monitoring techniques be used and that further speciation of indoor-generated, ambient, and personal PM mass be accomplished. This should enable measurement (or estimation) of both ambient and nonambient components of personal exposure and evaluation of the extent to which personal exposure to ambient-generated PM, personal exposure to nonambient PM, or total personal exposure (to ambient-generated plus nonambient PM) contribute to observed health effects.

9.6.3 Coherence of Reported Epidemiologic Findings

Interrelationships Between Health Endpoints. Considerable coherence exists across newly available epidemiologic study findings. For example, it was earlier noted that effects estimates for total (nonaccidental) mortality generally fall in the range of 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ 24-h PM_{10} increment. These estimates comport well with those found for cause-specific cardiovascular- and respiratory-related mortality. Furthermore, larger effect sizes for cardiovascular (in the range of 3 to 6% per 50 $\mu g/m^3$ 24-h PM_{10} increment) and respiratory (in the range of 5 to 25% per 50 $\mu g/m^3$ 24-h PM_{10}) hospital admissions and visits are found, as would be expected versus those for PM_{10}-related mortality. Also, several independent panel studies, evaluating temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects, provide generally consistent indications of decreased heart rate (HR) variability being associated with ambient PM exposure (decreased HR variability being an indicator of increased risk for serious cardiovascular outcomes, e.g., heart attacks). Other studies point toward changes in blood characteristics (e.g., increased C-reactive protein levels) related to increased risk of ischemic heart disease as also being associated with ambient PM exposures.

Spatial Interrelationships. Both the NMMAPS and Cohort Reanalyses studies had a sufficiently large number of cities to allow considerable resolution of regional PM effects within the “lower 48" states, but this approach was taken much farther in the Cohort Reanalysis studies than in NMMAPS. There were 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in Pope et al. (1995) and in the reanalyses using the

original data; and, in the additional analyses by the cohort study reanalysis team, 63 cities with $PM_{2.5}$ data and 144 cities with sulfate data. The relatively large number of data points allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers. Information drawn from the maps presented in Figures 16-21 in Krewski et al. (2000) is summarized below.

The patterns are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski, Figure 18) has peak levels in the industrial midwest, including the Chicago and Cleveland areas, the upper Ohio River Valley, and around Birmingham, AL. Lower, but elevated, $PM_{2.5}$ is found almost everywhere else east of the Mississippi, as well as in southern California. This is rather similar to the modeled sulfate surface (Krewski, Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only region with elevated SO_2 concentrations is the Cleveland-Pittsburgh area. A preliminary evaluation is that secondary sulfates in particles derived from local SO_2 is more likely to be important in the industrial midwest, south from the Chicago-Gary region and along the upper Ohio River region. This intriguing pattern may be related to the combustion of high-sulfur fuels in the subject areas.

The overlay of mortality and air pollution is also of interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewksi, Figure 21) is highest for the upper Ohio River region, but also includes a significant association over most of the industrial midwest from Illinois to the eastern noncoastal parts of North Carolina, Virginia, Pennsylvania, and New York. This is reflected, in diminished form, by the sulfates map (Krewski, Figure 19) where the peak sulfate-mortality associations occur somewhat east of the peak $PM_{2.5}$-mortality associations. The SO_2 map (Krewski, Figure 20) shows peak associations similar to, but slightly east of, the peak sulfate associations. This suggests that, although SO_2 may be an important precursor of sulfates in this region, there may be other considerations (e.g., metals) in the association between $PM_{2.5}$ and long-term mortality, embracing a wide area of the midwest and northeast (especially noncoastal areas).

It should be noticed that, although a variety of spatial modeling approaches were discussed in the NMMAPS methodology report (NMMAPS Part I, pp. 66-71), the primary spatial analyses in the 90-city study (NMMAPS, Part II) were based on a simpler seven-region breakdown of the contiguous 48 states. The 20-city results reported for the spatial model in NMMAPS I show a much smaller posterior probability of a PM_{10} excess risk of short-term mortality, with a spatial

posterior probability versus a nonspatial probability of a PM_{10} effect of 0.89 versus 0.98 at lag 0, of 0.92 versus 0.99 at lag 1, and of 0.85 versus 0.97 at lag 2. The evidence that PM_{10} is associated with an excess short-term mortality risk is still moderately strong with a spatial model, but much less strong than with a nonspatial model. In view of the sensitivity of the strength of evidence to the spatial model, the model assumptions warrant additional study. Even so, there is a considerable degree of coherence between the long-term and short-term mortality findings of the studies, with stronger evidence of a modest but significant short-term PM_{10} effect and a larger long-term fine particle ($PM_{2.5}$ or sulfate) effect in the industrial midwest. The short-term effects are larger but less certain in southern California and the northeast, whereas the long-term effects seem less certain there. Possible differences should be further explored.

9.6.4 Toxicologic Insights on Biological Plausibility

Toxicological studies can play an integral role in answering key questions regarding biological plausibility of health effects associated with ambient PM. The materials presented below focus on the progress that toxicological studies have made towards answering the following two key questions.

(1) What are the potential mechanisms by which PM causes health effects?

(2) What specific component or components of ambient PM cause health effects?

9.6.4.1 Mechanisms of Action

Various studies using particulate matter having diverse physicochemical characteristics have shown that these characteristics have a great impact on the specific response that is observed. Thus, there may, in fact, be multiple biological mechanisms responsible for observed morbidity/mortality because of exposure to ambient PM, and these mechanisms may be highly dependent on the type of particle in the exposure atmosphere. However, it should be noted that many controlled exposure studies used concentrations of PM that were much higher than those occurring in ambient air. Thus, some of the effects elicited may not occur with exposure to lower levels. Clearly, controlled exposure studies as yet have not been able to unequivocally determine the particle characteristics and the toxicological mechanisms by which ambient PM may affect biological systems. There is growing toxicological and epidemiological evidence that both the cardiovascular and respiratory systems are affected by ambient PM. Nonetheless, understanding

how particulate air pollution causes and exacerbates cardiovascular or respiratory diseases remains an important goal. The pathophysiological mechanisms involved in PM-associated cardiovascular and respiratory health effects remain unclear, but progress has been made since the 1996 PM AQCD was written. This section summarizes current hypotheses and reviews the toxicological evidence for potential pathophysiological mechanisms.

9.6.4.1.1 Direct Respiratory System Effects

Emerging new toxicological evidence for three key mechanisms hypothesized as underlying direct effects of PM on the respiratory system is summarized below.

Lung Injury and Inflammation. In the last few years, numerous studies have shown that instilled and inhaled ROFA, a product of fossil fuel combustion, can cause substantial lung injury and inflammation. The toxic effects of ROFA largely result from its high content of soluble metals, and the pulmonary effects of ROFA can be reproduced by equivalent exposures to soluble metal salts. In contrast, controlled exposures of animals to sulfuric acid aerosols, acid coated carbon, and sulfate salts cause little lung injury or inflammation even at high concentrations. Inhalation of concentrated ambient PM (which contains only small amounts of metals) by laboratory animals at concentrations in the range of 100 to 1000 $\mu g/m^3$ have been shown in some (but not all) studies to cause mild pulmonary injury and inflammation. Rats with SO_2-induced bronchitis and monocrotaline-treated rats have a greater inflammatory response to concentrated ambient PM than healthy rats. These studies suggest that exacerbation of respiratory disease by ambient PM may be caused, in part, by lung injury and inflammation.

Increased Susceptibility to Respiratory Infections. There are no published studies on the effects of inhaled concentrated ambient PM on host susceptibility to infectious agents. In vivo exposure of mice to acid-coated carbon particles at a mass concentration of 10,000 $\mu g/m^3$ causes decreased phagocytic activity of alveolar macrophages even in the absence of lung injury (Ohtsuka et al., 2000). More studies are needed on the effects of concentrated ambient PM on the pulmonary immune defense system.

Increased Airway Reactivity and Asthma Exacerbation. The strongest toxicologic evidence supporting this hypothesis is from studies on diesel particulate matter (DPM). Diesel particulate matter has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 8.2.4.3). In vitro studies have suggested that the organic fraction of DPM is involved in the increased IgE production. The ROFA leachate also enhances antigen-specific airway reactivity in mice (Goldsmith et al., 1999), indicating that soluble metals also can enhance an allergic response. However, in this same study, exposure of mice to concentrated ambient PM did not affect antigen-specific airway reactivity. It is premature to conclude from this one experiment that concentrated ambient PM does not exacerbate allergic airways disease because the chemical composition of the PM (as indicated by studies with DPM and ROFA) may be more important than the mass concentration.

9.6.4.1.2 Systemic Effects Secondary to Lung Injury

When the 1996 PM AQCD was written, it was thought that cardiovascular-related morbidity and mortality most likely would be secondary to impairment of oxygenation or some other consequence of lung injury and inflammation. There is some toxicological evidence for the following mechanisms for adverse systemic effects secondary to lung injury.

Impairment of Heart Function by Lowering Blood Oxygen Levels and Increasing the Work of Breathing. Instillation of ROFA has been shown to cause a 50% mortality rate in monocrotaline- treated rats (Watkinson et al., 2000). Although blood oxygen levels were not measured in this study, there were ECG abnormalities consistent with severe hypoxemia in about half of the rats that subsequently died. Given the severe inflammatory effects of instilled ROFA and the fact that monocrotaline-treated rats have increased lung permeability as well as pulmonary hypertension, it is plausible that instilled ROFA can cause severe hypoxemia leading to death in this rat model. However, results from studies in which animals (normal and compromised) were exposed to concentrated ambient PM (at concentrations many times higher than would be encountered in the United States) indicate that ambient PM is unlikely to cause severe disturbances in blood oxygenation or pulmonary function. However, even a modest decrease in oxygenation can have serious consequences in individuals with ischemic heart disease. For example, reducing arterial blood saturation from 98 to 94% by either mild hypoxia

or by exposure to 100 ppm CO significantly reduced the time to onset of angina in exercising volunteers (Kleinman et al., 1998). Thus, more information is needed on the effects of PM on arterial blood gases and pulmonary function to fully address the above hypothesis.

Lung Inflammation and Cytokine Production Leading to Systemic Hemodynamic Effects. It has been suggested that systemic effects of particulate air pollution may be caused by activation of cytokine production in the lung (Li et al., 1997). In support of this idea, monocrotaline-treated rats exposed to inhaled ROFA showed increased pulmonary cytokine gene expression, bradycardia, hypothermia, and increased arrhythmias (Watkinson et al., 2000). However, spontaneously hypertensive rats had a similar cardiovascular response to inhaled ROFA (except they also developed ST segment depression) with no increase in pulmonary cytokine gene expression. Studies in dogs exposed to concentrated ambient PM showed minimal pulmonary inflammation and no positive staining for IL-8, IL-1, or TNF in airway biopsies. However, the time of onset of ischemic ECG changes following coronary artery occlusion decreased significantly (Godleski et al., 2000). Thus, there is not a clear-cut link between changes in cardiovascular function and production of cytokines in the lung. Because human and animal exposure studies of ambient PM are using increasingly sophisticated and sensitive measures of cardiac function, basic information on the effects of mild pulmonary injury on these cardiac endpoints is needed to understand the mechanisms by which inhaled PM may affect the heart.

Increased Risk of Heart Attacks and Strokes Because of Increasing Blood Coagulability Secondary to Lung Inflammation. There is abundant evidence linking risk of heart attacks and strokes to small prothrombotic changes in the blood coagulation system; and some new epidemiologic evidence (discussed earlier above) indicates that ambient PM may affect blood coagulation and/or other blood characteristics related to increased risk of serious cardiac outcomes. However, there is no published experimental evidence as of yet that moderate lung inflammation increases blood coagulability; a high dose (8,300 μg/kg) of instilled ROFA did cause increased levels of fibrinogen, but no effect was seen at lower doses (Gardner et al., 2000). Also, exposure of dogs to concentrated ambient PM also had no effect on fibrinogen levels (Godleski et al., 2000). The coagulation system is as multifaceted and complex as the immune

system, and there are many other sensitive and clinically significant parameters that should be examined in addition to fibrinogen. Thus, it is premature to draw any strong conclusions about ambient PM exposure effects on cardiovascular morbidity or mortality being mediated via PM effects on blood coagulability or other blood characteristics.

Particulate Matter and Lung Interactions Potentially Affecting Hematopoiesis. Instillation of fine carbon particles (20,000 μg/rabbit) stimulated release of PMNs from the bone marrow (Terashima et al., 1997). In support of this hypothesis, Gordon and colleagues reported that the percentage of PMNs in the peripheral blood increased in rats exposed to ambient PM in some but not all exposures. On the other hand, Godleski et al. (2000) found no changes in peripheral blood counts of dogs exposed to concentrated ambient PM. Thus, direct evidence that ambient concentrations of PM can affect hematopoiesis is still needed.

9.6.4.1.3 Direct Effects on the Heart

Changes in heart rate and heart rate variability associated with ambient PM exposure have been reported in animal studies (Godleski et al., 2000; Gordon et al., 2000), in several human panel studies (described in Chapter 6), and in a reanalysis of data from the MONICA study (Peters et al., 2000). Some of these studies included endpoints related to respiratory effects, but few significant adverse respiratory changes were detected. This raises the possibility that ambient PM may have effects on the heart that are independent of adverse changes in the lung. There is precedent for this idea: tobacco smoke (a mixture of combustion-generated gases and particles) causes cardiovascular disease by mechanisms independent of its lung effects.

Heart Rate Variability. Epidemiological studies have linked fine particulate air pollution with cardiopulmonary morbidity and mortality (Schwartz and Morris, 1995; Burnett et al., 1995; Morris et al., 1995; Schwartz, 1997), but the underlying biologic mechanisms remain unclear. Recently, attention has focused on possible effects on heart rate (HR) variability as a potential mechanism underlying cardiovascular morbidity and mortality effects associated with ambient PM. During recent decades, a large clinical database has developed describing a significant relationship between autonomic dysfunction and sudden cardiac death. Moreover, low HR variability has been implicated as a marker for a number of pathophysiological conditions

including myocardial infarction (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Bigger et al., 1992; Hayano et al., 1990; Kleiger et al., 1987; Martin et al., 1987; Singer et al., 1988). This is further elaborated in Appendix 6-B.

Some studies (Liao et al., 1999; Pope et al., 1999b) provide new evidence for relationships between ambient PM and decreased HR variability. Pope et al. (1999b) reported an association between particulate air pollution, heart rate, and HR variability. A relationship between PM and HR variability also is supported by laboratory animal studies. Combustion particles instilled into rat lungs produce arrhythmias and a doubling of mortality (Watkinson et al., 1998). Concentrated ambient air particles breathed by dogs elicited electrocardiographic changes, including T-wave alterans and arrhythmias (Godleski et al., 1998).

Autonomic Control of the Heart and Cardiovascular System. There is growing evidence for the idea that inhaled particles could affect the heart through the autonomic nervous system. Activation of neural receptors in the lung is a logical area to investigate. Studies in conscious rats have shown that inhalation of wood smoke causes marked changes in sympathetic and parasympathetic input to the cardiovascular system that are mediated by neural reflexes (Nakamura and Hayashida, 1992). Although research on airway neural receptors and neural-mediated reflexes is a well-established discipline, the cardiovascular effects of stimulating airway receptors continue to receive less attention than the pulmonary effects. Previous studies of airway reflex-mediated cardiac effects usually have employed very high doses of chemical irritants, and the results may not be applicable to air pollutants. There is a need for basic physiological studies to examine cardiovascular system effects when airway and alveolar neural receptors are stimulated in a manner relevant to air pollutants.

Uptake of Particles and Distribution of Soluble Substances into the Systemic Circulation. Drugs can be delivered rapidly and efficiently to the systemic circulation by inhalation (as occurs with nicotine from inhaled cigarette smoke). This implies that the pulmonary vasculature absorbs inhaled materials, including charged substances such as small proteins and peptides. It is likely that soluble materials absorbed onto airborne PM find their way into the bloodstream, but it is

not clear whether the particulate materials themselves enter the blood. It is anticipated that more information will be available on this important question in the next few years.

9.6.4.2 Links Between Specific Particulate Matter Components and Health Effects

Key to enhancing confidence in the biological plausibility of ambient PM health effects is the need to identify those components of airborne PM responsible for the health effects and for placing susceptible individuals at risk. The plausibility of epidemiologically demonstrated associations between ambient PM and increases in morbidity and mortality has been questioned because associations with health effects have been observed at very low PM concentrations. To date, toxicology studies on PM have provided only limited evidence for specific PM components being likely responsible for cardiovascular or respiratory effects of ambient PM. The latest available experimental information concerning potential contributions of individual physical and chemical factors of particles to cardiorespiratory effects is summarized below.

Acid Aerosols. There is relatively little new information on the effects of acid aerosols, and the basic conclusions of the 1996 PM AQCD remain unchanged. It previously was concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects, but asthmatics may experience small decrements in pulmonary function. These conclusions are further supported by a recent study by Linn and colleagues (1997), in which healthy children (and children with allergy or asthma) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 h. There were no significant effects on symptoms or pulmonary function when the entire group was analyzed, but the allergy group had a significant increase in symptoms after the acid aerosol exposure (albeit to distinctly higher than typical ambient acid concentrations).

Although pulmonary effects of acid aerosols have been the subject of extensive research, the cardiovascular effects of acid aerosols have received much less attention. However, inhalation of acetic acid fumes has been reported to cause reflex mediated increases in blood pressure in normal and spontaneously hypertensive rats (Zhang et al., 1997). Thus, acid components should not be ruled out as possible mediators of PM health effects. In particular, the cardiovascular effects of acid aerosols (at realistic concentrations) need further investigation.

Metals. The previous 1996 PM AQCD mainly relied on data related to occupational exposures to evaluate the potential toxicity of metals in particulate air pollution. Since that time, in vivo and in vitro studies using ROFA or soluble transition metals have contributed substantial new information on the health effects of particle-associated soluble metals. Although there are some uncertainties about differential effects of one transition metal versus another, water soluble metals leached from ROFA, albeit at high concentrations, consistently have been shown to cause cell injury and inflammatory changes in vitro and in vivo.

Even though it is clear that combustion particles that have a high content of soluble metals can cause lung injury and even death in compromised animals, it has not been established that the small quantities of metals associated with relatively low concentrations of ambient particles are sufficient to cause health effects. In studies in which various ambient and emission source particulates were instilled into rats, the soluble metal content did appear to be the primary determinant of lung injury. However, one published study compared the effects of inhaled ROFA (at 1 mg/m^3) to concentrated ambient PM (of 475 to 900 $\mu g/m^3$) in normal and SO_2-induced bronchitic rats. A statistically significant increase in at least one lung injury marker was seen in bronchitic rats in only one out of four of the concentrated ambient PM exposures, and inhaled ROFA had no effect, even though the content of soluble iron, vanadium, and nickel was much higher in the ROFA sample. Thus, the potential roles of metals in contributing to health effects of ambient PM remains to be more clearly established. There has been increasing attention focused in recent years on the possibility of ultrafine particles playing a major role in observed ambient PM health effects due to large absolute number counts and/or surface area of ultrafine particles deposited in the lung.

Ultrafine Particles. When this subject was reviewed in the 1996 PM AQCD, it was not known whether the pulmonary toxicity of freshly generated ultrafine Teflon particles was because of particle size or a result of absorbed fumes. Subsequent studies with other types of ultrafine particles have shown that the chemical constituents of ultrafines substantially modulate their toxicity. Inhalation of MgO particles, for example, produces far fewer respiratory effects than does ZnO (Kuschner et al., 1997). Also, inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge caused minimal lung inflammation (Elder et al., 2000) compared to ultrafine Teflon or metal particles. On the other hand, instillation of ultrafine

carbon black caused substantially more inflammation than did the same dose of fine particles of carbon black, suggesting that ultrafine particles cause more inflammation than larger particles (Li et al., 1997). However, the chemical constituents of the two carbon black sizes were not analyzed and it is uncertain that the chemical composition was the same. As with acid aerosols, studies of ultrafine particles have focused largely on effects in the lung, but it is possible that inhaled ultrafine particles may have systemic effects that are independent of lung effects. It is also important to note that at least one very recent new epidemiology study (Wichmann et al., 2000) provides interesting new evidence implicating both ultrafine (nuclei-mode) and accumulation-mode fine particles in PM-mortality relationships.

Diesel Exhaust Particulate Matter. As described in Section 8.2.4.2, there is growing toxicological evidence that diesel exhaust particulate matter (DPM) exacerbates the allergic response to inhaled antigens. The organic fraction of diesel exhaust has been linked to eosinophil degranulation and induction of cytokine production suggesting that the organic constituents of DPM are responsible for the immune effects. It is not known whether the adjuvant-like activity of DPM is unique or whether other combustion-related particles have similar effects. It is important to compare the immune effects of other source-specific emissions, as well as concentrated ambient PM, to DPM to determine the extent to which exposure to diesel exhaust may contribute to the incidence and severity of allergic rhinitis and asthma. Other types of noncancer and carcinogenic (especially lung cancer) effects are of concern with regard to DPM exposures, as discussed in a separate EPA Health Assessment Document for Diesel Exhaust (U.S. Environmental Protection Agency, 2000b).

Organic Compounds. Published research on the acute effects of particle-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles. Like metals, organics are common constituents of combustion-generated particles and are found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial portion of the mass of ambient PM (10 to 60% of the total dry mass [Turpin, 1999]). The organic fraction of ambient PM has been evaluated for its mutagenic effects. Although the organic fraction of particulate matter is a poorly characterized heterogeneous mixture of a widely

varying number of different compounds, strategies have been proposed for examining the health effects of potentially important organic constituents (Turpin, 1999).

Bioaerosols. Recent studies support the conclusion of the 1996 PM AQCD that bioaerosols, at the concentrations present in the ambient environment, do not likely account for the health effects of ambient PM. Dose response studies in healthy volunteers exposed to 0.55 and 50 μg endotoxin, by inhalation, showed the threshold for pulmonary and systemic effects for endotoxin to be between 0.5 and 5.0 μg (Michel et al., 1997). Available information suggests that ambient concentrations of endotoxin are very low and do not exceed 0.5 ng/m^3. Also, Monn and Becker (1999) found cytokine induction by human monocytes, characteristic of endotoxin activity, in the coarse size fraction of outdoor PM but not in the fine fraction.

Concentrated Ambient Particle Studies (CAPS). Ambient particle studies are potentially among the most relevant in improving our understanding of the susceptibility of individuals to PM and underlying mechanisms of toxicity. New studies have used collected urban PM for intratracheal administration to healthy and compromised animals, and some recent work with inhaled concentrated ambient PM has reported cardiopulmonary changes in rodents and dogs at high concentrations of fine PM. Thus, despite difficulties in extrapolating from the bolus delivery used in such studies, they are contributing some new evidence enhancing the plausibility of health effects of fine particles observed in epidemiologic studies.

Animal Models of Susceptibility. Progress has been made in understanding the role of individual susceptibility to ambient PM effects. Studies have shown consistently that animals with compromised health, either genetic or induced, are more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models has created problems. Moreover, because PM seems to affect broad categories of disease states ranging from altered cardiac rhythms to pulmonary infection, it can be difficult to know what disease models to use in understanding the biological plausibility of the adverse health effects of PM. Thus, the identification of susceptible animal models has been slow, but, overall, it represents solid progress when one considers the numbers of people necessary in epidemiology studies to develop the statistical power to detect small increases in morbidity and mortality.

9.7 RISK FACTORS AND POTENTIALLY SUSCEPTIBLE POPULATION GROUPS

9.7.1 Introduction

The 1996 PM AQCD identified several population groups as likely being at increased risk for experiencing health impacts of ambient PM exposure. Elderly individuals (>65 years) were most clearly identified, along with those having preexisting cardiovascular or respiratory disease conditions. The latter likely include smokers and ex-smokers as individuals comprising large percentages of cardiovascular and respiratory disease (e.g., COPD) sufferers. Individuals with asthma also were, albeit more tentatively, identified as a likely susceptible population group as well, as were children. The new studies appearing since the 1996 PM AQCD, as assessed earlier in this document and chapter, provide considerable additional evidence substantiating all of the above named groups as likely being at increased risk for ambient PM-related morbidity or mortality effects. Information related to factors contributing to such increased susceptibility or useful in placing the potential public health impacts in perspective is presented below.

9.7.2 Preexisting Disease as a Risk Factor for Particulate Matter Health Effects

Earlier available information reviewed in the 1996 PM AQCD has now been extensively augmented by new studies that substantiate well that preexisting disease conditions are among the most important key risk factors for ambient PM health effects. Cardiovascular- and respiratory-related diseases have been shown to be of greatest concern, thus far, in relation to increasing risk for PM mortality and morbidity. Table 9-9 shows the numbers of U.S. cases reported for COPD, asthma, heart disease, and hypertension.

9.7.2.1 Ambient Particulate Matter Exacerbation of Cardiovascular Disease Conditions

Exacerbation of heart disease has been epidemiologically associated, not only with ambient PM, but also with other combustion-related ambient pollutants such as CO. Thus, while leaving little doubt that ambient PM exposures importantly affect CVD mortality and morbidity, the quantitation of the proportion of risk for such exacerbation specifically attributable to ambient PM exposure is difficult. Recent studies (e.g., concentrated ambient particle studies [CAPS]) have demonstrated cardiovascular effects in response to ambient particle exposures, and

TABLE 9-9. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND BY GEOGRAPHIC REGION, 1996
(reported as incidence per thousand population and as number of cases in thousands)

	Age					Regional			
Chronic Condition/Disease	All Ages	Under 45	45-64	Over 65	Over 75	NE	MW	S	W
COPD*									
Incidence/1,000 persons	60.4	50.6	72.3	95.9	99.9	57.8	67.6	59.4	56.6
No. cases × 1,000	15,971	9,081	3,843	3,047	1,334				
Asthma									
Incidence/1,000 persons	55.2	58.9	48.6	45.5	48.0	61.8	56.6	51.8	52.9
No. cases × 1,000	14,596	10,570	2,581	1,445	641				
Heart Disease									
Incidence/1,000 persons	78.2	33.1	116.4	268.7	310.7	88.5	78.0	77.0	70.4
No. cases × 1,000	20,653	5,934	6,184	8,535	4,151				
HD-ischemic									
Incidence/1,000 persons	29	2.5	51.6	140.9	154.6	28.9	30.0	30.7	25.0
No. cases × 1,000	7,672	453	2,743	4,476	2,065				
HD-rhythmic									
Incidence/1,000 persons	33	24.3	40.7	69.1	73.1	40.2	34.0	28.1	32.9
No. cases × 1,000	8,716	4,358	2,164	2,195	977				
Hypertension									
Incidence/1,000 persons	107.1	30.1	214.1	363.5	373.8	109.3	108.2	113.5	93.7
No. cases × 1,000	28,314	5,391	11,376	11,547	4,994				

*Total chronic bronchitis and emphysema.

Source: Adams et al. (1999).

studies utilizing other techniques also have produced various results suggesting some plausible mechanisms for cardiovascular effects. However, much remains to be resolved with regard to delineation of dose-response relationships for the induction of such effects and the extrapolation of such to estimate effective human equivalent exposures to ambient PM (or specific constituent) concentrations.

Schwartz (1999) has argued that independent effects of both PM and other pollutants are biologically plausible. In the case of PM_{10}, Schwartz's plausibility argument draws on the emerging literature, which has demonstrated effects of ambient PM on pulmonary inflammation in laboratory animals and human volunteers (Gilmour et al., 1996; Salvi et al., 1999), toxicity of transition metals carried by combustion- generated particles (Costa and Dreher, 1999), effects on cardiac dysfunction in animals with preexisting cardiopulmonary disease (Godleski et al., 1996; Watkinson et al., 1998), and new epidemiologic evidence of associations between ambient PM and physiologic changes in cardiac function (Pope et al., 1999a,b; Liao et al., 1999; Peters et al., 1999b; Gold et al., 1998, 2000) and plasma viscosity (Peters et al., 1997a) in humans. For CO, his argument is based on well-established effects of CO on oxygen transport by hemoglobin, although such an impact typically is observed only at much higher CO concentrations than those seen in these ambient studies. Although much more research is needed to clarify and confirm the hypothesized linkages among these new findings, these arguments provide an initial framework for such a linkage.

One very recently published HEI report on an epidemiologic study conducted by Goldberg et al. (2000) in Montreal, Canada, provides especially interesting new information regarding types of medical conditions potentially putting susceptible individuals at increased risk for PM-associated mortality effects, and obtained results suggestive of other diseases with cardiovascular complications being affected by ambient PM. First, the immediate causes of death, as listed on death certificates, were evaluated in relation to various ambient PM indices (TSP, PM_{10} estimated $PM_{2.5}$, COH, sulfates, and extinction coefficients) lagged for 0 to 4 days. Significant associations were seen between each of the PM measures and total nonaccidental deaths, respiratory diseases, and diabetes, with an approximate 2% increase in excess nonaccidental mortality being observed per 9.5 $\mu g/m^3$ interquartile increase in 3-day mean estimated $PM_{2.5}$ exposure. When underlying clinical conditions identified in the decedents' medical records were then evaluated in relation to ambient PM measures, all three measures (COH, sulfate, and

estimated $PM_{2.5}$) were associated with acute lower respiratory disease, congestive heart failure, and any cardiovascular disease. Predicted $PM_{2.5}$ and COH also were reported to be associated with cancer, chronic coronary artery disease, and any coronary artery disease, whereas sulfate was associated with acute and chronic upper respiratory disease. None of the three PM measures were related to airways disease, acute coronary artery disease, or hypertension. These results both tend to confirm previous findings identifying those with preexisting cardiopulmonary diseases as being at increased risk for ambient PM effects and implicate another possible risk factor, diabetes (which involves cardiovascular complications as it progresses), as a potential susceptibility condition putting individuals at increased risk for ambient PM effects.

To the extent that observed associations of ambient PM with heart disease exacerbation prove to be causal and specific to PM, they would be of genuine public health concern. In the U.S. in 1997, there were about 4,188,000 hospital discharges with heart disease as the first-listed diagnosis (Lawrence and Hall, 1999). Among these, about 2,090,000 (50%) were for ischemic heart disease, 756,000 (18%) for myocardial infarction or heart attack (a subcategory of ischemic heart disease), 957,000 (23%) for congestive heart failure, and 635,000 (15%) for cardiac dysrhythmias. Also, there were 726,974 deaths from heart disease (Hoyert et al., 1999). Even a small percentage reduction in admissions or deaths from heart disease would predict a large number of avoided cases.

9.7.2.2 Ambient Particulate Matter Exacerbation of Respiratory Disease Conditions

Many investigators also have observed associations of short-term fluctuations in ambient PM with daily frequency of respiratory illness. In most cases, exacerbation of preexisting respiratory illness has been assessed, although some cases of acute respiratory infection may be considered as occurrence of new illness, especially in young people. Symptoms of acute respiratory distress in children have been linked to elevated PM concentrations in studies in the United States and other countries, with asthmatics apparently more susceptible than nonasthmatics. However, some studies also have found associations between child respiratory symptoms or reduced lung function and other pollutants (such as O_3) in addition to PM or no significant relationship with air pollution. The credibility of ambient PM plausibly being linked to exacerbation of preexisting respiratory disease (e.g., asthma) is enhanced by newly reported dosimetry data noted earlier, which show greater lung deposition of 1-μm particles in people

with varying degrees of airway obstruction than in healthy subjects. The increased deposition was greatest for COPD patients and asthmatics, but smokers also showed increased deposition as well.

In the United States in 1997, there were 3,475,000 hospital discharges for respiratory diseases: 38% for pneumonia, 14% for asthma, 13% for chronic bronchitis, 8% for acute bronchitis, and the remainder not specified (Lawrence and Hall, 1999). Of the 195,943 deaths recorded as caused by respiratory diseases, 44% resulted from acute infections, 10% for emphysema and bronchitis, 2.8% for asthma, and 42% for unspecified COPD (Hoyert et al., 1999). Again, even a small percentage reduction in respiratory-related diseases could calculate out to a large number of avoided cases.

9.7.3 Aged-Related At-Risk Population Groups: The Elderly and Children

Why are the very young and the very old apparently among those most affected by PM air pollution? One major factor in increased susceptibility to air pollution is the presence of a preexisting illness, as shown by Zanobetti and Schwartz (2000). The youngest children have the highest rates of respiratory illnesses, as shown in the Table 9-10, which may be an important factor in their apparently greater susceptibility to the adverse effects of PM air pollution.

TABLE 9-10. NUMBER OF ACUTE RESPIRATORY CONDITIONS PER 100 PERSONS PER YEAR, BY AGE: UNITED STATES, 1996

						45 Years and Over		
Type of Acute Condition	All Ages	Under 5 Years	5-17 Years	18-24 Years	25-44 Years	Total	45-64 Years	65 Years and Over
Respiratory Conditions	78.9	129.4	101.5	86.0	76.9	53.3	55.9	49.0
Common Cold	23.6	48.6	33.8	23.8	18.7	16.1	16.4	15.7
Other Acute Upper Respiratory Infections	11.3	13.1	15.0	16.1	11.6	7.0	7.5	6.1
Influenza	36.0	53.7	44.3	40.5	38.1	23.3	26.1	18.6
Acute Bronchitis	4.6	*7.2	4.3	*3.9	5.1	3.8	3.5	*4.4
Pneumonia	1.8	*3.9	*1.7	*1.4	*1.3	*2.0	*0.9	*3.8
Other Respiratory Conditions	1.7	*2.9	*2.4	*0.4	*2.0	*1.1	*1.5	*0.5

Source: Adams et al. (1999).

In addition to their higher incidences of preexisting respiratory conditions, several other factors may render children and infants more susceptible to PM exposures, including a greater amount of time spent outdoors, greater activity levels and breathing rates, higher doses per body weight and lung surface area, and potential irreversible effects on children's developing lungs. For example, PM doses on a per kilogram body weight basis are much higher for children than for adults. This is displayed graphically in the Figure 9-14, which indicates that the amount of air inhaled per kilogram body weight increases dramatically as age decreases below adult levels, with the inhalation rate (in cubic meters per kilogram a day) of a 10-year-old being roughly twice that of a 30-year-old person, and this estimate does not consider higher personal exposure concentrations that a child is usually exposed to as a result of higher activity levels. Thus, on a per unit body weight basis, children receive higher doses of air pollution than adults, consistent with lung deposition information discussed earlier in this chapter.

Child-adult dosage disparities are even greater when viewed on a per lung area basis. This may be more important than body weight if the number of particle "hits" per unit lung surface is an important health impact metric, which it may well be for ultrafine particles. A newborn infant has approximately 10 million alveoli versus some 300 million as an adult. The alveolar surface area increases from approximately 3 m^2 at birth to about 75 m^2 in adulthood, causing the dose delivered per lung surface area for infants and children to be much higher than in adults, even given the same personal exposures (which is not the case, as they generally have greater PM_{10} personal exposures than adults, as noted above). Thus, observed high PM air pollution-hospital admissions associations for infants may result from PM doses that are significantly higher in children than in adults, when one considers children's higher personal exposures, their greater activity rates, and their smaller body weights and lung surface areas.

As discussed by Plopper and Fanucchi (2000), the limited experimental and epidemiologic studies currently available identify the early postneonatal period of lung development as a time of high susceptibility for lung damage created by exposure to environmental toxicants. This is likely the reason for the above noted high rate of respiratory infectious diseases in young children. In addition to their diminished immune status, infants are growing rapidly, and some recent (though limited) evidence supports the hypothesis that environmental pollution can significantly alter development of the respiratory system at that period of life. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been

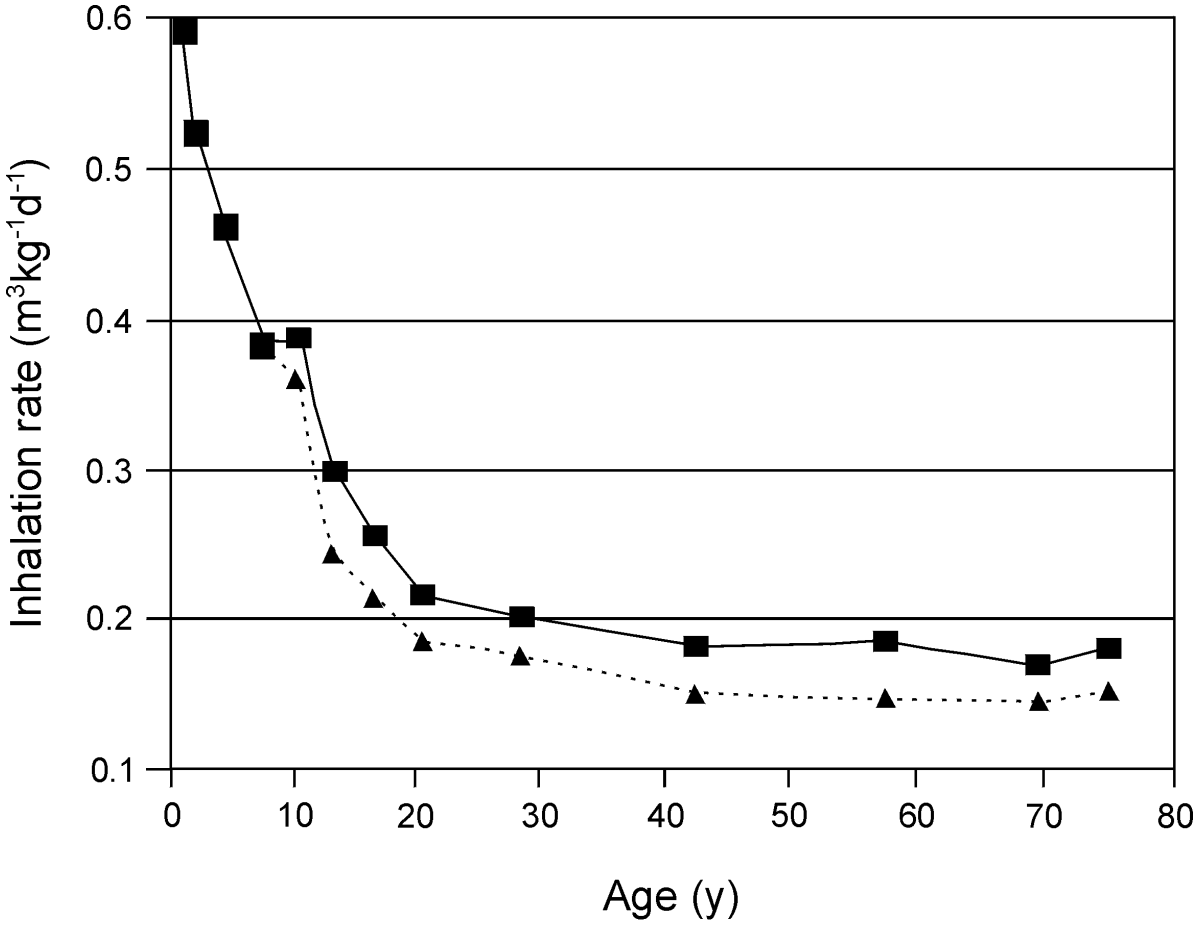

Figure 9-14. Inhalation rates on a per body-weight basis for males (■) and females (▲) by age (Layton, 1993).

reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000; Fanucchi and Plopper, 1997). In addition, acute injury to the lung during early postnatal development causes a failure of normal repair processes, including down-regulation of cellular proliferation at sites of injury (Smiley-Jewel et al., 2000, Fanucchi et al., 2000). Both infants' diminished defenses and pollution-induced impairment of repair mechanisms therefore can coincide during infancy, making the neonatal and postneonatal period one of potentially especially elevated susceptibility to damage by environmental toxicants like PM.

Other information reviewed earlier in this document and chapter highlighted new evidence pointing toward enhanced asthma symptoms, pulmonary function decrements, and asthma-

related doctors' visits and hospital admissions being associated with ambient PM exposures. Generally higher activity levels in children and other factors related to attaining adequate medical control of asthma in children may put asthmatic children (especially physically active mild to moderate asthmatics) at particular risks for untoward effects of ambient PM among pediatric population groups.

These and other types of health effects in children are emerging as a more important area of concern than in the 1996 PM AQCD. Unfortunately, relatively little is known about the relationship of PM to the most serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in older children). Also, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue because childhood illness or death may cost a very large number of productive life-years. Lastly new epidemiologic studies of ambient PM associations with increased non-hospital medical visits (physician visits) and asthma effects suggest likely much larger health impacts and costs to society due to ambient PM effects on children than just those indexed by mortality and/or hospital admissions/visits.

In contrast to information noted above for children, elderly adults do not appear to be put at increased risk because of difference in lung deposition, clearance, or retention of inhaled particles associated with aging, per se. However, the possible gradual focal accumation of previously inhaled PM material at bifurcations and carinal ridges in TB airways and release of previously accumulated inhaled PM-derived materials from lymph nodes could contribute to enhanced susceptibility of elderly adults, especially those residing for long periods of time in high PM exposure areas.

Probably of much more importance in placing elderly adults at increased risk for PM effects is the higher propensity for such individuals to have preexisting cardiovascular or respiratory disease conditions. Increased breathing rates due to compromised (e.g., obstructed) lungs and airways or altered particle deposition patterns resulting from such conditions could be among important factors increasing the risk for the elderly.

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APPENDIX 9A

Key Quantitative Estimates of Relative Risk for Particulate Matter-Related Health Effects Based on Epidemiologic Studies of North American Cities Assessed in the 1996 Particulate Matter Air Quality Criteria Document

TABLE 9A-1. EFFECT ESTIMATES PER 50-$\mu g/m^3$ INCREASE IN 24-HOUR PM_{10} CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR (±CI) Only PM in Model	RR (±CI) Other Pollutants in Model	Reported PM_{10} Levels Mean (Min/Max)[†]
Increased Total Acute Mortality			
Six Cities[a]		—	
Portage, WI	1.04 (0.98, 1.09)	—	18 (±11.7)
Boston, MA	1.06 (1.04, 1.09)	—	24 (±12.8)
Topeka, KS	0.98 (0.90, 1.05)	—	27 (±16.1)
St. Louis, MO	1.03 (1.00, 1.05)	—	31 (±16.2)
Kingston/Knoxville, TN	1.05 (1.00, 1.09)	—	32 (±14.5)
Steubenville, OH	1.05 (1.00, 1.08)	—	46 (±32.3)
St. Louis, MO[c]	1.08 (1.01, 1.12)	1.06 (0.98, 1.15)	28 (1/97)
Kingston, TN[c]	1.09 (0.94, 1.25)	1.09 (0.94, 1.26	30 (4/67)
Chicago, IL[h]	1.04 (1.00, 1.08)	—	37 (4/365)
Chicago, IL[g]	1.03 (1.02, 1.04)	1.02 (1.01, 1.04)	38 (NR/128)
Utah Valley, UT[b]	1.08 (1.05, 1.11)	1.19 (0.96, 1.47)	47 (11/297)
Birmingham, AL[d]	1.05 (1.01, 1.10)	—	48 (21, 80)
Los Angeles, CA[f]	1.03 (1.00, 1.055)	1.02 (0.99, 1.036)	58(15/177)
Increased Hospital Admissions (for Elderly > 65 years)			
Respiratory Disease			
Toronto, Canada[i]	1.23 (1.02, 1.43)[‡]	1.12 (0.88, 1.36)[‡]	30-39[*]
Tacoma, WA[j]	1.10 (1.03, 1.17)	1.11 (1.02, 1.20)	37 (14, 67)
New Haven, CT[j]	1.06 (1.00, 1.13)	1.07 (1.01, 1.14)	41 (19, 67)
Cleveland, OH[k]	1.06 (1.00, 1.11)	—	43 (19, 72)
Spokane, WA[l]	1.08 (1.04, 1.14)	—	46 (16, 83)
COPD			
Minneapolis, MN[n]	1.25 (1.10, 1.44)	—	36 (18, 58)
Birmingham, AL[m]	1.13 (1.04, 1.22)	—	45 (19, 77)
Spokane, WA[l]	1.17 (1.08, 1.27)	—	46 (16, 83)
Detroit, MI[o]	1.10 (1.02, 1.17)	—	48 (22, 82)

TABLE 9A-1 (cont'd). EFFECT ESTIMATES PER 50-μg/m^3 INCREASE IN 24-HOUR PM_{10} CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR (±CI) Only PM in Model	RR (±CI) Other Pollutants in Model	Reported PM_{10} Levels Mean (Min/Max)[†]
Pneumonia			
Minneapolis, MN[n]	1.08 (1.01, 1.15)	—	36 (18,58)
Birmingham, AL[m]	1.09 (1.03, 1.15)	—	45 (19, 77)
Spokane, WA[l]	1.06 (0.98, 1.13)	—	46 (16, 83)
Detroit, MI[o]	—	1.06 (1.02, 1.10)	48 (22, 82)
Ischemic HD			
Detroit, MI[p]	1.02 (1.01, 1.03)	1.02 (1.00, 1.03)	48 (22, 82)
Increased Respiratory Symptoms			
Lower Respiratory			
Six Cities[q]	2.03 (1.36, 3.04)	Similar RR	30 (13,53)
Utah Valley, UT[r]	1.28 (1.06, 1.56)[τ]	—	46 (11/195)
	1.01 (0.81, 1.27)[π]		
Utah Valley, UT[s]	1.27 (1.08, 1.49)	—	76 (7/251)
Cough			
Denver, CO[x]	1.09 (0.57, 2.10)	—	22 (0.5/73)
Six Cities[q]	1.51 (1.12, 2.05)	Similar RR	30 (13, 53)
Utah Valley, UT[s]	1.29 (1.12, 1.48)	—	76 (7/251)
Decrease in Lung Function			
Utah Valley, UT[r]	55 (24, 86)[**]	—	46 (11/195)
Utah Valley, UT[s]	30 (10, 50)[**]	—	76 (7/251)
Utah Valley, UT[w]	29 (7,51)[***]	—	55 (1,181)

References:

[a]Schwartz et al. (1996a).
[b]Pope et al. (1992, 1994)/O_3.
[c]Dockery et al. (1992)/O_3.
[d]Schwartz (1993).
[g]Ito and Thurston (1996)/O_3.
[f]Kinney et al. (1995)/O_3, CO.
[h]Styer et al. (1995).
[i]Thurston et al. (1994)/O_3.
[j]Schwartz (1995)/SO_2.
[k]Schwartz et al. (1996b).
[l]Schwartz (1996).
[m]Schwartz (1994a).
[n]Schwartz (1994b).
[o]Schwartz (1994c).
[p]Schwartz and Morris (1995)/O_3, CO, SO_2.
[q]Schwartz et al. (1994).
[r]Pope et al. (1991).
[s]Pope and Dockery (1992).
[t]Schwartz (1994d).
[w]Pope and Kanner (1993).
[x]Ostro et al. (1991).
[†]Min/Max 24-h PM_{10} in parentheses unless noted otherwise as standard deviation (±SD), 10 and 90 percentile (10, 90). NR = not reported.
[τ]Children.
[π]Asthmatic children and adults.
[*]Means of several cities.
[**]PEFR decrease in mL/s.
[***]FEV_1 decrease.
[‡]RR refers to total population, not just >65 years.

TABLE 9A-2. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-HOUR CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES

Acute Mortality	Indicator	RR (±CI) per 25 $\mu g/m^3$ PM Increase	Reported PM Levels Mean (Min/Max)[†]
Six City[a]			
Portage, WI	$PM_{2.5}$	1.030 (0.993, 1.071)	11.2 (±7.8)
Topeka, KS	$PM_{2.5}$	1.020 (0.951, 1.092)	12.2 (±7.4)
Boston, MA	$PM_{2.5}$	1.056 (1.038, 1.0711)	15.7 (±9.2)
St. Louis, MO	$PM_{2.5}$	1.028 (1.010, 1.043)	18.7 (±10.5)
Kingston/Knoxville, TN	$PM_{2.5}$	1.035 (1.005, 1.066)	20.8 (±9.6)
Steubenville, OH	$PM_{2.5}$	1.025 (0.998, 1.053)	29.6 (±21.9)
Increased Hospitalization			
Ontario, Canada[b]	$SO_4^=$	1.03 (1.02, 1.04)	R = 3.1-8.2
Ontario, Canada[c]	$SO_4^=$	1.03 (1.02, 1.04)	R = 2.0-7.7
	O_3	1.03 (1.02, 1.05)	
NYC/Buffalo, NY[d]	$SO_4^=$	1.05 (1.01, 1.10)	NR
Toronto[d]	H^+ ($Nmol/m^3$)	1.16 (1.03, 1.30)[*]	28.8 (NR/391)
	$SO_4^=$	1.12 (1.00, 1.24)	7.6 (NR, 48.7)
	$PM_{2.5}$	1.15 (1.02, 1.78)	18.6 (NR, 66.0)
Increased Respiratory Symptoms			
Southern California[f]	$SO_4^=$	1.48 (1.14, 1.91)	R = 2-37
Six Cities[g]	$PM_{2.5}$	1.19 (1.01, 1.42)[**]	18.0 (7.2, 37)[***]
(Cough)	$PM_{2.5}$ Sulfur	1.23 (0.95, 1.59)[**]	2.5 (3.1, 61)[***]
	H^+	1.06 (0.87, 1.29)[**]	18.1 (0.8, 5.9)[***]
Six Cities[g]	$PM_{2.5}$	1.44 (1.15-1.82)[**]	18.0 (7.2, 37)[***]
(Lower Resp. Symp.)	$PM_{2.5}$ Sulfur	1.82 (1.28-2.59)[**]	2.5 (0.8, 5.9)[***]
	H^+	1.05 (0.25-1.30)[**]	18.1 (3.1, 61)[***]
Decreased Lung Function			
Uniontown, PA[e]	$PM_{2.5}$	PEFR 23.1 (-0.3, 36.9) (per 25 $\mu g/m^3$)	25/88 (NR/88)

References:

[a]Schwartz et al. (1996a).
[b]Burnett et al. (1994).
[c]Burnett et al. (1995) O_3.
[d]Thurston et al. (1992, 1994).
[d]Neas et al. (1995).
[f]Ostro et al. (1993).
[g]Schwartz et al. (1994).

[†]Min/Max 24-h PM indicator level shown in parentheses unless otherwise noted as (±SD), 10 and 90 percentile (10,90) or R = range of values from min-max, no mean value reported.
[*]Change per 100 nmoles/m^3
[**]Change per 20 $\mu g/m^3$ for $PM_{2.5}$; per 5 $\mu g/m^3$ for $PM_{2.5}$ sulfur; per 25 nmoles/m^3 for H^+.
[***]50th percentile value (10,90 percentile).

TABLE 9A-3. EFFECT ESTIMATES PER INCREMENTS[a] IN ANNUAL MEAN LEVELS OF FINE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect and Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels Means ($\mu g/m^3$)
Increased Total Chronic Mortality in Adults		Relative Risk (95% CI)	
Six City[b]	$PM_{15/10}$	1.42 (1.16-2.01)	18-47
	$PM_{2.5}$	1.31 (1.11-1.68)	11-30
	$SO_4^=$	1.46 (1.16-2.16)	5-13
ACS Study[c] (151 U.S. SMSA)	$PM_{2.5}$	1.17 (1.09-1.26)	9-34
	$SO_4^=$	1.10 (1.06-1.16)	4-24
Increased Bronchitis in Children		Odds Ratio (95% CI)	
Six City[d]	$PM_{15/10}$	3.26 (1.13, 10.28)	20-59
Six City[e]	TSP	2.80 (1.17, 7.03)	39-114
24 City[f]	H^+	2.65 (1.22, 5.74)	6.2-41.0
24 City[f]	$SO_4^=$	3.02 (1.28, 7.03)	18.1-67.3
24 City[f]	$PM_{2.1}$	1.97 (0.85, 4.51)	9.1-17.3
24 City[f]	PM_{10}	3.29 (0.81, 13.62)	22.0-28.6
Southern California[g]	$SO_4^=$	1.39 (0.99, 1.92)	—
Decreased Lung Function in Children			
Six City[d,h]	$PM_{15/10}$	NS Changes	20-59
Six City[e]	TSP	NS Changes	39-114
24 City[i,j]	H^+ (52 nmoles/m^3)	−3.45% (-4.87, -2.01) FVC	—
24 City[i]	$PM_{2.1}$ (15 $\mu g/m^3$)	−3.21% (-4.98, -1.41) FVC	—
24 City[i]	$SO_4^=$ (7 $\mu g/m^3$)	−3.06% (-4.50, -1.60) FVC	—
24 City[i]	PM_{10} (17 $\mu g/m^3$)	−2.42% (-4.30, -.0.51) FVC	—

[a]Estimates calculated annual-average PM increments assume: a 100-$\mu g/m^3$ increase for TSP; a 50-$\mu g/m^3$ increase for PM_{10} and PM_{15}; a 25-$\mu g/m^3$ increase for $PM_{2.5}$; and a 15-$\mu g/m^3$ increase for $SO_4^=$, except where noted otherwise; a 100-nmole/m^3 increase for H^+.
[b]Dockery et al. (1993).
[c]Pope et al. (1995).
[d]Dockery et al. (1989).
[e]Ware et al. (1986).
[f]Dockery et al. (1996).
[g]Abbey et al. (1995).
[h]NS Changes = No significant changes.
[i]Raizenne et al. (1996).
[j]Pollutant data same as for Dockery et al. (1996).

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EXECUTIVE SUMMARY

Air Quality Criteria for Particulate Matter (March 2000)

The Executive Summary of this Second External Review Draft of the Air Quality Criteria for Particulate Matter is under preparation and will be completed following public comment and CASAC review of the earlier, more detailed chapters of this Second External Review Draft. It will be included in subsequent drafts of the document.