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April 1995
External Review Draft

EPA

Air Quality Criteria for Particulate Matter

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Volume III of III

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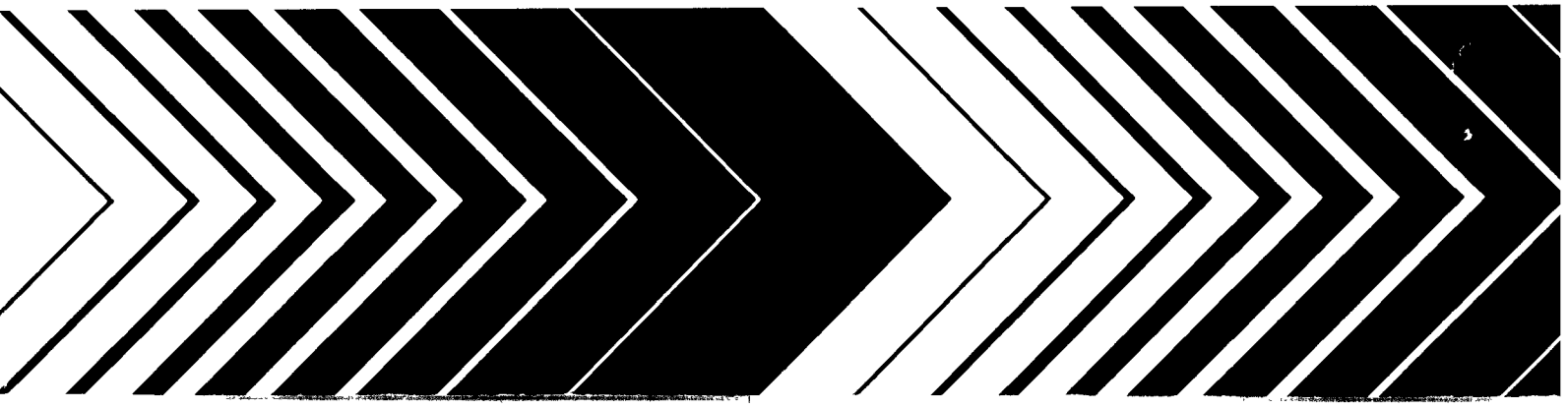

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Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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Air Quality Criteria for Particulate Matter

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AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHAPTER 12. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES/ACID AEROSOLS

Principal Authors

Dr. Lester D. Grant-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Office, Research Triangle Park, NC 27711

Dr. Vic Hasselblad-29 Autumn Woods Drive, Durham, NC 27713

Dr. Kazuhiko Ito-New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo, NY 10987

Dr. Laurence Kalkstein-University of Delaware, Center of Climatic Research, Newark, DE 19716-2541

Dr. Dennis Kotchmar-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Fred Lipfert-23 Carll Court, Northport, NY 11768

Dr. Allan Marcus-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. George Thurston-New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo, NY 10987

Contributors and Reviewers

Dr. Philip Bromberg-University of North Carolina, School of Medicine, Chapel Hill, NC 27599-0126

Dr. Bert Brunekreef-The University of Wageningen, Department of Epidemiology and Public Health, P.O. Box 238, 6700 A E Wageningen, The Netherlands

Dr. Richard Burnett-Health and Welfare Canada, 203 Environmental Health Center, Tunney's Pasture, Ottwaw, Ontario, Canada K1A 0L2

Dr. Robert Chapman-Health Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John Creason-Health Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers (cont'd)

Dr. Douglas Dockery-Harvard School of Public Health, Environmental Epidemiology, 665 Huntington Avenue, Boston, MA 02115

Dr. Laurence Saul Kalkstein-University of Delaware, Center for Climatic Research, Department of Geography, Newark, DE 19716-2541

Dr. Klea Katsouyanni-University of Athens, School of Medicine, Department of Hygiene and Epidemiology, 1327 Athens, Greece

Dr. Patrick Kinney-New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo, NY 10987

Dr. Aparna Koppikar, Human Health Assessment Group, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, (8602), Waterside Mall, 401 M. St. S.E., Washington, DC 20460

Dr. Dennis Kotchmar-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Fred Lipfert-23 Carll Ct., Northport, NY 11768

Dr. Thomas Louis-University of Minnesota, School of Public Health, A-460 Mayo Building, Box 197, 420 Delaware Street, S.E., Minneapolis, MN 55455

Dr. Joseph Lyon-University of Utah, Department of Family and Preventative Medicine, 50 North Medical Drive, Salt Lake City, UT 84132

Dr. David Mage-Atmospheric Research and Exposure Assessment Laboratory (MD-75), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Allan Marcus-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Suresh Moolgavkar-Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104

Dr. William Nelson-Atmospheric Research and Exposure Assessment Laboratory (MD-56), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Bart Ostro-California Environmental Protection Agency, 2151 Berkeley Way, Annex 11, Berkeley, CA 94704

Contributors and Reviewers (cont'd)

Dr. C. Arden Pope, III-Brigham Young University, Department of Economics, Provo, Utah 84602

Dr. James Quackenboss-Environmental Monitoring Systems Laboratory, U.S. Environmental Protection Agency, P.O. Box 93478, Las Vegas, NV 89193-3478

Dr. H. Daniel Roth-Roth Associates, 6115 Executive Boulevard, Rockville, MD 20852

Dr. Carl Shy-University of North Carolina, Department of Epidemiology, School of Public Health, Campus Box 7400, Chapel Hill, NC 27599

Dr. Duncan Thomas-University of Southern California, Preventative Medicine Department, 1420 San Pablo Street, Los Angeles, CA 90033-9987

Dr. Dianne Wagener-National Center for Health Statistics, Mortality Statistics Branch, Division of Vital Statistics, Center for Disease Control, 6526 Belcrest Road, Hyattsville, MD 20782

Dr. William Wilson-Atmospheric Research and Exposure Assessment Laboratory (MD-75), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Mary C. White-Centers for Disease Control, National Center for Environmental Health, 4770 Buford Highway, NE, Atlanta, GA 30341-3724

Dr. Ronald Wyzga-3420 Hillview Avenue, Palo Alto, CA 94304

CHAPTER 13. INTEGRATIVE HEALTH SYNTHESIS

Principal Authors

Dr. Lester D. Grant-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Annie A. Jarabek-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Allan Marcus-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Principal Authors (cont'd)

Dr. James McGrath-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Wilson-Atmospheric Research and Exposure Assessment Labatory (MD-75), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Judith A. Graham-Environmental Criteria and Assessment Office (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jeannette Wiltse, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency (8601), Waterside Mall, 401 M. St. S.E., Washington, DC 20460

12. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES/ACID AEROSOLS

12.1 INTRODUCTION

A rapidly growing body of epidemiologic data examines relationships between PM concentrations and human health effects, ranging from respiratory function changes and symptoms to exacerbation of respiratory disease and excess mortality associated with premature death.

The purpose of this chapter is to review the epidemiological evidence relating health effects to exposure to airborne particles. Much new information has appeared since EPA's publication of the 1982 document on Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982a), its second Addendum (U.S. Environmental Protection Agency, 1986a), and a later Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989). Information from these previous documents is only concisely considered here to provide a background context for this chapter and to help form the basis for evaluation of more recent publications.

12.1.1 Definition of Particulate Matter and Measurement Methods

As discussed in Chapter 3, "Particulate matter" is the generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety of stationary and mobile sources and may be emitted directly or formed in the atmosphere by transformation of gaseous emissions such as sulfur oxides (SO_x), nitrogen oxides NO_x), and volatile organic compounds (VOCs). The chemical and physical properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the assessment of health and welfare effects. Particles in ambient air usually occur in two somewhat overlapping bimodal size distributions: (1) fine (diameter less than 2.5 μm) and (2) coarse (diameter larger than 2.5 μm). The two size fractions tend to have different origins and composition, as discussed in Chapter 3 along with other aspects concerning particle size and atmospheric chemistry.

On July 1, 1987 (Federal Register, 1987), EPA published revisions to the PM NAAQS. The principal revisions in 1987 included replacing TSP as the indicator for the ambient standards with a new indicator that includes only particles with an aerodynamic diameter less than or equal to a nominal 10 μm (PM_{10}).

The NAAQS revision to PM_{10} standards was based on several key conclusions as summarized below:

(1) Health risks posed by inhaled particles are influenced by both the penetration and deposition of particles in the various regions of the respiratory tract and the biological responses to these deposited materials. Smaller particles penetrate furthest in the respiratory tract. The largest particles are deposited predominantly in the extrathoracic (head) region, with somewhat smaller particles depositing in the tracheobronchial region; still smaller particles can reach the deepest portion of the lung, the pulmonary region.

(2) The risks of adverse health effects associated with deposition of typical ambient fine and coarse particles in the thoracic region (tracheobronchial and pulmonary deposition) are markedly greater than those associated with deposition in the extrathoracic region. Maximum particle penetration to the thoracic region occurs during oronasal or mouth breathing.

(3) The size-specific indicator for primary standards should represent those particles small enough to penetrate to the thoracic region. The risks of adverse health effects from extrathoracic deposition of typical ambient PM are sufficiently low that particles depositing only in that region can safely be excluded from the indicator.

A variety of PM sampling and measurement methodologies have been used in the epidemiology studies discussed in this chapter. Some studies used earlier measures such as British Smoke (BS), Coefficient of Haze (COHs) and Total Suspended Particulate Matter (TSP). The use and limitations on interpreting studies using such PM measures are discussed in U.S. Environmental Protection Agency (1982, 1986). Additionally, current measures used in more recent studies (e.g., $PM_{2.5}$ and PM_{10}), are defined and discussed earlier in this document in Chapter 4 (Sampling and Analysis of Particulate Matter). Methodologies for strong acid measurement are also discussed in U.S. Environmental Protection Agency (1989) and in Chapter 4 of this document.

12.1.2 Epidemiologic Designs and Strategies

The recent epidemiology studies to be discussed generally fall into four categories:

(1). short-term exposure studies related to acute effects, typically on a time scale of one or a few days;

(2). prospective cohort studies, in which health outcomes for individuals recruited at the same time are followed over a period of time, typically several years;

(3). cross-sectional epidemiology studies comparing at a single point in time the health effects of long term-exposures to air pollution of different populations, typically assuming that exposure has occurred over a time interval of several years;

(4). metaanalyses and other syntheses of research studies.

Different studies have differing strengths and weaknesses. One limitation common to all of the above different study designs is that only community-level air pollution information is available, generally from one or a few air monitoring stations used to characterize PM and other air pollution and weather exposures over a city or county. However, the acute studies attempt to relate counts of the number of individuals with a specified health outcome to PM exposures during the day when air pollution was measured in the region or possibly within a few days after such exposure. The health endpoints reviewed here include death, hospital admissions for respiratory or cardio-pulmonary causes, respiratory symptoms reported in a diary by individuals on a selected panel of people who reside in the region, school absences, and results of standard pulmonary function tests (PFT). Sometimes the health outcome data are divided into demographic subgroups by age group, sex, or race. Some studies have also divided the mortality data by primary and contributing causes of death on death certificates, such as respiratory causes or cardio-vascular causes, compared with "control" causes that were believed to have little relation to air pollution.

The strength of acute health effects/short-term exposure studies is that they allow evaluations of a single region or community, comparing the response of a population of individuals on one day with one set of pollution exposures to the response of the same population (nearly) on another day with a different set of pollution and weather exposures. In general, the daily health effects data are detrended so that only daily fluctuations in outcome related to daily changes in exposure are evaluated. The detrending includes a

variety of techniques to eliminate the effects of season and yearly changes in population demographics, as well as control or adjustment for unpredictable variables that may affect health outcome, including weather-related variables and shorter-term random events such as influenza epidemics. The analyses of longitudinal data for London during 14 consecutive winters was an important element of the 1986 Addendum and helped to establish a relationship between excess mortality in London and high concentrations of airborne particles measured as British Smoke (BS). Other indicators of airborne particulate matter (PM) have been used in many recent studies.

One limitation in the analysis of acute effects of recent PM exposure is the potential for confounding of PM effects with those of other air pollutants or with meteorological variables. The potential for confounding with other air pollutants may arise because processes that produce PM may also produce the other pollutants. For example, incomplete combustion of fossil fuels used in electrical power generation may produce sulfur dioxide (SO_2) as well as PM, so that emissions of both PM and SO_2 emissions are high or low at the same time. Moreover, SO_2 may also form atmospheric sulfates, which constitute an important part of fine particle mass in many eastern U.S. cities. Likewise, incomplete combustion of fossil fuels in motor vehicles may directly generate PM and primary pollutants such as carbon monoxide (CO) and NO_x and indirectly contribute to secondary air pollutants such as ozone (O_3) and nitrates, with nitrates also being a PM component. Weather may be a contributing factor to emissions, for example by increasing demand for electric power on very hot summer days or very cold winter days, but meteorological conditions such as inversions are also responsible for high concentrations of air pollutants. However, it is important to remember that the potential for confounding of PM effects with weather or other air pollutants does not necessarily mean that confounding actually biased the results in any given study. Confounding must be evaluated on a case-by-case basis. Comparison of estimated PM effects across different communities having different levels of a potentially confounding factor may help to resolve questions about the role of any given potential confounder. This is discussed in more detail in Section 12.2 below.

Prospective cohort studies follow individuals over an extended period of time. The strength of such studies is that individual risk factors can be controlled or adjusted. Known risk factors for mortality include age, sex, race, occupation, economic status, smoking status,

use of alcoholic beverages, and body mass index. If the individuals selected are representative of PM exposures across different communities, the effects of individual risk factors can be separated from PM exposure effects. This epidemiologic design also allows the evaluation of cumulative exposure to PM over the years, whereas the acute effects study design only allows assessment of effects due to short-term exposure changes. One interesting question is whether there are cumulative effects of chronic PM exposure greater than the sum of daily acute effects, since chronic effects must include short-term effects. These strengths of prospective cohort studies are greatly reduced if only occasional air pollution measurements are available, so that only crude exposure comparisons across cities or regions can be made.

Cross-sectional studies look only at highly aggregated community health outcomes, such as mortality rates. With no individual-level exposure available, it is only possible to compare different cities by statistical adjustment for demographic and climatological differences and for average differences in levels of air pollutants or other community-wide health risk factors. However, the data for such analyses may be obtained and analyzed relatively easily, and such studies have served a useful historic role in hypothesis generation.

There is still much discussion about the appropriateness of using formal mathematical methods known as "metaanalysis" in research syntheses (Shapiro, 1994). This approach used in various other EPA documents, when applied properly, can provide useful guidance in combining the results of diverse studies. Ultimately, synthesis of the results of the studies reviewed here is clearly desirable, but must be guided by substantive knowledge about the individual studies evaluated. For this reason, important methodological issues that affect pertinent studies are discussed next, followed by evaluation of the studies themselves.

12.1.3 Guidelines for Assessment of Epidemiologic Studies

An important concept of epidemiologic information reviewed here concerns its usefulness in demonstrating cause-effect relationships versus merely establishing associations (which may be non-causal in nature) between PM exposures and various health effects. The interpretation of epidemiologic data as an aid to inferring causal relationships between presumed causal agents and associated effects has been previously discussed by several expert committees or deliberative bodies faced with evaluation of controversial biomedical issues

(Surgeon General of the United States, 1964; U.S. Senate, 1968). Criteria selected by each for determination of causality included: (1) strength of the association; (2) consistency of the association, as evidenced by its repeated observation by different persons, in different places, circumstances and time; (3) specificity of the association; (4) temporal relationship of the association; (5) coherence of the association in being consistent with other known facts; (6) existence of a biological gradient, or dose-response curve for the association; and (7) biological plausibility of the association.

Hill (1965) further noted that strong support for likely causality suggested by an epidemiologic association may be derived from experimental or semi-experimental evidence, where manipulation of the presumed causative agent (its presence or absence, variability in intensity, etc.) also affects the frequency or intensity of the associated effects. Importantly, both Hill (1965) and the deliberative bodies or expert committees were careful to emphasize, regardless of the specific set of criteria selected by each, that no one criterion is definitive by itself nor is it necessary that all (except temporal relationship) be fulfilled in order to support a determination of causality. Also, Hill (1965) and several of the expert groups noted that statistical methods alone cannot establish proof of a causal relationship in an association nor does lack of "statistical significance" of an association according to arbitrarily selected probability criteria necessarily negate the possibility of a causal relationship. That is, as stated by the U.S. Surgeon General's Advisory Committee on Smoking and Health (Surgeon General of the United States, 1964): "The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." Apropos to this, Bates (1992) has emphasized the importance of assessing the overall coherence of epidemiologic findings of both morbidity and mortality effects at varying pollutant concentrations in making judgements on likely causal relationships.

Taking into account the above considerations, the following guidelines can be stated by which to judge the relative scientific quality of epidemiologic studies and their findings reviewed here and to assist in their overall interpretation:

(1). Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?

(2). Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3). Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4). Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

(5). Were likely important confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

(6). Are the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

Few, if any, epidemiologic studies deal with all of the above points in a completely ideal fashion; nevertheless, these guidelines provide benchmarks for judging the relative quality of various studies and for selecting the best for use in criteria development. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is beyond the scope of this document. Of most importance for present purposes are those studies which provide useful quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

Accordingly, the following criteria were employed in selecting studies for detailed discussion in the ensuing text:

(1). Concentrations of PM and/or other pollutants were reported, allowing for evaluation of their separate or combined effects.

(2). Study results provide information on quantitative relationships between health effects and ambient air PM levels of current concern (i.e., generally ≤ 250 $\mu g/m^3$ PM_{10}).

(3). Key methodological issues were addressed, especially (a) in controlling for likely important confounding factors and (b) in data collection, analysis, and interpretation so as to minimize errors or potential biases.

(4). The study results have been reported in the open literature or are in press, typically after having undergone peer review.

Extensive epidemiologic literature on the effects of occupational exposures to various PM specific components is not reviewed here for several reasons:

(1). Such literature generally deals with effects of exposures to PM chemical species at levels many times higher than those encountered in the ambient air by the general population.

(2). Populations exposed occupationally mainly include healthy adults, self-selected to some extent in terms of being better able to tolerate exposures to PM substances than more susceptible workers seeking alternative employment or other groups often at special risk among the general public (e.g., the old, the chronically ill, young children, and asthmatics).

(3). Extrapolation of observed occupational exposure-health effects relationships (or lack thereof) to the general public (especially population groups at special risk) could, therefore, be potentially misleading in terms of demonstrating health effects among healthy workers at higher exposure levels than would affect susceptible groups in the general population.

The occupational literature does, however, demonstrate links between acute high level or chronic lower level exposures to many different PM chemical species and a variety of health effects, including: pulmonary function changes; respiratory tract diseases; morphological damage to the respiratory system; and respiratory tract cancers. Some consideration of such literature is provided in Chapter 11 on the toxicology of specific PM constituents as useful to elucidate important points on observed exposure-effect relationships.

12.2 METHODOLOGICAL CONSIDERATIONS

Studies assessed in this chapter were evaluated for several factors of importance for interpreting epidemiological studies. These include: (1) exposure measurement errors; (2) misclassification of health outcomes; (3) model specification for acute studies; (4) model specification for chronic studies; (5) covariates and confounders; (6) selection bias; (7) publication bias; (8) internal consistency and strength of effects; and (9) plausibility of observed effects.

12.2.1 Exposure Measurement Error

Measurement error in exposure is potentially one of the most important methodological problems in epidemiologic studies of PM. Ideally, personal monitors would be placed on all subjects for the entire period of a study. Even then, some error associated with the monitoring device itself would remain. Such intensive personal monitoring is generally not feasible for large scale epidemiology studies of PM effects. Even personal monitoring, because of the integrated multi-day sampling, does not adequately measure short-term peaks nor long-term chronic exposures. Instead, PM exposure may also be estimated by source description, personal monitors, in-home monitors, and fixed-site outdoor monitors.

The effect of exposure measurement error on epidemiologic estimation of exposure-effect relationships has been studied by several authors: Shy et al. (1978), Gladen and Rogan (1979), Clark (1982), Stefanski and Carroll (1985), Walker and Blettner (1985), Fuller (1987), Lebret (1987), Schafer (1987), Whittemore and Keller (1988), Samet and Utell (1990), Yoshimura (1990), Louis (1991), and Thomas et al. (1993). In general, exposure measurement error independent of the health outcome results in estimated effects being biased towards the null. For example, Whittemore and Keller (1988) found a 20% misclassification rate of the exposure category to result in an underestimate of the logistic regression coefficient by up to 50%. Also, Stefanski and Carroll (1985) found that even without the independence of error related to outcome, the bias is towards the null in situations where the probabilities of response are not extremely close to 0 or 1. Clark (1982) reported measurement error to be biased towards the null in logistic regression when that error was sampled from a normal or logistic regression, and also found bias towards the null for certain multiple logistic models.

Several types of PM measurement errors can affect PM-mortality associations. One type is analytical measurement error, including errors in weighing filters and in instrumental response (e.g., light transmittance). The error, in this case, is the discrepancy between the 'true' concentration at the sampling point and the value obtained through certain analytical techniques. Another type of error relates to exposure misclassification on an individual level (e.g., activity patterns) and on a population level (e.g., a monitoring site's location relative to population density center). Effects of individual level errors are harder to determine since this requires data collection on human activity patterns. Population level exposure

misclassification errors may be explored using demographic data in conjunction with information regarding the spatial variability of air pollution data.

The spatial variability in PM may affect PM mortality regression coefficients either systematically or randomly (see appendix for an illustration). Systematic error may bias the coefficient either upward or downward. Random errors bias the PM-mortality relationship toward the null. The downward bias is, in general, a function of error-to-signal variance ratio (Snedecor and Cochran, 1983). While extensive discussions exist on effects of measurement errors and possible methods of correction for more traditional epidemiologic studies (Thomas et al., 1993), there has been virtually no systematic assessment of the nature and impact of measurement errors in the time-series context (e.g., does averaging multiple-day PM data reduce error?). Also, without knowledge about differential effects of errors for each air pollution index, interpreting the relative significance of regression coefficients vis-a-vis causality (e.g., those for PM vs. SO_2) can be misleading.

A few examples in earlier literature, however, considered spatial variability errors for PM and other pollutants (e.g., Clifton et al., 1959; Stalker et al., 1962). In Stalker et al's study in Nashville, TN, a lower spatial precision was found for SO_2 than TSP. More recently, Kotchmar et al.'s (1987) study of five U.S. cities found fine particles ($d < 2.5\ \mu m$) to be more uniformly spatially distributed than coarse particles ($2.5 < d < 15\ \mu m$). Some epidemiologic reports also describe spatial variability of sulfates and ozone (Burnett et al., 1994) and PM_{10} (Ito et al., 1995) by plotting the temporal correlation of data from multiple sites, as a function of separating distance. This information could be more systematically and quantitatively incorporated into PM-mortality/morbidity analyses.

Measurement error may complicate the modeling of exposure-effect relationships based on epidemiologic data. For example, exposure-response relationships with a threshold may appear more nearly linear; or, conversely, linear relationships may appear to be nonlinear, depending on specific measurement error (Louis, 1991). Hasselblad et al. (1975) discuss the practical difficulties in distinguishing between continuous and threshold-type dose-response or concentration-effect functions. Also, Lipfert and Wyzga (1994) showed by data simulation and by numerical experiments with mortality and air quality data from Philadelphia that differences in the reliability of exposure estimates can be critical in estimating the implied relationships between correlated variables in multiple (joint) regressions. The variable

having the least exposure error tends to dominate in such situations, even for the same underlying relationships. In further simulation studies, Lipfert (1994b) showed that exposure error also tends to obscure the true shape of the dose-response function.

12.2.2 Misclassification of Health Outcomes

Misclassification of the health outcome can occur whether the outcome is continuous, such as a measure of pulmonary function, or dichotomous, such as the presence or absence of respiratory symptoms. Lung function is typically measured with spirometry, a well-standardized (Ferris, 1978) technique; measurement errors of the instruments collecting the data have been carefully estimated, and random errors add to the error variance. On the other hand, respiratory symptoms and disease are usually measured by questionnaire. Responses to symptom questions are typically positively correlated and depend on the interpretation of the respondent. A specific respiratory disease is likely to be reflected by reporting of a constellation of symptoms; and, so, aggregate as well as single specific symptom reports need to be considered. Obviously, questionnaire measurements that depend on recent recall are better than those based on recall of events that occurred several years ago. Questionnaires for cough and phlegm production, such as the British Medical Research Council (BMRC) questionnaire (American Thoracic Society, 1969) and revisions of the BMRC questionnaire (Ferris, 1978; Samet, 1978), have been standardized and validated for English-speaking populations. These questionnaires and modified versions have also been used to evaluate respiratory symptoms in non-English speaking populations, with varying degrees of standardization or validation for specific populations studied. Misclassification of primary cause of death on death certificates may also occur.

12.2.3 Model Specification for Short-Term Exposures

No single 'standard' statistical technique has been developed to examine short-term associations of PM with mortality or morbidity, and a variety of approaches have been employed by different researchers. This is partly due to lack of knowledge as to biological mechanism(s) involved in the hypothesized link between population PM exposure and response in the population (e.g., excess premature deaths). There are, however, a several common issues that must be addressed in analyses of PM mortality/morbidity associations:

- Treatment of long-term patterns and trends
- Duration-dependence of exposure/response
- Functional form of exposure/response
- Data Distribution
- Lag structure

No given statistical technique fully addresses all of these issues, and computational complexity and limitations in the available data (e.g., only every-6th-day sampling frequency) may not allow all investigators to employ all appropriate available statistical techniques. Nevertheless, these issues are important not only to statistical validity, but also to possible elucidation of biological mechanisms. This section considers such issues and some of the techniques currently being used to model PM-mortality associations.

Treatment of long-term patterns and trends

Time-series observations of daily mortality are generally not random, but include 'long-term' components (generally referring to peaks or cycles longer than two weeks or one month). These long-term components include: sinusoidal annual cycles that are often regular in their shapes (Rogot et al., 1976; Sakamoto-Momiyama, 1977); more irregular long-term components, such as influenza epidemics (Glezen et al., 1982; Choi and Thacker, 1981; Serfling, 1963), and; long-term trends that may be significant over many years.

Long-term components in mortality cause problems in the analyses of short-term association of PM-mortality in two ways: (1) they can create a spurious (confounding) mortality-PM association that can mask or bias short-term effects (Thurston and Kinney, 1995); and (2) they may induce significant autocorrelations in the residuals, which violate the assumption of independent error in two of the most commonly used statistical methods, the Ordinary Least Squares (OLS) and the Generalized Linear Models (GLMs), potentially biasing significance tests (Cochrane and Orcutt, 1949; Liang and Zeger, 1993).

To address these problems, long-term components can be estimated by several methods including: (1) weighted moving averages (e.g., Schimmel, 1978; Shumway et al., 1983; Schwartz and Marcus, 1990); (2) trigonometric fit (e.g., Hexter and Goldsmith, 1971; Schwartz, 1993); (3) Autoregressive Integrated Moving Average (ARIMA) fit (Box and Jenkins, 1977), and; (4) Seasonal and Trend decomposition using Loess or STL (Cleveland et al., 1990). Long-term components estimated by these methods may be included in the

mortality regression or subtracted from each series to obtain deviation series, which in turn may be used in subsequent regression analyses (see Appendix A). Distributional characteristics of the original series, however, may be altered in such deviation series.

Removal of long-term components by filtering or by inclusion of long-term components as covariates in the regression does not necessarily result in unautocorrelated regression residuals. If the residuals are still autocorrelated, the error term would need to be further modeled for such time dependent structures. Irregular systematic autocorrelations (e.g., day-of-week effects) can be modeled by indicator dummy variables. When other than normal distributions are assumed, an extension of the GLM procedure designed for correlated data may also be used. This option is discussed below. While not controlling for these long-term components can create bias and spurious associations, the majority of recent PM-mortality studies have addressed this issue in various ways. However, an unintended consequence of controlling for these long-term cycles (cycles $>$ 1 month) is elimination of information regarding possible delayed or prolonged effects.

Data Distribution

In theory, the underlying distribution of spontaneous death counts in a population in a short time interval should follow the Poisson distribution, in which the only possible values are whole numbers, the mean is proportional to the variance, and non-negative. A class of statistical models, Generalized Linear Models (GLM), includes log-linear models suitable for such count data (McCullagh and Nelder, 1989). The form of the relationship between the expected dependent variable and covariates is: $\log(E(Y_i))=X_ib$, where Y is death count on day i, and X_i is a matrix of covariates on day i (in contrast to the ordinary linear model: $E(Y_i)=X_ib$). The maximum-likelihood estimates of the parameters are obtained by iterative reweighted least squares with the adjusted dependent variable in the model. In the GLM log-linear model, systematic effects are modeled as multiplicative, rather than additive, as in the case of the classical linear model. This ensures that the counts are non-negative. In recent U.S. studies of data from relatively small areas, these characteristics were apparent (e.g., in Steubenville: mean=3.1, variance=3.1), and these Poisson regressions were employed. Some studies (e.g., Schwartz, 1992) also included a parameter to allow for the greater-than-predicted (by Poisson) variance of mortality ("over-dispersion"), which may result from

model misspecifications (e.g., omitting some long-term components). In large cities, the data distribution approximates normality, and use of OLS or Poisson model does make much difference in the estimated coefficients (e.g., see Schwartz, 1993; Kinney et al., 1995).

While the GLM log-linear model can accommodate the Poisson distributed data found in mortality series of small populations, GLM models share the same independent observations assumption as the classical linear regression models. Thus, without modification, they can not be adequately applied to correlated data, including serially correlated time series data. Statistical problems with ignoring correlations in the data include the inflation/deflation of variance of the estimated parameter and loss of efficiency, in the sense that the uncertainty in the estimated parameter is greater than the uncertainty in the best unbiased estimate (Liang and Zeger, 1993). Liang and Zeger extended GLM to the analysis of longitudinal data (1986, 1986, 1988) by introducing a class of estimation equations (i.e., Generalized Estimating Equations [GEEs]) that give consistent estimates of regression parameters when there is dependence within observations. While the GEE has been used in some recent PM-mortality studies (e.g., Schwartz , 1992; Pope et al., 1992), issues exist regarding differences in specifications of covariance structures and sensitivity to its application.

Duration Dependence of Exposure/Response

From the viewpoint of biological plausibility, the duration of exposure is likely to influence the biological response. For example, a 24-h exposure to 200 $\mu g/m^3$ of PM_{10} would likely produce a different biological stress than a 96-h consecutive exposure to the same level of PM. If this is the case, the PM-mortality regression coefficient or slope may be dependent upon the duration of exposure. This potential phenomenon may be examined via frequency (reciprocal of duration) domain time series analyses (see, for example, Bloomfield (1976) or Shumway (1988)). In frequency domain analysis, the frequency dependence of the 'slope' can be assessed using gain spectra; the strength of association, or correlations for each periodicity can be assessed using coherence spectra. Any inconsistency between the 'long-term' and the 'short-term' PM-mortality associations may be evaluated in these spectra, and may suggest filtering of certain frequency regions. Most recent time-series studies of PM-mortality associations have not explored these issues. One exception is an analysis of the

historical London data by Shumway et al. (1983), who reported that the strongest pollution-mortality associations occur at cycles ranging between seven and 21 days (after filtering mortality with a high-pass linear filter), implying that a pollution and temperature episode must persist for effects to be seen. While such frequency domain analyses may give comprehensive frequency break-downs of exposure-response relationships, they may still miss certain complexities of exposure-response relationships, such as seasonal dependence, even for a given segment of periodicity. Also, application of frequency domain techniques is limited to data collected daily for a long period.

Lag structure

In evaluating epidemiological findings for consistency with causality, one of the criteria suggested by Hill (1965) is a temporal relationship of the association: the exposure must precede the biological response. Given sufficient number of observations, such temporal relationship of exposure/response can be statistically examined through the cross-correlation function (CCF) or the pair-wise correlation with lags. Any autocorrelations in the exposure and/or response series may have to be removed prior to the CCF examination to obtain 'rational' CCF (Haugh and Box, 1977). A significant association found on the 'right' side lag (exposure leading response) is less convincing if a similar extent of association is found on the 'wrong' side lag (response leading exposure).

When PM has more than one significant lag (on the 'right' side), a *distributed lag model* is suggested. The shape of distributed lag coefficients may also reflect duration dependency of exposure/response relationship. In recent U.S. PM-mortality studies (see Table 12-1), the length of the lagged PM variables used in the regression analyses range from single day (current or previous day) to up to 4 previous days. The extent of description regarding the lag length is not always comparable in these studies (some report CCF's, others report the most significant lag and averaging length), and the choice of covariates' lags likely influence significance of PM lags. Also, it should be noted that there is a difference between the inclusion of multiple lagged PM variables and the inclusion of a multi-day averaged PM variable (a form of constrained distributed lag model). Averaging over multiple days may enhance relevant PM signals if a multi-day exposure is more effective in causing health effects than a single day elevated PM level. On the other hand, if

alternating high and low PM levels are more effective in producing health effects, then the averaging would attenuate such signals. The existing literature seems to suggest the former.

What has been rarely described in detail is the lag structure among the covariates, especially those between weather variables and pollutants. Elucidation of the lag structure among covariates should explain the sequence of events occurring in the atmosphere (e.g., the passage of a weather front, a change in temperature, and a build-up of air pollution), and may help understand the nature of 'confounding' among the weather and pollution covariates. The diversity of PM and weather lag structures used in the published studies complicates the intercomparison of results and the identification of an appropriate PM exposure metric for use in setting standards (e.g., is a 24-h standard adequate?).

Functional form of exposure/response and threshold

Examination of possible functional forms of PM-mortality/morbidity associations is complicated by several issues: (1) exposure duration dependence; (2) 'harvesting'; (3) sensitive sub-population; and (4) interaction with other covariates.

If the response is dependent on the duration, as well as the level, of PM exposure, then separate exposure level/response curves for a range of duration may be needed. The slope observed in a scatter plot of mortality vs. PM levels does not take into account differences in exposure duration. Log-normally distributed PM levels suggest, in a time-series context, that very high PM values do not persist except for a few unusual persisting pollution episodes. Therefore, the shallower slope at high levels sometimes observed in the literature may simply reflect the relatively ineffective impact of very short-term high level PM exposures.

'Harvesting' or more properly, 'mortality displacement', refers to a decrease in daily mortality that follows the day(s) of elevated pollution levels. This phenomenon is postulated because the people who die from the stress of air pollution are assumed to be those who already suffer from pre-existing cardio-respiratory conditions and the degree of prematurity of deaths may only be a few days. While there are some suggestions of this (e.g., Spix et al., 1994), it was not apparent in past major episodes such as the 1952 London fog incident. Also, statistical examination of this phenomenon is complicated by the necessary process of time-series modeling (e.g., detrending and filtering).

TABLE 12-1. SAMPLE SIZE, SIGNIFICANCE, AND OTHER CHARACTERISTICS OF RECENT STUDIES ON DAILY PM/MORTALITY IN U.S. CITIES

Area	Period	Sample Size	t-ratio	Population	Daily Number Deaths	PM measure and mean[a]	Lag and Average	Reference
Birmingham, AL	1985-1988	1,087	2.52	884,000	17	PM10; 48	same + 2 prev-day	Schwartz (1993)
Cincinnati, OH	1977-1982	2,191	3.47	873,224	21	TSP; 76	same-day	Schwartz (1994)
Cook Co., IL	1985-1990	1,357	3.43	5,300,000	117	PM10; 38	same-day	Ito et al. (1995)
Detroit, MI	1973-1982	3,652	3.76	1,200,000	53	TSP; 87	prev. day	Schwartz (1991)
Kingston, TN	1985-1986	330	1.07	640,887	16	PM10; 30	prev. day	Dockery et al. (1992)
Los Angeles, CA	1985-1990	364	1.96	8,300,000	153	PM10; 58	same-day	Kinney et al. (1995)
Santa Clara, CA	1980-1986	549	2.86	1,400,000	18	COH; 67[b]	same-day	Fairley (1990)
St. Louis, MO	1985-1986	311	2.17	2,356,460	56	PM10; 28	prev. day	Dockery et al. (1992)
Steubenville, OH	1974-1984	4,016	4.66	163,099	3	TSP; 111	prev. day	Schwartz and Dockery (1992b)
Philadelphia, PA	1973-1980	2,726	5.04	1,688,710	48	TSP; 77	same+prev-day	Schwartz and Dockery (1992a)
Utah Valley, UT	1985-1989	1,706	4.78	260,000	3	PM10; 47	same+4prev-day	Pope et al. (1992)

[a] $\mu g/m^3$, unless otherwise noted
[b] 12XCOH, unitless

Note: When multiple models were presented, the model with single pollutant (PM) and weather, season variables for the entire year was chosen.

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The shape of the exposure/response relationship must be different for various segments of the dying population. In fact, a certain fraction of non-accidental deaths is likely to be from those not even subject to day-to-day changes in PM levels. The extent of prematurity of deaths may be a few days for some, but could be many months for others. Characterization of sensitive sub-populations is important in establishing meaningful exposure/response curves.

Exposure/response curves may also be different depending upon the levels of other factors (e.g., temperature, ozone). An addition of interactive terms in regression models is not usually practiced in time-series studies, probably because of already highly collinear variables. Some recent studies have examined interactions between weather variables and air pollution variables, as noted in Section 12.2.5. Possible interactive effects may be examined through more exploratory techniques, such as the Classification and Regression Trees, or CART (Breiman et al., 1984). An exposure/response 'surface' of mortality on PM and other factors may be estimated using these techniques.

In exploring the shape of possible exposure/response curves, rather than forcing a certain functional form for the entire range of the data, smoothing, such as locally-weighted regressions, or LOWESS (Cleveland, 1979), may be useful. Smoothing may be extended to multivariate models using the Generalized Additive Model, or GAM (Hastie and Tibshirani, 1990), in which parametric and semi-parametric terms can also be included simultaneously. These techniques have been used in some of the PM-mortality studies (e.g., Schwartz, 1992 and 1994). Some caution is required, however, in determining the functional form and any 'threshold' from these curves. PM data (TSP and PM_{10}) for example, are often positively skewed in their distributions and do not have very 'low' values (e.g., <20 $\mu g/m^3$ PM_{10}). Also, the stability of the results depends on the neighborhood and the interval of PM scale, or "span", used to compute each segment of the curve. Thus, it would be useful to report the data density associated with these curves and information regarding the weights and the span used in the construction of exposure/response curves.

Thresholds

The existence of thresholds can be argued both biologically and statistically. The biological arguments have been given by several authors, including Stokinger (1972),

Dinman (1972), and Waldron (1974). Methods for estimating threshold models have been given by several authors including Quandt (1958), Hudson (1966), Hasselblad et al. (1976), Crump (1984a,b), Crump and Howe (1985), Cox (1987), and Ulm (1991). However, the concept of a threshold may be confused with the concept of a non-zero background. A threshold model starts out completely flat, possibly above zero, and at some point begins to curve upwards (see Figure 12-1). A non-zero background model begins above zero and continually curves upward. However when fitting data, "... an additive background dose is generally not distinguishable from a threshold" (Cox, 1987). Cox (1987) gives 10 real data sets where thresholds have been estimated, and in every one of them it is possible to fit a non-threshold model which fits nearly as well. Thus, for epidemiologic studies, the question of thresholds may be difficult to resolve because of difficulties in estimation. When there is substantial measurement error in the exposure variable or heterogeneity in threshold values in a population, it may not be possible to identify a threshold using aggregate response data such as mortality counts or hospital admissions.

However, many epidemiological studies reviewed in this section were structured to develop linear or log-linear models with no such threshold, and in many cases, this assumption has been supported by the data plots presented. However, it has also been shown that it may be difficult to distinguish among alternative regression models with confidence, presumably because the main outlying observations are controlled by factors not included in the model. In such cases, linear and threshold models may have essentially equivalent predictive power, and the most useful regression model will be one that admits the possibility of a threshold and develops confidence limits for its value.

12.2.4 Model Specification for Long-Term Exposures

Cross-sectional studies are intended to reveal associations between air pollution and health by virtue of similarities in spatial patterns, averaged over some suitably long term. In order to be able to interpret any resulting statistical associations as potentially causal, all other spatial factors that covary with air pollution or mortality rates must be accounted for or "controlled." Rumford (1961) noted the necessity of considering the "total socioeconomic complex" if valid estimates of the pollution effects are to be obtained. There may also be

spatially varying temporal factors, such as flu epidemics, heat waves, etc., that might influence health differentially in certain locations.

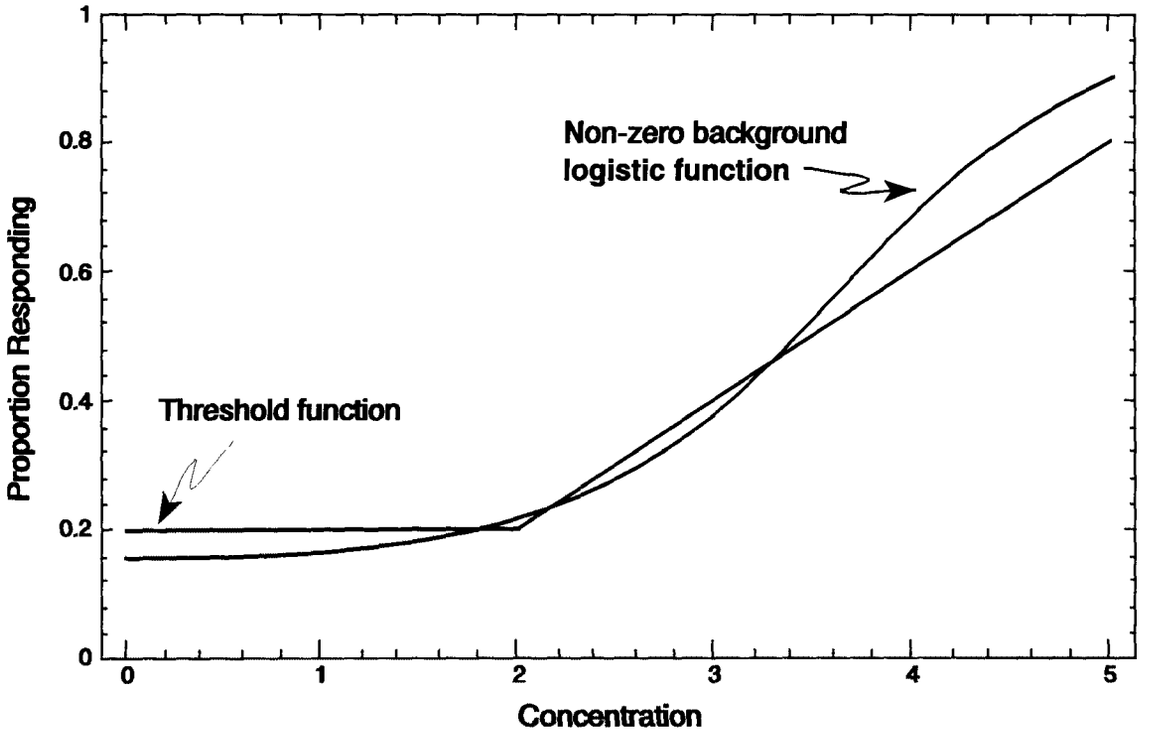

Figure 12-1. Examples of threshold function and non-zero background logistic function.

Chronic epidemiological studies of the health effects of community air pollution are typically beset by two fundamental difficulties:

(1). The health endpoints of interest are also affected by factors other than air pollution. Samet and Speizer (1993) noted that, "Few adverse effects of environmental pollutants are specific, that is, uniquely associated with a single agent." At current ambient conditions, in many instances, including mortality or hospital utilization, air pollution plays a relatively minor role in the overall etiology.

(2). As a result, it is necessary to study large populations in order to attain statistical significance. This makes it difficult if not impossible to determine individual exposures. Given that most people spend the majority of their time indoors and that routine air sampling is conducted outdoors, often at considerable distances away, the exposure measure used in air pollution epidemiology is usually subject to potential bias and to considerable uncertainty.

Uncertainties in exposure may be characterized on several different levels, listed in approximate decreasing order of importance:

(1). the difficulty in partitioning observed health effects among collinear pollutants;

(2). effects of subjects' microenvironment, including outdoor air, workplace exposures, indoor air in residences and other buildings, and air quality inside vehicles;

(3). selection of the appropriate exposure metric, with options ranging from hourly or less to averages over multi-day episodes;

(4). within-city variations in outdoor air quality, with spatial variability depending strongly (inversely) on averaging times and proximity to pollution sources; and

(5). instrumental and analytical errors, with the importance of such errors depending on the study design (cross-sectional versus time-series) and whether they are random or involve biases (e.g., filter artifacts as a source of bias in gravimetric determination of suspended particle mass).

In general, the difference between measured outdoor concentrations and actual exposures may be expected to vary from day-to-day and by pollutant species and particle size. Some pollutants are distributed more uniformly throughout a community than others, and some penetrate into indoor environments more readily than others. Thus the true exposure collinearity among the components of urban air quality may be quite different from the collinearity indicated by outdoor monitoring data.

It is common when analyzing a data set to discover that one or more key covariates for the analysis were not measured. Schenker et al. (1983a) discuss socioeconomic status (SES), passive smoking, and gender as important covariates in childhood respiratory disease studies. Other covariates include age; temperature; and other pollutants, such as ozone or SO_2. The concern is that, had an omitted covariate been measured, then the estimate of the regression coefficient for a dependent variable of interest would have been significantly different. Although the problem is faced by many investigators, the literature on the field is relatively sparse. For example, Kupper (1984) shows that high correlations between the variables just described will result in "unreliable parameter estimates with large variances." Gail (1985) considered the special case of omitting a balanced covariate from the analysis of a cohort study and concluded that "In principle, the bias may be either toward or away from zero, though in typical examples—the bias is toward zero. In applications with additive or

multiplicative regression, there is no bias." Neither paper provided information on how to attempt to correct for the bias or to investigate the possible bias in a given situation.

Most studies of respiratory disease and PM exposures discussed here measured important covariates such as age, socioeconomic level of the parents, gender, and parental smoking habits. The estimated effect (regression coefficient of disease on PM exposure) will be overestimated if a missing covariate is positively (or negatively) correlated with both exposure and outcome. The estimated effect will be underestimated if positively correlated with either exposure or outcome but negatively correlated with the other. For example, Ware et al. (1984), found that parents with some college education were more likely to report respiratory symptoms but less likely to use a gas stove, leading to an underestimate of the health effect of exposure to gas stove emissions if education were left out of the analysis.

The Ecological Fallacy

Epidemiological studies of air pollution health effects are necessarily observational, that is, involving naturally occurring rather than manipulated environmental conditions (Kleinbaum et al., 1982). Since the characterization of individual environmental exposures is clearly impractical in the large populations that are required, such a study is likely to be "ecological" as well as observational, i.e., involving the study of group attributes rather than those of individuals (Piantidosi et al., 1988). According to Kleinbaum et al. (1982), the primary feature of an ecological study is the lack of knowledge of the joint distribution of the study factor (i.e., exposure to air pollution) and the disease within each group. The primary weakness in ecological regression relates to the lack of specificity of the affected individuals and the exposed individuals, because groups are used in the regression analysis. This problem is most critical when the pollutant is very localized (such as emissions from a toxic waste dump) or when the disease is relatively rare (such as leukemia). In such cases, an ecological analysis may identify the incorrect agent.

However, the problem diminishes for broadly distributed regional pollutants, such as fine particles or sulfates, and for mortality from all causes or from very common causes (such as heart disease). In such instances, it is reasonable to assume that all the cases were exposed at least to some degree, although the particulars of their exposures will vary

because of indoor-outdoor pollutant relationships and other local factors. In these cases, the DRFs may be incorrect in shape or magnitude.

Greenland and Morganstern (1989) present examples in which ecological analyses clearly derive incorrect results. The concept of "effect modification" is one example in which the effect (i.e., slope of the dose-response function) depends on the proportion of exposed subjects in each of the regions used for ecological regression. (In the time-series analog, the slope may vary from day to day.) In this case, the esophageal cancer rate for non-smokers was constant across all regions, but rates for smokers increased as the proportion of smokers in the region decreased. Such a situation might occur due to selective survival: a low proportion of smokers could result from smokers' higher rates of cancer and heart disease and subsequent demise from these conditions. In this example, the numbers of smokers' cancer deaths was constant across regions even though the absolute numbers of smokers varied by a factor of 1.67. It is hard to conceive a physiological rationale for such a situation, since mortality rates are much too low to deplete the population, even for smokers. Greenland and Morgenstern's other two examples also had special situations involving two competing cancer risks, smoking being the "confounding" variable. In both examples, the regional rates for the two risk factors were strongly negatively correlated ($r = -1$ and -0.7). One of the most important checks to be made in a multifactor ecological analysis is for the existence of such confounding situations. If the desired risk factor is strongly correlated (+ or -) with other variables, disentanglement will be difficult if not impossible in all cases, ecological or not. These examples also involve use of a linear regression model in situations where the effects are established as multiplicative. The confounding factor (smoking) increased the risk by factors of five and ten, respectively. In such extreme situations, it is not surprising to find anomalous results. In Greenland and Morgenstern's examples, the difficulties arise from assumed properties of the regions, not from differences between group and individual behavior. One might thus argue that the chances of such situations seriously affecting an analysis diminish as the size of the groups decreases and their numbers and diversity increase (Robinson, 1950). However, Piantidosi et al. (1988) compared regression coefficients for a group of physiological and dietary variables, contrasting the "true" values obtained from individuals with those obtained from

various aggregations. In four out of the thirteen cases, the true values lay outside the confidence limits for the aggregated values, with errors in both directions.

For cross-sectional analyses, spatial variation constitutes the within-group variance at issue with respect to the ecological fallacy. Here, the ecological hypothesis is that each of the cities or locations studied has the same within-city spatial distribution of air quality (assuming that adequate monitoring networks are not always available) and the same within-city distributions of potential confounding variables such as age, race, poverty neighborhoods, etc. This is not likely to be true in general, but it can be seen that these considerations favor the use of the smallest practical units for geographic analysis. As larger geographic units are used for analysis, for example, Standard Metropolitan Statistical Areas (SMSAs) or larger, the representativeness of air monitoring is likely to diminish. In some of the studies reviewed below, only one monitoring station was available in a given metropolitan area.

"Overcontrol." This term refers to indiscriminate use of large numbers of nonpollutant variables in a cross-sectional regression. In U.S. Environmental Protection Agency (1986), the example cited (Selvin et al., 1984) involved use of 17 socioeconomic and four weather variables in a cross-sectional analysis of 3082 counties and 410 county groups. Some of the variables in this study that might be considered questionable included divorce rate, elevation, and land area, among others. In this case, there were adequate degrees of freedom to accommodate these many independent variables; but the question then becomes does inclusion of a particular variable act to obscure a "true" pollution relationship? Although some answers to this question may well be idiosyncratic, the questionable variable must be correlated with mortality and with air pollution for such obscuration to occur. However, in the typical interrelated data sets found in national cross-sectional studies, the relationship with the dependent variable must be evaluated dynamically, after control for other important variables like age, race, and income.

A good rule of thumb to preclude the "overcontrol" criticism may be to only consider those independent variables for which a relationship with the health endpoint can be shown exogenously, preferably with individual level data. Since it is generally not possible to make such a showing for air pollution variables at current ambient levels, the burden of proof will

rest on showing that the pollutant still has an effect even when all known non-pollution factors are included in a joint regression. In general, this may require the detailed evaluation of a range of models, rather than the selection of an a priori "best" model. Certainly, given the likelihood of some confounding in any event, maximizing the effects of the pollution variables should not be the rationale for selecting a particular regression model.

12.2.5 Covariates and Confounders

Confounding

Stellman (1987) stated that confounding is the "cause of great angst among epidemiologists." The term refers to the incorrect assignment of an effect to a given agent when in fact a third variable (the confounder) is responsible. Such a situation requires that the confounder have an effect on the outcome variable and be correlated with the first agent. In other words, a confounder must have the property of different distributions for exposed and nonexposed subjects (Miettinen and Cook, 1981). Smoking may be a good example, since it increases exposure to fine particles and adversely affects health. Heat waves may be another, since urban air pollution often increases with temperature as do mortality and hospitalization rates. In ecological case-control studies of environmental factors, in which an exposed city is compared to an unexposed city, confounding is likely because there are many other ways in which two population groups may differ. As numbers of locations or time periods increase and regression methods become appropriate, opportunities for serious confounding are diminished. It is possible to devise examples which feature serious confounding (i.e., Greenland and Morganstern, 1989); but according to Stellman (1987, p. 165); "Rarely, however, does confounding itself, especially from unidentified sources, live up to its reputation by introducing seriously spurious associations."

Confounders and choice of covariates

To pose a problem in epidemiologic analyses, confounders must: (1) be a risk factor for the outcome; (2) be associated with the exposure variable; and (3) not be an intermediate step in the causal path between the exposure and the outcome (Rothman, 1986). The risk factor need not be causal in this case. Thus, many weather variables, as well as co-pollutants, qualify as potential confounders for PM-mortality or morbidity associations.

The causality of various weather and pollution variables may or may not be clear, however. For example, an extreme (hot or cold) temperature is known to cause excess mortality, and laboratory human and animal studies support biologically plausible mechanisms for such observations. Thus, simultaneous inclusion of temperature and pollution variables in a time-series regression seems reasonable, although there also is a chance that this may result in under-estimation of pollution coefficients because temperature is also correlated with meteorological conditions that cause air pollution build-up. Wind speed is clearly a good predictor of air pollution build-up, but is not directly causally related to health outcomes. Therefore, inclusion of wind speed in mortality/morbidity regression is not recommended for air pollution epidemiology. Barometric pressure is an example of a variable whose effect (within the range of day-to-day variation) on physiological functions is less clear (Tromp, 1980). It is associated with certain physiological changes such as blood pressure, but this may be due to its association with temperature change, which is also related to change in blood pressure. Barometric pressure is also correlated with air pollution levels. Thus, while there is a need to address potential confounders, care must be taken that the regression model selected is not over-specified.

Common air pollution variables, such as SO_2, O_3, NO_2, and CO are all known to cause health effects, independent of PM, at some level. On a day-to-day basis, the concentrations of these air pollutants, as well as PM, are all correlated to varying degrees, due to the meteorological conditions that control dispersion of these pollutants. Care must therefore be taken when including these correlated pollution variables in a health effect regression, as their coefficients may be unstable. Furthermore, the significance of coefficients for each variable may be influenced by their measurement errors, rather than their causal strengths. Thus, without external information regarding differential error and some description of collinearity among the covariates, interpretation of these multiple regressions with collinear variables can be misleading. Under circumstances where various collinear variables are present, and each one of the pollutants is suspected of causality to differing degrees, a single pollutant model may result in over-estimation of the coefficient for that pollutant, while a multiple pollutant model may result in under-estimation of each pollutant's coefficient. Thus, ideally both results should be considered. Separation of possible effects from these various correlated pollutants may be difficult from a single study, but may be possible by

evaluating the consistency of coefficients across studies in which the levels and the extent of collinearity of co-pollutants vary. To facilitate such collective understanding (or even meta-analysis), it is crucial for each study to include systematic description of collinearity among the covariates (e.g., correlation of the estimated parameters), levels of each pollutant, and discussion of biological plausibility for each variable at the observed levels.

While the parsimony of a model is generally desirable, blind reliance on the automatic variable selection schemes based on the F-statistic, such as stepwise regressions, or the use of other criteria, based on residual error and number of parameters (Akaike, 1973; Schwarz, 1978) is not appropriate for epidemiologic purposes, as the objective is not to develop a parsimonious model, but to assess the impact of pollution while adequately 'controlling' for other covariates.

Season specific exposure/response

Removal or control of long-term seasonal cycles alone does not eliminate the possible differences in short-term PM exposure/response relationships across different seasons. This is likely because: (1) exposure patterns may be different among seasons due to the difference in human activity patterns (e.g., percent of time spent outdoors); (2) differences exist in indoor/outdoor air exchange patterns (e.g., open windows, air conditioning); (3) there can be a lack of PM signals in certain seasons and/or a lack of certain chemical components (e.g., sulfates exist more in the summer) in PM that may have health effects; and (4) the influence of other factors, such as temperature and co-pollutants, likely varies over time. Not only the strength of associations, but also the lag structure of PM-mortality associations, may therefore vary across seasons.

The seasonal specificity in PM-mortality associations may be explored by examining cross-correlation functions for each season, provided sufficient sample size is available. If such non-uniformity of PM-mortality relationships exists across the seasons, the year-round relationship may underestimate or mask within-season associations. Thus, it may be naive to apply one model specification without considering possible changes in lags. Season specific analyses may be more appropriate in certain cases. However, when the total data base is not large, the small sample size in such season specific analysis may compromise statistical power to detect 'small' PM-mortality/morbidity associations.

Weather and Climate: Factors in Studies Relating PM to Mortality

The confounding impact of weather on acute mortality can be significant, and determination of the differential and/or synergistic impacts of weather and PM on death rates is necessary in any PM-mortality analysis. There is much variation among studies as to how weather should be considered or controlled. Also, weather and PM concentrations are themselves related, and this collinearity problem can render any effort to adjust for weather rather difficult. The role of weather, e.g., day-to-day meteorology (especially extreme events) is very important when analyzing PM effects on acute mortality.

Some authors have conducted weather/pollution/mortality evaluations in Steubenville, OH; Philadelphia, PA; London, England; Birmingham, AL; and Utah County, UT as well as other locales (Table 12-2). In all of these studies reported significant associations are reported between human mortality and PM; and, in some cases, the relationship extends to levels well below the current PM NAAQS. Several also allude to significant weather-mortality relationships. For Steubenville, a positive non-linear relationship among temperature, dew point, and mortality was detected. When dummy variables were used to denote hot days, humid days, and hot/humid days, the hot/humid days were a significant regression models however, neither temperature nor dew point proved to be significant mortality predictor. When seasonal variations were controlled for in their Poissonpredictors of mortality (Schwartz and Dockery, 1992b). In a study of British Smoke in London, Schwartz and Marcus (1990) controlled for temperature and humidity and improved the goodness of fit of the model significantly compared to the model with no meteorological variables. The reduction of otherwise unexplained variability in the daily mortality series had little effect on the regression coefficient for British Smoke, but increased its statistical significance.

More recent analyses (Kalkstein et al., in press) suggest that controls for weather may have not been fully adequate in the studies cited above. Many PM-mortality studies used temperatures, categories by temperature percentiles, squared temperature and dewpoint values, moving averages of temperature, and mean temperatures for groupings of days (see Table 12-2), which may not provide adequate bases to detect true weather-mortality relationships. It is also probably not feasible to assume that cities within a wide range of climates demonstrate similar responses of daily mortality to daily changes in

TABLE 12-2. ADJUSTMENTS FOR METEOROLOGICAL FACTORS IN SOME RECENT STUDIES RELATING MORTALITY TO PARTICULATE MATTER

Location Studied and Authors	Pollution Data and Treatment	Mortality Data and Treatment	Weather Data and Treatment	Pollution/ Weather Impact
London Schwartz and Marcus (1990)	British Smoke measurements from 7 stations; logarithmic and square root transformations;	Daily total death counts, including respiratory and cardiovascular causes; sensitivity to filtering	Temperature and RH; grouped plots of temperature and humidity versus mortality; autoregressive model.	British Smoke is significant predictor of mortality; temp/humidity control increased significance, as did autocorrelation adjustment
Philadelphia Schwartz and Dockery (1992a)	TSP samples collected routinely at two monitors; supplemented by sampling every sixth day at several sites; daily means and lags used	Daily total, elderly, <65, pulmonary disease, pneumonia, cardiovascular and cancer mortality; Poisson regression using GEE;	Mean 24 h temp and DP including squared transformation; indicator variables for season, hot, cold, humid, and hot humid days, and year.	Significant TSP association mortality, strongest among elderly and respiratory patients; hot days, mean DP, other weather factors also associated
Steubenville Schwartz and Dockery (1992b)	TSP from one monitor; ranked by levels and sorted into quartiles;	Daily total mortality; Poisson and weather model regressions;	Mean 24 h temp and DP; year as random effect; indicator variables for hot, humid, and hot humid days;	Nonlinear association between TSP and daily mortality; hot humid days associated with daily total mortality;
Utah Pope, Schwartz and Ransom (1992)	PM_{10} level from one site; up to 7-day lagged moving averages; divided into quintiles used as dummy variables;	Daily total, non-accidental respiratory, cardiovascular, and all other causes of non-accidental mortality; Poisson regression;	Temp and RH; dummy variables used for 10 °F ranges, previous day's temp, 5-day temp moving average, and humidity; linear time trend, random year effect;	Relative risk of death increased monotonically with the mean PM_{10} level for each quintile; also observed when weather controlled;
Erfurt, East Germany Spix et al. (1993)	Suspended particulates; 0-3 day lags; logarithmic transformation;	Daily total mortality; Poisson regression; autocorrelation adjustment for "harvesting"	Daily mean temp, RH, precipitation; indicator variables used for very cold days and hot days for different thresholds, various lags;	Effects of air pollution smaller than influenza and weather effect; significant SO_2
Birmingham Schwartz (1993)	PM_{10} level averaged from all (1-2) city monitors; divided into quartiles used as dummy variables;	Daily total mortality; Poisson regression using GEE; dummy variables for year and day of week; biannual cycle filters;	Mean 24 h temp and DP; dummy variables same as Utah study, plus cold days; 3-day moving lags;	Significant association between PM_{10} and daily mortality; extremely hot weather also associated with excess mortality; relation to temperature.
Steubenville Moolgavkar et al. (1995)	TSP from one monitor and SO_2 (two series)	Daily total non-accidental mortality; Poisson regression; with and without GEE; full year and season; serial correlation unimportant.	Mean 24 h temp and DP; indicator variable for hot and humid days; temperature quintiles;	TSP influence on mortality greatly reduced when SO_2 included in analysis; choice of SO_2 series and season had large impact on mortality results.
Philadelphia Wyzga and Lipfert (1994)	24 h averages of O_3 and TSP from several city monitors; lags of 0 to 4 days tested	Daily non-accidental deaths (non-elderly and elderly); linear filtering; variable for time over entire period in stepwise regression and forced OLS.	Daily maximum temp.; daily change in barometric pressure; dummy variables for winter and seasonality	Strong relationship between temp. and mortality; seasonal adjustments very important; TSP-temp. interaction; most mortality with TSP on hot days.

weather or in air pollution, and there are possibly some regional similarities in response which have not been adequately explored. In a reanalysis of Philadelphia PM-mortality

relationships, Schwartz (1994) took a more flexible approach to examine the possibility of confounding weather impacts. The reanalysis utilized Hastie and Tibshirani's (1990) "Generalized Additive Model" to detect and control for nonlinearities in the dependence of daily mortality on weather; nevertheless, and yielded findings similar to the original Philadelphia study. On the other hand, Moolgavkar (1995) asserts that the role of weather was improperly evaluated within the Steubenville study, and suggests that weather-related variables be evaluated more comprehensively in future PM-mortality analyses.

To further interpret possible weather impacts, Schwartz (1994) stated that the similar responses to air pollution in the mild weather of Philadelphia (mean daily temperature of 57 °F) and the cold weather of London suggest that weather does not seriously confound the PM-mortality relationship. Schwartz (1994) further noted that similarity in temperature and humidity on high and low air pollution days (when different mortality responses are seen), "... also would seem to eliminate weather as a potential confounder." However, it is possible that these studies do not remove the total confounding influence of weather, especially because of their dependence on mean temperatures and other meteorological surrogates which may not fully reflect weather variation associated with biological responses.

Other studies have attempted to assess the differential impact of PM and weather on acute mortality. For example, Ostro (1993) summarized studies which show strong associations between exposures to PM_{10} and total daily mortality for many urban areas in the U.S., Europe, and Canada and noted remarkably consistent results across regions.

Ito et al. (1993) showed that daily mortality in London was significantly associated with aerosol acidity levels and British Smoke. The amount of variation explained by weather was smaller than that explained by air pollution. Ito's work confirms results obtained by others on London's mortality/PM/weather relationship (Schwartz and Marcus, 1990; Thurston et al., 1989; Mazumdar et al., 1982). However, it should be noted that London's marine climate is rather benign when compared to many large American cities, as thermal extremes are unusual, so that the mortality variations attributable to variations in weather during London winters may be relatively smaller than in most U.S. cities studied.

Some studies for cities exhibiting higher climate variation yielded somewhat different results. Wyzga (1978) used COH as a surrogate measure of PM concentration, and determined that high COH values are associated with increased mortality in Philadelphia.

However, he recognized the potential impact of extreme weather as well, and noted that heat waves may also be responsible for large numbers of extra deaths. In a recent study in which weather was treated in a more sophisticated manner (Wyzga and Lipfert, 1995), the impact of O_3 concentrations and weather on acute mortality were evaluated and results were compared to TSP. The authors concluded that a determination of O_3 and TSP impacts is most difficult because of the influence of confounders, particularly weather. Also, use of different explanatory models yields disparate results, with pollution impacts ranging, "...from essentially no effect to response similar to that associated with a 10 °F increase in ambient temperature" (Wyzga and Lipfert, 1995). This evaluation appeared to find a synergistic relationship between weather and pollution, as days with maximum temperatures exceeding 85 °F contributed most to the TSP-mortality associations.

Several other studies have uncovered synergistic relationships. Ramlow and Kuller (1990) found that daily mortality was most closely associated with the daily average temperature of the previous day rather than any pollution measure in Allegheny County, PA where the mortality effect varied with temperature. In a study which attempts to determine synergistic relationships between weather and pollution on mortality in Los Angeles, Shumway et al. (1988) determined that mortality is, "...an additive nonlinear function of temperature and pollution, whereas there may be significant interactions present, especially when low or high temperatures are combined with high pollution levels." The authors found that model-predicted average mortality values increased at both temperature extremes when particulate levels were held constant. Two evaluations in the Netherlands found also temperature extremes in summer and winter to be significantly correlated with mortality variation. Kunst et al. (1993) and Mackenbach et al. (1993) determined that the relationship between temperature and mortality is linear, producing a U-shaped temperature curve, with minimum mortality rates observed between 10 to 15 °C. Kunst found that summer acute mortality was not influenced by air pollution variations.

Although weather seems to induce mortality increases when temperatures are either very warm or very cold, the impact of weather as a confounder or as a modifier of the effect of air pollution varies seasonally. For example, the impact of weather on acute mortality in winter is much more difficult to evaluate, and thermal relationships are decidedly weaker (WHO/WMO/UNEP, in press). Thus, although the temperature/mortality relationship might

follow the U-shaped curve discussed in Kunst et al. (1993), the variation of mortality around the cold portion of the curve is much larger, and the magnitude of mortality change for a given change at low temperatures is smaller. This implies that adjustment procedures for weather as a confounder should not be identical for summer and winter.

Another means of evaluating weather as a differential seasonal confounder within PM-mortality studies is to include variables to adjust for seasonal cycles. A recent Chicago and Los Angeles (Ito et al., in press) study, where seasonal cycles were determined using sine/cosine curves, found only 10 to 20% of the PM variance attributable to seasonal cycles in Los Angeles and an even lower percentage of explained variance in Chicago.

In general, either air pollution or weather (especially temperature) can appear as an additive main effect (possibly nonlinear) in a mortality time series model. Which is more important depends on both the range of variation in pollution and weather, and on the strength of their association with mortality in any study.

Many studies used mean meteorological data (e.g., mean daily temperature or relative humidity) or running means, which may underestimate the impact of meteorological extremes upon human mortality. Thus some mortality attributed to weather variation may have been appropriated to PM due to inadequate control for meteorology within the models used. Some studies have effectively evaluated maximum or minimum daily temperature, but virtually none have determined how weather situations (comprised of combinations of several variables) contribute to heightened mortality. This implicitly assumes that humans respond to specific individual meteorological variables such as temperature, rather than to the interaction of numerous meteorological variables which comprise a weather situation (e.g., combined temperature and relative humidity stress).

Application of Synoptic Weather Patterns for Adjusting Daily Mortality Series

The use of arbitrary temperature increments, various weather "dummy variables", and moving averages may have the effect of dampening the true meteorological confounding impact within PM-mortality studies (Kalkstein, 1991). These approaches ignore the fact that the meteorology of a locale is defined by discrete, identifiable weather situations, and humans, animals, and pollution concentration respond to these situations. One means of identifying the meteorological character of these situations (which vary through space) is to

graph the frequency of daily temperature-dewpoint temperature combinations for a particular location. Such a plot clearly demonstrates that certain temperature-dewpoint modes exist, containing a high proportion of days. These modes represent "air masses", which frequently invade a region. Many fewer days reside between the modes (these represent "transition situations" between air masses). Thus, days can be clustered within air mass categories, which represent meteorologically realistic combinations of weather elements occurring at a locale. A more comprehensive picture of weather can be determined if air mass designators are inputted within PM-mortality analyses, rather than arbitrary thermal divisions, which are not based on meteorological reality. Since the air masses tend to persist for several days for any city, they also provide a natural method for defining weather episodes and duration of exposure during these episodes. This "synoptic climatological approach" is gaining increasing favor among climatologists, health scientists, and ecologists, but has been distinctly under-utilized to date within available PM-mortality analyses.

The synoptic climatological classification method proposed by Kalkstein is easily implemented. The amount of subjective meteorological and bioclimatological judgement used in defining distinct weather regimes can vary, with some approaches nearly completely automated (Davis and Kalkstein, 1990; Eder et al., 1994). One approach requires use of 24 daily meteorological measurements: temperature, dewpoint, surface barometric pressure, East-West and North-South components of windspeed, and cloud cover observed at 6-h intervals. Principal component scores (linear combinations of variables measured at each time point) are then grouped using several cluster formation strategies. This generally results in 9 to 11 distinct weather regimes, some with only a few days being clearly transitional between two primary regimes. It is generally possible to assign meaningful meteorological characterizations to the major groupings.

A "synoptic climatological approach" was employed to model climate as a holistic unit composed of multiple meteorological elements in a study of the impact of summer weather and pollution on St. Louis mortality (Kalkstein, 1991). The methodology provides a more complete depiction of the weather than any one-variable surrogate (e.g., temperature), as it assumes that people respond to combined characteristics of the entire umbrella of air (or "air mass") that surrounds them (Kalkstein, 1993). Each day is designated by air mass type, and those air masses associated with heightened mortality are deemed "offensive". In the St.

Louis study, an offensive air mass was determined which possessed mean daily mortality values of 33% above baseline levels (Kalkstein, 1991). Those days within the offensive air mass with the highest mortality totals were the hottest and/or part of a multiple-day sequence. However, PM values within all offensive category days averaged close to the summer mean for St. Louis and were found to have little effect on mortality.

A more complete study using the synoptic methodology for four U.S. cities (Philadelphia, Birmingham, Cleveland, Seattle) supported the St. Louis findings (Kalkstein et al., in press; Kalkstein and Smoyer, 1993). In addition, an attempt was made to determine if PM contributed to heightened mortality in a differential manner during offensive and non-offensive air mass situations in Philadelphia. Days were divided into two groups of PM concentration quintiles: one for the offensive air mass and the second for all days within non-offensive air masses. Mean daily mortality was then calculated for each quintile (Figure 12-2). The results indicated that PM had little impact on mortality when the offensive air mass was present. In fact, mean mortality was lower in the highest PM concentration quintile than in the lowest PM quintile during offensive air mass days. It is noteworthy that the mean daily mortality for all PM quintiles within the offensive air mass was well above the baseline and, in some cases, approached or exceeded 10 additional deaths per day. Kalkstein suggested that the magnitude of the mortality totals on offensive air mass days was due almost exclusively to the associated stressful weather and that PM concentration played almost no role. However, for days not within the offensive air mass, a small systematic increase in mortality (which was not statistically significant) was noted as PM concentration increased. Nevertheless, mean daily mortality was below the baseline even within the highest PM concentration quintile when the weather was not offensive. Kalkstein concluded that PM has small impact on mortality in these cities during nonstressful weather, and when the weather is stressful, the "add-on" effect of high PM concentration is undetectable.

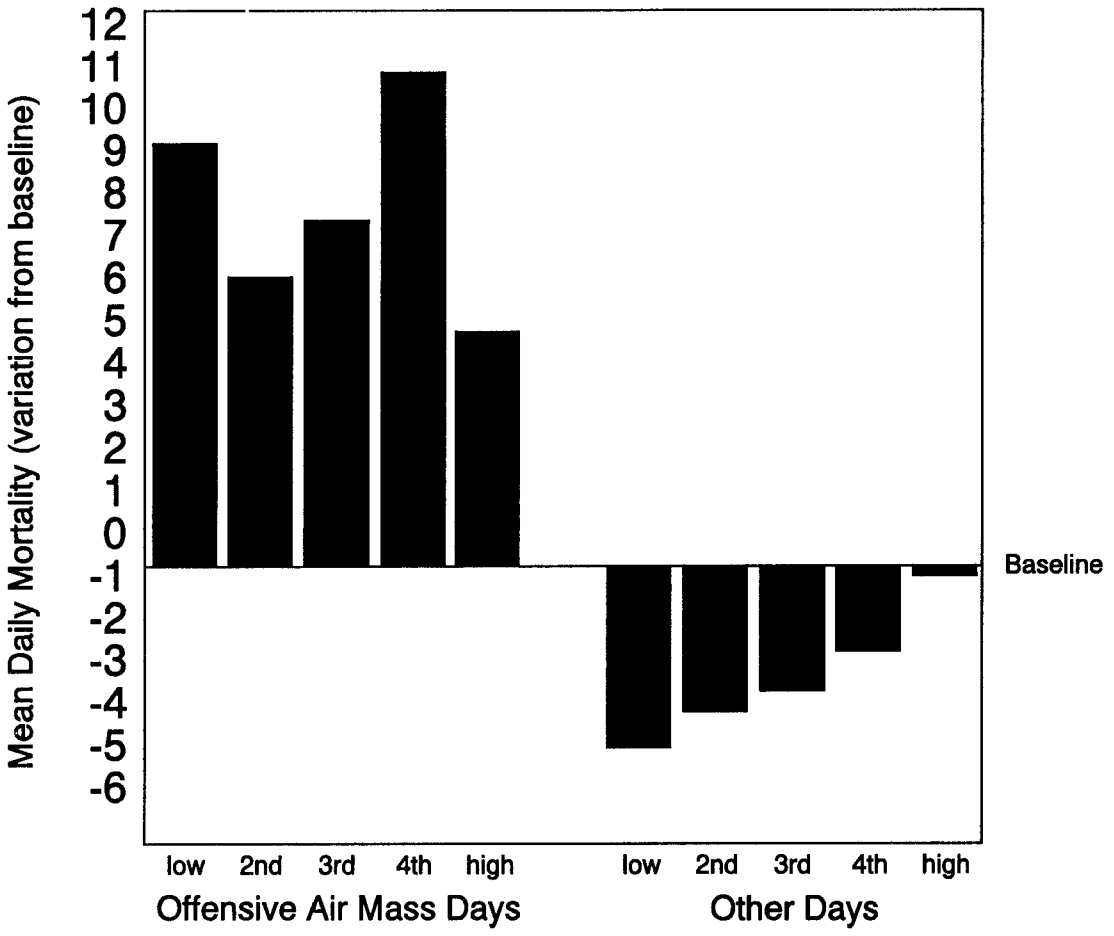

Figure 12-2. Mean daily mortality for PM quintiles, Philadelphia, PA.

Source: Kalkstein et al. (in press).

The above discussion illustrates current lack of agreement on (1) the differential impact of weather and PM on acute mortality, and (2) the proper means to control for weather in PM-mortality studies. However, the evidence to support a synergistic PM-weather impact is not strong, and some studies have found no apparent indications of synergism. Also, growing evidence suggests that the PM impact on mortality may only be detectable when the weather is benign. In most locales, meteorologically offensive days which contribute to heightened mortality occur about 15% of the time in a typical summer. However, according to one recent study, weather-related mortality in summer was estimated as more than double PM-induced mortality in Philadelphia, even though the number of meteorologically stressful days is comparatively small (Kalkstein et al., in press).

Thus, disparate results from several studies suggest that relative roles of meteorology and PM concentration in contributing to human mortality are not readily differentiated. However, there is growing evidence that weather is, at minimum, a significant confounder that must be considered in attempting to estimate PM/mortality relationships. See Appendix 12A for more discussion of specific weather impacts on mortality.

Confounding by Epidemics

Concern exists that the increased incidence of illness or mortality associated with changes in air pollution during the winter season may not indicate a causal relationship because of confounding influences of contagious illnesses epidemics. Infectious respiratory illness (e.g., the "flu") strongly influences mortality. An underlying or contributing cause for changes in air pollution or in contagious illness may be weather changes. Confounding due to epidemics may be adjusted statistically to some extent by use of filtering, but this is at best suitable for time series with a normally distributed response, and filtering of time series may perform better when there is some recurrent medium-to-long wave pattern to outbreaks of the disease in a given population. Without some recurrence pattern, filtering may only eliminate evidence of longer-term persistence of health effects related to air pollution. Close inspection of the time course of infectious respiratory illness outbreaks in populations reveals that outbreaks do not appear on a regular schedule from year to year (Henderson et al., 1979; Murphy et al., 1981; Chapman et al., 1981; Denny et al., 1983). In any given year, a number of important respiratory pathogens may not appear at all in a given population. Thus, fixed-cycle curve-smoothing techniques may not accurately describe the time course of respiratory illness outbreaks in populations. Several investigators have subsequently used long-term nonparametric methods such as lowess smoothers or generalized additive models (GAM) to adjust mortality series for aperiodic fluctuations that may include time-extended outbreaks of respiratory disease (Pope, 1994; Schwartz, 1994, 1995).

It is sometimes possible to evaluate the effect of epidemics on health outcome time series by comparison with adjacent communities. Pope (1991c) evaluated the possible effect on hospital admissions of contagious illnesses such as influenza (which is known to cause a substantial number of deaths in the elderly) and respiratory syncytial virus (RSV, which affects a substantial number of children and is often mistakenly diagnosed as influenza).

There was particular interest in the possibility that infectious diseases occurred more often during the winters when the Utah Valley steel mill was open, and less often during the winter when the steel mill was closed, purely by chance. Pope writes that "The few diagnoses where the agent of disease was specified limited opportunities to directly observe epidemics of any specific infectious agent. Bronchitis and asthma admissions for preschool-age children were more than twice as high in Utah Valley during periods when the mill was operating than when it was closed. The potential of highly localized epidemics of contagious respiratory disease that were correlated coincidentally with the operation of the steel mill cannot be completely ruled out. If the association were strictly spurious, however, the same correlation would probably be observed in neighboring communities unaffected by the mill's pollution. Such correlations were not observed."

The ability to directly observe diagnosed cases of influenza or RSV would allow a direct adjustment of health outcome time series for community-wide incidence of occurrence of the disease, which could in turn be exacerbated by co-occurring air pollution. Some progress in obtaining data on outbreaks of influenza-like illnesses (ILI) may be possible using recently established data bases, such as the CDC volunteer physician surveillance network. Evidence exists that these 140 family physicians make good sentinels for epidemics of ILI (Buffington et al., 1993). Data are provided to CDC on a weekly basis, which seems appropriate to the level of filtering that may be needed to adjust daily time series of health outcomes and air pollution for co-occurring respiratory diseases.

12.2.6 Selection Bias

The possibility of selection bias is a concern of every assessment. Selection bias would require selection of participants based on exposure and also health outcome. Because most epidemiologic studies of these exposures are population based, there is little possibility of selection bias affecting health end-points. Nevertheless, the possible loss of subjects by non-participation and attrition differentially associated with both exposure and health studies must be considered.

12.2.7 Publication Bias

Publication bias, and the related "file drawer problem", refers to increased likelihood of publication of studies that have positive results, leading to a bias in the literature reviewed towards positive results (Rosenthal, 1979). The "file drawer problem" is used to describe negative studies not submitted or published. However, large scale epidemiological studies are published regardless of their results. In fact, the study design and methods usually appear as papers prior to publication of results. Analyses of preexisting data sets such as mortality and hospital admissions present a different problem. Here the results can be calculated using fewer resources, and the likelihood of unpublished negative results increases. There is no adequate way to ascertain or correct for this bias; it does suggest, however, that more weight be attached to the large scale epidemiological studies.

12.2.8 Internal Consistency and Strength of Effects

Internal consistency is always a check on the validity of a study, but often the authors do not report sufficient detail by which to check for such consistency. For known risk factors for respiratory effects, a study should provide evidence of expected associations. Furthermore, certain patterns of age or gender relationships to observed health outcomes should be expected. For example, studies of lung function should show a decrease as a function of increasing age if the subjects are old enough and the follow-up time is long enough. Consistency between studies provides a further indication of the overall strength of the total data base.

Sample size and power of reported PM-mortality associations

Since the size of the 'relative risks' and the extent of associations found in recent observational studies of PM-mortality are not 'large', such associations are unlikely to be shown in a 'small' sample size (i.e., a limited number of days). This can be particularly problematic if one plans to analyze the data using PM data collected at the current U.S. sampling frequency (i.e., every-6th-day). It should be noted that a majority of the existing studies that reported significant PM-mortality associations used PM data that were collected daily. A determination of the sample size required to find the observed association in a given community is not simple, because power may be dependent on not only sample size, but also

on: (1) the population size of the community (to produce certain number of deaths per day); (2) the levels of PM; (3) the proportion of susceptible populations (e.g., age/race/gender distribution); (4) the location and number of PM sampling sites to estimate representative PM exposure of the population, and; (5) the model specification. Also, determining the expected 'effect' size from the published studies alone may be misleading because of potential 'publication bias' towards significant effects. With this caveat in mind, one can illustrate the effects of sample size and the above mentioned factors on the significance of PM/total daily mortality associations, by examining the t-ratios of the PM coefficients reported by recent U.S. PM-mortality studies (Table 12-1). When both multi-pollutant models and single pollutant models were presented, a single pollutant model was selected here. All the models included weather variables. When both Poisson models (log-linear GLM) and OLS models were presented (Schwartz, 1993; Kinney et al., 1995), both gave essentially identical t-ratios, and therefore the results for Poisson models are shown. Despite the magnitude of differences in various studies' population/mean deaths, the key predictor of t-ratio appears to be the number of study days (sample size).

In a simple linear regression, the t-ratio for the null hypothesis of a regression coefficient being zero is a function of square-root of sample size, with its slope being $r/(1-r^2)^{0.5}$, where r is the underlying size of the correlation between the dependent variable (e.g., mortality) and the explanatory variable (e.g., PM). The plot (Figure 12-3) of these t-ratios versus square-root of sample days from Table 12-1 in fact shows the t-ratio's strong linear dependency on the square-root of sample size. The magnitude of PM-mortality associations seen in these studies, as reflected in the slope ($r=0.083$, if the slope is equated to $r/(1-r^2)^{0.5}$, requires about $n=600$ days for the association to be significant at 0.05 (two-tailed), or $n=400$ for one-tailed test at 0.05 level. The required sample size observations to detect this size of r with 80% power is about 800 days. Therefore, findings of statistical non-significance of PM effect may reflect inadequate power to detect an effect of this magnitude if sample size is limited.

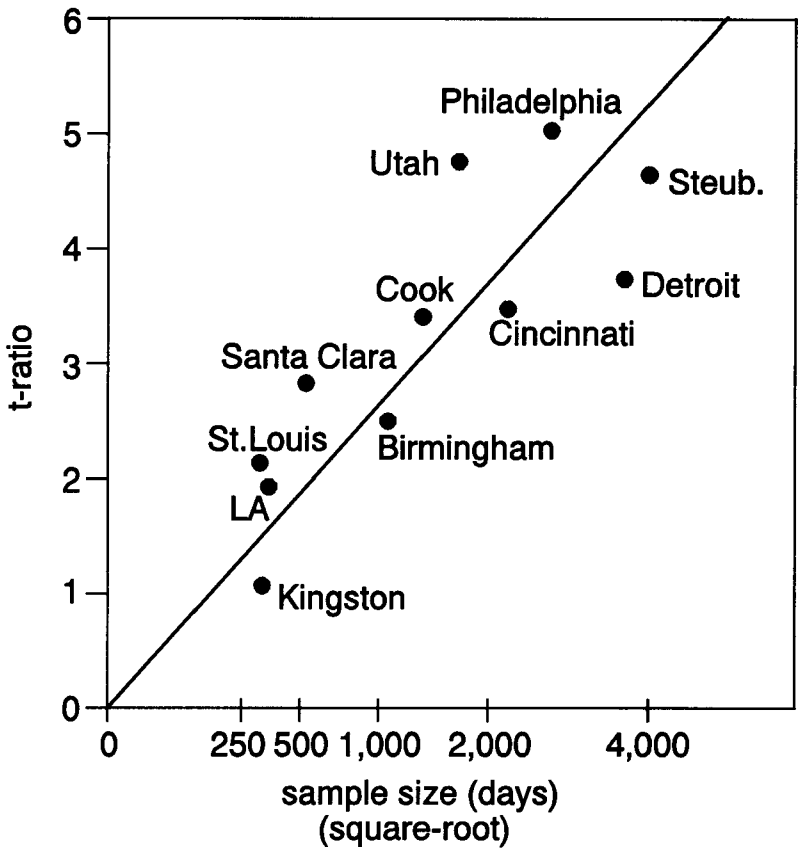

Figure 12-3. t-ratios of PM coefficients versus sample size (days) from 11 recent U.S. studies.

12.2.9 Plausibility of Effects

Health outcomes measured should be ones for which there are plausible bases to suspect that they could be affected by PM exposure. Health outcome measures of greatest interest in PM epidemiologic studies include: lung function measurements, respiratory symptoms and illness occurrence, hospital admissions, and mortality.

12.2.10 Qualitative Versus Quantitative Studies

Studies which do not measure PM exposure but only infer it from some other related indicator (e.g., coal consumption, level of mining activity, etc.) are by definition qualitative. Other studies that measure PM exposures in broad categories (e.g., low, medium, high) and do not relate the exposure to the health effects in an exposure-response fashion are also qualitative. A quantitative study is one in which PM exposures are estimated with reasonable

accuracy as a continuous variable, important potential covariates are adequately controlled, and the response variable reliably varies as a function of increased PM exposure.

12.3 HUMAN HEALTH EFFECTS ASSOCIATED WITH SHORT-TERM PM EXPOSURE

Some of the earliest indications that short-term ambient air particulate matter or acid aerosols exposure may be associated with human health effects were derived from the investigation of historically well-known, major air pollution episode events. These include the Meuse Valley (Belgium), Donora, PA (USA), and London (UK) episodes.

Firket (1931) described December 1930 fog in the Meuse Valley and morbidity and mortality related to them. More than 60 persons died from this fog and several hundred suffered respiratory problems, with a large number becoming complicated with cardiovascular insufficiency. The mortality rate during the fog was more than 10 times higher than normal. Those persons especially affected were the elderly, those suffering from asthma, heart patients and other debilitated individuals. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of pollutants in ambient air during the episode are available by which to establish clearly their relative roles in producing the observed health effects.

Schrenk et al. (1949) reported on the atmospheric pollutants and health effects associated with the Donora smog episode of October 1948. A total of 5,910 persons (or 42.7%) of the Donora population experienced some effect. The air pollutant-ladened fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths occurred, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed through all age groups and, on average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population and was evenly distributed through all age groups. Dyspnea (difficulty in breathing) was the most frequent symptom in the more severely affected, being reported by 12% of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea. While no single substance could be clearly identified as being responsible for the

October 1948 episode, the observed health effects syndrome seemed most likely to have been produced by two or more of the contaminants, i.e., SO_2 and its oxidation products together with PM, as among the more significant highly elevated contaminants present.

Based on the Meuse Valley mortality rate, Firket (1931) estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to the Meuse Valley one occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of 1952, as noted by Martin (1964). During the fog of 1952, evidence of bronchial irritation, dyspnea, bronchospasm and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners. There was a considerable increase in sudden deaths from respiratory and cardiovascular conditions. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute anoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) reported that in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. It is possible that sulfur trioxide, dissolved as sulfuric acid in fog droplets, appreciably augmented the harmful effects of PM and/or other pollutants.

The occurrence of the above episodes and resulting marked increases in mortality and morbidity associated with acute exposures to very high concentrations of air pollutants (notably including PM and SO_2 in the mix):

(1) left little doubt about causality in regard to induction of serious health effects by very high concentrations of air pollutants;

(2) stimulated the establishment of air monitoring networks in major urban areas and control measures to reduce air pollution; and

(3) stimulated research to identify key causative agents contributing to urban air pollution effects and to characterize associated exposure-response relationships.

Besides evaluating mortality associated with major episodes, the 1982 criteria document (U.S. Environmental Protection Agency, 1982) also focused on epidemiology studies of more moderate day-to-day variations in mortality within large cities in relation to

PM pollution. Evaluating risks of mortality at lower exposure levels, the 1982 criteria document concluded that studies conducted in London by Martin and Bradley (1960) and Martin (1964) yielded useful, credible bases by which to derive conclusions concerning quantitative exposure-effect relationships. The 1986 addendum to the 1982 criteria document (U.S. Environmental Protection Agency, 1986) also considered several additional acute exposure mortality studies of London, England during the 1958-1959 through 1971-1972 winter periods conducted by Mazumdar et al. (1982), Ostro (1984), Shumway et al. (1983), and by EPA (later published in Schwartz and Marcus, 1990). After reviewing these various data analyses, and taking into account the previously reviewed London results and the above noted epidemiological considerations, the following conclusions were made (U.S. Environmental Protection Agency, 1986):

(1). Markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1,000 $\mu g/m^3$, especially during episodes when such pollutant elevations occurred for several consecutive days;

(2). During such episodes, coincident high humidity or fog was also likely important, possibly by providing conditions leading to formation of H_2SO_4 or other acidic aerosols;

(3). Increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1,000 $\mu g/m^3$, for SO_2 most clearly at concentrations in excess of ≈ 700 $\mu g/m^3$; and

(4). Convincing evidence indicates that relatively small, but statistically significant, increases in the risk of mortality exist at BS (but not SO_2) levels below 500 $\mu g/m^3$, with no indications of any specific threshold level having been demonstrated at lower concentrations of BS (e.g., at ≤ 150 $\mu g/m^3$). However, precise quantitative specification of the lower PM levels associated with mortality is not possible, nor can one rule out potential contributions of other possible confounding variables at these low PM levels.

The extensive epidemiological research that ensued has greatly advanced our knowledge regarding the above issues, especially roles played by PM and SO_2 in mortality and morbidity associated with both episodic and non-episodic (lower level) exposures to these and/or other co-occurring pollutants. Key studies and findings from such research on mortality associated with short-term exposures to particulate matter are evaluated in the

following section. Additional discussion on validity of model specification is in Section 12.6.2.

12.3.1 Mortality Effects Associated With Short-Term Particulate Matter Exposures

Mortality is a synonym for death rate, the ratio of the total number of deaths in a specified area to the population, generally figured in terms of a number of deaths per i.e., 100,000 of population. For a mortality rate, the numerator is the number of persons dying during a stated period; the denominator is the total population within which the deaths occurred (MacMahon and Pugh, 1970). Thus, the mortality rate expresses the frequency with which members of a general population die. The difference between an increase in the death rate and the cessation of life for an individual is important. Mortality is a population statistic, death relates to an individual. Factors effecting changes in population mortality in relation to population exposure to PM may exert themselves in both similar and dissimilar ways as contrasted to factors associated with the cessation of life for an individual and personal PM exposure. Also, premature death and the related aspect of length of time of potential life lost are important aspects of the end point of interest. The biological plausibilities of mortality and population PM exposure may be different and involve different factors than death and exposure for an individual.

The National Center for Health Statistics (NCHS) mortality statistics used in most U.S.-mortality studies published were compiled in accordance with the World Health Organization (WHO) regulations, which specify that member nations classify causes of death by the current Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organization, 1977). Causes of death for 1979-91 were classified according to the manual. For earlier years, causes of death were classified according to the revisions then in use—1968 through 1978, Eighth Revision; 1958 through 1967, Seventh Revision; and 1949 through 1957, Sixth Revision. Changes in classification of causes of death due to these revisions may result in discontinuities in cause-of-death trends.

National Center for Health Statistics tabulations of cause-of-death statistics are based solely on the underlying cause of death. The underlying cause is defined by WHO as the disease or injury that initiated the sequence of events leading directly to death, or as the

circumstances of the accident or violence that produced the fatal injury. It is selected from the conditions entered by the physician in the cause-of-death section of the death certificate. When more than one cause or condition is entered by the physician, the underlying cause is determined by the sequence of conditions on the certificate, provisions of the ICD, and associated selection rules.

One index of the quality of reporting causes of death is the proportion of death certificates coded to the Ninth Revision, Chapter XVI, Symptoms, signs, and ill-defined conditions (ICD-9 Nos. 780-799). Although deaths occur for which the underlying causes are impossible to determine, this proportion indicates the care and consideration given to the certification by the medical certifier. This proportion also may be used as a rough measure of the specificity of the medical diagnoses made by the certifier in various areas. In 1991, 1.12% of all reported deaths in the United States were assigned to Symptoms, signs, and ill-defined conditions, the same as 1990. However, trends in the percent of deaths assigned to this category vary by age. Although the percent of deaths from this cause for all ages combined generally has remained stable since 1980, decreases have occurred for the age group 55 to 64 years since 1983; and for 10-year age groups from 15 to 44 years since 1988. Between 1990 and 1991, the percent increased for all age groups, except for those 15 to 44 and 55 to 64 years.

Mortality statistics are based on information code by the States and provided to NCHS through the Vital Statistics Cooperative Program and from copies of the original certificates received by the NCHS from the State Registration Offices. The National Center for Health Statistics (1993) reported that in 1991, in the United States, the death rate was 860.3 deaths per 100,000 population. In 1991 a total of 2,169,518 deaths occurred in the United States. The first leading causes of death — diseases of the heart; malignant neoplasms; and cerebrovascular diseases accounted for 64% of deaths. Chronic obstructive pulmonary disease and allied conditions surpassed accidents in 1991 as the fourth leading cause.

In 1991, life expectancy at birth reached a record high at 75.5 years. For those between 65 and 70 years of age, the average number of years of life remaining is 17.4 years. Women currently are expected to outlive men by an average of 6.9 years and white persons are expected to outlive black persons by an average 7.0 years. In 1991, the age-adjusted death rate for males of all races was 1.7 times that for females. In 1991, the age-adjusted

death rate for the black population was 1.6 times that for the white population. The annual asthma death rate was constantly higher for blacks than for whites during the period 1980 through 1990; for blacks, the rate increased 52% (from 2.5 to 3.8 per 100,000), compared with a 45% increase (from 1.1 to 1.6 per 100,000) for whites. (United States Center for Disease Control, 1994). National Centers for Health Statistics (1994) reported that for January 1985 through December 1992 trends in mortality from diseases of the heart (including coronary heart disease) showed that for the modeled period, provisional death rates decreased. Mortality also showed a seasonal pattern with death rates higher in winter.

12.3.1.1 Review of Short-Term Exposure Studies

The decade or so since the previous criteria document addendum was released (U.S. Environmental Protection Agency, 1986a) has been an active period for the reporting of time series analyses of associations between human mortality and acute exposures to PM. In the beginning of this period, various PM measures of only indirect applicability to the standard setting process (e.g., TSP, BS, KM, or COH) were usually employed. However, in the last few years the analyses have more often employed PM_{10} as a measure of PM. This is because sufficient routine PM_{10} ambient measurement data have finally begun to be available for such statistical analyses to be conducted in a wide variety of locales. The focus of this section is on detailed assessments of those studies conducted since the PM criteria document addendum (U.S. Environmental Protection Agency, 1986a). Of special interest are studies that have employed PM_{10} in their analyses of the human mortality effects of acute exposures to PM; although studies employing other indices of PM exposures are be summarized in tables and discussed in the text, as appropriate.

As shown in Table 12-3 a variety of PM metrics have been employed in time-series studies relating PM to acute mortality. These have included gravimetric measures, such as total suspended particulate matter (TSP) and PM_{10}, the former of which includes a significant portion of nonrespirable particles. In addition, many studies have employed data from various samplers that yield BS or KM optical measurements of particle reflectance of light, or coefficient of haze (COH) optical measurements of particle transmission of light. All of these latter metrics are most directly related to ambient elemental carbon concentration (e.g., see Bailey and Clayton, 1982, and Cass et al., 1984), but only indirectly related to particle

mass, as the relationship with mass will vary as sampled particle size, shape, color, and surface characteristics vary over time and between sites. Hence, unless side-by-side calibrations of these optical measurements are made against direct mass measurements obtained by collocated gravimetric monitoring instruments, such optical measurements cannot be readily converted to quantitative estimates of ambient PM mass concentrations or associated PM-mortality relationships. Thus, given the diversity of nonequivalent PM metrics employed across many of the reviewed epidemiology studies, attempting quantitative intercomparisons between results of all of the various reviewed epidemiologic studies necessarily introduce additional uncertainties, although attempts have been made using assumed conversion factors (Schwartz, 1991; Ostro, 1993, 1993; Dockery and Pope, 1994; and Pope et al., 1995).

The two studies using KM as the PM metric employed very different approaches to the same data set from Los Angeles during 1970 to 1979. The study by Shumway et al. (1988) evaluated long-wave associations and found significant KM-mortality associations, but this analysis failed to account for seasonal effects. The KM study by Kinney and Ozkaynak (1991) more appropriately studied the short-wave associations of multiple pollutants, finding KM to be significantly associated with total mortality, but collinearities among KM, NO_2, and CO made it impossible to separately estimate a PM association.

Similar to the KM studies, BS studies are quite varied in approach. Thurston et al. (1989) applied a high pass filter (similar to that employed by Kinney and Ozkaynak, 1991) to the 1963 to 1972 London, England wintertime mortality-pollution data set, whereas Ito et al. (1993) analyzed a subset of the same data using prewhitening and autoregressive techniques. In both, BS, SO_2, and H_2SO_4 were all found to be significantly associated with mortality, but the effects of each were not separable due to the high collinearity among these pollution metrics. Katsouyanni et al. (1990) similarly found an association between total mortality and all pollutants measured in Athens, Greece, during 1975 to 1987, though they reported that BS was the most strongly associated of the pollutants. A separate randomized block analysis of SO_2 and by-cause mortality during this same period (Katsouyanni, 1990) found significant SO_2 effects, but also noted that SO_2 and BS were correlated at $r = 0.73$, suggesting that BS may also have been associated. A subsequent analysis by Katsouyanni et al. (1993) of summer heat wave periods found a significant temperature-SO_2 interaction term, and the suggestion of an interaction ($p < 0.2$) for BS.

TABLE 12-3. SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
KM (mean = 25; SD = 11)	Total, respiratory, and cardiovascular mortality in Los Angeles County during 1970 to 1979 related to O_3, CO, SO_2, NO_2, HC, daily max. temperature, relative humidity, and KM (a particulate matter metric of optical reflectance by particles, related to the ambient carbon concentration). Low pass filter used to eliminate short-wave, so that only long-wave associations are studied.	Frequency domain analyses indicated significant short- and long-wave associations with KM. The filtered (i.e., long-wave) data analysis indicated that air pollution (including KM) was significantly associated with seasonal variations in LA mortality.	Shumway et al. (1988)
TSP (OECD Method) (Lyons, France: 3 year mean = 87 $\mu g/m^3$) (Marseilles, France 3 y mean = 126 $\mu g/m^3$)	Daily total, respiratory, and cardiac mortality for persons $\geq$65 years of age tested for associations with SO_2 and TSP during 1974 to 1976 in Lyons and Marseilles, France. Temperature also considered in analyses.	No significant mortality associations found with TSP, while SO_2 was reportedly associated with total elderly deaths in both cities. Seasonality addressed by analyzing deviations from 3-year average of 31-day running means of variables. However, lags of temperature not considered and probable seasonal differences in winter/summer temperature-mortality relationship not addressed.	Derriennic et al. (1989)
BS (mean = 90.1 $\mu g/m^3$) (24-h avg. daily max. = 709 $\mu g/m^3$)	Daily total mortality analyzed for associations with BS, SO_2, and H_2SO_4 in London, England, during 1963 to 1972 winters. Mean daily temperature and relative humidity also considered.	PM, SO_2, and H_2SO_4 all indicated as having significant associations with mortality (0, 1 day lag). Temperature also correlated (negatively) with mortality, but with a 2-day lag. Seasonality addressed by studying only winters and by applying a high-pass filter to the series and analyzing residuals.	Thurston et al. (1989)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
COH (monthly mean range = 9 to 12)	Daily total, respiratory, cancer, and circulatory associations with daily COH in Santa Clara County, CA, during 1980 to 1982 and 1984 to 1986 winters. Daily mean temperature and relative humidity at 4 PM also considered.	An association found between COH and increased mortality, even after making adjustments for temperature, relative humidity, year, and seasonality.	Fairley (1990)
BS	Daily total mortality in Athens, Greece, and surrounding boroughs during 1975 to 1987 related to BS, SO_2, NO_2, O_3, and CO_2 using multiple regression.	During winter months 1983 to 1987, the daily number of deaths was positively and statistically significantly associated with all pollutants, but the association was strongest with BS.	Katsouyanni et al. (1990a)
BS (annual mean range = 51.6 to 73.3 $\mu g/m^3$) (maximum daily value = 790 $\mu g/m^3$)	For the period 1975 to 1982 in Athens, Greece, 199 days with high SO_2 (>150 $\mu g/m^3$) were each matched on temperature, year, season, day of week, and holidays with two low SO_2 days. Mortality by-cause comparisons made between groups by analysis of variance by randomized blocks. BS correlated with SO_2 at r = 0.73, but not directly employed in the analysis.	Mortality was generally higher on high SO_2 days, with the difference being most pronounced for respiratory conditions. BS levels for each group not provided, and BS-SO_2 confounding not addressed, limiting interpretability of results.	Katsouyanni et al. (1990b)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
KM (mean = 25; SD = 11)	Shumway et al. (1988) 1970 to 1979 Los Angeles mortality dataset analyzed using a high-pass filter to allow investigation of short-wave (acute) associations with environmental variables (by removing seasonality effects). Environmental variables considered in regression analyses included temperature, relative humidity, extinction coefficient, carbonaceous particulate matter (KM), SO_2, NO_2, CO, and O_3.	Analyses demonstrated significant associations between short-term variations in total mortality and pollution, after controlling for temperature. Day-of-week effects found not to affect the relationships. The results demonstrated significant mortality associations with O_3 lagged 1 day, and with temperature, NO_2, CO, and KM. The latter three pollutants were highly correlated with each other, making it impossible to separately estimate particulate matter associations with mortality.	Kinney and Ozkaynak (1991)
TSP (mean = 87 $\mu g/m^3$) (24-h avg. range: 46 to 137 $\mu g/m^3$, 5th to 95th percentiles)	Total deaths in Detroit, MI, 1973 to 1982 analyzed using Poisson methods. Environmental variables considered included TSP, SO_2, O_3, temperature, and dew point. Seasonality controlled via multiple dummy weather and time variables.	Significant associations reported between TSP and mortality in autoregressive Poisson models (RR of 100 $\mu g/m^3$ TSP = 1.06). However, most TSP data estimated from visibility, which is best correlated with the fine aerosol (and especially sulfate) portion of the TSP. Thus, results suggest a fine particle association.	Schwartz (1991)
TSP (mean = 77 $\mu g/m^3$) (max. = 380 $\mu g/m^3$) (5th to 95th percentiles = 37 to 132 $\mu g/m^3$)	Total and cause specific daily mortality in Philadelphia, PA during 1973 to 1980 related to daily TSP and SO_2 (n $\approx$2,700 days). No other pollutants considered in the analysis. Poisson regression models, using GEE methods, included controls for year, season, temperature, and humidity. Autocorrelation addressed via autoregressive terms in model.	Strongest associations found with pollution on the same and prior days. Total mortality (mean = 48/day) estimated to increase 7% (95% C.I. = 4 to 10%) for a 100 $\mu g/m^3$ increase in TSP. Cause-specific effects of TSP were larger (as %). SO_2 associations were non-significant in simultaneous models with TSP, but correlations of their coefficients not reported	Schwartz and Dockery (1992a)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 69 $\mu g/m^3$) (5th to 95th percentiles = 32 to 120 $\mu g/m^3$)	Age and cause-specific daily mortality in Philadelphia, PA during 1973 and 1990 related to daily TSP, SO_2, and O_3. Other environmental variables included were: temperature, barometric pressure, humidity, and precipitation. Various models employed, including poisson and autoregessive. Prefiltering methods also applied to remove long-waves in data.	TSP effect found only in winter season. TSP never significant in by-cause analyses of those <15 or ≥ 65 years of age. TSP effects weakened by the addition of other pollutants (TSP-SO_2 r = 0.57). However, the inclusion of barometric pressure and precipitation in these models may have acted as surrogates for PM, potentially confounding results. Correlations between TSP and these variables not presented.	Li and Roth (1995)
TSP (mean = 111 $\mu g/m^3$) (24-h avg. range: 36 to 209 $\mu g/m^3$, 10th to 90th percentiles)	Daily total mortality in Steubenville, OH, between 1974 to 1984 related to TSP, SO_2, temperature, and dew point. Poisson regression employed, because of very low death counts/day (mean = 3.1). Regressions controlled for season by including dummy variables for winter and spring, and autoregressive methods also used to address any remaining autocorrelation.	In regressions controlling for season and weather, previous day's TSP was a significant predictor of daily mortality. SO_2 was less significant in regressions, becoming nonsignificant when entered simultaneous with TSP. Auto-regressive models gave similar results.	Schwartz and Dockery (1992b)
TSP (mean = 113 $\mu g/m^3$) (10th to 90th percentiles = 38 to 212 $\mu g/m^3$)	Daily mortality in Steubenville, OH during 1974 to 1984 related to TSP, SO_2, temperature, and dew point (to allow comparisons of results with Schwartz and Dockery, 1992b). Poisson method employed. Analyses done overall and by-season.	In single pollutant models, the TSP coefficient was the same as Schwartz and Dockery (1992b), but TSP effects were found to be attenuated by SO_2 inclusion in the model. SO_2 was also attenuated by the addition of TSP. It is concluded that TSP and SO_2 effects cannot be separated in this dataset. Intercorrelations among these variables not presented.	Moolgavkar et al. (1995)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
BS (mean = 90.1 $\mu g/m^3$) (range = 0 to 350 $\mu g/m^3$)	Further analysis of London, England data (1965 to 1972) examined by Thurston et al. (1989). Spectral and advanced time series methods applied, including prewhitening and auto- regressive (AR) moving average (MA) methods. Environmental variables considered included BS, SO_2, H_2SO_4, temperature, and relative humidity.	Estimated pollution mean effect of 2 to 7% of all London winter deaths (mean = 281/day). However, the various pollutants' effects were not separated. Independent model test on the 1962 episode confirmed the appropriateness of such methods. Long-wave addressed by considering winters only and by prewhitening the data.	Ito et al. (1993)
BS (range = 50 to 250 $\mu g/m^3$)	Daily total mortality in Athens, Greece, during July, 1987 (when a major "heat wave occurred) compared to the deaths in July during the previous 6 years. Environmental variables considered included: temperature, discomfort index (DI), BS, SO_2, and BS. Confounding effects of day-of-week, month, and long-term trends addressed via dummy variables in OLS regression models.	Mean daily temperature above 30 °C found to be significantly associated with mortality. The main effects of all air pollutants nonsignificant, but the interaction between high air pollution and temperature were significant for SO_2 and suggestive ($p < 0.20$) for ozone and BS.	Katsouyanni et al. (1993)
Suspended Particles (SP) (range = 10 to 650 $\mu g/m^3$)	Daily total mortality in Erfurt, East Germany, during 1980 to 1989 (median = 6/day) related to SO_2, SP, T, RH, and precipitation. SP measurements made only 1988 to 1989. Autoregresssive Poisson models employed (due to low deaths/day) also included indicator variables for extreme temperatures and adjustments for trend, season, and influenza epidemics.	Both SO_2 and SP were found to be significantly associated with increased mortality. In a simultaneous regression, SP remained significant while SO_2 did not. Correlations of these coefficients not provided, however. Pollution effect size similar to that for meteorology.	Spix et al. (1993)
BS (mean = 83 $\mu g/m^3$) (range = 18 to 358 $\mu g/m^3$)	Daily total mortality in Athens, Greece, during 1984-1988 (mean = 38/day) related to BS, SO_2, CO, T, and RH. Autoregressive OLS models employed also included indicator variables for season, day of week, and year.	BS, SO_2, and CO all found to be individually significantly associated with increased mortality. In simultaneous regressions, the size of all coefficients declined, with SO_2 still significant and BS approaching significance. CO was no longer significant, but was highly correlated with BS (r = 0.74) in the data.	Touloumi et al. (1994)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 52 $\mu g/m^3$; SD = 19.6 $\mu g/m^3$)	Daily total and cause-specific mortality in Cincinnati, OH, (mean total = 21/day) during 1977 to 1982 related to TSP, temperature, and dew point. Poisson model employed with dummy variables for each month and for eight (unspecified) categories of temperature and dew point. Linear and quadratic time trend terms also included. Spline and nonparametric models also applied. Autocorrelation not directly addressed.	TSP was significantly associated with increased risk of total mortality. The relative risk was higher for the elderly and for those dying of pneumonia and cardiovascular disease. However, the analysis failed to consider other pollutants, and there remains the potential for within-month, long-wave confoundings.	Schwartz (1994a)
TSP (mean = 375 $\mu g/m^3$) (maximum = 1,003 $\mu g/m^3$)	Daily deaths during 1989 in two residential areas in Beijing, China, (mean total deaths = 21.6/day) related to TSP and SO_2 using Poisson methods. Controlling indicator variables for quintiles of temperature and humidity, as well as for Sunday also included. Long-wave confounding and autocorrelation not directly addressed. However, season-specific results presented.	Significant mortality associations found for ln (SO_2) and ln (TSP). Associations were strongest for chronic respiratory diseases. In simultaneous regressions, SO_2 was significant, but not TSP. However, the two pollutants were highly correlated with each other (r = 0.6), as well as with temperature. In season-specific analyses, both pollutants were significant in summer, but only SO_2 in winter.	Xu et al. (1994)
PM_{10} (mean = 47 $\mu g/m^3$) (24 h max. = 365 $\mu g/m^3$) (5 day max. = 297 $\mu g/m^3$)	Total, respiratory, and cardiovascular mortality in Utah County, UT, during 1985 to 1989 related to 5-day moving average PM_{10}, temperature, and humidity. Time trend and a random year terms also included in autoregressive Poisson models employed. Seasonality not directly addressed in this basic model, but the addition of four seasonal dummy variables changed results little.	A significant positive association between total non-accidental mortality and PM_{10} was observed, the strongest association being with the 5-day moving average of PM_{10}. The association was largest for respiratory disease, the next largest for cardiovascular, and the lowest for all other. Association noted below 150 $\mu g/m^3$ PM_{10}. The possible influence of other pollutants discussed, but not directly addressed.	Pope et al. (1992)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} St. Louis, MO: (mean = 28 $\mu g/m^3$) (24 hr max. = 97 $\mu g/m^3$) Kingston/Harriman, TN (mean = 30 $\mu g/m^3$) (24 h max. = 67 $\mu g/m^3$)	Total mortality in St. Louis, MO, and Kingston/Harriman, TN (and surrounding counties), during September 1985 to August 1986 related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temperature, dew point, and season using auto-regressive Poisson models.	Statistically significant daily mortality associations found with PM_{10} and $PM_{2.5}$ in St. Louis, but not with other pollutants. In Kingston/Harriman, PM_{10} and $PM_{2.5}$ approached significance, while other pollutants did not. Seasonality was reduced by season indicator, variables, but within season long wave cycles not directly addressed.	Dockery et al. (1992)
PM_{10} (mean = 48 $\mu g/m^3$) (24 h max. = 163 $\mu g/m^3$)	Total daily mortality in Birmingham, AL, from August 1985 to December 1988 related to PM_{10}, temperature, and dew point. Poisson models employed addressed seasonal long wave influences by the inclusion of 24 sine and cosine terms having periods ranging from 1 mo to 2 years. Autoregressive linear models also applied.	Significant associations found between total mortality and prior day's PM_{10}. Various models gave similar results, as did eliminating all days with $PM_{10} > 150$ $\mu g/m^3$. However, the possible role of other pollutants not evaluated.	Schwartz (1993)
PM_{10} (mean = 40 $\mu g/m^3$) (24 h max. = 96 $\mu g/m^3$)	Total, cardiovascular, cancer, and respiratory mortality in Toronto, Canada, during 1972 to 1990 related to PM_{10}, TSP, SO_4, CO, O_3, temperature, and relative humidity. Nineteen-day moving average filtered data used in OLS regressions. Sixty-three hundred and three PM_{10} values estimated based on TSP, SO_4, COH, visibility (B_{ext}) and temperature data, using model developed from 200 PM_{10} sampling days during the period.	Significant associations found between all pollutants considered and mortality, after controlling for weather and long wave influences. However, it was not possible to separate the PM_{10} association from other particulate measures considered. Simultaneous PM and ozone regressions gave significant coefficients for each, but intercorrelations among the pollutants not presented.	Ozkaynak et al. (1994)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 58 $\mu g/m^3$) (24 h max. = 177 $\mu g/m^3$)	Total mortality in Los Angeles, CA, during 1985 to 1990 related to PM_{10}, O_3, CO, temperature, and relative humidity. Poisson models employed addressed seasonal long-wave influences by including multiple sine and cosine terms ranging from 1 mo to 2 years in periodicity. OLS and long linear models also tested. Winter and summer analyzed separately also.	Association between PM_{10} and mortality found to be only mildly sensitive to modeling method. CO also individually significant. The addition of either CO or O_3 lowered the significance of PM_{10} in model somewhat, but the PM_{10} coefficient was not as affected, indicating minimal effects on the PM_{10} association by other pollutants in this case.	Kinney et al. (1995)
PM_{10} (mean = 38 $\mu g/m^3$) (24 h max. = 128 $\mu g/m^3$)	Total mortality in Los Angeles, CA and Chicago, IL during 1985 through 1990 related to PM_{10}, O_3, and temperature. Analysis focused on importance of monitor choice to modeling results. Poisson models used addressed seasonal long wave influences by including multiple sine/cosine terms ranging from 1 mo to 2 years in periodicity.	Average of multiple sites' PM_{10} found to be significantly associated with mortality in each city after controlling for season, temperature and ozone. Other pollutants and relative humidity not yet considered. Individual sites' PM_{10} varied from non-significant to strongly significant. Also, dividing the data by season diminished the significance of the multi-site average PM_{10} in mortality regressions. Both site selection and sample size concluded to influence results.	Ito et al. (1995)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 115 $\mu g/m^3$) (24 h max. 367 $\mu g/m_3$)	Total, respiratory, and cardiovascular daily deaths/day (means = 55, 8, and 18, respectively) in Santiago, Chili during 1989 through 1991 related to PM_{10}, O_3, SO_2, NO_2, temperature and humidity. Seasonal influences addressed by various methods, including seasonal stratification, the inclusion of sine/cosine terms for 2.4, 3, 4, 6, and 12 month periodicities, prefiltering, and the use of a nonparametric fit of temperature. Log of PM_{10} modeled using OLS with first order autoregressive terms.	Significant association found between PM_{10} and daily mortality, even after addressing potential confounders (e.g., weather), other pollutants, lag structure, and outliers. Strongest associations found for respiratory deaths. SO_2 and NO_2 also significantly associated individually, but only PM_{10} remained significant when all were added simultaneously to the regression. Correlations of the coefficients not reported.	Ostro et al. (1995a)
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Respiratory mortality among children < 5 years old (mean = 3/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to PM_{10}, SO_2, NO_x, O_3, CO, temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables in regressions. Mortality data adjusted for non-normality via a square root transformation.	Significant association found between respiratory deaths and NO_x, but no other pollutants. No such association found for non-respiratory deaths. However, auto-correlation not addressed. Also, inter-correlations of the pollutant coefficients not reported (but NO_x - PM_{10} correlation = 0.68)	Saldiva et al. (1994)
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Total mortality among the elderly (≥ 65 years old) (mean = 63/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to two day avg. of PM_{10}, SO_2, NO_x, O_3, and CO, and to temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables. Temperature addressed using three discrete dummy variables.	Significant associations found between total elderly deaths and all pollutants considered. In a simultaneous regression, PM_{10} was the only pollutant which remained significant. The PM_{10} coefficient actually increased in this regression, suggesting interpollutant interactions. Correlations of the pollutant coefficients not provided.	Saldiva et al. (1994)

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TABLE 12-3 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (Cook County median = 37 $\mu g/m^3$; max = 365 $\mu g/m^3$) (Salt Lake County median = 35 $\mu g/m^3$; max = 487 $\mu g/m^3$)	Total, respiratory, circulatory, and cancer mortality in Cook County, 1985 to 1990. Elderly, total by race and sex also evaluated. Poisson regression with seasonal adjustments, meteorological variables, and pollen tested. In Salt Lake Count, total and elderly mortality. One daily station in Cook County and two daily monitoring stations in Salt Lake County, plus multiple __-day stations.	Average and single site PM_{10} were significant predictions of PM_{10} in Cook County for total, elderly, cancer, and elderly white mortality, marginal for respiratory, circulatory, and elderly black. Significant Fall and Spring mortality in Cook County, not Summer or Winter. No significant effects in Salt Lake County. No copollutants.	Styer et al. (1995)
PM_{10} (variable by month and year)	Reanalysis of Utah County mortality, 1985 to 1992, broken down by year, season cause and place of death. PM_{10} was entered as a dichotomous variable, less or greater than 50 $\mu g/m^3$. No adjustment for copollutants or for weather in Poisson regression, except for daily minimum temperature. Poisson regression, not GEE.	Variations in RR did not appear to be associated with high or low PM_{10} days. High RR for cancer deaths, age < 60, at home. Highest RR in spring. Increased RR for sudden infant death syndrome. Patterns appear noncausal.	Lyon et al. (1995)

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A PM study using BS as the particulate matter index which has carefully addressed the potential confounding effects of other pollutants and temperature was recently conducted by Touloumi et al. (1994) for daily all-cause mortality in Athens, Greece during 1984 through 1988. In this study, BS (mean = 83 $\mu g/m^3$), SO_2 (mean = 45 $\mu g/m^3$), CO (mean = 6 $\mu g/m^3$), temperature, and relative humidity were all modeled separately and simultaneously, giving a range of estimates for PM effects, depending on the model specification. The five years of data employed provided ample numbers of records for the analysis (e.g., n = 1684 for BS). Temperature associations were simply but effectively modeled. The authors examined the bivariate temperature-mortality plot and noted that a mortality minimum occurred at approximately 23 °C daily mean temperature. They then defined two temperature variables: one as the daily mean temperature deviation below 23 °C; the other as the daily deviation above 23 °C, whichever was relevant, thereby allowing a separate modeling of the cold and hot weather effects on mortality. It was found that the square of each of these (lagged one day) gave the best fit of the mortality, and these terms were used in subsequent pollutant models. Multiple monitoring stations were averaged (e.g., 5 for smoke) after filling in missing observations from available data on the same day at other sites, providing spatially representative exposure estimates. Ordinary least squares modeling was applied, which is acceptable in this case, given the relatively large number of mortality counts/day (mean = 38 deaths/day, SE = 12) in this metropolitan area. In mortality regressions on pollutants, day-of-week, season, hot (> 23 °C) and cold (<23 °C) temperature deviations squared, and relative humidity terms were also included. Although the use of only a dummy term for each season could not have fully addressed the within-season long wave mortality trends shown in time series plots, autoregressive modeling did address any resulting residual autocorrelation. Also, the use of a single annual sine curve with a periodicity of 1 year (phase not reported) gave similar results.

Separating the effects of the various air pollutants was attempted in this analysis of Athens mortality, but proved challenging. The log of pollutant concentrations were entered into the basic model both individually and simultaneously. All pollutants considered were individually significant at the p = 0.0001 level. When copollutants were entered simultaneously, SO_2 was the least affected, both in terms of coefficient size and statistical significance. The BS coefficient dropped in size by 50% when entered with SO_2 in the

model, and its statistical significance weakened, as expected when correlated variables are entered together, but remained significant ($p = 0.02$, two-tailed test). However, SO_2 declined by less than 30 percent and remained significant at the $p = 0.002$ level in simultaneous regressions. The CO coefficient decreased in size by 75% and became clearly non-significant when entered with either SO_2 or BS. The authors noted, however, that these pollutants are highly intercorrelated over time (e.g., for CO and BS, $r = 0.79$). Thus, while the most consistent mortality association, both in terms of size and significance of its coefficient, appears to be with SO_2 in this city, the colinearities among these primary, combustion-related, air pollutants prevents a quantitative apportionment of effects to individual pollutants. The authors acknowledged this fact, concluding that relatively low-level air pollution has a small but real effect on mortality. Using BS alone as the index of ambient air pollution, the authors report that a 10% decrease in BS was associated with a 0.75% decrease in total mortality. Using an on-site calibration with PM_{10} ($PM_{10} = 8.70 + 0.832 \times BS$) developed for this city (Katsouyanni, 1995) yields a mean PM_{10} of 77.7 $\mu g/m^3$, and a relative risk (RR) of 1.07 for a 100 $\mu g/m^3$ increase in PM_{10} (i.e., to 203 $\mu g/m^3$ BS). However, when the BS coefficient from the simultaneous regression with other pollutants is employed, the estimated RR of that 100 $\mu g/m^3$ increase in PM_{10} drops to 1.03. Thus, the estimate of the total mortality RR of a one day 100 $\mu g/m^3$ increase in PM_{10} implied by this work ranges from 1.07 to 1.03, depending on whether the PM metric is entered into the regression singly or in combination with other pollutants, respectively.

Total suspended particulate matter studies have also yielded mixed results as to the relative role of PM, versus other pollutants, in mortality. For example, Schwartz (1991) examined total mortality in Detroit during 1973 to 1982, finding TSP to be more strongly associated with mortality than SO_2. However, the correlation between SO_2 and TSP was not reported, other pollutants likely to have been present (e.g., CO and NO_2) were not considered in the analysis, and most of the TSP values were estimated from visibility records, which are most strongly correlated with fine particles (e.g., see Ozkaynak et al., 1986). Schwartz and Dockery's analysis of 1974 to 1984 mortality in Steubenville, OH (1992), similarly concluded that TSP was more significant than SO_2, but failed to consider other pollutants and did not report the correlation between SO_2 and TSP in this valley locale. A Schwartz (1994a) analysis of Cincinnati, OH, mortality during 1977 to 1982 also found a

TSP-mortality association, but did not consider other pollutants. Derriennic et al. (1989) examined mortality among the elderly in two French cities during 1974 to 1976 and found mortality associations with SO_2, but not with TSP (though the model specification for temperature did not address possible lag structure or season). Spix et al. (1993) found significant suspended particle (SP) and SO_2 associations with mortality in Erfurt, East Germany, during 1980 to 1989, with SP remaining significant in simultaneous regressions, despite very high SO_2 levels. Xu et al. (1994) found significant SO_2 and TSP associations (other pollutants not considered) in Bejing, China, but found that SO_2 (not TSP) remained significant in simultaneous regressions.

Overall, qualitatively examining the KM, BS, and TSP time-series studies summarized in Table 12-4 reveals that these various PM metrics are often associated with mortality. The strength and interpretation of that association can vary depending on the number of other pollutants included and on the way they are considered in the analysis. In the above discussed cases where more pollutants were considered, other pollutants were often found to also be associated with mortality, sometimes less strongly and sometimes more strongly than for the PM metric. Moreover, in the cases where the correlations among the significant pollutants were reported, it was consistently found that the PM metric was correlated with these other pollutants. Also, the relationships of all these various PM metrics with PM_{10} mass are not generalizable, and likely vary between seasons and from place to place. Thus, although these various analyses are strongly supportive of an ambient air pollution effect on mortality throughout the world, and are generally consistent with the hypothesis of a PM effect on mortality, they are of more limited usefulness in trying to quantitatively assess PM mortality associations (e.g., as a relative risk per $\mu g/m^3$).

Table 12-4 includes summaries of numerous recently reported PM_{10}-mortality studies. Among the first was a study of total, respiratory, and cardiovascular mortality in Utah County, UT during 1985-1989 (Pope et al., 1992). In this study, the various daily counts of mortality were regressed on the 5-day moving average PM10, as well as on temperature, humidity, a time-trend term, and random year terms. While only one site was used to represent the whole county's PM_{10} level, comparisons with two other PM_{10} sites indicated spatial consistency (correlation between sites ≥ 0.95). Autoregressive Poisson methods were used because of the low total mortality counts (mean = 2.7/day) in this relatively small

TABLE 12-4. SUMMARIES OF PUBLISHED PM_{10}-ACUTE MORTALITY EFFECTS STUDIES BASED ON VARIOUS PM MEASURES

Health Outcome	Synthesis Study	Location	Original PM Measurement	Mean Equivalent PM_{10}	Percent Change Per 10 $\mu g/m^3$ PM_{10} Equivalent	95 Percent Confidence Interval
Total Mortality	Ostro (1993)	London UK	BS	80	0.3	(0.29, 0.31)
		Steubenville OH	TSP	61	0.6	(0.44, 0.84)
		Philadelphia PA	TSP	42	1.2	(0.96, 1.44)
		Santa Clara CA	COH	37	1.1	(0.73, 1.51)
	Dockery and Pope (1994)	St. Louis MO	PM_{10}	28	1.5	(0.1, 2.9)
		Kingston TN	PM_{10}	30	1.6	(-1.3, 4.6)
		Birmingham AL	PM_{10} (3d)	48	1.0	(0.2, 1.5)
		Utah Valley UT	PM_{10} (5d)	47	1.5	(0.9, 2.1)
		Philadelphia PA	TSP (2d)	40	1.2	(0.7, 1.7)
		Detroit MI	TSP	48	1.0	(0.5, 1.6)
		Steubenville OH	TSP	61	0.7	(0.4, 1.0)
		Santa Clara CA	COH	35	0.8	(0.2, 1.5)
Respiratory Mortality	Dockery and Pope (1994)	Birmingham AL	PM_{10} (3d)	48	1.5	(-5.8, 9.4)
		Utah Valley UT	PM_{10} (5d)	47	3.7	(0.7, 6.7)
		Philadelphia PA	TSP (2d)	40	3.3	(0.1, 6.6)
		Santa Clara CA	COH	35	3.5	(1.5, 5.6)
Cardiovascular Mortality	Dockery and Pope (1994)	Birmingham AL	PM_{10} (3d)	48	1.6	(-1.5, 3.7)
		Utah Valley UT	PM_{10} (5d)	47	1.8	(0.4, 3.3)
		Philadelphia PA	TSP (2d)	40	1.7	(1.0, 2.4)
		Santa Clara CA	COH	35	0.8	(0.1, 1.6)

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population (260,000). Using this model, a significant positive association was found between total non-accidental mortality and PM_{10}, and the authors concluded that a 100 $\mu g/m^3$ increase in the 5-day average PM_{10} concentration was associated with a 16% increase in mortality. Analyses presented indicate that the use of concurrent day PM_{10}, rather than a 5-day average, would have resulted in an effect estimate roughly half that reported in terms of the 5-day average PM_{10} (in deaths per $\mu g/m^3$). A "control" disease category (i.e., one unlikely to be affected by air pollution) was not considered, per se. However, deaths due to causes other than respiratory or cardiovascular were considered, and found not to be associated with PM. Respiratory deaths were more strongly associated with PM_{10} than any other cause. Both of these results support the biological plausibility of a PM-mortality association. Furthermore, the PM_{10}-mortality association was noted by the authors to be present well below the existing 24-h average PM_{10} standard of 150 $\mu g/m^3$. The authors dismiss other air pollutants as having negligible influence by comparing them to their respective present air quality standards without directly modeling the possibility that other (correlated) air pollutants might also influence mortality. On the other hand, Pope (1995) reported that PM_{10}, and SO_2 were only weakly correlated ($r = 0.19$), acid aerosol (H_+) levels were below 8 nmoles/m^3, and the introduction of O_3 into the model actually strengthened the PM_{10} association. Thus, other pollutants appear unlikely to be a major confounder in this analysis, and this study supports the hypothesis of a PM_{10} air pollution effect on human mortality.

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during the one year period between September 1985 and August 1986 in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered is Knoxville, TN, some 50 Km from the air pollution monitoring site employed. In each study area, total daily mortality was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's PM_{10} and PM2.5, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, PM_{10} and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar PM_{10} coefficients are reported, implying a 16 to 17 percent increase in total mortality per 100$\mu g/m^3$ of PM_{10}. While autocorrelation was

accounted for, seasonality was only addressed by season indicator (dummy) variables, which could not address any within-season long wave influences. However, in both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites are provided (e.g., correlations with other sites' data). Also, using mortality data for Knoxville, TN (50 km from the Kingston/Harriman, TN monitoring site at which PM concentrations were measured) in the PM-mortality analysis raises questions about the representativeness of the exposure estimates in that city. Furthermore, the number of days for which pollution data are available for time-series analyses is limited in this data set, especially for H^+ (e.g., only 220 days had H^+ values at the St. Louis site). In the words of the authors: "Because of the short monitoring period for daily particulate air pollution, the power of this study to detect associations was limited." However, despite this limitation, consistent PM_{10} coefficients were found in each of these two cities.

A longer record was examined for a total mortality-PM_{10} relationship in Birmingham, AL during August, 1985 through December, 1988 (Schwartz, 1993). In this work, Poisson modeling was used to address small count effects (mean mortality = 17.1 deaths/day), season was addressed by the inclusion of 24 sine and cosine terms having periods ranging from 1 to 24 mo, and weather was modeled using various specifications of temperature and relative humidity. Autocorrelation was addressed using autoregressive parameters, as required, and day of week dummy variables were also included. In these analyses, significant associations were found between total daily mortality and the average of the three prior day's PM_{10} concentration. It was noted that averaging fewer days weakened the PM_{10}-mortality association, which is consistent with expectation that multiple day pollution episodes are of the greatest health concern. The analysis did not look at any other pollutants, making it impossible to directly assess whether the association noted is due to PM_{10} alone, or also in part to some other collinear pollutant (e.g., SO_2) not considered in the analysis. However, a variety of modeling approaches gave similar results, as did eliminating all days with $PM_{10} > 150\ \mu g/m^3$, indicating that the PM-mortality associations noted are not dependent on model choice, or limited to elevated pollution days only.

Ozkaynak et al (1994) related total daily mortality in Toronto, Ontario during 1972-1990 to daily PM_{10}, TSP, SO_4, CO, O_3, temperature, and relative humidity. A 19-day

moving average equivalent high-pass filter was used to prefilter out long-wave cycles in the data and to reduce autocorrelation. OLS regression was employed, as the distribution of mortality data tend toward the normal in larger cities such as Toronto (mean deaths = 40/day) once seasonal cycles are removed. In this dataset, 6,303 PM_{10} daily values were estimated based on TSP, SO_4, COH, visibility (i.e., Relative Humidity corrected B_{ext}, the extinction coefficient derived from airport visibility observations), and temperature data, using a model developed from 200 actual PM_{10} sampling days during the study period. This limits the usefulness of the results for distinguishing PM_{10} in the analyses, as it is derived from other particulate matter metrics and from variables which may themselves be causally related to mortality (e.g., temperature). For example, estimated PM_{10} is correlated at $r = 0.95$ with TSP, and $r = 0.27$ with temperature. In the analyses, all pollutants considered were significantly associated with daily mortality. The simultaneous regression of total mortality on both O_3 and PM_{10} yielded significant coefficients for each. The PM_{10} mean effect (at 41 $\mu g/m^3$) was reported to be 2.3% of total mortality. However, the authors found that it was not possible to separate the PM_{10}-mortality association from that for the other particulate matter metrics considered.

Kinney et al. (1995) investigated total daily mortality in Los Angeles, CA during 1985-1990 (mean = 153 deaths/day), relating it to PM_{10}, O_3, CO, temperature, and relative humidity in order to assess the sensitivity of the PM-mortality association to model type and model specification. Pollution data were averages of all sites available (e.g., 4 for PM_{10} and 8 for O_3 and CO) after first filling in missing days at each site based on available data from other sites (thereby addressing error from day to day variation in site availability). Although the data were collected over 6 years, the PM_{10} sampling was conducted only every sixth day, so only 364 days could be included in the analyses, limiting the power of the analysis to detect associations. Poisson models were employed which addressed seasonal long wave influences by including sine and cosine terms ranging in periodicity from 1 to 24 mo in periodicity. OLS and log-linear models also considered. Weather was modeled initially by including only same-day maximum temperature and relative humidity in regressions, but sensitivity analyses also considered dummy variables for extreme temperature and up to 3-d lags of all weather variables. Winter and summer were also modeled separately. In these various analyses, PM_{10} was generally found to be significantly associated with mortality after

controlling for weather and season, with a relative risk (RR) estimate of approximately 1.05 (CI = 1.0 to 1.10) reported for a 100 $\mu g/m^3$ increase in PM_{10}. Durbin - Watson (DW) statistics indicated only modest autocorrelation in these models ($1.8 < DW < 2.0$). The PM_{10}-mortality association was found to be only mildly sensitive to modeling method. However, CO was also significantly associated with mortality, and the simultaneous inclusion of either CO or O_3 to the PM_{10} model lowered the significance of PM_{10} in the model noticeably, but affected the coefficient less. The correlations among the pollutant's coefficients in this model were, however, significant ($r_\beta(PM_{10}\text{-}CO) = -0.4$; $r_\beta(PM_{10}\text{-}O3) = -0.5$). Therefore, despite the effort made to maximize the quality of the exposure estimates and to appropriately address the statistical and multi-pollutant aspects of the analysis, the PM-mortality association was not completely separable from other copollutants. In this sense, these results are quite similar to those found previously for L.A. (Kinney and Ozkaynak, 1991).

Ito et al. (1995) considered total daily mortality during 1985-1990 in L.A., CA (mean = 153 deaths/day) and Chicago, IL (mean = 117 deaths/day) in their investigation of the role of monitoring site choice on PM_{10} health effects analyses results. Poisson models were used which included four sine and cosine terms ranging from 1 to 24 mo in periodicity to control for season, day of week dummy variables, a linear trend term, and temperature. In each city, multi-site averages were computed for each pollutant considered (PM_{10} and O_3) after missing day's values were estimated at each site from other data available for that day. Also, simple daily averages of all available data were computed (without filling missings), and each site's raw data were also individually analyzed. The average of the multiple sites' PM_{10} was found to be significantly associated with total mortality in each city after controlling for season, temperature, and O_3. However, while the O_3 coefficient was only moderately correlated with the PM_{10} coefficient ($r_\beta = -0.2$), other potentially more correlated pollutants (e.g., CO, SO_2, or NO_2) were not considered in this basic model specification. Also, the size and significance of the PM_{10} coefficient in mortality regressions varied widely among the individual sites. The authors concluded that: "Thus, identification of a single causal pollutant, based simply on the strength of association with a health effect outcome without evaluation of attenuation/enhancement due to random/systematic errors in exposure estimates, may be misleading." Dividing the data by season also diminished the significance of PM_{10} in mortality regressions, as would be

expected due to reduced sample size. However, the PM_{10} coefficient was not as affected by season-specific analyses, indicating consistent associations throughout the year. Overall, multi-site averaging and larger sample sizes were shown to strengthen the PM_{10}-mortality association, but the results (and the fact that a very basic model specification was employed) leaves open the possibility that other co-pollutants or more elaborate weather specifications could account for part of the Chicago PM_{10}-mortality association.

Styer et al. (1995) considered total, respiratory, circulatory, and cancer deaths in Cook County, IL (Chicago) and elderly total deaths in Salt Lake County, UT. The mean number of total, respiratory circulatory, and cancer deaths in Cook County were 117 for all nonaccidental causes, 83 of them elderly (age 65 and over), 10 from respiratory causes (ICD 9 codes 11, 35, 472 to 519, 710.0, 710.2, 710.4), 56 from circulatory causes (ICD 9 codes 390 to 459), 28 from cancer (ICD 9 codes 140 to 209) per day. They also broke down total mortality by race and by sex. There were two daily PM_{10} stations in Salt Lake County, one daily station and up to 12 measurements per day from other monitoring stations in Cook County. Models were fitted using Poisson regression, with adjustments for mean daily temperature, specific humidity, and average daily pressure, but with no other air pollutant in the model. Pollen counts and other meteorological variables were evaluated but were not found to significantly improve one fitted model; semi-parametric and parametric models for PM_{10} were tested, with lags up to 5 days. Seasonal adjustments were significant.

The overall PM_{10} effect was found to be statistically significant overall in Cook County. Spring and Autumn showed significant PM_{10} effects, whereas Winter and Summer did not. Elderly mortality had twice the excess risk of total mortality. Respiratory deaths in Cook County had nearly three times the response to PM_{10} as total mortality, but was only marginally significant. The cancer death effect of PM_{10} was about twice as high as for all cause mortality and statistically significant, unlike findings by Schwartz and Dockery (1992a) for Philadelphia using TSP. Styer et al. (1995) also found no effect of PM_{10} on elderly mortality in Salt Lake County. The best PM_{10} predictor for most of the Cook County analyses performed by Styer et al. (1995) was a 3-day moving average (lags 0, 1, 2). While often PM_{10} lags were evaluated, no other pollutants were tested. Relative risks are reported in Tables 12-3, 12-5, and 12-6. The total mortality RR for 50 $\mu g/m^3$ in Cook County can be estimated as 1.04 (95% confidence interval 1.00 to 1.08) and is consistent with other studies.

Ostro et al. (1995a) considered total, respiratory, and cardiovascular daily deaths (mean = 55, 8, and 18 deaths/day, respectively) in Santiago, Chile during 1989-1991, examining their relationship to ambient PM_{10}, O_3, SO_2, and NO_2, and to daily minimum and maximum temperature and humidity. To improve exposure estimate representativeness, multiple sites' daily data were averaged for each pollutant (e.g., 4 sites for PM_{10}), though the maximum from all 4 PM_{10} sites for each day was also considered in some analyses. In this work, most regressions employed the log of PM_{10}, as it showed the highest associations with total mortality in exploratory analyses. OLS regression was employed for most total mortality regressions because a test of normality was not rejected for the total mortality data, though Poisson regressions were employed for cause-specific analyses, in view of their lower daily counts. Also, sensitivity analyses were conducted for various model types: the total mortality RR of the mean PM_{10} concentration (115 $\mu g/m^3$) ranged from 1.04 to 1.09 (1.12 with a 3-day average mean PM_{10} employed). Seasonal influences were alternatively addressed by various methods, including seasonal stratification, the inclusion of sine/cosine trigonometric terms for 2.4, 3, 4, 6, and 12 mo periodicities, prefiltering, and the use of various non-parametric fits of temperature: the PM_{10} RR estimate ranged from 1.04 to 1.11, with the lowest mean PM_{10} risk provided by the OLS model with 5 trigonometric terms included (RR = 1.04). Investigations of mortality by-cause and age indicated that the strongest PM_{10} associations were for respiratory-specific deaths (RR = 1.15) and for the elderly (RR = 1.11). Other pollutants were also considered separately and simultaneously with PM_{10} in a total mortality regression which also contained 36 dummy variables (one for each month of the study). In this model, the individually significant pollutants were: log(PM_{10}) (RR at mean = 1.05 ; CI = 1.01 to 1.08); SO_2 (RR at mean = 1.01; CI = 1.00 to 1.03), and; NO_2 (RR at mean = 1.02 ; CI = 1.01 to 1.04). Thus, all three pollutants had similar levels of significance in this model. Neither the log of SO_2 nor the log of NO_2, were investigated, however. In multi-pollutant regressions, only log(PM_{10}) stayed significant. The intercorrelations of the various pollutants' coefficients in this model were not reported, but they were likely high, given that the pollutants themselves were highly intercorrelated over time, e.g., r(PM_{10}-NO_2) = 0.73. Overall, these results suggest that, of the pollutants considered, PM_{10} is the air pollutant most strongly associated with mortality in

TABLE 12-5. COMPARISON OF RELATIVE RISK (RR) ESTIMATES FOR TOTAL MORTALITY FROM 50 $\mu g/m^3$ CHANGE IN PM_{10}, USING STUDIES WHERE PM_{10} WAS MEASURED OR WAS CALIBRATED FOR THE SITE

Study	Reference	PM_{10} ($\mu g/m^3$)		Other Pollutants In Model	Lag Times, d	RR per 50 $\mu g/m^3$	95 Percent Confidence Interval
		Mean	Maximum				
Utah Valley, UT	Pope et al.(1992)	47	297	None	≤ 4 d	1.08	(1.05, 1.11)
				None, winter	≤ 4 d	1.085	(1.03, 1.35)
				None, summer	≤ 4 d	1.11	(0.92, 1.35)
				Max O_3, summer	≤ 4 d	1.19	(0.96, 1.47)
				Avg O_3, summer	≤ 4 d	1.14	(0.92, 1.41)
St. Louis, MO	Dockery et al. (1992)	28	97	None	≤ 3 d	1.08	(1.005, 1.15)
				O_3	≤ 3 d	1.06	(0.98, 1.15)
Kingston, TN	Dockery et al. (1992)	30	67	None	≤ 3 d	1.085	(0.94, 1.25)
				O_3	≤ 3 d	1.09	(0.94, 1.26)
Birmingham, AL	Schwartz (1993)	48	163	None	≤ 3 d	1.05	(1.01, 1.10)
Athens, Greece	Touloumi et al. (1994)	78	306	None	1 d	1.034	(1.025, 1.044)
				SO_2, CO	1 d	1.015	(1.00, 1.03)
Toronto, ON Canada	Özkaynak et al. (1994)	40	96	None	0 d	1.025	(1.015, 1.034)
Los Angeles, CA	Kinney et al. (1995)	58	177	None	1 d	1.025	(1.00, 1.055)
				O_3, CO	1 d	1.017	(0.99, 1.036)
Chicago, IL	Ito et al. (1995)	38	128	O_3, CO	≤ 3 d	1.025	(1.005, 1.05)
Santiago, Chile	Ostro et al. (1995a)	115	367	None	1 d	1.04	(1.035, 1.06)
				None	≤ 4 d	1.07	(1.04, 1.10)
				None, Poisson	1 d	1.022[a]	(1.003, 1.042)
				SO_2, Poisson	1 d	1.026[a]	(1.005, 1.047)
				NO_2, Poisson	1 d	1.043[a]	(1.020, 1.066)
				O_3, Poisson	1 d	1.026[a]	(1.005, 1.047)
Chicago, IL	Styer et al. (1995)	37	365	None	3 d	1.04	(1.00, 1.08)

[a]Calculated on basis of 50 $\mu g/m^3$ increase, from 50 to 100 $\mu g/m^3$.

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TABLE 12-6. BASIS FOR EVALUATION OF TIME SERIES STUDIES ON PM_{10}-MORTALITY CITED IN TABLE 12-5.

Study	Reference	Period	Other Pollutants In Model	Lag Addressed		Multiple Methods	Correl. of B's Given	
				Pollutants	Temp			
Utah Valley, UT	Pope et al. (1992)	1985-1989	None	0-4 d	≤ 1 d	Yes	No	1,436
St. Louis, MO	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, NO_2, O_3	≤ 3 d	≤ 1 d	No	No	311
Kingston, TN	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, $NO_{2.5}$, O_3	≤ 3 d	≤ 1 d	No	No	330
Birmingham, AL	Schwartz (1993)	1985-1988	None	0-3 d	≤ 3 d	Yes	No	1,087
Athens, Greece	Touloumi et al. (1994)	1984-1988	SO_2, CO	1 d	1 d	Yes	No	1,684
Toronto, ON Canada	Özkaynak et al. (1994)	1972-1990	TSP, $PM_{2.5}$, SO_4, O_3, COH, NO_2, SO_2	0 d	0 d	No	No	6,506
Los Angeles, CA	Kinney et al. (1995)	1985-1990	O_3, CO	1 d	≤ 3 d	Yes	Yes	364
Chicago, IL	Ito et al. (1995)	1985-1990	O_3, CO	≤ 3 d	≤ 3 d	No	Yes	1,357
Santiago, Chile	Ostro et al. (1995a)	1989-1991	O_3, SO_2, NO_2	≤ 4 d	1 d	Yes	No	779
Chicago, IL	Styer et al. (1995)	1985-1990	None	≤ 5 d	≤ 2 d	Yes	No	1,357

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this setting. Moreover, sensitivity analysis suggest that the elderly having respiratory diseases are most susceptible to adverse effects from ambient air pollution excursions.

A reanalysis of deaths in Utah Valley, UT, from 1985 to 1992 was carried out by Lyon et al. (1995). The data were extensively categorized by year, season, cause, age, and place of death. Based on quintile plots, the authors concluded that excess mortality increased steeply at about 50 $\mu g/m^3$ and consequently used only a dichotomous indicator of PM_{10} greater than 50 $\mu g/m^3$, rather than any linear or nonlinear function of PM_{10}. No other pollutants were used, and the only meteorological variable used in the model was minimum daily temperature. Relative risk (called rate ratio) was calculated from a Poisson regression model without time series structure adjustment by GEE. However, a linear time trend was used to adjust for decreasing mortality rates over the years. The authors found an apparently random pattern of increased RR, by year, season, age, cause, and place of death. Among their results, they noted the following: strongest effect in spring, not winter; largest contribution to excess mortality from age 75 and over dying in hospital; largest RR for ages 15 to 59 dying at home from cancer; increased RR for sudden infant death syndrome.

The choice of a 5-day mean PM_{10} as the exposure metric was based on an earlier study (Pope et al., 1992). However, dichotomizing the PM_{10} metric at 50 $\mu g/m^3$ may have cost a great deal of useful information, possibly including a substantial exposure measurement error or misclassification problem. Since this PM_{10} metric cannot be scaled to RR increments over other ranges of values, we were not able to include this study in the subsequent tables of this section. However, the authors estimate an excess mortality of 4% for PM_{10} above 50 $\mu g/m^3$, roughly consistent with other studies.

12.3.1.2 Short-Term PM_{10} Exposure Associations With Total Daily Mortality: Syntheses of Studies

Most of the studies summarized in Table 12-3 and discussed in more detail above considered daily mortality in the entire population (i.e., all ages) and due to all causes, though some also considered sub-populations. Considering all these studies in one overall assessment of PM effects on mortality is not a straightforward task, given the variety of models and model specifications employed but, as noted above, this has been attempted previously. Table 12-4 presents a synthesis of two recently published summaries of the PM literature which attempted to convert all results to a PM_{10}-equivalence basis and provide

quantitative intercomparisons (Ostro, 1993; Dockery and Pope, 1994). As also noted above, other such summaries have been conducted using TSP as the reference PM metric (Schwartz, 1991; Schwartz, 1994b), but many of the same studies were considered in those two PM_{10}-equivalent summaries, so the TSP-equivalent results are not tabulated here.

The results presented in Table 12-4 suggest about a 1 percent change in acute total mortality for a 10 $\mu g/m^3$ change in PM_{10}, but the estimates range from 0.3 to 1.6% (i.e., a factor of 5). While most of the 95% confidence intervals (CI's) of these estimates overlap, CI's of the highest and lowest estimates do not overlap, indicating significant differences between these estimates. Note that the effects indicated here for a 10 $\mu g/m^3$ change cannot be consistently converted to other PM increments (e.g., 50 or 100 $\mu g/m^3$ PM_{10}), as differences in model specification (e.g., linear versus log models) will cause them to differ in their conversions to other particle concentration levels. The reasons for the approximately five-fold effect estimate difference noted among studies are not obvious from the information provided by these references, but one factor appears to be the PM exposure averaging time, as estimates using multiple day PM_{10} averages are all 1% or higher. This is not unexpected, given that any lagged effects from prior days of PM_{10} exposure will be added to the effects estimate when a multi-day average is employed, increasing the estimated effect on a per $\mu g/m^3$ basis. It is also important to note that other air pollutants have generally not yet been addressed in reaching the coefficients reported here. Also, coefficient variation is to be expected, given that the composition (and, therefore, toxicity) of the PM, as well as the population make-up, in each city can be expected to differ. Moreover, the conversions from other PM metrics to PM_{10} must necessarily introduce additional uncertainty. This is made apparent here when comparing the estimates for Santa Clara, CA from these two sources, each having its own, somewhat different, estimate of the equivalent PM_{10} and of the PM_{10} effect. Although not all of these results may therefore be the most appropriate available for quantifying a PM_{10} effect, they do consistently indicate an association between acute PM exposure and increased daily mortality. Moreover, the by-cause results also reported in these summaries indicate that PM effect estimates are greater for respiratory causes, lending support to the biological plausibility of the PM associations being causal.

In an attempt to better quantify the daily PM_{10}-total acute mortality association indicated by the above discussions, Table 12-5 presents a summary of the total mortality

relative risks (RR) of a 50 $\mu g/m^3$ increase in PM_{10} estimated from nine studies reviewed in the above section which employed PM_{10} data in their analysis of total mortality data (or which had on-site PM_{10} reference data to convert other PM metrics with more certainty). This selection of studies does not in any way mean to dismiss the other studies discussed above as less important: these studies are selected for this analysis solely because they can most readily be intercompared and referred to the present PM_{10} standard. The RR's calculated were based upon a 50 $\mu g/m^3$ increase above the mean PM_{10}, which is the order of magnitude of the difference between the maximum and mean in these cities and roughly approximates the estimated effects of a typical day experiencing an exceedance of the present PM_{10} standard, relative to the average case. This is important to note, because in non-linear models such as were often employed in the studies in Table 12-4, the RR estimate associated with a given $\mu g/m^3$ PM_{10} increase will vary depending upon the baseline concentration to which it is added.

From the results presented in Table 12-5, it is apparent that these studies generally have yielded at least marginally significant PM_{10} coefficients, but that the resultant excess risk estimates vary by a factor of five across these studies (from 1.5% to 8.5% per 50 $\mu g/m^3$). The mean and maximum PM_{10} concentration data are noted for each study. If the PM_{10} coefficient decreased as the mean level of PM_{10} decreased, then confounding would be suggested. However, the data presented indicate that the variability in coefficients is not a function of PM_{10} level, as sites with high or low PM_{10} concentrations can report either high or low RR's. In Table 12-6, an attempt is made to concisely summarize the statistical methodology characteristics of each study, in order to determine if any of these factors are important to the variability observed from study to study in the PM_{10} RR estimate. Of all factors examined in this table, the one consistently present with higher PM_{10} RR's is when other pollutants have not been simultaneously considered in the model. Indeed, those studies which considered PM_{10} both alone and with other pollutants in the model yielded consistently smaller (and usually more marginally significant) PM_{10} relative risks when the other pollutants were simultaneously considered. This influence ranges from roughly a 20 to 50 percent reduction in the excess risk associated with 100 $\mu g/m^3$ in PM_{10} (e.g., in Athens, Greece, the PM_{10} RR declines from 1.07 to 1.03 when other pollutants are considered). However, such a reduction is to be expected when co-linear variables are added, and the

"true" PM_{10} RR is likely to lie between the single pollutant and multi-pollutant model estimates.

Another factor which clearly affected the PM_{10} RR from some of the studies listed in Table 12-5 was the PM_{10} averaging period. Both of the studies which utilized multi-day averages of PM_{10} in their regressions (i.e., Utah Valley, UT and Birmingham, AL) are among the higher RR estimate studies. As discussed above, this would be expected, but the increase indicated for these studies is not as large as might be expected. Indeed, in sub-analyses included by Pope et al. (1992), the PM_{10} mortality risk is indicated to be roughly doubled by using a five day average versus a single day concentration, while sub-analyses presented by Ostro et al. (1995) for Santiago also indicate approximately a doubling in the PM_{10} RR when a 3 day average is considered (i.e., from RR = 1.04 for a single day PM_{10} value to RR = 1.07 for a 3d average PM_{10} value). This may be due to the fact that, since autocorrelation exists in the PM_{10} concentrations from day to day, the single day concentration is "picking up" some of the effect of multi-day pollution episodes, even though they are not explicitly modeled. Also, most studies show a maximum same-day or one day lag PM-mortality association, with the PM_{10} "effect" dropping off on subsequent days. These results suggest that a multi-day average PM_{10} concentration may provide a more relevant index to gauge the effects of acute PM_{10} exposures than the present single-day based PM_{10} standard. However, the present standard is in terms of a one-day concentration, so these estimates, while no more valid than those for a multi-day average, are more directly relevant to the present regulatory process, and will be examined further.

It appears from Table 12-5 that the total acute mortality relative risk estimate associated with a 50 $\mu g/m^3$ increase in the one-day 24-h average PM_{10} can range from 1.015 to 1.085, depending upon the site (i.e., the PM_{10} and population composition) and also upon whether PM_{10} is modeled as the sole index of air pollution or not. Relative Risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the PM_{10} RR with multiple pollutants in the model range from 1.015 to 1.025. The former range might be viewed as approximating an upper bound of the best estimate, as any mortality effects of co-varying pollutants are likely to be "picked up" by the PM_{10} index, while the multiple pollutant model range might be viewed as approximating a lower bound of the best estimate, as the inclusion of highly correlated covariates are likely to weaken the PM_{10}

estimate, even if they are not themselves causal. Both estimates should be considered in assessing the potential effects of PM_{10}. Overall, consistently positive PM-mortality associations are seen throughout these analyses, despite the use of a variety of modeling approaches, and after controlling for major confounders such as season, weather, and co-pollutants, with the 24-h average 50 $\mu g/m^3$ PM_{10} total mortality effect estimate apparently being in approximately the RR = 1.025 to 1.05 range.

12.3.1.3 Short-Term PM_{10} Exposure Associations with Daily Mortality in Elderly Adults

Of the studies in Table 12-3 and/or discussed above, only a few directly examined the elderly as a potentially sensitive sub-population. Certainly, since the highest mortality rates are among the elderly, this is a population which surely dominated the total mortality analyses discussed above, and it is therefore logical to assume that the bulk of the total mortality effects suggested by these studies are among the elderly. Also, as noted earlier, during the historic London, 1952 pollution episode the greatest increase in mortality rate was among older citizens and those with respiratory diseases. However, the analysis of deaths in the elderly population in France by Derriennic et al. (1989) discussed previously found no associations with TSP, while SO_2 was associated with total elderly deaths in both cities studied. No PM_{10} or fine particle metric was considered, however. Similarly, Li and Roth (1995) did not find a significant association between TSP and daily deaths in the elderly. However, an analysis by Schwartz (1994c) of mortality in Philadelphia, PA during 1973 through 1980 comparing mortality during the 5% highest versus the 5% lowest TSP days found the greatest increase in risk of death in those aged 65 to 74 and those >74 year of age (mortality risk ratios = 1.09 and 1.12, respectively, between high and low TSP days). Also, in their time series analyses of Philadelphia daily mortality during this period, Schwartz and Dockery (1992a) found a significantly higher TSP-mortality coefficient ($\beta = 0.000910 \pm 0.000161$) for persons older than 65 years of age than for the younger population ($\beta = 0.000271 \pm 0.000206$). These coefficients indicated an effect size for the elderly roughly three times that for the younger population (10% versus 3%, respectively, for a 100 $\mu g/m^3$ TSP increase).

In addition, two recent PM_{10} analyses directly considered the question of PM_{10}-mortality associations among the elderly population ($\geq$ 65 years of age), and these provide further relevant insights into this question. The first of these two analyses was conducted by Saldiva and Bohm (1994) during May 1990 through April 1991 in Sao Paulo. Environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but was instead evaluated via beta gauge instruments calibrated to mass. Pollutants were considered in the analysis in the form of 2-day moving averages of concentration (i.e., averages of the same-day and the prior day's concentration). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8

sites for PM_{10}). Multiple regression models estimated the association between daily mortality and air pollution controlling for month of year, temperature, relative humidity, and day of week. Because of the large number of daily deaths (mean = 63/day), Gaussian regression models were appropriately used for the basic analysis. Poisson models using the generalized estimating equation of Liang and Zeger (1986) were also applied for comparison. Temperature effects were crudely accounted for through the use of three dummy variables ($T < 8$ °C; 8 °C $\leq T \leq$ 12 °C; 13 °C $\leq T \leq$ 18 °C) in the basic = model. Regression results indicated that, when studied separately, PM_{10}, SO_2, NO_x, and CO were all significantly associated with mortality. In a simultaneous regression of mortality on all pollutants, however, PM_{10} was the only pollutant that remained significant. In fact, the PM_{10} coefficient actually increased, suggesting confounding among these correlated pollutants. Thus, as noted by the authors, "the close interdependence exhibited by the concentrations of measured pollutants suggests that one has to be cautious when ascribing to a single pollutant the responsibility of causing an adverse health effect". Nevertheless, multiple regression models, including those considering all pollutants simultaneously, consistently attributed the association found with mortality among the elderly to PM_{10}. The reported PM_{10} relative risk (RR = 1.13 for a 100 $\mu g/m^3$ increase) is higher than noted above for total mortality studies addressing multiple pollutants (100 $\mu g/m^3$ RR $\approx$ 1.03 to 1.05), supporting past observations that the elderly represent a population especially sensitive to health effects of air pollution.

A second recent study directly examining PM_{10}-mortality associations in the elderly was that by Ostro et al. (1995) in Santiago, Chile. For the overall population, the PM_{10} 100 $\mu g/m^3$ RR estimate was 1.08, but for the population aged 65 and greater, it rose to an estimate of RR = 1.11 in the same model specification. Thus, these directly comparable estimates (i.e., using the same model specification and population) suggest that the elderly experience roughly a 40 percent higher excess risk from exposure to PM air pollution than the total population.

Overall, considering the historical pollution episode evidence and the results of recent PM_{10}-mortality analyses considering elderly populations, it seems evident that elderly adults represent a population especially at risk to the mortality implications of acute exposure to air pollution, including PM.

12.3.1.4 Short-Term PM_{10} Exposure Associations with Daily Mortality in Children

As with analyses of PM-mortality associations for the elderly, few studies have directly examined PM-mortality associations in children. While the previously discussed London Fog episode yielded the greatest increased risk in the older population (e.g., the episode mortality risk versus the week before the episode increased by a factor of 2.74 for persons >45 years old), the second highest increase in risk was in the neo-natal group (ratio = 1.93 for children < 1 year) (United Kingdom Ministry of Health, 1954). More recently, as described above, Schwartz (1994c) examined increased risk of death in Philadelphia, PA for relatively high versus low TSP days during 1973 to 1980 by age, concluding that no pattern of increased risk emerged until age 35 and above (e.g., the high/low TSP mortality ratio for < 1 year of age was 1.01). The author noted increased risk of death on high PM days for children 5 to 14 years old, which he suggested may be due to their greater time spent outdoors than other ages, though he notes that the small numbers of deaths in this age group suggest caution in such interpretations.

A recent analysis of PM_{10} pollution and mortality in Sao Paulo, Brazil provides further insight into the potential mortality effects of PM_{10} on children. Saldiva et al. (1994) studied respiratory mortality among children < 5 yrs old in Sao Paulo during May 1990 to April 1991. The environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but was evaluated via beta gauge instruments calibrated to mass. Pollutants were considered in the analysis in the form of 3-day moving averages of concentration (i.e., averages of the same-day and the two prior day's concentrations). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8 sites for PM_{10}). Prior to the analysis, mortality counts were adjusted using a square root transformation to address their non-normal distribution, which results in part from low daily counts (mean = 3.0 deaths/day). Season was addressed by including both seasonal and monthly dummy variables in all regressions. Weather was only crudely addressed, in that only two dummy variables for extreme temperature and two for extreme relative humidity were considered. Day-of-week effects were addressed by the inclusion of six dummy variables, but none were significant. Autocorrelation was not directly addressed in the analyses. Despite the limited data set size, a significant mortality association was found with NO_x, but not with any other pollutant. No such association was found for

non-respiratory mortality, which is supportive of the interpretation of the air pollution-respiratory mortality association as causal. In the multiple pollutant model, the PM_{10} coefficient actually becomes negative (though non-significant), which is likely due to its high intercorrelation with NO_x over time ($r = 0.68$). The high interdependence between NO_x and most of the other pollutants caused the authors to note that "interplay among pollutants causing respiratory damage is very difficult to exclude". Thus, while there appeared to be an air pollution association with mortality in children in this case, this study found the strongest association with NO_x, though the high intercorrelation among pollutants makes it difficult to designate the effects noted to any one pollutant in this case.

Overall, there is an indication among these various analyses that children may be more susceptible to the mortality effects of air pollution exposure than the population in general, but it is difficult, given the limited and somewhat conflicting available results to ascribe any such association to PM pollution in particular.

12.3.1.5 Short-Term PM_{10} Exposure Associations with Daily Mortality in Other Susceptible Subgroups

Throughout the results and discussions presented above regarding the effects of acute PM exposure on human mortality, a consistent trend was for the effect estimates to be higher for the respiratory mortality category. As discussed above, this lends support to the biological plausibility of a PM air pollution effect, as the breathing of toxic particles would be expected to most directly affect the respiratory tract, and these results are consistent with this expectation. For example, the respiratory mortality relative risk estimates presented in Table 12-4 are all higher than the risks for the population as a whole. Of particular interest is to compare the relative risk values for each study, which yield the most direct and appropriate comparisons. In the case of the Santa Clara study (Fairley, 1990), the respiratory mortality RR of PM was 4.3 times as large as for deaths as a whole (i.e., 3.5/0.8, in Table 12-4). In the case of the Philadelphia, PA study (Schwartz and Dockery, 1992a), the respiratory mortality RR of PM was 2.7 times as large as for death as a whole (i.e., 3.3/1.2, in Table 12-4). In the case of the Utah Valley study (Pope et al., 1992), the respiratory mortality RR of PM_{10} was 2.5 times as large as for deaths as a whole (i.e., 3.7/1.5, in Table 12-4). In the case of the Birmingham, AL study (Schwartz, 1994), the respiratory mortality RR of PM_{10} was 1.5 times as large as for deaths as a whole (i.e.,

1.5/1.0, in Table 12-4). More recently, the Santiago, Chile PM_{10} study by Ostro et al. (1995a), reported that the respiratory mortality RR of PM_{10} was 1.8 times as large as for deaths as a whole (i.e., 1.15/1.08 RR for a 100 $\mu g/m^3$). Thus, in these studies, the PM RR for respiratory diseases is indicated to range from 50 to over 400% higher for respiratory disease categories than for all causes of death, indicating that increases in respiratory deaths are a major contributor to the overall PM-mortality associations noted previously. Moreover, since evidence suggests that an acute pollution episode is most likely be inducing its primary effects by stressing already compromised individuals (rather than, for example, inducing chronic respiratory disease from a single air pollution exposure episode), the above results indicate that persons with pre-existing respiratory disease represent a population especially at risk to the mortality implications of acute exposures to air pollution, including PM.

In overall summary, the time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution can cause increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels, and suggest that such effects extend below the present U.S. air quality standards. Furthermore, these new PM studies are consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. Overall, the PM_{10} relative risk estimates derived from the most recent PM_{10} total mortality studies suggest a 24-h average 50 $\mu g/m^3$ PM_{10} acute exposure effect of the order of RR = 1.025 to 1.05 in the general population, with higher relative risks indicated for the elderly sub-population and for those with pre-existing respiratory conditions, both of which represent sub-populations especially at risk to the mortality implications of acute exposures to air pollution, including PM.

12.3.2 Morbidity Effects of Short-Term PM Exposure

12.3.2.1 Hospitalization and Emergency Visit Studies

Introduction to Hospitalization Studies

Hospitalization for a respiratory illness diagnosis can provide a measure of the respiratory morbidity status of a community during a specified time frame. Such respiratory diagnosis include hospitalization for asthma, pneumonia and influenza. Various factors affect the epidemiology of admissions for these diagnosis. Thomson and Philion (1991) suggest

some factors shown to be independently associated with respiratory hospitalization include poor socioeconomic level, lack of breast feeding, type of heating, and exposure to second-hand tobacco smoke.

In the last decade, large increases have occurred in asthma hospitalization rates in the pediatric population. While this pattern has been seen in all age, race and gender groups the most severely affected group were urban blacks (Gerstman et al., 1993). This increase was largest among 0 to 4 years old with blacks having approximately 1.8 times the increase of whites (Gergen and Weiss, 1990). During this time total hospitalization decreased while admissions for lower respiratory tract disease also had a slight decrease (Gergen and Weiss, 1990).

There are differences in the frequency of admission for asthma by age and gender (Skobeloff et al., 1992). Asthma morbidity is known to exhibit seasonal periodicity. For persons ages 5 through 34 years hospitalization peaked in September through November whereas mortality trends peaked in June through August. For individuals 65-years-old or older, both asthma hospitalization and mortality demonstrated increases during December through February (Weiss, 1990). Crane et al. (1992) states that the most valid and reliable marker of asthma readmission is the number of hospitalization admissions for asthma in the previous 12 mo. In New York City, Carr et al. (1992) found large geographic variations for asthma hospitalization with the highest rate concentrated in the city's poorest neighborhoods. The patients are heavily dependent on hospital outpatient departments and emergency rooms for their ambulatory care. Differences in medical practice styles, reflecting the exercise of physicians discretion in the way illnesses are treated, are important determinants of temporal variation and geographic variation in hospital utilization for many medical conditions.

Storr and Lenney (1989) observed a long term variation in children's hospitalization for asthma and school holidays. The admission rate fell during holidays and there were two or more peaks during terms. The pattern is consistent with a largely viral etiology for asthmatic attacks throughout the year. They postulated that school holidays disrupt the spread of viral infectious in a community, with synchronization of subsequent attacks. Travel during holidays may facilitate acquisition of new viral strains by the community.

Based on a total of 450,000 hospitalizations for asthma and an estimated U.S. population of 10,000,000 asthmatics, the incidence of hospitalization for all asthmatic subjects is about 45 per 1,000 asthmatics (National Institutes of Health, 1991).

Beard et al. (1992) evaluated interobserver variability during data collection for a population based study of asthma using medical record information. The results suggested that data collection was carried out reliably in this study. Osborne et al. (1992) evaluated the diagnosis of asthma in 320 inpatient and outpatient records bearing the diagnosis of asthma for the period 1970 through 1973 and 1980 through 1983 in a health maintenance organization (HMO). The majority of charts examined exhibited a clinical picture consistent with asthma. The increases in "definite asthma" among outpatients from the 1970s to the 1980s reflected increasing chart documentation among physicians. Jollis et al. (1993) study of hospital insurance claim information to include medicare indicated that insurance claim data lack important diagnostic and pragmatic information when compared with concurrently collected clinical data in the study of ischemic heart disease as an example.

Wennberg et al. (1984) found that hospital admissions for the following diagnosis related groups showed a very high variation by hospital market area: pediatric pneumonia, pediatric bronchitis and asthma, chronic obstructive lung disease, and adult bronchitis and asthma. Richardson et al. (1991) found that adjusted admission rates for respiratory distress (COPD, asthma, bronchitis, and pneumonia) varied up to 3.09-fold between the highest and lowest hospital market areas in 1986 for the state of Ohio. The reasons for differences between hospital market areas are found in the incidence of illness, variability of local resources, access to care, practice styles of area physicians, numbers of physicians and pulmonologists, inconsistencies in diagnoses, conflicting treatment methodologies, lack of consensus of care, quality of outpatient care, and varying criteria for admission among principal variables. For example, Wennberg et al. (1984) documented great geographic variability in hospital admission rates for adult community acquired pneumonia. This variation suggests that physicians do not use consistent criteria for hospitalization. Specific indications for admission do exist such as the Appropriateness Evaluation Protocol (AEP). Substitution of outpatient for inpatient care is a major strategy promoted to reduce health care cost and as such the majority of patients with community acquired pneumonia are treated as outpatients.

Fedson et al. (1992) state that vaccination practices may play a role in hospitalization rates for influenza and associated respiratory disorders. Despite public health recommendations for influenza vaccination for elderly persons, the vaccine has not been widely used, in the United States only 32% of elderly persons may be vaccinated each year. During the influenza outbreak period most persons with respiratory conditions requiring hospitalization (92%) resided in the community rather than in personal care homes. Also while previous epidemiologic studies arbitrarily defined outbreak periods as the first three months of the year this study indicated that hospitalization discharges for influenza occurred during the period December 1 through February 28.

The number and rate of patients discharged by age and first-listed diagnosis in the United States in 1991 are shown in Table 12-7 for all conditions, respiratory disease, heart and circulatory diseases and neoplasma. The number and rate for pneumonia of the respiratory diseases listed are highest for all ages primarily due to the high number and rate for 65 years and over. Disease of the respiratory system approximately represent 10% of all conditions. Specific diseases of the respiratory system are shown in Table 12-8 for 1992 in which five groupings predominate. Pneumonia organism unspecified is the largest group.

Hospital Admission Studies

This section discusses studies of hospital admissions, outpatient visits and emergency room visits, both within the United States and from countries with different medical care systems which may have different medical care practices. Most hospitalization studies consider at least two different classes of admissions. Thus, the studies were not grouped by class, but the tabled results are presented by class.

Bates and Sizto (1983, 1986, 1987) reported results of a study relating hospital admissions in southern Ontario to air pollution levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1985 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and $S0_2$ or COHs in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory admissions (both asthma and nonasthma) in summer and sulfates and ozone, but not to summer COH levels. However, Bates and Sizto note that the data analyses are now complicated by long-term trends in respiratory disease

TABLE 12-7. NUMBER AND RATE OF PATIENTS DISCHARGED FROM SHORT-STAY HOSPITALS, BY AGE AND FIRST-LISTED DIAGNOSIS: UNITED STATES, 1991[a]

First-listed diagnosis	ICD-9-CD code	All ages	Under 15 years	15-44 years	45-64 years	65 years and over	All ages	Under 15 years	15-44 years	45-64 years	65 years and over
		Number of patients discharged in thousands					Rate of patients discharged per 10,000 population				
All conditions		31,098	2,498	11,620	6,173	10,806	1,241.1	453.2	993.4	1,321.6	3,403.1
Diseases of the respiratory system	460-519	3,052	736	500	530	1,286	121.8	133.6	42.7	113.4	405.2
Acute respiratory infections	460-466	518	220	68	75	156	20.7	39.8	5.8	16.0	49.2
Pneumonia	480-486	1,088	214	133	152	589	43.4	38.9	11.4	32.5	185.5
Asthma	493	490	187	128	85	90	19.6	33.9	10.9	18.2	28.5
Diseases of the circulatory system including heart disease	390-459	5,338	28	396	1,509	3,405	213.1	5.1	33.9	323.1	1,072.4
Neoplasms	140-239	2,001	52	363	626	960	79.9	9.5	31.0	133.9	302.3

[a]Discharges from non-Federal hospitals. Excludes newborn infants. Diagnostic groupings and code number inclusions are based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CD).

Adapted from National Center for Health Statistics (1993).

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TABLE 12-8. NUMBER OF FIRST-LISTED DIAGNOSES FOR INPATIENTS DISCHARGED FROM SHORT-STAY NON-FEDERAL HOSPITALS, BY ICD-9-CM CODE, AGE OF PATIENT, AND GEOGRAPHIC REGION OF HOSPITAL: UNITED STATES, 1992-CON

First-listed diagnosis	ICD-9-CM code	Total	Age				Region			
			Under 15 years	15-44 years	45-64 years	65 years and over	Northeast	Midwest	South	West
		Number of first-listed diagnoses in thousands								
Diseases of the respiratory system	460-519	2,923	735	460	501	1,227	635	704	1,139	445
Acute Bronchitis	466	251	149	21	23	58	49	64	104	33
Viral Pneumonia	480	39	27	*	*	*	*	12	12	10
Pnuemoccal pneumonia	481	53	6	10	10	27	10	14	17	12
Other bacterial pneumonia	482	202	11	26	31	134	34	47	87	35
Pneumonia, other specified organisms	483	20	*	*	*	8	*	5	8	*
Broncho pneumonia, organism unspecified	485	45	16	*	*	22	9	9	22	5
Pneumonia, organism unspecified	486	700	145	87	108	360	134	177	287	101
Influenza	487	13	*	*	*	6	*	*	*	*
Bronchitis, unspecified	490	23	9	*	6	*	*	*	11	*
Chronic Bronchitis	491	201	*	7	52	141	45	40	86	30
Emphysema	492	29	--	*	8	18	6	8	12	*
Asthma	493	463	193	117	78	76	116	113	152	83

*Figure does not meet standard of reliability or precision.
Adapted from National Center for Health Statistics (1994).

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admissions unlikely related to air pollution, but they nevertheless hypothesize that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer but not in the winter. In a more recent paper, Bates and Sitzo (1987) extend the time period through 1983 and include additional air sampling data not available previously. The monitoring was from 17 air sampling stations and included O_3, sulfate fraction, SO_2, NO_2, and COH. Stepwise multiple regressions confirmed the earlier findings that there was a consistent summer relationship between sulfates and O_3 with hospital admissions. The analyses did not adjust for time trends, trends within the summer season, or serial correlation.

Lipfert and Hammerstrom (1992) conducted a 6-year study of hospital admissions in southern Ontario for 1979 to 1985. Daily hospital admissions were obtained from the Ontario Ministry of Health, the same data base used by Bates and Sitzo (1983, 1986, 1987). The primary focus of the study was on respiratory illness in one of the following ICD codes: 466 acute bronchitis, 480 to 482 or 485 pneumonia, 490 to 492 chronic bronchitis, emphysema, or 493 asthma. Three regions were defined with slightly different air pollution exposures, based on data from the Ontario Ministry of the Environment for SO_2, NO_2, O_3, sulfate fraction, COH, and TSP. Some stations monitored every three or six days and averages were taken by region for those monitors present. A Box-Jenkins ARIMA multiple regression model was used to analyze the data. Bivariate correlations were calculated between the pollutants and respiratory illness. Stepwise multiple regressions did not include TSP as a significant factor, but O_3 was significant for January and February and SO_2 was significant for some regions in July and August.

Burnett et al. (1994) studied hospital admissions in southern Ontario, using a broader area than that used by Bates and Sitzo (1983, 1986, 1987). The respiratory admissions were for 1983 to 1988 and were restricted to the ICD9 codes of 466, 480 to 486, 490 to 494, and 496. The non respiratory control admissions included the codes of 280 to 281.9, 345 to 347, 350 to 356, 358 to 359.5, 530 to 534, 540 to 543, 560 to 569, 571, 572, 574 to 578, 594, and 600. Twenty-two monitoring stations were used to estimate daily O_3 and sulfate fraction data; meteorological data came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random

effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). In general, O_3, sulfate fraction, and temperature were all predictors of hospital admissions; but O_3 tended to be more significant than did sulfate fraction. The models predicted about a 3% increase in respiratory hospital admissions for about a 14 $\mu g/m^3$ concentration of sulfate fraction.

Thurston et al. (1994) studied hospital admissions in the Toronto metropolitan area. during the months of July and August of 1986, 1987, 1988 and restricted to the following causes: total respiratory (ICD9 codes 466, 480, 481, 482, 485, 490 to 493), asthma (493), and non respiratory control (365, 430, 431, 432, 434, 435, 531, 543, 553.3, 537, 540, 541, 542, 543, 590). There were no stated restrictions on age. Pollution data consisted of acidity (H^+) and sulfate data measured at three sites during the three summer seasons. In addition, O_3, NO_2, and SO_2 and daily 24-h $PM_{2.5}$ and PM_{10} were measured at several other stations. Meteorological measurements were available from two of the monitoring sites. Ordinary least squares analyses were calculated after the environmental variables were detrended. The data for the three summers were combined. In general, O_3 was the strongest predictor of hospital admissions above the strong effect of temperature. There was some suggestion of an effect from PM_{10}, especially for total respiratory admissions. Non-linear temperature terms were not fitted.

Sunyer et al. (1991, 1993) studied daily emergency room admissions for COPD in adults in Barcelona, Spain. The original study included admissions for the years 1985 and 1986. A specially trained physician collected data from clinical records from the four largest hospitals in Barcelona. A panel of chest physicians defined expressions used to determine the diagnosis of COPD. Seventeen manual samplers and two automatic samplers took 24-h measurements of SO_2, black smoke, CO and O_3. Neither SO_2 nor black smoke exceeded the European Community standards. A Box-Jenkins ARIMA (auto-regressive integrated moving average) time series model was used to analyze the results. COPD was found to be related to SO_2, black smoke, and CO. The relationship with black smoke was especially pronounced for temperatures greater than 11.7° C. In the later paper, Sunyer et al. (1993) included the larger time period of 1985 to 1989. The study was restricted to individuals in the four largest hospitals at least 14 years of age. Fifteen manual samplers provided SO_2 and black

smoke measurements. Ridge regression (a modification of standard multiple linear regression) was used to analyze the daily admissions, but the analyses were done separately by season. Ridge regression is a conservative method of handling collinear variables, but it does not take into account the effects of non-normality of counts. Lag variables to adjust for the autocorrelation were selected according to the methodology of Box and Jenkins (1979). Significant changes in admissions were found for both SO_2 and black smoke for the winter season, but only SO_2 was significant in the summer.

Hospital admissions for all hospitals in the Birmingham, AL, SMSA were studied by Schwartz (1994e). The admissions were restricted to pneumonia (ICD-9 codes 480 to 487) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Birmingham stations reporting on a given day. The author used three different models for the analysis including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of pneumonia was found to be about 1.16 (1.05 to 1.28) corresponding to an increase of 100 $\mu g/m^3$ of PM_{10}. The relative risk of COPD was found to be about 1.24 (1.05 to 1.45) for an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with O_3 were found to be slightly weaker.

Schwartz (1994d) also studied hospital admissions for the elderly in Detroit, restricted to pneumonia (ICD-9 codes 480 to 486) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 or older were included in the analysis. Separate counts were constructed for asthma (493) and all other COPD (491 to 492 and 494 to 496). Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Detroit metropolitan area stations reporting on a given day. The author used three different approaches to the analysis, including a nonparametric approach. Serial correlation was adjusted for using autoregressive terms which were estimated using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The multiple logistic regression coefficient for

pneumonia was 0.00115 (0.00039) which corresponds to an odds ratio of about 1.06 (1.02 to 1.10) for an increase of 50 $\mu g/m^3$ of PM_{10}. The multiple logistic regression coefficient for COPD was 0.00202 (0.00059) which corresponds to an odds ratio of about 1.11 (1.04 to 1.17) for an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with O_3 were also found, but the dose response relationship was not as consistent.

Schwartz (in press) studied hospital admissions for all hospitals in Spokane, WA. The admissions were restricted to respiratory disease (ICD-9 codes 460 to 519) from January 1, 1988 to December 31, 1990. Only individuals $\geq$ 65 yrs were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Spokane stations reporting on a given day. PM_{10} values averaged 46 $\mu g/m^3$ with 10 and 90 percentile values of 16 and 83 $\mu g/m^3$. The author used three different models for the analysis, including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of respiratory disease was about 1.08 (1.04 to 1.14) corresponding to an increase of 50 $\mu g/m^3$ of PM_{10}. Associations were also found with O_3, giving a relative risk of 1.24 (1.00 to 1.54) for an increase of 50 $\mu g/m^3$. Inclusion of both pollutants in the model had little effect on either estimate.

Pönkä and Virtanen (1994) studied hospital admissions for exacerbations of chronic bronchitis (ICD-9 code 491) and emphysema (ICD-9 code 492) in Helsinki, Finland during 1987 to 1989. Individuals with the diagnosis of asthma (ICD9 code 493) were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two stations, and O_3 at one station; TSP was measured every other day at four stations and every third day at two stations. Meteorological information was available from a single station but the location was not specified. Daily admissions were analyzed using Poisson regression as described by McCullagh and Nelder (1989). The model included variables for season, day of week, year, and influenza epidemics. The authors report that the day of week variables effectively reduced the autocorrelation, and so autocorrelation terms were not included due to their difficulty of interpretation. For persons < 65 years old, the only effects seen were with SO_2 on the same day or three days previous. For individuals older than age 64, the only effect

seen was for NO_2 six days previous. Although these results are difficult to interpret, the study did not find any results suggesting a PM effect.

Pönkä (1991) also studied hospital admissions for asthma (ICD9 code 493) in Helsinki during 1987 to 1989. Persons with the diagnosis of bronchiolitis were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two and O_3 at one; TSP was measured every other day at four stations and every third day at two. Meteorological information was available from a single station. The analysis was done using simple and partial age specific correlations of asthma admissions with mean daily concentrations of SO_2, NO_2, NO, CO, TSP, O_3, temperature, wind speed and humidity. No adjustment was made for season or serial correlation. TSP was found to be significantly correlated with hospital admissions, but was less correlated than some of the other pollutants.

White et al. (1994) studied asthma outpatient clinic visits of children at Grady Memorial Hospital in Atlanta. The encounter forms for each child between June 1, 1990 and August 31, 1990 were abstracted, excluding visits when pneumonia or bronchiolitis was mentioned. Hourly O_3 measurements were available from two stations in the area. PM_{10} data were available from the middle of July, but data before that time had to be estimated using visibility data from Hartsfield International Airport. Clinic visits were increased when O_3 exceeded 0.11 ppm. Using a Poisson regression model, the estimated increase, as measured by a rate ratio, was 1.02 (CI = 0.96, 1.13) for a 10 $\mu g/m^3$ increase in PM_{10}.

Tseng et al. (1992) studied quarterly hospital discharges for asthma (ICD-9 Code 493) from the computerized hospital inpatient data base of the Medical and Health Department of Hong Kong. The study ran from the second quarter of 1983 to the last quarter of 1989. The discharges were split into four groups: under age 1, age 1 to 4, age 5 to 14, and adult. Quarterly averages of SO_2, NO_2, O_3, TSP and RSP values were obtained from the environmental protection unit of the Hong Kong Government. Multiple regression analyses were performed on the hospitalization rates using the four different age groups as the dependent variables and the pollution values as the independent values. Season and year were used as covariates, but no meteorological variables were included in the analyses. The significant correlations were between TSP and hospitalization rates for children aged 1 to 4 and children aged 5 to 14. The correlations for RSP tended to be similar, but smaller in magnitude.

Queirós et al. (1990) studied asthmatic admissions and Emergency Room visits to the Pediatric Department of the hospital de S. Joäo during the period from 1983 to 1987. The hospital serves the Oporto area of Portugal. Air pollution was estimated from measurements of SO_2 and black smoke (BS) taken daily at four stations. The admissions were adjusted so that the values represented deviations from the average for a particular month or year. No correlation was found between daily, monthly, or quarterly mean admissions or visits and BS levels but SO_2 levels were correlated with monthly mean admissions. The authors concluded that there was no evidence for pollution effects on admissions or visits.

During January 1985, large parts of Europe from western Germany to Great Britain experienced a pollution event that was traced to emission sources in Central Europe. This event was tracked by monitoring stations in several countries as it moved from east to west, and then finally dissipated over the North Sea. Very high levels of PM, SO_2, and NO_x were reported. Wichmann et al. (1989) studied mortality, hospital admissions, ambulance transports and outpatient visits for respiratory and cardiovascular disease in West Germany during the 1985 event. During that time, daily suspended particulate matter reached 600 μg/m, SO_2 reached 830 $\mu g/m^3$, and NO_2 reached 410 $\mu g/m^3$. Total mortality rose immediately with the increase in pollution (January 16, 1985), and reached a maximum on January 18. The increase in mortality was about 8 percent. Similarly, increases in hospital admissions (15 percent), outpatient visits (12 percent), and ambulance transports (28 percent) were seen. Wichmann et al. (1988a,b) reported on other events in 1986 and 1987 which related lung function changes to SO_2 levels but did not report PM data.

Walters et al. (1994) studied hospital admissions in Birmingham, England. The admissions were restricted to asthma or acute respiratory disease (ICD9 codes of 466, 480 to 486, and 490 to 496) for the period of April 1988 to March 1990. No age restrictions were indicated. Seven monitoring stations were used to estimate British standard black smoke and sulfur dioxide. Meteorological information came from the University of Birmingham Department of Geography. The data were divided into four seasons for analysis to control for seasonal variation in all variables. Stepwise multiple regression models were fitted to the hospital admissions data using pollution and meteorological variables as independent variables. Marginally significant regression coefficients were found for both pollutants for both endpoints, especially in the winter season. Additional analyses were run using 2-day

lags of the pollution variables, and some of these were marginally significant. This study adds little to the effect of particulate matter on respiratory hospital admissions because of the difficulties in comparing black smoke to particulate fractions.

In another study, (Schwartz et al., 1993), emergency room visits for 8 hospitals in the greater Seattle area were abstracted for the period September 1, 1989 to September 30, 1990. Asthma was defined as a diagnosis of ICD9 Codes 493, 493.01, 493.10, 493.90 and 493.91. Sulfur dioxide was measured at an industrial site, PM_{10} was available from a residential area north of town, and O_3 was measured at a site 20 km east of town. Poisson regression as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on asthma visits with adjustments for serial correlation using the method of Zeger and Liang (1986). Logistic regression coefficient estimated from the Poisson regression gave a values of .0036 (.0012) for PM_{10}. The pollution monitors were located far from the study population, but the analyses of partial data suggested that the station produced estimates that were highly correlated with the local data.

Urgent hospital admissions for respiratory illnesses in Montreal, Canada were collected from 14 hospitals from 1984 to 1988, and were split into asthma and non-asthma admissions Delfino et al. (1994). The definitions were similar to those used by Bates and Sitzo (1987). City-wide averages of O_3, PM_{10}, and sulfate fraction were calculated from seven selected monitoring stations. PM_{10} was measured every sixth day, and values for the other five days were estimated. A high-pass filter was used to eliminate yearly seasonal trends (see Shumway et al., 1983). Weather variables included temperature and humidity. Regression analyses with and without autoregressive terms found few significant relationships between the health endpoints and the various pollutants.

Duclos et al. (1990) studied hospital admissions for respiratory and non-respiratory conditions during several forest fires in northern California. The fires commenced on August 30, 1987, and TSP levels increase to about 300 $\mu g/m^3$ from a background level generally below 100 $\mu g/m^3$. The analysis consisted of comparing observed versus expected rates without adjustment for serial correlation or other factors. Although there was a significant increase in visits for respiratory conditions, the same pattern appeared for visits for injuries.

Pope (1991) studied hospital admissions in the Salt Lake Basin during the period surrounding the shut-down or strike of the steel mill. According to Pope (1991), PM_{10} pollution in the Utah Valley came from many sources, but the primary source was a 45-year-old integrated steel mill with coke ovens, blast furnaces, open hearth furnaces, and a sintering plant. When in operation, the mill emitted 82 to 92% of the valley's industrial PM_{10} pollution and 50 to 70% of the total Utah Valley PM_{10} emissions. The steel mill shut down from August 1, 1986 to September 1, 1987. Winter PM_{10} levels were approximately twice as high when the mill was open compared to when it was closed. Three mountain areas of central and north central Utah were monitored for admissions to three local hospitals. Daily admissions for asthma, bronchitis, and pneumonia were recorded. PM_{10}, SO_2, and NO_2 levels were monitored at a site 5 km northeast of the steel mill. Admissions for bronchitis and asthma were higher during periods of operation of the steel mill when compared to other areas of Utah. Logistic regressions were generally not significant, but respiratory hospital admissions were associated with monthly mean PM_{10} levels.

Hefflin et al. (1994) compared the number of emergency room visits in southeast Washington state for twelve respiratory disorders for each day of 1991 with daily PM_{10} levels. During two dust storms on October 16 and 21, 1991 PM_{10} reached 1,689 and 1,035 $\mu g/m^3$, respectively. Other pollutants were not measured. Particulates in rural eastern Washington, which are volcanic in origin, fall mostly in the PM_{10} fraction and belong to the plagioclase (glass) mineral class of aluminum silicates and other oxides. The authors used a Poisson regression model to predict daily emergency room visits as a function of season, relative humidity, and one and 2-day lags of PM_{10} pollution. Variances were estimated using the generalized estimating equations with an exchangeable correlation structure as described by Liang and Zeger (1986). Daily emergency room totals for each disorder, except respiratory allergy, had a statistically significant inverse correlation with mean daily temperature. The maximum observed/ expected ratio for respiratory disorders from the dust storms on October 16 and 21 was 1.2. The author considered this relatively low ratio for such high pollution days as indicating that the high PM_{10} levels probably had a minimal public health impact. A statistically significant relationship between a year of daily PM_{10} levels for emergency room visits for bronchitis and sinusitis was found, although the

estimated regression coefficient indicated a small effect. Ten other disorders, including asthma, pneumonic influenza, and COPD did not show this relationship.

Thurston et al. (1992) studied hospital admissions for respiratory disease among all ages in Buffalo, Albany, and New York City during July and August, 1988-1989. Three monitoring stations (one per city) measured sulfate, H+, and ozone. A linear regression analysis on filtered data showed relative risk of 1.05 (1.01, 1.10) for sulfate. No results were given for measures of PM.

Schwartz (1994f) studied hospital admissions for elderly patients in Minneapolis during 1986 to 1989. Exposure measurements were obtained from 6 monitoring stations which measured PM_{10} and O_3. The mean PM_{10} value was 36 $\mu g/m^3$, the 10th percentile was 18 and the 90th was 58. The mean O_3 value was 26 ppb, the 10th percentile was 11 and the 90th was 41. An autoregressive Poisson model with 8 categories of temperature and dew point, month, year, linear and quadratic time trend was used to analyze the data. The estimated odds ratio for a 50 $\mu g/m^3$ increase in PM_{10} was 1.25 (1.10, 1.44) for COPD (ICD9 490 to 496) and 1.08 (1.01, 1.15) for pneumonia (ICD9-480 to 487).

Schwartz (in press) studied respiratory hospital admissions (ICD9-460-519) for elderly patients in New Haven and Tacoma during 1988 to 1990. For New Haven, the PM_{10} data was averaged from all monitoring stations giving data. The mean PM_{10} was 41, the 10th percentile 19 and the 90th percentile 67 $\mu g/m^3$. The mean O_3 percentile 16 and the 90th percentile 45 $\mu g/m^3$. The mean SO2 was 30 ppb, the 10th percentile 9 and the 90th percentile 61. A Poisson log-linear regression model using with a 19 day moving average filter was used to analyze the data. Temperature and dew point were adjusted for in the moving average. The odds ratio for respiratory hospital admissions for a 50 $\mu g/m^3$ increase in PM_{10} was 1.06 (1.00, 1.13). Using a two day lag SO_2 term in the model, the odds ratio was 1.07 (1.01, 1.14). The same analysis was run for the Tacoma data. The odds ratio for respiratory hospital admissions for a 50 $\mu g/m^3$ increase in PM_{10} was 1.10 (1.03, 1.17). Using a two day lag SO_2 term in the model, the odds ratio was 1.11 (1.02, 1.20).

Schwartz and Morris (in press) studied ischemic heart disease hospital admissions (ICD9 410 to 414, 427 and 428) for the elderly in Detroit from 1986 to 1989. There were from 2 to 11 PM_{10} monitoring stations operating during the study period, and data were available for 82% of possible days The mean PM_{10} was 48 $\mu g/m^3$, the 10th percentile 22

and the 90th percentile 82. The mean SO2 was 25 ppb, the 10th percentile 11 and the 90th percentile 44. A Poisson auto-regressive model using GEE was used to analyze the data with dummy variables for temperature, month, and linear and quadratic time trend. The odds ratio for hospital admissions for ischemic heart disease for a 50 $\mu g/m^3$ increase in PM_{10} was 1.06 (1.02, 1.10). Using O_3, CO and SO_2 in the model resulted in an odds ratio of 1.06 (1.02, 1.10).

Cardiac and respiratory hospital admissions in 168 acute care hospitals in Ontario, CA for 1983 to 1988 calendar years were studied by Burnett et al. (in press). The cardiac admissions were defined as ICD9 codes 410, 413, 427, and 428, and the respiratory admissions as codes 466, 480 to 486, 490 to 494 and 496. No other age restrictions were given. Twenty-two monitoring stations were used to estimate daily O_3 zone and sulfate fraction data. Meteorological information came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). The sulfate fraction, O_3, and temperature were all predictors of hospital admissions, with O_3 more significant than the sulfate fraction. The models tended to predict about a 3 to 4% increase in respiratory admissions and about a 2 to 3% increase in cardiac admissions with about a 13 $\mu g/m^3$ increase in the concentration of sulfate fraction.

Hospital Admission Studies Summary

Hospitalization data can provide a measure of the morbidity status of a community during a specified time frame. Hospitalization data specific for respiratory illness diagnosis or more specifically for COPD and pneumonia give a measure of the respiratory status. Such studies provide an outcome measure that relates to mortality studies for total and specified respiratory measures. Tables 12-9 through 12-12 summarize these studies. These studies associate hospitalization data with PM measures. Many of the same factors and concerns related to the mortality studies are at issue for these studies also.

Both COPD and pneumonia hospitalization studies show moderated but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$

in PM_{10} or its equivalent. There is a possible suggestion of a relationship to heart disease, but the evidence is very inconclusive. The admission studies of respiratory disease show a similar effect. The hospitalization studies in general use very similar analysis methodologies and the majority of the papers are written by a single author. Overall, these studies are indicative of health outcome related to PM. They are also supportive of the mortality studies, especially with the more specific diagnosis relationships.

Schwartz (in press) reviewed the hospital admission and mortality studies of particulate matter and ozone. The hospitalization results were based on the studies of Thurston et al., (1992), Schwartz (1994e), Burnett et al. (1994), Schwartz et al. (1995), Schwartz (1994f), Sunyer et al. (1993), Schwartz (1994d), and Burnett et al. (1995). Summary tables for all respiratory admissions showed relative risks ranging from 1.10 to 1.20 per 100 $\mu g/m^3$ PM_{10} (or equivalently, 1.05 to 1.10 per 50 $\mu g/m^3$ PM_{10}). Summary tables for COPD admissions showed relative risks ranging from 1.15 to 1.57 per 100 $\mu g/m^3$ PM_{10} (or equivalently, 1.07 to 1.25 per 50 $\mu g/m^3$ PM_{10}). Schwartz (in press) argues that because there is no significant heterogeneity in the relative risks across studies that

> "This suggests that confounding by other pollutants or weather is not the source of these associations, since the coincident weather patterns and levels of other pollutants varied greatly across the studies. In particular, studies in the western United States (Spokane, Tacoma) had very low levels of sulfur dioxide, and much less humidity than [sic] in the eastern United States locations."

However, tests for homogeneity are known to have very little power against specific alternatives, and so this conclusion may not be appropriate (Hunter and Schmidt, 1989).

The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may be appropriately associated with concurrent admission, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined.

TABLE 12-9. HOSPITAL ADMISSIONS STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Burnett et al. (1994) All ages in Ontario, Canada, 1983-1988	9 monitoring stations measuring sulfate	sulfate means ranged from 3.1 to 8.2 $\mu g/m^3$	108	Lin. regress. on filtered data, 1-d lag best	Ozone	Temperature	none	1.03 (1.02, 1.04)
Thurston et al. (1994) All ages in Ontario, Canada, July and August, 1986-1988	3 monitoring stations measuring sulfate, TSP, and PM_{10}	mean sulfate ranged 38 to 124 (nmole/m^3), PM_{10} 30 to 39 $\mu g/m^3$, TSP 62 to 87 $\mu g/m^3$	14.4	Linear regression on filtered data, 0-d lag best	Ozone, H+, SO_2, NO_2	Temperature	none	PM_{10} 1.09 (0.96, 1.22)
							ozone	PM_{10} 1.01 (0.87, 1.15)
Thurston et al. (1992) All ages in Buffalo, Albany, New York City, July and August, 1988-1989	3 monitoring stations (one per city) measuring sulfate, H+	(values not given)	Buffalo, 24 Albany, 12, New York, 137	Linear regression on filtered data	Ozone, H+	Temperature	ozone	(not given for PM measures)
Schwartz (in press) Elderly in New Haven, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 41, 10% tile = 19, 90% tile = 67	8.1	Poisson log-linear regression, 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 29; 10% tile = 16; 90% tile = 45; SO_2 (ppb): mean = 30; 10% tile = 9; 90% tile = 61	Temperature and dew point adjusted for in the moving average	none	1.06 (1.00, 1.13)
							SO_2 (2 day lag)	1.07 (1.01, 1.14)
Schwartz (in press) Elderly in Tacoma, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 37, 10% tile = 14, 90% tile = 67	4.2	Poisson log-lin. regress. 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 25; 10% tile = 13; 90% tile = 36; SO_2 (ppb): mean = 17; 10% tile = 6; 90% tile = 28	Temperature and dew point adjusted for in the moving average	none	1.10 (1.03, 1.17)
							SO_2 (2 day lag)	1.11 (1.02, 1.20)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 12-10. HOSPITAL ADMISSIONS STUDIES FOR COPD

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Sunyer et al. (1993) Adults in Barcelona, 1985-1989	15 monitoring stations measuring black smoke	winter 33% tile = 49, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	12	Autoregressive linear regression analysis, 0-d lag best	Sulfur dioxide, winter 33% tile = 49 $\mu g/m^3$, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	min temp, dummies for day of week and year	none	winter: 1.15 (1.09, 1.21) summer: 1.05 (0.98, 1.12)
							SO_2	winter: 1.05 (1.01, 1.09) summer: 1.01 (0.97, 1.05)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% 2.2 tile = 18, 90% tile = 58	2.2	Autoregressive Poisson model, 1-d lag best	Ozone, mean = 26 ppb, 10% tile = 11, 90% tile = 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.25 (1.10, 1.44)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

TABLE 12-11. HOSPITAL ADMISSIONS STUDIES FOR PNEUMONIA

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10%tile = 18, 90% tile = 58	6.0	Autoregressive Poisson mod., 1-d lag best	Ozone: mean 26 ppb; 10% tile 11; 90% tile 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.08 (1.01,1.15)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19. 90% tile = 77	5.9	Autoregressive Poisson mod., 0-d lag best	Ozone: mean 25 ppb; 10% tile 14; 90% tile 37	7 cat. of temp. & dew pt., month, year, lin. & quad. time trend	none	1.09 (1.03, 1.15)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson auto-regress. mod. using GEE, 0-d lag best	Ozone: mean 21 ppb; 10% tile 7; 90% tile 36	Dummy variables for temp, month, lin. & quad. time trend	ozone	1.06 (1.02, 1.10)

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TABLE 12-12. HOSPITAL ADMISSIONS STUDIES FOR HEART DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz and Morris (in press) Elderly in Detroit 1986-1989 Ischemic Heart Disease	2 to 11 PM_{10} monitoring stations, data available for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	44.1	Poisson auto-regressive model using GEE, 0-d lag best	SO_2, mean = 25 ppb, 10% tile = 11, 90% tile = 44 CO, mean 2.4 ppm, 10% tile 1.2, 90% tile = 3.8	Dummy vars. for temp, month, lin. & quad. time trend	none	1.06 (1.02, 1.10)
							ozone, CO, SO_2	1.06 (1.02, 1.10)
Burnett et al. (in press) All ages in Ontario, Canada, 1983-1988 Cardiac disease admission	22 sulfate monitoring stations	station means ranged from 3.0 to 7.7 in the summer and 2.0 and 4.7 in the winter	14.4	Linear regression on a 19 day linear filter, 1-d lag best	Ozone averaged 36 ppb	Temperature included in separate analyses by summer and winter	none	1.04 (1.03, 1.06)
							ozone	1.04 (1.03, 1.05)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

12.3.2.2 Respiratory Illness Studies

Respiratory illness and the factors determining its occurrence and severity are important public health concerns. This section discusses epidemiologic findings relating estimates of PM exposure to respiratory illness. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common (Samet et al., 1983; Samet and Utell, 1990). Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage (Glezen, 1989; Samet et al., 1983; Gold et al., 1989).

The PM studies generally used several different standard respiratory questionnaires that evaluated respiratory health by asking questions about each child's and adult's respiratory disease and symptom experience daily, weekly or over a longer recall period. The reported symptoms and diseases characterize respiratory morbidity in the cohorts studied. A brief discussion of aspects of epidemiology of respiratory morbidity provides a background for studies examining PM exposure in relation to respiratory health. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader syndromes such as upper and lower respiratory illnesses.

Asthma is characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to stimuli (National Institutes of Health, 1991). The prevalence of physicians diagnosed asthma among children under age 18 is 6.3/100 (U.S. Department of Health and Human Services, 1994). From 1982 through 1992, the prevalence of asthma among persons aged 5 to 34 years (for whom the diagnosis is likely most accurate) increased 42%, from 3.4 (401 deaths) to 4.9 (569 deaths) (United States Center for Disease Control, 1995). Overall, an estimated 4.9% of the total U.S. population or over 12 million people, have asthma (U.S. Department of Health and Human Services, 1994). Asthma patients develop clinical symptoms such as wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms associated with decreased levels of various measures of forced expiratory volume. Although viral respiratory tract infections are common asthma triggers, especially in young children (National Institutes of Health, 1991), symptoms such as wheezing may occur without an infectious cause.

Chronic bronchitis in adults is defined as a clinical disorder characterized by excessive mucous secretion in the bronchial tube with an associated chronic productive cough on most days for a minimum of 3 months of the year for not less than 2 successive years (American Thoracic Society, 1962). The diagnosis can only be made after excluding other disorders with similar symptoms. In contrast, Morgan and Taussig (1984) state that a clear definition and etiology of chronic bronchitis in childhood have not yet been described. They characterize chronic bronchitis in children as a symptom complex consisting of a chronic or recurrent "wet" cough, increased phlegm production, and wheezing that may be associated with evidence of airway inflammation. Symptoms and findings observed in children with physician-diagnosed chronic bronchitis commonly include recurrent respiratory infections and wheezing, with chronic phlegm production and chronic cough being less prevalent (Burrows and Lebowitz, 1975). Respiratory syncytial virus (RSV) and parainfluenza virus are isolated in cases of bronchitis (Chanock and Parrott, 1965), but symptoms of bronchitis may occur without an infectious cause.

Viral respiratory illnesses can be subdivided by predominant anatomic site of involvement in the respiratory tract: rhinitis (the common cold), pharyngitis, laryngitis, laryngotracheo bronchitis (croup), tracheobronchitis, bronchiolitis, and pneumonia. In many instances, signs and symptoms referable to more than one site (e.g., pharyngitis, laryngitis, and rhinitis) may occur at the same time in the same patient.

The common cold is the leading acute upper respiratory illness in the United States. Rhinoviruses lead the list as the most common group of viruses that cause colds in adults and children. Other common viruses include coronaviruses, parainfluenza virus, respiratory syncytial virus, and influenza virus. The number of colds acquired per year decreases with age. Infants and preschool children have the highest incidence (4 to 8 colds per year), and adults generally have two to five colds per year. Rhinovirus accounts for about 30% of colds with a defined etiologic cause and has a characteristic seasonal pattern with the highest prevalence of rhinovirus colds in early fall and a second smaller peak in the spring. Many factors, including age of the patient, season of year, geographic location, and type of population are important determinants of etiology. In most adults and older children signs and symptoms of the common cold are marked by a dry, scratchy or sore throat. Usual progression leads to a watery nasal discharge associated with the feeling of irritated nasal

mucosa and sneezing. Typically, symptoms and responses on respiratory questionnaire for upper respiratory illness include throat irritation, acute cough, cough with phlegm, wheeze, runny nose, breathing difficulty, fever, and earache.

Lower respiratory illnesses are generally classified into one of four clinical syndromes: croup (laryngotracheobronchitis), tracheobronchitis, bronchiolitis, and pneumonia (Glezen and Denny, 1973; Wright et al., 1989; McConnochie et al., 1988). In a study in Tucson, the most common diagnosis during the first year of life was bronchiolitis, which accounts for 60% of all lower respiratory illness (Wright et al., 1989). The most common signs and symptoms associated with lower respiratory illnesses were wet cough (85%), wheeze (77%), tachypnea (48%), fever (54%), and croupy cough (38%) as reported by Wright et al. (1989). A few infectious agents are presumed to cause the majority of childhood lower respiratory illness. Bacteria are not thought to be common causes of lower respiratory illness in nonhospitalized infants in the United States (Wright et al., 1989). Seventy-five percent of the isolated microbes were one of four types: RSV, parainfluenza virus types 1 and 3, and *Mycoplasma pneumoniae* (Glezen and Denny, 1973; McConnochie et al., 1988). Respiratory syncytial virus is particularly likely to cause lower respiratory illness during the first two years of life. More than half of all illnesses diagnosed as bronchiolitis, for which an agent was identified, were positive for RSV (Wright et al., 1989). Wright et al. (1989) noted that studies that rely on parental reports of symptoms may underestimate illness. Asking parents about illnesses at the end of the first year of life revealed that one-third of them failed to report illnesses diagnosed by pediatricians.

Various studies of lower respiratory illness have reported rates based on visits to physicians ranging from about 20 to 30 illnesses/100 children in the first year of life (Glezen and Denny, 1973; Wright et al., 1989; Denny and Clyde, 1986; McConnochie et al., 1988). Glezen and Denny (1973) reported that the rate for lower respiratory illnesses ranged from 24/100 person-years in infants under one year of age and decreased steadily each year through the preschool years, tending to level off in school children (age 12 to 14 years) to about 7.5 illnesses/100 person-years. Several factors affect the rate of lower respiratory illness in children, including age, immunologic status, prior viral infections, siblings of early school age, level of health, SES (Chanock et al., 1989), day care attendance, home dampness and humidity, environmental tobacco smoke, NO_2, PM, and other pollutants. Rates also

depend on method of illness ascertainment. Studies in the United States (Wright et al., 1989; Denny and Clyde, 1986; McConnochie et al., 1988) indicated that the overall pattern and incidence of lower respiratory illness is consistent in different geographic regions during the two decades covered by the studies, suggesting that diagnosis and infectious agents have changed little in that time period. Lower respiratory illness remains one of the major causes of childhood morbidity in the United States (McConnochie et al., 1988).

Over the past 4 decades, a large body of epidemiologic evidence has accumulated that indicates that respiratory illness events in childhood (mostly viral) are important determinants (risk factors) for the future risk of chronic respiratory symptoms and disease in adult life (Samet et al., 1983; Denny and Clyde, 1986; Britten et al., 1987; Glezen, 1989; Gold et al., 1989). Based on such data, it seems likely that any factor such as PM that could be responsible for increasing the risk of childhood respiratory illness and symptoms would be of considerable public health importance not only with regard to immediate morbidity, but also in relation to its contribution to long-term morbidity from chronic respiratory disease.

Studies of Respiratory Illness in Children

Schwartz et al. (1994) analyzed respiratory symptoms in children from the Harvard Six Cities Studies. The cities included Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubinville, OH; and Topeka, KS. Daily diaries of respiratory symptoms were collected from the parents of 1844 school children for one year starting in September, 1984. A centrally located residential monitor measured SO_2, NO_2, and O_3 on a continuous basis, $PM_{2.5}$ and PM_{10} were collected by a dichotomous sampler and aerosol acidity was measured daily. A multiple logistic regression model was used to analyze the data, adjusting for serial correlation by autoregressive terms estimated using the generalized estimating equations of Liang and Zeger (1986). The only weather variable included in the model was temperature, using both linear and quadratic terms.

In order to avoid the seasonal component of respiratory illness, the analysis was restricted to the months of April through August. During this period the $PM_{2.5}$ values had a median value of 18 $\mu g/m^3$ with 10th and 90th percentile values of 7.2 and 37.0 $\mu g/m^3$. The PM_{10} values had a median value of 30 $\mu g/m^3$ with 10th and 90th percentile values of 13 and 53 $\mu g/m^3$. Sulfate fractions were estimated from the $PM_{2.5}$ filters. Cough was significantly

related to all pollutants except acidity. The strongest relationships for cough were found with PM_{10} and O_3, and these effects appeared to be independent of each other. An increase of 30 $\mu g/m^3$ in PM_{10} was associated with an odds ratio for cough of 1.28 (1.07 to 1.54). Fitting a Generalized Additive Model (non-parametric) showed that cough incidence increased monotonically with PM_{10} concentration, and there was no evidence of non-linearity. Lower respiratory symptoms (LRS) were also related to all pollutants except acidity. Strongest relationships were found with PM_{10} and sulfate fraction, and these effects appeared to be independent of each other. An increase of 30 $\mu g/m^3$ in PM_{10} was associated with an odds ratio for lower respiratory symptoms of 1.53 (1.20 to 1.95). There was no evidence of non-linearity, as shown in Figure 12-4. Comparable analyses for SO_2 and H^+ are shown in Figures 12-5 and 12-6. Note that these curves show an inconsistent relationship at lower exposure estimates. Although these non-parametric models do not provide confidence intervals, it is clear that the relationship between cough and PM10 is stronger than for either SO_2 or H^+.

Pope et al. (1991) studied respiratory symptoms in asthmatic school children in the Utah Valley. Participants were selected from samples of 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon, Utah and were restricted to those who responded positively to one of: (a) ever wheezed without a cold; (b) wheezed for 3 days out of a week for a month or longer; (c) had a doctor say the "child has asthma". This resulted in 34 subjects who were included in the final analyses. PM_{10} monitors operated by the Utah State Department of Health collected 24 hr PM_{10} samples from midnight to midnight (range 11 to 195 $\mu g/m^3$). There was limited monitoring of SO_2, NO_2, and O_3. Lower respiratory disease was defined as the presence of at least one of: trouble breathing, dry cough, or wheezing. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. Estimated odds ratios for upper respiratory disease per PM_{10} increase of 50 $\mu g/m^3$ was 1.20 (1.03, 1.39); for lower respiratory illness, it was 1.28 (1.06, 1.56).

Pope et al. (1991) also studied asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects who were included in the final analysis. PM_{10} monitors operated by the Utah State Department of Health collected 24 hr samples from midnight to midnight; and values ranged from 11 to 195 $\mu g/m^3$.

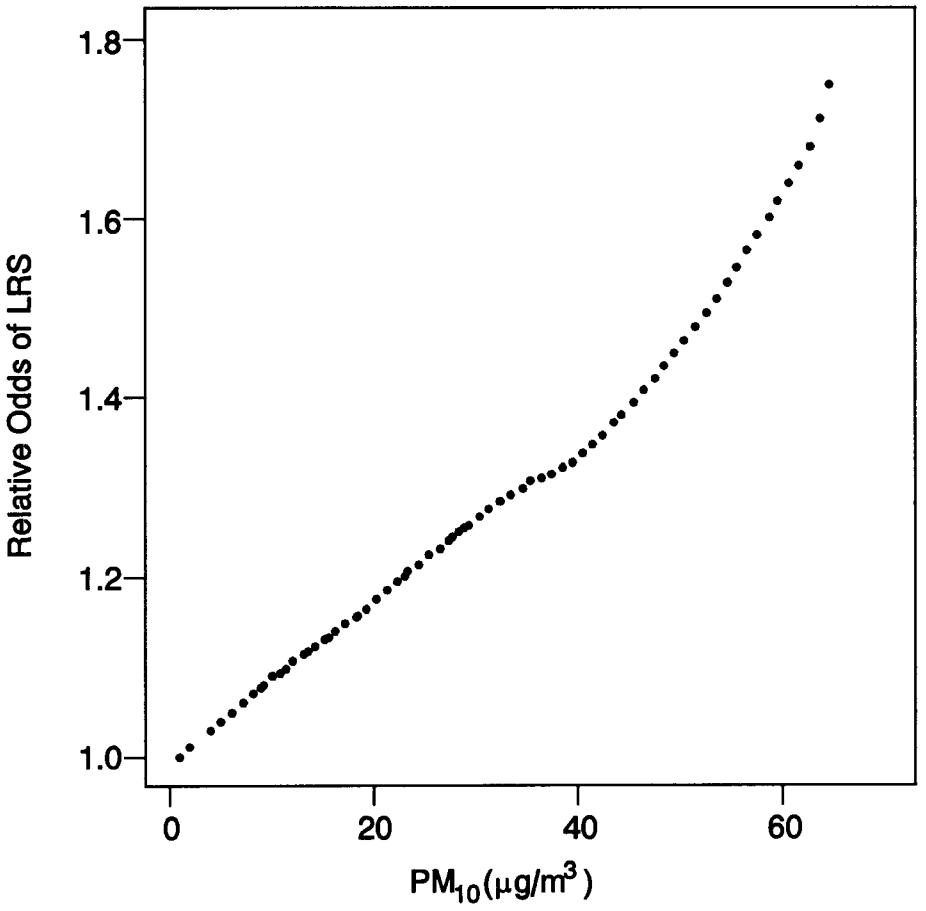

Figure 12-4. Relative odds of incidence of lower respiratory symptoms (LRS) smoothed against 24-h mean PM_{10} ($\mu g/m^3$) on the previous day controlling for temperature, day of the week, and city.

Source: Schwartz et al. (1994).

There was limited monitoring of SO_2, NO_2, and O_3. Lower respiratory disease was defined as the presence of at least one of: trouble breathing, dry cough, or wheezing. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. The estimated odds ratio for upper respiratory disease per PM_{10} increase of 50 $\mu g/m^3$ in PM_{10} was 0.99 (0.81, 1.22). For lower respiratory illness, it was 1.01 (0.81, 1.27).

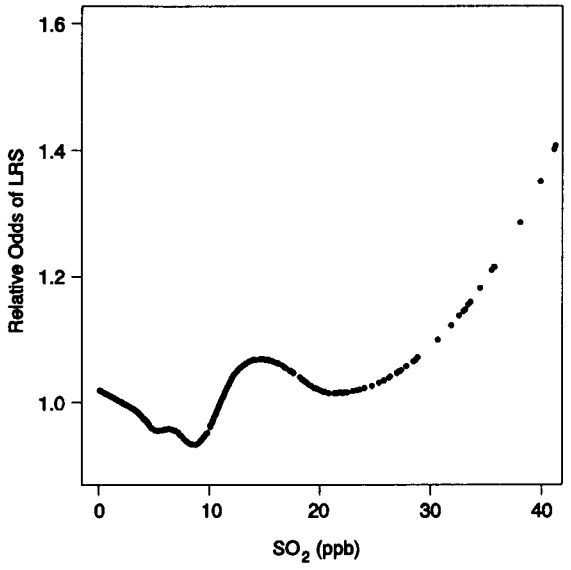

Figure 12-5. **Relative odds of incidence of LRS smoothed against 24-h mean SO_2 concentration on the previous day, controlling for temperature, city, and day of the week.**

Source: Schwartz et al. (1994)

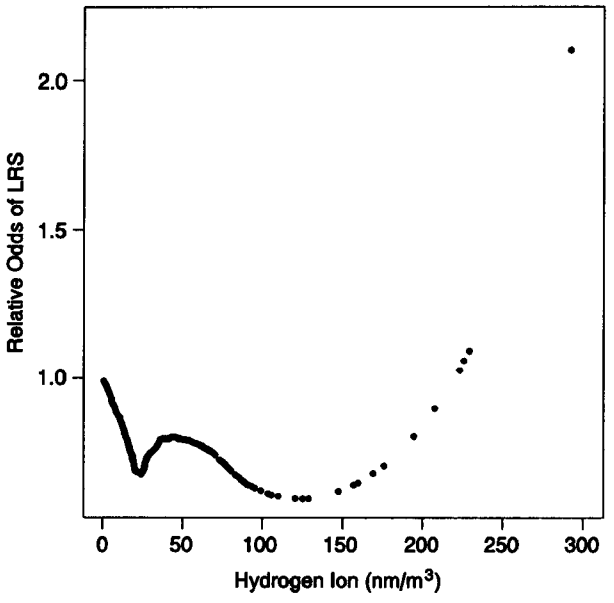

Figure 12-6. **Relative odds of incidence of LRS smoothed against 24-h mean H^+ concentration on the previous day, controlling for temperature, city, and day of the week.**

Source: Schwartz et al. (1994)

In a follow up study, Pope and Dockery (1992) enrolled non-asthmatic symptomatic and asymptomatic children in the Utah Valley, selected from samples of 4th and 5th grade elementary students in three schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon Utah. A questionnaire identified 129 children who were mildly symptomatic and 60 were selected. An additional 60 with no symptoms were recruited. PM_{10} monitors operated by the Utah State Department of Health collected 24 hr samples from midnight to midnight; PM_{10} values ranged from 11 to 195 $\mu g/m^3$. Limited SO_2, NO_2, and O_3 monitoring was conducted. Low temperature was used to adjust for weather, but no adjustment was made for humidity. Upper respiratory symptoms had a logistic regression coefficient of .00519 (.00203) and lower respiratory symptoms had a coefficient of .00658 (.00205) in the symptomatic sample using a 5-day moving average of PM_{10}. These correspond to odds ratios of 1.30 and 1.39 respectively for an increase of 50 $\mu g/m^3$ in PM_{10}. No consistent effects were seen in the asymptomatic sample, although all effects tended to increase with PM. Only minimum temperature was used to adjust for weather.

Ostro et al. (1995b) studied a panel of 83 African-American asthmatic children aged 7 to 12 recruited from four allergy and pediatric clinics in central Los Angeles and two asthma camps in the summer of 1992. The analysis focused on the daily reporting of respiratory symptoms including shortness of breath, cough, and wheeze. Daily air monitoring at three fixed sites included O_3, PM_{10}, NO_2, and SO_2. PM_{10} levels ranged from 20 to 101 $\mu g/m^3$ and O_3 from 10 to 160 ppb. Daily temperature, humidity, rainfall, pollens and molds were also used as covariates. A logistic regression allowing for repeated measures with variances estimated by generalized estimating equations was used to estimate effects of the pollutants and covariates. Both PM_{10} and O_3 were associated with increased shortness of breath, and the authors could not separate the effect of the two pollutants. The odds ratio for an increase of 56 $\mu g/m^3$ PM_{10} was 1.58 (1.05, 2.38). No effects were seen with cough or wheeze.

Schwartz et al. (1991) analyzed acute respiratory illness in children in five German communities. Children's hospitals, pediatric departments and pediatricians were asked to fill out a short questionnaire for each visit for croup or obstructive bronchitis over a 2-year period. A diagnosis of croup was defined as acute stenotic subglottic laryngotracheitis. Not all doctors reported for the full 2 years—a loss of about 50%. Thus, participation was about 50%. Areas chosen to represent a wide range of air pollution exposure included: Duisburg

and Köhn in the highly industrialized areas of Northrhine-Westfalia and Stuttgart, and Tubingen/Reutlingen and Freundenstadt in South Germany. Two to four monitors were located in each study areas and 24 hr measurements were taken of TSP, SO_2, and NO_2. TSP was measured by low volume sampler, NO_2 by chemiluminescence, and SO_2 by the conductometric method, and were expressed in $\mu g/m^3$. Poisson regression analysis as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on croup and obstructive bronchitis, with adjustments for serial correlation using the method of Zeger and Liang (1986). The model included terms for season (annual and biannual sine and cosine terms), weather (temperature and relative humidity), and drop-outs. Logistic regression coefficients estimated from the Poisson regressions gave values of 0.1244 admissions/log(TSP) (.0309), 0.4161 (.156) for NO_2, and 0.0831 (.0352) for SO_2. The log TSP coefficient was not significant with either NO_2 or SO_2 were included in the model.

Hoek and Brunekreef (1993) and Hoek (1992) studied a general population sample of 112 children aged 7 to 12 who lived in a non-urban area proximal to Wageningen, ND. Acute respiratory symptoms of the children were recorded in a diary by their parents, including throat irritation, cough, cough with phlegm, wheeze, runny nose, and a variety of other symptoms. PM_{10} was measured daily (3PM to 3PM) with an instrument similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured using fluorescence, and NO_2 was measured using chemiluminescence. Logistic regression analyses including first order autoregressive terms were used to analyze the data and included ambient temperature and day of study as covariates. The PM_{10} coefficient for any upper respiratory illness was 0.0026 (0.0013). This corresponds to an odds ratio of 1.14 (95% confidence interval of (1.00 to 1.30) for an increase of 50 $\mu g/m^3$ PM_{10}. Most other coefficients were not significant.

Braun-Fahrländer et al. (1992) studied daily respiratory disease symptoms in preschool children in 4 areas of Switzerland. A sample of 840 children was chosen from Basel and Zurich. One-twelfth of the sample was recruited each month from November 1985 to November 1986. A physician conducted a standardized questionnaire with the parents. Parents recorded daily symptoms including cough without runny nose, breathing difficulty, and fever with earache and sore throat. TSP was measured daily (method not given) and NO_2 by Palmes tubes both outside the apartment and inside the room where the child stayed most frequently. Children lived within 6 km of an outdoor monitor which measured TSP,

NO_2, SO_2, and O_3. Multiple logistic regression analysis was used to explain differences in upper respiratory symptom incidence. Analysis terms included temperature, season, city, and a risk strata based on a cross-sectional analysis. Variances were adjusted using the method of Liang and Zeger (1986). The TSP coefficient for upper respiratory symptoms was 0.00454 (0.00174), corresponding to an odds ratio of 1.57 per TSP increase of 100 $\mu g/m^3$. Neither NO_2, SO_2, or O_3 were significant.

Hoek and Brunekreef (1994) studied respiratory function and pulmonary symptoms in more than 1000 children in 4 towns in the Netherlands. Children aged 7 to 11 in Deurne, Enkhuizen, Venlo, and Nijmegen were studied during one of three winters (1987/88, 1988/89, 1989/90). During the study, respiratory symptoms data were collected daily by diary. PM_{10} was measured daily (3PM to 3PM) with an instrument similar to the Sierra Anderson 241 dichotomous sampler, SO_2 by fluorescence, and NO_2 by chemiluminescence. Separate logistic regressions were performed for 9 locations (six groups of subjects of Deurne and one in each other town) using a first order autoregressive model. The coefficients were combined using the inverse variance weighting method. The odds ratio for the incidence of cough associated with 100 $\mu g/m^3$ PM_{10} increase was 1.10 (0.67,1.79). PM_{10} odds ratios for upper and lower respiratory illness were also not statistically significant. Nor was the incidence of acute respiratory symptoms significantly related to PM_{10}, SO_2, NO_2, or sulfate.

In a study by Roemer et al. (1993) of children with chronic respiratory symptoms, parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Seventy-four of the 313 children with positive responses (cough or shortness of breath) were included in the study. PM_{10} was measured daily using the Sierra Anderson 24 dichotomous sampler. SO_2, NO_2, and black smoke were also measured. Several symptoms including asthma attack, wheeze, and cough were marginally associated with PM_{10}. The logistic regression coefficient for wheeze was .00224 (.00115) per unit increase in the same day's PM_{10} level. The coefficient for broncho-dilator use was .00210 (.00085). SO_2 and black smoke were also marginally related to several of the symptoms. Seasonal variation did not appear to be considered in the model.

Hoek and Brunekreef (1995) studied respiratory symptoms in 300 children aged 7 to 11 years in Duerne and Enkhuizen, The Netherlands. The study was designed as an ozone

study, but SO_2, NO_2, and PM_{10} were also measured (PM_{10} ranged 13 to 124 $\mu g/m^3$; O_3 ranged 22 to 107 ppb). A symptom diary similar to that used in the Harvard Six Cities Study was used to obtain daily information on cough, phlegm, wheeze, runny nose, and other respiratory symptoms. A multiple logistic model with first order autoregressive residuals was used. Additional analyses using ARIMA models to allow for autocorrelation confirmed results of the logistic analyses. Nearly all logistic regression coefficients were non-significant and negative. The analyses of cough in Deurne gave an estimated odds ratio of 0.93 for a 50 $\mu g/m^3$ increase in PM_{10} on the same day. Analyses of other endpoints, lag times, and pollutants gave similar results.

Relationships between air pollution indices for 84 standard metropolitan statistical areas (SMSA's) mostly of 100,000 to 600,000 people in size and indices of acute morbidity effects were studied by Ostro (1983), Hausman et al. (1984), and Ostro (1987), using data derived from the National Center for Health Statistics (NCHS) Health Interview Survey (HIS) of 50,000 households comprising about 120,000 people. Ostro (1983) used HIS data to assess the prevalence of illness and illness-related restrictions in activity in the United States. Data on either restricted activity days (RADs) or work loss days (WLDs) were aggregated over a year, and correlated with annual TSP levels, controlling for temperature, wind, precipitation, population density, and smoking. Using the 1976 survey, a significant relationship between TSP and both outcomes was found, with RAD's being more significant. Sulfate fractions were not significantly related to either outcome. Ozone was not measured. The explained variation was much higher for RADs than for WLDs. The average of air pollution monitors for each city was used, rather than aerometric data aggregated for smaller geographic units in relationship to individuals residing nearby for whom HIS data were included in the analysis. Hausman et al. (1984) analyzed the same data, but used Poisson regression analysis using a fixed effects model that compared deviations from the city mean levels of illness and short-term pollution as the exposure variable. Significant associations between 2-week average TSP levels and RADs or WLDs were found. The magnitude of the within city effects was similar to the magnitude of the between city effects seen earlier. Demographic factors were controlled for on an individual basis, along with climatic conditions.

Ostro (1987) applied the Hausman et al. (1984) techniques to analyze HIS results from 1976 to 1981 in relation to estimates of fine particle (FP) mass. That is, for adults aged

18 to 65, days of work loss (WLDs), restricted activity days (RADs) and respiratory-related restricted activity days (RRADs) measured for a 2-week period before the day of the survey were used as measures of morbidity and analyzed in relation to estimated concurrent 2-week averages of FP or lagged in relation to estimated 2-week FP averages from two to four weeks earlier. The FP estimates were produced from the empirically derived regression equations of Trijonis. These equations incorporated screened airport data and 2-week average TSP readings at population-oriented monitors, using data taken from the metropolitan area of residence. Various potentially confounding factors (such as age, race, education, income, existence of a chronic health condition, and average 2-week minimum temperature) were controlled for in the analyses. The morbidity measures (WLDs, RADs, RRADs), for workers only or for all adults in general, were consistently found to be significantly ($p < 0.01$ or < 0.05) related to lagged FP estimates (for air quality 2 to 4 weeks prior to the health interview data period), when analyzed for each of the individual years from 1976 to 1981. However, less consistent associations were found between the health endpoints and more concurrent FP estimates.

Ostro and Rothschild (1989) studied acute respiratory morbidity based on an analysis of 1976 to 1981 HIS data. Ozone measurements were taken from EPA's SAROAD monitoring network, and FP measurements were estimated from airport visibility data. The endpoints of the analysis included minor restrictions in activity and work loss. Using a multiple regression analysis, both endpoints showed a relationship to FP.

School Absences Studies

Most school absences are due to acute conditions (Klerman, 1988). Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. School absences are also caused by injuries, digestive system conditions and ear infections. Kornguth (1990) notes the following characteristic of school absent children: (1) as mothers level of education or family income increased the likelihood of their children being absent decreased; and (2) days absent due to illness are related to source of medical care and to type of health insurance coverage. Children with a wide range of chronic illnesses miss more school than their healthy peers. There is only tentative evidence that school absent rates of individual children vary directly with the severity of their health

problem (Weitzman, 1986). Parcel et al. (1979) found that children with asthma have a significantly higher absentee rate than do nonasthmatic children. Children who smoke and whose parents smoke are more likely to be absent from school for minor ailments (Charlton and Blair, 1989). Whether this increased likelihood of absence is due to genuine health problems or to a generally negative attitude to school in children who take up smoking to boost their self-esteem, is unclear.

Most excessive school absence is probably the result of factors outside the health care sphere (Klerman, 1988). Chaotic family environments, lack of achievement motivation, understaffed and uninviting schools, and other societal problems, are undoubtedly the major reason for absenteeism. Excessive school absence is a profound educational and social problem in the United States (Weitzman et al., 1986). Despite the fact that the majority of school absences are reported as being health related, data suggest that demographic and educational characteristics of students have a much greater influence on absence behavior than do health-related factors. Since school absence rates reflect both health and non-health related factors, it is important that investigators recognize the nonspecific nature of the measure and account for non-health related influences appropriately (Weitzman, 1986). Such non-health related potential problems with the data include the following: data are difficult to collect, individual data as compared to aggregate data; different coding in schools for tardy or leaves school early for sickness; and, records may not be computerized at school making retrospective studies more difficult (Weitzman, 1986).

Ransom and Pope (1992) studied elementary school absences in connection with the steel strike in the Utah Valley. Data for school absences from 1985 to 1991 were obtained from two sources: (1) district-wide attendance averages by grade level from the Provo School District, and (2) daily absenteeism records from the Northridge Elementary School in Orem. The Northridge School was much closer to the steel mill than were the schools in the Provo School District. Daily PM_{10} measurements were made at three sites (Linden, Provo, and Orem), but only the Linden site collected daily measurements for the entire time period of the study. Some SO_2 and O_3 measurements were available, but these values tended to be well below the National Ambient Air Quality standards. Meteorological information was available from the Brigham Young University weather station. Regression analyses were conducted, taking into account several covariates including month of study, snowfall,

Christmas and Thanksgiving holidays, and low temperature. The best PM_{10} predictor was a 4-week moving average. A highly significant increase of about 2% in the absence rates (absolute increase) for an increase of 100 $\mu g/m^3$ increase in the 4-week average PM_{10} was found both sets of data, and the coefficient was similar even when a dummy variable was added for the strike. No adjustments were made for periods of increased influenza cases.

Studies of Respiratory Illness in Adults

Lawther et al. (1970) reported on studies carried out from 1954 to 1968 mainly in London, using a diary technique for self-assessment of day-to-day changes in symptoms among bronchitic patients. A daily illness score was calculated from the diary data and related to BS and SO_2 levels and weather variables. Pollution data for most of the London studies were mean values from the group of sites used in the mortality/morbidity studies of Martin (1964). In early years of the studies, when pollution levels were generally high, well defined peaks in illness score were seen when concentrations of either BS or SO_2 exceeded 1,000 $\mu g/m^3$. With later reductions in pollution, the changes in condition became less frequent and of smaller size. From the series of studies as a whole, up to 1968, it was concluded that the minimum pollution levels associated with significant changes in the condition of patients was a 24-h mean BS level of $\sim$250 $\mu g/m^3$ together with a 24-h mean SO_2 concentration of $\sim$500 $\mu g/m^3$ (0.18 ppm). A later study reported by Waller (1971) showed that, with much reduced average levels of pollution, there was an almost complete disappearance of days with smoke levels exceeding 250 $\mu g/m^3$ and SO_2 levels over 500 $\mu g/m^3$ (0.18 ppm). As earlier, some correlation remained between changes in the conditions of the patients and daily concentrations of smoke and SO_2, but the changes were small at these levels and it was difficult to discriminate between pollution effects and those of adverse weather. The analysis of the Lawther et al. (1970) study was made prior to the availability of current statistical methods such as poisson regression using generalized estimating equations. The large differences seen by Lawther et al. (1970) at high levels would undoubtedly remain significant regardless of the analysis technique. Marginally significant results must be viewed with caution.

Dusseldorf et al. (1994) studied respiratory symptoms in 32 adults living near a large steel plant in Wijk aan Zee, The Netherlands. During the study period PM_{10} levels ranged

from 36 to 137 $\mu g/m^3$. Diary information on acute respiratory symptoms, medication use, and presence of fever was collected. Peak flow measurements were also taken. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. A logistic regression model was used and to control autocorrelation, a linear time series model was also fitted. Both models gave similar results and so the logistic regression coefficients converted to odds ratios for 100 $\mu g/m^3$ were reported. These were converted to odds ratios for 50 $\mu g/m^3$. The odds ratio for cough on PM_{10} (lag zero) was 1.31 (0.9, 1.76). The other endpoints of phlegm, shortness of breath and wheeze showed lesser effects. Using PM_{10} lagged one, two, and three days showed little effect.

Lebowitz et al. (1982) studied 117 families in Tucson, AZ selected from a stratified sample of families in geographical clusters from a representative community population included in an ongoing epidemiologic study. Both asthmatic and non-asthmatic families were evaluated over a 2-year period using daily diaries. The health data obtained were related to various indices of environmental factors derived from simultaneous micro-indoor and outdoor monitoring in a representative sample of houses for air pollutants, pollen, fungi, algae and climate. Monitoring of air pollutants and pollen was carried out simultaneously. Two-month averages of indoor TSP ranged from 2.1 to 169.6 $\mu g/m^3$. Cyclone measurements of respirable particulate (RSP) ranged from below minimum detectable limits up to 28.8 $\mu g/m^3$; CO and NO_2 measurements were also taken, but no $S0_2$ monitoring was reported. TSP and pollen were reported to be related to symptoms in both asthmatics and non-asthmatics, but the authors reported that the statistical analyses used were all qualitative (because of low sample size) and statistical significance was not computed.

Whittemore and Korn (1980) studied asthmatics in seven communities in the Los Angeles area. Panelists were located by consulting local physicians and were followed for 34 weeks from May 7 to December 30 in the years 1972 to 1974 from the communities of Santa Monica, Anaheim, Glendora, Thousand Oaks, Garden Grove, and Covina. Dairies were filled out weekly by the participants who gave daily information on symptoms. Monitoring stations were placed in each community near an elementary school. TSP, RSP, suspended sulfates, suspended nitrates, SO_2, and photochemical oxidants were measured. NO_2 was also measured but the data were determined to be unreliable. Because of the colinearities and measurement errors, only TSP and photochemical oxidants were actually

included in the analyses. A logistic model was used for each individual that included the presence of an attack on the previous day, meteorology, day of study, day of week, and pollutants. Regression coefficients were combined using both a fixed and random effects model. Both photochemical oxidants and TSP were found to be significantly related to symptoms, even when the other pollutant was included in the model. The coefficient for TSP for both models was .00079 (standard error not given). This corresponds to an odds ratio of 1.08 for a 100 $\mu g/m^3$ increase in TSP.

Ostro et al. (1991) studied adult asthmatics recruited from clinic patients in Denver. Diagnosis of asthma was based on physical exam confirmed by lung function tests. The panel of 207 recorded daily symptoms and medication use from November 1987 to February 1988. Ambient air pollutants measured were sulfates, nitrates, $PM_{2.5}$, nitric acid, H^+, and SO_2 at a downtown Denver monitor two miles from the clinic. Logistic regression analysis was used with adjustment for autocorrelation by creating an instrumental variable; the final regression used Proc Autoreg in SAS. The coefficient for $\log(PM_{2.5})$ was .0006 (.0053) for asthma and .0012 (.0043) for cough. H^+ was the only pollutant near statistical significance, having an estimate coefficient of .0031 (.0042) for asthma and .0076 (.0038) for cough. The coefficients cannot be compared directly with other studies because of the log transformation, and attempts to convert them based on mean values give unreasonable answers.

Ostro et al. (1993) studied respiratory symptoms in non-smoking adults aged 18 or more in Southern California from September 1978 to March 1979. The analysis was restricted to those 321 subjects who completed diaries for the entire 181-day period. The health endpoints included upper respiratory illness, lower respiratory illness, and eye irritation. Air pollution data for the Glendora, Covina, and Azusa areas were obtained from the Los Angeles County Air Pollution Control District Station in Azusa and included O_3, NO_2, SO_2, and sulfate fraction of PM. Temperature, rain, and humidity were used as meteorological covariates. A multiple logistic regression analysis was run using the three health endpoints. Ozone, sulfate fraction, and gas stove use were associated with significant odds ratios for lower respiratory tract illness. The odds ratio for gas stove use, 1.23, was well within the range reported in a meta-analysis of studies of nitrogen oxides by Hasselblad et al. (1992), but COH was not significantly related to lower respiratory illness. Only ozone

was related to upper respiratory illness or eye irritation. The author did not report that adjustments were made for serial correlation of the health outcomes.

Acute Respiratory Illness Studies Summary

This category include several different endpoints, but the majority of authors reported results on at least two of: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (See Table 12-13). The results for upper respiratory illness are very inconsistent: two studies estimate a relative risk near 1.00 whereas four others obtain estimates between 1.14 and 1.55. These relative risks are all estimated for an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent The relative risks for lower respiratory illness are spread between 1.01 and 2.03, but all are positive. The relative risks for cough include two below 1.0 and go as high as 1.51. All of these are suggestive of an effect. Whereas the hospital admission studies were all done in a similar manner and resulted in very similar results, these studies are done with very different designs and give very inconsistent results.

12.3.2.3 Pulmonary Function Studies

Pulmonary function studies are part of any comprehensive investigation of possible effects of any air pollutant. Measurements can be made in the field, they are noninvasive, and their reproductibility has been well documented. Guidelines for reference values and interpretative strategies of lung function tests have been prepared (American Thoracic Society, 1991). Various factors are important determinants of lung function measures.

Lung function in childhood is primarily related to general stature (as measured by height) and as children enter late childhood, by age. The growth patterns differ between males and females. Compared to girls, boys show larger size-adjusted (usually height or $height^2$) average values for various measures of lung function (Wang et al., 1993a,b). Moreover, growth of measures derived from forced expiratory maneuvers (e.g., forced vital capacity-FVC and forced expiratory volume one-second-FEV_1) continues for a longer period of time in males, beyond the time when height growth is complete (Wang et al., 1993a,b). Lung function begins to decline with age in the 3rd to 4th decades (Tager et al., 1988) and continues to do so monotonically as people age. Cigarette smoking, the presence of chronic

TABLE 12-13. ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1994) 300 elementary school children in Six-Cities in U.S., 1984-1988	PM_{10} monitoring in each city	median 30 $\mu g/m^3$ 10th percentile = 13, 90th percentile = 53	3.1	Autoregressive logistic regression using GEE	Ozone, NO_2, SO_2	Temperature	none SO_2 ozone	1.51 (1.12, 2.05) 1.39 (0.98, 1.96) 1.49 (1.10, 2.01)
Pope et al. (1991), students in the Utah Valley, winter 1989-1990	PM_{10} monitoring stations at 3 sites	mean = 46 $\mu g/m^3$, range = 11 to 195	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and ozone. Values were well below the standard	Variables for temperature and time trend	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.28 (1.06, 1.56)
Pope et al. (1991), asthmatic children in the Utah Valley, winter 1989-1990	PM_{10} monitoring stations at 3 sites	mean = 46 $\mu g/m^3$, range = 11 to 195	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and ozone. Values were well below the standard	Variables for low temperature and time trend	none	Upper resp. 0.99 (0.81, 1.22) Lower resp. 1.01 (0.81, 1.27)
Pope and Dockery (1992), symptomatic children in the Utah Valley, winter 1990-1991	PM_{10} monitoring stations at 2 sites	mean = 76 $\mu g/m^3$, range = 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temperature	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.27 (1.08, 1.49) Cough 1.29 (1.12, 1.48)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 12-13 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Pope and Dockery (1992), asymptomatic children in the Utah Valley, winter 1990-1991	PM_{10} monitoring stations at 2 sites	mean = 76 $\mu g/m^3$, range = 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temperature	none	Upper resp. 0.99 (0.78, 1.26) Lower resp. 1.13 (0.91, 1.39) Cough 1.18 (1.00, 1.40)
Hoek and Brunekreef (1993), respiratory disease in school children aged 7 to 12 in Wageningen, Netherlands, winter 1990-1991	Two to 4 monitoring stations measured PM_{10}	max = 110 $\mu g/m^3$	(not given)	Autoregressive logistic regression using GEE	Max SO_2 = 105 $\mu g/m^3$, max NO_2 = 127 $\mu g/m^3$	Variable for ambient temperature and day of study	none	Upper resp. 1.14 (1.00, 1.29) Lower resp. 1.06 (0.86, 1.32) Cough 0.98 (0.86, 1.11)
Schwartz et al. (1991) Study of acute respiratory illness in children in 5 German communities, 1983-1985	Two to 4 monitoring stations in each area measured TSP	medians ranged from 17 to 56 $\mu g/m^3$, 10% tiles from 5 to 34, 90% tiles from 41 to 118	0.5 to 2.9	Autoregressive Poisson regression using GEE	median SO_2 levels ranged from 9 to 48 $\mu g/m^3$, median NO_2 levels ranged from 14 to 5 $\mu g/m^3$	Most significant terms of day of week, time trend, and weather (terms not listed)	none (TSP was not significant when NO_2 added to model)	1.26 (1.12, 1.42)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 12-13 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1994) Study of respiratory symptoms in 6 U.S. cities, 1984-1988	Daily monitoring of PM_{10}, $PM_{2.5}$ at each city	median PM_{10} = 30 $\mu g/m^3$, 10% tile = 13, 90% tile = 53 median $PM_{2.5}$ = 18 $\mu g/m^3$, 10% tile = 7, 90% tile = 37	(not given)	Autoregressive logistic regression using GEE	SO_2, median = 4 ppb, 10% tile = 1, 90% tile = 18 NO_2, median = 13 ppb, 10% tile 5, 90% tile = 24, ozone	temperature, day of week, city or residence	all two pollutant models were fitted with minimal effect on PM	Cough (PM_{10} lag 1) 1.51 (1.12, 2.05) Upper resp. (PM_{10} lag 2) 1.39 (0.97, 2.01) Lower resp. (PM_{10} lag 1) 2.03 (1.36, 3.04)
Braun-Fahrländer et al. (1992) Study of preschool children in four areas of Switzerland	Daily monitoring of TSP	(not given)	4.4	Logistic regression	SO_2, NO_2, and ozone levels not given	city, risk strata, season, temperature	none	Upper resp. 1.55 (1.10, 2.24)
Roemer et al. (1993) Study of children with chronic respiratory symptoms in Wageningen, The Netherlands	Daily monitoring of PM_{10}	6 days above 110 $\mu g/m^3$	.094 incidence rate	Autoregressive logistic regression	SO_2 and NO_2 means not given	(not given)	none	Cough (not given, probably less than one)
Dusseldorf et al. (1994) Study of adults near a steel mill in The Netherlands	Daily monitoring of PM_{10}, iron, sodium, silicon, and manganese	mean PM_{10} = 54 $\mu g/m^3$, range = 4 to 137)	(not given)	Logistic regression	Geometric mean iron = 501 ng/m^3, manganese = 17 ng/m^3, silicon = 208 ng/m^3	(not given)	none	Cough 1.14 (0.98, 1.33)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 12-13 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Ostro et al. (1991) Study of adult asthmatics in Denver, Colorado November 1987 to February 1988	Two monitors provided daily measurements of $PM_{2.5}$	22 $\mu g/m^3$, range = 0.5 to 73	15 (out of 108)	Autoregressive logistic regression	nitric acid, sulfates, nitrates, SO_2, and hydrogen ion	day of survey, day of week, gas stove, minimum temperature	none	Cough 1.09 (0.57, 2.10)
Ostro et al. (1993) Study of non-smoking adults in Southern California	Apparently one site (Azusa). PM measurements included sulfate fraction and COHS	mean sulfate = 8 $\mu g/m^3$, range = 2 to 37 mean COHS = 12 per 100 ft, range = 4 to 26	4.2/person for lower, 10.2/person, upper	Logistic regression	ozone, mean = 7 pphm, range = 1 to 28	temperature, rain humidity	none	Sulfates: Upper resp. 0.91 (0.73, 1.15) Lower resp. 1.48 (1.14, 1.91)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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obstructive lung disease and, in some cases, asthma are some factors related to more rapid declines in lung function in adults (Tager et al., 1988; Vedal et al., 1986).

Factors in the environment undoubtedly influence the natural history of the growth and decline of lung function. Three such factors, viral respiratory illness, active smoking and passive exposure to tobacco smoke products, are briefly summarized here. As in older children and adults clinically inapparent alteration in lower airway function occur during URI in infants (Martinez et al., 1990). Both differences in the caliber or length of the airway and differences in the elasticity of the lungs and chest wall may exist between infants who subsequently have wheezing with a viral lower respiratory tract illness and those who do not have wheezing with a similar illness. Thus the initial airway caliber, length, or both (and perhaps the structure of the lung parenchyma) may predispose infants to wheezing in association with common viral respiratory infection (Martinez et al, 1988; Tager et al., 1993; Martinez et al., 1991; Martinez et al., 1995).

Active smoking is the major risk factor for chronic airflow limitation. As a group, cigarette smokers have more rapid reductions in lung function with age relative to non-smokers. In approximately 15 to 20% of long-term regular smokers, this increased loss of lung function leads to the development of symptomatic chronic obstructive lung disease. Smoking cessation can be associated recovery of a very small amount of function and a lessening of the rate of decline of function (Dockery et al, 1983). However, such cessation amongst persons with far advanced chronic obstructive lung disease has little effect on the overall course of the disease.

Passive exposure to products of tobacco smoke generated by parental smoking consistently has been associated with alterations in lung function in infants and children. Maternal smoking, in particular, has demonstrated an exposure-response association with reduced lung function. The extensive body of evidence in support this association has been reviewed by the U.S. Environmental Protection Agency (1992). The issue of passive exposure to tobacco smoke has particular conceptual relevance to the issue of the health effect of ambient PM, since tobacco smoke is a major PM source in indoor environments.

Studies of Pulmonary Function in Children

Dockery et al. (1982) studied changes in lung function in school age children as the result of air pollution episodes in Steubenville, OH — one of the cities in Harvard Six City studies. Steubenville was known to have large changes in SO_2 and TSP exposures, and these occurred in the fall of 1978, the fall of 1979, the spring of 1980, and the fall of 1980. During each period, lung function measurements ($FEV_{0.75}$ and FVC) were taken prior to the episode and within a week after the episode. Linear regression was used to estimate the effect of pollution on each child separately. The slopes were summarized by period and combined in a total summary. The pooled slopes were significantly different from zero for both TSP and SO_2 for both $FEV_{0.75}$ and FVC. The median slope for $FEV_{0.75}$ with TSP was -0.018 ml per $\mu g/m^3$ and for FVC it was -0.081 ml per $\mu g/m^3$.

During November, 1984, Dassen et al. (1986) obtained baseline pulmonary function data for a sample of more than 600 children aged 6-11 in the Netherlands. Then, a subset of the same children (N = 62) was retested again in January, 1985, during an air pollution episode when 24-h mean values for TSP (hi-vol samples), RSP (respirable suspended particulate, cyclone sampler), and S02 (acidimetric technique) measured via a 6-station network all reached the range of 200 to 250 $\mu g/m^3$. Lung function values of 62 children were taken at the end of the episode. Growth adjusted FVC values decreased by an average of 62 ml (11), $FEV_{1.0}$ values decreased by 50 ml (10), and PEFR values decreased by 219 ml/sec (62). These decreases were all statistically significant. Several lung function parameters showed statistically significant average declines of 3 to 5% at second (episode) testing in comparison with each child's own earlier baseline values, including decrements seen on the second day of the episode in both FVC and FEV levels, as well as in measures reflecting small airway functioning (i.e., maximum mid-expiratory flow and maximum flow at 50% vital capacity). Declines from their original baseline values for these parameters were still observed 16 days after the episode upon retesting of another subset of the children, but no differences were found between baseline and retest values for a third subset of children reevaluated 25 days after the episode. The 24-h mean TSP, RSP, and SO_2 levels measured in the 100 to 150 $\mu g/m^3$ range just prior to the last lung function tests may not have been sufficient to cause observable pulmonary function effects in children.

Quackenboss et al. (1991) reported results of a lung function study of asthmatic children aged 6 to 15 years in Tuscon, AZ. The data were collected over two week periods from May 1986 to November 1988. Peak flow rates (PEFR) were measured with mini-Wright peak flow meters with three tests during each of the four times per day (morning, noon, evening, bed). Activity patterns were recorded in diaries, as well as symptoms and medication use. $PM_{2.5}$, PM_{10}, and NO_2 measurements were made both inside and outside the home during the two week period for 50% of the homes. $PM_{2.5}$ levels were elevated in homes with environmental tobacco smoke. Exposures for the remaining homes were estimated statistically. A random effects linear model was used to estimate the effect of pollutants and other covariates on PEFR. The NO_2 levels had the greatest effect on PEFR rates, but the indoor $PM_{2.5}$ levels were associated with a 15 ml/s decrease in morning PEFR (within day change) per unit increase of $PM_{2.5}$ in $\mu g/m^3$. The relationships were unaffected by the inclusion of weather variables such as temperature, wind speed, and dew point.

Pope et al. (1991) studied pulmonary function (PEFR) in asthmatic school children in the Utah Valley. The group of participants was selected from samples of 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon Utah. Participants were restricted to those who responded positively to one of: ever wheezed without a cold, wheezed for 3 days out of a week for a month or longer or had a doctor say the "child has asthma". This resulted in 34 subjects being included in the final analyses. PM_{10} monitors were operated by the Utah State Department of Health. 24 hr samples were collected from midnight to midnight, and PM_{10} values ranged from 11 to 195 $\mu g/m^3$. There was limited monitoring of SO_2, NO_2, and ozone. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0110 l/min (0.0082). This coefficient corresponds to a 9.2 ml decrease in PEFR for a 50 $\mu g/m^3$ increase in PM_{10}. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope et al. (1991) also studied pulmonary function (PEFR) in asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects being included in the final analysis. PM_{10} monitors operated by the Utah State

Department of Health collected 24 hr samples from midnight to midnight (PM_{10} range 11 to 195 $\mu g/m^3$). There was limited monitoring of SO_2, NO_2, and ozone. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0175 l/min (0.0092), corresponding to a 14.6 ml decrease in PEFR for a PM_{10} 50 $\mu g/m^3$ increase. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope and Dockery (1992) studied non-asthmatic symptomatic and asymptomatic Utah Valley children selected from samples of 4th and 5th grade elementary students in three schools near PM_{10} monitors in Orem and Lindon, Utah. A questionnaire identified 129 children who were mildly symptomatic and 60 were selected; and 60 more with no symptoms were selected. Utah State Department of Health PM_{10} monitors collected 24 hr samples from midnight to midnight; PM_{10} ranged from 11 to 195 $\mu g/m^3$. For purposes of analyses, five day moving averages of PM_{10} were used for exposure estimates. Limited monitoring of SO_2, NO_2, and O_3 was conducted. Mean deviations of PEF were computed for each individual. Weighted least squares regression found a -0.00060 (0.00020) decrease in PEF per unit increase in PM_{10} in symptomatic children and a -0.00042 (0.00017) change in PEF per unit increase in PM_{10} in asymptomatic children. No relationship between low temperature and PEF was found.

Koenig et al. (1993) studied two groups of elementary school children, one during the school year 1988 to 1989 and another during the school year 1989 to 1990. The subjects in the first study included 326 children, 24 of whom were asthmatics. During the second year, only 20 asthmatics were studied (14 of which were in the original study). The FVC and $FEV_{1.0}$ were measured for each child in September, December, February, and May of each year. Fine particulates were considered to be the primary pollutant of interest and were measured by light scattering using a nephelometer. 12 hour averages (7:00 PM to 7:00 AM) were used as the exposure measure. Additional information on $PM_{2.5}$ was collected and shown to be linearly related to light scattering ($r^2 = 0.945$). A mixed model was used to analyze the data. The model included random effects terms for the individuals and fixed effects terms for height, temperature, and light scattering. No relationship was found

between light scattering and lung function in the larger sample, but a significant relationship was found in the asthmatics. When converted to $PM_{2.5}$ units, the decrease in $FEV_{1.0}$ was -0.0017 (0.0006) liters/($\mu g/m^3$). Effects of other pollutants were not considered.

Silverman et al. (1992) studied 36 asthmatic children over a 10-day period in the summer and a 10-day period in the winter in Toronto, Canada. The first study (17 subjects) and the second study (19 subjects) were selected from a pool of 800 asthmatic children from the Gage Research Institute in Toronto. Patients were selected if they had a diagnosis of asthma and if they experienced wheezing at least a few times a week. Lung function measurements were obtained at the start and end of each day. Subjects carried a portable monitor which measured SO_2, NO_2, and particulate matter. The first study measured particles less then 25 microns, the second less than 10 microns. The regression coefficient of $FEV_{1.0}$ on PM was -.00078 liters/($\mu g/m^3$) for the summer and .00018 liters/($\mu g/m^3$) for the winter for Study 1, and $-.00165$ and .00283 for the summer and winter in Study 2. No standard errors were given. The SAS analysis procedure was not specified, and there was no mention of a repeated measures design. Results from analyses using SO_2 and NO_2 as exposure variables were not reported.

Hoek and Brunekreef (1993) studied pulmonary function in 112 children aged 7 to 12 who lived in a non-urban area near Wageningen, ND. Spirometry was performed every three weeks for a total of six times. One more measurement was made during an air pollution episode. PM_{10} was measured daily (3PM to 3PM) with an instrument similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured by fluorescence and NO_2 by chemiluminescence. Linear regression analysis using the SAS procedure AUTOREG yielded an estimated coefficient for FEV_1 with PM_{10} of -.00055 liters/($\mu g/m^3$) (.00010) and for PEF of -.00082 (liters/s)/($\mu g/m^3$) (.00050). Lagged PM_{10} values gave similar coefficients. SO_2 and black smoke coefficients were similar in magnitude. Thus both FEV_1 and PEF showed decreases related to pollution measures, but it was not possible to assign the effects to a particular pollutant.

Hoek and Brunekreef (1994) studied pulmonary function and respiratory symptoms in children aged 7 to 11 in the towns of Deurne, Enkhuizen, Venlo, and Nijmegen, The Netherlands. Each child was studied six to ten times during one of three winters (1987/88, 1988/89, 1989/90). Measurements of FEV were obtained along with information on

respiratory symptoms. PM_{10} was measured daily (3 pm to 3 pm), as were SO_2 and NO_2. Linear regression analysis using the SAS procedure MODEL with the %AR macro was used. The estimated coefficient for FEV_1 with PM_{10} was -.00010 liters/($\mu g/m^3$) (.00006) and the estimated coefficient for PEF was $-.00082$ (liters/s)/($\mu g/m^3$) (.00029). Lagged PM_{10} values gave similar coefficients. PM_{10} and NO_2 coefficients remained significant after adjusting for ambient temperature, but pollutants such as SO_2, HONO, sulfate and nitrate did not. Other adjustments for factors such as relative humidity, self-reported colds, and learning effects did not affect magnitudes of estimated coefficients.

Brunekreef et al. (1991) further analyzed data from Dockery et al. (1982) on pulmonary function in children in Steubenville, OH as part of the Harvard Six-Cities Study discussed earlier. Linear decreases in forced vital capacity (FVC) with increasing TSP concentrations were found, and slopes were determined for linear relationships fitting the data for four different observation periods (fall, 1978; fall, 1979; spring, 1980; fall, 1980). The slope of FVC vs. TSP was calculated for 335 children with three or more observations during any of the four study periods, with 194 having been tested during more than one study period. Individual regression coefficients for each child using pollution as the independent variable were calculated. The distribution of coefficients was then trimmed to eliminate outliers. Slopes for TSP using one and five day averages were significantly lower than zero for both FVC and $FEV_{0.75}$. No overall dose-response relationship was estimated.

Dusseldorf et al. (1994) studied pulmonary function in 32 adults living near a large steel plant in Wijk aan Zee, The Netherlands. During the study period PM_{10} levels ranged from 36 to 137 $\mu g/m^3$. Peak flow measurements (PEFR) were measured twice daily using a Mini Wright peak flow meter. Diary information on acute respiratory symptoms, medication use, and presence of fever was also collected. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. Multiple linear regression analysis with adjustment for first order autocorrelation. The regression coefficient for evening PEFR on PM_{10} (lag zero) was -.054 l/min/$\mu g/m^3$ (0.022), and the regression coefficient for morning PEFR on PM_{10} (lag zero) was -.092 l/min/$\mu g/m^3$ (0.026). These correspond to an estimated decrease in PEFR for an increase of 50$\mu g/m^3$ PM_{10} of 45 and 77 ml/sec respectively. Lags of one, two, and three days were also fitted, but they gave smaller estimated coefficients.

Lebowitz et al. (1992) studied 30 children with a current diagnosis of asthma using PEFR measurements twice daily. A total of 674 PEFR measurements were analyzed. Individual activity patterns were collected. $PM_{2.5}$ and PM_{10} samples were collected in 50% of the homes. Local monitoring stations were used to measure outdoor exposure. Using a random effects model, PEFR was found to be significantly lower in the morning in children who lived in homes with higher concentrations of PM.

Johnson et al. (1982) studied lung function in children as part of the Montana Air Pollution Study, designed to collect sequential pulmonary function data on children from November 1979 to April 1980 at six different time points. By adding a 7th round of testing on May 23, 1980, the study took advantage of the natural experiment created by the eruption on May 18, 1990 of the Mt. St. Helens volcano in Washington state. Approximately 100 children had been measured for FVC, $FEV_{1.0}$, and FEF_{25-75} on six earlier occasions. During five of these measurement periods the 3-day TSP average was relatively low (98 to 154 $\mu g/m^3$), but in one period, the average was 440 $\mu g/m^3$. The eruption of the volcano on May 18, 1980 forced nearly everybody indoors for the following three days. Most children who ventured out did so with masks on. By May 23, the air had cleared enough so that children returned to school, and their pulmonary function was measured. The TSP values for the four preceding days ranged from 948 to 11,054 $\mu g/m^3$. The authors used an unusual method of analysis which was described in their appendix. The results indicated that there was a bigger decrease in lung function on the 400 $\mu g/m^3$ day than there was on the day following the high volcanic ash episode.

Johnson et al. (1990) studied pulmonary function in 120 3rd and 4th grade children in Missoula, MT during 1978 to 1979 who were tested up to six times between October 1978 and May 1979. FVC, $FEV_{1.0}$, and FEF_{25-75} were measured. TSP was monitored daily near the center of the study area. RSP was measured every third day and estimated from TSP and other variables on the other days. The average of the current day's pollution and the previous two day's pollution was used as the estimate of exposure. Each child who had at least three readings was used as his own control. Percent changes in FVC, $FEV_{1.0}$, and FEF_{25-75} on higher pollution days as compared with the same measurements on days with lower pollution exposure were used as the response variable. FVC averages on days with RSP 31 to 60 $\mu g/m^3$ were decreased about 0.40% and on days with RSP $>$ 60 were

decreased about 0.75%. Similar but smaller changes were seen in $FEV_{1.0}$ and FEF_{25-75}. All changes were marginally significant. The authors did not mention any other pollutants.

Roemer et al. (1993) studied children with chronic respiratory symptoms in the Netherlands. Parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Seventy-four of the 313 children with positive responses cough or shortness of breath were included in the study. Peak flows were measured in the morning and evening. PM_{10} was measured daily using an Anderson dichotomous sampler. Sulfur dioxide and NO_2, and black smoke were also measured. Regression coefficients for both morning and evening current day's PM_{10} levels were significant. Lagged PM_{10} values were not significant. The coefficient for current days PM_{10} with morning PEF was -0.00090 (liters/s)/($\mu g/m^3$) (0.00028). SO_2 was also significantly related to evening peak flow but not to morning peak flow. Black smoke was not related to peak flow.

Bock et al. (1985) and Lioy et al. (1985) examined pulmonary function of 39 children at a camp in Mendham, New Jersey during a 5-week period in July to August, 1982. Ozone was continuously monitored using chemiluminescent analysis. Ambient aerosol samples were collected on Teflon filters with a dichotomous sampler having a 15 μm fractionation inlet and a coarse/fine cut size of 2.5 μm (Sierra Mod 244-E). Aerosol acidity was measured by strong acid (H^+) content, using the pH method. Highly significant changes in peak expiratory flow rate (PEFR) were found to be related to ozone exposure, as well as a baseline shift in PEFR lasting approximately one week following a haze episode in which the ozone exposure exceeded the NAAQS for four consecutive days that included a maximum concentration of 185 ppb. There was no apparent effect of H^+ on pulmonary function. The authors did state, however, that the persistent effects associated with the ozone episode could have been due to acid sulfates as well as, or in addition to, ozone but additional uncollected data were needed to evaluate this possibility.

Lioy et al. (1987) and Spektor et al. (1988) measured respiratory function of 91 active children who were residing at a summer camp on Fairview Lake in northwestern New Jersey during a 4-week period in 1984. Continuous data were collected for ambient temperature, humidity, wind speed and direction, and concentrations of ozone, H_2SO_4, and total sulfates. Ozone was measured by U.V. absorbance, and H_2SO_4 and total sulfates were determined by

a flame photometric sulfate analyzer (Meloy Model 285) preceded by a programmed thermal pretreatment unit. The ambient aerosol samples were collected on quartz fiber filters with a dichotomous sampler having a 15 μm fractionating inlet (PM_{15}) and a coarse/fine cut-size of 2.5 μm (Sierra Model 244-E). Aerosol acidity, as measured by strong acid (H^+) content, was determined using the pH method. The maximum values recorded for H_2SO_4 and NH_4HSO_4 were 4 and 20 μg/m3 respectively. While effects were reported as being associated with exposure to ozone, no effects were found to be related to exposure to the acid aerosol concentrations experienced in this study.

Studnicka et al. (1995) studied acidic particles in a summer camp study in southern Austria between June 28 and August 28, 1991. Daily spirometry was measured in three panels of children age 7 or greater with a total of 133 subjects. On site measurements were taken for H^+, sulfate, ammonia, PM_{10}, and ozone. A repeated measures linear regression model was fitted using a SAS macro. Pulmonary function measurements were made using a rolling-seal-type instrument which gave flow-volume tracings. From these, $FEV_{1.0}$, FVC, and PEFR were measured. The results from all three panels combined suggested that PM_{10} was marginally related to a decrease in $FEV_{1.0}$, but was less related to FVC and PEFR. Other pollutants showed less of a relationship than did PM_{10}. The coefficient for FVC suggested that an increase of 50 $\mu g/m^3$ in PM_{10} would result in a 66 ml (39) decrease in FVC, and a 99 ml/s (99) decrease in PEFR.

Neas et al. (1995) studied peak expiratory flow rates in 83 children living in Uniontown, Pennsylvania. PEFR rates were measured over an 87 day period during the summer of 1990 using a Collins recording survey spirometer. Air pollution data was collected from a monitoring site located 2 km north of the center of the town, and included PM_{10}, $PM_{2.5}$, ozone, SO_2, sulfate fraction, and H^+. The $PM_{2.5}$ values had a mean of 24.5 $\mu g/m^3$ with an interquartile range of 18.9. The PEFR values were analyzed using the autoregressive integrated moving average procedure of SAS. The model included terms for temperature, time trend, and second-order autocorrelations. The largest decreases in PEFR were related to H^+, but they were also related to both $PM_{2.5}$ and ozone.

Studies of Pulmonary Function in Adults

Pope and Kanner (1993) studied adults in the Salt Lake Valley, using spirometric data taken from the Salt Lake City Center of the Lung Health Study supported by NHLBI; 624 participants were selected based on presence of mild COPD and willingness to participate in a 5-year smoking cessation study. Analyses were based on two initial screening visits before randomization into the NHLBI Study; 399 subjects had adequate data to be in the analyses. PM10 monitors were operated by the Utah State Department of Health collected 24-h samples midnight to midnight. Limited monitoring of SO_2, NO_2, and O_3 showed these pollutants to be always well below their respective NAAQS and none were included in the analyses. Regression analyses on change in FEV_1 (liters) per change in PM_{10} ($\mu g/m^3$) found a coefficient of -0.00058 liters/($\mu g/m^3$) (0.00022). Changes were also seen in ratio of FEV_1 to FVC. PEF was not measured.

Perry et al. (1983) conducted a longitudinal study of 24 Denver area asthmatics' pulmonary function, symptoms, and medication use followed daily January through March, 1979. Peak flows (from Mini-Wright Peak Flow Meters), symptoms, and medication use were measured twice a day. Fine and coarse mass as well as sulfate and nitrate fractions were available from an east and west Denver site. CO, SO_2, and O3 were also measured. Dichotomous, virtual impactor samplers provided daily measurements of inhaled PM (total mass, sulfates, and nitrates), for coarse (2.5 to 15 μm) and fine fractions (<2.5 μm) with all PM measures being relatively low during the study. Temperature and barometric pressure were also measured. Individual subject data were analyzed separately by regression analysis. The coefficients were then tested using a non-parametric Wilcoxon signed rank test. None of the PM measures were associated with changes in any of the health endpoints. This study had very low power, given the small sample size and lack of high PM levels.

Acute Pulmonary Function Studies Summary

The acute pulmonary function studies (summarized in Table 12-14) are suggestive of a short term effect resulting from particulate pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The results appear to be larger in symptomatic groups such as asthmatics. The effects are

seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent.

12.4 HEALTH EFFECTS FROM LONG-TERM EXPOSURE TO PM

12.4.1 Mortality Effects of Long-Term PM Exposures

The long-term effects of air pollution may be examined by considering gradual changes over time (the longitudinal study) or by contrasting spatial differences at a given point in time (the cross-sectional study). Longitudinal studies require long-term changes in air quality, such as those that accompany pollution abatement campaigns. Only a few such studies have been published (Lipfert, 1994a); none recently. Cross-sectional studies are designed to infer the accumulated long-term effects of the environment by contrasting spatial differences. As with all epidemiology, such spatial gradients may only be credibly attributed to air quality after the potential confounders have been controlled.

Mortality rates or probabilities of survival may differ by location for any of a number of reasons:

(1). geographic variations in the presence of specific endemic diseases, such as malaria or influenza.

(2). geographic variations in risk factors, which may either be associated with the location per se or with the people who tend to live there, such as climate or the quality of the environment, the age and racial distributions of the population, its dietary and smoking habits, or occupational factors associated with local industry.

(3). geographic variations in the frequencies of acute events, such as heat waves, accidents, or natural disasters.

Epidemiological studies of the long-term effects of community air pollution on mortality are most likely to be concerned with the second and third categories, since (aside from occupational lung disease) there are no diseases specific to these pollutants.

The second category of geographic factors relates to chronic effects on health, and it is the task of the analyst to distinguish the effects of air pollution from those of other risk factors in much the same way that it is necessary to adjust for seasonal trends in time-series

TABLE 12-14. ACUTE PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Dockery et al. (1982) School age children in Steubenville, OH, measured at three times between 1978 and 1980	Single station measuring TSP	up to 455 $\mu g/m^3$	individual regression analyses for each child, coefficients pooled across time	SO_2	average temperature	TSP	FVC: 8.1 ml $FEV_{0.75}$: 1.8 ml Note: decreases were statistically significant
Dassen et al. (1986) School age children in The Netherlands, measured in November, 1984 and January, 1985	Six station network measuring TSP, RSP (PM_{10})	TSP and RSP both exceeded 200 $\mu g/m^3$	multiple linear regression	SO_2	technician, appliance, presence of colds	RSP	slopes not given but FVC, FEV_1, and PEFR were significantly reduced during episodes
Quackenboss et al. (1991) Asthmatic children aged 6 to 15 years in Tuscon, AZ, measured in May and November, 1988	Individual monitoring of homes of $PM_{2.5}$, PM_{10}		Random effects linear model	NO_2	temperature, wind speed, dew point	$PM_{2.5}$	PEFR: 375 ml/s Note: these are diurnal rather than daily changes
Pope et al. (1991) Study of asthmatic children in the Utah Valley	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 11 to 195 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	low temperature	PM_{10}	PEFR: 55 ml/s (24, 86)
Pope and Dockery (1992) Study of non-asthmatic symptomatic and asymptomatic children in the Utah Valley	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 11 to 195 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	low temperature	PM_{10}	Symptomatic PEFR 30 ml/s (10, 50) Asympto-matic PEFR 21 ml/s (4, 38)

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TABLE 12-14 (cont'd). ACUTE PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Koenig et al. (1993) Study of asthmatic and non-asthmatic elementary school children in Seattle, WA in 1989 and 1990	$PM_{2.5}$ calibrated from light scattering	$PM_{2.5}$ ranged from 5 to 45 $\mu g/m^3$	Random effects linear regression	none	height, temperature	$PM_{2.5}$	Asthmatics FEV_1 42 ml (12, 73) FVC 45 ml (20, 70) Non-asthmatics FEV_1 4 ml (-7, 15) FVC -8 ml (-20, 3)
Hoek and Brunekreef (1993) Study of children aged 7 to 12 in Wageningen, Netherlands	Single site measure black smoke. PM_{10} was measured during episodes	range of PM_{10} was 30 to 144 $\mu g/m^3$	SAS procedure AUTOREG	SO_2, NO_2	day of study	PM_{10}	PEFR 41 ml/s (-8, 90)
Roemer et al. (1993) Study of children with chronic respiratory symptoms in The Netherlands	Single site measure black smoke. PM_{10} was measured using an Anderson dichot	range of PM_{10} was 30 to 144 $\mu g/m^3$	multiple linear regression analysis	SO_2, NO_2	none	PM_{10}	PEFR 34 ml/s (9, 59)
Pope and Kanner (1993) Study of adults in the Utah Valley from 1987 to 1989	PM_{10} was collected daily from the north Salt Lake site	PM_{10} daily mean = 55 $\mu g/m^3$, ranged from 1 to 181 $\mu g/m^3$	Linear regression on difference in PFT as a function of PM_{10}	Limited monitoring of SO_2, NO_2, and ozone	low temperature	$PM_{2.5}$	FEV_1 29 ml (7, 51) FVC 15 ml (-15, 45)

*Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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studies. Long-term health risk factors may be further subdivided into factors that relate to the population of a given place (age, race, education, lifestyle, for example) and factors that relate to the physico-chemical environment of that place (climate, air and water quality). There are also likely to be interactions between these two subcategories, since places with desirable environments may attract as in-migrants that portion of the population that is better off economically while the disadvantaged part of the population may be forced to remain in less desirable locations and in those with depressed economies.

The third category above is included in long-term studies because annual mortality rates must also reflect the net sum of acute events that took place that year (Evans et al., 1984a). If the increases in daily death rates associated with acute events are not subsequently canceled by decreases (a phenomenon referred to as "harvesting"), annual rates will indicate the history of these acute effects. Thus, differences in long-term mortality rates associated with air pollution are likely to reflect some combination of acute and chronic effects. Although both types of information are useful contributions to the overall understanding of the health effects of air pollution, their distinction may be difficult if based on statistical criteria alone.

Long-term mortality studies are considered here in two groups:

1. Cross-sectional studies based entirely on the characteristics of groups averaged across various geopolitical units, referred to as population-based studies.

2. Prospective cohort studies based on data on individuals. The available studies of this type are also cross-sectional in design, because their air pollution exposure data were based on community-wide averages in much the same way as the population-based studies.

Because none of the studies available for review had individual data on personal exposures to air pollution, they must all be classed as "ecological," in the strictest application of the definition. The population-based studies used annual mortality rates and annual average air quality data, usually for coincident periods centered on decennial census years. Brief considerations have been given to lagged exposures in several instances, in an attempt to deduce effects of exposures over longer periods. The prospective studies consider the net survival rates over a multi- year period of follow-up; various assumptions were made by the different investigators about the appropriate timing of air pollution exposures. The studies

thus varied in terms of their ability to provide either a measure of lagged chronic effects or an integrated measure of acute effects during a given period.

12.4.1.1 Methodological Considerations

Methods for analysis were considered in a general way in the Methodology discussion (Section 12.2). However, there are some specific guidelines that should be considered with respect to the estimation of long-term effects on the basis of spatial gradients. In general, the most difficult problems are collinearity among pollutants, variable and inadequate characterizations of pollutant exposure, and confounding by non-pollutant variables.

The study of long-term or chronic health effects of air pollution began with population-based studies and became fraught with difficulty and controversy, more so than the short-term studies (Smith, 1975; Lipfert, 1980; Ware et al., 1981; Ricci and Wyzga, 1983; Evans et al., 1984b). The primary method of analysis involves comparing the health statistics of populations of places which have had different environments over the long-term. However, the comparisons are often complicated or even compromised by other differences that may be related to the sources and effects of air pollution, such as industrialization or climate. Cross-sectional studies often use data from only one specific year that may or may not be truly representative of long-term environmental conditions.

Spatial Patterns in the United States

Spatial patterns of U.S. mortality rates show some well-defined trends that have existed for decades (Lipfert, 1994a). Such patterns are sometimes called the "geography of disease." In general, heart disease is higher east of the Mississippi and ischemic heart disease shows even sharper gradients and peaks in the Northeast (part of this gradient could be due to differences in diagnostic practices). Cancer death rates tend to be higher in the Northeast, but not exclusively in industrialized states (Vermont, New Hampshire and Maine are relatively high). Gorham et al. (1990) argue that breast cancer is higher in northern latitudes because of reduced intake of vitamin D; such patterns were also seen in the former Soviet Union, for example. Lung cancer deaths are more evenly distributed and include some of the states with high tobacco use (Nevada, Kentucky, Virginia, but not North

Carolina). Pneumonia and influenza deaths are distributed across the country but tend to be higher north of about the 36th parallel.

Spatial trends in air pollution have both local and regional patterns. Local patterns within cities reflect the presence of primary pollutants from local sources (CO from traffic, particles from industrial operations, SO_2 and NO_2 from combustion sources, for example). There are also multi-state regional patterns in secondary pollutants, such as sulfates and other fine particles in Appalachia and the "rust belt," and ozone in Southern California and along the Northeast corridor from Washington to Boston. Collinearity among pollutants results from common spatial patterns of their major sources.

Associations between air pollution and health may be suggested by coincident spatial patterns; the challenge to the epidemiologist is to establish whether such associations are causal or merely circumstantial, since there are also many lifestyle parameters that vary spatially, such as smoking, diet, exercise and employment status. Furthermore, some of these factors have much stronger effects on mortality than air pollution: for example, a difference of 11 years in life expectancy according to whether all the "good" health practices are followed (Belloc, 1973), and 55% higher mortality for unemployed white men, aged 25 to 64 (Sorlie and Rogot, 1990). (See Yeager et al. [1995] for a recent showing of the significant correlation between sedentary lifestyle and coronary heart disease mortality at the state level that remained after controlling for smoking and hypertension; the relative risk for sedentary lifestyle was about 1.8.) Unfortunately, suitable data on these potential confounders are not always available. The possibilities for confounding by regional factors vary with the scale of the analysis; comparisons within regions may thus be less susceptible than comparisons across the whole country. For this reason, consistency between different types of studies becomes very important in considering causality.

Risk Measures

Most of these studies consider deaths from all causes. Some of them subtract deaths from accidents, homicides, and suicides, yielding a quantity referred to by various authors as "nonexternal" deaths, "deaths from all natural causes," or "all-disease deaths." Measures of the risks attributed to air pollution differ by type of study and regression model. Some

studies report relative risks (mortality ratios) due to specified but arbitrary pollution "reference" levels, such as 100 $\mu g/m^3$ of particulate matter or 50 ppb of ozone. These figures are obtained by multiplying the regression coefficient (the relative risk per unit of pollution) times the desired pollution level. This practice is convenient for comparing studies of the same pollutant but is less suitable for comparing the relative effects of different pollutants, because the actual relationship between pollutants in a given city may not correspond with that assumed by the reference levels. Others report ordinary least-squares regression coefficients in the original units of the study, such as change in annual death rate per unit of pollution. These coefficients are specific to the measures used for both dependent and independent variables, but may be converted to approximate log-linear coefficients or relative risk by dividing by the mean value of the dependent variable.

One measure that is free of measurement units is the "elasticity," a term taken from economics defining a nondimensional regression coefficient of y on x_i (at the mean) as

$$e_i = b_i \bar{x}_i / \bar{y} \qquad [12.4.1\text{-}1]$$

Elasticities may be expressed as decimals or in percent and offer another measure of attributable risk, based on the mean values of the x_i. An elasticity of 0.04 thus corresponds to a relative risk of 1.04 at the mean pollution level. Comparison of two elasticities may be misleading if the mean values differ widely. Note that when the "effect" of a variable ($b_i x_i$) is expressed as a percentage of the mean total response, "effect" and elasticity are synonymous.

Model Specifications for Long-term Mortality Studies

By and large, identification of environmental influences on longevity has not been part of the medical "mainstream," although epidemiological studies have included the effects of both air quality and drinking water quality (mainly water hardness; see Pocock et al., 1980, for example). Because of the large number of potential confounding variables in spatial analysis, multiple regression has been the statistical method of choice. Models for population studies may be either linear or log-linear, and some investigators have included pollutant

thresholds (hockey-stick models). For population-based studies, the dependent variable is usually an annual mortality rate for the geographic unit in question. Rosenbaum and Rubin (1984) argue that if age adjustment is used for the dependent variable, it must also be used for any independent variable that may also exhibit age dependency (such as smoking or air pollution exposure).

Prospective studies of individuals have featured the proportional hazards model, in which the risk factors are multiplicative (these coefficients correspond to elasticities). The dependent variable is thus dichotomous (alive or dead). The range in survival probability among adult individuals is quite large, encompassing more than two orders of magnitude in mortality rate, which indicates the very large effects of individual risk factors. Years of medical research have identified some of these risk factors as genetic predisposition, exposure to infectious diseases, access to medical care, and personal lifestyles, including diet, exercise, and smoking habits.

In contrast, the variability among cities and Standard Metropolitan Statistical Area (SMSA) mortality rates is relatively modest, with a coefficient of variation (CV) of about 17% (Lipfert, 1993a), most of which is due to differences in age distributions. This reduction in variability occurs because areas as large as SMSAs in the United States tend to be similar in terms of their average characteristics, especially within regions; i.e., much of the variability in individual risk factors is "averaged out." It is thus much easier to accurately predict with a mathematical model the death rate averaged over some geopolitical unit than the probability of survival of an individual over a given time. In any case, the ability to accurately predict the effects of exposure to air pollution depends on the validity of the model. Unfortunately, it is ineluctable that all such models are incomplete and thus contain the potential for bias (Cohen, 1994).

As discussed in more detail above, to confound, a variable must be correlated with both the dependent variable and the independent variable of interest. This limits consideration to established mortality risk factors that may vary spatially in ways similar to the spatial patterns of air pollution. In many cases, appropriate data on confounders are not available and surrogates must be used for the actual mortality risk factors. Education is an example; staying in school longer per se does not prolong life, but better educated individuals are

likely to have higher incomes and thus access to better medical care; they may also have healthier personal lifestyles. However, the relationship between education and health is likely to be nonlinear, as is the relationship between income and longevity (Rogot et al., 1992). Greenland and Robins (1994a) point out with examples that control of potential confounders "crucially hinges on adequate measurement of the potential confounders." It therefore follows that the assumption of linearity may not be always be appropriate for surrogate risk factors. Alcohol consumption and body mass are two of the risk factors that have been shown to have non-linear relationships with mortality (see Gronbaek et al., 1994, for example).

In cross-sectional regressions, confounding is inevitably a matter of degree, especially for those pollutants that exhibit broad spatial patterns. Sulfate is a case in point; the following correlations were given by Lipfert et al. (1988) among U.S. cities, ca. 1980:

% with college education	-0.44
population change, 1970-80	-0.39
% below poverty	0.33
% Hispanic	-0.22
% Asian	-0.28
smoking index	0.15
drinking water hardness	0.00

In contrast, the correlation between SO_4^{2-} and crude city mortality rate was 0.44, but after taking the above variables into account in a multiple regression, the correlation dropped to 0.2 to 0.3, depending on the data set considered. Since this publication, state-level survey data on many other behavioral risk factors has become available (Siegel et al., 1993), and many of these factors are also correlated with sulfate concentrations. For example, the state-level correlation with "% 65 and over with sedentary life-style" was 0.64. The spatial collinearity between sulfate and these demographic/lifestyle factors is similar to that between daily air pollution and weather, and presents a challenge to the analyst to separate cause from circumstance.

The need for confounder control may also vary with the scale of the cross-sectional analysis and the spatial variability of the air pollutants of concern. For example, in many

cases, ambient air quality monitors are sited near the locations of the worst air quality, near point sources or in the densest part of a city, in keeping with their intended regulatory function. They may thus overestimate the exposures of persons living in more distant suburban areas. This is most likely to be the case for primary pollutants, such as CO, NO_2, SO_2, and PM_{10} (or TSP). The opposite may be true for ozone, because of the tendency for levels to be reduced near sources of NO. Secondary sulfate and other fine particles tend to have much longer lifetimes and thus to be more uniformly distributed over entire states or regions. Note that such differences in the reliability of exposure estimates will tend to bias the regression coefficients, giving an advantage to those pollutants with smoother distributions (Lipfert and Wyzga, 1995). Because the socioeconomic characteristics of the population and thus their mortality risk factors are also nonrandomly distributed, especially at the local level within an SMSA, collinearity may result between their actual population exposures and these other mortality risk factors. More simply put, persons employed by a local pollution source may tend to live closer to that source, and it may thus be difficult to distinguish between their ambient exposures, their occupational exposures, and the personal characteristics that led to their employment and residence there. As a result, all cross-sectional studies, prospective or ecological, have the same obligation to demonstrate that potential confounders have been adequately controlled.

12.4.1.2 Population-Based Cross-Sectional Mortality Studies

In this section, cross-sectional studies employing averages across various geopolitical units (cities, SMSAs, etc.) are reviewed, in chronological order. The "ecological" label applies to this group of studies without reservation, since no data on individuals are used; the community- based study seeks to define the (average) community characteristics that are associated with its overall average health status, in this case annual mortality rate. Extension of these associations to imply causality (an individual concern) may thus require additional information.

Studies published after 1985 are emphasized here, but it is also useful to refer to some of the earlier influential studies for context. Table 12-15 summarizes some of the findings from these "background" studies, which analyzed mortality from 1960 to 1974. Studies that

analyzed spatial variability in 1980 mortality are summarized in Table 12-16. Many of these studies comprise a large numbers of individual regressions; the Tables indicate which ones were selected for discussion here, but the numerical column headings are more convenient for the discussion that follows.

Background and Critiques of Some Older Studies

Although there had been a few earlier intracity cross-sectional studies (Lipfert, 1994a), the current "model" for the cross-sectional population-based study was introduced by Lave and Seskin (1970, 1977). They published an extensive national cross-sectional regression analysis and concluded that about 9% of annual U.S. metropolitan mortality (ca. 1960) was associated with air pollution, considering TSP and SO_4^{2-} jointly. The analysis was based on multiple linear regression analysis of annual mortality rates in the major SMSAs in relation to coincident annual air quality levels (as measured at city centers) and to selected other explanatory variables, listed in Table 12-15. This study was the first to attempt to characterize the air pollution exposure of an entire SMSA using (often fragmentary) data from a single monitoring station. Previous cross-sectional studies had tried to characterize city-wide averages by using multiple monitoring stations or surrogate variables such as fuel use patterns (Lipfert, 1994a). Lave and Seskin also introduced the idea of using more than one metric for each pollutant in the same regression; they used the annual means as well as the minimum and maximum values observed during the year, thus jointly regressing 6 pollutant variables. This led to excessive collinearity, unstable results, and, with the ca. 1960 data, bias because the smaller cities (many of which were in the industrial states) often recorded only 4 composite SO_4^{2-} values during the year while other cities had readings every two weeks. Later studies by several investigators showed that the annual mean was the preferred pollution metric. As shown in the first two studies in Table 12-15, introduction of a home-heating fuel variable resulted in loss of significance and reduced relative risks for both pollution variables. There are other examples of this type of instability in Lave and Seskin (1977).

TABLE 12-15. COMMONLY-BASED CROSS-SECTIONAL STUDIES (1960-74 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Lave and Seskin (1978) Regr. 3.3-1	Total mortality	1960, 117 SMSA, USA	TSP, min SO_4	118 4.7	(41) (3.1)	1	447,000[2]	OLS, joint	none	none	Pct. ≥ Age 65, Pct. Nonwhite, Pop. density, Pct. Poor, Population	1.050 TSP 1.104 SO_4	(1.01-1.09) (1.03-1.18)	0.059 0.033
Lave and Seskin (1978) Regr. 5.2.2	Total mortality	1960, 117 SMSA, USA	TSP min SO_4	118 4.7	(41) (3/1)	1	447,000[2]	OLS, joint	none	none	Pct. ≥ Age 65, Pct. nonwhite, Pop. density, Pct. Poor, Pop., Home heating fuel	1.019 TSP 1.030 SO_4	(0.98-1.05) (0.97-1.09)	0.022 0.01
Lave and Seskin (1978) Regr. 7.1-4	Total mortality	1960, 112 SMSA, USA	TSP min SO_4	95 3.5	(29) (1.9)	1	570,000[2]	OLS joint	none	none	Pct. ≥ Age 65, Pct. nonwhite, Pop. density, Pct. poor, Population	1.091 TSP 1.129 SO_4	(1.04-1.14) (1.01-1.25)	10.087 0.030
Lipfert (1984) Regr. 4.2	Total mortality	1970, 111 SMSA, USA	TSP SO_4	96 10.9	(29) (4.5)	1	989,000	OLS, joint	none	none	Pct. ≥ Age 65, Pct. Afr. Amer., Pct. other nonwhite, Pop. density, Pct. poor, pop. adj. cig. sales, coal, wood, homeheat	1.044 TSP 1.057 SO_4	(0.98-1.07) (1.01-1.11)	0.034 0.042
Lipfert (1984) Regr. 4.7	Total mortality	1970, 69 SMSA, USA	TSP SO_4	96 10.9	(29) (4.5)	1	989,000	OLS, joint	none	O_3	same as above, with water quality, without pop.	1.052 TSP 1.035 SO_4	(0.99-1.12) (0.98-1.09)	0.054 0.026
Lipfert (1984) Tbl. 6, Line 10	Total mortality	1970, 69 SMSA	non-S TSP, SO_4	80.5 11.0	(25) (4.4)	1	989,000	OLS, joint	none	O_3	Pct. ≥ Age 65, Pct. Afr. Amer., Pct. other nonwhite, Pop. density, Pct. poor, adj. cig. sales, coal, wood, home heating, drinking water, pop. migration	1.074 1.019	(1.00-1.14) NS	0.05 0.014

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TABLE 12-15 (cont'd). COMMONLY-BASED CROSS-SECTIONAL STUDIES (1960-74 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Chappie and Lave (1982) Regr. 2-6	Mortality from natural causes	1974, 104 SMSA	TSP SO_4	75 9.6	(41) (3.8)	1	527,000[2]	OLS, joint[3]	none	SO_4[3]	Pct. ≥ Age 65, Pct. nonwhite, pop. density, income, population	0.99 TSP 1.23 SO_4	NA NA	-0.01 0.15
Chappie and Lave (1982) Regr. 3-6	Mortality from natural causes	1974, 102 SMSA	TSP SO_4	75 9.6	(41) (3.8)	1	527,000[2]	OLS, joint[3]	none	SO_4[3]	Pct. ≥ Age 65, Pct. nonwhite, pop. density, income, pop., tobacco sales, alcohol sales, pct. college grads, industries	0.985 TSP 1.18 SO_4	NA NA	-0.015 0.12

[1]At TSP = 100, SO_4 = 15, concentration adjusted for migration.
[2]Median value.
[3]Regression used minimum, maximum, and mean values for TSP and SO_4 in the same model; relative risks were calculated from combined elasticity for each pollutant.

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Lave and Seskin also tested the hypothesis that current mortality patterns might be more influenced by previous air pollution patterns than by coincident patterns. They found that 1969 mortality was slightly more correlated with 1960 air pollution than with 1969 pollution values, although this may have been due to the "minimum" sulfate error that was only present in the 1960 data base.

For credibility, findings on air pollution should be robust to changes in the locations studied and to reasonable changes in the regression model. In the late 1970s and early 1980s, the Lave and Seskin model was subjected to several tests of robustness (Crocker et al., 1979; Lipfert, 1978; Evans et al., 1984b). In general, the Lave and Seskin results were found to lack robustness, especially for the sulfate variable, which was shown to be sensitive to the inclusion of certain socioeconomic variables. Lipfert (1978) found that the Fe and Mn content of TSP was more highly correlated with city mortality than was SO_4^{2-}, for example. He also found that TSP values lagged 10 years were about as successful as current values in predicting ca. 1970 mortality.

Lipfert (1984) reanalyzed Lave and Seskin's 1969 total mortality data set for 112 SMSAs (third study in Table 12-15), using corrected data and many new independent variables, including 1970 mortality (to correspond better with the socioeconomic variables obtained from the 1970 Census (fourth through sixth studies in Table 12-15). The objective was to provide a more rigorous analysis of the portion of the Lave and Seskin data that had valid sulfate data, and to compare it with the original analysis by Lave and Seskin (1978) using the same set of locations. The dependent variables were total SMSA mortality, mortality by sex, and mortality for two broad age groups cut at age 65. The main conclusion drawn from this analysis of 1970 SMSA mortality was that pollution effects on mortality were sensitive to both model specification and the data set used. Specifically:

- Minimum $SO_4^=$ had no advantage over mean $SO_4^=$ and was less significant, other things being equal. When a complete model specification was used, sulfate was rarely significant (as either measure) but significance occurred more often for females. TSP was more important for deaths of those under 65 years of age. Non-sulfate TSP (obtained by subtracting the mass equivalent of SO_4^{2-} from each reading) was just as important as TSP (Column 6).

- Drinking-water quality, ozone, migration, and racial distribution variables all had important effects on the regressions. Only when a complete model specification was

TABLE 12-16. COMMONLY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model[1] Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[2] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Özkaynak and Thurston (1989) Table VI	Total mortality	1980 98 SMSA	TSP	78	(26)	1	NA	OLS sep.	none	none	Pct. ≥ Age 65, median age,	1.012 TSP	(0.96, 1.06)	0.01
			SO_4	11.1	(3.4)						Pct. nonwhite, pop. density,	1.17 SO_4	(1.09, 1.24)	0.086
											Pct. poor, pct. w/ 4 yrs college.			
Özkaynak and Thurston (1987) Table VII	Total mortality	1980, 38 SMSA	PM_{15}	38	(7.3)	1	NA	OLS sep.	none	none	Same as above.	1.059 PM_{15}	(0.95, 1.16)	0.045
			$PM_{2.5}$	20	(3.8)							1.085 $PM_{2.5}$	(0.96, 1.21)	0.068
Lipfert et al. (1988) Table 24	Total mortality	1980 172-185 cities	Fe,	1.2	(0.61)	1	57,500	OLS sep.	none	none	Pct. ≥ Age 65, birth rate;	1.044 Fe	(1.02-1.07)	0.041
			SO_4	9.5	(3.5)						Pct. Afr.-Amer. pop. density, pct. poor; Pct. pop. change, pct. w/ 4 yrs. college; Pct. Hispanic, adj., cig., sales; Pct. prior res., hard water	1.13 SO_4	(1.06-1.20)	0.071
Lipfert et al. (1988) Table 24	Total mortality	1980 68 cities	PM_{15}	38	(121)	1	57,500	OLS sep.	none	none	Same as above.	1.036 PM_{15}	NS[3]	0.027
			$PM_{2.5}$	18	(6)							1.082 $PM_{2.5}$	NS[3]	0.059
Lipfert et al. (1988) Page 60	Total mortality	1980 122 cities	TSP	88	(29)	1	about 60,000	OLS joint	10 years	none	Pct. ≥ Age 65, birth rate, pct. nonwhite, pop. density, pct. poor, adj. cig. sales, pct. w/ 4 yrs. college	about 1.0	NS[3]	NS
			SO_4	9.0	(1.8)							1.072 SO_4	(1.0, 1.14)	0.037
Lipfert (1993a) Regr. 6.1, 6.2	Mortality from natural causes	1980 149 SMSA	TSP	68	(17)	10.6 (TSP)	928,000	OLS sep.	none	none	Pct. ≥ Age 65, Pct. Afr.-Amer., Pct. Hispanic, Pct. other nonwhite, pct. poor, pct. pop. change, adj. cig. sales, pct. w/ 4 yrs. college, hard water, heating degr. days pop. density	1.038 TSP	(0.97, 1.10)	0.026
			SO_4	9.3	(3.1)							1.059 SO_4	(0.99, 1.12)	0.037

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TABLE 12-16 (cont'd). COMMONLY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Lipfert (1993) Regr. 13.1, 13.3	Mortality from natural causes	1980 62 SMSA	PM_{15}	38	(29)	1	928,000	OLS sep.	none	none	Same as above	1.036 PM_{15}	(0.98, 1.10)	0.027
			$PM_{2.5}$	18	(4.5)							1.060 $PM_{2.5}$	(0.99, 1.13)	0.043
Lipfert (1993) Regr. 9.1, 9.3	Mortality from natural causes	1980 62 SMSA	TSP	68	(17)	10.6 (TSP)	928,000	Log-linear	none	none	Same as above without other nonwhite, heating degr. days, pop. density	1.066 TSP	(1.006, 1.13)	0.044
			SO_4	9.3	(3.1)							1.021 SO_4	NS	0.012
Lipfert (1993) Regr. 13.5	Major CVD	1980 62 SMSA	SO_4 (IP)	4.3	(2.5)	1	928,000	OLS	none	none	Same as above with other nonwhite, heating degree days, pop. density	1.04 SO_4	NS	0.011
Lipfert (1993) Regr. 12.1	Major CVD	1980 62 SMSA	SO_4 (IP)	4.3	(2.5)	1	928,000	OLS	none	none	Pct. ≥ Age 65, median age, pct. nonwhite, pop. density, pct., poor pct. w/ 4 yrs. college	1.19 SO_4	(1.03, 1.35)	0.054
Lipfert (1993) Regr. 10.3, 10.4	COPD	1980 149 SMSA	non-TSP*	56.4	(18)	10.6	928,000	Log-linear	none	none	Pct. ≥ Age 65, pct. Afr.-Amer., Pct.	1.50 TSP	(1.22, 1.83)	0.23
			TSP	68.5	(17)						Hispanic, pop. density, pct. poor, adj. cig. sales	1.43 TSP	(1.20, 1.71)	0.25

[1]All regression models used PM indicators one at a time (separate models) except as noted.
[2]At TSP = 100 $\mu g/m^3$, SO_4 = 15 $\mu g/m^3$, corrected for migration.
[3]NS = not statistically significant, confidence limits not available.

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used did the coefficients for age, race, poverty, and smoking take on values consistent with exogenous estimates; this implies that these additional variables were also necessary to derive appropriate values for the air pollution variables.

- The analysis was incapable of distinguishing between linear and threshold models and thus could not rule out the applicability of a threshold or hockey-stick model.

Chappie and Lave (1982) replicated the 1960 and 1969 Lave/Seskin results with data for 1974 mortality using essentially their original model and found that sulfate had become even more important than in previous years (relative risk was about double), in spite of lower average concentrations, while TSP became insignificant (studies 7 and 8). Chappie and Lave retained the multiple measures of pollutants and attempted to rebut earlier criticisms about the lack of data on smoking by using retail trade sales data as a surrogate for smoking behavior; however, this variable was not important in their analysis, probably because it is a poor measure of actual tobacco consumption (Lipfert, 1994a).

In summary, at this point in the development of the methodology for population-based cross-sectional studies (which was discussed in the 1982 CD and the 1986 Addendum [U.S. Environmental Protection Agency, 1982a, 1986a]), it appeared that the findings of national cross-sectional analyses were largely investigator-dependent. Table 12-15 shows that including additional socioeconomic variables in the model reduced the apparent effects of sulfate for the 1970 time period. However, the 1974 study found even larger effects of sulfate, but it could not be ascertained whether this was due to the regression model used or to the particular data set considered. Evans et al. (1984b) critically reviewed some of the published cross-sectional mortality studies, including a quantitative comparison of regression coefficients and a reanalysis of the Lave and Seskin (1978) 1960 data with new variables added. For this reanalysis, the dependent variable was total 1960 mortality for 66 to 98 SMSAs. The independent variables included percentage over 65, median age, percentage of nonwhites, log of population density, percentage of college graduates, smoking index, percentage of poverty, and mean sulfate concentration. Other variables explored included occupational, home heating, climate and housing variables; mean values for TSP, Fe, Mn, and B(a)P. In general, the sulfate variable lost statistical significance in this reanalysis; the

elasticity with respect to total mortality was about 0.03. None of the other pollutants provided any better results.

Kim (1985) analyzed total mortality data for 1970 in an ecological analysis of 49 U.S. cities. Pollutants considered were TSP and the benzene-soluble organic fraction of TSP (BSO), in 5 different formats: averaged over the single years 1968, 1969, and 1970; averaged for 1969 to 70, and for 1968 to 70. This analysis was intended to test for lagged effects, but one might also expect the multiple-year averages to be superior because of the reduction of random sampling errors. Socioeconomic/demographic (SES) variables included: percent aged 65 and over, population density, percent unemployed, and percentage of housing built before 1950. Four climate variables were also used: annual mean wind speed, annual precipitation, and mean January and July temperatures. All climate and SES variables were included in each regression, and both joint and single-pollutant models were evaluated. Racial differences were not included in this model, which may have had the effect of increasing the apparent climate (temperature) effects, since the black population has higher mortality rates and constitutes a higher fraction of Southern cities. The wind coefficients were highly nonsignificant, but positive coefficients were shown for precipitation. This may reflect the lower mortality rates in the Western states, rather than a harmful effect of precipitation per se.

Kim's lag analysis was largely inconclusive. He concluded "the effects of total mortality in 1970 may be due to the air pollution in 1969, although it is not possible to pinpoint a lag-effect between the time of exposure to air pollution and the time of death." The TSP coefficients for the single year 1968 were the lowest by far, but the opposite was true for BSO. It is possible that BSO affects different diseases (such as cancer) than TSP and thus exhibits a different lag relationship. However, in spite of the advantage of three times as many observations, the results for 1968 to 70 did not have larger t-values than the single years. It is not possible to speculate what effect the model specification used by Kim in this analysis might have had on the outcome of this lag analysis. It is clear, however, that one must be careful in interpreting regression coefficients literally (e.g., the climate variables) when an incomplete model specification is used.

Studies of 1980 SMSA Mortality

Ozkaynak and Thurston (1987) analyzed 1980 total mortality in 98 SMSAs, using data on PM_{15} and $PM_{2.5}$ from the EPA inhalable particle (IP) monitoring network for 38 of these locations. The sulfate data from this network were not used in this study. The independent variables used are given in Table 12-16 (first two studies); in general, the regression modeling approach was similar to that of Lave and Seskin (1970). The results presented in Table 12-16 are from their "basic" regression model. Additional variables were explored, including spatial correlation variables intended to examine regionality and latitude and longitude variables. The sulfate measurements that Ozkaynak and Thurston used may have been affected by artifacts from the high-volume sampler filters (Lipfert, 1994b); this is also suggested by the fact that their mean SO_4^{2-} value exceeds those of previous years and the mean from the IP data set (compare studies 1 and 9 in Table 12-16).

Ozkaynak and Thurston (1987) ranked the importance of the various pollutants mainly by relative statistical significance in separate regressions. They concluded that the results were "suggestive" of an effect of particles on mortality decreasing with particle size, although in the basic model only SO_4^{2-} was significant. In some of the other models, $PM_{2.5}$ was also significant and PM_{15}, nearly so. However, if the effects are judged by elasticities rather than significance levels, SO_4^{2-}, $PM_{2.5}$, and PM_{15} would be judged as equivalent, with TSP ranking somewhat lower. The indicated effect of SO_4^{2-} would be reduced from an elasticity of 0.086 to about 0.05 by accounting for filter artifacts (Lipfert, 1994b). Ozkaynak and Thurston (1987) also used source apportionment techniques to estimate that particles from coal combustion and from the metals industry appeared to be the most important.

The coefficients and significance levels obtained for TSP by Ozkaynak and Thurston (1987) may be the result of the TSP data they used, which were based on a single monitoring station in each SMSA and thus are unlikely to be fully representative of population exposures. Thus, alternative interpretations of these findings are certainly possible. In addition, because smoking, diet, and other socioeconomic or lifestyle variables were not considered in the regression model, the pollution coefficients may have been biased. Finally, this study did not specifically address the question of acute vs. chronic responses by exploring lagged pollution variables.

The analysis by Lipfert et al. (1988) comprised a statistical analysis of spatial patterns of 1980 U.S. central city total mortality (all causes), evaluating demographic, socioeconomic, and air pollution factors as predictors (Studies 3 to 5 in Table 12-16). The advantages of studying central cities vs. SMSAs include potentially better measures of exposure because of the smaller areas, and sufficient numbers of observations to allow analysis of subsets of locations. In this study, sulfate and iron particles were significant (joint) predictors of all-cause mortality in about 180 cities. If the elasticities for SO_4^{2-} were corrected to account for the filter artifacts, they would be reduced by about 50% in this study. The data on PM_{15} and $PM_{2.5}$ were only available for 68 cities; neither pollutant was significant in this data set but their elasticities were in the same range found for other pollutants (0.013 to 0.05). This study also allowed a test of lagged pollution data as a means of attempting to distinguish acute from chronic responses; using 1970 TSP and SO_4^{2-} data to predict 1980 city mortality was slightly less effective than using ca. 1980 data for these pollutants as predictors.

Data from up to 149 metropolitan areas (mostly SMSAs) were analyzed in a study of the relationships between community air pollution and "excess" mortality due to various causes for the year 1980 (Lipfert, 1993a). Several socioeconomic models, including the model proposed by Ozkaynak and Thurston (1987), were used in cross- sectional multiple regression analyses to account for non- pollution effects; the variables are listed in Table 12.16 (Studies 6 to 11). Cause-of-death categories analyzed include all causes, nonexternal causes (ICD9 0-800), major cardiovascular diseases (ICD9 390-448), and chronic obstructive pulmonary diseases (COPD) (ICD9 490-96). The patterns for the first three groupings were quite similar but differed markedly from the patterns of COPD mortality, which tend to be higher in the Western U.S. Regressions were performed for these cause-of-death groupings as annual mortality rates ("linear" models) and as their logarithms ("log-linear" models). The original regressions used base-10 logarithms; the results have been converted to natural logarithms for this review. Two different sources of measured air quality data were utilized: data from the EPA AIRS database (TSP, $SO_4^{=}$, Mn, and ozone from a long-term average isopleth map) and data from the inhalable particulate (PM_{15}) network; the latter data (PM_{15},$PM_{2.5}$ and $SO_4^{=}$ from the IP filters) were only available for

63 locations. All particulate data were averaged across all the monitoring stations available for each SMSA; the TSP data were restricted to the year 1980 and were based on an average of about 10 sites per SMSA.

The associations between mortality and air pollution were found to be dependent on the socioeconomic factors included in the models, the specific locations included in the data set, and the type of statistical model used, as was the case with 1970 data (Lipfert, 1984). In the expanded analysis, stepwise regressions were run for each mortality variable and a "parsimonious" model was developed that had statistically significant coefficients for the non-pollution variables. Most of these coefficients also agreed with exogenous estimates of the "correct" magnitudes. Using these models, statistically significant associations were found between TSP and mortality due to non-external causes with the log-linear models evaluated, but not with a linear model. Sulfates, manganese, inhalable particles (PM_{15}), and fine particles ($PM_{2.5}$) were not significantly ($P < 0.05$) associated with mortality with any of the parsimonious models, although $PM_{2.5}$ and Mn were close with linear models ($p=0.07$) and significance may have been affected by the use of smaller data sets. This study showed that $PM_{2.5}$ was the "strongest" particulate variable with linear models, but that TSP performed better in log-linear models. Scatter plots and quintile analyses suggested that a TSP threshold might be present for COPD mortality, at around 65 $\mu g/m^3$ (annual average).

This study supported the previous findings of associations between TSP and premature mortality and also the hypothesis that improving the accuracy of pollutant exposure data tends to increase statistical significance. Similarly, the lack of significance for $SO_4^=$ may partly relate to the flawed measurement methods used at the time. The ambiguity between linear and log-linear models probably reflects the effects of influential observations.

Cross-Sectional Mortality Studies by Age and Cause of Death

Only a few of the many published ecological mortality studies analyzed subgroups by age and cause. Lave and Seskin (1978) used very broad age groups (0 to 14, 15 to 44, 45 to 64, 65+) with 1960 and 1969 data, which limited the usefulness of the analysis because of the failure to account for age differences within these groupings. Lave and Seskin also examined a large number of disease-specific mortality rates using 1960 and 1961 data.

Cancers and cardiovascular diseases were associated with the flawed "minimum" sulfate variable, but respiratory causes tended to be associated with TSP. Lipfert (1978) considered for U.S. cities, 1969 to 71, infant mortality, ages 1 to 44, and from 45 to 85 by 10-year groups. Very little significance was found below age 65; for ages 75+, SO_4^{2-}, TSP, Fe and Mn were significant (one at a time). By cause of death, Lipfert (1978) considered nonexternal causes, total cancers, respiratory cancer, respiratory disease (asthma, bronchitis, emphysema) and all other diseases (mainly cardiovascular). Only Fe was significantly associated with total cancers, only Mn with respiratory cancer, Fe was positively associated with respiratory diseases but SO_4^{2-} was strongly negatively associated with respiratory disease mortality. Lipfert (1993a) found that PM was not significantly associated with mortality from major cardiovascular causes for 1980 SMSA mortality, which implies that other causes of death must be involved for this pollutant. Note that between 1960 and 1980 there were major improvements in cardiovascular mortality, resulting in some changes in the geographic patterns. For 1980 SMSA mortality, COPD mortality was strongly associated with TSP with a variety of regression models. Significant associations were found between TSP and COPD mortality for both linear and log-linear models (Study 11 in Table 12-16). When the sulfate contribution to TSP was subtracted, the relationship with COPD mortality was slightly strengthened. $PM_{2.5}$ was a significant predictor of heart disease mortality only when the regression model was restricted to the variables used by Ozkaynak and Thurston (1987).

Cross-Sectional Infant Mortality Studies

Bobak and Leon (1992) studied neonatal mortality (ages less than 1 month) and post-neonatal mortality (ages 1 to 12 months) from 1986 to 88 in 46 administrative districts in the Czech Republic, in relation to annual averages of PM_{10}, SO_2, and NO_2. The observations comprised 121 combinations of districts and years, ranked into quintiles by mean pollution level for analysis (5 districts had insufficient data). The analysis was ecological in design, in that the outcome variable was the death rate per 1,000 live births and district-wide averages were used as the control variables (mean income, mean savings, mean number of persons per car, proportions of total births outside of marriage, and the rate of legal abortions. In the

United States, for example, infant mortality is a strong function of income or poverty status, reflecting the effects of access to pre- and post-natal medical care.

The mean pollutant values were 68.5, 31.9, and 35.1 $\mu g/m^3$ for PM_{10}, SO_2, and NO_2, respectively. This study appears to be based on a denser air monitoring network than many of its predecessors in the U.S.; the mean population per monitor was only about 50,000 and many ecological studies in the U.S. are based on values an order of magnitude higher than this. Two of the three pollutants were highly correlated ($R = 0.80$ for SO_2 vs. NO_2), indicating a common source (combustion). Correlations with PM_{10} were lower (0.15 and 0.26), reflecting the fact that the particle sources were more diverse and included cement production. The maps presented in the paper suggested little likelihood for spatial autocorrelation, although this topic was not discussed directly. Bobak and Leon (1992) addressed the pollutant collinearity problem by presenting results for each pollutant alone and for the combination of all three. Results were also presented with and without socioeconomic adjustments.

The statistics used to indicate significant associations were chi-square p-values for trend across the 5 quintiles, with the relative risks set to 1.0 for the lowest quintiles. Highly significant trends ($p < 0.01$) were seen after socioeconomic adjustment for postneonatal mortality only with PM_{10}, even after including the other pollutants. Post-neonatal respiratory mortality showed highly significant trends for all 3 pollutants, but only PM_{10} retained significance ($p=0.013$) with all 3 pollutants. Because of the use of multiple years of data for 41 common locations and the strong likelihood of temporal persistence in annual average air quality, the true number of degrees of freedom may be 41 rather than 121. For this reason, a higher standard of association should be applied to these results ($p < 0.01$ rather than $p < 0.05$). Although Bobak and Leon (1992) elected to analyze their data in terms of linear responses over the entire pollutant range, their results were suggestive of a threshold at the third quintile or higher (mean $PM_{10} = 67$ $\mu g/m^3$).

It is not clear from the design of this study whether the reported effects are acute or chronic. Pollution values were averaged over the same years used to aggregate deaths; thus it is possible that exposure did not precede death in all cases. In any event, it may be difficult to distinguish delayed acute from chronic responses for lifetimes as short as a few

months. Among the previous U.S. studies reviewed, Lave and Seskin (1978) found infant mortality to be associated with TSP; Lipfert (1978) found marginal significance for the Fe and Mn portions of TSP and a negative association with SO_4^{2-} (ca. 1970).

Summary of Population-based Cross-Sectional Mortality Studies

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the numbers of independent variables considered, including the air pollutants. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the specific pollutants associated with mortality varied. However, all of these studies found at least some association between air pollution and mortality on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. The finding of significant associations with metals (Lipfert, 1978, 1984, 1993) and with cement plant particles (Bobak and Leon, 1992) suggests that many different types of particles may be involved. Analyses by age and cause of death were limited; the most consistent associations were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP (but not SO_4^{2-}).

12.4.1.3 Prospective Mortality Studies

Studies considered in this section utilized data on the relative survival rates of individuals, as affected by age, sex, race, smoking habits, and certain other individual risk factors. This type of analysis has a substantial advantage over the population-based studies, because the identification of the actual decedents allows stratification according to important risk factors such as smoking. Such stratification allows tests of the hypothesis that certain segments of the population may be more sensitive to air pollution than others, which is a major shortcoming of population-based studies. However, analyzing individuals also entails dealing with increased variability in outcome and thus requires large sample sizes if effects as small as those typically found in population studies are to be detected with significance. Unfortunately, none of the prospective cohort studies had data on personal exposures to air

pollution, which precludes analysis within cities or by type of exposure (primarily indoor vs. outdoor, or coincident vs. accumulated, for example). In this limited sense, these studies are also "ecological."

Although the newer prospective studies (Abbey et al., 1991, Dockery et al., 1993, and Pope et al., 1995), are of most interest, brief comments on two older studies are included here to allow additional comparison of effects by gender and smoking. The studies are reviewed in chronological order. The main findings from the three most recent studies are summarized in Table 12-17.

Comparison of Two Pennsylvania Towns

Morris et al. (1976) followed survival rates cohorts of volunteers in Seward (n=938) and New Florence, PA, (n=732) from 1960 to 1972. Based on 1960 to 61 air quality data, Seward had worse air quality for both sulfur oxides and suspended particulates. Although the small sample size precluded definite conclusions about the effect of air pollution alone (i.e., in nonsmokers), the data suggested a relative risk of 1.2 ($p < 0.2$) for mortality from all causes for males with more than 20 years' residence in Seward, which would correspond to a slope of about 0.005 per $\mu g/m^3$ when the mortality gradient is assigned to TSP. The effects of smoking and air pollution appeared to be additive. This study did not control for occupation, education, other life-style variables or non-response bias.

Comparison of Two Residential Areas in Cracow, Poland

Nonaccidental mortality rates from random samples of two areas in Cracow were compared after 10 years of follow up (1968-78) by Kryzanowski and Wojtyniak (1982). This study tracked 4,355 individuals; their individual characteristics were identified (including smoking habits) and used in categorical mortality models. The two residential areas were characterized as: high pollution, average smoke = 180 $\mu g/m^3$, SO_2 = 114 $\mu g/m^3$; lower pollution, average smoke = 109 $\mu g/m^3$ and SO_2 = 53 $\mu g/m^3$. A total of 20 air samplers was used, from 1968 to 73; the smoke samplers collected particles less than 10 μm in diameter and concentrations were based on filter staining.

TABLE 12-17. RELATIVE MORTALITY RISKS IN SIX CITIES ADJUSTED RISKS

Risk Factor	$PM_{2.5}$ Data ($\mu g/m^3$)	Crude Risk	Adjusted Risks		
			All[2]	Men[2]	Women[2]
Residence					
Portage	11.0 (1980-7)[3]	1.0[1]	1.0	1.0	1.0
Topeka	12.5 (1980-8)	0.90	1.01	1.04	0.97
Watertown	14.9 (1980-5)	1.16	1.07	0.94	1.22
Harriman	20.8 (1980-7)	1.16	1.17	1.21	1.07
St. Louis	19.0 (1980-6)	1.48	1.14	1.15	1.13
Steubenville	29.6 (1980-7)	1.51	1.26	1.29	1.23
Smoking Status					
Current			1.59	1.75	1.54
Previous			1.20	1.25	1.18
No high school education			1.19	1.22	1.13
Body mass index of 4.5			1.08	1.03	1.11

[1]Baseline annual crude death rate = 10.73 per thousand population
[2]Adjusted for age, smoking, education, and body mass
[3]Period of $PM_{2.5}$ air monitoring

Source: Dockery et al. (1993)

The authors found a marginally statistically significant (p=0.05) (positive) effect of air pollution on male mortality (after age adjustment and consideration of confounding variables including education, density of living conditions, and occupational factors), but a marginally significant (p=0.05) negative effect on female mortality. The most important factors for both sexes (neglecting interactions) were smoking; occupational exposure to heat, humidity, or dust; in-migration; and education. The finding that in-migrants tended to be healthier (especially males) was consistent with the findings of Morris et al. (1976). However, neither

analysis is capable of distinguishing whether the effect is due to longer residence in the polluted area or to selective migration of healthier people.

The relative risk for smoking for males was similar to that found by Morris et al. (1976), as was the finding of stronger air pollution effects for males. The strong effects of occupational exposure to heat and dust for both sexes are noteworthy. The effects of education were seen to be about the same as those found in the U.S. by Rogot et al. (1992), for males, but much stronger for females. The Cracow study should be viewed as providing qualified support for the hypothesis that long-term exposure to air pollution is associated with increased mortality in males, although it provides no specific information as to the harmful pollutants.

California Seventh-Day Adventists.

Abbey et al. (1991a) described a prospective study of about 6,000 white, non-Hispanic, nonsmoking, long-term California residents who were followed for 6 to 10 years, beginning in 1976. The study was designed to test the use of cumulative exposure data as an explanatory factor for disease incidence and chronic effects. Ambient air quality data dating back to 1966 were used, and the study was restricted to those who lived within 5 miles of their current residence for at least 10 years. All of the air quality monitors in the state were used to create individual exposure profiles (duration of exposure to specific minimum concentration levels) for each participant, by interpolating to their zip code centroids based on the 3 nearest monitoring stations. Pollutant species were limited to TSP and ozone in this paper; oxidant concentrations were used in the early part of the monitoring record. Endpoints evaluated and the numbers of cases included: newly diagnosed cancers (incidence at any site) for males, 115; any cancer site for females, 175; respiratory cancer, 17; definite myocardial infarction, 62; mortality from any external cause, 845; and respiratory symptoms, 272. The Cox proportional hazards model was used, considering age, sex, past smoking, education, and presence of definite symptoms of airway obstructive disease[1] (AOD) in 1977 as individual risk factors, together with various exposure indices for TSP or ozone

[1]Symptoms of asthma, chronic bronchitis, or emphysema.

(considered separately). Data on occupational exposures and history of high blood pressure were available but were not used in the mortality model. No data were available on climate, body mass, income, migration, physical activity levels or diet. Separate results by gender were not reported for nonexternal mortality.

Of these endpoints, respiratory symptoms and female cancers (any site) were associated with TSP exposure. Neither heart attacks or nonexternal mortality was associated with either pollutant. The authors felt that possible errors in their estimated exposures to air pollution may have contributed to the lack of significant findings, and a later version of the data base include estimates of attenuation resulting from time spent indoors (Abbey et al., 1993), but mortality was not considered in the 1993 paper.

The follow-up analysis (Abbey et al., 1995) considered exposures to SO_4^{2-}, PM_{10} (estimated from site-specific regressions on TSP), $PM_{2.5}$ (estimated from visibility), and visibility per se (extinction coefficient). No significant associations with nonexternal mortality were reported, and only high levels of TSP or PM_{10} were associated with AOD or bronchitis symptoms.

This study used an unique air quality data base which was developed for the express purpose of studying the effects of long-term cumulative exposures to community air pollution (Abbey et al., 1991b). The technique was shown to provide reliable spatial interpolations that were somewhat better for O_3 than for TSP, in keeping with expectations based on the regional nature of O_3. However, no attention was given to temporal matching of air quality and health; the studies using this data base were intended to evaluate the hypothesis that health is affected by cumulative long-term pollution exposure at some undetermined time, as opposed to acute or coincident exposures. Note that the data base began in 1966 and the mortality follow-up began 10 years later. Because air quality generally improved during this period, the highest concentrations are likely to have occurred in the earlier part of the record, and thus we would not expect spatially-based correlations to also reflect the sum of acute effects, as would be the case when air quality and health data are also matched in time. Note that the range of air quality levels experienced in California from 1966 onward is at least as large as that currently experienced in the rest of the United States, including the nation's highest O_3 levels, annual average TSP up to about 175 $\mu g/m^3$, and annual average

SO_4^{2-} up to about 9-11 $\mu g/m^3$ (Lipfert, 1978). Thus, lack of adequate range in the pollution variables does not appear to be a valid reason for the lack of statistical significance. However, levels of SO_2 and of certain trace metals such as Mn tend to be lower in California than in the midwestern parts of the United States with larger concentrations of heavy industry.

The finding of Abbey et al. (1991a) of no association between long-term cumulative exposure to TSP or O_3 and all natural-cause mortality may be interpreted as showing the absence of chronic responses after 10 years but not necessarily the absence of (integrated) acute responses, since coincident air pollution exposures were not considered. It is also possible that the latency period for chronic effects may exceed 10 years and that additional follow-up might still reveal chronic effects. The magnitudes of the other risk factors considered were not given by Abbey et al. (1991), which precludes comparison with the other studies.

Prospective Cohort Study in Six U.S. Cities.

Dockery et al. (1993) analyzed survival probabilities among 8,111 adults who were first recruited in the mid-1970s in six cities in the eastern portion of the United States. The cities are: Portage, WI, a small town north of Madison; Topeka, KS; a geographically-defined section of St. Louis, MO; Steubenville, OH, an industrial community near the West Virginia-Pennsylvania border; Watertown, MA, a western suburb of Boston; and Kingston-Harriman, TN, two small towns southwest of Knoxville. This selection of locations thus comprises a transect across the Northeastern and Northcentral United States, from suburban Boston, through Appalachia, and into the upper Midwest.

The adults were white and aged 25 to 74 at enrollment. In each community, about 2,500 adults were selected randomly, but the final cohorts numbered 1,400 to 1,800 persons in each city (Ferris et al., 1979). Follow-up periods ranged from 14 to 16 years, during which from 13 to 22% of the enrollees died. Of the 1,430 death certificates, 98% were located, including those for persons who had moved away and died elsewhere. However, no information was given in the paper about the actual locations of death. The bulk of the

analysis was based on all-cause mortality; no mention was made of subtracting external causes.

These cohorts have been studied extensively for respiratory health (Dockery et al., 1985). Air monitoring data were obtained from routine sampling stations and from special instruments set up by the research team. Individual characteristics of the members (and thus of the decedents) considered included smoking habits, an index of occupational exposure, body mass index, and completion of a high school education. The Cox proportional hazards model was used to estimate coefficients for the individual risk factors after stratifying ny sex and age (5-year groups). the effects of air pollution were evaluated in two ways: by evaluating the relative risks of residence in each city relative to Portage (the city with the lowest pollution levels for most indices), and by including the community-average air quality levels directly in the models. Since only six different values were available for each pollutant, the effective degrees of freedom are greatly reduced by this procedure.

Most of the air quality measures were averaged over the period of study, in an effort to study long-term (chronic) responses; the specific averaging periods varied by pollutant. Steubenville, Kingston-Harriman, and St. Louis were the most polluted cities and also had the oldest and least educated cohorts and the heaviest rates of smoking among the six cities.

The index of smoking rate used in this study was pack-years, defined as the average number of packs of cigarettes smoked per day times the number of years of smoking. This metric is also a function of age. Current and former smokers were treated separately. This smoking metric assumes that health impacts are defined by the cumulative tobacco consumption rather than by the current rate of consumption; the fact that the risk per pack-year was higher for former smokers (0.015 per pack year), compared to current smokers (0.01 per pack year), and the finding of a risk per pack year for current smokers that increased with consumption rate suggest that the current rate of smoking may also have merit as a health impact index (especially if the age of starting smoking varies). The total effect of smoking was thus defined as the relative risk of being a smoker plus the risk associated the number of pack-years in question.

The index of socioeconomic status used was having less than a high school education; Rogot et al. (1992) show that this index is a good measure of mortality differences due to

differences in education for white men but not for white women. For women, relative mortality risk continues to increase for educational attainments less than completion of high school. The index of occupational exposure to air pollution (dusts or fumes) did not take into account the length or degree of exposure or the nature of the agents involved. Occupational exposure to dusts or fumes was not found to be a significant risk factor; this outcome may have resulted from the lack of specificity of the index used. The average percentages having occupational exposure were high, ranging from 28 to 53%, with an average across all cities of 45%.

The index of physiology used was the body mass index (BMI), defined as weight divided by height squared (kg/m^2), treated as a linear relationship. The relative risk of increased body mass was similar to that found by Sandvik et al. (1993), where it was not statistically significant, but other investigators have found that the relationship is U-shaped rather than linear and may interact with other risk factors, especially smoking (Gronbaek et al., 1994).

No consideration was given to possible independent effects of occupation classification, other personal lifestyle variables such as diet or physical activity, migration, or income. Presumably, each subject was characterized by his status at entry to the study; follow-up data on possible changes in risk factors over time were not mentioned. Since the air quality data used in this study were largely obtained from "private" monitoring rather than from public archives, comparisons of the average levels with routine monitoring data were of some interest. No serious disagreements were found, except that it might have been preferable to consider peak rather than average levels of ozone, as has been done in most of the studies of acute effects of ozone on mortality. However, the size-classified particulate data began in 1980 while TSP data began in 1974; from 1974 to 1980 there were large reductions in TSP (and probably in the size-classified particles as well), so that it appears that the size-classified data are less representative of cumulative exposures than TSP. Sulfate appeared to be intermediate in this regard. In this sense, there is a mismatch in time between the air quality data, which were obtained after the study began, and the descriptive data on individuals, which pertain to the period before entry into the study.

Based on statewide mortality data, substantial differences in survival rates would be expected across this transect of the Northeastern U.S. and were observed (Table 12-17). The long-term average mortality rate in Steubenville was 16.2 deaths per 1,000 person-years; in Topeka, it was 9.7, yielding a range in average (crude) relative risk of 67% among the six cities. After individual adjustment for age, smoking status, education, and body-mass index, the range in average relative risk was reduced to 26%. The relative importance of the adjustments for age, smoking, education, and body mass in determining the final ranks of the cities may be seen from the table. Also, there is more scatter for men and women separately than when combined, presumably because of the reduction in sample size.

Dockery et al. (1993) report that "mortality was more strongly associated with the levels of fine, inhalable, and sulfate particles" than with the other pollutants, which they attributed primarily to factors of particle size. They provided relative risk estimates and confidence limits based on the differences between air quality in Steubenville and in Portage for these three pollutants. However, it is relatively simple matter to estimate these coefficients from the adjusted risks and pollutants levels in each of the six communities. Such estimates correspond quite closely to the figures given by Dockery et al. based on output from the Cox proportional hazards model. However, because there are only 6 degrees of freedom for the air quality data, the resulting confidence limits are considerably wider than those for the risk factors having individual data. These estimates are given in Table 12-18, as a means of comparing the various pollutants and combination of pollutants. As in the original paper, the relative risks are based on the difference in air pollution between Steubenville and Portage. The data for 1970 TSP (corresponding to a lag of about 12 years) were obtained from Lipfert (1978), assuming that Madison could represent Portage, WI.

Table 12-18 shows only small differences among many pollutants, including SO_2 and NO_2, owing in part to the strong collinearity present. Note that TSP and the coarse particle variables created by subtracting PM_{15} from TSP and $PM_{2.5}$ from PM_{15} were not significant, suggesting that particles larger than about 15 μm in aerodynamic diameter may be less important; this outcome may reflect in part greater spatial variability within the communities for these measures. The non sulfate portion of $PM_{2.5}$ had the tightest confidence limits

(SO_4^{2-} was multiplied by 1.2 before subtraction, assuming an average composition of NH_4HSO_4). Note also that the estimated 1970 TSP variable performed better than the TSP data used by Dockery et al. (ca. 1982). However, all of the differences in relative risks and their confidence limits could have occurred due to chance, given the availability of only 6 observations. Dockery et al. noted that the mean ozone level varied little among cities. This might not have been the case if some measure of peak concentration had been used instead of the overall mean (24-hr averages). No relationship was found for aerosol acidity (H^+), but only limited data were available.

TABLE 12-18. ESTIMATED RELATIVE RISKS IN SIX U.S. CITIES ASSOCIATED WITH A RANGE OF AIR POLLUTANTS

Species	Regr. Coeff.	Standard Error	Range	Rel. Risk	95% CIs (n=6)
PM_{15}	0.0085	(0.0026)	28.3	1.27	(1.04-1.56)
$PM_{2.5}$	0.0127	(0.0034)	18.6	1.27	(1.06-1.51)
SO_4^{2-}	0.0297	(0.0081)	8.5	1.29	(1.06-1.56)
TSP	0.0037	(0.0014)	55.8	1.22	(0.99-1.53)
TSP-PM_{15}	0.0042	(0.0032)	27.5	1.12	(0.88-1.43)
PM_{15}-$PM_{2.5}$	0.0178	(0.0098)	9.7	1.19	(0.91-1.55)
$PM_{2.5}$-SO_4	0.0255	(0.0029)	8.4	1.24	(1.16-1.32)
PM_{15}-SO_4	0.0121	(0.0034)	18.1	1.24	(1.05-1.48)
SO_2	0.0093	(0.0032)	19.8	1.20	(1.01-1.43)
NO_2	0.0126	(0.0046)	15.8	1.22	(1.00-1.49)
1970 TSP	0.0014	(0.00044)	154.0	1.25	(1.03-1.50)

In comparing the most and least polluted cities, Dockery et al. also report elevated risks for cardiopulmonary causes (1.37, [1.11 to 1.68]) and lung cancer (1.37, [0.81 to 2.31], not significant). The relative risk for all other causes of death was 1.01 (0.79 to 1.30). When the six cities were considered individually, only Steubenville showed a statistically significant ($p < 0.05$) elevated risk with respect to the least polluted city (Portage).

Comparison of the pollution risks among the various cohort subsets considered is one of the most important outcomes of a study on individuals. Such comparisons must account for the higher variability among subgroups, however, and the study was not capable of distinguishing excess risks between subgroups less than about 18% (i.e., an excess risk of 1.18 cannot be distinguished from one of 1.36, for example). Although none of these subgroup differences were statistically significant, the mortality risks associated with area of residence (and thus air pollution) were higher for females and for smokers and the risks were also higher for those occupationally exposed compared to the nonexposed. Because of reduced uncertainties about their exposure to air pollution not reflected in the outdoor monitoring data used in this study, it is possible that the relative risk estimates for nonsmokers and the nonoccupationally exposed might be the most reliable estimates (1.19 and 1.17, respectively).

In correspondence, Moolgavkar (1994) raised issues of residual confounding, age adjustment and smoking controls. In their response, Dockery and Pope (1994) agreed that confounding is a potential concern but did not address the possibility that variables other than the ones they considered might be important. They dealt with the age adjustment issue quantitatively and pointed out that the air pollution risk estimates were reasonably stable over different subgroups by smoking status.

The authors of this study appear to have made the most of the available individual data on some of the most important mortality risk factors. They were quite cautious in their conclusions, stating only that the results suggest that fine-particulate air pollution "contributes to excess mortality in certain U.S. cities." There are several other important outcomes:

- None of the population subgroups examined appeared to be significantly more sensitive to air pollution than any other. Since the relative risks were virtually unchanged by excluding subjects with hypertension and diabetes, this finding might also be extended to those with pre- existing chronic diseases. This apparent homogeneity of response has implications regarding the acceptability of population-based studies in which such stratification is not possible.

- The implied regression coefficients are much larger (about an order of magnitude) than those found in either type of cross-sectional study. This could be interpreted as evidence that the chronic effects of air pollution far exceed the acute effects, or that not all of the spatial confounding has been controlled. Use of linear models for non-linear effects (body-mass index) and failure to control for alcohol consumption, diet,

exercise and migration may have contributed to the relatively large effects indicated for air pollution.

- If the responses to air pollution truly are chronic in nature, it is logical to expect that cumulative exposure would be the preferred metric (Abbey et al., 1991). Pollution levels 10 years before this study began were much higher in Steubenville and St. Louis, as indexed by TSP from routine monitoring networks. Estimates of previous levels of fine particles are more difficult, but atmospheric visibility data suggest that previous levels may have been higher in winter, but not necessarily in summer. These uncertainties make it difficult to accept quantitative regression results based solely on coincident monitoring data. For example, annual average TSP in 1965 in Steubenville was about three times the value used by Dockery et al.

Because it seems unlikely that any of the perceived shortcomings of this study could have resulted in bias sufficient to reduce the risk estimates to levels less than those found in acute mortality studies, the study of Dockery et al. (1993) appears to provide support for the hypothesis that the results of long-term air pollution studies must also reflect the presence of acute effects on mortality as integrated over the long term, as suggested by Evans et al. (1984a). It may also be concluded that support has been shown for the existence of chronic effects; these two possibilities are not mutually exclusive. However, these conclusions must be qualified by the realization that not all of the relevant socioeconomic factors may have been properly controlled in this study.

American Cancer Society Study

Pope et al. (1995) analyzed 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS). The Cox proportional hazards model was used to define individual risk factors for age, sex, race, smoking (including passive smoke exposure), occupational exposure, alcohol consumption, education, and body-mass index. The deaths, about 39,000 in all, were assigned to geographic locations using the 3-digit zip codes listed at enrollment into the ACS study in 1982. Relative risks were then computed for 151 metropolitan areas defined by these zip codes and were compared to the corresponding air quality data, ca. 1980. The sources of air quality data used were the EPA AIRS system for sulfates, as obtained from high-volume sampler filters for 1980, and the Inhalable Particulate Network for fine particles ($PM_{2.5}$). The latter data were obtained from

dichotomous samplers during 1979-81; Pope et al. used the values from this data base reported by Lipfert et al., 1988 (this study is discussed above), but only 50 $PM_{2.5}$ locations could be matched with the death data. The correlation between the two pollutants was 0.73. The sulfate values from the inhalable particle filters, which are thought to be free from artifacts, were not used in this study. Causes of death considered included all causes, cardiopulmonary causes (ICD-9 401-440, 460-519), lung cancer (ICD-9 162), and all other causes.

This study took great care with the potential confounding factors for which data were available. Several different measures of active smoking were considered, as was the time exposed to passive smoke. The occupational exposure variable was specific to (any of) asbestos, chemicals/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel exhaust, or formaldehyde. The education variable was an indicator for having less than a high-school education. However, alcohol use and body-mass index were considered as linear predictors of survival, whereas other studies have indicated these effects to be non-linear (U or J-shaped) (Doll et al., 1994; Gronbaek et al., 1994). Pope et al. (1995) did not report the relative risk coefficients they obtained for these cofactors, which is unfortunate since correspondence of findings for the non- pollution variables with exogenous estimates from independent studies adds to the confidence in the results for the pollution variables.

Risk factors not considered by Pope et al. (1995) include income, employment status, dietary factors, drinking water hardness and physical activity levels, all of which have been shown to affect longevity (Sorlie and Rogot, 1990; Belloc, 1973; Pocock et al., 1980). In addition, they did not discuss the possible influences of other air pollutants. For example, Lipfert et al. (1988) found that it was not possible to separate the effects of SO_2, SO_4^{2-}, and NO_x from one another, and Lipfert (1992) found some evidence for the effects of ozone in cross-sectional mortality regressions for U.S. metropolitan areas in addition to associations between TSP and all-disease and COPD mortality.

The ACS cohort is by no means a random sample of the U.S. population; it is 94% white and better educated than the general public, with a lower percentage of smokers than in the Six City Study. The (crude) death rate during the 7.25 years of follow-up was just under 1% per year, which is about 20% lower than expected for the white population of the

U.S. in 1985, at the average age reported by Pope et al. In contrast, the corresponding rates for the Six- Cities study (Dockery et al., 1993) discussed above tended to be higher than the U.S. average.

No mention was made of residence histories for the decedents; matching was done on residence location at entry to the study. The 1979 to 1981 pollution values were assumed to be representative of long-term cumulative exposures, in keeping with the objective of analyzing chronic effects. However, the previous decade was one of extensive pollution cleanup in most of the nation's dirtiest cities (TSP dropped by a factor of 2 in New York City, for example [Ferrand, 1978]). In contrast, air quality would have remained relatively constant in cities that already met the standards. Thus, it is reasonable to expect that the contrast between "clean" and "dirty" cities would have been greater in 1970 than in 1980.[2] If the excess mortality found in this study were in fact due to cumulative exposures, the regression coefficients would have been biased upward (in terms of relative risk per $\mu g/m^3$) by using the more recent data. The typically long latency period for lung cancer (ca. 20 yr.) suggests that data on prior exposures may be particularly important for this cause of death.

The adjusted total mortality risk ratios (computed for the range of the pollution variables) were 1.15 (95% CL = 1.09 to 1.22) for sulfates and 1.17 (95% CL = 1.09 to 1.26) for $PM_{2.5}$. When expressed as log-linear regression coefficients, these values were quite similar for both pollution measures: 0.0070 (0.0014) per $\mu g/m^3$ for SO_4^{2-} and 0.0064 (0.0015) for $PM_{2.5}$, suggesting that particle chemistry may be relatively unimportant as an independent risk factor (it is possible that the SO_4^{2-} results have been biased high by the presence of filter artifacts). Pope et al. (1995) found that the pollution coefficients were reduced by 10 to 15% when variables for climate extremes were added to the model. Expressed as the percentage of mortality associated with air pollution at the mean values and corrected for filter artifact for SO_4^{2-} using the data of Lipfert (1994), this study found mean

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[2]For example, the ranges of TSP and SO_4^{2-} across the U.S. in 1970 were from 40 to 224 and from 3 to 28 $\mu g/m^3$, respectively (Lipfert, 1978). In 1980, these ranges decreased to 41-142 and 2-17 eeg/m^3 (Lipfert, 1993), which suggests that the dirtiest cities became cleaner while the "clean" cities stayed about the same. The change in pollution range is about a factor of 1.8.

effects of about 5% for sulfate and 12% for $PM_{2.5}$. No significant excess mortality for the "other" causes of death was attributed to air pollution in this study.

Pope et al. (1995) found very consistent pollution risks for males and females and for ever-smokers and never-smokers for all-cause mortality. However, the relative risks for air pollution were slightly higher for females for cardiopulmonary causes of death. The lung cancer- sulfate association was only significant for males, except for male never-smokers.

The ACS study is unique in having attempted to control for passive smoking exposure. It is unfortunate that passive smoking results were not reported and compared with the air pollution risks.

The results of the American Cancer Society prospective study were qualitatively consistent with those of the Six City study with regard to their findings for sulfates and fine particles; relative standard errors were smaller, as expected because of the substantially larger database. However, no other pollutants were investigated in the ACS analysis, so that no further progress was made in attempting to identify the "responsible" pollutants. In addition, the ACS regression coefficients were about 1/4 to 1/2 of the corresponding Six City values and were much closer to the corresponding values obtained in various acute mortality studies. Thus it is not clear to what extent chronic effects (as opposed to integrated acute effects) are indicated by these results and to what extent the limited air quality data base used was responsible for this outcome.

Summary and Conclusions from Prospective Studies

Table 12-19 summarizes the three newer prospective studies considered here. The California and Six-City studies suffer from small sample sizes and inadequate degrees of freedom, which partially offsets the specificity gained by considering individuals instead of population groups. All of them may have neglected some important risk factors. The two early studies not shown in this table were largely inconclusive and the studies of California nonsmokers by Abbey et al. (1991, 1994) that had the best cumulative exposure estimates found no significant mortality effects of previous air pollution exposure. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess

TABLE 12-19. PROSPECTIVE COHORT MORTALITY STUDIES

Source	Health Outcome	Population	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Total Deaths	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at SO_4 = 15, PM_{15} = 50, $PM_{2.5}$ = 25	RR. Confidence Interval	Elasticity
Abbey et al. (1991)	Total mortality from disease	Calif. 7th Day Adventist	1977-82 Defined by air monitoring sites	24 h TSP > 200	102	25-175 (annual avg)	NA	845	Cox proportional hazards	10 yrs	none	age, sex, race, smoking, education, airway disease	0.99 TSP[1]	(0.87-1.13)[1]	NS[2]
Dockery et al. (1993) p. 1758	Total mortality	White adult volunteers in 6 U.S. cities[3]	1974-91	PM_{15} $PM_{2.5}$ SO_4	29.9 18 7.6	18-47 11-30 5-13	1	1429	Cox proportional hazards	none	none	age, sex, smoking, education, body mass, occup. exposure hypertension[4], diabetes[4]	1.42 PM_{15} 1.31 $PM_{2.5}$ 1.46 SO_4	(1.16-2.01) (1.11-1.68) (1.16-2.16)	0.25 0.22 0.23
Pope et al. (1995) Table 2	Total mortality	American Cancer Society, adult volunteers in U.S.	1982-89 $PM_{2.5}$ 50 cities SO_4 151 cities	$PM_{2.5}$ SO_4	18.2 11[5]	9-34 4-24	1 1	20,765 38,963	Cox proportional hazard	none	none	age, sex, race, smoking, education, body mass, occup. exposure, alcohol consumption, passive smoking, climate*	1.17 $PM_{2.5}$ 1.10 SO_4	(1.09-1.26) (1.06-1.16)	0.117 0.077

[1]For 1,000 h/yr > 200 $\mu g/m^3$.
[2]NS = non significant, confidence limits not shown.
[3]Portage, WI; Topeka, KS; Watertown, MA; Harrisman-Kingston, TN; Steubenville, OH.
[4]Used in other regression analyses not shown in this table.
[5]Value may be affected by filter artifacts.

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mortality, but it is unfortunate that the ACS study did not consider a wider range of pollutants so as to also confirm the lack of importance for other pollutants. In addition, the timing of the critical exposures remains an open question. It is also important that a range of pollutants be considered in both chronic and acute studies, since it is possible that acute effects may be exhibited by one pollutant and chronic effects by another.

12.4.1.4 Summary of Long-Term Studies

Previous Summaries of Cross-Sectional Studies

There have been many previous reviews and summaries of air pollution-mortality studies, including those by Ricci and Wyzga, 1983; Lipfert, 1977, 1978, 1980, 1985; International Electric Research Exchange, 1981; Evans et al., 1984b; Lave and Seskin, 1970; Landau, 1978, Cooper and Hamilton, 1979; Thibodeau et al., 1980; Ware et al., 1981. However, few of these adequately considered the effects of errors in estimating air pollution exposures, and there are now some new results that were not available to previous reviewers. For example, Thibodeau et al. (1980) reanalyzed the Lave and Seskin data set (1978) using the same basic data (including the flawed "minimum" $SO_4^=$ data) and variables, but correcting for errors in the data and adding some statistical techniques. This type of reanalysis provides confidence in the results of the original authors with respect to the absence of numerical errors but cannot provide insight into robustness with respect to choices of variables and observations, which can be a more important issue.

With respect to cross-sectional studies, Ware et al. (1981) concluded that "...The model can only be approximately correct, the surrogate explanatory variables can never lead to an adequate adjusted analysis, and it is impossible to separate associations of mortality rate with pollutant and confounding variables. This group of studies, in our opinion, provides no reliable evidence for assessing the health effects of sulfur dioxide and particulates...." However, they did not support this conclusion by attempting to explain the important differences among study results. Obviously, Ware et al. (1981) did not have access to the recent large prospective cohort studies nor the more recent population-based cross-sectional studies, which should allow some of these issues to be addressed and some of the differences in study results to be explained.

Evans et al. (1984) concluded that "...important questions related to the interpretation of cross-sectional studies remain unanswered. For example, it is unclear which specific pollutants are responsible for any observed effect; the shape of the exposure-response relationship is unresolved; and it is possible that the observed effects are due, in part, to confounding or systematic misclassification...." Nevertheless, the authors were of the opinion that "...the cross- sectional studies reflect a causal relationship between exposure to airborne particles and premature mortality...." Several observers have arrived at this conclusion with respect to the acute mortality studies; it is thus important to consider the entire body of air pollution-mortality studies.

Comparison of Prospective and Population-based Cross-Sectional Study Results

The literature on long-term health effects of air pollution has been substantially enriched by the publication of the recent prospective studies. Their ability to stratify by smoking habit or occupational exposure provides valuable information not previously available. These studies also provide a basis with which to evaluate the reasonableness of the "ecologic assumptions" that are required in order to interpret ecological studies. In this section, we consider the two types of studies on an equal footing, following the admonition of Greenland and Robins (1994b) that ecological studies should not be discounted just because they are ecological.

Table 12-20 compares regression coefficients from the two prospective studies that reported significant pollution risks with corresponding estimates made on an "ecologic" basis, i.e., using SMSA-wide mortality rates. Pope et al. (1995) introduced this concept by comparing age-race-sex-adjusted SMSA mortality rates with their prospective findings, but without adjusting the SMSA-wide values for cofactors such as smoking or education. They noted the similarity in relative risk estimates between their prospective study findings and the SMSA-wide "ecologic" estimates, but they did not discuss whether the risks predicted by ecological studies would drop substantially if the equivalent confounding variables had been considered in both types of studies. Table 12-20 also makes this comparison and goes on to show how the ecologic estimates of the pollution effects diminish and become negative and/or non-significant as additional cofactors are entered into the regression model. Each of

TABLE 12-20. COMPARISON OF LOG-LINEAR REGRESSION COEFFICIENTS FROM PROSPECTIVE AND "ECOLOGIC" ANALYSES FOR U.S. METROPOLITAN AREAS

Factors Accounted For	SO_4^{2-} coeff. (SE)	FP coeff. (SE)
A. Prospective studies		
1. Dockery et al. (1993)	(n=6)	(n=6)
age, sex, active smoking, body mass, education.	**0.0308 (0.011)**	**0.0124 (0.005)**
2. Pope et al. (1995)	(n=151)	(n=50)
age, sex, race, active & passive[a] smoking, education[a], body mass[a], alcohol[a], occupational exposure[a]	**0.007 (0.0014)**	**0.0064 (0.0015)**
B. "Ecologic" regressions[b]	(n=149)	(n=63)
1. **age, race**	**0.0092 (0.0019)**	**0.0048 (0.0019)**
2. **age, race,** smoking	**0.0040 (0.00083)**	**0.0048 (0.00195)**
3. **age, race,** smoking, **education**	**0.0058 (0.00195)**	0.0018 (0.00195)
4. **age, race, smoking, education, migration**	-0.00044 (0.0021)	0.00012 (0.0016)
5. **age, rage, smoking, education, migration,** drinking water hardness	-0.00055 (0.0021)	0.00035 (0.0016)

Bold factors are significant ($p < 0.05$).
[a]Significance of cofactors not stated.
[b]Data from Lipfert, 1993.

these factors has been shown (by others) to exert an influence on health, and all of them were significant in the ecologic model except drinking water hardness (for which t=1.6). This comparison suggests that the mortality risks assigned to air pollution by the prospective studies may have diminished had individual data on additional risk factors been available and included in the analysis.

It is also interesting that introduction of the smoking variable (statewide cigarette sales) into the ecologic regressions had little or no effect on the pollution coefficients, whereas the

other variables had relatively large effects (the correlation between this smoking variable and SO_4^{2-} was only 0.15). The relative risk corresponding to the ecologic smoking risk coefficient was somewhat less than those found by the prospective studies, probably because this variable is a poor surrogate for individual smoking rates.

Figures 12-7 to 12-9 were prepared to illustrate the overlapping confidence intervals of the various studies using mortality data ca. 1980 and later. For SO_4^{2-}, Figure 12-7, the two prospective studies and Ozkaynak and Thurston's (1987) ecological study overlap, mainly because of the very wide confidence limits of the Six City Study. However, all of these studies accounted for a somewhat limited range of potential confounding variables; the 1980 SMSA study by Lipfert (1993) found SO_4^{2-} to lose significance when additional variables were entered into the model. More overlap is shown for $PM_{2.5}$ (Figure 12-8), even though significance was not achieved with either ecological study. Overlapping confidence intervals are also seen with TSP (Figure 12-9), including the California prospective study. These plots thus suggest that much of the apparent contrast among studies could be due to chance variation.

The important contribution of the prospective studies is the proper accounting for individual risk factors, mainly smoking. The question thus arises, could inadequate control for smoking in an ecological study lead to an underestimate of the air pollution relationship? This would require a negative correlation between smoking and air pollution. However, based on state-level data, the correlations between smoking and both SO_4^{2-} and $PM_{2.5}$ are weakly positive. Thus it does not appear that inadequate control for smoking explains the difference in results. One is thus led to the conclusion that either some other factor is negatively correlated with air pollution or that the prospective studies are affected by some confounder that is more important at the individual level than at the community-average level. Of course, much of the range in results seen in these plots could also be due to chance.

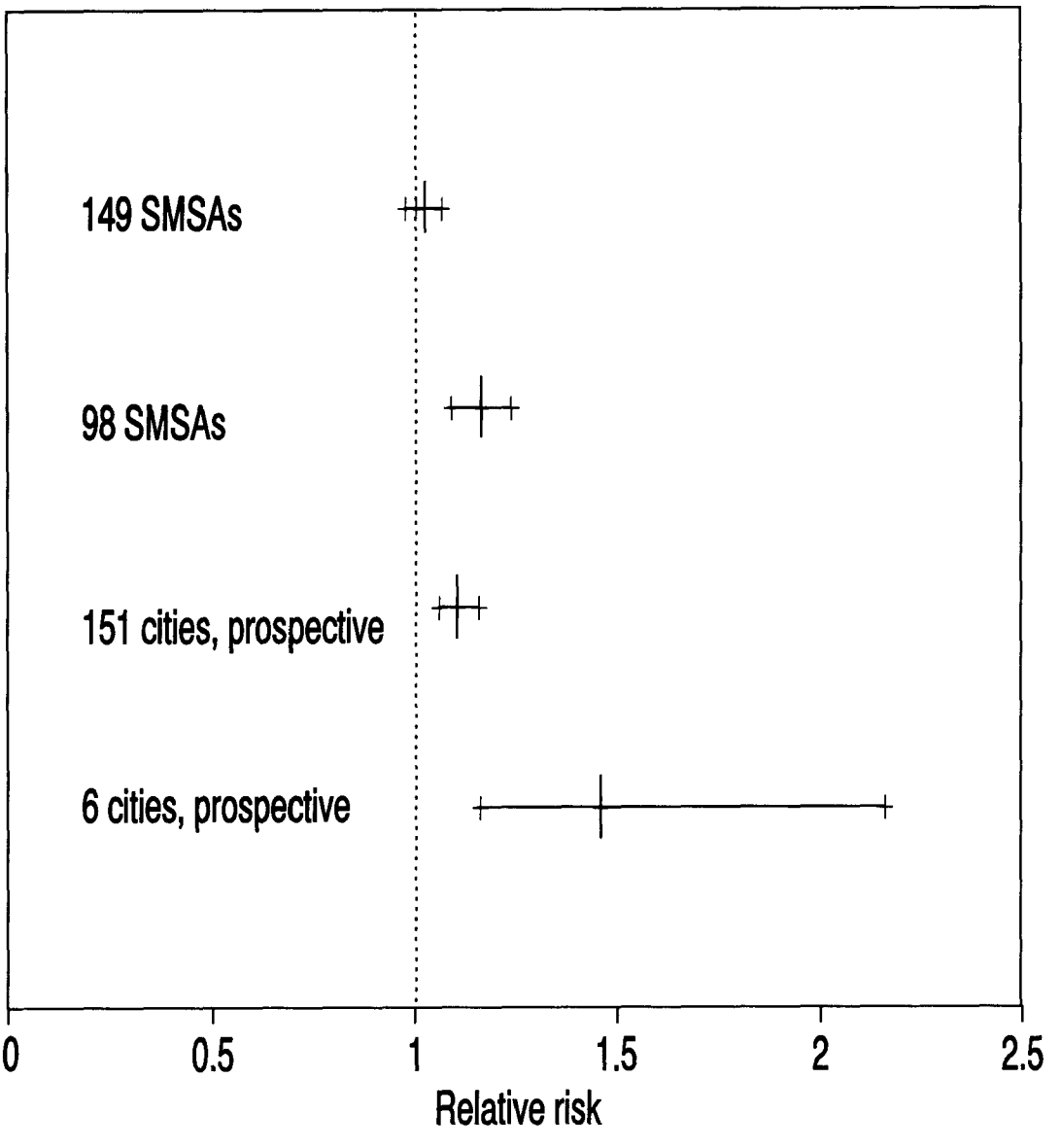

Figure 12-7. **Comparison of relative risks of exposure to 15 $\mu g/m^3$ of SO_4, as estimated by Dockery et al., 1993 (6-cities, prospective), Pope et al., 1995 (151 cities, prospective), Ozkaynak and Thurston, 1987 (98 SMSAs, ecological), and Lipfert, 1993 (149 SMSAs, ecological).**

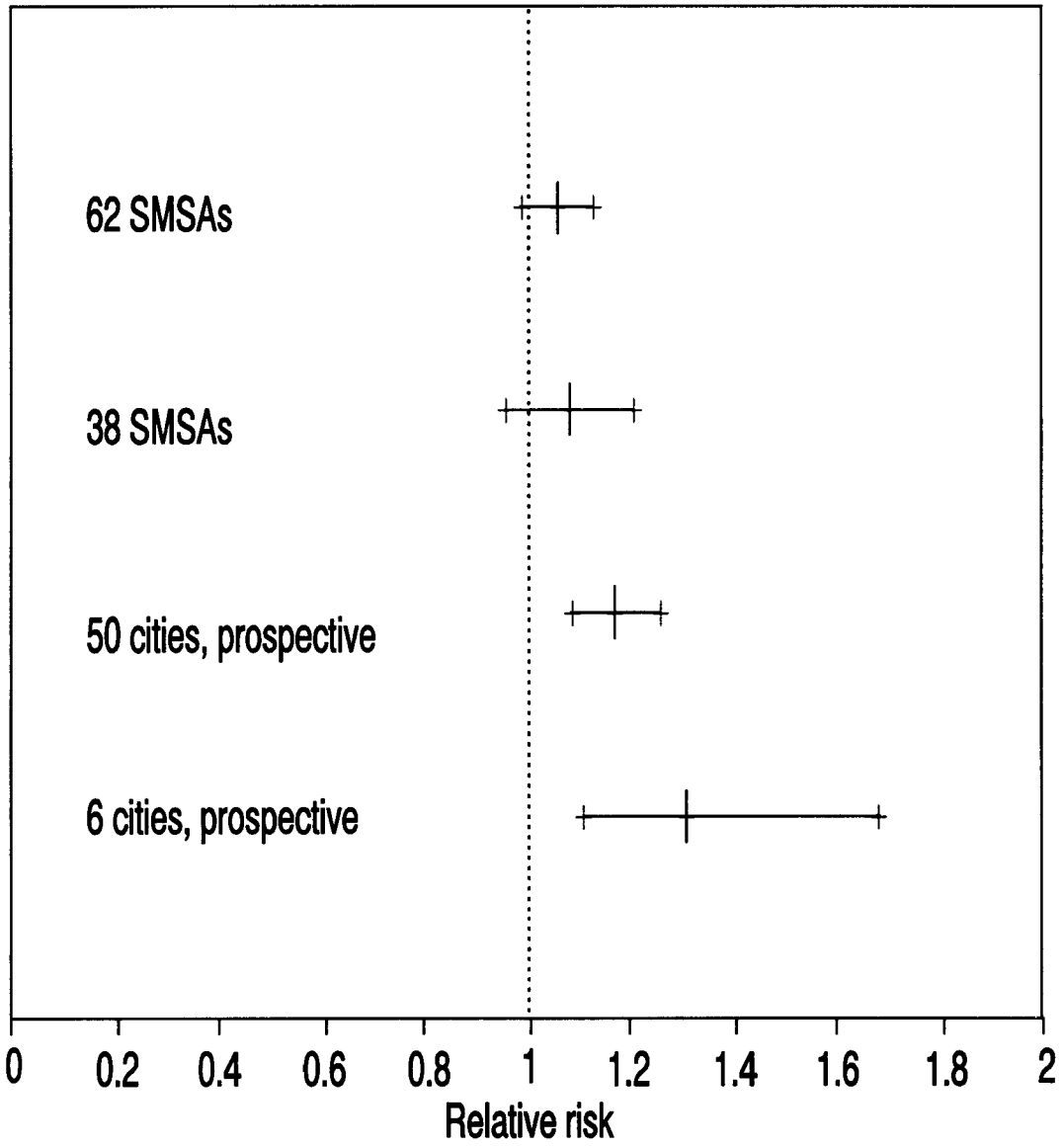

Figure 12-8. **Comparison of relative risks of exposure to 25 $\mu g/m^3$ of $PM_{2.5}$, as estimated by Dockery et al., 1993 (6-cities, prospective), Pope et al., 1995 (50 cities, prospective), Ozkaynak and Thurston, 1987 (38 SMSAs, ecological), and Lipfert, 1993 (62 SMSAs, ecological).**

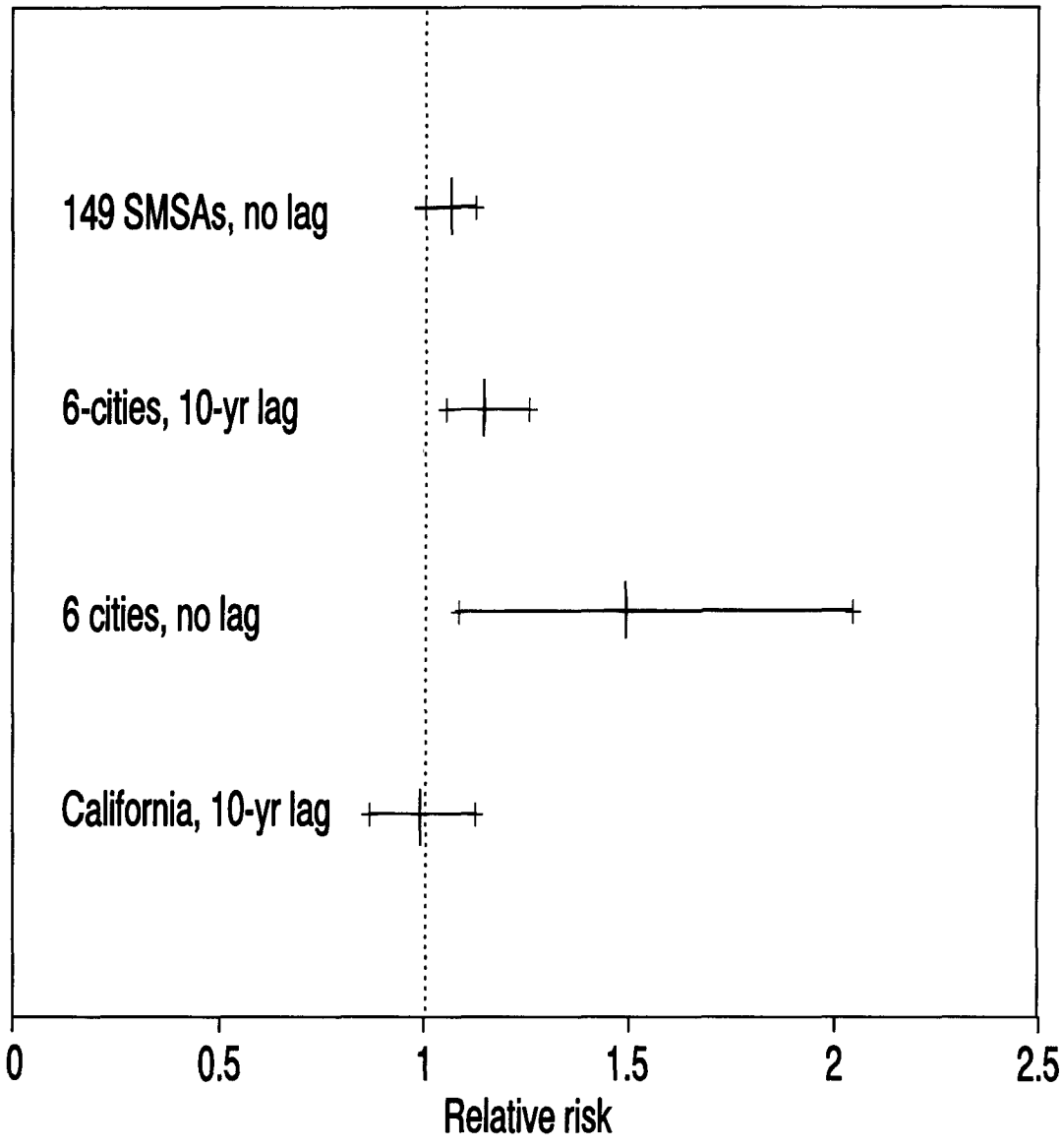

Figure 12-9. **Comparison of relative risks of exposure to 100 $\mu g/m^3$ of TSP, as estimated by Abbey et al., 1991 (California), and as estimated from the data of Dockery et al., 1993, with and without a 10-year lag (6-cities, prospective), and Lipfert, 1993 (149 SMSAs, ecological).**

Concluding Discussion

Referring back to the original goals of long-term mortality studies, several questions appear worthy of reconsideration:

1. Have potentially important confounding variables been omitted? The generic criticisms of (previous) cross-sectional studies should be revisited in this context. The effects of selective migration (i.e., population loss), lifestyle (diet, physical fitness, etc.), drinking water hardness, and income were not investigated in any of the prospective studies. The analysis protocols used by Abbey et al. (1991) and by Pope et al. (1995) included possible effects of passive smoking, but results were not reported for this risk factor. In view of the sensitivity of other cross-sectional (population- based) studies to some of these factors, the conclusion follows that the potential for biased results exists in all of the cross-sectional studies.

2. Can the most important pollutant species be identified? Abbey et al. found no significance for any pollutant for all-disease mortality. In the Six City Study, "importance" must be identified in terms of relative fit between residual risk and air pollution across the six cities, since the aggregate risk level is the same for all species. Unfortunately, with only six observations, the air pollution confidence limits are quite wide and it is difficult to discriminate among the various possibilities. In addition, the pollutants that seem to fit best have the shortest periods of monitoring data. Comparisons between pollutants in the ACS study were limited since only two pollutants were considered (and these were highly correlated) and because of the inherent differences in reliability of the different data bases used for each pollutant. Thus, although support exists for fine particles or sulfates as important mortality predictors, other pollutants cannot be ruled out.

3. Can the studies discriminate between the effects of current and of cumulative exposures, i.e., between truly chronic effects and the integral of acute responses over time? Abbey et al. only examined previous exposures, while the Six City Study looked mainly at coincident exposures and the periods of record were shortest for the pollutants that seem to fit the best ($PM_{2.5}$, PM_{15}, and SO_4^{2-}). The ACS study was even more limited, since only one year of sulfate data was used and the fine particle data were limited to a few years and a subset of locations. This question must thus be considered as still open. Since the acute effects of air pollution seem to be manifested much more strongly on the elderly, it might be useful to stratify the prospective cohorts by age. The chronic effects of cancer and heart disease might show up at earlier ages, leading to a clearer distinction between the two types of responses.

The overarching conclusion from long-term mortality studies is that they may be easier to carry out than they are to interpret. To some extent, the results are still somewhat investigator-dependent, although a high degree of support has been shown for the hypothesis

that the result from a cross-sectional study for a given year reflects at least the sum of the acute effects experienced during that year. However, one must also conclude that support for the finding of truly chronic effects from cumulative exposures cannot be excluded.

In the 1982 OAQPS Staff Paper (U.S. Environmental Protection Agency, 1982b), the use of cross-sectional analyses in setting standards was discouraged, based on the admonitions of Ware et al. (1981) that, "these models can only be approximately correct, the surrogate explanatory variables can never lead to an adequately adjusted analysis, and separating associations between mortality rates and pollutant and confounding variables is impossible. Thus these studies deal with unknown levels of exposure of ill-defined groups of individuals to unspecified pollutants for unstated periods of time and fail to control for many variables known to affect health status." Given the large number of studies that have appeared in the ensuing years, this rather harsh indictment should be revisited to determine what progress has been made (most of these criticisms also apply to time-series studies, which should be examined in the same light).

"Models can only be approximately correct."
This is true for all of the studies reviewed above, including the prospective studies. However, the most relevant question here is to what extent the estimates of pollution effects have been confounded by model shortcomings.

"Surrogate explanatory variables."
Surrogates are heavily used in the population-based studies and less so in the prospective studies, for which some individual-level data were available. This question may be addressed in part in population-based studies by comparing the effects obtained for a given factor (like age, race, or education) with those obtained at the individual level.

"Separating collinear associations is impossible."
On its face, this is an overstatement for population-based cross-sectional studies, while it may be more applicable to time-series studies or to prospective studies involving only a few locations. For example, using 1980 data for cities (Lipfert et al., 1988), SO_4^{2-} was the pollutant most associated with other (nonpollutant) factors, and the highest such correlation was only about 0.5. Among pollutants, however, correlations tend to be higher: SO_4^{2-} vs $PM_{2.5}$, 0.76; PM_{15} vs. $PM_{2.5}$, 0.61; Mn vs. Fe, 0.78; PM_{15} vs. Fe, 0.69.

"Unknown exposures for unstated periods of time."
Some of the prospective studies (e.g., Abbey et al., 1991) have defined specific chronic exposure levels; they were not found to be statistically significant in that

instance. Other studies have been more vague, and population-based studies in general have not found important differences between concurrent and lagged pollution data (see for example, Kim, 1985). Lipfert (1993) found that the TSP-mortality relationship was better defined when concentrations were averaged across SMSAs for the same year as the mortality data and when a migration variable was included. This supports the hypothesis that the integrated sum of acute responses is reflected in the long-term response.

"Ill-defined groups of individuals."

This deficiency was addressed directly by prospective cohort studies. Results were found to be consistent for various subsets of individuals defined by smoking and occupational exposures. However, population-based studies tend to find somewhat unstable results when subsets defined by age and gender are analyzed (Lipfert, 1984).

Failure to control for known confounders.

All of the studies reviewed are subject to this criticism, but to varying degrees. None controlled for lifestyle differences such as diet or exercise. Most of the studies ignored the effects of population migration and some of the population- based studies did not control for smoking. However, the extent to which these variables actually confound varies with the situation and absolute levels of bivariate correlation are not always a good indicator. This arises in part from the general tendency for mortality to be more weakly associated with air pollution than with many of the potential confounders.

Thus, it appears that, as with most epidemiology, consistency among studies of widely varying design must be sought in order to respond to the shortcomings that were noted earlier, since different designs have different strengths and weaknesses. Among the long-term exposure studies, it is important to find consistency in terms of geographic scale, time periods, pollutant levels, and regional locations. It will also be important to contrast the findings from short- and long- term exposures and to examine coherence among various health endpoints.

Summary of Conclusions

Cross-sectional studies may find a significant association between mortality and a specific air pollutant for any of several reasons:

- The association may reflect a non-zero integral of the acute effects of that pollutant over the period of study.

- The association may reflect a chronic effect from previous long-term exposures.

- The association may have resulted from confounding, either with another pollutant, with the characteristics of the sources that produced that pollutant (occupational hazards or exposures), or with human elements spatially associated with pollution sources such as differential migration of the healthy, less desirable housing near sources, or other socioeconomic factors.

The studies reviewed above probably all reflect some varying combinations of these possibilities. It is possible that a given regression coefficient may reflect the acute effects of one pollutant and the collinear portion of the chronic effects of another, for example. Convincing evidence of causal associations requires demonstration of specific disease-pollution combinations that are physiologically plausible. Supporting evidence may be obtained by showing that the statistical relationship improves when more reliable exposure data are used in the analysis.

Some of the prospective studies demonstrated that additional pollutant exposures (cigarette smoke, occupational exposure) not reflected in the outdoor measurements lead to a stronger statistical mortality relationship with the outdoor measurements. This suggests two possibilities (there may be others):

- The indoor and outdoor exposures may reinforce each other and thus must have similar physiological effects. This may provide some clues as to the most likely of several collinear outdoor pollutants. The responses could be either chronic or acute.

- The indoor or occupational exposures may have created a disease state (independent of the outdoor exposures) that makes the individual more susceptible to outdoor pollution effects. This hypothesis suggests that the outdoor effects in the prospective studies are acute, since it is unlikely that normally healthy people will experience acute effects at the air pollution levels now seen in U.S. cities.

Distinguishing between these two scenarios will likely require additional research, probably including temporal studies of long-term changes in air quality in different places.

At this time, the long-term studies provide support for the existence of short-term increase in mortality which are not subsequently canceled by decreases below normal rates. However, they do not exclude the existence of chronic effects. They provide no convincing evidence as to the specific pollutant(s) involved, and they do not rule out the existence of pollutant thresholds.

12.4.2 Morbidity Effects of Long-Term PM Exposure

Acute exposures to PM are associated with increased reporting of respiratory symptoms and with small decrements in several measures of lung function (Section 12.3.2.3). As a consequence, cross-sectional studies of the relationship between long-term exposure to PM (or any air pollutant) and consequent chronic effects on respiratory function and/or respiratory symptoms may be limited by the inability to control for effects of recent exposures on function and symptoms. Moreover, such studies are further handicapped by: (1) limited or no ability to characterize accurately lifetime exposure to PM other than through "area-based" ecological assignments or assignments inferred from short-term, acute measurements; and (2) their inherent limited ability to characterize correctly other relevant exposure histories (e.g., past histories of respiratory illnesses, passive exposure to tobacco smoke products, active smoking in older subjects).

Longitudinal studies offer a number of obvious advantages over cross-sectional studies in terms of PM exposure characterization and characterization of relevant covariates. Nonetheless, to the extent to which such studies try to base their inference with regard to the occurrence of long-term morbidity on the effects observed over relatively short durations of cohort follow-up (e.g., incident respiratory illness in relationship to ambient PM, short-term relationship between ambient PM and lung function), their result need to be accepted with circumspection. These approaches do not establish long-term effects but only suggest the coherence of the possibility of such long-term effects. The optimal longitudinal studies would provide data on incident chronic conditions such as physician diagnosed asthma and/or evidence for altered patterns of lung function growth and decline for children and adults, respectively.

12.4.2.1 Respiratory Illness Studies

Studies of Children

The 1982 Criteria Document (U.S. Environmental Protection Agency, 1982a) indicated that apparent quantitative relationships between air pollution and lower respiratory tract illness in children were reported by Lunn et al. (1967), who studied respiratory illnesses in 5- and 6-year old school children living in four areas of Sheffield, England. Positive

associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56% more frequent in the higher pollution areas than in the low-pollution area ($p < 0.005$). Also, decrements in lung function, measured by spirometry tests, were closely associated with respiratory disease symptom rates. Lunn et al. (1970) also reported results for 11-year-old children studied in 1963 to 1964 that were similar to those found earlier for the younger group. These Lunn et al. (1967, 1970) findings have been widely accepted (World Health Organization, 1979; Holland et al., 1979; U.S. Environmental Protection Agency, 1982a,b) as valid. On the basis of the results reported, it appears that increased frequency of lower respiratory symptoms and decreased lung function in children may occur with long-term exposures to annual BS levels in the range of 230 to 301 $\mu g/m^3$ and SO_2 levels of 181 to 275 $\mu g/m^3$. However, these are only very approximate observed-effect levels because of uncertainties associated with estimating PM mass based on BS readings. Also, it could not then be concluded, based on the 1968 follow-up study, that no-effect levels were demonstrated for BS levels in the range of 48 to 169 $\mu g/m^3$ because of: (1) the likely insufficient power of the study to have detected small changes given the size of the population cohorts studied, and (2) the lack of site-specific calibration of the BS mass readings at the time of the later (1968) study. In summary, the Lunn et al. (1967) study provided the clearest evidence cited in the 1982 EPA criteria document (U.S. Environmental Protection Agency, 1982a) for associations between both significant pulmonary function decrements and increased respiratory disease illnesses in children and chronic exposure to specific ambient air levels of PM and SO_2.

Dockery et al. (1989) studied respiratory symptoms in children as part of the Harvard Six Cities Study. The cities included Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS. A cross-sectional survey was done in 1980 to 1981. The survey included questions on the presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to 5,422 10 to 12-year-old white children. A centrally located air monitoring station was established in each community starting in 1974 measuring TSP, SO_2, NO_2, and ozone. Starting in 1978 dichotomous samplers were used to measure PM_{15}. Multiple logistic regression analyses

were performed on each health endpoint. The estimated relative odds of bronchitis from comparing the most polluted community to the least was 2.5 (1.1 to 6.1). This corresponded to a 38.7 $\mu g/m^3$ increase in the PM_{15} level. For chronic cough the odds ratio was 3.7 (1.0 to 13.5) and for chest illness it was 2.3 (0.8 to 6.7). The odds ratios corresponding to the other pollutants including TSP, $PM_{2.5}$, sulfate fraction, SO_2, NO_2, and O_3 were not significant, although they all were greater than 1.

Ware et al. (1986) had previously studied respiratory illness and symptoms in children in the same six communities as Dockery et al. (1989). The earlier survey included questions on the presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to white children enrolled during one of the first three visits to each city who were six through nine years of age. At least one centrally located air monitoring station was established in each community starting in 1974 measuring TSP, SO_2, water soluble sulfate, NO_2, and ozone. The cities of St. Louis, Steubenville and Kingston-Harriman were divided into two regions based on exposure. Multiple logistic regression coefficients were significant for cough, bronchitis, and lower respiratory illness for both TSP and water soluble sulfate. The between city coefficients for TSP ($\mu g/m^3$) were .0101 (.0018) for cough, .0103 (.0046) for bronchitis, and .0076 (.0035) for lower respiratory illness. TSP coefficients for within city analyses tended to be negative.

Neas et al. (1994) analyzed a cohort of white children aged 7 to 11 from the same Six Cities Study. Respiratory illness history and other background information was collected on a parent-completed questionnaire administered between September, 1983 and June, 1986. A stratified one-third random sample of the questionnaire respondents (300 to 350 households per city) was invited to participate in a program of indoor air quality measurements. Indoor air quality was measured in two consecutive 1-week sampling periods in both winter and summer. Measurements included respirable particulates ($PM_{2.5}$) and nitrogen dioxide. Health endpoints reported on the questionnaire included shortness of breath, persistent wheeze, chronic cough, bronchitis, asthma, hayfever, earache, and chest illness. Odds ratios (OR) were calculated using multiple logistic regression for an increase of 30 $\mu g/m^3$ in $PM_{2.5}$, after adjusting for gender, age, parental education, parental history of asthma, and city. Most of the health endpoints showed little effect from $PM_{2.5}$ except for bronchitis

(OR = 1.18, CI = 0.99, 1.42) and any lower respiratory symptom (OR = 1.13, CI = 0.99, 1.30).

Stern et al. (1994) studied respiratory illness and lung function in five towns in southwestern Ontario (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and five communities in south-central Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton. Self-administered parental questionnaires were distributed between October 1985 and March 1986. Pollution monitoring was not begun until late 1985, and included SO_2, NO_2, and O_3. Inhalable particulates were measured at each town using a high-volume Sierra Instruments sampler. PM_{10} was measured once every six days in the Ontario towns and once every three days in the Saskatchewan towns. Odds ratios were computed (presumably using multiple logistic regression with a random effects model) comparing the endpoints of cough, phlegm, wheeze, asthma, bronchitis, and chest illness for the Ontario towns versus the Saskatchewan towns. No significant differences were found, even after adjusting for gender, parental smoking, parental education, and gas cooking. Actual exposure estimates for the individual towns were not used. The overall mean PM_{10} level in the Ontario towns was 23.0 $\mu g/m^3$ compared with 18.0 $\mu g/m^3$ for Saskatchewan.

Studies of Adults

The earlier 1982 criteria document (U.S. Environmental Protection Agency, 1982a) discussed one series of studies, reported on from the early 1960s to the mid-1970s, that was conducted by Ferris, Anderson, and others (Ferris and Anderson, 1962; Kenline, 1962; Anderson et al., 1964; Ferris et al., 1967, 1971, 1976). The initial study involved comparison of three areas within a pulp-mill town (Berlin, New Hampshire). In the original prevalence study (Ferris and Anderson, 1962; Anderson et al., 1964), no association was found between questionnaire-determined symptoms and lung function tests assessed in the winter and spring of 1961 in the three areas with differing pollution levels, after standardizing for cigarette smoking. The study was later extended to compare Berlin, New Hampshire, with the cleaner city of Chilliwack, British Columbia in Canada (Anderson and Ferris, 1965). The prevalence of chronic respiratory disease was greater in Berlin, but the

authors concluded that this difference was due to interactions between age and smoking habits within the respective populations.

The Berlin, New Hampshire, population was followed up in 1967 and again in 1973 (Ferris et al., 1971, 1976). During the period between 1961 and 1967, all measured indicators of air pollution fell (e.g., TSP from about 180 $\mu g/m^3$ in 1961 to 131 $\mu g/m^3$ in 1967). In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg $SO_3/100\ cm^2$ day) while TSP values fell from 131 to 80 $\mu g/m^3$. Only limited SO_2 data were available (the mean of a series of 8-h samples for selected weeks.) During the 1961 to 1967 period, standardized respiratory symptom rates decreased and there was an indication that lung function also improved. Between 1967 to 1973, age-sex standardized respiratory symptom rates and age-sex-height standardized pulmonary function levels were unchanged. Although some of the testing was done during the spring versus the summer in the different comparison years, Ferris and coworkers attempted to rule out likely seasonal effects by retesting some subjects in both seasons during one year and found no significant differences in test results. Given that the same set of investigators, using the same standardized procedures, conducted the symptom surveys and pulmonary function tests over the entire course of these studies, it is unlikely that the observed health endpoint improvements in the Berlin study population were due to variations in measurement procedures, but rather appear to have been associated with decreases in TSP levels from 180 to 131 $\mu g/m^3$. The relatively small changes observed and limited aerometric data available, however, argue for caution in placing much weight on these findings as quantitative indices for effect or no-effect levels for health changes in adults associated with chronic exposures to PM measured as TSP.

The earlier criteria review (U.S. Environmental Protection Agency, 1982a) also noted a cross-sectional study conducted by Bouhuys et al. (1978) in Ansonia (urban) and in Lebanon (rural) Connecticut towns in which differences in respiratory and pulmonary function were examined in 3,056 subjects (adults and children). Bouhuys et al. (1978) found no differences between Ansonia and Lebanon for chronic bronchitis prevalence rates but did note that a history of bronchial asthma was highly significant for male resident of Lebanon (the cleaner town) as compared to Ansonia (the higher-pollution area). No differences were

observed between the communities for pulmonary function tests adjusted for sex, age, height and smoking habits. However, prevalence for three of five symptoms (cough, phlegm, and plus one dyspnea) were significantly higher for adult non-smokers in Ansonia ($p < 0.001$). The mix of positive and negative health effect results found by this cross-sectional study make it difficult to interpret.

Schwartz (1993) analyzed the NHANES data on respiratory illness diagnosed by a physician. The NHANES survey was conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The survey used a complex design and the Schwartz analysis was restricted to 53 urban sampling units. Endpoints included asthma, bronchitis, respiratory illness and dyspnea. EPA's SAROAD data base was used to obtain data from population oriented monitors in the 53 areas. Average TSP concentrations ($\mu g/m^3$) for previous years were used as the exposure measure. No other pollutants were considered. Multiple logistic regression analysis was used that included terms for cigarette consumption per day, former smoking, age, race, and gender. The coefficient for chronic bronchitis was .0068 (.0023) and for respiratory illness it was .0058 (.0019). The coefficients were slightly larger when restricted to non-smokers.

Yano et al. (1990) studied chronic respiratory illness in females aged 30 to 59 in two cities in Japan. One city, Kanoya is 25 km from an active volcano, and Tashiro is 50 km from the volcano. The winter concentrations of TSP in Kanoya average 341 $\mu g/m^3$ whereas the average is 119 $\mu g/m^3$ in Tashiro. Respiratory conditions were assessed using a Japanese version of the ATS-DLD questionnaire. No significant difference in rates of bronchitis, asthma, wheezing, or other related illnesses were found.

A number of studies have been published that attempt to define chronic respiratory system health effects in relationship to ambient pollutants to include PM and O_3 (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b). Among these, the series of publications from the Adventist Health Smog Study (AHSMOG) (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b) will be discussed first and as a set.

The basic population for these studies represents California-resident, Seventh-Day Adventists aged ≥ 25 years of age who had lived 11 years or longer (as of August 1976) in either a high-oxidant-polluted area (South Coast Air Basin [Los Angeles and vicinity] and a

portion of the nearby Southeast Desert Air Basin) or a low-pollution area (San Francisco or San Diego). This sample was supplemented by an additional group of subjects who met the 11-year residence requirement but who came from low-exposure rural areas in California. The total, baseline sample (March 1977) comprised 8,572 individuals, of whom 7,267 enrolled. From this group, 109 current smokers and 492 subjects who had lived outside of the designated areas for a portion of the previous 11 years were excluded. Detailed respiratory illness and occupational histories were obtained. In these studies, "COPD" refers to "definite chronic bronchitis", "definite emphysema", and "definite asthma" as defined by the study questionnaire. Measures of pulmonary function are not included.

Air monitoring data were obtained from the California ARB monitoring system. Ninety-nine percent of the subjects (excluding the rural supplement) lived at a distance from the nearest ARB monitoring site that was considered to provide relatively reliable concentration estimates for the outdoor, ambient environment at their residence. Concentrations at the monitors were interpolated to the centroid of each residential zip code from the three nearest monitoring sites with the use of a $1/R^2$ interpolation. Subsequent development of exposure indices took account of the improvements in ARB data after 1973. Data were available for total oxidants, O_3, TSP, SO_2, NO_2, CO, and SO_4 (excluding 1973 to 1975).

The initial report from this study (Hodgkin et al., 1984) was summarized in the 1986 ozone criteria document (U.S. Environmental Protection Agency, 1986c). Based upon a multiple logistic regression that adjusted for smoking, occupation, race, sex, age, and education, it was estimated that residence in the South Coast Air Basin conferred a 15% increase in risk for prevalent COPD. No estimates of exposure were provided, and the data were considered to be of limited utility.

Next, Euler et al. (1988) assessed the risk of chronic respiratory disease symptoms due to long-term exposure to ambient levels of TSP, oxidants, SO_2, and NO_2. Symptoms were ascertained using the National Heart, Lung, and Blood Institute questionnaire on 8,572 Southern California Seventh-Day Adventists (nonsmokers—25 years and older) who had lived 11 years or longer in their 1977 residential area. Tobacco smoke (active and passive) and occupational exposures were assessed by questionnaires, as were lifestyle

characteristics relative to pollution exposure, such as time spent outside and residence history. For each of the 7,336 participants who responded and qualified for analysis, cumulative exposures to each pollutant were estimated using monthly residence zip code histories and interpolated exposures from state air monitoring stations.

Multiple logistic regression analyses were conducted for pollutants individually and together with eight covariables, including environmental tobacco smoke exposure at home and at work, past smoking, occupational exposure, sex, age, race, and education. Statistically significant associations with chronic respiratory symptoms were seen for (1) SO_2 ($p = 0.03$), relative risk of 1.18 for 13% of the study population with 500 h/year of exposure above 0.04 ppm; (2) oxidants ($p < 0.004$) relative risk of 1.20 for 18% with 750 h/year above 0.1 ppm; and (3) TSP ($p < 0.00001$), relative risk of 1.22 for 25% with 750 h/year above 200 $\mu g/m^3$. When these pollutant exposures were analyzed together, TSP was the only one showing statistical significance ($p < 0.01$). Individuals working with smokers for 10 years had relative risks of 1.11 and those living with a smoker for 10 years had relative risks of 1.07.

A major improvement in the methods for assessment of exposure was presented in Abbey et al (1991a). Previous exposure estimates were refined by the computation of "excess concentrations" (concentration minus cutoff, summed over all relevant time periods and corrected for missing data). Exposures also were corrected for time spent at work and time away from residence, with estimates provided for the environments where work occurred and for geographic areas away from residence. The quality of the interpolations (in terms of distance of monitor from residence zip codes) also was evaluated and incorporated into the estimates. Adjustments were made for the time spent indoors by individuals. New indices were developed that were based on O_3, rather than on total oxidants. Comparison of actual versus interpolated cumulative exceedance frequencies and mean concentrations at monitoring stations (1985 through 1986) for TSP and O_3 were assessed. The actual versus interpolated 2-y mean concentrations did not differ significantly and were correlated with a Pearson correlation coefficient of 0.78 for TSP and 0.87 for O_3.

The above estimates were applied to data that included 6 years of follow-up of the study population (Abbey et al., 1991b). This analysis focused on incident occurrence of

obstructive airways disease (AOD—same definition as for COPD above). Incident symptoms of AOD were significantly associated with hours above several TSP thresholds, but not with hours above any O_3 threshold. Incidence of definite symptoms of AOD and chronic bronchitis were statistically significantly ($P < 0.05$) elevated for average annual hours in excess of 100, 150, and 200 $\mu g/m^3$ and mean concentrations of TSP but not for 60 $\mu g/m^3$. For incidence of asthma, there was significantly elevated risks only for average annual hours above thresholds of 150 and 200 $\mu g/m^3$. Relative risks for concentrations above 200 $\mu g/m^3$ of TSP for bronchitis were 1.33 (95% CL = 1.07 to 1.81); and asthma was 1.74 (95% CL = 1.11 to 2.92). Cumulative incidence estimates were adjusted with the use of Cox proportional hazard models for the same variables noted in the original publication of Hodgkin et al. (1984), as well as the presence of possible symptoms in 1977 and childhood respiratory illness history. None of the analyses included both O_3 and TSP thresholds. No data were provided on the details of the subjects available for the prospective analysis and their representativeness versus the entire base population.

Another analysis by Abbey et al. (1993) evaluated changes in respiratory symptom severity with the TSP and O_3 thresholds noted above. In this analysis, logistic regression, rather than Cox proportional hazard modeling, was used to assess cumulative incidence of components of the COPD/AOD complex; and multiple, linear regression was used to evaluate changes in symptom severity. When O_3 was considered by itself, there was a trend toward an increased risk of asthma for a 1,000-h average annual increment in the OZ (10) criterion (RR = 2.07, 95% CL = 0.98 to 4.89). In this analysis, there was a suggestion that recent ambient O_3 concentrations were more related to cumulative incidence than past concentrations. Change in asthma severity score was associated significantly with the 1977 to 1987 average annual exceedance frequency for O_3 thresholds of 10 and 12 pphm. No significant effects were found for COPD or bronchitis alone. In contrast to the above study of cumulative incidence, the investigators carried out an analysis in which TSP (200) and OZ (10) were allowed to compete for entry into a model to evaluate asthma cumulative incidence and changes in severity. In the cumulative incidence model that employed exceedance frequencies (number of hours above threshold), TSP (200) entered before OZ (10); when average annual mean concentrations were used, O_3 entered before TSP.

From this, the authors concluded that both TSP and O_3 were relevant to asthma cumulative incidence. In no case did both pollutants remain significant simultaneously in the same regression. No interactions were observed between TSP and O_3 for either metric. A similar result was observed for change in asthma severity. As in previous analyses, there was a high correlation between TSP (200) and OZ (10) exceedance frequencies (0.72) and their respective average annual mean concentrations (0.74).

Some researchers used case-control approaches to study chronic respiratory system health effects in relationship to ambient pollutants such as PM. In Athens, Greece, Tzonou et al. (1992) studied the relation of urban living and tobacco smoking to the development of COPD. Their findings suggested that air pollution or another aspect of the urban environments can be an important contribution to the development of COPD. Specific PM levels were not studied. Katsouyanni et al. (1991) conducted a case-control study in Athens exploring the role of smoking and outdoor air pollution and their relationship to lung cancer. Air pollution levels were associated with an increased risk for lung cancer but the relative risk was small and not statistically significant. Xu et al. (1989) studied air pollutants and lung cancer in China, the findings of which suggested that smoking and environmental pollution combined to allow for elevated rates of lung cancer mortality. In Poland, Jedrychowski et al. (1990) found similar findings as the above studies. (See Chapter 11 for other discussions of these studies).

Robertson and Ingalls (1989) studied male workers in the seven U.S. plants producing carbon black. The exposures ranged from 60 to 1700 $\mu g/m^3$. The study was analyzed as a matched case-control study. No differences in the time weighted average exposure were found for any cancers or respiratory disease.

Rothman et al. (1991) reported that wildland firefighters experience a small cross-seasonal decline in pulmonary function and an increase in several respiratory symptoms. Hours of self-reported fire-fighting activity were used as a surrogate for fire smoke exposure. At wildland fires, the concentration of a variety of pulmonary irritants, including respirable particulate, acrolein and formaldehyde may exceed occupational safety and health administration permissible exposure limits. Other compounds are also produced in wildland fires.

Shusterman et al. (1993) report the smoke-related disorders in Alameda County, California related to the October 20, 1991 grass fire in the Oakland-Berkeley hills. Bronchospaitic and irritative reactions to smoke constituted more than half of the emergency department visits related to the fire. Many of these patients had a history of asthma. The intensity and duration of smoke exposure ranged from mild and transient (among residents of surrounding areas) to intense and prolonged (among firefighters and some residents of the fire area).

Chronic Respiratory Disease Studies Summary

Three studies based on a similar type of questionnaire but done by two different groups of researchers, provide data on chronic respiratory disease and PM. All three studies suggest a chronic effect of particulate matter on respiratory disease, but the studies suffer from the usual difficulty of cross sectional studies. The effect of particulate matter is based on variations in exposure which are determined by the different number of locations. In the first two studies there were six locations and in the second there were four. The results seen were consistent with a particulate matter gradient, but it is impossible to separate out the effect of particulate matter and any other factors or pollutants which have the same gradient (See Table 12-21).

12.4.2.2 Pulmonary Function Studies

Studies of Children

Dockery et al. (1989) also studied lung function in children in the same six cities. A cross-sectional survey was done in 1980 to 1981. Lung function was measured at the time of the survey using a water filled recording spirometer. The analysis was restricted to 5,422 10 to 12-year white children. A centrally located air monitoring station was established in each community starting in 1974 measuring TSP, SO_2, NO_2, and ozone. Starting in 1978 dichotomous samplers were used to measure PM_{10}. Separate regressions of the adjusted city-specific pulmonary function levels on air pollution for children with and without asthma or wheeze did not show any associations.

TABLE 12-21. CHRONIC RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Overall Symptom Rate	Model Type & Lag Structure	Other pollutants measured	Other Covariates	Other pollutants in model	Result* (Confidence Interval)
Ware et al. (1984) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1974-1977	Daily monitoring of TSP, SO_2, NO_2, and ozone at each city	City TSP means ranged from 39 to 114 $\mu g/m^3$	Cough, .08, Bronchitis .08, Lower resp. .19	Logistic regression	SO_2, NO_2, and ozone	age, gender, parental education, maternal smoking	none	Cough 2.75 (1.92, 3.94) Bronchitis 2.80 (1.17, 7.03) Lower resp. 2.14 (1.06, 4.31)
Dockery et al. (1989) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1980-1981	Daily monitoring of PM_{15}, sulfate fraction at each city	City PM_{15} means ranged from 20 to 59 $\mu g/m^3$	Cough, .02 to .09, Bronchitis .04 to .10, Lower resp. .07 to .16	Logistic regression	SO_2, NO_2, and ozone	age, gender, maternal smoking	none	Cough 5.39 (1.00, 28.6) Bronchitis 3.26 (1.13, 10.28) Lower resp. 2.93 (0.75, 11.60)
Chapman et al. (1985) Study of persistent cough and phlegm (bronchitis) in adults in four Utah communities. Survey done in 1976.	Daily monitoring of TSP, and sulfate fraction at each city	Previous 5 year TSP ranged from 11 to 115 $\mu g/m^3$	.02 to .05 by city	Logistic regression	SO_2, NO_2	smoking	none	Mothers 1.75 (1.21, 2.54) Fathers 1.94 (1.16, 3.25)
Neas et al. (1994) Study of children aged 7 to 11 from six cites in U.S. Survey done 1983-1986.	$PM_{2.5}$	Not given	Not given	Logistic regression	NO_2	household smoking, gas stove, age, gender	none none none	Cough 1.08 (0.76, 1.53) Bronchitis 1.32 (0.98, 1.79) Lower resp. 1.23 (0.98, 1.55)

* Estimates calculated from data tables assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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Ware et al. (1986) also studied lung function in children in an earlier study of the same six cities. A cross-sectional survey was done between 1974 and 1977. Lung function was measured at the time of the survey using a water filled recording spirometer. $FEV_{1.0}$ and FVC measurements were used in the analyses. Starting in 1978 dichotomous samplers were used to measure PM_{10}. Adjusted logarithms of the pulmonary function values were not related to TSP concentrations. The change in $FEV_{1.0}$ per $10\mu g/m^3$ change in TSP was .06% (.17%) at the first examination and -0.09% (.17%) at the second examination.

Neas et al. (1994) analyzed a cohort of white children aged 7 to 11 from the same Six Cities Study for pulmonary function. Five pulmonary function measures were studied: FVC, $FEV_{1.0}$, the ratio of $FEV_{1.0}$ to FVC, FEF_{25-75}, and the ratio of FEF_{25-75} to FVC. The regression model used the logarithm of the lung function value as the dependent variable and included gender, parental education, history of asthma, age, height, weight, and city as covariates. No significant effects of $PM_{2.5}$ on lung function could be found. The use of logarithms of the dependent variables as well as the lack of overall mean lung function values makes it impossible to directly compare the results of this study with other studies.

Stern et al. (1994) studied lung function and respiratory illness in five towns in southwestern Ontario (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and five communities in south-central Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton. Lung function measurements were made between October 1985 and March 1986. Self-administered parental questionnaires were distributed at the same time. Pollution monitoring was not begun until late 1985, and included SO_2, NO_2, and O_3. Inhalable particulates were measured at each town using a high-volume Sierra Instruments sampler. PM_{10} was measured once every six days in the Ontario towns and once every three days in the Saskatchewan towns. Lung function measurements included FVC, $FEV_{1.0}$, PEFR, FEF_{25-75}, and V_{50}max. Lung function measurements were adjusted for age, gender, weight, standing height, parental smoking, gas cooking, and standing height by gender interaction. Ontario children had statistically significant decrements in FCV (1.7%) and $FEV_{1.0}$ (1.3%) compared with Saskatchewan children, but no differences were found in the flow parameters. Actual exposure estimates for the individual towns were not used. The overall mean PM_{10} level in the Ontario towns was 23.0 $\mu g/m^3$ compared with 18.0 $\mu g/m^3$ for Saskatchewan.

Spektor et al. (1991) studied pulmonary function in children living in Cubatao, Brazil. PM_{10} and SO_2 measurements were made at six sites in Cubatao which is located about 44 km from Sao Paulo. Average annual PM_{10} levels ranged from 64 to 104 $\mu g/m^3$. Pulmonary function measurements were made monthly from March to November in 1988. Individual regressions were performed using height, weight, and pollution was covariates. Average slopes were reported for each of six schools, but no confidence intervals were given. Both $FEV_{1.0}$ and PEFR were significantly related to PM_{10} at the six schools. The average decrease in PEFR per 50 $\mu g/m^3$ was about 100 ml/sec. This value is much larger than the values seen in other studies.

He et al. (1993) studied lung function in children in areas of Wuhan, China, in 1988. The children (aged 7 to 13 years) were from six urban and one suburban school. Pollution measurements, including TSP, SO_2, oxides of nitrogen, and CO, were collected by the Wuhan Environmental Protection Agency Air Pollution Monitoring Network from 1981 to 1988. All pollutants were higher at the urban site, with TSP values averaging 251 $\mu g/m^3$, as compared with 100 $\mu g/m^3$ at the suburban site. The cross sectional study was conducted in May and June of 1988. The hypothesis was that the relationship between lung function and height would be less in the urban city. Lung function growth curves were constructed by regressing $FEV_{1.0}$ and FVC on height for males and females for both areas. The curves were significantly steeper for the suburban children than for the urban children.

Arossa et al. (1987) studied lung function in approximately 2000 children in Turin, Italy, during a time period when both TSP and SO_2 were being reduced. Three areas of Turin (central city, peripheral area, and suburban area) were studied during the winters of 1980 to 1981 and 1982 to 1983. Each child's respiratory health was assessed at the beginning and end of the study using a questionnaire which also obtained demographic information. Lung function measurements included FVC, $FEV_{1.0}$, FEF_{25-75}, and MEF_{50}. Daily SO_2 and TSP measurements were available from seven monitoring sites in the area. The pollution data confirmed that the large SO_2 differences across areas in 1980 to 1981 were reduced substantially by 1982 1983. The differences in TSP remained small but constant during the time period. A general linear model analysis was used to calculated adjusted lung function values. From these values, individual slopes were estimated and these

became the unit of analysis. Average slopes were significantly higher within the city of Turin when compared with the suburban area, suggesting to the authors that a decrease in pollution (primarily SO_2) resulted in an improvement of lung function.

Studies of Adults

Chestnut et al. (1991) analyzed the NHANES data on pulmonary function. The NHANES survey was conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The survey used a complex design and the Chestnut et al. (1991) analysis was restricted to 49 urban sampling units where TSP measurements were available. A subsample of 6,913 adults (aged 25 to 74) were given spirometric tests using an Ohio Medical Instrument Corporation Model 800 electronic spirometer. Endpoints included FVC, $FEV_{1.0}$, and MMEF. EPA's SAROAD data base was used to obtain data from population oriented monitors in the 49 areas. Average TSP concentrations for previous years were used as the exposure measure. All individuals with reproducible results were included in a multiple regression analysis that included terms for age, height, gender, ethnic group, obesity, and TSP. Both a nonparametric analysis and a regression analysis suggested that TSP was associated with decrease FVC at TSP levels greater than 60 $\mu g/m^3$.

Xu et al. (1991) studied lung function in adults in areas of Beijing, China, in 1986. A stratified sampling plan over three areas with historically different pollution was used. A trained interviewer obtained information on history of chest illness, respiratory symptoms, cigarette smoking, occupational exposure, residential history, educational level, and type of fuel used for cooking. Pulmonary function measurements were made according to guidelines of the American Thoracic Society. Outdoor particulate matter (TSP) and SO_2 were obtained from 1981 to 1985 from World Health Organization Global Air Monitoring Stations. Multiple linear regression was used to assess the impact of air pollution on $FEV_{1.0}$ and FVC. Highly significant decreases in $FEV_{1.0}$ and FVC as a function of $\log(SO_2)$ and log(TSP) were found.

Tashkin et al. (1994) reported on the results of a long term lung function study of adults living in three areas of southern California. The areas were (1) Lancaster, with moderate levels of photochemical oxidants and low levels of other pollutants, (2) Glendora,

with very high levels of photochemical oxidants, sulfates, and particulate matter, and (3) Long Beach, with high levels of sulfates, oxides of nitrogen, and moderate levels of sulfur oxides. A mobile lung function laboratory was used to gather pulmonary function measurements and collect information on a modified NHLBI questionnaire. Residents of each area were tested twice over a 5 or 6-year interval, but during the same month each time. The testing schedule was as follows: (1) Lancaster, 1973 to 1974 and 1978 to 1979, (2) Glendora, 1977 to 1978 and 1982 1983, and (3) Long Beach, 1974 1975 and 1980 to 1982. Significantly larger annual decreases in $FEV_{1.0}$ were found in both Long Beach and Glendora as compared with Lancaster. These results were consistent across gender, and were adjusted for age, height, smoking status, and allergies. The decrease was largest in Long Beach, but only slightly larger than in Glendora. Smoking showed a larger effect than did area of residence. Because of the design of the study, it is impossible to attribute the effects to a single pollutant, or to develop any quantitative relationships.

Chronic Pulmonary Function Studies Summary

The chronic pulmonary function studies are less numerous than the acute studies (Table 12-22). The one study with good monitoring showed no effect from particulate pollution. Cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus the lack of statistical significance cannot be taken as proof of no effect.

12.5 HUMAN HEALTH EFFECTS ASSOCIATED WITH ACID AEROSOL EXPOSURE

One key consideration in the evaluation of PM-health effects is: Are there specific chemical components of PM responsible for the noted associations between PM and human health? The presence of known toxic constituents within ambient particles would add to the strength of the association. Since the time of the London Fog of 1952 and other major pollution episodes earlier in this century, the acidity of aerosols is one characteristic

TABLE 12-22. CHRONIC PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Neas et al. (1994) Study of lung function in children in 6 cities in the U.S. Data collected from 1983-1988.	Daily monitoring of $PM_{2.5}$, sulfate fraction at each city	not given	Linear regression using logarithm of PFT value	SO_2, NO_2, and ozone	city, gender parental education, history of asthma, age, height, weight	$PM_{2.5}$	FVC and FEV_1 not changed. Values could not be converted to mls.

* Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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suspected of contributing to health effects by PM air pollution. Though certainly not the only PM component with potentially toxic effects, acidic aerosols have received more epidemiologic study than have other PM components, to date. The epidemiologic evidence available regarding acidic aerosols as a potential contributor to PM-health effects associations is evaluated below.

Several epidemiologic studies have examined the health effects associated with ambient particulate strong acid aerosol (H^+) exposures. The historical scarcity of such analyses was due in large part to the absence of adequate ambient acid measurement techniques in the past and to the lack of routine acid aerosol monitoring in more recent years. Some studies now exists which suggests that human health effects maybe associated with exposures to ambient acid aerosols, both: (1) as derived from reexamination of older, historically important data on air pollution episode events in North America and Europe, and; (2) as can be deduced from recent epidemiology studies carried out in the U.S., Canada, and Europe. This section concisely reviews their studies, first as they relate to acute exposure effects, and then as they pertain to chronic exposure effects. Because of the relative scarcity of direct acid aerosol measurements until recent years, part of this section is also devoted to identifying studies of situations in which there is good reason to suspect that high ambient acid concentrations existed in the evaluated study areas. From all of these studies, the nature of any observed health associations are summarized as a basis for drawing health effects conclusions, and for suggesting directions for future research. The material in this review was based upon the acid aerosols issue paper prepared by the U.S. Environmental Protection Agency (1989), as well as more recent evidence, as appropriate.

12.5.1 Historical Evidence Evaluating the Relationship between Acid Aerosols and Health Effects

Some of the earliest indications of associations between ambient air acid aerosols and human health effects can be discerned upon reexamination of historically important air pollution episode events. These include, for example, the Meuse Valley (Belgium), Donora, PA (USA), and well-known London (UK) episodes, as discussed below.

12.5.1.1 Meuse Valley

Firket (1931) described the fogs of December 1930 in the Meuse Valley in Belgium and the morbidity and mortality related to them. A detailed discussion of the causes was presented, and he concluded that, while multiple pollutants existed in this atmosphere, the main component of the fog that caused the health effects that occurred was sulfuric acid. This conclusion was based both upon consideration of the emissions in the valley, the weather conditions and the aerometric chemistry required for the production of sulfuric acid. Additionally, the pathophysiology seen was thought to relate to sulfuric acid exposure more so than to other possible agents. More than 60 persons died from this acid fog and several hundred suffered respiratory problems, with a large number becoming complicated with cardiovascular insufficiency. The mortality rate during the fog was over ten times higher than the normal rate. Those persons especially affected by the fog were the elderly, those suffering from asthma, heart patients and the debilitated. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of acid aerosols in ambient air during the episode are available by which to establish clearly their role in producing the observed health effects versus the relative contributions of other specific pollutants.

12.5.1.2 Donora

Schrenk et al. (1949) reported on atmospheric pollutant exposures and the health effects of the smog episode of October 1948 in Donora, PA. A total of 5,910 persons (or 42.7 percent) of the total population of Donora experienced some effect from the smog. The air pollutant-laden fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths took place, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed through all age groups and, on the average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population, and was evenly distributed through all age groups. Dyspnea was the most frequent symptom in the more severely affected, being reported by 13 percent of the population, with a steep rise

as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea.

It seems reasonable to state that, while no single substance can be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome could have likely been produced by two or more of the contaminants, i.e., sulfur dioxide and its oxidation products together with particulate matter, as among the more significant contaminants present. Hemeon (1955) examined the water soluble fraction of solids on a filter of an electronic air cleaner operating during the smog in Donora and concluded that acid salts were an important component.

12.5.1.3 London Acid Aerosol Fogs

Based on the mortality rate in the Meuse Valley, Firket (1931) had estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to that in the Meuse Valley occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of December 1952, as noted by Martin (1964). During the fog of December 1952, evidence of bronchial irritation, dyspnea, bronchospasm and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners. There was a considerable increase in sudden deaths from respiratory and cardiovascular conditions. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute anoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) reported that, in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. It is probable, therefore, that sulfur trioxide, dissolved as sulfuric acid in fog droplets, appreciably augmented the harmful effects of sulfur dioxide and/or other particulate matter species.

Martin and Bradley (1960) reported increases in daily total mortality among the elderly and persons with preexisting respiratory or cardiac disease in relation to SO_2 and PM (measured as British Smoke; BS) levels in London during the winter of 1958 to 1959. The

pathological findings in 12 fatal cases and the clinical evidence of practitioners seem to indicate clearly that the harmful effects of the fog were produced by the irritating action of polluted air drawn into the lungs. These effects were more obvious in people who already suffered from a chronic respiratory disease and whose bronchi were presumably more liable to bronchospasm.

Waller (1963) reported that sulfuric acid was one of the pollutants considered as a possible cause of the increased morbidity and mortality noted during the London fog of December 1952. As noted earlier, following the 1952 pollution episode daily measurements of BS and SO_2 made in London starting in 1954. Concentrations of sulfuric acid, calculated from net aerosol acidity, were also measured during air pollution episodes and, later, on a daily basis, starting in 1963. All of these historical acid measurements must be viewed with caution, since filter artifact formation is possible for these samples. For example, there was no attempt to protect the sample filters from ambient SO_2 or NH_3, which could result in excess acid formation or in acid neutralization, respectively, on the samples. No regular measurements of sulfuric acid were made during the winter of 1955 to 1956, but some was detected at times of high pollution. For example, Waller and Lawther (1957) detected the presence of acid droplets in samples collected in January of 1956. Insufficient measurements were made, however, during the rest of the winter of 1955 to 1956 to study the effects of the acid aerosol present. Waller (1963) later reported measuring acid droplets in London in the winter of 1958 to 1959 with mass median diameter of 0.5 μm. Commins (1963) measured particulate acid in the city of London and found concentrations especially high at times of fog reaching H^+ levels of 678 $\mu g/m^3$ of air (calculated as sulfuric acid). Typical winter daily concentrations were 18 $\mu g/m^3$ compared to 7 $\mu g/m^3$ in the summer. The sulfuric acid content of the air in the city of London at the time could range up to 10 percent of the total sulfur.

Acid aerosol data collected by Commins and Waller (1967) during the December 1962 London Fog episode, which occurred almost exactly 10 years after the 1952 episode, provide some of the strongest evidence that acid aerosols were elevated during the 1950's episodes. As shown in Figure 12-10, 24 h average acid concentrations reached 378 $\mu g/m^3$ (as H_2SO_4) on the peak mortality day during this later, less severe, London episode. Both BS and SO_2

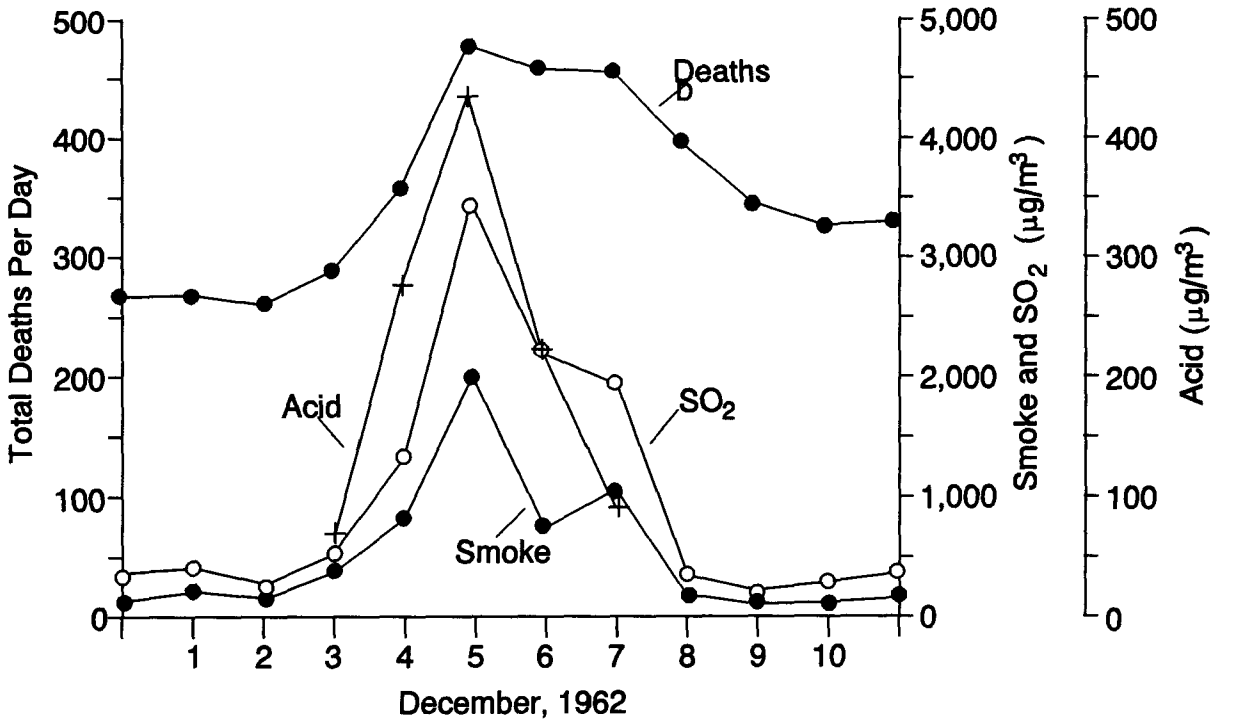

Figure 12-10. December 1962, London pollution episode.

were similarly elevated on these episode days, however, so it is not possible to identify H_2SO_4 as the sole causal pollutant. Not all of the measured acids during fog episodes would necessarily be respirable, reducing their health effects from that implied by the total H_2SO_4 concentration. However, these H^+ data from the 1962 episode do support past anecdotal evidence that elevated strong acid concentrations were present during the major London Fog pollution episodes.

Lawther et al. (1970) reported an association between daily pollutant levels (BS and SO_2) and worsening of health status among a group of over 1,000 chronic bronchitis patients in London during the winters of 1959 to 1960 and 1964 to 1965. A daily technique for self-assessment of day-to-day change in health status was used. The concentration of acid aerosol rose with that of smoke, and it is likely to have been partly responsible for health effects observed in these chronic bronchitic patients. Since many patients' symptoms become worse even at times of relatively low humidity, this suggests that small droplets of strong acid had

more effect than larger ones. An interesting study was also conducted on a smaller sample of the patients during in the winters of 1964 to 1965 and 1967 to 1968 when pollutant levels were somewhat lower than in earlier years. Approximately 50 subjects selected for their susceptibility to air pollutant effects formed the cohort. Daily apparent sulfuric acid, measured at St. Bartholomew Hospital Medical College, was reported as having a relatively high correlation with health effects in the 1964 to 1965 winter. For 1967 to 1968, all these correlation coefficients were lower, but still significant. The authors comment that the patients selected must have been particularly sensitive to pollution, since from past experience no correlation would have been expected with such very low levels of pollution encountered by such a small group.

The studies discussed above suggest that mortality and morbidity effects may be associated with pollutant mixes which included elevated levels of ambient air concentrations of acid aerosols. The calculations and measurements of sulfuric acid levels (estimated to range up to 678 $\mu g/m^3$ for a 1-h average) during some London episodes in the late fifties and early sixties provide a plausible basis for hypothesizing contributions of sulfuric acid aerosols to the health effects observed during those episodes.

12.5.2 Quantitative Analysis of Earlier Acid Aerosol Studies

12.5.2.1 London Acute Mortality and Daily Acid Aerosol Measurements

Thurston et al. (1989) conducted a reanalysis of the London mortality data for a multi-year period in which daily direct acid aerosol measurements were made at St. Bartholomew's Medical College. The data considered in this analysis include pollution and mortality records collected in Greater London during winter periods (November 1 to February 29) beginning in November 1963 and ending in February 1972. The air pollution data were compiled from one of two sources. First, BS and SO_2 data (as reported in $\mu g/m^3$) were compiled as daily means of seven sites run by the London County Council and spatially distributed throughout London County. A second data set of BS, SO_2 and aerosol acidity (calculated as $\mu g/m^3$ sulfuric acid) was also compiled for one central London site run by the Medical Research Council Air Pollution Research unit at the St. Bartholomew's Medical College. The Greater London mortality data were obtained from the London General Register Office for winter

periods (November to February) beginning in 1958, and for all days commencing in April 1965. Total mortality, respiratory mortality, and cardiovascular mortality were all compiled daily during these periods, but only total mortality was considered in this work. The Greater London population was fairly stable during the period considered in this research (1963 to 1972), averaging about 8 million people. The pollution and mortality data for each of the nine winters of data were combined into one data set for analysis. This is reasonable in this case because the period under study, late 1963 to early 1972, is subsequent to the implementation of the London smoke control zones (1961 to 1963), and is therefore a period of fairly constant average winter pollutant concentrations. Prior to combining the data, each year's total mortality data were also prefiltered using a high-pass filter that weights the mortality data in a manner very similar to the calculation of deviations from a 15-day moving average of mortality, except that it eliminates the undesirable long-term cyclical fluctuations. Although the filtered total mortality has largely removed slow moving fluctuations in the mortality data, the winters of 1967 to 1968 and 1969 to 1970 were still slightly nonstationary, probably due to influenza epidemics in those years. It may have been desirable to also control for these remaining effects by considering an influenza epidemic dummy variable in subsequent regression analyses of these data. The resulting data set comprised a total of 921 observations of daily pollution, total mortality, and filtered total mortality data for the nine-winter data set.

In the Thurston et al. (1989) results, the log of H_2SO_4 measured at the central site was much more strongly correlated with raw total daily mortality than any measure of BS or SO_2 especially when it was correlated with the next day mortality ($r = 0.31$). It is also clear that the logarithm transformation "helps" the acid-mortality association more than is true for BS or SO_2. For the filtered mortality variable, however, the H_2SO_4 correlation is weakened versus raw total mortality (e.g., $r = 0.19$ for log (H_2SO_4) with next day filtered mortality). Thus, the St. Bartholomew's College H_2SO_4 measurements appear to be correlated with Greater London mortality, especially before the mortality data are filtered for slow moving fluctuations. Mortality-pollution crosscorrelation analyses indicated that mortality effects usually followed pollution in time even after filtering both series (Thurston et al., 1989), a basic consideration in inferring casual association.

The superiority of the log of H_2SO_4 concentration versus the raw H_2SO_4 data in correlations with total mortality agrees with the previous analyses of British Smoke-total mortality associations. This may imply that a "saturation" of mortality effects is indeed occurring over two or more days, and that a cumulative effect of several episode days may be more relevant than modeling a single day effect alone. This may be due to avertive behavior, especially since episode warnings were publicized at the time of high pollution. Most likely, however, the "saturation" of effects is due to the premature death of the most susceptible people on prior moderate pollution days.

A more extensive analysis of the London total mortality and acid aerosol data was conducted by Ito et al. (1993) for 1965 to 1972, when daily acid measurements were available year-round and the air pollution levels were non-episodic (see Figure 12-11). BS, SO_2, H_2SO_4, and weather variables (temperature and humidity) were examined for their short-term associations with daily mortality after removal of long-term components from each series via prewhitening, in order to obtain "rational" crosscorrelations. Power spectra of the variance of mortality, pollution, and temperature variables were employed in the development of this model. Also, first order autocorrelations were found to be significant, and were evaluated. Significant associations with same day and following days' mortality were found for all three pollutants considered. In the most extensively controlled model the winter mean pollutant effect was estimated to range from 2 to 3% of the mean 278 deaths/day total mortality, but all three pollutants gave similar results (for mean H_2SO_4 = 5.0 $\mu g/m^3$, SO_2 = 293 $\mu g/m^3$, or BS = 72 $\mu g/m^3$) and their respective effects could not be separated, due to their high intercorrelation. These models were fit to the (separate) 1962 London acid/mortality episode data and found to fit well, supporting the validity of such deviation-derived mortality estimates.

Lippmann and Ito (1995) conducted a preliminary graphically-based analyses of the year-round 1965 to 1972 London pollution and mortality data set that controlled for same-day temperature effects by analyzing restricted temperature ranges in each season. This was done to provide an alternative to more empirical approaches applied to these data in prior analyses. In each season, the majority of days fell within one or two temperature ranges, within which the mortality also fell within narrow ranges. Within these restricted ranges,

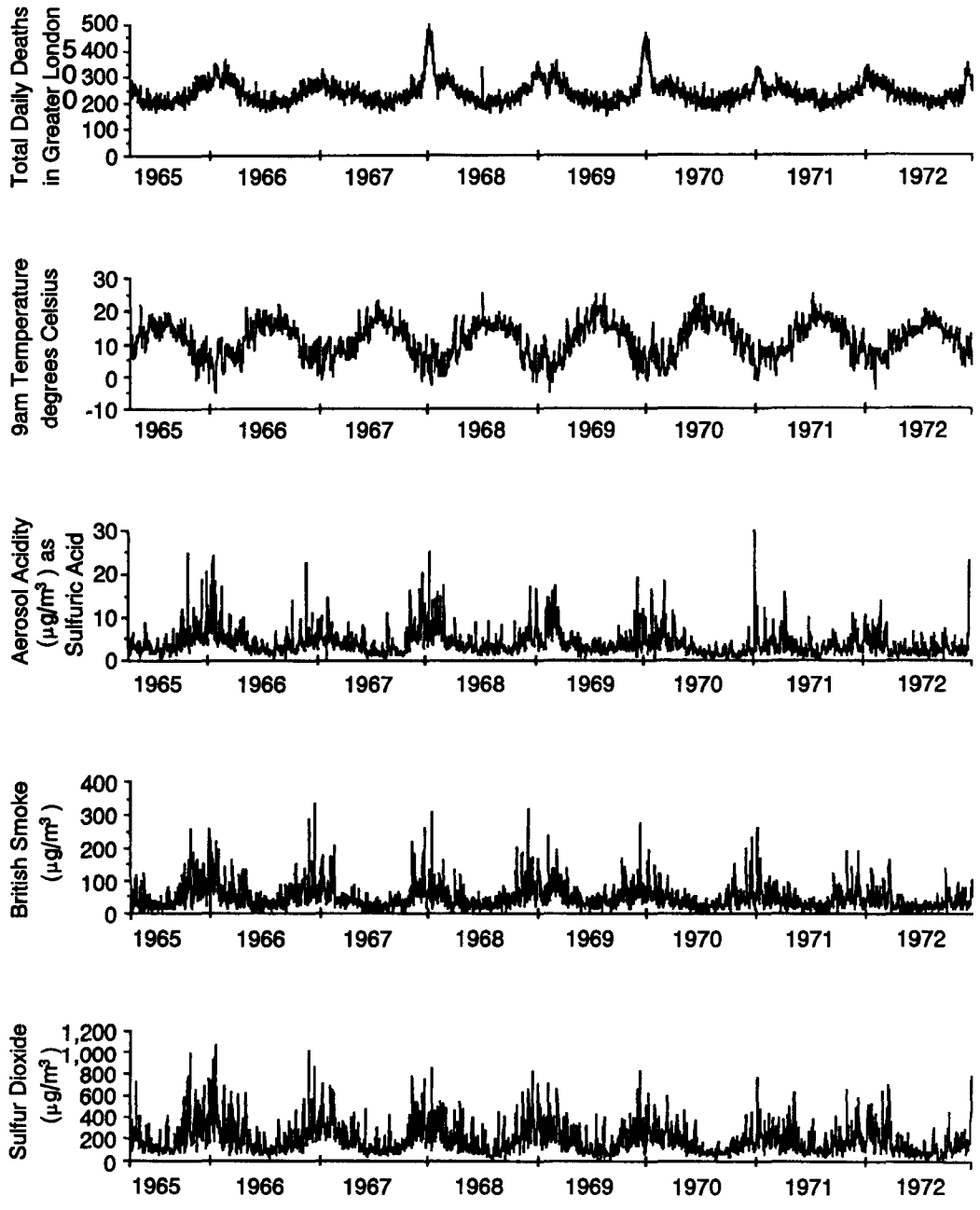

Figure 12-11. Time Series Plots of Daily Mortality, Pollution and Temperature in London, England 1965 to 1972. (Ito et al., 1993)

analyses indicated that there were relatively strong associations between daily mortality and the daily logs of the concentrations of H^+ and SO_2. By contrast, the mortality association with BS was much weaker, especially in the winter and summer. The authors indicate that more comprehensive analyses are needed, but assert that such analyses provide a useful complement to model-based approaches. Things as yet not addressed by this analysis include the need to control for the potential effects of prior days' extreme temperatures (i.e., lagged effects), which are known to be important in winter, and the direct addressing of potential temperature effects within the ranges considered. Probably the most interesting result of these analyses is that the H^+-mortality association is found even in the summertime, when the daily H^+ concentrations do not exceed approximately 10 $\mu g/m^3$, as H_2SO_4 ($\sim$ 200 nmoles H^+/ m^3), which are concentrations not unlike those presently experienced during the summer in the eastern United States.

These recent analyses by Thurston et al. (1989) and by Ito et al. (1993) of daily direct acid aerosol measurements over a long span of time (1963 to 1972) in London are especially important in providing more data to examine for associations between acute exposures to ambient acid aerosols and mortality at H^+ levels more relevant to those presently experienced in North America. Also, the work of Lippmann and Ito (1995) suggests that this acute H^+-mortality association may exist at concentrations below 200 nmoles/m^3 H^+, and under summertime conditions. However, as noted above, the several pollutants considered were correlated over time, making a discrimination of their respective effects difficult, and the historical London acid measurement techniques may or may not be directly comparable with present day measurements.

12.5.3. Studies Relating Acute Health Effects to Sulfates

Sulfate species usually represent the principal component of particulate strong acid aerosols (primarily as H_2SO_4 or NH_4HSO_4). As a result, variations in measured sulfate levels have been found to represent a reasonably reliable surrogate for variations in strong particulate acid aerosol levels over time at a site. However, sulfates are not necessarily as useful for intercomparing aerosol particulate acidity levels between sites. This is because measurements of total sulfate levels comprise not only strongly acidic sulfates, but, in fact,

are usually dominated by sulfates that are only weakly acidic (e.g. $(NH_4)_2SO_4$). Moreover, it has been found that local ammonia levels can diminish the ambient $H^+/SO_4^=$ ratio experienced at a site by neutralizing the strongly acidic sulfates (Suh et al., 1994). For this reason, two sites located in differing environs (e.g. urban versus suburban) may have similar $SO_4^=$ levels but different $H^+/SO_4^=$ ratios, merely because the population density around the two sites is different (Ozkaynak et al., 1994). Therefore, cross-sectional studies using sulfates may be limited in the insight they may provide into the potential health effects of acid aerosol exposures, especially if they compare sites with differing surrounding land uses. However, if two monitoring sites are in the same airshed, they will usually still be highly correlated over time, as their particulate H^+ concentrations will rise and fall together from day to day as regional sulfate levels rise and fall (e.g., see Thurston et al. 1994a). Thus, while the surrounding land use dependence of the $H^+/SO_4^=$ ratio may limit somewhat the usefulness of sulfates as an index of H^+ differences between sites, this will not adversely affect longitudinal (i.e., correlation based) studies using sulfate data as an index of particulate aerosol strong acidity.

12.5.3.1 Canadian Hospital Admissions Related to Sulfate Acute Exposure Studies

Bates and Sizto (1983, 1986) reported results of an ongoing correlational study relating hospital admissions in southern Ontario to air pollutant levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1986 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and SO_2 or COH in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory (both asthma and non-asthma) admissions in summer and sulfate and ozone concentrations, but not to summer COH levels. However, Bates and Sizto noted that the data analyses were complicated by long-term trends in respiratory disease admissions unlikely related to air pollution. They nevertheless hypothesized that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer, but not in the winter.

Bates and Sizto (1987) later studied admissions to all 79 acute-care hospitals in Southern Ontario, Canada (i.e., the whole catchment area of 5.9 million people) for the months of January, February, July and August for 1974 and for 1976 to 1983. Means of the hourly maxima for O_3, NO_3, SO_2, coefficient of haze (COH), and aerosol sulfates were obtained from 17 stations between Windsor and Peterborough. Sulfates were measured every sixth day. Total admissions and total respiratory admissions declined about 15 percent over the course of the study period, but asthma admissions appeared to have risen. Evaluating the asthma category of admissions is complicated by the effects of a change in International Classification of Disease (ICD) coding in 1979. The analyses demonstrated that there was a consistent summertime relationship between respiratory admissions (with or without asthma) and sulfates, ozone, and temperature. This conclusion was strengthened by the continuing lack of any association of these variables with non-respiratory conditions. The 1987 paper raised the question of whether the association of increased respiratory admissions in the summer in this region could be associated with ozone or sulfates. It was aerosol sulfates that, in summertime, explained the highest percentage of the variance in respiratory admissions; yet these were not correlated with respiratory admissions in the winter. In view of this, the authors hypothesized that the observed health effects might be attributable neither to ozone nor to sulfates, but to some other air pollutant species that "travel" with them over the region in the summer (but not in the winter).

Bates and Sizto (1987) noted that recent observations had suggested the presence of peaks of H^+ aerosol of small particle size in this region of Canada in the summer, concomitant with elevated O_3 and $SO_4^=$ levels. On two days in July 1986 in eastern Toronto when ozone and sulfate levels were elevated, but not higher than on other days, peaks of H^+ acid aerosol lasting for up to two hours were recorded at levels of 10 to 15 $\mu g/m^3$. The particle size was small (about 0.2 μm). Similar observations were recorded on the same days by another H^+ air sample operation southwest of Toronto. This raises the possibility that the types of health effects noted above might be attributable neither to ozone, nor to sulfates, but rather perhaps to acid aerosols. Thus, the evidence from Bates and Sizto (1983, 1986, 1987, 1989) neither conclusively relates sulfates nor ozone to hospital admissions.

Instead, the results appear to suggest that some other pollutant(s) may be responsible, e.g., the strong acidic aerosols that have since been measured in the region.

Lipfert and Hammerstrom (1992) reanalyzed the Bates and Sizto (1989) hospital admissions dataset for 79 acute-care hospitals in southern Ontario, incorporating more elaborate statistical methods and extending the dataset through 1985. Pollutants considered included SO_2, NO_2, O_3, $SO_4^=$, COH, and TSP. Long-wave influences were reduced by using the short study periods previously employed by Bates and Sizto (e.g. July and August only for summer), as well as by employing very conservative prewhitening procedures to the data. Day of week effects were also controlled. In addition, the models were more extensively specified, including a variety of new meteorological variables such as wind speed (correlated at r=-0.5 with COH). Despite this possible model overspecification, however, summerhaze pollutants (i.e. O_3, $SO_4^=$, and SO_2) were found to have significant associations with on hospital admissions in southern Ontario. In contrast, pollution associations with hospital admissions for accidental causes became nonsignificant in these models. While air pollution concentrations were generally within U.S. standards, the pollutant mean effect accounted for 19 to 24% of all summer respiratory admissions (mean admissions [a] 40/day, mean $SO_4^= \approx 11\ \mu g/m^3$), though the "responsible" summertime haze pollutant(s) could not be discerned by the authors with certainty.

Burnett et al. (1994) related the number of emergency or urgent daily respiratory admissions daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. No other pollutants were directly considered in this analysis, although the authors reported that SO_2 and NO_2 were only weakly correlated with SO_4 in these data ($r \leq 0.3$), so these pollutants were unlikely to be confounders. Daily levels of sulfates were recorded at nine monitoring stations located throughout the province. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model, wherein hospital effects were assumed random, was employed using the generalized estimating equations (GEE) of Liang and Zeger (1986). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone

and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, and 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 12-12. In simultaneous regressions, five percent of daily respiratory admissions in the province during May to August (mean = 107.5/day) were found to be associated with O_3 (at 50 ppb), and one percent with $SO_4^=$ (at 5 $\mu g/m^3$). Positive and significant air pollution associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and H^+ are highly intercorrelated with sulfates in the summer months ($r > 0.8$), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work.

12.5.3.2 Other Health Effects Related to Sulfate Exposures

Ostro (1987) also conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979 to 1981 annual Health Interview Surveys (HIS) to test if there were acute morbidity associations coherent with those found for mortality by Ozkaynak and Thurston (1987) during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of zeros in the dependent variables (i.e. days with morbidity), and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data, but the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This indicates that, while presumably important to morbidity, smoking is not a confounder to pollutants in such cross-sectional analyses. Ostro concluded

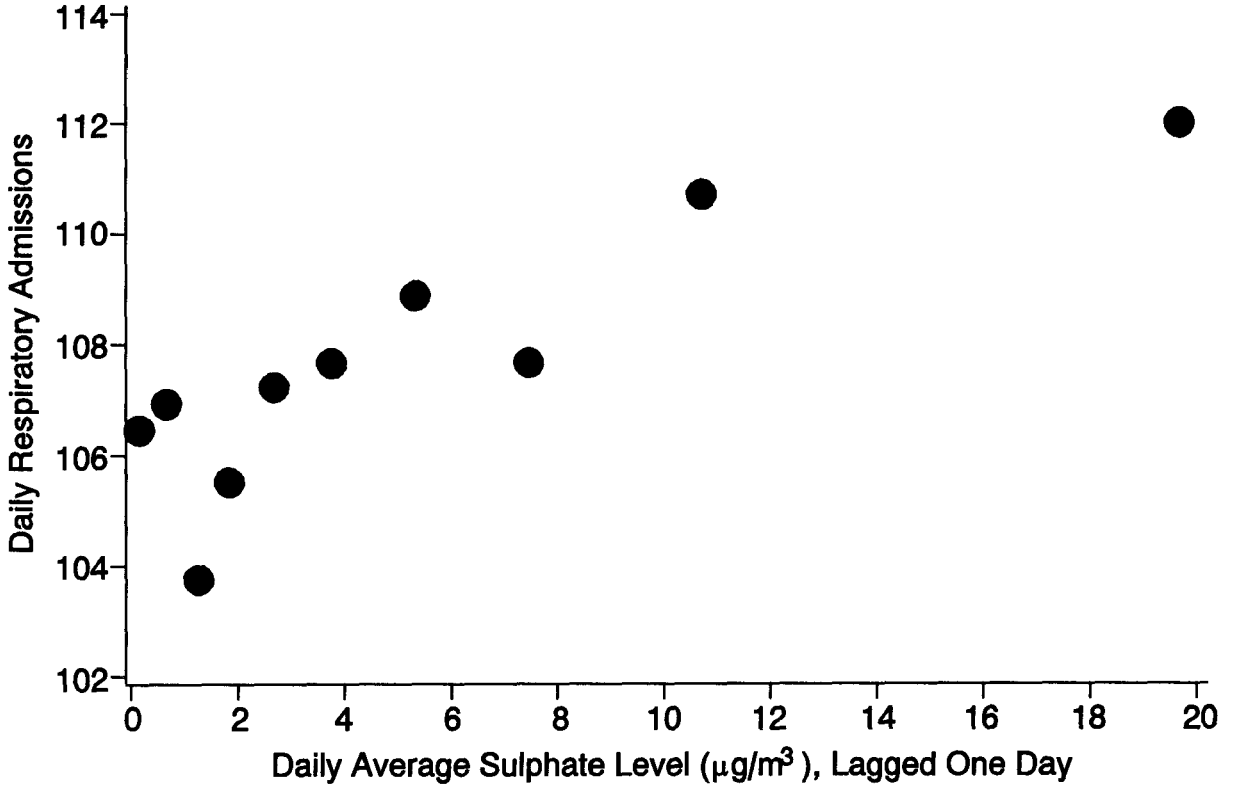

Figure 12-12. Average number of adjusted respiratory admissions among all 168 hospitals by decile of the daily average sulfate level ($\mu g/m^3$), lagged 1 day (Burnett et al., 1994).

that his findings were consistent with the results of prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates.

12.5.3.3 Studies Relating Acute Health Effects to Acidic Aerosols

In recent years, a number of new studies have been conducted of acute health effects employing direct measurements of particulate strong acid aerosols. These allow a more direct test of the hypothesis that it is the H^+ that is responsible for the sulfates-health effects associations noted in past work.

12.5.3.4 Acute Acidic Aerosol Exposure Studies of Children

Several studies have recently been carried out in the United States and Canada that examine the effects of exposures to air pollutants on pulmonary function in children at summer camps. Some of the available data derived from these studies allow evaluation of the possible involvement of acid aerosols in the health effects observed. Furthermore, recent children's diary studies have also investigated acid aerosol effects on respiratory symptoms in the general population.

Studies of Pulmonary Function in Children at Summer Camp

Lippmann et al. (1983) studied 83 nonsmoking, middle class, healthy children (ages 8 to 13) during a 1980 2-week summer camp program in Indiana, PA. The children were involved in camp activities which resulted in their exercising outdoors most of the time. At least once, each child had height and weight measured and performed spirometry on an 8 liter Collins portable recording spirometer in the standing position without nose clip. During the study, peak flow rates were obtained by Mini-Wright peak flow meter at the beginning of the day or at lunch and adjusted for both age and height. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler on the rooftop of the day camp building. Ozone levels were estimated using a model that used ozone data from monitoring sites located 32 and 100 km away. The hi-volume samples were collected on H_2SO_4 treated quartz fiber filters for the determination of the concentration of H^+ and total suspended particulate matter (TSP). H^+ was determined from filter extract using a Gran titration. Peaks in acid concentration occurred on four days, when the acid values ranged between 4 and 6.3 $\mu g/m^3$ (if as H_2SO_4). On many occasions, there was no measurable H_2SO_4 in the atmosphere. While effects were reported as being significantly associated with exposure to ozone, no effects were found to be related to exposure to H_2SO_4 at the relatively low levels observed during the study.

Bock et al. (1985) and Lioy et al. (1985) examined pulmonary function of 39 children at a camp in Mendham, New Jersey during a 5-week period in July to August, 1982. Ozone was continuously monitored using chemiluminescent analysis. Ambient aerosol samples were collected on Teflon filters with a dichotomous sampler having a 15 μm fractionation inlet and

a coarse/fine cut size of 2.5 μm (Sierra Model 244-E). Aerosol acidity as measured by strong acid (H^+) content, was determined using the pH method. Highly significant changes in peak expiratory flow rate (PEFR) were found to be related to ozone exposure, as well as a baseline shift in PEFR lasting approximately one week following a haze episode in which the O_3 exposure exceeded the NAAQS for four consecutive days that included a maximum concentration of 185 ppb. There was no apparent effect of H^+ on pulmonary function. The authors did state, however, that the persistent effects associated with the ozone episode could have been due to acid sulfates as well as, or in addition to, ozone, but additional uncollected data were needed to evaluate this possibility.

During a 4-week period in 1984, Lioy et al. (1987) and Spektor et al. (1988) measured respiratory function of 91 active children who were residing at a summer camp on Fairview Lake in northwestern New Jersey. Continuous data were collected for ambient temperature, humidity, wind speed and direction, and concentrations of O_3, H_2SO_4, and total sulfates were determined. Ozone was measured by U.V. absorption, and H_2SO_4 and total sulfates were alternately determined by a flame photometric sulfate analyzer (Meloy Model 285) preceded by a programmed thermal pretreatment unit. The ambient aerosol samples were collected on quartz fiber filters with a dichotomous sampler having a 15 μm fractionating inlet (PM_{15} and a coarse/fine cut-size of 2.5 μm (Sierra Model 244-E). Aerosol acidity, as measured by strong acid (H^+) content, was determined using the pH method. The maximum values recorded for H_2SO_4 and NH_3HSO_4 were 4 and 20 μg/m3 respectively. While effects were reported as being associated with exposure to ozone, no effects were found to be directly related to exposure to the acid aerosol concentrations experienced in this study.

Raizenne et al. (1987) reported analyses of data from a study in Ontario, Canada. In 1983, fifty two campers (23 were asthmatics) at a summer camp were studied to examine lung function performance in relation to daily pollutant concentrations. The health assessment included a pre-camp clinical evaluation, a telephone administered questionnaire on respiratory health, daily spirometry and symptoms measurements. Pollutants measured included O_3, respirable particles, sulfates, NO_2, and SO_2. Respirable sulfates were highly variable and ranged from 10 to 26 $\mu g/m^3$. Sulfate as sulfuric acid was usually very low. Raizenne et al. (1989) report that O_3, sulfate, and $PM_{2.5}$ were associated with decrements in

lung function of children. Evidence of decrements in specific lung function indices were related to current pollution levels and to a 12 to 24 h lag function for $PM_{2.5}$, SO_4, O_3 and temperature. Although both asthmatic and non-asthmatics had similar data trends, only responses in the non-asthmatic group reached statistical significance. The authors note that all of the air pollutants were highly correlated, and thus it was not possible to apportion health effects to the individual pollutants.

Raizenne et al. (1989) studied 112 young girls who participated in one of three 2-week camp sessions at camp Kiawa, Ontario, Canada during June to August, 1986. They examined the subjects in relation to four ambient acid aerosol events (the highest H_2SO_4 level was 47.7 $\mu g/m^3$ during one event on July 25, 1986). The influence of air pollution on lung function was evaluated first by comparing responses on the day of a pollutant event (high acid and ozone levels) to the mean of the responses on corresponding days of low pollutant levels. For $FEV_{1.0}$ there was tendency for the lung function decrements on the event day to be greater than the response on the corresponding control days, except for the last event (when an increase in function was observed). The largest decrements for $FEV_{1.0}$ and PEFR (48 to 66 mL decline for $FEV_{1.0}$) were observed on the morning after the highest H_2SO_4 event, on July 25, 1986. No analyses were presented, however, that attempted to separate out pollutant effects of H_2SO_4 from those of O_3.

Airway hyper-responsiveness was assessed using a methacholine bronchial provocation test for 96 of the subjects in the Raizenne et al. (1989) study. Children with a positive response to methacholine challenge had larger decrements compared to their nonresponsive counterparts. These preliminary results do not allow definitive statements to be made on the susceptibility of methacholine sensitive subjects. However, there are indications in these data of differential lung function profiles and responses to air pollutants in children with and without airway hyper-responsiveness. Further analyses and research are indicated.

At the same camp, twelve young females (9 to 14 years old) performed pre- and post-exercise spirometry on a day of low air pollution and at the peak of an air pollution episode. Clinical interview, atopy, and methacholine airway hyper-responsiveness tests were performed at the camp on the first 2 days of the study. Seven subjects had positive responses to methacholine challenge ($^+$MC) and five did not ($^-$MC). A standardized

ergonometric physical capacity test was also administered, in which minute volume, heart rates, and total work achieved were recorded. Air monitoring was performed on site and, during the episode, air pollution concentrations were: O_3 exceeded 130 ppb; H_2SO_4 exceeded 40 $\mu g/m^3$ during a 1-h period. Additional discussion of the aerometric monitoring is given by multivariate normal methods on the indicator of airway hyper-responsiveness. For the entire group (N = 12), post exercise FVC and $FEV_{1.0}$ were observed to increase on the control day and decrease on the episode day. On the control day, an average 40 mL increase in FVC due to exercise was observed ($p < .05$) for the whole group, with a 71 mL increase in +MC subjects and a 17 mL increase in -MC subjects. Although not statistically significant at the 10 percent level, mean FVC for the entire group was 30 ml less on the day of high pollution versus low pollution, and this difference was more pronounced in -MC (-65 mL) than +MC (-4 mL) subjects. The effect of exercise in the model was statistically significant ($p < .05$), whereas the pollution day effect was not. These results suggest that lung function responses to exercise differ in +MC and -MC subjects under field research conditions, and that the expected normal FVC response to exercise in both groups is altered during periods of elevated ambient pollution. However, no analyses were presented that directly evaluated possible acid aerosol relationships to health effects.

It is of interest to compare results obtained in this summer camp study to findings of certain controlled human exposure studies, or to other epidemiology studies. For example, Spengler et al. (1989) calculated that the children in the Raizenne et al. (1989) study received an average 1-h respiratory tract dose of 1050 nmoles of H^+, based on a exposure model which takes into account not only the concentration of exposure, but also minute ventilation rate. Spengler et al. (1989) further noted that the asthmatic subjects in the human clinical studies of Utell et al. (1983) and Koenig et al. (1983) had experienced an airway dose of approximately 1,200 nmoles of H^+, which evoked a response at reported concentrations of 450 $\mu g/m^3$ and 100 $\mu g/m^3$ H_2SO_4, respectively. These calculations suggest that, because of differences in minute ventilation rates, the peak levels occurring at Camp Kiawa during an ambient acid aerosol event may have produced exposures similar to those seen in clinical studies of asthmatic subjects. It remains to be determined as to what extent comparable C x T total respiratory tract dose(s) for H^+ ions may be effective in producing pulmonary

functions decrements beyond the short exposure times employed in the controlled human exposure studies or in producing other types of effects. For example, Spektor et al. (1989) found that the effect of increasing the length of exposure to 100 $\mu g/m^3$ sulfuric acid from one to two hours increased average tracheobronchial clearance half-time from 100 to 162 percent, relative to control.

Studnicka et al. (1995) conducted a study of the effects of air pollution on the lung function of three consecutive panels of children participating in a summer camp in the Austrian Alps during the summer of 1991. On-site environmental assessment consisted of 24-h measurements of PM10, H^+, and $SO_4^=$, as well as continuous measurements of O_3, temperature, and relative humidity. Pollen counts were sampled daily using a Burkhardt spore trap. SO_2 and NO_2 data were obtained from routine monitoring stations located at the same altitude 20 to 30 km from the camp. For 47, 45, and 41 subjects, daily FEV1, FVC, and peak expiratory flow were recorded. While mean levels of ambient pollutants were generally 15% higher for Panel 1, the Panel 1 H^+ concentrations averaged twice as high as for the other two panels. The maximum H^+ exposure (during Panel 1) was 84 $nmol/m^3$ ($4\mu g/m^3$ H_2SO_4 equivalent). Compared with other camp studies discussed above, peak H^+ exposure was of lesser concentration, but of longer duration. For FEV1, a significant decrease of -.099 ml per $nmol/m^3$ H^+ ($p = 0.01$) during Panel 1. Exclusion of the first 5 days, or excluding the maximum H^+ day did not significantly alter this result. The FEV1/H^+ coefficient was found to be similar (-0.74 ml per $nmol/m^3$ H^+; $p = 0.28$) for Panel 2, but was in the opposite direction and clearly non-significant during Panel 3 (0.10 ml per $nmol/m^3$ H^+; $p = 0.83$). The decrease in FEV1 during Panel 1 was more pronounced when the mean exposure during the previous 4-d was employed (-2.99 m; FEV1 per $nmol/m^3$ H^+; $p = 0.004$), suggesting greater effects from multiple-day episodes. However, it is important to note that, while O_3 levels were low and not significantly correlated with FEV1 throughout this study, PM10 measurements showed associations of similar strength with FEV1 during Panel 1 as found for H^+ ($r_{PM10-H^+} = 0.94$). However, in simultaneous model of FEV1 on H^+ with PM10, O_3, and pollen in the model, the previous 4-d mean H^+ variable's coefficient was of similar magnitude as for the single pollutant model (though the coefficient SE did rise). This suggests that the H^+ association with FEV1 remained, even

after controlling for other potentially confounding factors. The authors conclude that a significant FEV1 decrease of 200 ml was observed in children at this camp during a summer haze episode in the Austrian Alps, and the acidic PM may, therefore, be associated with transient decreases in lung function in children.

Studies of Respiratory Symptoms and Pulmonary Function in Schoolchildren

As part of the 6-Cities study conducted by Harvard University, a cohort of approximately 1800 children in grades two through five from six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Portage, WI; Steubenville, OH, and; Topeka, KS) was enrolled in a diary study in which parents completed a bi-weekly report on each child's daily respiratory symptoms (Schwartz et al., 1994). The study extended over 4 school years (1984 to 1988), but data were collected for only one year in each city. Environmental variables measured daily at a central site in each city included PM_{10}, $PM_{2.5}$, $PM_{2.5}$ sulfur, H^+, H_2SO_4, SO_2, O_3, and nephelometry (a measurement of aerosol scattering of light, which provides an index of sub-micron particle concentration). The H_2SO_4 data were not analyzed in this work. The reported analysis was limited to April through August in each city to reduce seasonal confounding (n = 153). Statistical analyses involved the use of ordinary logistic regression, in which the logarithm of the odds of the response rate is modeled as a linear function of covariates, followed by the application of logistic methods incorporating corrections for autocorrelation using the GEE model proposed by Liang and Zeger (1986) and Zeger and Liang (1986) for such repeated measures studies. Regressions included a temperature and a temperature squared term, as well as city-specific and day of week dummy variables and interaction terms for city-specific temperature terms. Exploratory analyses considered pollution lags of up to 14 days. Pollutants were considered individually in the regressions, and those which were significant individually were considered in multiple pollutant models.

Lower respiratory symptoms (LRS) is defined as the reporting of at least two of: cough, chest pain, phlegm, or wheeze. Analyses of daily LRS found in individual pollutant regressions that PM_{10}, $PM_{2.5}$, $PM_{2.5}$ sulfur (i.e., sulfates), nephelometry, SO_2, and O_3 were all significant predictors. Of all these pollutants, $PM_{2.5}$ sulfur (i.e., sulfates) and PM_{10}

yielded the highest levels of significance (t = 3.35 and t = 3.47, respectively), suggesting that it is the sulfur containing fine aerosol component which was driving the PM relationships found with LRS. In the overall data analysis, aerosol acidity was not significantly associated with LRS, but associations were noted for H^+ above 110 nmoles/m^3, with a relative odds ratio of LRS estimated to be greater than 2.0 at 300 nmoles/m^3 H^+. Similarly, the 6-City diary analysis of upper respiratory symptoms (URS, defined as any two of hoarseness, sore throat, or fever) showed no consistent association with H^+ until concentrations exceeded 110 nmoles/m^3. The authors hypothesize that the acid may enhance the effects of PM_{10} on such subjects (i.e. healthy children) if the H^+ is present in high enough concentration.

A separate analysis of upper respiratory symptoms was also conducted using similar data and methods for three of the cities only: Watertown, MA; Kingston-Harriman, TN, and; St. Louis, MO (Schwartz et al., 1991b). Why these cities alone were analyzed in this work is not stated. In these cities, the pollutant with the largest regression coefficient was H_2SO_4 , with the strongest association falling on the prior two days. Unfortunately, comparative details about other pollutants are not provided in this paper. While sketchy, these results provide further support of the hypothesis that ambient acid aerosols in general, and H_2SO_4 in particular, may be associated with adverse health effects in children.

In a study of ambient air pollution and lung function in children reported by Neas et al. (1995), a stratified sample of 83 children living in Uniontown, PA reported twice daily peak expiratory flow rate (PEFR) measurements on 3,582 child-days during the summer of 1990. Upon arising and before retiring, each child recorded the time, three PEFR measurements, and the presence of cold, cough, or wheeze symptoms. Environmental factors were monitored, including ambient temperature, O_3, SO_2, fine particle mass, PM10, and particle strong acidity, which was measured separately during the day (8 am to 8 pm) and night. Each child's maximum PEFR for each session was expressed as the deviation from their mean PEFR over the study and adjusted to a standard of 300 liters/minute. The session-specific average deviation was then calculated across all the children. A second order autoregressive model for PEFR was developed which included a separate intercept for evening measurements, trend, temperature, and 12-hour average air pollutant concentration weighted by the number of hours each child spent outdoors during the previous 12-hour

period. A 12-hour exposure to a 125 nmole/m_3 increment in H^+ was associated with a -2.5 liters/minute deviation in the group mean PEFR (95% CI = -4.2 to -0.8) and with increased cough incidence (odds ratio, OR = 1.6; 95% CI = 1.1 to 2.4). It should be noted, however, that H^+ was highly correlated with sulfates (r = 0.92) and fine particles (r = 0.86). A 30 ppb increment in ozone for 12-hours was associated with a similar deviation in PEFR levels (-2.8; 95% CI = -6.7 to 1.1). However, when both O_3 and H^+ were entered into the model simultaneously, the H^+ effect size was only slightly reduced and remained significant. Although monitored, PM10 results were not presented for comparison. The association between PEFR and particle strong acidity was observed among the 60 children who were reported as symptomatic on the prior symptom questionnaire (-2.5; 95% CI = -4.5 to -0.5). The authors concluded that summertime occurrences of elevated acid aerosol and particulate sulfate pollution are associated with acute declines in peak expiratory flow rates and increased incidence of cough episodes in children.

Overall, these recent camp and school children studies proved evidence indicating an acute acidic PM effect on both children's respiratory function and symptoms. However, given the usually high correlation between acidic PM and PM in general, it is difficult to identify these effects solely with the acid portion of PM.

12.5.3.5. Acute Acid Aerosol Exposure Studies of Adults

Acute Acid Aerosol Exposures and Asthma Symptoms in Adults

The hypothesis that human exposures to ambient H^+ concentrations are associated with exacerbations of pre-existing respiratory disease was tested by a recent study of asthmatic responses to airborne acid aerosols (Ostro et al., 1989, 1991). Data on daily concentrations of aerosol H^+, SO_4, NO_3, and FP, as well as gaseous SO_2 and HNO_3, were tested for correlation with daily symptom, medication usage, and other variables for a panel of 207 adults with moderate to severe asthma in Denver, CO between November 1987 and March 1988. However, CO and NO_2, potentially confounding pollutants, were not considered in the analyses. The H^+ concentrations ranged from 2 to 41 neq/m^3 (0.01 to 2.0 $\mu g/m^3$ of H_2SO_4 equivalent), and were significantly related to both the proportion of the survey respondents reporting a moderate or worse overall asthma condition, and the

proportion reporting a moderate or worse cough. However, it is important to note that these concentrations are near to or below the level of detection of H^+, and that, of the 74 H^+ values used in the analysis, 47 were predicted from the observed $SO_4^=$ value on that day (H^+ - $SO_4^=$ correlation = 0.66), which is more accurately measured at such low levels. $PM_{2.5}$ was also highly correlated with sulfates during this study (r = 0.86). Both logit models and ordinary least squares with a log pollution term, autoregressive terms, and terms for trend, weekend, use of gas stove, and maximum daily temperature were modeled.

Of all the pollutants considered in these analyses, H^+ displayed the strongest associations with asthma and cough. In the first analysis, the magnitudes of effects were compared by computing elasticities, or the percent change in the health effect due to a given percent change in the pollutant. The results for asthma indicated elasticities with respect to SO_4, FP, and H^+ of 0.060, 0.055 and 0.096, respectively (Ostro et al., 1989). This indicates that a doubling of the concentration of H^+ (from 8 to 16 nmoles/m^3) would increase the proportion reporting a moderate to severe asthma condition by 10 percent. In their follow-up report on this study, Ostro et al. (1991) examined evidence for lagged effects, and concluded that contemporaneous measures of H^+ concentration provided the best associations with asthma status, and that meteorological variables were not associated with the health effects reported. They also examined the effects of exposure to H^+, adjusting for time spent outdoors, level of activity, and penetration of acid aerosol indoors. Based on the adjusted exposures, the effect of H^+ on cough increased 43%, suggesting that dose-response estimates that do not incorporate behavioral factors affecting actual H^+ exposures may substantially underestimate the impact of the pollution. The associations of exposure adjusted H^+ with moderate to severe cough and with asthma status are shown in Figures 12-13 and 12-14, respectively. Although the H^+ concentrations on some days had to be estimated from sulfates, and potentially confounding pollutants were not considered simultaneously with H^+ in the model, these results allow the consideration that human exposures to present day ambient H^+ concentrations may be associated with exacerbations of pre-existing respiratory disease.

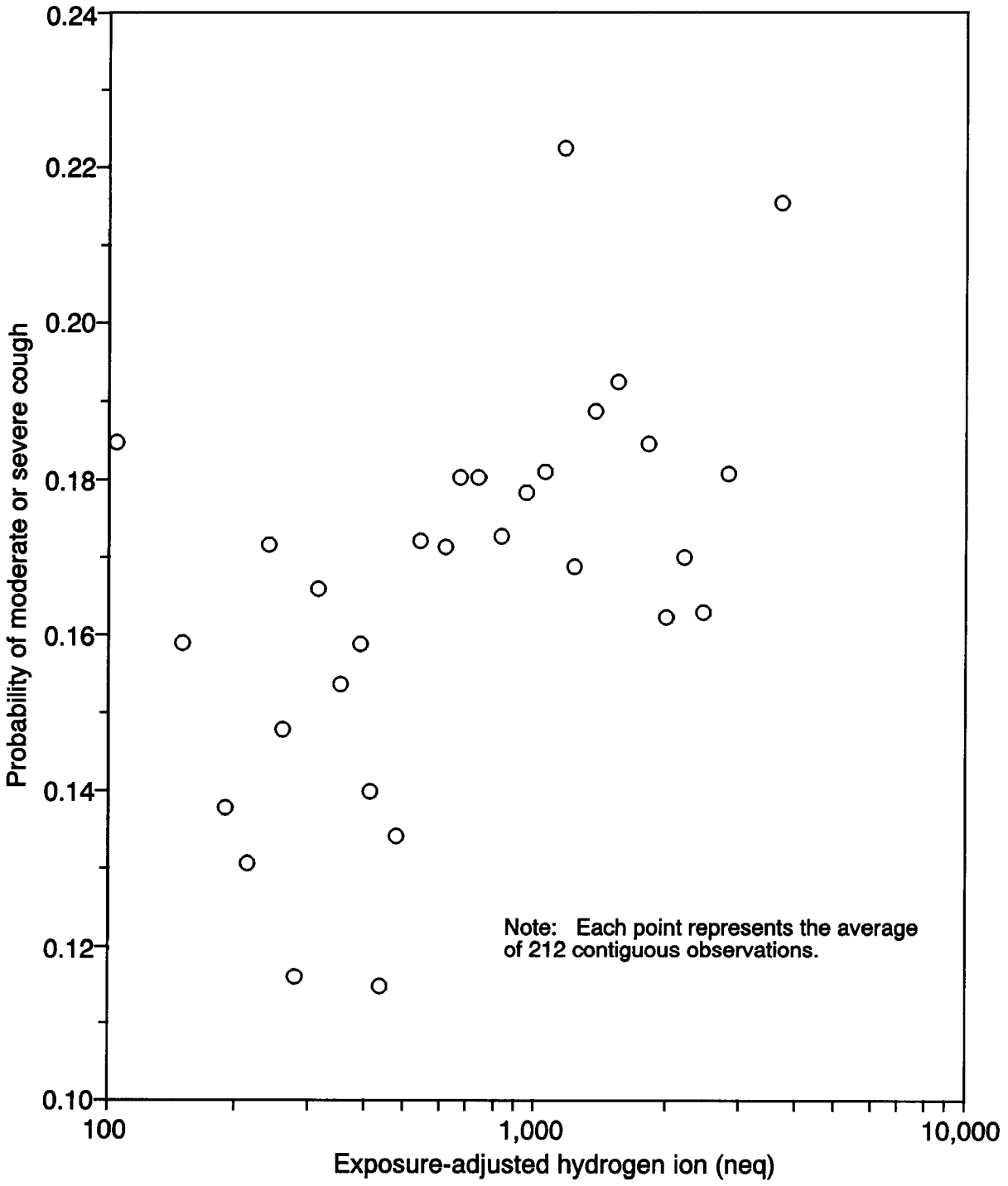

Figure 12-13. Association of moderate or severe cough with exposure-adjusted hydrogen ion.

Source: Ostro et al. (1991).

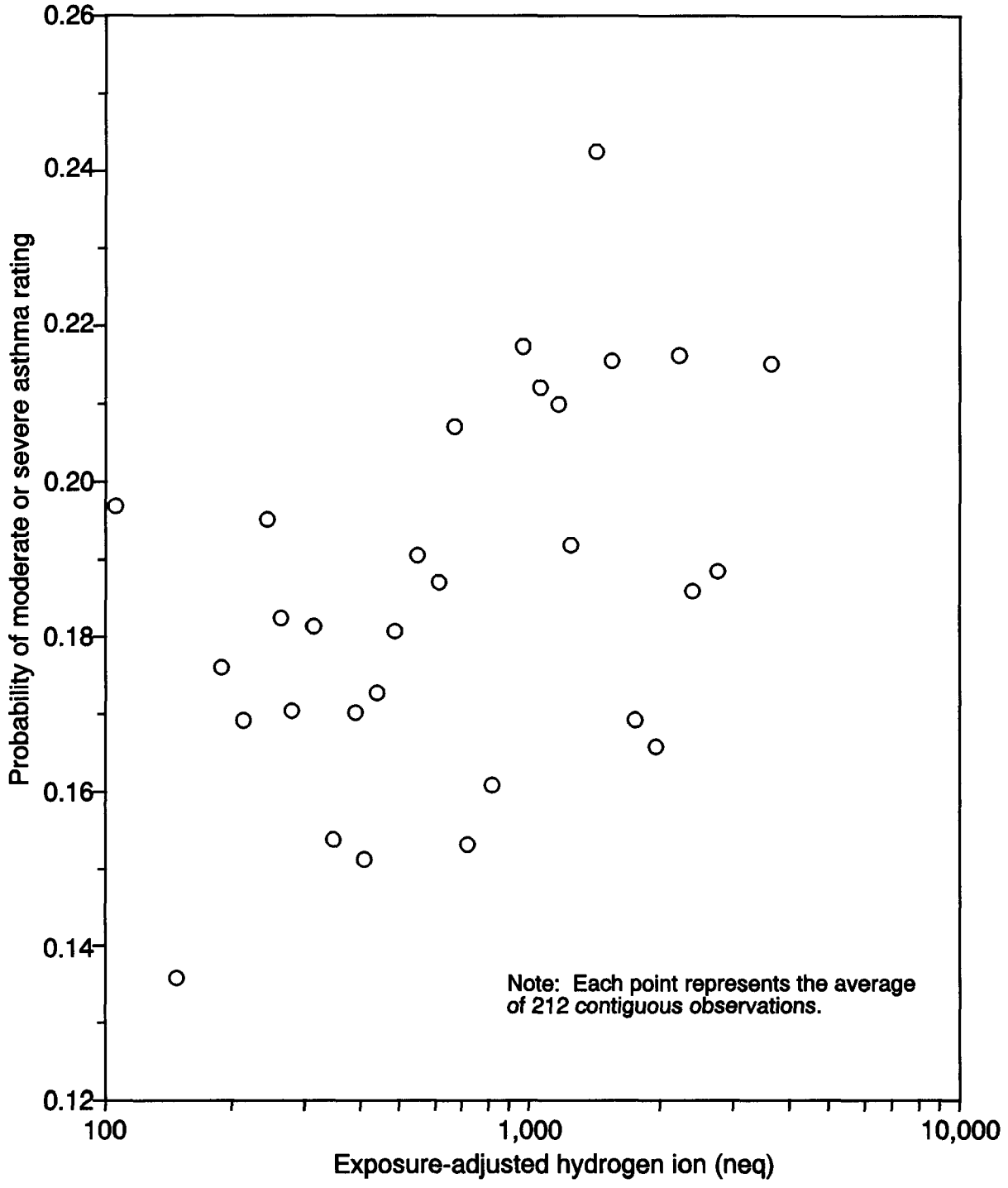

Figure 12-14. Association of moderate or severe asthma rating with exposure-adjusted hydrogen ion.

Source: Ostro et al. (1991).

12.5.4.2.2 Acute Acidic Aerosol Associations with Respiratory Hospital Admissions

The reported sulfate-respiratory hospital admissions associations discussed above were interpreted as potentially being due to the presence of strongly acidic aerosols on high sulfate days. Two follow-up studies of respiratory hospital admissions were conducted in New York State and in Toronto, Ontario to directly test this hypothesis.

Thurston et al. (1992) analyzed unscheduled (emergency) admissions to acute care hospitals in three New York State metropolitan areas during the summers of 1988 and 1989. Environmental variables considered included daily 1-h maximum ozone, 24-h average sulfate, and particulate strong acid aerosol (H^+) concentrations, as well as daily maximum temperature recorded at central sites in each community. For this study, acid aerosols were sampled in residential suburbs of Buffalo, Albany, and New York City (NYC), NY. In the case of NYC, the site was located well outside the urban core (in White Plains, 10 mi. north of the city), so the acid levels are likely to be overestimates of the levels experienced directly in the city. However, comparisons between sulfates in the White Plains site and at a site in Manhattan during part of the study period showed a high correlation ($r = 0.9$), supporting the assumption that the White Plains H^+ data are indicative of particulate strong acid exposures in NYC. Long wave periodicities in the data were reduced by selecting a June through August study period. However, because of remaining within-season long wave cycles in the data series, they were prefiltered using sine and cosine waves with annual periodicities. Day of week effects were also controlled via regression. These adjustments resulted in non-significant autocorrelations in the data series and also improved the pollution correlations with admissions. The strongest pollutant-respiratory admissions associations found by Thurston et al. (1992) were during the high pollution 1988 summer, and in the most urbanized communities considered (i.e. Buffalo and New York City). Correlations between the pollution data and hospital admissions for non-respiratory control diseases were non-significant both before and after prefiltering. After controlling for temperature effects via simultaneous regression, the summer haze pollutants (i.e. $SO_4^=$, H^+, and O_3) remained significantly related to total respiratory and asthma admissions. However, multiple pollutant regressions were not attempted, preventing a clear discrimination of these pollutants respective effects. Other community pollutants (e.g. NO_2, SO_2, and CO) were not

considered, but are generally low and unlikely to be highly correlated with the studied pollutants during July and August in these cities. After filtering, $SO_4^=$ and H^+ were highly correlated in these cities (e.g. r = 0.86 in Buffalo, and 0.79 in NYC during the summer of 1988), supporting the contention that SO_4 is a useful index of H^+ in such time-series analyses. In regressions for the summer of 1988 for Buffalo and New York City, both H^+ and $SO_4^=$ had similar mean effects (3 to 4% of respiratory admissions in NYC, at mean H^+ = 2.4 $\mu g/m^3$ as H_2SO_4, and mean $SO_4^=$ = 9.3 $\mu g/m^3$; and 6 to 8% in Buffalo, at mean H^+ = 2.2 $\mu g/m^3$ as H_2SO_4, and mean $SO_4^=$ = 9.0 $\mu g/m^3$). Ozone mean effects estimates were always larger than for H^+ or $SO_4^=$, but the impact of the highest day was greatest for H^+ in all cases. This is the case in part because H^+ episodes are more extreme, relative to the mean, than are O_3 episodes (e.g. in Buffalo in 1988, the summer max./mean H^+ = 8.5, while the max./mean O_3 = 2.2). Thus, the maximum H^+ day in Buffalo (18.7 $\mu g/m^3$ as H_2SO_4, or 381 nmoles H^+/m^3, on August 4, 1988), was estimated to be associated with a 47% increase above the mean number of total respiratory admissions in this metropolitan area (mean = 25/day). Thus, the H^+ effects estimates reported in this work are dominated by the two or three peak H^+ days per year experienced in these cities (e.g. $H^+ > 10$ $\mu g/m^3$, or ~200 nmoles/m^3, as a 24-h average).

Thurston et al. (1994b) focused their analysis of respiratory hospital admissions in the Toronto metropolitan area during the summers (July to August) of 1986 to 1988, when they directly monitored for strong particulate acidity (H^+) pollution on a daily basis in that city. This study was designed specifically to test the hypothesis that the $SO_4^=$ associations found in southern Ontario by Bates and Sizto were due to H^+ exposures. Acid measurements were made at three sites in the Toronto metropolitan area, and were found to be highly correlated across sites (Thurston et al., 1994a). The H^+ data from the center city site (Breadalbane St.) were used for the health effects analyses, as there were a full 3 summers of data there (the other two sites were not operated in 1988), and because other pollutants were measured there daily, as well. The 9AM to 5PM average H^+ was employed in these analyses. Long wave cycles, and their associated autocorrelations, were removed by first applying an annual periodicity sine-cosine fit to the data (as well as day of week dummy variables) and analyzing the resulting residuals. Strong and significant positive associations with both asthma and

respiratory admissions were found for both O_3 and H^+, and somewhat weaker significant associations with $SO_4^=$. No such associations were found for SO_2 or NO_2, nor for any pollutant with non-respiratory control admissions. Other PM metrics examined included the mass of fine particles less than 2.5 μm in d_a (FP), the mass of particles greater than 2.5 μm and less than 10 μm in d_a (CP), PM_{10} (= FP+CP), TSP, and non-thoracic TSP (= TSP-PM10). Temperature was only weakly correlated with respiratory admissions, and became non-significant when entered in regressions with air pollution indices.

Simultaneous regressions and sensitivity analyses indicated that O_3 and H^+ were the summertime haze constituents of greatest importance to respiratory and asthma admissions in Toronto during these three summers. Indeed, as shown in Table 12-23, of the PM metrics considered, only H^+ remained significant in the respiratory admissions regression with both O_3 and temperature also included. The correlation of the H^+ and O_3 coefficients in this simultaneous model was non-significant (r=-0.11), indicating that these two pollutants have independent associations with respiratory admissions. As shown in Table 12-24, the 1988 results for Toronto are consistent with (i.e. not statistically different from) those found previously for nearby Buffalo, NY (approximately 100 km to the south, across Lake Ontario). As in these authors' Buffalo analysis, the maximum H^+ day in Toronto (August 4, 1988: H^+ = 391 nmoles/m^3) was estimated to be associated with the greatest relative risk of total respiratory and asthma admissions (1.50 and 1.53, respectively), again indicating an especially large adverse respiratory effect by summertime haze air pollutants during the few H^+ episode days each summer. However, a sensitivity analysis eliminating the six days having $H^+ \geq 100$ nmoles/m^3 yielded a similar, and statistically significant, H^+ coefficient in the total respiratory admissions regression, suggesting that the association is not limited to the highest pollution days alone. The authors reviewed A.B. Hill's criteria for causality (Hill, 1965), and concluded that the associations they report between summertime haze air pollutants (i.e. O_3 and H^+) and acute exacerbations of respiratory disease (i.e. respiratory hospital admissions), are causal. It is of particular interest to note that, assuming the H^+ to be in the form of NH_4HSO_4, the "effect" per $\mu g/m^3$ of mass implied by these Toronto coefficients indicate that H^+ is six times as potent (per $\mu g/m^3$) as non-acidic PM10.

TABLE 12-23. SIMULTANEOUS REGRESSIONS OF 1986 TO 1988 TORONTO DAILY SUMMERTIME TOTAL RESPIRATORY ADMISSIONS ON TEMPERATURE AND VARIOUS POLLUTION METRICS

Temp, pollutant model specification	Pollutant Regression Coefficients (adm/poll unit[a])	*P* value (one-way)
	Two pollutant models	
T(LG0), O_3(LG0)	0.0503 ± 0.0205	0.008
H^+(LG1)	0.0153 ± 0.0089	0.044
T(LG0), O_3(LG0)	0.0508 ± 0.0207	0.008
$SO_4^=$(LG1)	0.0062 ± 0.0046	0.089
T(LG0), O_3(LG0)	0.0404 ± 0.0233	0.043
FP(LG0)	0.0434 ± 0.0429	0.157
T(LG0), O_3(LG0)	0.0388 ± 0.0241	0.055
PM_{10}(LG0)	0.0339 ± 0.0344	0.164
T(LG0), O_3(LG0)	0.0360 ± 0.0228	0.059
TSP(LG0)	0.0127 ± 0.0175	0.235

[a]Pollution units are nmole/m^3 for H^+ and $SO_4^=$, ppb for O_3, and $\mu g/m^3$ for FP, CP, PM_{10}, TSP, and TSP-PM_{10}.

Source: Thurston et al. (1994b)

These two new studies of daily respiratory hospital admissions in New York State cities and in Toronto, Ontario support the hypothesis that the summertime sulfate concentrations previously found to be correlated with respiratory admissions are indeed accompanied by acidic aerosols in Eastern North America. Furthermore, in these recent analyses, the H^+ associations with respiratory hospital admissions were found to be stronger than for sulfates, or any other PM component monitored. The facts that: (1) these were studies designed specifically to test the hypothesis that H^+ is associated with increased respiratory hospital admissions; (2) consistent results were found, both qualitatively and quantitatively across these studies, and; (3) in one of them, many other pollutants and PM metrics were directly intercompared with H^+ in the analyses, collectively indicate that these studies provide evidence that acidic aerosols may represent a component of PM which is particularly associated with increases in the incidence of exacerbations in pre-existing respiratory disease.

TABLE 12-24. COMPARISON OF REGRESSIONS OF DAILY SUMMERTIME RESPIRATORY ADMISSIONS ON POLLUTION AND TEMPERATURE IN TORONTO, ONTARIO, AND BUFFALO, NEW YORK 1988 SUMMER

City and year	Respiratory admissions category	Temp, pollutant model specification	Pollutant Regression Coefficient (adm/$\mu g/m^3/10^6$, persons ±SE)	Pollutant mean effect (% ±SE)	Max/mean pollutant rel risk (±SE)
Toronto, 1988 summer	Total respiratory (mean = 14.1/day)	T(LG2), $SO_4^=$(LG1)	0.07 ± 0.03[a]	13.3 ± 5.3	1.41 ± 0.16
		T(LG2), H^+(LG1)	0.18 ± 0.009[b]	7.7 ± 3.9	1.50 ± 0.25
		T(LG2), O_3(LG1)	0.011 ± 0.005[b]	26.4 ± 11.8	1.34 ± 0.15
Toronto, 1988 summer	Total asthma (mean = 9.5/day)	T(LG2), $SO_4^=$(LG1)	0.04 ± 0.02[b]	13.0 ± 6.8	1.40 ± 0.21
		T(LG2), H^+(LG0)	0.13 ± 0.07[b]	8.1 ± 4.5	1.53 ± 0.29
		T(LG2), O_3(LG1)	0.007 ± 0.004[b]	25.3 ± 14.9	1.32 ± 0.19
Buffalo, 1988 summer	Total respiratory (mean = 25.0/day)	T(LG2), $SO_4^=$(LG0)	0.11 ± 0.04[a]	8.0 ± 2.7	1.22 ± 0.12
		T(LG2), H^+(LG0)	0.35 ± 0.12[a]	6.4 ± 2.2	1.47 ± 0.16
		T(LG2), O_3(LG2)	0.015 ± 0.008[b]	18.4 ± 9.9	1.25 ± 0.09
Buffalo, 1988 summer	Total asthma (mean = 7.1/day)	T(LG2), $SO_4^=$(LG1)	0.03 ± 0.02[b]	7.0 ± 3.9	1.29 ± 0.12
		T(LG2), H^+(LG1)	0.09 ± 0.05[b]	5.6 ± 3.3	1.43 ± 0.26
		T(LG2), O_3O(LG3)	0.006 ± 0.002[a]	23.9 ± 10.1	1.25 ± 0.14

[a]$P<0.01$ (one-way test).
[b]$P<0.05$ (one-way test).

Source: Thurston et al. (1994b).

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12.5.4.2.3 Acute Acid Aerosol Exposure Associations with Mortality

As discussed in the methodological discussions at the outset of this chapter, relatively long records of daily mortality and pollution are required to have sufficient power to discern mortality-pollution associations. Due to the dearth of sufficiently long records of H^+ concentration measurements (other than the historical London measurements discussed previously), only one study has yet attempted to evaluate the acute mortality effects of acidic aerosols.

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during the one year period between September 1985 and August 1986 in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered is Knoxville, TN, some 50 Km from the air pollution monitoring site employed. In each study area, total daily mortality was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, $SO_4^=$, H^+, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's PM_{10} and $PM_{2.5}$, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, PM_{10} and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar PM_{10} coefficients are reported, implying a 16 to 17 percent increase in total mortality per $100\mu g/m^3$ of PM_{10}. While autocorrelation was accounted for, seasonality was addressed by season indicator (dummy) variables, which may not remove within-season long wave influences. However, the chief areas of concern regarding this study relate to the exposure data. In both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites are provided (e.g., correlations with other sites' data). More importantly in the case of H^+ analyses, the number of days for which pollution data are available for time-series analyses is limited in this data set (e.g. only 220 days had H^+ values at the St. Louis site). As discussed in the methodological section, it is expected that roughly at least twice this number of study days are needed to be able to reliably detect PM associations with mortality. Thus, in the words of the authors: "Because of the short

monitoring period for daily particulate air pollution, the power of this study to detect associations was limited."

Thus, the only available attempt to correlate human mortality with present day ambient acid aerosol concentrations was unable to find a significant association, but it is not clear to what extent this result was due to the severe lack of power in the analysis (because of the many fewer H^+ observations than available for other pollutants). Clearly, there is a critical need for present day replications of the London mortality-acid aerosol studies to be conducted, in order to determine whether these London associations (dominated by wintertime H^+, occurring in reduction-type atmospheres) are pertinent to the U.S., where acid aerosol peaks occur primarily in the summertime, in oxidation-type atmospheres.

12.5.4 Studies Relating Health Effects to Long-Term Exposure

A limited but growing amount of epidemiologic study data currently exist by which to evaluate possible relationships between chronic exposures to ambient acid aerosols and human health effects. These include one study from Japan relating effects to estimated or measured acidity, and many other North American studies which relate effects to sulfate levels or other surrogate measures thought to roughly parallel acid aerosol concentrations. Moreover, newer epidemiologic studies, which consider measured acid aerosols, now provide more direct insight into the potential chronic effects of particulate strongly acidic aerosols.

12.5.4.1 Acid Mists Exposure in Japan

Kitagawa (1984) examined the cause of the Yokkaichi asthma events (1960 to 1969) by examining the potential for exposure to concentrated sulfuric acid mists and the location and type of health effects noted. He concluded that the observed respiratory diseases were due not to sulfur dioxide, but to concentrated sulfuric acid mists emitted from stacks of calciners of a titanium oxide manufacturing plant located windward of the residential area. This was based on the fact that the SO_3/SO_2 ratio of 0.48 was much higher than the normal range of 0.02 to 0.05. The higher ratio indicates a higher acid aerosol level. The acid particles were fairly large (0.7 to 3.3 μm) compared with acid aerosols usually seen in the United States of America (see Chapter 3), but were still were in the respirable range. Between 1960 and

1969, more than six hundred patients with respiratory disease were found to have chronic bronchitis, allergic asthmatic bronchitis, pulmonary emphysema and sore throat. In 1969, measures of acid aerosol exposures were obtained from litmus paper measurements collected near the industrial plant which showed that acid mist particles were distributed leeward of the industrial plant. The author notes that the physiological effects of concentrated sulfuric acid mists (per estimated mass concentration) may be quite different from that of dilute sulfuric acid mists formed by atmospheric oxidation of sulfur dioxide, and that the distinction between the two types of acid mists is very important. It should be noted that morbidity fell markedly after the installation of electrostatic precipitators which reduced H_2SO_4 and other particulate matter emissions.

12.5.5.2 Studies Relating Chronic Health Effects to Sulfate Exposures

Franklin et al. (1985) and Stern et al. (1989) reported on a cross-sectional epidemiologic study investigating the respiratory health of children in two Canadian communities that was conducted in 1983 to 1984, in Tillsonburg, Ontario and Portage la Prairie, Manitoba. There were no significant local sources of industrial emissions in either community. Seven hundred and thirty-five children aged 7 to 12 were studied in the first town and 895 in the second. Respiratory health was assessed by the measurement of the forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) of each child, and by evaluation of respiratory symptoms and illnesses using a questionnaire self-administered by the parents. While NO_2 and inhalable particles (PM_{10}) differed little between these communities, SO_2, SO_4, and NO_3 were higher in Tillsonburg. Historical data in the vicinity of Tillsonburg indicate that average levels of sulfates, total nitrates and ozone (O_3) did not vary markedly in the 9-year period proceeding the study. The results show that Tillsonburg children had statistically significantly ($p < 0.001$) lower levels of FVC and $FEV_{1.0}$ than the children in Portage la Prairie (2% and 1.7% lower, respectively). These differences could not be explained by parental smoking or education, cooking or heating fuels, pollution levels on the day of testing or differences in age, sex, height or weight. The differences persisted when children with either cough with phlegm, asthma, wheeze, inhalant allergies or hospitalization before age 2 for a chest illness were excluded from analysis. With the

exception of inhalant allergies, which occurred more frequently in Tillsonburg children, the prevalence of chronic respiratory symptoms and illnesses was similar in the two communities. Thus, sulfates were among the pollutants which were higher in the community experiencing reduced lung function and increased inhalant allergies, while PM_{10} mass concentrations were not different between cities.

Ware et al. (1986) have reported results of analyses from the ongoing Harvard study of outdoor air pollution and respiratory health status of children in six eastern and midwestern U.S. cities. Between 1974 and 1977, approximately 10,100 white preadolescent children were enrolled in the study during three successive annual visits to the cities. On the first visit, each child underwent a spirometric examination, and a parent completed a standardized questionnaire regarding the child's health status and other important background information. Most of the children (8,380) were seen for a second evaluation one year later. Measurements of TSP, SO_4, and SO_2 concentrations at study-affiliated outdoor stations were combined with data from other public and private monitoring sites to create a record of pollutant levels in each of nine air pollution regions during a one-year period preceding each evaluation, and for TSP during each child's lifetime up to the time of evaluation. Annual mean TSP levels ranged from 32 to 163 $\mu g/m^3$. Sulfur dioxide levels ranged from 2.9 to 184 $\mu g/m^3$, and sulfate levels ranged from 4.5 to 19.3 $\mu g/m^3$.

Analyzing these data across all six cities, Ware et al. (1986) found that frequency of chronic cough was significantly associated ($p < 0.01$) with the average of 24-h mean concentrations of TSP, SO_2, and SO_4 air pollutants during the year preceding the health examinations. Furthermore, rates of bronchitis and a composite measure of lower respiratory illness were significantly ($p < 0.05$) associated with annual average particle concentrations. However, within the individual cities, temporal and spatial variation in air pollutant levels and symptom or illness rates were not found to be significantly associated. The history of early childhood respiratory illness for lifetime residents was significantly associated with average TSP levels during the first two postnatal years within cities, but not between cities. Also, pulmonary function parameters (FVC and $FEV_{1.0}$) were not associated with pollutant concentrations during the year immediately preceding the spirometry test or, for lifetime residents, with lifetime average concentrations. Ferris et al. (1986), however, reported a

small effect on lower airway function (MMEF) related to fine particle concentrations. Spengler et al. (1986) report the occurrence of acid aerosol peak concentrations of 30 to 40 $\mu g/m^3$ (1 h average) in two of the cities during recent monitoring. Overall, these results appear to suggest that risk may be increased for bronchitis and some other respiratory disorders in preadolescent children at moderately elevated levels of TSP, SO_4, and SO_2 concentrations, which do not appear to be consistently associated with pulmonary function decrements. However, the lack of consistent significant associations between morbidity endpoints and air pollution variables within individual cities argues for caution in interpreting these results.

Dockery et al. (1989) presented further results from the cross-sectional assessment of the association of air pollution with chronic respiratory health of children participating in the Six Cities Study of Air Pollution and Health. Air pollution measurements collected at quality-controlled monitoring stations included total suspended particulate matter (TSP), particulate matter less than 15 μm (PM_{15}) and 2.5 μm ($PM_{2.5}$) aerodynamic diameter, fine fraction aerosol sulfate ($SO_4^=$), SO_2, O_3, and NO_2. This analysis was restricted to the 5,422 10 to 12 years old white children examined in the 1980 to 1981 school year. Five respiratory illness and symptom responses obtained by questionnaire were considered: bronchitis, cough, chest illness, wheeze, and asthma. Each symptom was analyzed using a logistic regression model including sex, age, indicators of parental education, maternal smoking, gas stove, and city. Reported rates of bronchitis, chronic cough, and chest illness during the 1980 to 1981 school year were positively associated with all measures of particulate pollution (TSP, PM_{15}, $PM_{2.5}$, and SO_4) and positively, but less strongly, associated with concentrations of two of the gases (SO_2 and NO_2). For children experiencing wheeze, the estimated relative odds (and 95% CI) for $SO_4^=$ between the most and least polluted cities were: 3.1 (0.6 to 16.8) for bronchitis; 2.4 (0.1 to 60.6) for chronic cough, and; 2.9 (0.5 to 15.6) for chest illness. Frequency of earache also tended to be associated with particulate concentrations, but no significant associations were found with asthma, persistent wheeze, hay fever, or non-respiratory illness. No associations were found between pollutant concentrations and any of the pulmonary function measures considered (FVC, $FEV_{1.0}$, FEV0.75, and MMEF). Children with a history of wheeze or asthma had a much

higher prevalence of respiratory symptoms, and there was some evidence that the association between air pollutant concentrations and symptom rates was stronger among children with these markers for hyperreactive airways. Results suggest that children with hyperreactive airways may be particularly susceptible to other respiratory symptoms when exposed to these pollutants. The lack of statistical association between pollutant concentrations and measures of both pulmonary flow and volume suggests, however, that these increased rates of illness are not associated with permanent loss of pulmonary function, at least during the preadolescent years. Overall, these data provide further evidence that rates of respiratory illnesses and symptoms are elevated among children living in cities with high particulate pollution, including sulfates, which are known to be correlated over time and across cities with H^+, based on direct $SO_4^=$ and H^+ monitoring subsequently conducted in each of these cities as part of this study.

Dodge et al. (1985) reported on a longitudinal study of children exposed to markedly different concentrations of SO_2 and moderately different levels of particulate sulfate in Southwestern U.S. towns. In the highest pollution area, the children were exposed to 3 h peak SO_2 levels exceeding 2,500 $\mu g/m^3$ and annual mean particulate sulfate levels of 10.1 $\mu g/m^3$. The prevalence of cough (measured by questionnaire) correlated significantly with pollution levels (chi-square for trend = 5.6, p = 0.02). No significant differences existed among the groups of subjects over 3 years, and pulmonary function and lung growth over the study were roughly equal over all groups. The results tend to suggest that intermittent high level exposure to SO_2, in the presence of moderate particulate sulfate levels, produced evidence of bronchial irritation (increased cough), but no chronic effect on lung function or lung function growth. These results suggest a bronchitis - H^+ relationship, assuming that SO_2 or sulfates are indicative of acidic aerosols.

Chapman et al. (1985) report the results of a survey done in early 1976 that measured the prevalence of persistent cough and phlegm among 5,623 young adults in four Utah communities. The communities were stratified to represent a gradient of sulfur oxides exposure. Community specific annual mean SO_2 levels had been 11, 18, 36, and 115 $\mu g/m^3$ during the five years prior to the survey. The corresponding annual mean sulfate levels were 5, 7, 8, and 14 $\mu g/m^3$. No gradients for TSP or suspended nitrates were observed. The

analyses were made using multiple logistic regression, in order to adjust for confounding factors such as smoking, age and education. Persistent cough and phlegm rates in fathers were about 8 percent in the high SO_2/SO_4 exposure community, versus about 3 percent in the other communities. For mothers, the rates in the high SO_2/SO_4 exposure community were about 4 percent, as opposed to about 2 percent in the other communities. Both differences were statistically significant, suggesting that communities with higher SO_2 and SO_4 pollution, which may be associated with higher H^+ concentrations, experience chronically higher respiratory symptom rates in adults.

Stern et al. (1994) reported on a Canadian survey assessing the effects to transported acidic pollution on the respiratory health of children, regional differences in respiratory symptoms and lung function parameters. A cohort of about 4,000 Canadian school children, aged 7 to 11 years, residing in five rural communities in southwestern Ontario (high exposure area) and in five rural communities in central Saskatchewan (low exposure area) were examined. Respiratory health status was assessed through the use of parent-completed questionnaires and standard pulmonary function tests performed by the children in the schools. The levels of particulate sulfates and nitrates varied little among communities within each region, but sulfate means did differ between regions, with annual average sulfate readings for 1980 of 1.9 $\mu g/m^3$ and 6.6 $\mu g/m^3$ in Saskatchewan and Ontario, respectively. There were no significant differences in PM_{10} between these regions, however. After adjusting for the effects of age, sex, parental smoking, parental education and gas cooking, no differences in the prevalence of chronic cough, chronic phlegm, persistent wheeze, current asthma, bronchitis in the past year, or any chest illness that kept a child home for 3 or more days in the previous year most days and nights were observed. This differs with the results of the Harvard Six City Study (Dockery et al., 1989), which Stern et al. (1994) conclude may be due to a threshold of effects for chronic air pollution and respiratory symptoms effects. There were no regional differences in PEFR, FEF_{25-75}, FEF_{75-85}, $Vmax_{50}$, and $Vmax_{25}$. However, statistically significant decrements of 1.7% in FVC and 1.3% in $FEV_{1.0}$ were observed in Ontario children, as compared with those in Saskatchewan, after adjusting for age, sex, weight, standing height, parental smoking, and gas cooking. These results are noted to be similar to those reported by Schwartz (1989), but not with the

Six-Cites results (Dockery et al., 1989). It is hypothesized that this new study had greater power to detect such effects because the areas being contrasted are more similar, other than with respect to air pollution. The authors conclude that statistically significant decrement in the pulmonary volume parameters, FVC and $FEV_{1.0}$, of preadolescent children residing in rural southwestern Ontario are associated with moderately elevated ambient concentrations of sulfates and ozone.

Schenker et al. (1983b) studied 5,557 adult women in a rural area of western Pennsylvania using respiratory disease questionnaires. Air pollution data (including SO_2, but not particulate matter measurements) were derived from 17 air monitoring sites and stratified in an effort to define low, medium and high pollution areas. The four-year means (1975 to 1978) of SO_2 in each stratum were 62, 66, and 99 $\mu g/m^3$, respectively. Respiratory symptom rates were modeled using multiple logistic regression, which controlled for several potentially confounding factors, including smoking. A model was used to estimate air pollutant concentrations at population-weighted centroids of 36 study districts. The relative risk (odds ratio) of "wheeze most days or nights" in nonsmokers residing in the high and medium pollution areas was 1.58 and 1.26 ($p \leq 0.02$) respectively, as compared with the low pollution area. For residents living in the same location for at least five years, these relative risks were 1.95 and 1.40 ($p < 0.01$). Also, the increased risk of grade 3 dyspnea in nonsmokers was associated with SO_2 levels ($p \leq 0.11$). However, no significant association was observed between cough or phlegm and air pollution variables. The results of this study suggest that wheezing may be associated with SO_2 levels, but these results must be viewed with caution, since the gradient between areas was small and there were no particle or other pollutant measures. Lippmann (1985) suggested that it was plausible that the effects in this study are associated with submicrometer acid aerosol which deposits primarily in small airways, rather than with SO_2 levels.

Jedrychowski and Krzyzanowski (1989) related SO_2 and PM levels to increased rates of chronic phlegm, cough and wheezing in females living in and near Cracow, Poland. The authors suggest that the effects may have been due to hydrogen ions, but no direct measurements were available.

Several authors (Lave and Seskin, 1972, 1977; Chappie and Lave, 1982; Mendelsohn and Orcutt, 1979; Lipfert, 1984; Ozkaynak and Spengler, 1985; Ozkaynak and Thurston, 1987) have related annual mortality rates in U.S. Metropolitan Statistical Areas (MSA's) to sulfate and other pollution measurements using aggregate population cross-sectional analyses. There are significant problems and inconsistencies in results obtained across many of these analyses, as reviewed extensively by the U.S. Environmental Protection Agency (1986, 1982). For example, Lave and Seskin (1977) reported that mortality rates were correlated with sulfates. Lipfert (1984), reanalyzing the same data, found that it was not possible to conclude whether sulfates or particulate matter had a statistically significant effect on total mortality. These studies are reviewed in more detail in Section 12.4.1, but are included again in this section because of their relevance to acid aerosol epidemiology.

In one of the more extensive of these analyses, employing a variety of model specifications and controls for possible confounding, Ozkaynak and Spengler (1985), Ozkaynak et al. (1986), and Ozkaynak and Thurston (1987) used more sophisticated statistical approaches in an effort to improve upon some of the previous analyses of mortality and morbidity associations with air pollution in U.S. cities. The principal findings concern cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating information on particle size relationships and on a set of socioeconomic variables to control for potential confounding. Issues of model misspecification and spatial autocorrelation of the residuals were also investigated. Results from the various regression analyses indicated the importance of considering particle size, composition, and source information in modeling of PM-related health effects. In particular, particle exposure measures related to the respirable and/or toxic fraction of the aerosols, such as FP (fine particles) and sulfates were the most consistently and significantly associated with the reported (annual) cross-sectional mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., TSP and IP) were often found to be nonsignificant predictors of total mortality. In addition, an analysis of source-related fine particle trace element components for the 38 SMSA set found the

strongest mortality associations with industrial and combustion-related components of the fine aerosol, but not with soil-derived particles. Thus, these analyses indicated that sulfate containing fine combustion-related particles were most closely associated with mortality.

The Ozkaynak and Thurston (1987) results noted above for analysis of 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969 to 1970 U.S. mortality data, and to the findings of Lipfert et al. (1988) for the 1980 U.S. mortality data. In particular, whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Thurston (1987) found particle mass measures, including coarse particles (TSP, IP), often to be nonsignificant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Thurston (1987) found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. They estimated a range of particulate matter-total mortality mean effects of 4 to 9% of total U.S. mortality, when sulfates were used as the PM metric. When Lipfert (1988) conducted a reanalysis of the 1980 cross-sectional dataset, and added many more controllers for confounding (e.g. for smoking, water hardness and sulfate artifact), he also reports a significant sulfate coefficient having an elasticity of 2.8 to 13%, which is not statistically different from that reported by Ozkaynak and Thurston (see Lipfert and Morris, 1991, and; Thurston and Ozkaynak, 1992 for discussion). Thus, while results vary somewhat across studies, most cross-sectional analyses of the 1960, 1970, and 1980 are supportive of an association between chronic sulfate exposure and increased human mortality.

Taken as a whole, these various analyses are suggestive of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Without nationwide measurements of airborne acidity, however, it is difficult to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

12.5.4.3 Studies Relating Chronic Health Effects to Acid Aerosols

In an hypothesis generating discussion, Speizer (1989) presented city-specific bronchitis prevalence rates from the six cities. While no direct aerosol acidity measurements were actually made during or before the 1980/81 school year (when the children were examined), Speizer (1989) utilized pollution data that Spengler et al. (1989) gathered in Kingston/Harriman and St. Louis from December 1985 through September 1986 and in Steubenville and Portage from November 1986 to early September 1987. His plot of bronchitis prevalence as a function of PM_{15} is presented in Figure 12-15. Additional H^+ concentration data from Watertown, MA and Topeka, KS have since been published by Dockery (1993), and all these data are included in the updated version of Speizer's H^+ plot presented in Figure 12-16. It should be noted that these points may contain unaddressed bronchitis variation due to factors other than pollution. For example, illness and hospitalization rates are known to vary across areas, independent of health status factors (Wennberg, 1987; McPherson et al., 1982). Thus, the relationship of bronchitis rates with pollution in these preliminary analyses must be considered as being only suggestive. However, as seen in these figures, when the city-specific bronchitis rates are plotted against mean H^+ concentrations, instead of PM_{15}, there is a relative shift in the ordering of the cities which suggests a better correlation of bronchitis prevalence with H^+ than with PM_{15}.

Damokosh et al. (1993) has analyzed the 6-City children's bronchitis data, more thoroughly, it is an abstract incorporating controls for confounding variables, and has added a seventh locale, Kanahwa County, WV to the analysis. In that county, PM_{10}, $PM_{2.5}$, and H^+ were measured from 1987 to 1988 during the collection of data on the respiratory health status of 7,910 children in third through fifth grade. As in the 6-City study, respiratory health status was assessed in Kanahwa County via a parent completed questionnaire. Nine indicators of asthmatic and bronchitic symptom reports were considered. A two-stage logistic regression analysis was used, adjusting for maternal smoking and education, race, and any unexplained variation in symptom rates between the cities. Significant associations were found between summer mean H^+ and chronic bronchitis and related symptoms (cough, phlegm, and chest illness). The estimated relative odds for bronchitic symptoms associated with the lowest mean value of particle strong acidity (15.7 nmoles/m^3) to the highest

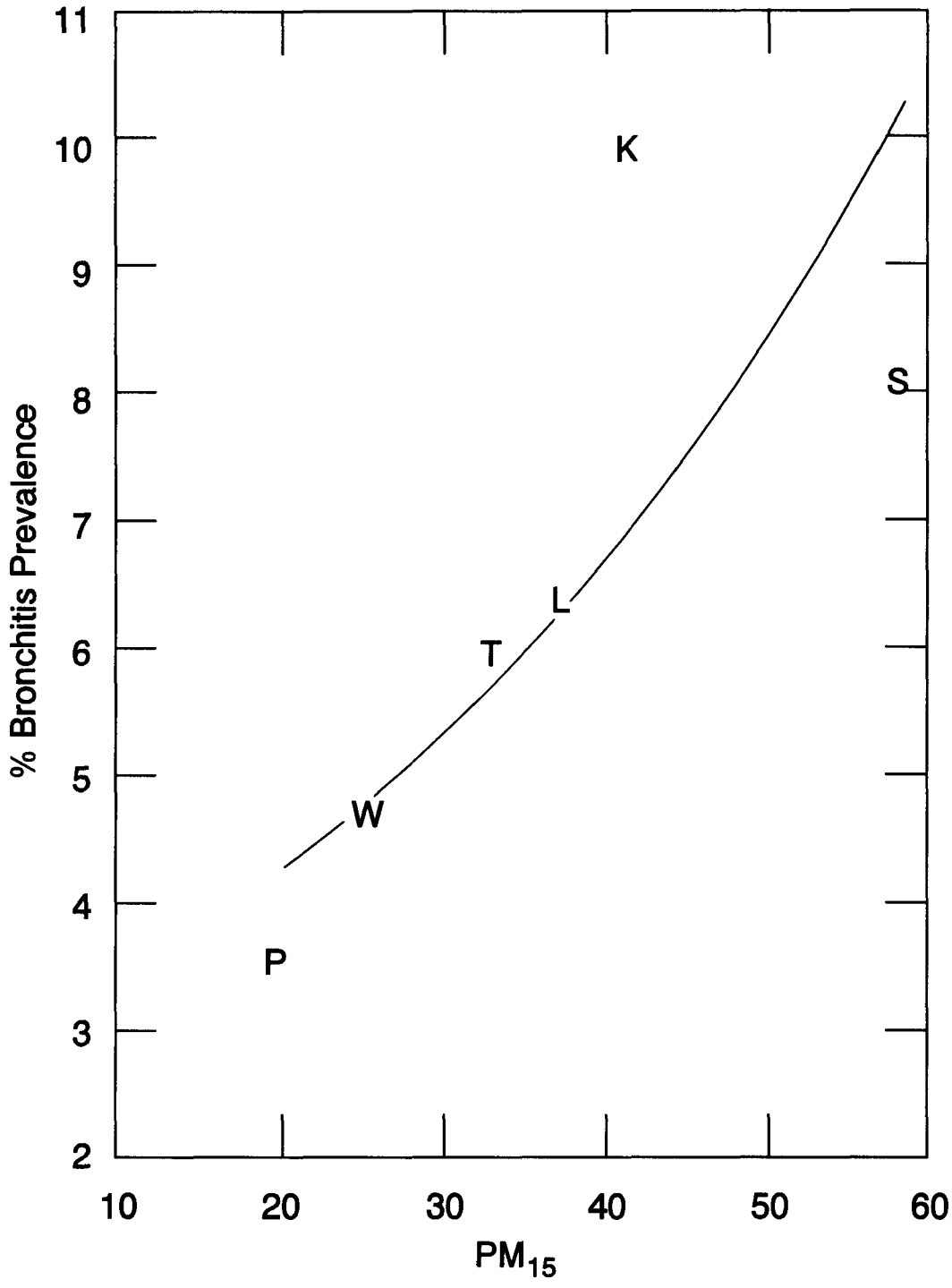

Figure 12-15. Bronchitis in the last year, children 10 to 12 years of age in 6 U.S. cities, by PM_{15}. (P = Portage, WI; T = Topeka, KS; W = Watertown, MA; K = Kingston, TN; L = St. Louis, MO; S = Steubenville, OH.)

Source: Speizer (1989).

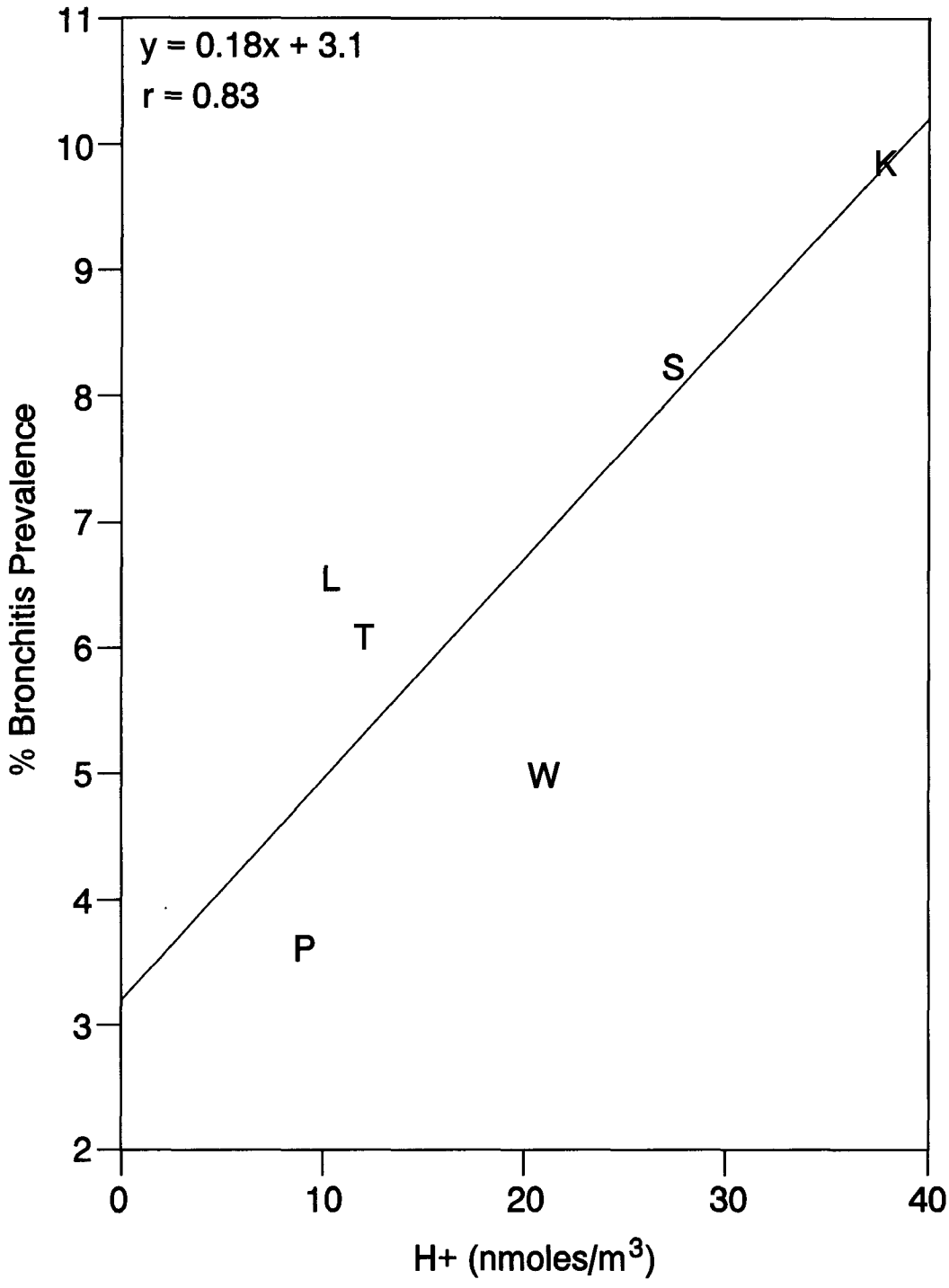

Figure 12-16. Bronchitis in the last year, children 10 to 12 years of age in six U.S. cities, by Hydrogen ion concentration. (K = Kingston, TN; L = St. Louis, P = Portage, WI; S = Steubenville, OH; T = Topeka, KS; W = Watertown, MA.)

Source: Dockery (1993); Speizer (1989).

(57.8 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). No associations were found for asthma or asthma related symptoms (doctor diagnosed asthma, chronic wheeze, and wheeze with attacks of shortness of breath). However, equivalent results were found with other particle mass measurements highly correlated with aerosol acidity.

As a follow-up to the 6-City study, the relationship of respiratory symptom/illness reporting with chronic exposures to acidic aerosols was tested among a cohort of schoolchildren in 24 rural and suburban communities in the United States and Canada (Dockery et al., 1993). Ambient air pollution concentrations were measured for one year in each community. Annual mean particulate strong acidity concentrations ranged from 0.5 to 52 nmoles/m^3 across the 24 communities. Questionnaires were completed by the parents of 15,523 schoolchildren 8 to 12 years of age. Both bronchitic symptoms, (reports of bronchitis, cough, or phlegm) and asthmatic symptoms, (reports of asthma, shortness of breath with wheeze) or persistent wheeze, were considered separately. City-specific reporting rates were first calculated after adjustment for the effects of gender, age, parental asthma, parental education, and parental allergies. Associations with ambient air pollution were then evaluated. Bronchitic symptoms were associated with particulate strong acidity: relative odds 1.7 (95% CI: 1.1 to 2.5) across the range of exposures. Increased reporting of bronchial symptoms were also associated with other measures of particulate air pollution including sulfate - relative odds 1.7 (95% CI: 1.1 to 2.4). However, associations of asthmatic symptom reports with any of the air pollutants, including particulate acidity, were not statistically significant. Stratified analyses did not show any evidence that asthmatics or other potentially sensitive groups of children had a greater response to particulate acidity.

Raizenne et al. (1993) report results from the 24-City follow-up to the Six Cities study designed by researchers at Harvard University to specifically examine the health effects in children of living in regions having periods of elevated ambient acidic air pollution (24 communities in the U.S. and Canada, 8 sites/year, 3 years) . Parents of children between the ages of 8 to 12 completed a questionnaire and provided consent for their child to perform a standardized forced expiratory maneuver on one occasion between October and May. Air and meteorological monitoring was performed in each community for the year preceding the pulmonary function tests. The annual mean particle strong acidity (H^+) ranged from 0.5 to

52 nmoles/m^3, PM_{10} ranged from 18 to 35 $\mu g/m^3$, and $PM_{2.1}$ from 6 to 21 $\mu g/m^3$. Annual H^+ was more highly correlated with PM2.1 (r = .72) and SO_4 (r = .91) than with PM_{10} (r = 0.29). FVC and FEV_1 measurements of 10,753 Caucasian children in 22 communities were used in the analyses. A two-stage logistic regression analysis was used adjusting for age, sex, height, weight, sex-height interaction and parental history of asthma. The reported effect estimates were expressed in terms of 52 nmoles/m^3 difference in H^+. The results indicated that residing in high particle strong acidity regions was associated, on average, with a 3.41% (95% CI 4.72, 2.09) and a 2.95% (95% CI 4.36, 1.52) lower than predicted FVC and $FEV_{1.0}$, respectively. For children with a measured FVC less than or equal to 85% of predicted, the odds ratio for lower lung function was 2.5 (95% CI 1.7, 3.6) across the range of H^+ exposures. Assuming that these exposures reflect lifetime exposure of the children in this study, the data suggest that long-term exposure to ambient particle acidity may have a deleterious effect on normal lung growth, development, and function.

As discussed in detail earlier in this chapter, Dockery et al. (1993) reported the results of a prospective cohort study in which the effects of air pollution on mortality were estimated, controlling for individual risk factors. Survival analysis, including Cox proportional-hazards regression modeling, was conducted with data from a 14 to 16 year mortality follow-up of 8,111 adults in six U.S. cities. After adjusting for smoking and other risk factors, statistically significant associations were found between air pollution and mortality. Using inhalable particles, fine particles, or sulfates as the indicator of pollution all gave similar results: an adjusted mortality-rate ratio for the most polluted city as compared to the least polluted city of 1.26 (95% CI = 1.08 to 1.47). Weaker mortality associations were found with H^+ in this analysis. However, this analysis did not demonstrate that H^+ was not a factor in the pollution related excess mortality, as the H^+ data employed was not appropriate for such an analysis. Of the pollutant data considered, the H^+ was the most limited. Less than one year of H^+ data were collected in each city, near the end of this study, and this was used to characterize lifetime exposures of adult study participants. This seems especially inappropriate in Steubenville, OH where the industrial (e.g. steel mill) pollution levels declined during the course of the study, as the steel industry in the valley declined. Indeed, in Steubenville, OH, the H^+ data were only collected from

mid-October, 1986 through early September, 1987 (Spengler et al., 1989). In contrast, the inhalable particle, fine particle, and sulfate data employed in each city were more representative, having been collected earlier and over roughly a five to six year period in these cities. Thus, the inability of this study to find a statistically significant correlation between H^+ and mortality (relative to sulfates and fine particles) may be due in large part to the fact that the limited H^+ data employed were not sufficient for this application.

12.5.4.4 Chronic Exposure Effects in Occupational Studies

The last remaining type of information considered here concerns the effects of chronic exposures to acid aerosols in occupational settings. Such studies are discussed mainly in order to provide some perspective on the variety of health effects associated with acid aerosol exposures, albeit at extremely high concentrations not likely to occur in ambient air.

Gamble et al. (1984a) studied pulmonary function and respiratory symptoms in 225 workers in five lead battery acid plants. This acute effect study obtained personal samples of H_2SO_4 taken over the shift. Most personal samples were less than 1 mg/m^3 H_2SO_4, and mass median aerodynamic diameter of H_2SO_4 averaged about 5 μm. The authors concluded that exposure to sulfuric acid mist at these plants showed no significant association with symptoms or with acute effect on pulmonary function. The ability of the body to neutralize acidity of H_2SO_4 was considered as one factor is this outcome. Additionally, the authors speculated that tolerance to H_2SO_4 may develop in workers habitually exposed.

In a related study of chronic effects of sulfuric acid on the respiratory system and teeth, Gamble et al. (1984b) measured in the same workers respiratory symptoms, pulmonary function, chest radiographs, and tooth erosion. Concentrations measured at the time of the study were usually 1 mg/m^3 or less. Exposure to the concentration of acid mist showed no significant association with cough, phlegm, dyspnea, wheezing, most measures of pulmonary function, and abnormal chest radiographs. Tooth etching and erosion were strongly related to acid exposure. The authors noted that the absence of a marked effect of acid exposure on respiratory symptoms and pulmonary function may be due to the size of the acid particles. The range of the mass median diameter in the 5 plants was 2.6 to 10 μm, which is much larger than (typically submicrometer) ambient H^+ aerosols. Moreover, the relative humidity

of the lung may cause at least a doubling of particle size, especially in the lower size range. Thus, most acid particles may be deposited in the upper respiratory tract, and many may not even reach the lung. Finally, the authors note that the lack of any convincing finding in this study relating to the acute respiratory symptoms is not completely unexpected, due to the relatively low exposure (<1 mg/m^3) compared to previous occupational studies.

Williams (1970) studied sickness absence and ventilatory capacity of workers exposed to high concentrations of sulfuric acid mist in the forming department of a battery factory (location not stated). Based on 38 observations made on two days, the forming department had a mean H_2SO_4 concentration of 1.4 mg/m^3, ranging from a trace to 6.1 μg/m^3. In a different forming department, the mass median diameter of the acid particles was 14 μm. Compared with control groups, men exposed to the high concentrations of sulfuric acid mist in the forming department had slight increases in respiratory disease, particularly bronchitis. There was no evidence of increased lower respiratory disease, which might be explained by the large particle size. After adjusting for circadian variations, there was no evidence of decreased ventilatory function.

Beaumont et al. (1987) studied mortality patterns in 1,165 workers exposed to sulfuric acid and other acid mists in steel-pickling operations. Workplace monitoring during the 1970's indicated worker personal exposures to average 190 μg/m^3 H_2SO_4. However, as discussed for battery plant operations, the particle size of these mists tend to be larger than ambient acid aerosols, so not all is likely to be respirable. Standardized mortality ratio (SMR) analysis of the full "any acid exposure" cohort (n = 1,165), with the use of U.S. death rates as a standard, showed that lung cancer was significantly elevated, with a mortality ratio of 1.64 (95%CI = 1.14 to 2.28, based on 35 observed deaths). The lung cancer mortality ratio for workers exposed only to sulfuric acid (n = 722) was lower (SMR = 1.39), but further restriction to the time 20 years and more from first employment in a job with probably daily sulfuric acid exposure ($\sim$0.2 mg/m^3) yielded a mortality ratio of 1.93 (95% CI = 1.10 to 3.13). An excess lung cancer risk was also seen in workers exposed to acids other than sulfuric acid (SMR = 2.24; 95% CI = 1.02 to 2.46). When comparison was made to other steel workers (rather than to the U.S. general population) to control for socio-economic and life-style factors such as smoking, the largest lung cancer excess was

again seen in workers exposed to acids other than sulfuric acid (SMR = 2.00; 95% CI = 1.06 to 3.78). However, the smaller rate ratios may have been partly due to the restriction of this sub-analysis to white males, which excluded the higher excess lung cancer risk in nonwhite males. Adjustment for potential differences in smoking habits showed that increased smoking was unlikely to have entirely explained the increased risk. Mortality from causes of death other than lung cancer was unremarkable, with the exception of significantly lower rates for deaths due to digestive system diseases. These results suggest that chronic acid aerosol exposures may promote lung cancer at high concentrations, perhaps via chronic irritation of respiratory tissues, or by some other mechanism (e.g. by affecting clearance rates in the lung).

12.5.5 Summary of Studies on Acid Aerosols

Historical and present-day evidence suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 $\mu g/m^3$ as H_2SO_4, or roughly 8,000 nmoles/m_3 H_+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2. In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels ($\leq$ 30 $\mu g/m^3$ as H_2SO_4, or $\leq$ approximately 600 nmoles/m_3 H_+), though these associations could not be separated from those for BS or SO_2. The only attempts to-date to associate present-day levels of acidic aerosols with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, respectively) were unable to do so, but there may not have been a sufficiently long series of H^+ data to detect H^+ associations. There is a critical need for present day replications of the London mortality-acid aerosol studies to be conducted, however, in order to determine if the London wintertime associations (which occurred in reduction-type atmospheres) are pertinent to present-day U.S. conditions, in which acid aerosol peaks occur primarily in the summer months (in oxidation-type atmospheres).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. Thurston et al. (1992) and Thurston et al. (1994b) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. In the Toronto analysis, the increase in respiratory hospital admissions associated with $^+$ was indicated to be roughly six times that for non-acidic PM10 (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes ($H^+ \geq 10\ \mu g/m^3$ as H_2SO_4, or $\approx$200 nmoles/m_3 H^+), which occur roughly 2 to 3 times per year in eastern North America. These studies provide evidence that present-day strongly acidic aerosols may represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms except at H^+ above 110 moles/m_3 (Dockery et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991). Recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of chronic H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested

associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1993a) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.7, 95% CI: 1.1 to 2.4). It was also found in the 24-Cities study that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1993). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children.

12.6 DISCUSSION

12.6.1 Introduction and Basis for Study Evaluation

The epidemiologic studies of human health effects related to PM exposure play a particularly important role because there is somewhat less supporting information on exposure-response information from toxicological or clinical studies compared to other criteria pollutants. We have therefore paid much greater attention to methodological issues in the studies that have been reviewed in this epidemiology chapter. Various health endpoints have been used in these studies, including respiratory function measures, respiratory symptom reports, hospital admissions, total non-accidental mortality, and mortality classified by medical cause of death such as respiratory or cardiovascular classifications. Each health outcome has many causes other than air pollution, and no specific air pollutant can be uniquely associated with a specific outcome, including PM and its components. Subject-specific (personal) exposure to PM or to other air pollutants is unmeasured in almost all of the studies, and exposure to PM, to other pollutants, or even to weather variables, is only estimated from one or a few monitoring sites in a large metropolitan area or region. Demographic information can be used with either longitudinal studies, prospective studies, or cross-sectional studies, but age is the only individual subject

variable that has been used in almost all studies. Other personal variables can be obtained in prospective studies. Comparisons across different cities must be adjusted for demographic and climatologic differences, and usually are in cross-sectional studies. Studies of acute responses to air pollutants, whether measured by respiratory function indices, respiratory symptoms, hospital admissions, or mortality, have been compared by various formal or informal meta-analytic techniques (Schwartz, 1992a, 1994c; Dockery and Pope, 1994b), but there has so far been no effort to adjust the results of the metaanalyses for quantitative differences among study groups or for differences in data-analytic methodologies.

Differences in results may also be attributed to differences in methods of data analysis. Many investigators of acute effects have expressed concerns about data analysis issues, including problems of non-Gaussian data distributions, mis-specification of exposure-response relationships, inappropriate adjustments for covariates such as weather and co-pollutants, mis-specification of the temporal lag structure between exposure and response, and inadequate adjustment for seasonality and other random or systematic long-wave (low frequency) effects. However, it has become clear that very similar estimates of the effects of PM can be obtained for a wide range of alternative data analysis methods. Many models seem to work well, but all adequate models for short-term effects must be adjusted for seasonality, for long-term and transient irregular events such as influenza epidemics, must include adjustments for auto- and cross-correlation structure when necessary, must be examined for sensitivity to distributional assumptions such as Poisson or hyper-Poisson variability and, if not based on demonstrably robust methods, must be carefully examined for sensitivity to unusual values among either predictor or response data. Some models used by different investigators have not met all of these criteria.

12.6.1.1 Differences Among Study Results

What is more disturbing is that, using ostensibly similar data sets, different investigators of acute mortality effects have come up with different estimates of PM effect size or statistical significance. There are at least two possible reasons for this. The first is that there may be some genuine confounders of PM effects on human health. In some studies, under some meteorological or seasonal conditions, co-pollutants will be emitted by

some of the same sources as emit PM, so that there will be a close intrinsic relationship between PM and some other pollutants. This may also extend to certain meteorological variables, which may be related both to atmospheric dispersion of all outdoor pollutants and to pollutant emissions rates. For example, an extremely hot day in summer may be associated with increased use of electrical power for air conditioning (increasing emissions of PM and other pollutants such as SO_2 from local electricity generating plants that burn fossil fuels) and, also, with increased motor vehicle use as people travel to less uncomfortable locations (increasing vehicle-generated pollutants from gasoline and other motor vehicle fuels, including O_3, CO, and NO_2). Primary gaseous pollutants may become secondary atmospheric sources of certain PM components, such as sulfates and nitrates. While there are a number of statistical diagnostics for intrinsic confounding, and even a few adequate methods for partially resolving seriously confounded predictors of response, these have rarely been used. Analyses in which only a single pollutant is used to predict a health effect are not wholly satisfactory without confirmation by multi-pollutant analyses, adjusted for confounding insofar as possible. In this regard, comparison across different studies, including those in which each potentially confounding factor is or is not present, may be needed to assess the effects of PM in the absence of detailed technical assessments of sensitivity to intrinsically confounded variables.

The second reason why different investigators may come up with different results for acute mortality is much more profound. In the absence of generally acceptable mechanistic relationships among potentially confounding variables, and in the absence of generally acceptable specifications for the exposure-response relationships for PM, for co-pollutants, and for weather, all modelling is data-driven and empirical. This has led almost all investigators into extensive model specification searches, in which numerous alternative models may be fitted to the same data or to subsets of the same data set until a "best fitting" or "statistically significant" model is obtained. It has long been known (Leamer, 1978) that data-driven model specification searches can seriously distort the actual significance level of the regression coefficients in ordinary linear regression models with independent Gaussian errors, and by extension we expect the same problem in Poisson and hyper-Poisson exponential regression models with complicated correlation structures. This is similar to the

better-known "multiple comparisons" problem, in which all possible subsets of a set of hypothesis tests in a linear analysis of (co)variance could be tested, with a corresponding artificial inflation of the statistical significance of the whole ensemble of tests. However, the complicated model specification searches that have produced the models reported in the published PM epidemiologic studies have a hypothetically limitless number of alternative specifications.

In evaluating numerous model specifications, on the one hand, a model specification search may be extended until some combination of correlation model or lag structure, adjustments for time trends, season, co-pollutants, and weather produces a model in which the study response data are fitted well and the PM coefficient is "statistically significant". Statistical significance for a PM coefficient means that either an asymptotic confidence interval or a more exact likelihood ratio-based confidence interval for the effect does not cover the null value (0 for effect size, 1 for relative risk). Or, on the other hand, the specification search may proceed towards the goal of establishing that some other pollutant in the model is a statistically significant predictor of changes in mortality rates or hospital admission rates (etc.) or that some combination of meteorological variables can fit the observed health effects data when the PM coefficient is not statistically significant. This could provide the basis of an argument that some factor(s) other than PM are accounting for the observed effects. Because of the confounding that exists between PM and other variables that may be used in the models, there may be many substantial points of similarity between the models with a significant PM effect and those without a significant PM effect, at least in some cities during some years. There may thus be little internal basis for choosing between two models, one with a significant PM effect and another, using similar specifications in many ways, without a significant PM effect.

There are several ways in which the indeterminacy of the models from different studies of the same data set could be resolved. The first method, and in many ways the best, is to see which of the competing models does the best job of predicting new information. Since new information is not readily at hand, a more realistic method would be "internal cross-validation". The model would be fitted to one subset of the data and then the parameters derived from the model based on one part of the data would be used to predict the other part.

In time series analysis, the use of the first part of the series to predict the last part of the series is known as "postdiction", to distinguish the exercise from a genuine forecast or prediction in which the future observations and their predictors are in fact unknown. A related approach would be to use the PM and co-pollutant models derived from one group of cities to estimate health effects in another group of cities, where "pre-models" specific to each of the second group of cities are used to adjust mortality rates for all non-pollution variables such as meteorological variables. In practice, we are not aware of any efforts to assess the predictive validity of any of the models, either in an absolute sense or relative to a competing model.

12.6.1.2 Importance of Comparisons Across Different Cities

We are therefore limited to evaluating models reported in different studies on the basis of comparisons of results for different geographic sites (cities, SMSA's, etc.) or during different periods of time. If the estimated PM effect is similar in magnitude across a range of different cities, differing in location, climate, co-pollutant inventories, demographics, or other relevant factors, we may argue that these effect estimates are relatively robust with respect to exact specifications of different models. This is discussed in more detail in Section 12.6.3.

Similarly, weather is an important confounding factor. Adjustments for meteorological variables may differ substantially from one study to another. It is easier to compare effect size estimates from studies with similar adjustment methods. However, there are likely to be real differences among cities that complicate the use of weather effect models found at one location to adjust for weather effects on human health in another location. This is particularly likely to affect adjustments made for extreme weather conditions, whether defined by a threshold for a temperature effect or by a weather-related synoptic category. It is, in any event, easier to identify a quantitative PM relationship during non-extreme weather conditions, or during non-offensive synoptic categories. Studies in which the size of the PM exposure-response relationship was estimated for non-extreme weather conditions, or for which appropriate adjustments were made in the analysis, are also accorded higher weight than those without such distinctions.

Finally, there is a question about how the effect size estimates in different cities should be combined, or whether there should be a combined estimate. Combined estimates using meta-analytic techniques have been published (Schwartz, 1994c; Dockery and Pope, 1994b), and additional meta-analyses for the more recent studies may be useful. However, there is a possibility that real differences exist among PM effect sizes in different communities. The differences may be due to differences in sub-populations, in pre-existing health status, in acclimatization to weather conditions, or to effects of other unmeasured air pollutants. If the differences among communities are substantial, it may be preferable to treat the PM effect on health outcome as a random effect across communities, even though the reasons for the differences are potentially explainable, but unknown at present.

12.6.2 Sensitivity of PM Effects to Model Specification in Individual Studies

12.6.2.1 Model Specification for Acute Mortality Studies

Many different statistical models have been used to interpret short-term mortality and morbidity studies. The model specifications and methods used to interpret the long-term studies are generally different from those used in analyzing the short-term studies. It is often difficult to compare estimates of PM effect in different studies when the estimates of effect size are obtained by different methods. Differences in effect size estimates may then occur because of differences in modelling approach as well as any real differences in response to PM exposure.

Many of the papers reviewed in this chapter provide enough information to assess the authors' choice of their "best" model, which we have reported in the summary tables. An extensive discussion of alternative modelling approaches for short-term exposure studies was already evident in earlier papers, such as the analyses of BS in London in the 1960's (Ostro, 1984; Thurston et al., 1989; Schwartz and Marcus, 1990; Ito, 1990), KM in Los Angeles (Shumway et al., 1988; Kinney and Ozkaynak, 1991), and COH in Santa Clara (Fairley, 1989). More recent work has moved in some substantially different directions, recognizing the non-Gaussian nature of discrete data such as daily death counts and hospital admissions, and incorporating a growing variety of data-driven non-parametric or semi-parametric models

for PM and other Covariates. We will here discuss the more recent studies, emphasizing those studies in which PM_{10} or TSP are used as PM indicators.

Model Specification for the Utah Valley Mortality Study (Pope et al., 1992)

One of the most comprehensive assessments of alternative model specifications was presented by Pope in a report for presentation at the EPA-sponsored workshop on daily mortality data and short-term changes in PM exposure in November, 1994 (Pope, 1994). The results of these additional analyses of the Utah Valley study were described briefly in Section 12.3.1. We will present the results graphically, with a view towards resolving model specification issues. For each comparison, we will exhibit a sequence of three graphs illustrating the results for total (non-accidental) mortality, for death from respiratory causes, and for death from cardiovascular causes. The horizontal bars show the 95 percent confidence limits for relative risk (denoted RR) corresponding to 50 $\mu g/m^3$ in PM_{10}.

Figures 12-17a through 12-17c show the RR estimates for Poisson regression models. The RR for PM quintiles given in the published paper (Pope et al., 1991) is denoted Model 0. The next group, Models 1 through 5, show the results of fitting increasingly adjusted parametric models, from those with only a linear PM_{10} effect (Model 1), and subsequently adding adjustments for time trend (Model 2), temperature (Model 3), humidity (Model 4), and operation of the mill (Model 5) to the preceding model. The relative risk for total mortality (Figure 12-17a) was little affected in Models 1 and 2, but dropped somewhat after temperature was included (Model 3). The relative risk for respiratory mortality (Figure 12-17b) was less affected by temperature, but shifted upward after humidity was added (Model 4). Cardiovascular mortality (Figure 12-17c), like total mortality, also dropped slightly after temperature was added to the model. The relative risk for the next four models (Model 6 through 9) are parallel to Models 2 through 5, except that a non-parametric smoothing function LOESS was used to model time trend, temperature, and humidity respectively in Models 6, 7, and 8; a dummy variable for mill operation was added in Model 9. Model 13 is the same as Model 8 without adjusting for time trend by a LOESS fit on day of the study. In general, RR using at least one LOESS smoother provided a

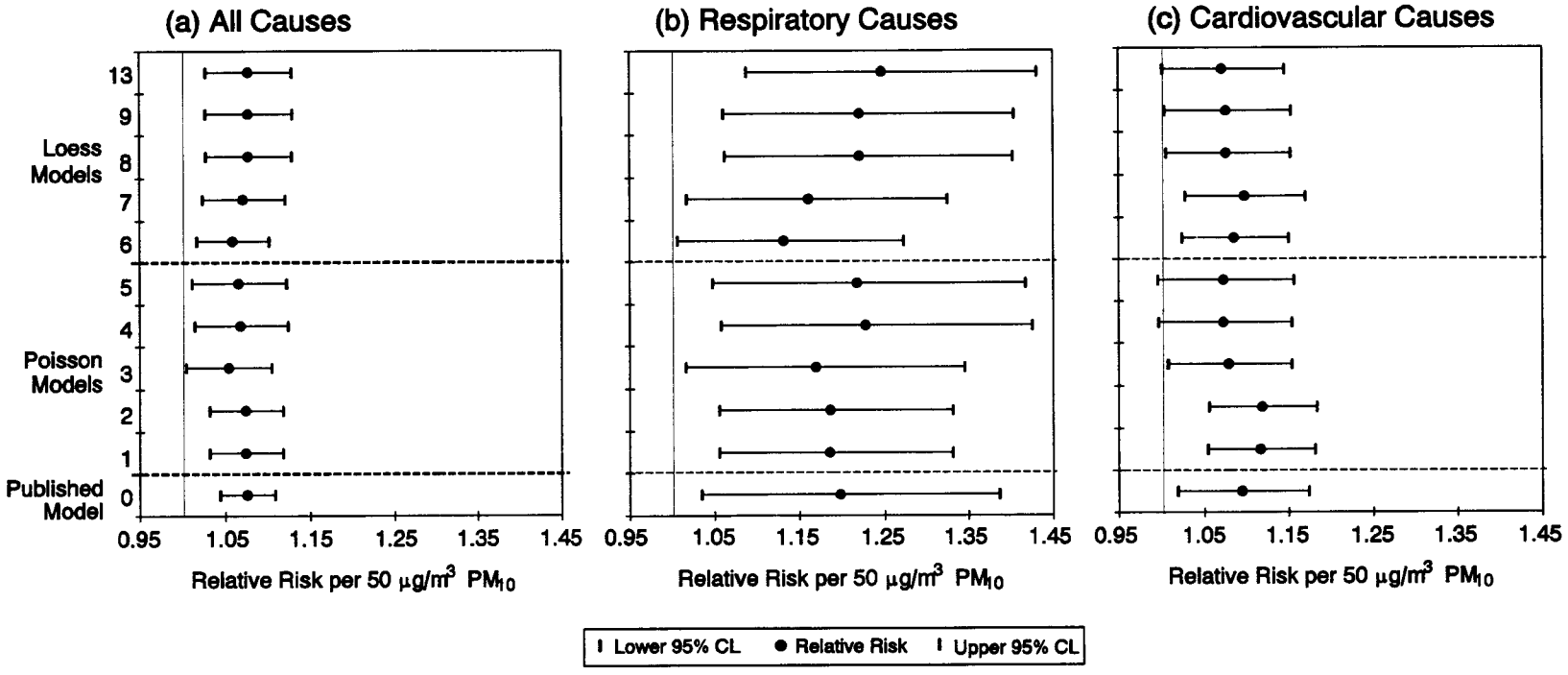

Figure 12-17a-c. Relative risk of mortality for PM_{10} in Utah Valley, as a function of several parametric and semi-parametric models of time, temperature, and dewpoint: (a) all causes; (b) respiratory causes; (c) cardiovascular causes.

somewhat higher RR for total mortality against PM_{10} in the Utah Valley study, but the difference in RR among these Poisson models is small. RR for respiratory mortality increased as each smoothed covariate was added, but never rose much beyond that for the published model. LOESS smoothers had little effect on RR for cardiovascular mortality.

The next group of model comparisons is shown as Figures 12-18a through 12-18c. These compare several parametric Poisson models with the analogous Gaussian ordinary least squares (OLS) linear models for mortality. Even though the distributional assumptions for a Gaussian distribution fail utterly, the regression coefficients and calculated RR are not very different than the analogous estimates from Poisson regression models.

Figures 12-19a through 12-19c show the effects of separating the annual data into segments, here called "summer" (April to September) and "winter" (October to March). The RR for total mortality (Figure 12-19a), respiratory mortality (Figure 12-19b), and cardiovascular mortality (Figure 12-19c) are all statistically significant on an annual basis, while differing substantially in magnitude. Most of this effect is seen to occur from the winter months when the PM_{10} concentrations were highest, whether or not the mill was operating, based on Model 13 in which temperature and humidity effects were adjusted using LOESS smoothing. The relative risk and its estimated uncertainty for all three mortality endpoints is nearly the same using whole year data as when using winter data alone. While PM level are generally much lower during the summer half of the year than in the winter half, the summer RR estimates are higher than the winter RR estimates, but not significantly different. However, the smaller range of summer PM values results in much larger uncertainty about the summer RR than the winter RR. This illustrates a general problem in subsetting the data by year, season, or month: the increased specificity of RR estimates for subsets of data is usually offset by the loss of precision in the estimates. In general, small increases in uncertainty of subset data RR estimates compared to whole data set RR estimates occur only for the subset(s) of the data that are most influential in establishing the whole data set RR estimate, such as the "winter" subset in this Utah Valley study.

Figures 12-20a through 12-20c extend these analyses to assessing the effect of a co-pollutant, ozone. Including either daily average ozone concentration or maximum one-hour ozone concentration as predictors of the three mortality endpoints leaves the PM_{10} RR

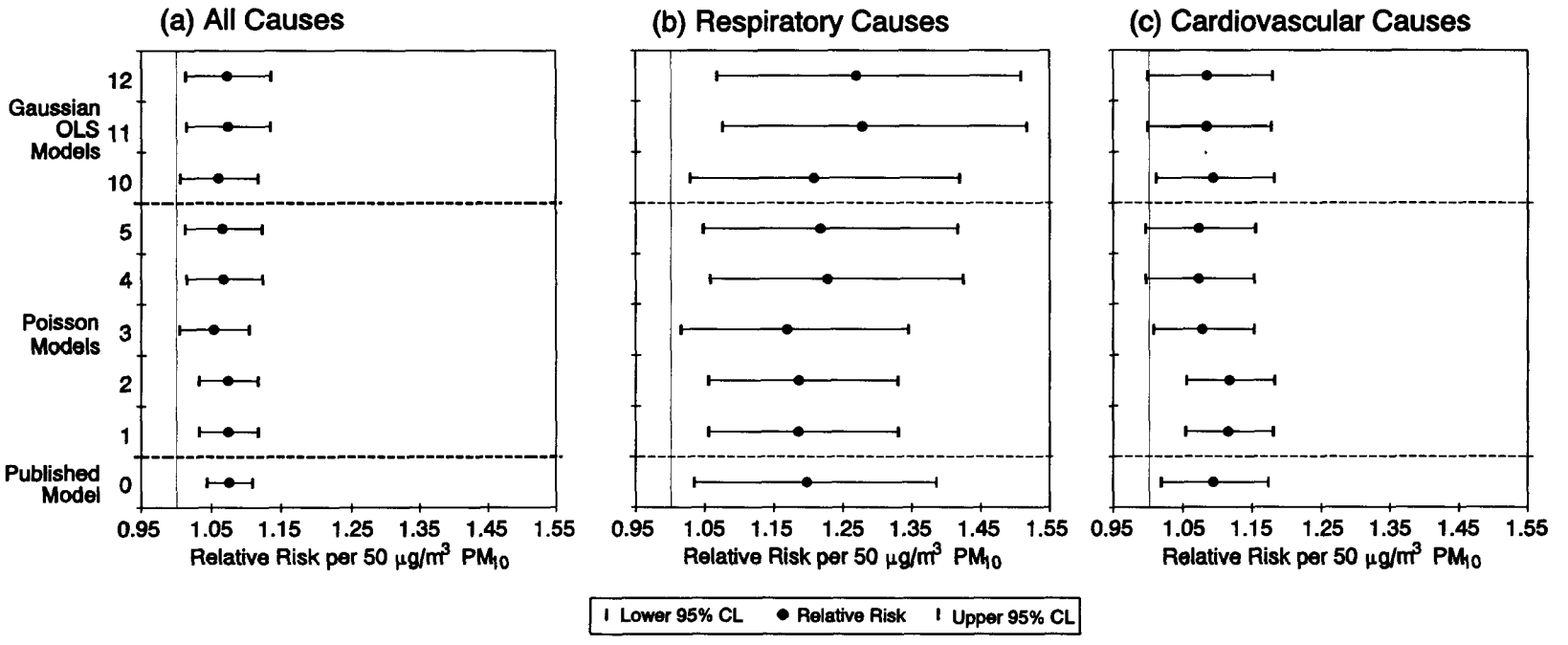

Figure 12-18a-c. Relative risk of mortality for PM_{10} in Utah Valley, as a function of several poisson and gaussian regression models of time, temperature and dewpoint: (a) all causes; (b) respiratory causes; and (c) cardiovascular causes.

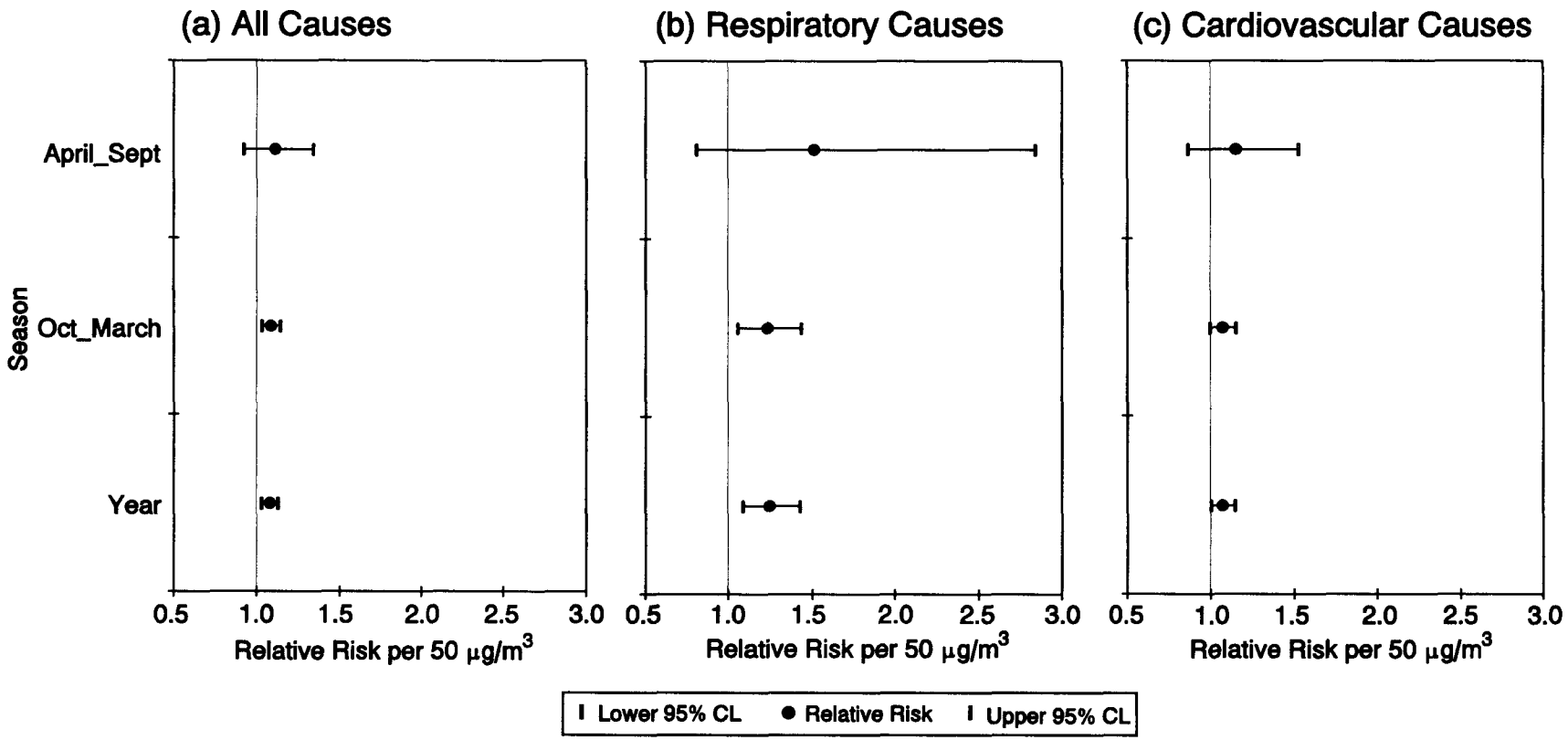

Figure 12-19a-c. Relative risk of mortality for PM_{10} in Utah Valley, as a function of season: (a) all causes; (b) respiratory causes; and (c) cardiovascular causes.

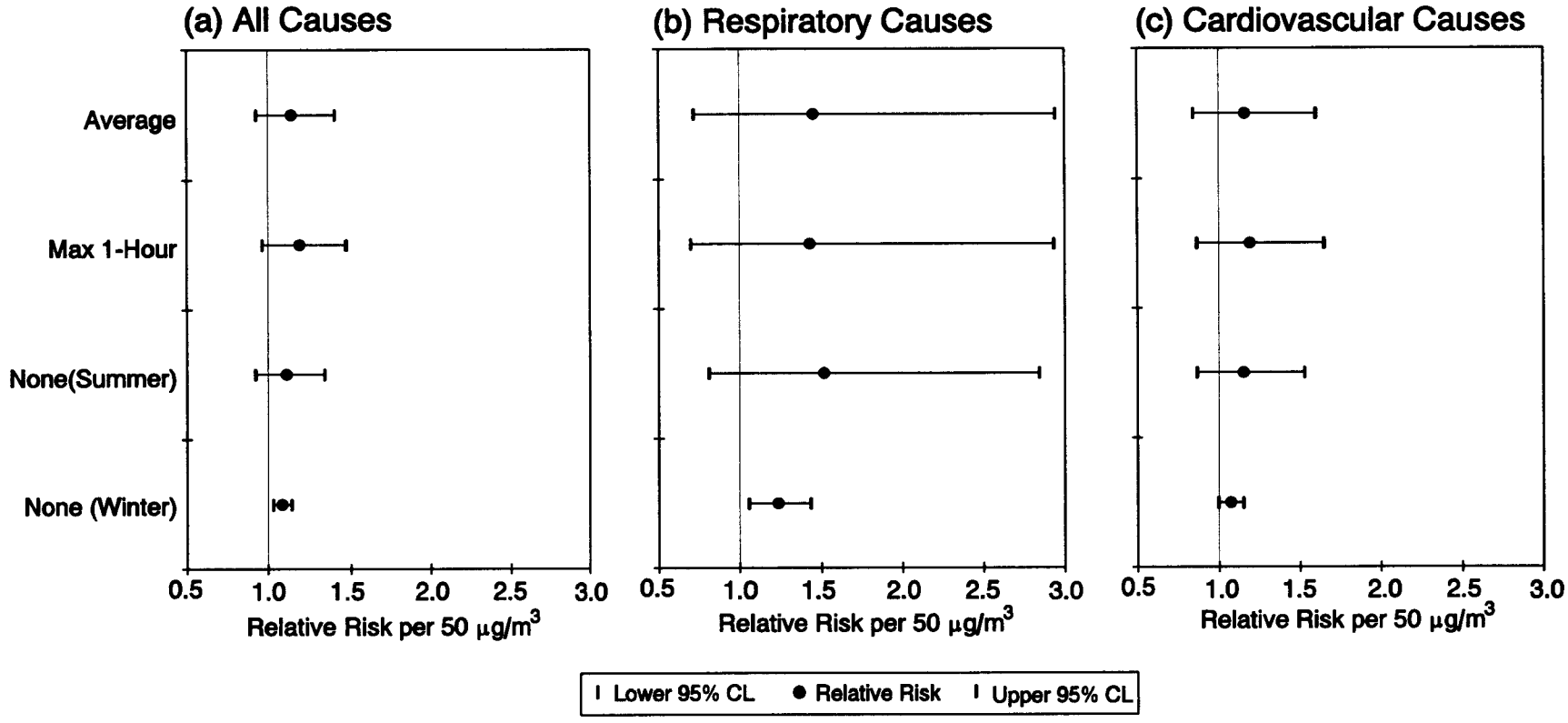

Figure 12-20a-c. Relative risk of mortality for PM_{10} in Utah Valley, as a function of ozone indicator in the model: (a) all causes; (b) respiratory causes; and (c) cardiovascular causes.

estimate nearly unchanged from the summer PM_{10} RR estimate obtained without including ozone as a predictor. Summer RR estimates for all models, with or without ozone, are somewhat larger than the winter or whole-year RR estimate for PM, and have much greater uncertainty. It may be argued that this indicates little confounding of the estimated PM effect with an estimated ozone effect, and by implication little potential for confounding with other pollutants generated by combustion of fossil fuels by mobile sources, at least in this study.

Figures 12-21a through 12-21c show that specification of PM averaging time may be a critical component of the modelling exercise. Moving averages of 4, 5, or 6 days would provide very similar estimates of a statistically significant PM effect on total mortality (Figure 12-21a) or respiratory mortality (Figure 12-21b). The 5-day moving average used by Pope in most analyses gave the better prediction of cardiovascular mortality (Figure 12-21c).

Model Specification for the Santiago, Chile, Mortality Study (Ostro, 1995)

Many model specifications were evaluated by Ostro et al. (1995). The study was discussed in Section 12.3.1. Model specification tests were designed to systematically examine important issues, and results were reported in detail. The results are shown graphically. Figure 12-22a shows the RR estimates and large-sample confidence intervals for 10 different Poisson regression models. We have recalculated the RR values in Table 3 of their paper to a base of 50 ug/m^3 for models that are linear in average or maximum PM_{10}, or for a change from 100 to 150 ug/m^3 for their logarithms. Inclusion of temperature-related variables reduced RR slightly, from about 1.13 to about 1.10. Inclusion of additional dummy variables for year, quarter, and day of week had little effect on RR, but adding variables for quarter and month reduced RR to about 1.05, which was still statistically significant. Figure 12-22b shows the results of an additional sensitivity tests controlling seasonality in a variety of different ways. The results are somewhat parallel to those of the Utah Valley study discussed above, but with somewhat smaller values. Summer and winter coefficients were very similar, but the RR effect was not quite statistically significant in summer using a two-tailed test with alpha = 0.05. All other model specifications showed a significant PM_{10} effect. The RR of the effect increased somewhat when the coldest days

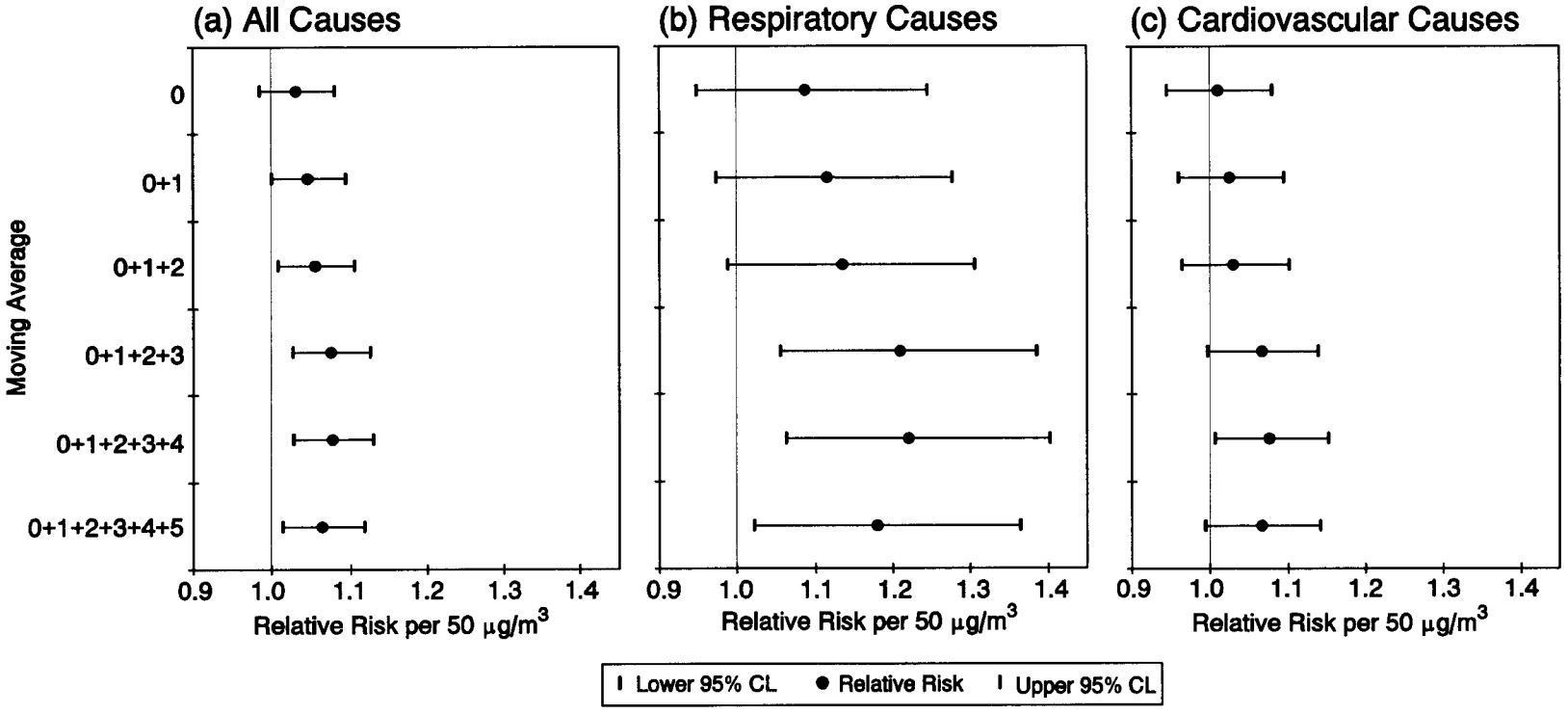

Figure 12-21a. **Relative risk of mortality for PM_{10} in Utah Valley, as a function of the moving average model: (a) all causes; (b) respiratory causes; and (c) cardiovascular causes.**

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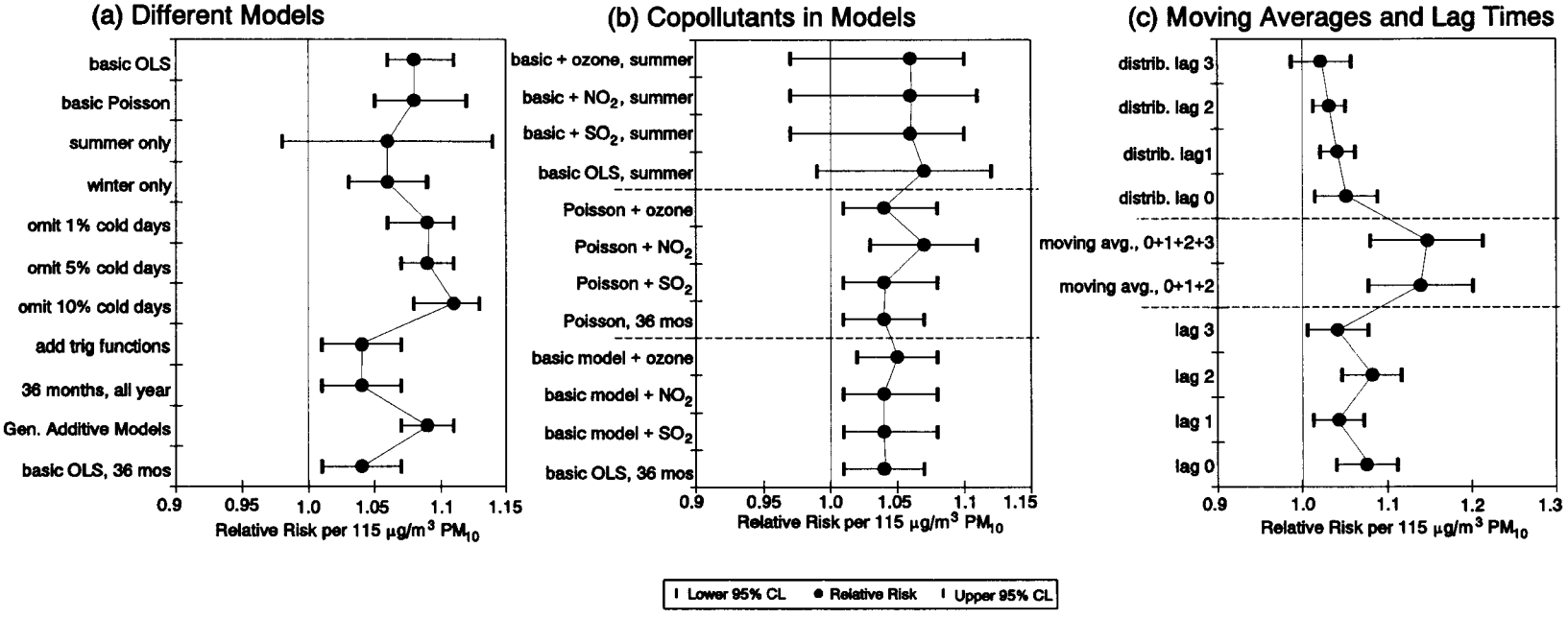

Figure 12-22a-c. Relative risk of total mortality for PM_{10} in Santiago, Chile, as a function of (a) different models; (b) models for co-pollutants; and (c) moving averages and lag times.

Source: Ostro et al. (1995).

were omitted. Including additional trigonometric terms, or including 36 dummy variables for combinations of year and month reduced the RR for PM, but did not eliminate PM as a significant contributor to total mortality. Control of seasonality by use of a generalized additive model to adjust for time effects gave a somewhat larger RR for PM_{10}, with small uncertainty.

Figure 12-22c evaluates a number of lag and moving average models for PM. The relative risks corresponding to each term have been recalculated from the regression coefficients (denoted b) in their Table 7, for a basis of 100 to 150 ug/m^3, by the formula

$$RR = \exp(b * \log(150/100)),$$

with confidence limits estimated analogously. All of the PM effects are statistically significant, with the exception of the 3-day lag term in the 4-day polynomial distributed lag (PDL) model. The 0-day and 2-day single lag models and the 3-day and 4-day moving average models perform almost as well at predicting total mortality as does the PDL model, of which they are each a special case.

Model Specification for the St. Louis and Eastern Tennessee Mortality Studies (Dockery et al., 1992)

The daily mortality data for St. Louis and for eastern Tennessee analyzed by Dockery et al. (1992) were discussed in Section 12.3.1. Additional results contributing to the analysis were presented by Dockery in a report for presentation at the EPA-sponsored workshop on daily mortality data and short-term changes in PM exposure in November, 1994 (Dockery, 1994c). Figure 12-23a,b illustrates the sensitivity of the PM_{10} RR to the lag time or moving average model in the Poisson regression for St. Louis total mortality, and Figure 12-24a,b shows the analogous plot for the eastern Tennessee area. Models were fitted for lags from 0 to 4 days, and for the lagged moving average from the two preceding days. The lag 1 and 2 RR estimates for St. Louis, and the lagged 2-day moving average were statistically significant for the St. Louis mortality series, but no PM indicator had a statistically significant RR for PM_{10} in the eastern Tennessee mortality series even though the RR estimates were numerically very similar. Longer-term moving averages were not evaluated,

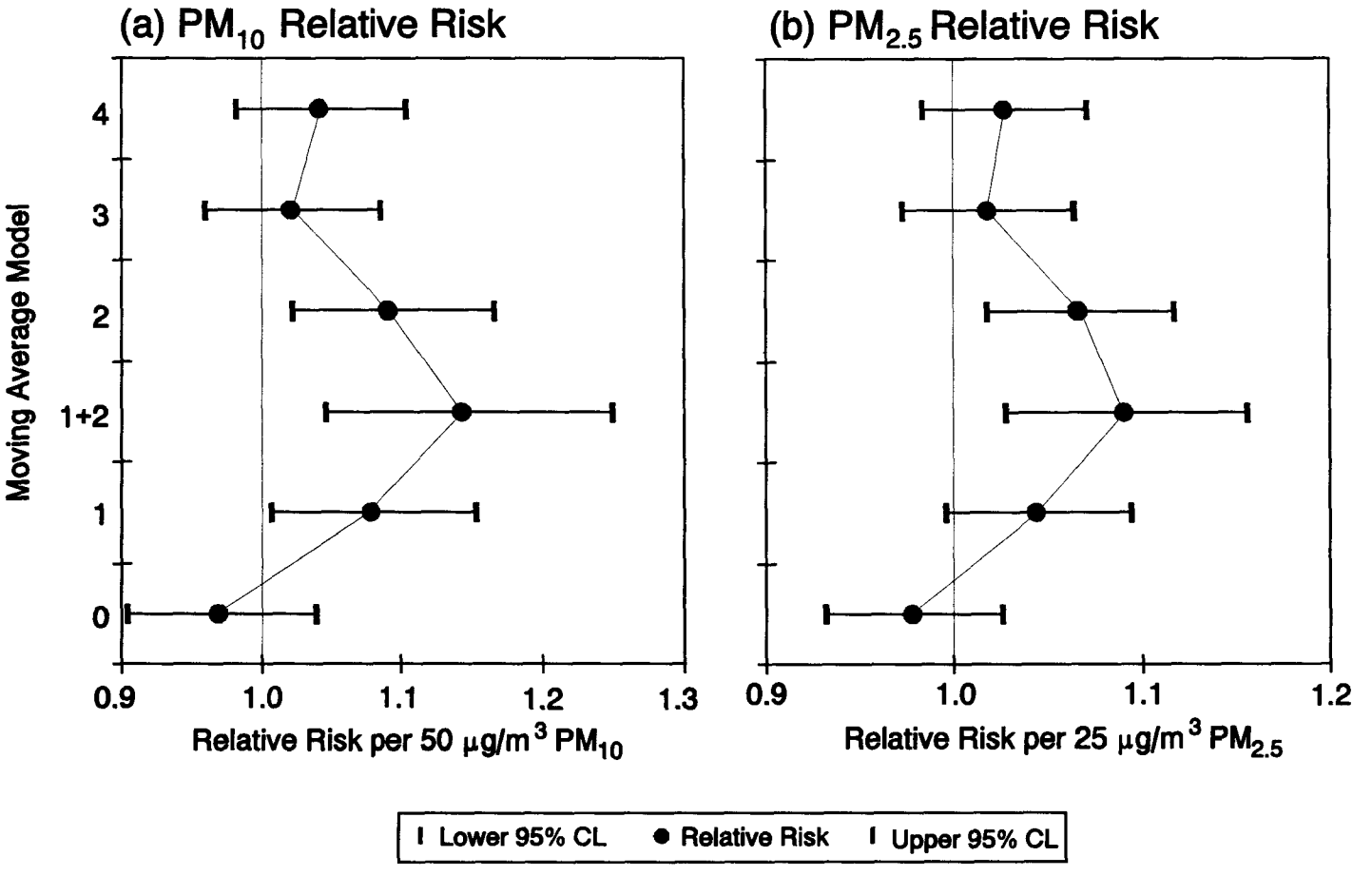

Figure 12-23a-b. Relative risk of total mortality for particulate matter in St. Louis, as a function of moving average and lag times: (a) PM_{10}; (b)$PM_{2.5}$.

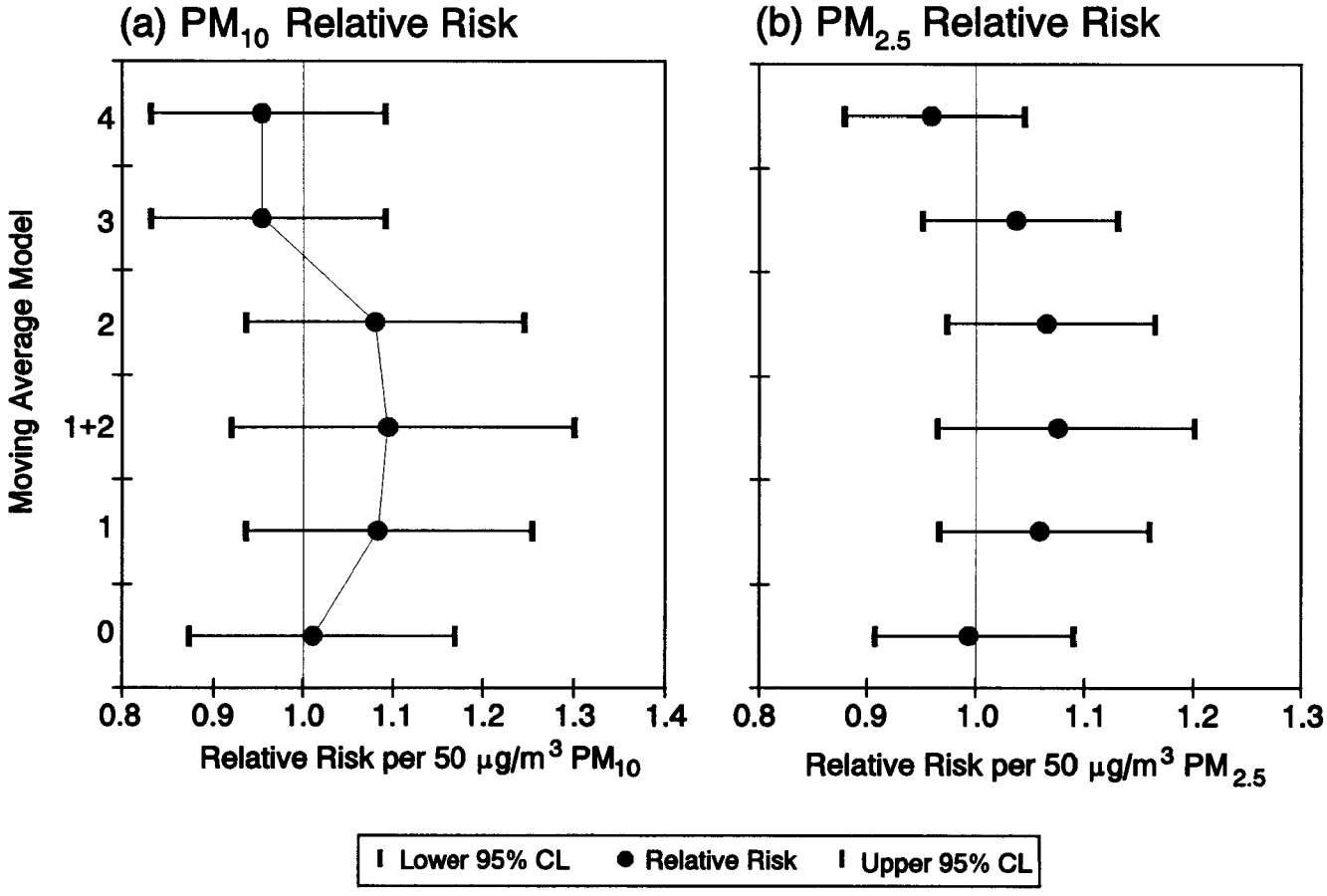

Figure 12-24a-b. Relative risk of total mortality for particulate matter in eastern Tennessee as a function of moving average and lag times: (a) PM_{10}; (b) $PM_{2.5}$.

but the effects of PM_{10} would probably have been much smaller than the RR calculated using the average of 1- and 2-day lagged PM. As in the Utah Valley and Santiago studies, PM lag structure needed to be identified in order to obtain a significant PM effect.

Model Specification for the New York City Respiratory Mortality Study (Thurston and Kinney, 1995)

Thurston and Kinney compared several Gaussian OLS time series models with a Poisson regression model, using respiratory mortality data for New York City for 1972-1975. Time series were done using both unfiltered mortality and pollution data, and filtered mortality and pollution time series using a 19-day moving average. Analyses were done using year-round unfiltered OLS, April-September OLS, April-September filtered OLS, April-September adjustments by sines and cosines, and April-September Poisson regression adjusted with sines and cosines. During the April-September ozone season, the unfiltered OLS model showed a strong significant COH effect, but the COH effect size decreased to small and nonsignificant values when the filtered or detrended analyses were performed. The ozone effect size decreased somewhat from the unfiltered OLS analysis, but was similar in magnitude and statistically significant using filtered or detrended OLS, or Poisson regression models.

Model Specification for the Los Angeles Mortality Studies (Kinney et al., 1995; Ito et al., 1995)

Kinney et al. (1995) have discussed a number of important model specification issues for an air pollution time series model. Figure 12-25a,b, taken from their paper, shows the RR estimates for 100 ug/m^3 PM_{10}, with alternative methods to control for temporal cycles. In general, most such adjustments for seasonal cycles using dummy variables or Fourier series (sines and cosines) reduced the RR slightly. Subsetting the data into winter and summer groups increased the uncertainty, but did not greatly affect the RR estimate. However, the summer-only RR adjusted with 4 sine/cosine terms was larger than the unadjusted annual RR, and statistically significant. Figure 12-25b shows the results of including co-pollutants, O_3 and CO. Including O_3 in the model, along with PM_{10}, did not change the RR for PM, but increased its uncertainty slightly so that the RR for PM was now only marginally significant (two-tailed test, $p < 0.05$). Including CO in the model reduced

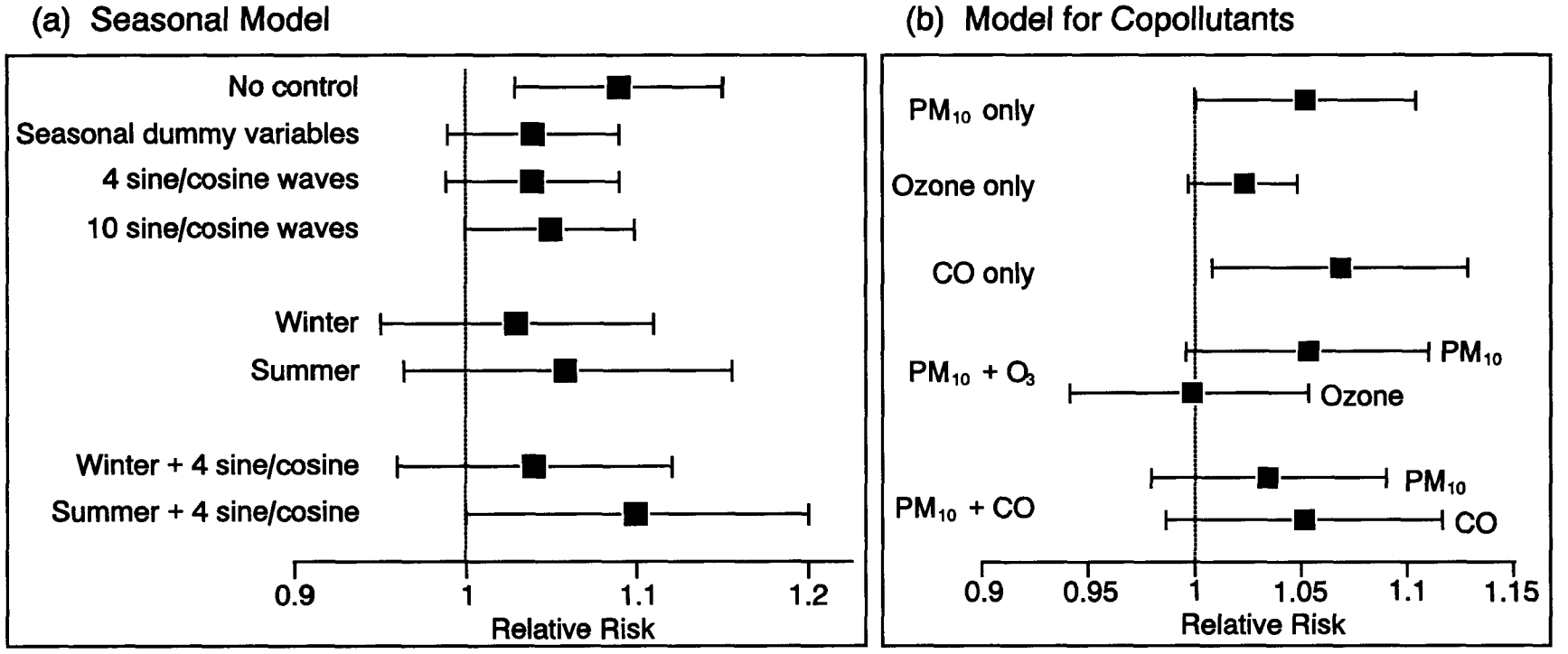

Figure 12-25a,b. Relative risk of total mortality for PM_{10} in Los Angeles, as a function of (a) seasonal model; and (b) models including copollutants.

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the RR for PM, which was also less significant. CO and O_3 were too highly correlated to use in a three-pollutant model.

Ito et al. (1995) have evaluated alternative model specifications for combining data from a network of urban monitoring stations, when one station collects data daily and others at an irregular schedule such as once-every-6-days with different days at different stations. While an important subject, this is not the primary source of concern about possible model mis-specification. The optimal use of monitoring data distributed over space and time is more likely to appear as a problem in exposure measurement error arising when any surrogate is used instead of the actual individual exposure.

Model Specification for the Chicago Mortality Studies (Ito et al., 1995; Styer et al., 1995)

Styer et. al. evaluated several alternative models for the Chicago PM_{10} study discussed in Section 12.3.1. These models assess the effects of dividing data by season. Figure 12-26 shows the RR for total elderly mortality per 50 ug/m^3 of PM_{10} in ten different models. Model 0 is their basic best-fitting model using all of the data and assuming a common PM effect for all seasons. The next eight models deal with pairs of model specifications for PM in each season. Models 1, 4, 6, 8 are based on a single model using all of the data with dummy variables for each season that allows separate PM effects in fall, spring, winter, and summer respectively. Models 2, 5, 7, and 9 are similar models fitted independently using subsets of the data for each season. Model 3 is also a separate model for elderly mortality in fall, similar to Model 2 except that the moving average for PM is 5 days, whereas all of the other models used 3-day moving averages. In general, the RR for each season did not show large differences when different estimation methods were used, but there were large differences among seasons in these analyses. The only statistically significant RR were fall and spring. The winter and summer seasons had RR for PM that did not differ significantly from 1.0.

Ito et al. (1995) also evaluated alternative model specifications for combining data from a network of urban monitoring stations in Chicago. Relative risks for models with daily

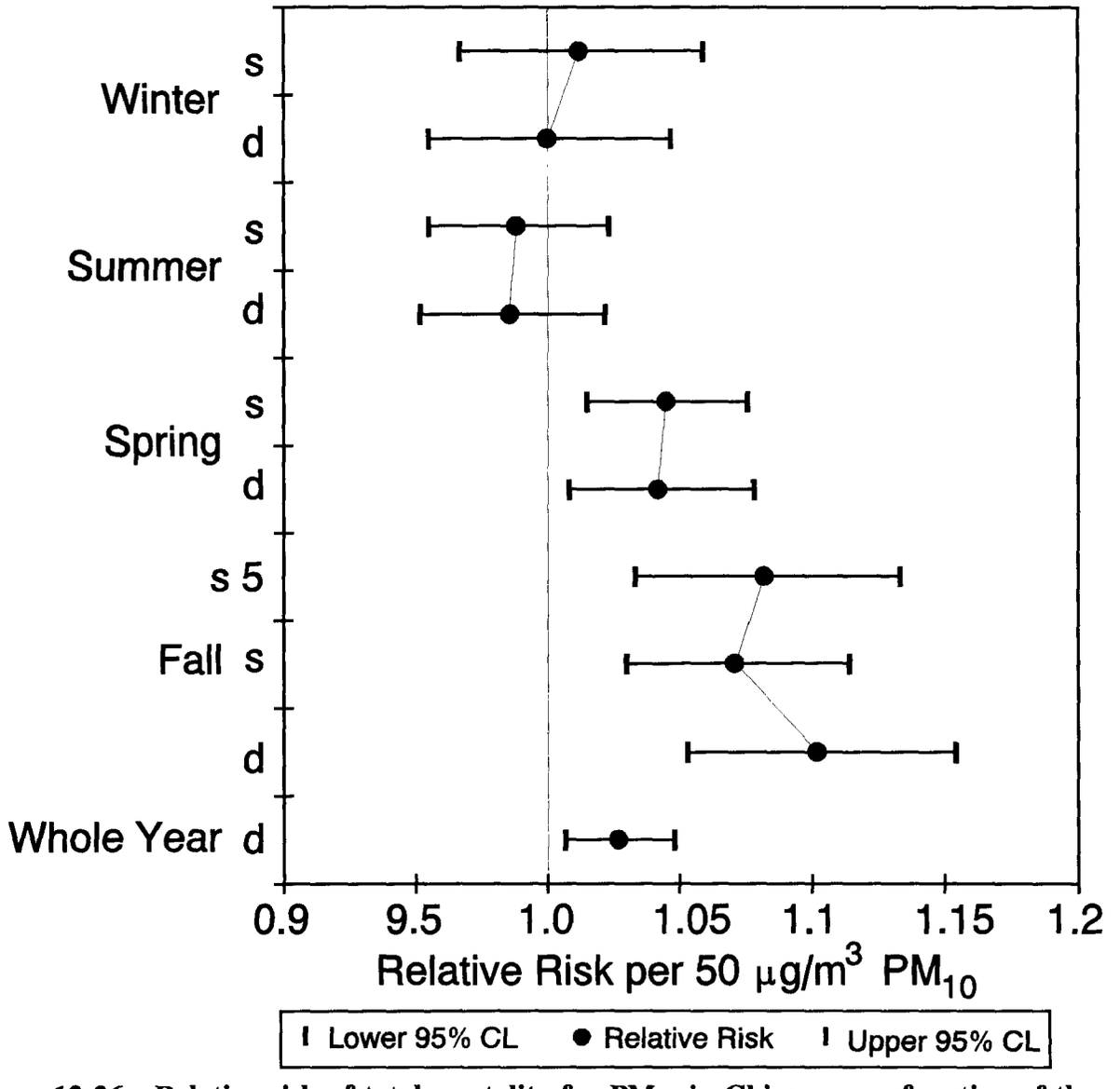

Figure 12-26. Relative risk of total mortality for PM_{10} in Chicago as a function of the model for co-pollutants.

Source: Styer et al., 1995.

PM_{10} were statistically significant using any of several alternative averaging models, such as averaging from all non-missing sites or averaging from all sites using regression-imputed PM_{10} for missing sites. Data from some individual sites also gave significant PM effects, but models using every-6-day data were generally not significant, typically because the estimated RR had greater uncertainty when only 1/6 as many data were available.

Model Specification for the Steubenville Mortality Studies (Schwartz and Dockery, 1992b; Moolgavkar et al. 1995a)

Two papers have assessed alternative treatments of a single data base, air pollution and mortality data from Steubenville for 1974-1984, and more recently 1981-1988 (Moolgavkar et al. 1995a). The initial analyses by Schwartz and Dockery (1992b) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (same day and lagged one day), and seasonal indicators. Neither same-day nor lagged temperature and dewpoint were statistically significant, nor the square of these variables, nor indicators for hot days ($>$ 70 °F). However, humidity measured by mean dewpoint temperature was nearly statistically significant at the 0.05 level, and an indicator for days that were both hot ($>$ 70°) and humid (dewpoint $>$ 65°) was a statistically significant predictor of mortality. Sensitivity analyses included putting both average of same-day and previous day TSP and SO_2 in the model, omitting weather and season variables, including year of the study as either a random effect or as a fixed effect (no year was significant), and including an autocorrelation structure. As expected, including SO_2 reduced the TSP effect, but the decrease was small, with RR for TSP decreased from 1.04 without including SO_2 to 1.03 per 100 ug/m^3 when SO_2 was included, and the SO_2 coefficient was not significant whereas the TSP coefficient was still statistically significant. As shown in Figure 12-27a, these had little effect on the estimated relative risk for 100 ug/m^3 TSP. This paper also demonstrated the use of TSP quartiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

Moolgavkar et al. (1995a) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. The whole-year models analogous to those of Schwartz and Dockery (1992b) are also shown in Figure 12-27a. The results are close to those of Schwartz and Dockery, but are not identical. The RR for 100 ug/m^3 TSP are somewhat smaller, but the decrease is only from about 1.032 to 1.025 when SO_2 is included in the model. These coefficients are for what Moolgavkar et al. define as the "restricted" mortality data set, which consists of deaths in Steubenville of people who resided

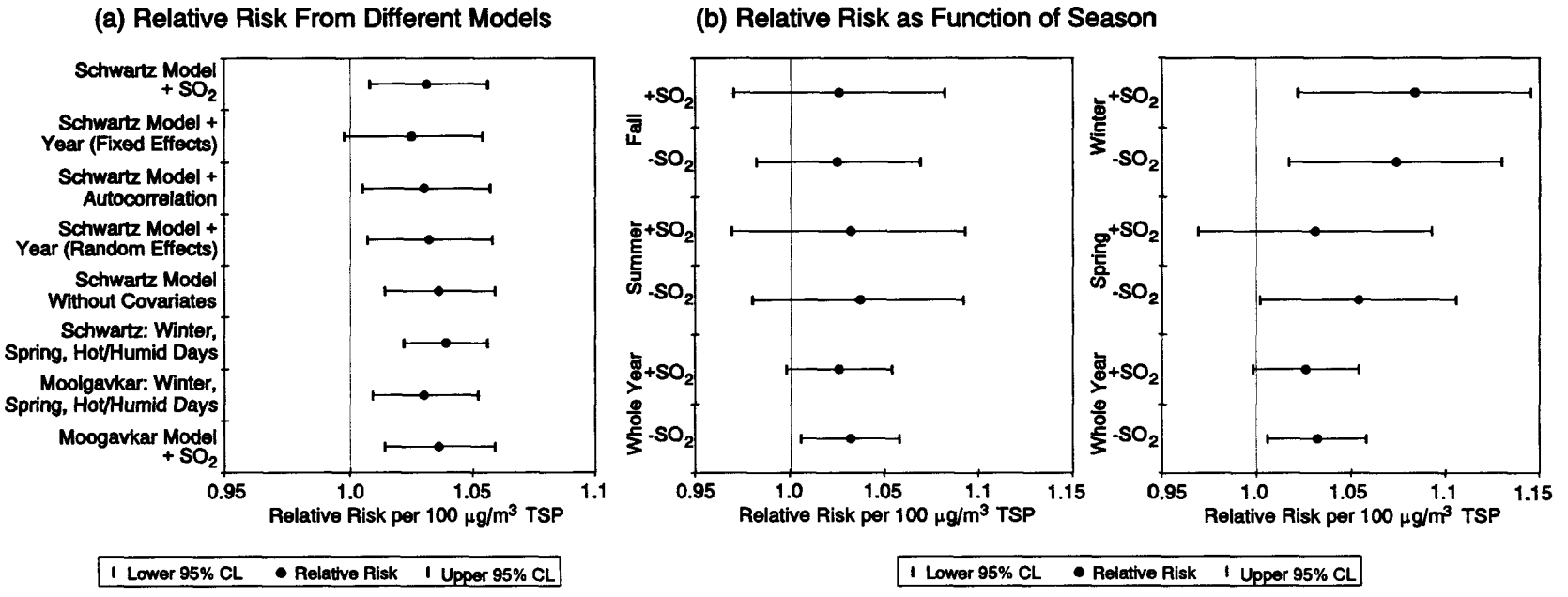

Figure 12-27a,b. Relative risk of total mortality for TSP in Steubenville: (a) different models (left); and (b) as a function of season (center, right).

Sources: Schwartz and Dockery 1992b; Moolgavkar et al. 1995a.

there. This is comparable to the data set used by Schwartz and Dockery in this study, and by Schwartz or Dockery and their associates in many other studies. The argument for use of the "restricted" mortality data is that community-based air monitors provide better exposure indicators for people who live in the community most of the time, as opposed to commuters or to other visitors who die in the community. Also, since many metropolitan areas contain medical facilities that may be better equipped than those in more remote areas, it is possible that some excess number of the deaths in elderly or ill patients transported from the more remote areas occur in urban centers such as Steubenville. Moolgavkar et al. (1995a) also show results for analyses of "full" mortality data, which includes individuals who did not reside in the location at which they died.

It is clear that season-to-season effects are present in these data. Schwartz and Dockery found that winter and spring mortality was significantly higher than summer and fall mortality. Moolgavkar separated the analyses by season. He found that whole-year RR for TSP was nearly the same as RR in the separate summer and fall models, with or without SO_2 in the model, and nearly the same in the spring model when SO_2 was included. However, TSP coefficients were higher in the winter, and in the spring model when SO_2 was not included. In fact, as shown in Figure 12-27b, the RR for TSP increased slightly in the winter model when SO_2 was included.

There is a possibility that the weather model used by Schwartz and Dockery, and by Moolgavkar et al., are not adequate to remove all of the seasonal effects. It is possible that additional variance reduction could have been achieved with the use of additional weather data, emphasizing more extreme conditions than the very moderate cutpoints of temperature and dewpoint, since temperature extremes are known to have effects on mortality (Kalkstein et al., 1991, 1995; Kunst et al., 1993). Variables used by other investigators, such as barometric pressure, could have been tested. The flexibility of the model to fit nonlinear relationships could be improved by the use of nonparametric or semi-parametric models, and classifying data by synoptic weather category may provide a useful alternative approach to evaluating the interaction between season and weather.

Moolgavkar found that the TSP coefficients were not statistically significant (two-tailed tests at 0.05 level) in any season except winter, nor in the whole-year model, when SO_2 was included in the model. However, the season-by-season TSP coefficients were not tested in a

whole-year model. Part of the non-significance may be attributable to the fact that confidence intervals for a regression parameter in a separate seasonal model, with about 1/4 of the data in a whole-year model, may be on the order of twice (= reciprocal square root of 1/4) as wide as the confidence interval for the corresponding season-by-pollutant regression coefficient in a whole-year model, everything else being equal.

The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and why those derived by Moolgavkar et al. are quantitatively different from those derived by Schwartz and Dockery (1992b), even though the differences are small in these studies. There may exist some residual confounding with weather, since other studies have found that substantial adjustment of weather by use of temperature and dewpoint categories, or nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in Steubenville models including the collinear co-pollutant SO_2. No adjustments were made for other pollutants such as CO, NO_x, and O_3.

These analyses of the Steubenville data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not PM_{10}. These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations. When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to SO_2. Differences in RR of TSP between analyses presented in the two papers are not regarded as large.

Model Specification for Philadelphia Mortality Studies (Schwartz and Dockery, 1992a; Li and Roth, 1995; Moolgavkar et al. 1995; Wyzga and Lipfert, 1995)

Several papers have recently appeared that allow assessment of alternative treatments of a single data base, the air pollution and mortality data from Philadelphia for the years 1973 to 1980, and more recently 1981 to 1988 (Moolgavkar et al. 1995b). The initial analyses by Schwartz and Dockery (1992a) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (lagged one day), winter season temperature (same day), and an indicator for hot days (> 80 F). Sensitivity analyses

included putting both average of same-day and previous day TSP and SO_2 in the model, stratifying analyses as above or below median SO_2 level (18 ppb), omitting weather and season variables, and including day of week. As shown in Figure 12-28, these had little effect on the estimated relative risk for 100 $\mu g/m^3$ TSP. RR for mortality in the elderly was greater than for other age groups. A more detailed assessment of the age structure was presented by Schwartz (1994), showing clearly that there was increased mortality in ages 65 to 74, and again higher at ages 75+. There was also significantly increased mortality at ages 5 to 14 years, based on a small number of cases. This paper also demonstrated the use of TSP quantiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

Li and Roth (1995) reanalyzed these data, but only reported results in the form of t-statistics. A wide range of model specifications were tested, although some models (such as those using deviations from mean values for day of year, or from monthly average) appear to assume an unrealistic level of seasonal recurrence of air pollution and weather effects. The model most directly comparable to the Poisson regression models used by Schwartz and Dockery (1992a). The autoregressive model they denoted AR(6) was somewhat comparable to models tested in the London analyses of Schwartz and Marcus (1990). The models with residual deviations of mortality from 7-, 15-, or 29-day moving averages did not have comparably filtered predictors on the "right" side of the prediction equation, however, so the regression coefficients are not readily interpretable as predictions of mortality deviations from mean pollution levels. The Poisson log models that are most comparable to those used by other investigators involved comparisons of model specifications for averaging times. The results only indicate statistical significance by use of statistics, not effect size in any form more useful in epidemiologic studies (Greenland et al., 1986). In a model that includes TSP, SO_2, and O_3, statistical significance of TSP is clearly highest with the moving average of 0+1 day lags, and diminishes sharply for all pollutants when longer lags are included. Models with longer weather averages are also more predictive. The lower significance of the TSP term may be related to the fact that it may have greater exposure measurement error

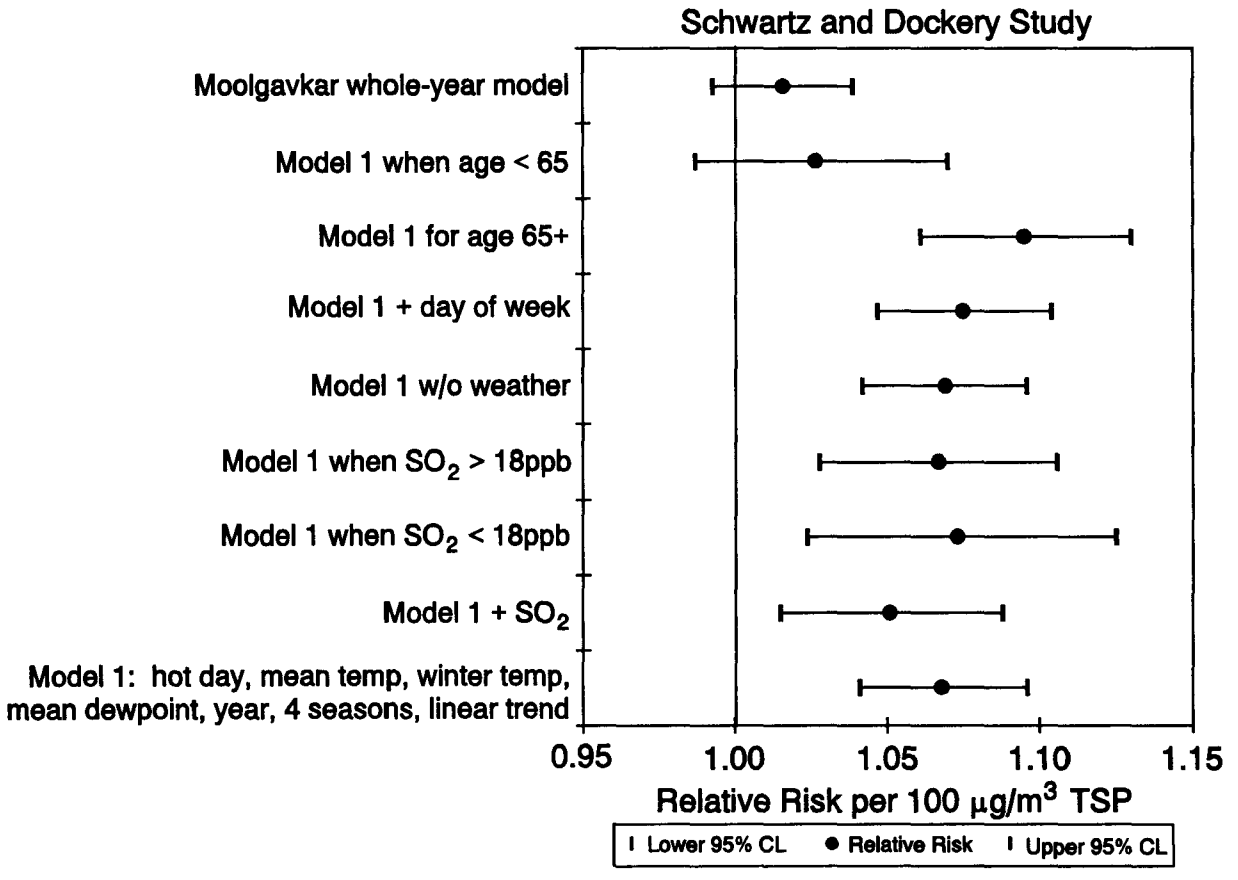

Figure 12-28. Relative risk of total mortality for TSP in Philadelphia.

Sources: Schwartz and Dockery 1992a; Moolgavkar et al. 1995b.

than the gaseous pollutants. The models being evaluated in this paper have not been adjusted for collinearity even though there are some fairly strong collinearities in the data, such as between TSP and SO_2, and between temperature and ozone, so that inclusion of several collinear variables is almost certain to greatly inflate the variance and thus to reduce the statistical significance of many of the regression coefficients.

Moolgavkar et al. (1995b) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. These are shown in Figure 12-29a-d. It is clear that season-to-season effects are present in these models. The models were adjusted for weather and time trend by using quintiles of temperature and indicators of year. There is a possibility that the weather model is not adequate to remove all of the seasonal effects. Subdividing the temperature range by quintiles will result in three or four closely spaced

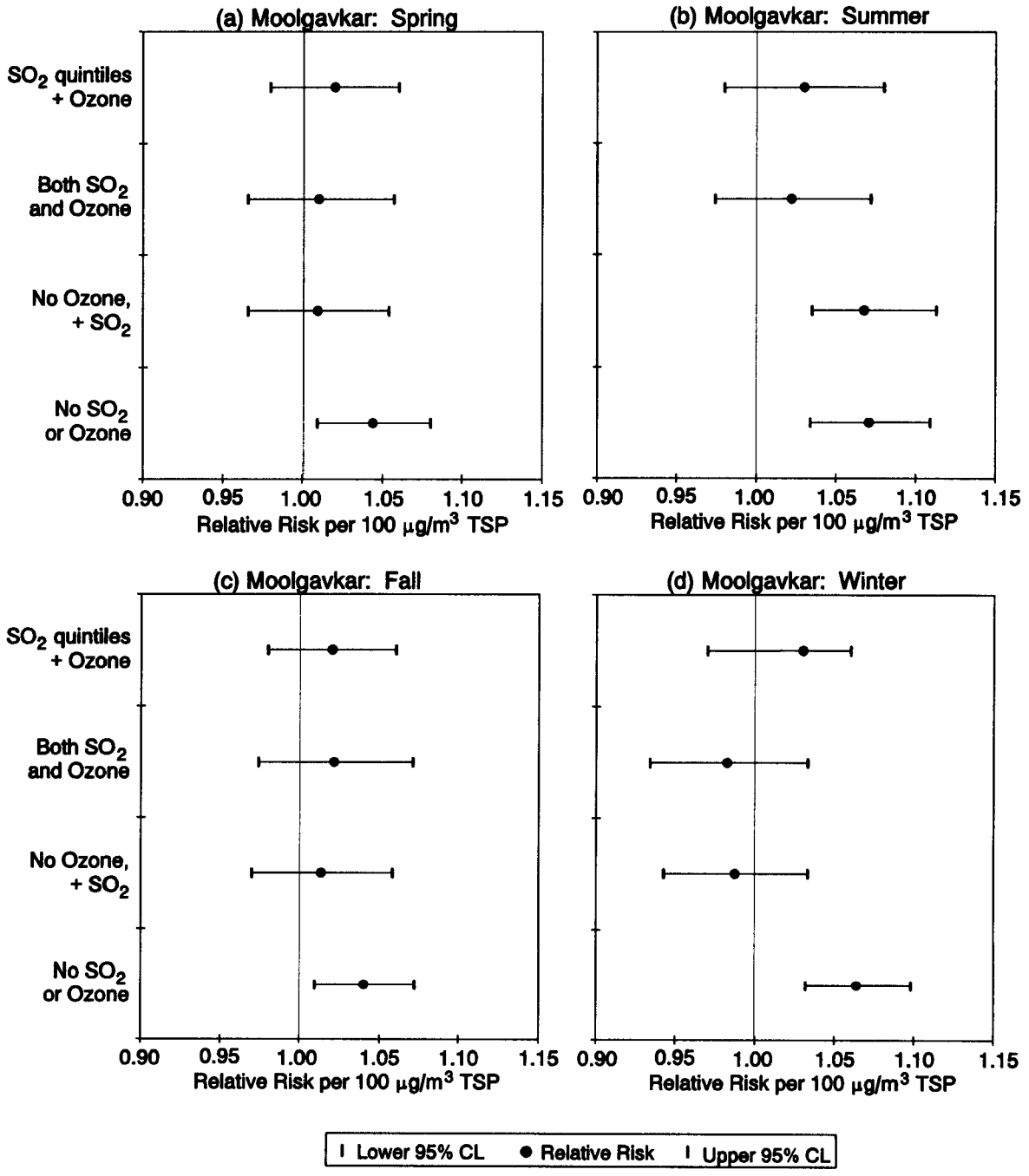

Figure 12-29a-d. Relative risk of total mortality for TSP in Philadelphia, in the (a) spring; (b) summer; (c) fall; and (d) winter.

Source: Moolgavkar et al., 1995.

quintiles corresponding to moderate temperatures which have little effect on mortality, and will not adequately take into account temperature extremes. Quintiles of temperature are not given here, but Li and Roth (1995) report values of maximum temperature at the 10th, 25th, 50th, 75th, and 90th percentiles as 37, 48, 63, 78, and 84 degrees F; (Schwartz and Dockery (1992a) report mean temperature percentiles corresponding to 25, 36, 52, 66, and 73 degrees F, respectively. This paper finds a significant effect for the highest quintile in the summer, and the lowest quintile in the other seasons. This suggests that additional variance reduction could have been achieved with the use of additional weather data, emphasizing more extreme conditions than the 20th and 80th percentiles, and possibly including information on dewpoint or barometric pressure, as used by other investigators. In general, replacing numeric data by grouped equivalents such as quintile classes involves some loss of information. The loss of information may be acceptable if there is a corresponding increase in the flexibility of the model to fit nonlinear relationships, but in this instance the loss of information may be substantial since extreme temperatures are known to have a quantifiable and increasing relationship with mortality as the temperatures become more extreme (Kunst et al., 1993). The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and are quantitatively different from those derived by Schwartz and Dockery (1992a). There may exist some residual confounding with weather, since other investigators have found that substantial adjustment of weather by use of temperature and dewpoint categories, or nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in models including collinear co-pollutants SO_2 and O_3.

Neither the Schwartz and Dockery (1992a) study nor the Moolgavkar et al. (1995b) study allows a complete assessment of the actual role of co-pollutants as confounders of a PM effect. While SO_2 is not as strongly correlated with temperature as is O_3, it is also subject to weather conditions that affect atmospheric dispersion along with TSP. Therefore, if there is an incorrect assignment of weather effects on mortality, some part of the mortality that could have been explained with weather-related variables will probably be allocated to various other predictors of mortality used in the models, especially TSP and the co-

pollutants. The development of a predictive model for mortality using weather and other time-varying covariates would probably have required use of humidity, since humidity along with temperature had been predictive of mortality in earlier studies such as London (Schwartz and Marcus, 1990) and Steubenville (Schwartz and Dockery, 1992b). If confounding can be explained by an unobserved (or in this case, unused) covariate, then omission of humidity from any of the models in the Moolgavkar et al. (1995b) study is certainly another candidate explanation for the differences in results between these papers. However, both papers may also have provided an inadequate adjustment for other medium-term effects on a scale longer than a day and shorter than a season or quarter, such as epidemics. The use of nonparametric smoothers such as LOESS, or GAM models of time, would allow subtraction of such trends. Even a simple alternative, such as including a dummy variable for every month in every year (96 parameters for the 1973-1980 series; another 96 parameters for the 1981-1988 series) would probably have greatly improved the ability of these analyses to evaluate short-term responses to short-term changes in air pollution and weather. The parameters that relate mortality to pollution and weather over intervals of a few days were likely the same or similar over periods of some years, and would require only a few more parameters. In view of these questions, we regard potential confounding among TSP, SO_2, and summer ozone in Philadelphia that was identified in the Moolgavkar et al. (1995b) study as possible, but not yet proven.

Another unresolved issue is that TSP may have relatively large exposure measurement error than the gaseous pollutants. Since TSP includes large particles, there is more association of TSP levels with local sources and transport near the air pollution monitors, and a weaker correlation with TSP at other monitors than is the case of smaller particles. In particular, TSP would be expected to show less correlation within the Philadelphia region than would PM_{10}, and even less yet than would $PM_{2.5}$ across the region. Therefore, TSP may be less predictive of individual PM exposure than the gaseous pollutants in Philadelphia. Since variables with larger exposure measurement error are more likely to show attenuated effects (bias towards smaller RR) than covariates with smaller measurement errors, it is at least possible that SO_2 may appear to be a more important predictor of pollution-related mortality than does TSP. There does not seem to be any way to evaluate these possibilities from the published reports.

Wyzga and Lipfert (1995) also reanalyzed the Philadelphia time series data for 1973 to 1990, using Gaussian OLS regression models with time-lagged predictors. In view of the moderately large number of deaths per day (21 deaths at ages less than 65 years, 34.5 deaths at ages 65 and older), the OLS regression coefficients are probably sufficiently accurate approximations to regression coefficients estimated from Poisson regression models. They evaluated model specifications for daily mortality, log mortality, and deviations of mortality from 15-day moving averages. The regression models were adjusted for maximum temperature dummy variables in 6 categories, winter season, daily changes in barometric pressure, and time trend. Maximum hourly ozone was used as a co-pollutant. RR estimates for TSP were calculated using regression coefficients and standard errors in their Table 3, plus data from their Figures 14 and 20. Figure 12-30a shows RR for ages <65 years, Figure 12-30b for ages 65+ years, for all days (N = 2380) and for N=390 hot days (maximum temperature at least 85 degrees), for different averaging times. The largest and most significant estimates of TSP effect, measured as deviations from 15-day moving averages, are in the elderly, especially on hot days. For the elderly on hot days, the TSP effect is nearly the same for averaging times from 2 to 5 days on hot days, but the 0+1 day moving average has only slightly greater statistical significance than thee 0+1+2+3 and 0+1+2+3+4 day averages. When all days are considered, the RR for TSP is only half as large, and statistically significant only for 0+1 day TSP averages. For deaths at age <65, none of the all-day TSP were significant; on hot days, the 0+1 average TSP was nearly significant, and the 0+1+2 day average TSP effect nearly as large, but other RR estimates were much smaller. The estimates were not calculated using filtered pollution series, but the moving averages of TSP had some of the same effect of removing long-term trends and effects. These estimates are in general similar to those found by Schwartz and Dockery, but larger differences were found for other model specifications. This paper did not attempt to include SO_2 as a covariate, since TSP was clearly collinear with SO_2.

These analyses of the Philadelphia data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not PM_{10}. These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations.

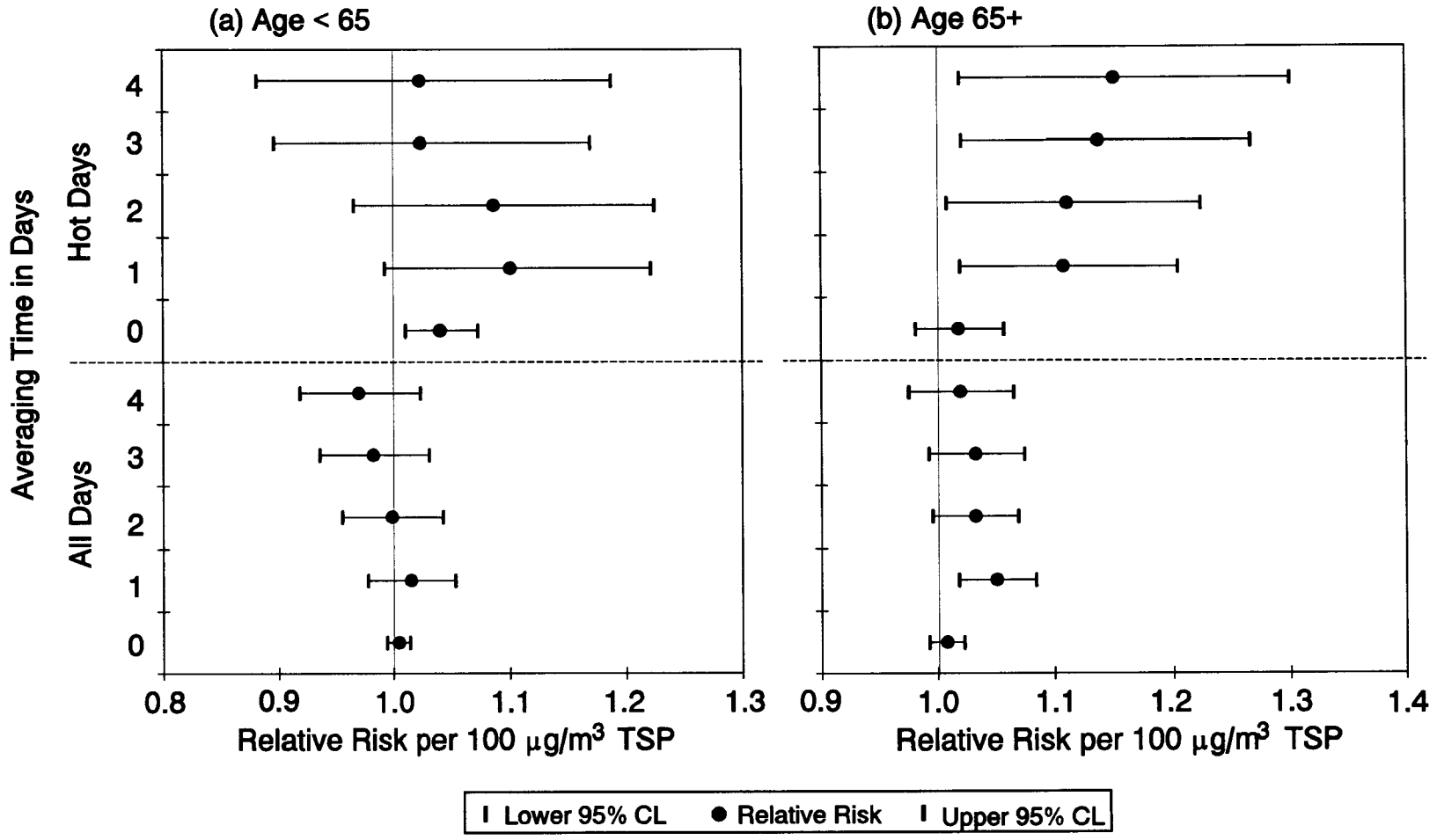

Figure 12-30a,b. Relative risk of mortality for TSP in Philadelphia, as a function of age, averaging time, and temperature: (a) Age < 65; (b) Age > 65.

Source: Wyzga and Lipfert, 1995.

When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to ozone, and that the ozone effect was more nearly confounded with temperature and season than with TSP. However, there was a substantial degree of confounding between TSP and SO_2 effects, which could be separated in some analyses but not in all analyses. The best averaging time for pollution was 0+1 days, but longer averages seemed useful in estimating RR among the elderly during hot weather.

Model Specification for Other Mortality Studies

Other studies on acute mortality have evaluated alternative model specifications. A number of OLS and time series regression models for COH in Santa Clara were compared by Fairley (1990). Mortality studies by Schwartz for Detroit (Schwartz 1991) and Birmingham (1993a) evaluated other regression and time series approaches. These are not reported in as much detail as the studies cited here, and the Detroit study also uses estimates for PM.

12.6.2.2. Model Specification for Morbidity Studies

There have been a large number of recent studies on hospital admissions related to PM (Schwartz, 1993b, 1994b, 1994e, 1995a, 1995b, 1995c). These have used generally similar strategies for evaluating alternative Poisson regression models. The basic model includes a set of variables for temperature and dewpoint (usually in 6 to 8 categories), linear and quadratic time trends, indicators or dummies for each month in each year (so that no assumptions need to be made about recurrent seasonal or monthly effects), and the PM indicator. Alternative model specifications usually include: (1) piecewise cubic spline functions for time trend, temperature, and dewpoint; (2) generalized additive models (GAM) for time trend, temperature, and dewpoint; (3) basic model, excluding all non-attainment days (PM_{10} > 150 ug/m^3, or ozone > 120 ppb, etc.); (4) basic model without hot days; (5) extended range of lag times or moving averages; (6) basic model plus co-pollutants. Differences in RR for PM among most specifications is small. RR estimates from the GAM method tend to be higher than most other specifications, but the conclusions about RR are fairly insensitive to alternative specifications. Since there have been no studies that disagree with these conclusions, we will not review these in detail, since the assessments are in many ways similar to those for the acute mortality studies.

12.6.2.3. Model Specification Issues: Conclusions

Published research articles have provided a substantial amount of evidence about the consequences of different model specifications for short-term and long-term models. The short-term studies have been generally consistent across many different kinds of model specifications. While it is tempting to conclude that differences in model specification produce only minor differences in estimates of PM effects, that is clearly not the case. The general concordance of PM effects, particularly in analyses of short-term mortality studies, is a consequence of certain appropriate choices in modelling strategy that most authors have adopted but the results are not dictated by the use or misuse of any specific model. Some features of the more useful models are described below.

12.6.3 Other Methodological Issues for Epidemiology Studies

The issues in air pollution epidemiology for PM are similar to those of many other pollutants. No single air pollutant, nor any mixture such as PM or an identifiable component of PM, is uniquely related to a specific health outcome and individual exposure measurements are generally lacking, with exposure to PM typically measured at only one site in an urban or regional airshed or, at most, at a few widely spaced sites. U.S. studies of acute mortality typically depend on combining three data bases: (1) mortality data tapes provided by the National Center for Health Statistics (NCHS); (2) air pollution data sets for urban areas, accessed through the Aerometric Information Retrieval System (AIRS) network; and (3) meteorological data for urban areas and smaller SMSA's, obtained from the National Climatic Data Center (NCDC). Hospital admissions data involve a more diverse set of sources. Merging the data sets has not always been a straight-forward task, and attempts to replicate results have sometimes been complicated by the fact that different investigators have used different approaches to creating a merged data set for subsequent analyses. As a simple example, the PM_{10} monitoring data for Chicago consists of every-day monitoring at one site and every-6-days monitoring at up to eight other sites. In that ease, different investigators may calculate different PM_{10} concentrations according to how the data from the intermittent monitoring sites are combined with data from the every-day site. In this section, we will discuss specific methodology issues encountered in the studies reviewed earlier.

12.6.3.1 Particulate Matter Exposure Characterization

PM_{10} measures the inhalable particles better than TSP. The NAAQS are specified by PM_{10} concentrations, which were not generally available before 1986. PM_{10} is also a better index of ambient fine particle exposure than TSP because it is more uniformly distributed in an urban area or region than TSP. Since fine particles from outside can also penetrate indoors and constitute a major fraction of indoor air concentrations, PM_{10} is also likely to be a better index of indoor air exposure to fine particles than TSP. Currently, data on AIRS do not allow discrimination among important components of PM_{10}, including fine particles, coarse particles, or sulfates. In the absence of any clearly demonstrated mechanistic relationship between PM components (by size, composition, or source) and specific health endpoints, there is little a-priori reason to believe that health endpoints related to PM should not be predicted well in different studies by different PM indices. The indices include PM_{10}, fine particles (defined as $PM_{2.5}$), coarse fraction of PM_{10} particles (defined as PM_{10} - $PM_{2.5}$), or surrogates that may be more closely correlated with fine particles than to coarse particles, including sulfates, SO_2, and even TSP. Results presented by Dockery and Pope (1994) suggest that $PM_{2.5}$ may be a more appropriate "proxy" of exposure to particles that are predictive of health effects.

While $PM_{2.5}$ particles are more likely to be uniformly distributed within an urban airshed, and are more likely to penetrate indoors so that outdoor ambient fine particle concentration becomes a better predictor of total fine particle exposure than ambient coarse particle concentration does for total coarse particle exposure, it is not clear that coarse particle concentration can be neglected in terms of its health effects. While sulfates are a significant part of fine particle levels in some places, they may be of more limited value as an indicator of a toxic component of PM_{10} due to measurement artifacts (filter artifacts). The usefulness of sulfate data may also be limited because high levels are reached only in the eastern and southeastern U.S., mainly during the summer. Information on other components of PM_{10}, including acidity, metal ions, and organic components, is often not available. Similarly, data deficiencies exist for most co-pollutants. In studies where SO_2 is a good proxy for PM_{10}, it may be difficult to assign effects to one or the other without evaluating the relationships linking the two, since SO_2 is the source of some fraction of particle sulfates.

Chapter 7 on Human Exposure to PM indicates that variations in ambient PM concentration may have limited influence on the variation of individual personal PM exposures as measured by personal monitors. However, although individual exposures may not be well correlated with ambient PM concentrations measured at representative fixed ambient monitoring site(s), the mean personal exposure of people in a community is expected to be better correlated to the ambient concentration. In terms of community air pollution, a properly sited ambient PM measurement is reasonably related to the mean personal PM exposure of the community, although it will not be a good indicator of any single individuals' daily PM exposure. The important consideration here is that the ambient monitors be properly sited. This would have to be evaluated study by study, which can be difficult or impossible if data has not been reported in the study. There must be limits to the acceptability to using a monitor for daily level changes in both distance from the population and terrain between population and monitoring site.

Data are available at more than one monitoring site in a few studies, including Birmingham AL (Schwartz, 1993, 1994), Utah Valley (Pope et al., 1992, 1994), Los Angeles (Kinney et al., 1991, 1995), San Francisco Bay area (Fairley, 1994), Philadelphia (Wilson et al., 1995), and Chicago (Ito et al., 1994, 1995; Styer et al., 1995). While PM_{10} varies from place to place, with a decreasing correlation across a metropolitan area, measurements are well correlated up to a few kilometers. FP ($PM_{2.5}$) is particularly well correlated across a metropolitan region.

Exposure Relevance

The majority of the PM data used in the PM/mortality literature are daily observations, rather than the standard every-6th-day observations. The ambient daily mean PM levels reported in these PM/mortality studies of U.S. cities range from 28 $\mu g/m^3$ (St. Louis, MO) to 58 $\mu g/m^3$ (Los Angeles, CA) for PM_{10}; 76 $\mu g/m^3$ (Cincinnati, OH) to 111 $\mu g/m^3$ (Steubenville, OH) for TSP. Other PM indices in the literature include COH in Santa Clara County, CA; and KM (mean = 25) in Los Angeles County, CA. The data description reported for these PM indices indicate a generally skewed distribution, and the maximum daily values deviate about 50 to 150 $\mu g/m^3$ from these means. The current 24-h standard, 150 $\mu g/m^3$, is rarely exceeded in these communities. Many of these communities studied

were urban, but the PM levels observed appeared to be representative of metropolitan areas where substantial fraction of U.S. population reside.

Size and Chemistries

In theory, since TSP includes particle sizes (d_a < 50 μm) that exceed those having thoracic deposition (d_a < 10-15 μm), it is expected that TSP would be a less reliable measure of particulate matter for health effects analyses. However, comparison of the significance of the PM regression coefficients in the recent U.S. PM/mortality studies do not show systematically lower significance for TSP than PM_{10}. This may be because, so long as TSP levels fluctuate together with smaller particles over time, TSP may still be a reasonable surrogate for inhalable particles. The error introduced by large particles depends on their availability, and therefore, is site-specific.

In most of the PM/mortality studies, only one PM index was employed. An exception is the study conducted in St. Louis, Mo. and Kingston, TN (Dockery et al., 1992). In this study, PM_{10}, $PM_{2.5}$, sulfates, and aerosol acidity were available. The regression results indicate that, for both cities, PM_{10} showed the most significant mortality associations, and the significance declined as the size of the index decreased. However, the sample size of this study was relatively small (n = 300; PM_{10} coefficient t-ratio = 2.17 in St. Louis, and 1.07 in Kingston), and the sample size for the aerosol acidity was even smaller (n = 200). Furthermore, we currently do not know the extent to which the measurement errors of these different PM measures affect PM/mortality significance. Thus, it is as yet premature to relate the significance of various PM measures to size or chemistry specific causality from this study. This inability, in a sense, to distinguish the possible difference in health effects from particles of various size and chemistries that fluctuate together, is one of the shortcomings of existing time-series studies. Cross-sectional studies reported more significant mortality associations for fine particles ($PM_{2.5}$: Dockery et al., 1993; sulfates: Ozkaynak and Thurston, 1987). However, significant PM/mortality associations have also been reported in areas where summertime sulfates are not the major component of PM (e.g., winter analysis of Santa Clara, CA; Los Angeles, CA). All the PM measures in the U.S. studies do include some type of combustion source originated particles (e.g., automobile emissions in Los Angeles, sulfates in the eastern U.S.). Overall, PM composition vary

widely, not only between sites, but also over time at a single site. This represents a major challenge to any attempts to quantify the health implication of PM.

12.6.3.2 Exposure-Response Functions, Including Thresholds

A PM threshold for mortality is difficult to detect because of small numbers of deaths (especially when broken down by age group and cause of death), and because the observed PM concentration is only a surrogate for exposure. In general, the threshold question has not been extensively examined. Other model specification issues that have had little examination include non-linear transformations of pollutant variables, interactions among pollutant variables, and interactions between meteorological variables and pollutants.

Thresholds

The question of threshold is critical when extrapolation of effects from episodes to non-episode (i.e., more usual) condition is attempted. Also, a key question of interest is whether effects extend below the current standard.

Many of recent U.S. PM/mortality studies have reported PM/mortality "exposure-response" curves of the data, after controlling for weather and seasonal variables (Schwartz, 1992, 1993, 1994; Pope et al., 1992). Some of these are shown in Figures 12-31 and 12-32. They were constructed either by using quintile or quartile indicator variables in the regression, or by nonparametric smoothing (in the Generalized Additive Models), both of which should allow for possible non-linear relationships. In all the figures presented, a generally monotonic increase in mortality, as PM increases, is suggested. However, a search for a threshold from these results is difficult because of the distribution of the data. For example, in the plots of the quintile (or quartile) PM versus relative risk, the resolution of the shape of slope is determined by the number (5 or 4) of indicator categories. The lowest quintile (or quartile) could be higher than a potential threshold level (e.g., the lowest quintile of TSP was about 50 $\mu g/m^3$ in Philadelphia). Because estimation of more stable coefficients require greater number of cases, even a large dataset may not allow smaller data division than quintiles. Thus, from these results, we cannot determine if any threshold exists below about 50 $\mu g/m^3$ for TSP or 20 $\mu g/m^3$ for PM_{10}. Nonparametric smoothing of relative risk versus PM can, in theory, allow greater resolution of the shape. However, the stability of

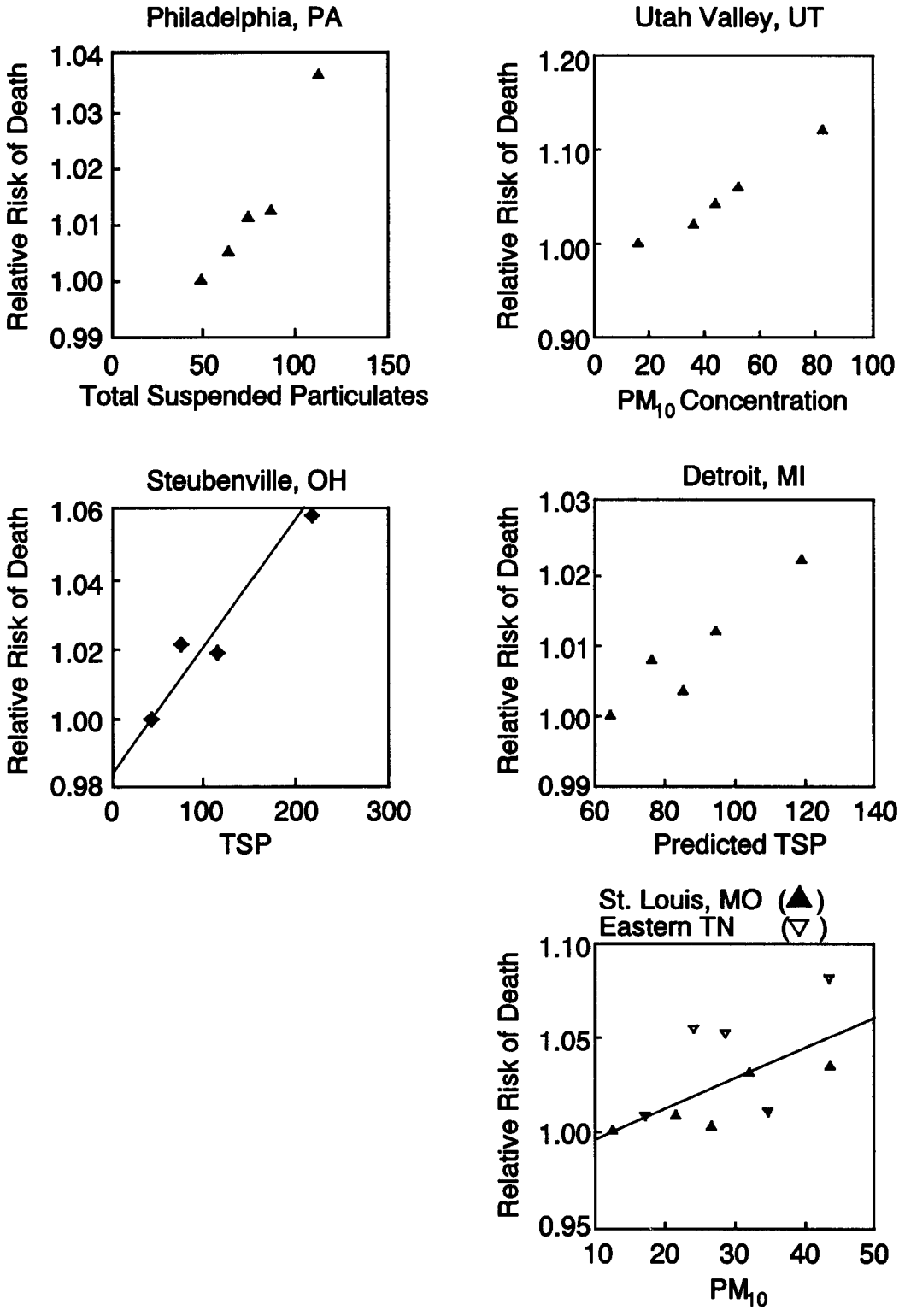

Figure 12-31 **Relative risk of mortality in five studies, where the particulate matter index is either total suspended particulates (TSP) or PM_{10}, in units of $\mu g/m^3$ grouped in quintiles. Figures are based on those in the original papers; note differences in scale.**

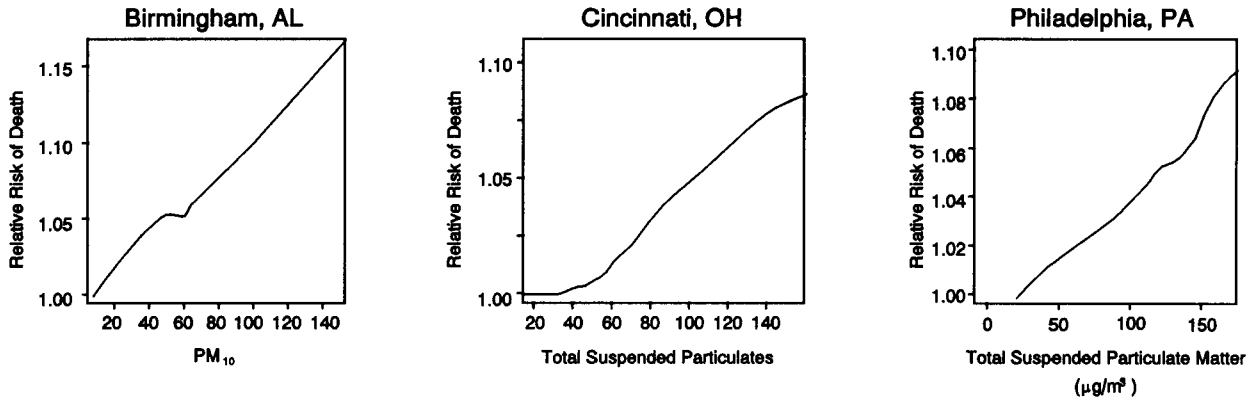

Figure 12-32. Smoothed non-parametric estimate of relative risk of mortality in three studies, where the particulate matter index is either total suspended particulates (TSP) or PM_{10}, in units of $\mu g/m^3$.

the results also depends on the weights of neighborhood and the interval of the PM, or "span", used to compute each segment of the curve (these parameters are not described in these publications). Again, these smoothed curves, as with the quintile approach, cannot describe the shape of the curve where data do not exist. For example, the smoothed curve shown for Cincinnati, OH, appears to suggest a threshold around 40 $\mu g/m^3$ of TSP, but the distribution (25th percentile TSP = 53 $\mu g/m^3$) indicates that there are not enough data points below 40 $\mu g/m^3$ to obtain stable curve shape below this level. Thus, while these figures do collectively suggest a linear-like PM/mortality relationship, any examination of a threshold level is limited by the data. Other studies did not consider or present graphical examination of the possible shape of any exposure/response relationship, and, thus, the results could have been constrained by the functional form specified in the regression model.

It is possible that there is a causal effect of airborne PM, but rather than altering the long term average mortality rate, peaks in exposure simply advance the date of death of otherwise terminally ill subjects. The terms "mortality displacement" or "harvesting" have generally been applied to this hypothesis. Under this scenario, lowering particulate matter concentrations might grant a few extra days life to a small part of the population, but have no effect on the general mortality rate. It is obviously extremely important for policy making purposes to resolve whether this is indeed the case.

Although the possibility has been discussed in several of the papers reviewed, only one (Spix et al., in press) seems to have offered a serious test of the hypothesis. They point out that the effect of harvesting should be to induce a negative effect on the autocorrelation, since " a high number of deaths on one day may leave a smaller number of vulnerable individuals at risk of dying on succeeding days." They further suggest that the magnitude of this effect should be proportional to the excess deaths due to pollution. Hence, they test the hypothesis by adding an interaction between the pollutant level on that day and the last k days mortality deviation from the expected value, where the expected value is based on a previously fitted model including trend, season, and influenza epidemics. A negative estimate for this interaction term would be interpreted as evidence for this phenomenon. Applying this test to data from Erfurt, East Germany, Spix et al. found a weak effect for suspended particles in the expected direction (nominal one-tailed $p = 0.07$ ignoring the multiple testing for k): the RR comparing the 5th and 95th percentiles of the exposure distribution was 1.51 if the previous 18 days mortality was above expected, 1.26 if it was below expected. A somewhat similar approach, examining mortality displacement from summer heat waves, has been described by Kalkstein (1994).

The statistical properties of this test merit further research. However, a full investigation of the performance of the test in realistic settings with the more sophisticated time series and GEE methods, including estimation of the harvesting parameter k is beyond the scope of this assessment.

In addition to statistical research, further epidemiologic research is warranted to better characterize the excess deaths in terms of age, cause of death, hospitalization status, prior morbidity, etc. It may be necessary to develop a multistage model, with recruitment of individuals from a healthy stage through one or more stages of morbidity until they reach a susceptible stage at which acute air pollution exposure may cause deaths.

12.6.3.3 Adjustments for Seasonality, Time Lags, and Correlation Structure

Trends, long-term and medium-term recurrent or cyclical effects, and effects of medium-term non-recurrent or random events such as influenza epidemics are removed from the data so that short-term responses to short-term changes in PM concentration can be detected without confounding or interference from longer-term effects. For Gaussian time

series models, this can usually be done well by filtering. However, filtering has the potential to remove longer-term effects of PM exposure, and therefore may underestimate the true PM effect. For example, death may occur from PM exposure during the first few days after exposure because the PM exposure may exacerbate pulmonary insufficiency in individuals whose respiratory capacity has already been compromised, especially the elderly and the ill. This may also contribute to excess short-term cardiovascular mortality. However, if PM exposure also compromises the immune system, the exposed individual may succumb to an infectious disease some weeks after the PM exposure, an effect that would be more likely to be cancelled out by application of filtering or other detrending techniques. Detrending could also be done by using regressors that are functions of the time or day of study. Candidate regressors are Fourier series (sums of sine and cosine terms), polynomial functions of time, dummy variables for year, season or quarter, month, or day of week. Fourier series are mathematically convenient, but require many terms in order to fit asymmetric seasonal variations, and cannot include random year-to-year differences in seasonal effects. Dummy variables for year, season, and month provide a great deal of flexibility, but may still be too "rough" in that such models allow abrupt changes between December 31, 1980 and January 1, 1981, between June 30 and July 1, etc. Non-parametric smoothers such as spline functions, LOESS smoothers, and generalized additive models are often good choices, but as with any other detrending procedure, the scale or span of the smooth detrender determines what medium-term effects are removed from the model.

A number of short-term studies have provided reasonable control over time-related exogenous changes. The use of tapered high-pass filters in Gaussian time series models, in connection with linear time trends or dummy variables for season or day of week, has been demonstrated in numerous papers, for example, among acute mortality studies: (Shumway et al., 1988; Schwartz and Marcus, 1990; Kinney and Ozkaynak, 1991; Ito et al., 1993; Thurston et al., 1995; Kinney et al. 1995; Ito et al., 1995).

Time-series models for non-Gaussian data (e.g., Poisson) require additional development. Various methods of accounting for longitudinal correlations have been proposed. One approach depends on filtering using either time or frequency domain methods followed by regressions based on the independence assumption. Another approach builds complicated correlation models for the residuals, and a third combines the foregoing. All

require care to avoid over-modeling that eliminates or reduces the opportunity to find the signal of interest. Random effects models are conceptually straightforward and recent developments make them relatively easy to develop. But, they cannot represent auto-regressive and other models where correlations depend on separation in time. Though one can put in lagged dependent variables to account for auto-regression, unless these are pre-whitened (represented as residuals from predicted), models may be deceptive. In models where defining residuals is a problem (e.g., logistic regression with 0/1 data), pre-whitening is a problem.

It is somewhat a matter of choice whether the analyst used covariates to remove spurious correlations or to build a covariance structure. In either approach, care must be taken to avoid inappropriately adjusting-away the effects of interest. For example, if filters are used for short-term patterns, or high-frequency sine and cosine effects are pulled from explanatory and dependent variables, they can remove the PM effect. There is no objective way to determine how far to go with these adjustments, and care is needed to remove confounders but retain power to detect an air pollution effect.

Filtering needs to be done on both sides of the equation. It may be better to include moving averages explicitly in covariate adjustments than to use filters. Unlike the acute mortality studies where some studies found that same-day or previous-day concentrations gave the best fit and other studies found that 3-day to 5-day moving averages were more predictive, the hospitalization studies found the strongest association with the current day's PM measurement. Only a few studies found strong effects with lagged measures. These studies found the greatest effect with the previous day's PM measurement, as well as an effect with the current day's PM measurement.

The analyst needs to worry about temporal correlation after pulling out fixed effects. Properly done, relatively little residual correlation should remain, but models should allow for the possibility. After filtering one still needs to include correlated error structures. Filtering can induce correlations and, more generally even filtered regressions need to be robust.

12.6.3.4 Adjustments for Meteorological Variables and Other Confounders

There has been relatively little progress in developing a systematic approach to the use of weather-related variables in daily mortality or morbidity studies. A variety of ad hoc procedures have been used. While various statistical methods for adjusting daily mortality or morbidity time series for weather effects appear to be successful on a case-by-case basis, there is little understanding of how to do this systematically in a way that appropriately characterizes current knowledge about the relationship between weather, weather changes, and changes in mortality. The empirical adjustments used in most studies are made with little theoretical basis and may be arguable for that reason alone. It is clear that the effects of some variables, such as temperature, are intrinsically nonlinear, and that it may be more useful to define the likelihood of excess weather-related mortality by the presence of clusters of related meteorological variables, such as the synoptic classes suggested by Kalkstein et al. (1994). While the synoptic class approach appears promising, it has so far been applied to relatively few cities, and may require further modification to be applicable in a general health effects modelling framework. The problem is that meteorological variables are confounded with other pollutants as well as with PM, so that any misspecifications of the relationship between health effects and weather can provide a distorted set of residual effects to be modelled using air pollution variables. A causal or mechanistic model could be useful in relating weather, season, pollutant emissions, pollutant concentrations, behavior as it affects exposure, and health endpoints. Remarkably, weather continues to be significantly related to mortality and other health effects, in spite of increasing use of air conditioning.

One interesting possibility in the use of synoptic categories has been demonstrated by Kalkstein et al. (1994). They showed that during the most offensive synoptic weather category, there may be little detectable relationship between PM and excess mortality since most of the excess is attributable to weather. During non-offensive weather categories, however, the excess mortality attributable to PM is readily detected since the weather effect is much smaller and there is a quantitative dose-response relationship between PM and excess mortality, as shown earlier in Figure 12-2 for Philadelphia.

Weather/climate control between studies has been discussed by Schwartz (1994a,b), Dockery and Pope (1994) and others as a qualitative issue rather than as a formal numerical evaluation. These papers present global comparisons of RR between cities studied that are

labeled as warm or cold cities, based on longer term mean temperature. Since the actual study analysis looked at day to day changes, long-term comparisons of means may not be as informative or appropriate to examine in such a global manner. First, it is not clear that the classification of a city as a warm or cold climate is correct. This dichotomy does not consider moderate climates in a continuum as a factor, so the comparison may not be appropriate. Second, the mortality in the studies is examined on a daily basis as is the temperature. Mean comparison over several months of temperature is an inappropriate control for the study design. Appendix 12A discusses aspects of these concerns in more detail.

Infectious Disease (Influenza)

Control for confounding with infectious diseases (influenza) by focusing on epidemics, rather than the day to day variation of the infectious disease, may not be the most appropriate model. Pollution may peak in one season and disease epidemics may peak in another season. Statistical adjustment may control for epidemics, but may not adequately account for the day to day variation below the epidemic level. The PM mortality effect has a small RR. The influenza factor which may control for epidemics may be small also. Influenza effects may be modeled more accurately using estimates of weekly or daily variation along with pollution and mortality.

Confounding: Is It a Real Problem?

In developing criteria for assessing epidemiologic studies, we have paid a great deal of attention to the potential confounding of PM effects on human health with the effects of other agents that are associated with PM. Confounding has both conceptual and technical aspects. We will first discuss some of the conceptual aspects.

There are three distinct options by which an analyst can deal with confounding in an epidemiology study: (1) control; (2) avoid; or (3) adjust by analysis. It is obviously preferable to control confounding by designing a study in such a way that all of the potential confounding effects are anticipated and avoided. If confounding is unavoidable, then all levels of the nominal causal agent (PM) and its confounding factors should be included in the study, preferably in a balanced design so as to simplify the analyses of the data. Since the

PM studies are all observational studies, study design rarely allows a representative sampling of all levels of all factors. For example, in a city or region where there are large stationary sources that burn fossil fuels containing sulfur,, both PM and SO_2 are likely to be high at the same time or low at the same time, being governed by similar patterns of generation and dispersion. Likewise, if mobile sources burning fossil fuel are the primary source of PM in a region, then PM during the summer is likely to be associated with some or all of the following factors: high temperatures, low wind speed, high concentrations of ozone, CO, and airborne nitrates. Therefore, avoiding situations in which confounding occurs is not usually an option.

However, there are some situations in which certain kinds of confounding are minimized. One example occurred in the Utah Valley studies. During the year that the mill was closed due to a strike, PM emissions from the mill were greatly reduced, but not quite eliminated since the coke ovens were banked during the closure, and not shut down. The years before and after the closure were years with high PM_{10} concentrations and typical weather. The year during the closure had generally typical seasonal weather, but much lower PM_{10} levels. Hence, confounding between PM_{10} and weather was relatively minimal during the study. Other studies by Pope et al. (1989, 1991) in surrounding counties showed little evidence of any change in the incidence of respiratory infections during the year of closure, so that confounding of winter health effects with epidemics of respiratory infection seems unlikely. Other pollutants were at low levels even when the mill was operating, particularly SO_2. Summer levels of ozone were high enough to merit covariate adjustment, but had little effect on the estimated RR for various health effects of PM_{10}.

In general, the potential for confounding of PM effects with the effects of other air pollutants is regionally distributed, with sulfates forming a higher percentage of particle mass in areas of the eastern U.S. and Canada, and nitrates a larger percentage than sulfates in the western U.S. and Canada. Thus, the **potential** for confounding with $SO_4^=$ and with SO_2 is greater in studies in eastern states, and the **potential** for confounding of PM effects with effects of NO_x, and (presumably) with other air pollutants such as CO and O_3 that are generated largely by mobile sources, is greater in the western states. Likewise, there is some confounding of health effects of PM with health effects from weather, since weather conditions may affect both generation of PM and its atmospheric dispersion (that is,

concentration). For this reason, it may also be helpful to take a multi-city or multi-study perspective in comparing the effects of potential confounding variables on RR for PM.

Schwartz (1994cd, 1995abc) has emphasized a multi-study and multi-endpoint perspective from several points of view. We believe that comparisons of study results across different studies is very useful, but the approach still leaves some unresolved questions about confounding. For example, a completely factorial design controlling for effects of weather and co-pollutants might require finding studies in both "hot" and "cold" cities, in "wet" and "dry" cities, in cities with "high" SO_2 and "low" SO_2, with "high" O_3 and "low" O_3. Thus, even a simple factorial design would require comparisons of at least $2^4 = 16$ cities, counties or SMSA's. Since the variables used in describing the cities are numeric, combining the results would be more appropriately done using a "meta-regression" in the same sense as in the cross-sectional analyses done for the long-term exposure studies, rather than a "meta-analysis". Meta-analyses are discussed below. In general, there have not been enough reported studies to do this "meta-regression". There are also problems in defining levels of weather effects, since Kalkstein et al. (1994) have shown that thresholds for excess mortality from high temperatures are different in different cities. That is, a "high" temperature in Minneapolis-St. Paul or Seattle, may not have the same effect in Birmingham or Los Angeles, and that differences may depend on other weather variables and on climate conditions. This approach also shares another concern about population-based cross-sectional studies, that populations in different cities are demographically different in ways that affect population-based health outcomes. Even the measure of effect size that we have used for most of our comparisons, relative risk of health outcome for PM or other factors, is relative to a base rate for the health outcome that one would expect to differ somewhat among different populations in different cities.

Avoidance of confounding is also possible for some co-pollutants. Gaseous chemical compounds such as SO_2, CO, and O_3 are likely to have very similar effects in different conditions, everything else (such as temperature and humidity) being equal. When levels of these pollutants are very low, such as SO_2 in most western studies, there is virtually no chance that these pollutants have a causal effect on health endpoints such as mortality and hospital admissions. While such effects cannot be absolutely excluded, the fact that they are

often found at levels very far below the NAAQS should control their contribution to some extent.

In spite of these concerns, the general similarity of RR estimates for acute mortality in different studies and the large differences in potential confounding variables among the studies, along with the similarity of RR to that found in studies where confounding effects seem relatively minimal, adds a great deal of credibility to the conclusion that the PM mortality effects are real, and similar in many locations, even if their magnitude is small and somewhat uncertain. This is not to say that there is no confounding with co-pollutants, particularly where pollutants such as SO_2 are generated by the same process that generates PM. Differences in RR for hospital admissions are somewhat greater, possibly reflecting differences in demographic factors or regional differences in hospital admissions criteria, but for similar reasons these estimates are not so seriously confounded in every study as to preclude concluding that, in some studies, there are real increases in hospital admissions rates for the elderly, and for certain classes of respiratory and cardiovascular conditions.

Control of Confounding By Covariate Adjustment

For most of the short-term studies, there is some unavoidable confounding with co-pollutants, with weather, and possibly with other medium-term and long-term events such as epidemics and seasons. Different model specifications of some studies in Section 12.3 were compared at length in Section 12.6.2. Weather variables and temporal variations over times longer than a few weeks can be adequately modeled using any of several approaches discussed above, such as polynomials, sinusoids, indicator variables for each month and year, indicators of synoptic climatological categories, nonparametric smoothers or generalized additive models, or high-pass filtering for Gaussian models. Careful examination of residuals for Poisson or Gaussian models have found that a large number of alternative models can provide regression residuals or Poisson expectations apart from air pollution variables that are independent of season, so that seasonal subsetting of time series data in short-term studies may not be necessary for adequately adjusted models. Sometimes, as in analyses of the London mortality series (U.S. EPA, 1986; Schwartz and Marcus, 1990), only seasonal monitoring data are available, but one should not make a virtue of necessity by subsetting time series, since statistical tests to detect PM effects of the magnitude currently

observed in the U.S. require long series of data, roughly at least 800 values. Apart from this sample size requirement, different methods for adjusting for weather and time trends provided adequate levels of adjustment to control for these factors. In addition to controlling confounding with air pollution, it is also important to fit very good models for weather and time trends in time series data, however, so as to help reduce residual variability in daily response data to the limiting or irreducible Poisson minimum variance, which is equal to the expected number on that day.

12.6.3.5 Adjustments for Co-pollutants

Not all studies contain data on the major co-pollutants, and a wide variety of approaches has been used to assess the importance of these co-pollutants as predictors of health effects that compete with PM in terms of explanatory power. Studies in which no other co-pollutant is assessed probably over-estimate the PM effect, but the use of a large number of more or less closely related pollutants to predict the health outcome almost guarantees that the statistical significance and size of the PM effect will be under-estimated. So far, none of these studies have used effective diagnostic techniques or alternative methods for dealing with correlated (e.g. multicollinear) predictor data.

Co-pollutants

Earlier discussion has indicated that other pollutants such as SO_2 are factors that play a role in modifying the relationship between PM and mortality when they are incorporated into models examining these relationships such that the RR is usually smaller. Other pollutants such as O_3 and CO also need to be considered. Indeed as more studies incorporate these other pollutants into the studies, concern for the role they play becomes more important. This applies to hospitalization studies where possible relationships with CO may be evident. The biological plausibility of CO and sudden death is established. The earlier major air pollution episode events in London involved relatively high levels of CO (Commins and Waller, 1967). Section 12.6.2 conducted an intense examination of the roles of copollutants with a focus on SO_2 but also O_3 and CO to determine what roles these copollutants play and what summary statements are possible to allow conclusions about PM effects to be stronger.

One of the more difficult problems in interpreting the analyses of the studies discussed here is that of separating the effects of several air pollutants. These pollutants are often fairly highly correlated, and the correlation is often causal, in that several pollutants may be emitted by the same mix of sources in a community, or that one pollutant is a precursor to another pollutant or to a component of that pollutant, such as the fractions of sulfates and nitrates in PM that are secondary pollutants formed from SO_2 or NO_x. There have been a number of studies in which several different model specifications were tested, involving PM as the only air pollutant, versus PM and other pollutants used jointly in the model. In many studies, such as TSP in Philadelphia (Schwartz and Dockery, 1992a) there was little effect of SO_2 on the RR for TSP, whereas other authors have found that SO_2 appeared to modify the TSP effect in some seasons, using a similar approach and data set, but with less comprehensive adjustment for weather variables and time trends. There are two ways in multi-pollutant models can cause differences in interpretation from a single-pollutant model: (1) the correlation between PM and the other pollutant(s) is (are) sufficiently high that the effect or health outcome attributable is shared among the pollutants and the individual RR for any one pollutant may be seriously biased. Measurement error in pollutants or other covariates may also bias the result, not necessarily towards the null, and the most poorly measured exposure covariate is usually the one that is driven towards no effect; (2) parameter variance estimates are seriously inflated among the entire group of nearly collinear covariates, increasing estimated standard errors and the width of the confidence intervals for the RR estimates and thereby also attenuating their apparent statistical significance.

Collinearity diagnostics have been developed for Gaussian OLS regression models (Belsley et al., 1980) and are implemented in most modern statistical programs. Analogous methods for Gaussian, logistic, or Poisson time series models are less well developed. Most programs allow calculation of the correlation coefficient between estimates of regression parameters (denoted B) based on the asymptotic covariance matrix. However, as noted in Table 13-6, correlation of the B's was given in only two out of ten studies relating acute mortality to PM_{10}. Pollutants with similar patterns and effects can be identified by B-correlation values close to -1. Numeric diagnostics for confounding of co-pollutants could be easily included in reports of long-term studies, many of which use Gaussian OLS linear or nonlinear regression methods for which these diagnostics are readily calculated.

Some investigators have noted that similarity of PM regression coefficients in single- and multiple-pollutant models is sufficient to show that PM is not confounded with the other pollutants. This is not the whole story, since there is a possibility that the B coefficient or RR for PM is unchanged, but the confidence limits are much wider because of the variance inflation of the parameter estimate for collinear pollutants. When the RR estimate for PM is relatively unchanged **and** there is little increase in the width of the confidence interval, then one can say there is little evidence of confounding. This has been done in a number of analyses discussed in this section, for example in the Utah Valley mortality study as shown in Figure 12-19. The RR estimates for the summer season and the width of the confidence intervals for PM_{10} are similar without ozone in the model, with daily average ozone, or with maximum daily one-hour ozone as the co-pollutant. The summer PM coefficient, with or without ozone, is similar to the winter value, when ozone levels were so low as to have little probable effect on mortality, which illustrates both covariate adjustment and confounder avoidance strategies in the same study.

There is some question about whether the confounding of certain co-pollutants such as PM and SO_2 should be regarded as true confounding when one pollutant is part of a causal pathway from pollution source to pollution monitor (Rothman, 1986). Our assessment of probable causal pathways in a hypothetical multivariate model relating source emissions, weather, air pollution, and health outcomes is shown in Figure 12-33. This could serve as a framework for a statistical analysis in which the direct and indirect effects of air pollutants and other factors could be disentangled using substantive scientific hypotheses and data.

In summary, confounding by weather and by time effects can be adjusted statistically so as to remove a substantial amount of confounding, but possibly at the expense of reducing the estimated PM effect by attributing it to weather or longer-term time effects not related to short-term PM exposure. Confounding by co-pollutants sometimes cannot be avoided, but should be diagnosed and reported more completely than in most studies now available. In studies where sensitivity analyses demonstrate that including other pollutants in the model causes little change in either the RR estimate for PM or on the width of the confidence interval for the PM effect, one may conclude that the model is not seriously confounded by co-pollutants. Since a number of mortality and morbidity studies have shown that the PM effect on health is not sensitive to other pollutants, we may conclude that the PM effects in

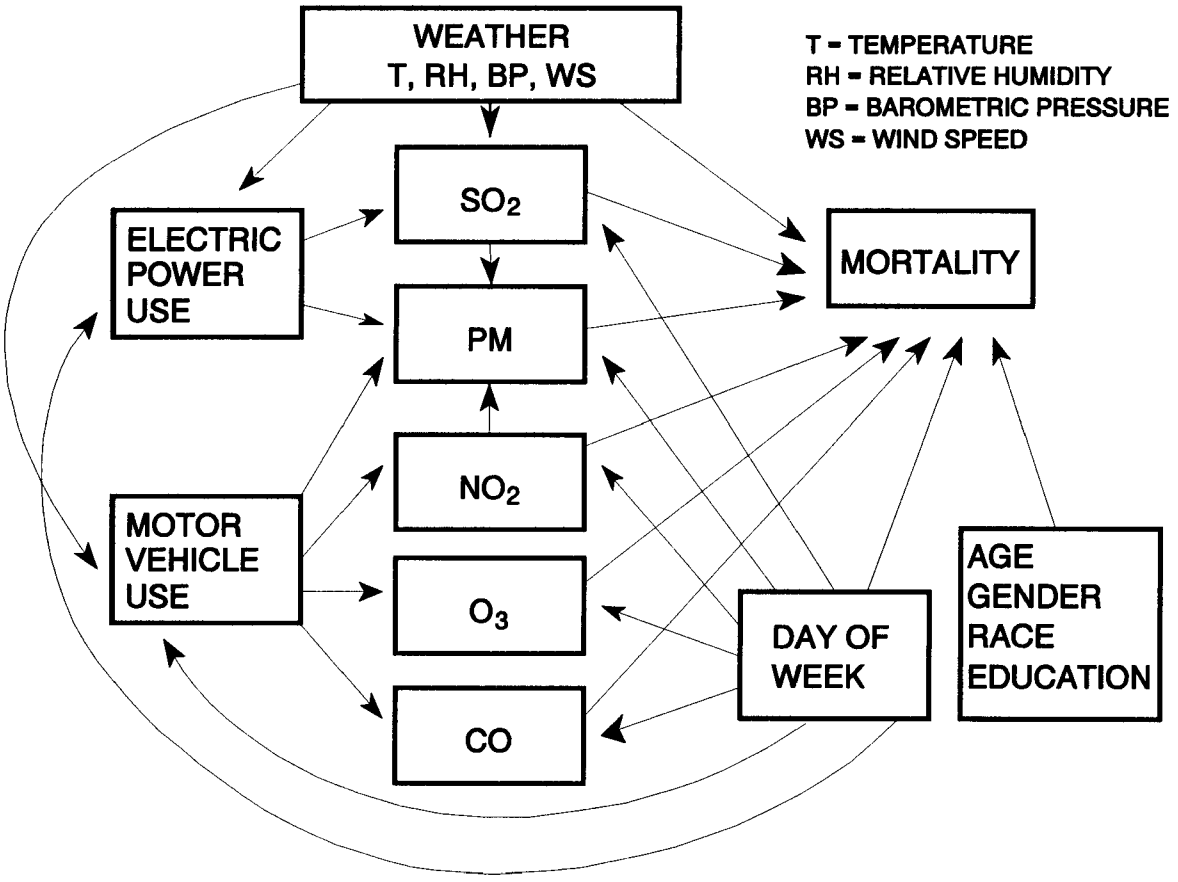

Figure 12-33. A conceptual model of sources and pathways for air pollution health effects such as mortality, including a causal model of potential confounding by co-pollutans.

these studies are real. This adds some credibility to the claim that a significant PM effect exists in the remaining studies where PM is statistically significant in a model without other pollutants, though similar in magnitude to the PM effect found in other studies with less co-pollutant confounding, but is not statistically significant when other pollutants are included in the model. This then provides a basis for the meta-analyses discussed below.

12.6.3.6 Ecological Study Design

Most of the studies considered are ecologic in design. Even in the daily longitudinal studies, individuals are grouped by region, SMSA, or catchment area for hospital admissions, and all are assumed to have exposure to PM and other covariates characterized by a single

numerical value for the area on that day. The "ecological fallacy" refers to the biases inherent in making individual-level predictions from aggregate-level data. However, such studies are often used because of the availability of data bases for air pollution, weather, and mortality or hospital admissions on a daily basis. Relative risk estimates for individuals should therefore be regarded as subject to much uncertainty, even for age-specific sub-populations, in the absence of subject-specific exposure and covariate data. Recent additions to the NCHS mortality data base, including demographic information such as educational attainment, may allow better resolution of the effects of socio-demographic covariates. While residential location might improve estimates of exposure in communities with several monitoring sites, there would still be considerable uncertainty about individual non-residential exposures in the absence of information about daily activity. Better individual-level exposure information would still be needed to reduce the substantial uncertainties about exposure.

12.6.3.7 Measurement Error

While there has been much discussion about the effects of measurement error, particularly with respect to exposure misclassification, few suggestions have been made as to how to deal with this question.

There have been few quantitative assessments of errors in measurements of particulate matter or other copollutants. There are at least two major components of these errors.

(1) Instrument error: Errors in measurement of pollutant levels at the point of measurement.

(2) Proxy error: Error in using levels at a point (even if correctly measured) as the levels to which study population members are exposed.

For studies of chronic effects, another potentially important problem is sometimes dealt with under the heading of "exposure definition":

(3) Construct error: Error in using a particular exposure summary other than the biologically relevant exposure (for example, using time-weighted average level when only time above a critical threshold is biologically relevant). This is also encountered in constructing moving averages for short-term studies.

It is often assumed that any measurement error is nondifferential, and that consequently any bias produced by the error would be towards the null. Neither assumption is necessarily

correct. There are several possible scenarios under which proxy measurement errors will be differential. For example, suppose monitor readings in low-pollution, low-mortality areas tend to understate exposure more than in high-pollution, high mortality areas because many residents of low-mortality areas commute to jobs in high-mortality areas. Then measurement errors will be differentially higher for low-mortality populations (and among noncases in an individual-level study based on these measurements and areas).

Contrary to popular treatments, nondifferential error does not guarantee that the resulting bias in effect estimates is towards the null. In ecologic designs, nondifferential error in individual-level exposure measurements can easily produce very large bias away from the null. In individual-level designs, nondifferential error may produce bias away from the null if errors are interdependent or if the dependence of measured on true levels is not monotonic. Interdependence of errors seem likely. For example, wind patterns would induce correlated proxy errors in all atmospheric pollutants. Effects of confounder errors can be in either direction, whether or not the errors are nondifferential. Under the best of circumstances the only predictable effect of nondifferential confounder errors is that they will tend to leave the exposure effect estimates partially confounded.

In summary, there has been no evidence presented that measurement errors are nondifferential. Even if there were such evidence, it would not imply that the biases produced by the errors are toward the null. Bias due to measurement error can be profound.

12.6.4 Assessment Issues for Epidemiology Studies

12.6.4.1 Significance of Health Effects/Relevancy

The "relative risks" derived from the regression coefficients in recent short-term PM/mortality studies appear to be consistently "small" (i.e., 1.04-1.05 per 100 $\mu g/m^3$ increase in PM_{10}), compared (at a face value) to the relative risks in other types of studies. In cancer epidemiology, for example, some (Shapiro, 1994) consider a relative risk of 1.7 as weak support, "at most", for a causal inference. However, much lower RR estimates of 1.2 to 1.3 have been regarded as sufficient for establishing a presumption of a causal relationship for health effects from environmental pollutants in recent EPA studies on environmental tobacco smoke (U.S. Environmental Protection Agency, 1992) and nitrogen oxides (U.S. Environmental Protection Agency, 1993).

The fact that a relationship is weak, or that an effect is small, does not mean that the relationship is not causal. As Rothman (1986, pp. 17-18) points out, "By 'strength of association', Hill [1965] means the magnitude of the ratio of incidence rates. Hill's argument is essentially that the strong associations are more likely to be causal than weak associations because if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. Nevertheless, the fact that an association is weak does not rule out a causal connection." Many of the studies cited in this chapter included substantial assessments of the effects of potential confounding factors, particularly age group, identifiable cause of death or hospital admission, weather or climate, and the levels of co-pollutants. In some cases, potentially confounding factors were either not present or present at such levels as to have an ignorable effect on the health outcome. Even when potential confounders were present, it was often possible to carry out a statistical adjustment for the confounder, with the PM effect size estimated with and without the potential confounder in the model. The PM effect size estimates and their statistical uncertainty in many studies showed little sensitivity to the adjustment for confounding variables. In a few other studies, there was substantial confounding with some co-pollutants such as SO_2 or O_3, but estimates of RR for PM without inclusion of the confounders in the statistical concentration-effect model used in these studies were quantitatively similar to RR estimates from other studies where confounding was either avoided or was shown statistically to have little effect. This bears out the comment by Rothman (1986, p. 18) that "... the strength of an association is not a biologically consistent feature, but rather a characteristic that depends on the relative prevalence of other causes," which here includes confounders such as weather and co-pollutants.

However, these two types of relative risks are not directly comparable. The "relative risk" estimates used in these short-term PM exposure studies are not only "acute" in their exposure/response relationship, but also represent "indirect" cause of deaths. A healthy person does not develop respiratory disease and die from an exposure to 100 $\mu g/m^3$ PM_{10} in one day. The causal hypothesis is that people with chronic respiratory or cardiovascular diseases, who may be near death from the preexisting conditions, are pushed toward death prematurely by the additional stress on the respiratory system imposed by an increased level

of air pollution. This is in contrast to a cancer risk from exposures to a chemical, through which a perfectly healthy person may develop cancer and die at the age of 50, when the person may otherwise have lived up to 70 years old. This difference may be obvious to the researchers analyzing these data, but needs to be clarified when such "risk estimates" are communicated to people who are not familiar with this field.

With this difference taken into consideration, there are several reasons why we may be concerned about the estimated "relative risks":

- The apparent "relative risk" estimates are often calculated for the entire death categories. Cause-specific "relative risk" estimates are often greater than for total mortality (e.g., in Pope et al.'s Utah study, the excess relative risk calculated for the respiratory category mortality was 43% as opposed to 16% for total mortality). If susceptible populations were defined and categorized, for example by age, the risk estimate would be even higher than for the general population.

- The apparent "relative risk" tacitly assumes a baseline death population in which all are subject to the change in PM exposures. It is likely that this is not the case. An unknown fraction of the population are not subject to the change in exposure levels of outdoor PM, thereby causing an underestimation of the risk of those actually exposed.

- There may be a downward bias in the estimated PM/mortality regression coefficients (and, therefore, in the estimated relative risk) due to the PM measurement errors. The extent of this bias is not known.

- The extent of prematurity of the deaths, which may range from days to years, is not known.

12.6.4.2 Biological Mechanisms

Most of speculation on the biological mechanism of PM mortality effects were made in the earlier major air pollution episodes. According to Firket's report (1936) on the fog episode of Meuse Valley in 1930, the autopsies with microscopical examinations found local and superficial irritation of the mucus membrane of the respiratory ducts and the inhalation of fine particles of soot in the pulmonary alveoli. The chemists concluded that "the SO_2 in the presence of oxidation catalysts such as ferric and zinc oxide, must have been partly transformed to sulfuric acid". The discussion of the report suggested sulfuric acid to be "the most probable cause" of deaths. In the 1952 London fog episode (United Kingdom Ministry of Health, 1954), the association of the air pollution and the observed increase in deaths,

estimated to be 4,000 excess deaths, was rather obvious. The report suggested "it is probable that sulphur trioxide dissolved as sulphuric acid in fog droplets, appreciably reinforced the harmful effects of sulphur dioxide." One immediate cause of death was speculated to be acute anoxia from bronchospasm.

Such extreme observations do not exist in recent PM/mortality studies. There are some speculations regarding possible mechanisms, identifying specific chemical components responsible for the effects such as acid aerosols. The pattern that does appear to resemble the past episodes in these more recent observational studies is the age and cause specificity of the deaths associated with PM. Both cardiovascular and respiratory deaths in the elderly population increased in the 1952 London episode. The estimated relative risks for these categories were found to be disproportionately higher and more significant in the analysis of Philadelphia (Schwartz, 1994). Other cause specific analyses (e.g., Fairley, 1990; Pope et al., 1992; Schwartz, 1994b) also reported higher estimated relative risks for respiratory and cardiovascular categories than total or other categories. While the excess deaths in the cardiovascular category, which was also apparent in past episodes, do not provide direct information on possible causal mechanisms, the analysis of contributing causes (Schwartz, 1994h) appears to suggest that the respiratory illness is contributing to the deaths of people with cardiovascular conditions. If a person has been suffering from a major cardiovascular disease, that person's death may be still categorized as cardiovascular, even if the respiratory condition causes the death. Such misclassification may also occur for other categories (e.g., cancer). More analyses using the contributing cause of deaths are needed to further characterize such mechanisms.

12.6.4.3 Coherence

The strength of an association and the consistence of an association can be evaluated by looking across the data base. The repeated observation by different persons, in different places, circumstances and time, and the consistency with other known facts of an association help demonstrate the strength of that association. This is related to the Bates (1992) discussion on the Question of Coherence. One can look for interrelationships between different health indices to provide a stronger and more consistent synthesis of available information. The various findings that support a picture of coherence would provide a

stronger case with quantitative studies as opposed to qualitative studies. Some studies may be inappropriate to use in such a discussion, and the quality of each study should be considered. Bates (1992) states that the difficulty with discussing any index of internal coherence is that this requires a series of judgements on the reliability of the individual findings and observations. The outcome of a coherence discussion then is a qualitative presentation in the end, not quantitative. Thus, coherence cannot be formally measured.

Bates (1992) noted that the strength of different health indices are important as are difficulties in assessing exposure. Bates (1992) suggests three areas to look for coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) between epidemiological, controlled human and animal data. Only the first is considered in this chapter. The other two are more appropriately discussed in the synthesis chapter (Chapter 13).

Coherence by its nature considers biological relationships of exposure to health outcome. In looking for coherence one should compare outcomes that look at similar time frames—for example, daily hospitalizations compared to daily mortality rather than monthly hospitalizations. Underlying mechanisms related to different effects should also be considered. Biologic mechanisms underlying a small acute PFT reduction in children in relation to a non-episodic PM exposure, for example, are unlikely to explain the acute basis for a change in the mortality rate of the sub-population group of individuals over 65 years of age in relation to a similiar PM exposure. Also, evidence for coherence is strongest when reported increases in morbidity endpoints are obtained for the same population segment (e.g., the elderly) in the same geographic locale as where PM-mortality effects were demonstrated. Most of the morbidity endpoints measured in available PM studies generally do not speak directly to coherence with a change in the mortality rate.

The various PFT and respiratory symptoms and disease endpoints studied do indicate that PM has a relationship with a continuum of health outcomes. However, the underlying mechanisms between the health outcomes studied may be different. The principal health outcome for which coherence is desirable is mortality, the death rate in a population. Of the various morbidity outcomes studied and discussed earlier in this chapter, the outcome potentially most related to mortality is hospitalization for respiratory or cardiovascular causes in the older age group (i.e., > 65 years old). In a qualitative sense, the hospitalization

studies reviewed in the chapter support this notion. The mortality studies suggest that these specific causes provide stronger relationships (i.e., RR) than total mortality in that age group. While a much larger increase in hospitalizations than deaths may have been expected, this is not evident in the data. The population of decedents may be fundamentally different from the underlying population of hospital users (Bates, 1992). The relationship between health outcomes may be more complex than a simple approach would suggest.

12.6.5 Meta-analyses and Other Methods for Synthesis of Studies

12.6.5.1 Background

Several reports have appeared in which results from different studies have been combined, formally or informally, to present an overall effect size estimate for acute health effects. For example, a synthesis of daily mortality studies for seven cities was published by Schwartz (1992). The seven cities included four TSP studies (Steubenville, Philadelphia, Detroit, Minneapolis) and three PM_{10} studies (St. Louis, Eastern Tennessee, Utah Valley). The daily mortality studies were further analyzed by Schwartz in a later paper (1994), which added studies from New York, from Birmingham, Alabama, later London studies (1959 to 1972), and a study in Athens, Greece. The RR estimates were combined in formal quantitative meta-analyses, using either unweighted RR estimates, or using a smaller set of estimates weighted by inverse of the estimation variance of the RR coefficient from studies in which the standard error was reported. Several methods were used, and several subsets of the data were tested according as to whether or not the study city was "warm" or the TSP coefficient was adjusted for copollutants.

A recent paper by Dockery and Pope (1994) extends the research synthesis to a variety of health outcomes, including hospital admissions studies and respiratory function tests. This paper is also based on conversion of different PM measures to an equivalent PM by applying a scaling factor: 1.0 for PM_{15} and BS, 0.55 for TSP, 4 for sulfates (SO_4), 1/0.60 for $PM_{2.5}$, and 1/0.55 for COH. This synthesis paper uses eight cities for total mortality, four cities for respiratory mortality and for cardiovascular mortality, three cities for hospital admissions for respiratory symptoms, four studies for asthma admissions, and combines three cities with different reasons for emergency room visits. The paper examines the effects of PM on exacerbation of asthma by combining results of two cities for bronchodilator use, and

combining three studies for asthmatic attacks. Pulmonary function tests are synthesized from four studies for Forced Expired Volume (FEV_1 and $FEV_{0.75}$), and six studies for Peak Expiratory Flow (PEF daily, weekly, or longer). Respiratory symptom results are divided into combining six studies reporting lower respiratory symptom results, upper respiratory symptom results, and six studies reporting cough symptom results. The authors conclude that these results demonstrate a coherence of effects across a range of related health outcomes, and a consistency of effects across independent studies by different investigators in different settings.

The synthesis of the epidemiologic evidence in this document presents some unusual problems. Many of the studies showing mortality and morbidity effects are based on relatively small increases estimated with great precision resulting from sophisticated analyses of long series of frequent events. As a result, relative risks (or odds ratios) of 1.06 are common and often statistically significant. A value of 1.06 would indicate that mortality (or morbidity) is increased by 6% when PM_{10} is increased a specified amount (usually 50 $\mu g/m^3$). Traditionally, relative risks less than 1.5 were considered to be of questionable biological meaning. Although relative risks near 1.06 are not large in magnitude, they may represent a large net effect because the events are so common. The question remains: are these effects real or are they an artifact of the analysis?

A careful review of the analysis techniques in Section 12.6.3 suggests that similar results are obtained as long as similar covariates and independent variables are included in the analysis. There are remaining questions about the accuracy of the variances and the assumptions upon which they are based. Even allowing for these problems, the estimated regression coefficients are consistently estimating the correct quantities although the exact p-values may be slightly in error.

The results do not appear to depend heavily on the form in which covariates were included in the model. Analyses that included the known covariates such as temperature and season usually gave similar results. The one factor which appeared to make a consistent difference was the inclusion of one or more copollutant(s) in addition to particulate matter. The inclusion of SO_2 tend to reduce the effect of particulate matter in most analyses, while O_3 generally had less of an impact on PM regression coefficients. This would be expected

because O_3 tends to be less correlated with PM than does SO_2. Although the PM coefficients were reduced by the inclusion of SO_2, most remained statistically significant.

One unresolved question is the possibility that the effects seen were the result of some covariate which, had it been included, would have reduced the PM coefficients to a non-significant level. Although this is always a concern with epidemiologic studies, the concern is often dismissed as improbable when the relative risks are large as 1.5 or 2.0. When the relative risks are less than 1.1, the question is of greater concern. There have been serious attempts by several authors to find such covariates, but none have so far been discovered.

12.6.5.2 Meta-analyses Using Studies Reviewed in This Document

In order to compare the results of the various studies relating acute exposure to PM to excess mortality, we selected studies that satisfied certain criteria: (1) the study has been published or is in press; (2) the study used PM_{10} or TSP as an index of particulate matter exposure; and (3) the study included adequate adjustments for seasonality, weather, other effects. The first criterion was imposed to provide adequate access to a description of study data, methods, and results; and the second so as to restrict consideration to studies with pollutants for which EPA has extensive air monitoring data. Even here, analyses were performed separately for PM_{10} studies and for TSP studies, so as to avoid having to make any assumptions about site-specific calibrations of one PM concentration or index into another. It may be possible to extend the meta-analyses to a wider range of studies when methods are developed for assessing the uncertainty associated with generic versus city-specific calibrations of one PM index to another.

The results of the analyses have been standardized for purposes of comparison. All of the acute exposure studies used Poisson or equivalent regression methods with the expected mortality an exponential function of a linear combination of predictors, or with the logarithm of the mortality rate as a linear combination of predictors including the PM index. This means that the **relative risk (RR)** -- the fractional increase in the mortality rate relative to a baseline value without pollution, everything else being equal -- can be expressed in terms of changes per unit of pollution. The base unit for change in risk was chosen differently for each pollutant. For PM_{10} studies, the effect was the odds ratio for mortality corresponding to an increase of 50 $\mu g/m^3$ in PM_{10}. Other ranges have been used in published papers, most

commonly 10 or 100 $\mu g/m^3$. We selected 50 $\mu g/m^3$ because it is closer to the range of values in various morbidity studies, whereas the range in mortality studies usually is larger than 100 $\mu g/m^3$. Since the range of values in TSP studies is typically much larger than in PM_{10} studies, we used 100 $\mu g/m^3$ as the base unit for TSP studies of mortality.

The basic data on effects size estimates, in appropriate units, are shown earlier in Tables 12-3 and 12-5. Note that the confidence intervals derived in the various papers are not always symmetric about the estimated RR. The data could be naturally sorted into five distinct groups:

- Estimates of PM_{10} effect on RR, not adjusted for copollutants, lags <2 d (4 studies, 4 cities)
- Estimates of PM_{10} effect on RR, not adjusted for copollutants, lags >2 d (6 studies, 6 cities)
- Estimates of TSP effect on RR, not adjusted for copollutants (4 studies, 3 cities)
- Estimates of PM_{10} effect on RR, adjusted for copollutants (3 studies, 3 cities)
- Estimates of TSP effect on RR, adjusted for SO_2 (3 studies, 2 cities)
- Estimates of PM_{10} effects on RR short, long lags (3 studies, 3 cities)

There are presently no methods for using results of different analyses of the same data set, such as the two studies on Steubenville (Schwartz and Dockery, 1992; Moolgavkar et al., 1995a). (For this assessment, we report results using each separately.)

The meta-analysis methods were similar to those used in the Nitrogen Oxides criteria document (US EPA 1994; Hasselblad et al. 1994). Differences among studies are regarded as random effects. Results are shown in Figures 12-34 through 12-39 and Table 12-25. The relative risk for PM_{10} exposure averaged ≤ 2 days is estimated as 1.032 per 50 $\mu g/m^3$ PM_{10}, with a 95% confidence interval of 1.025 to 1.038 per 50 $\mu g/m^3$ PM_{10}. There is overall evidence of an effect, even though one of the four studies in Figure 12-34 is not significant. The relative risk for PM_{10} exposure with longer averaging times, 3 to 5 d, is estimated as 1.064 with 95% confidence interval of 1.047 to 1.082. In Figure 12-35, one study is negative and another marginally significant. The combined estimate for TSP effect in Figure 12-36 depends on which study is used for the Steubenville estimate; with the Schwartz

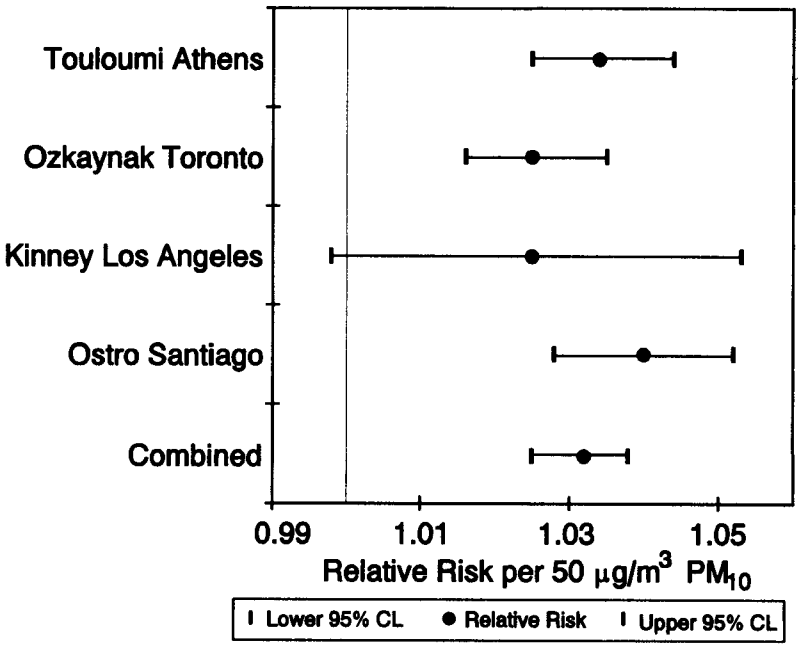

Figure 12-34. Summary of studies used in a combined EPA meta-analysis of PM_{10} effect on mortality with short averaging times (0-1 days), and co-pollutants in model.

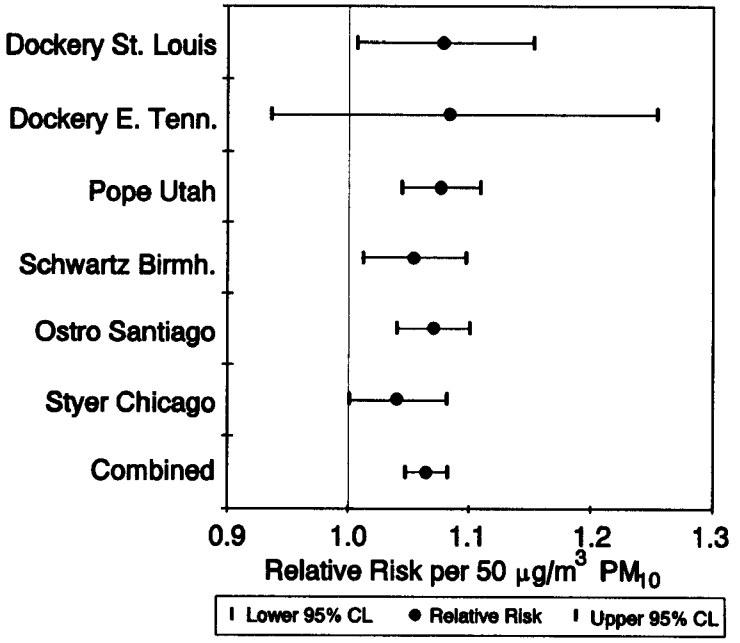

Figure 12-35. Summary of studies used in a combined EPA meta-analysis of PM_{10} effects on mortality with longer averaging times (3-5 d), and no co-pollutants in model.

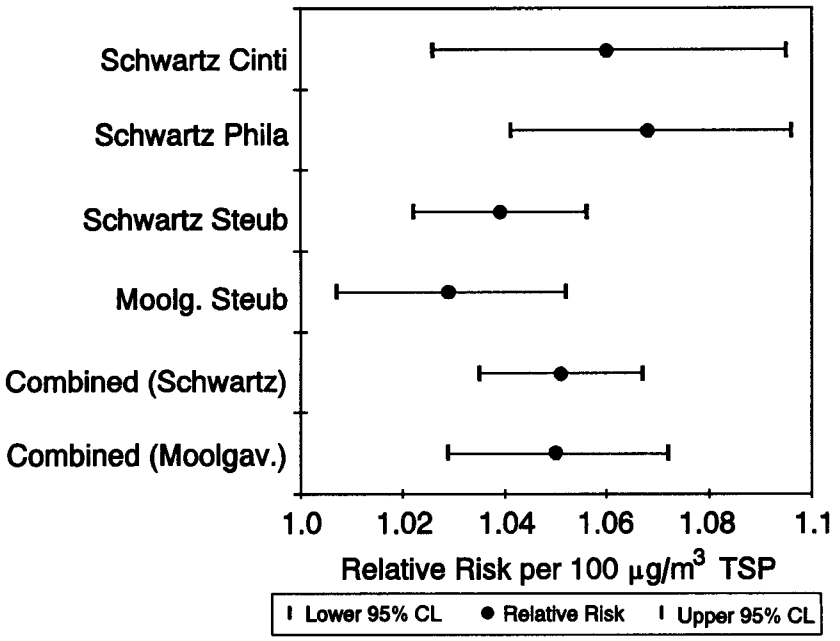

Figure 12-36. Summary of studies used in a combined EPA meta-analysis of TSP effects on mortality, with no co-pollutants in model.

study, the effect is 1.051 per 100 $\mu g/m^3$ TSP, whereas with the Moolgavkar study, the estimate is 1.050, but is less certain. However, none of these studies included SO_2, the most probable confounding co-pollutant. The analogous estimates for a TSP effect with copollutants in the model is less significant across three studies, RR = 1.018 with a 95% confidence interval from 1.007 to 1.029 per 50 $\mu g/m^3$ PM_{10}, as shown in Figure 12-37. Also, Figure 12-38 shows that when SO_2 is included in the model, estimated PM_{10} effects still remain significant. The overall EPA meta-analyses results are summarized in Table 12-25 and Figure 12-39.

We conclude that there is a short-term increase in mortality in response to acute PM exposures. This appears to be at least partly confounded with other pollutants, especially SO_2, but even with SO_2 included in the model the effect is on the order of 1 to 5% increase in relative risk per 100 $\mu g/m^3$ TSP. This is probably a minimum estimate of effect size. If SO_2 is in fact a proxy for fine particle exposure through the SO_2 to sulfate to fine particle pathway, then adjusting for SO_2 may overcontrol the estimate of PM effect, which could be as large as 1 to 5% per 100 $\mu g/m^3$ TSP, or 2 to 6% per 50 $\mu g/m^3$ PM_{10}. This also

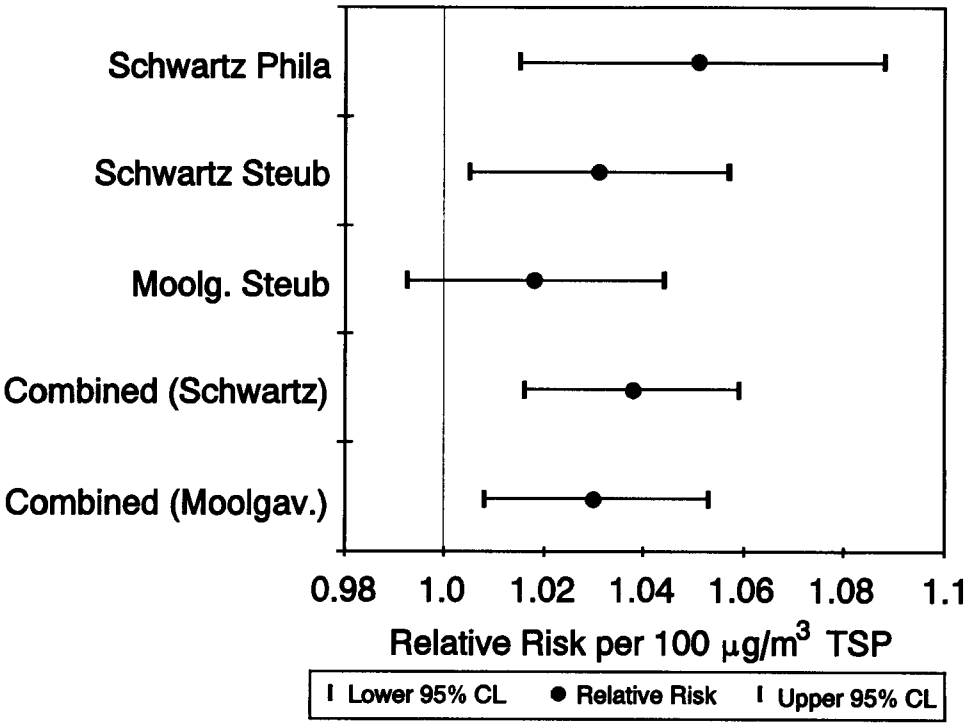

Figure 12-37. **Summary of studies used in combined EPA meta-analysis of TSP effects on mortality, with SO_2 in the model.**

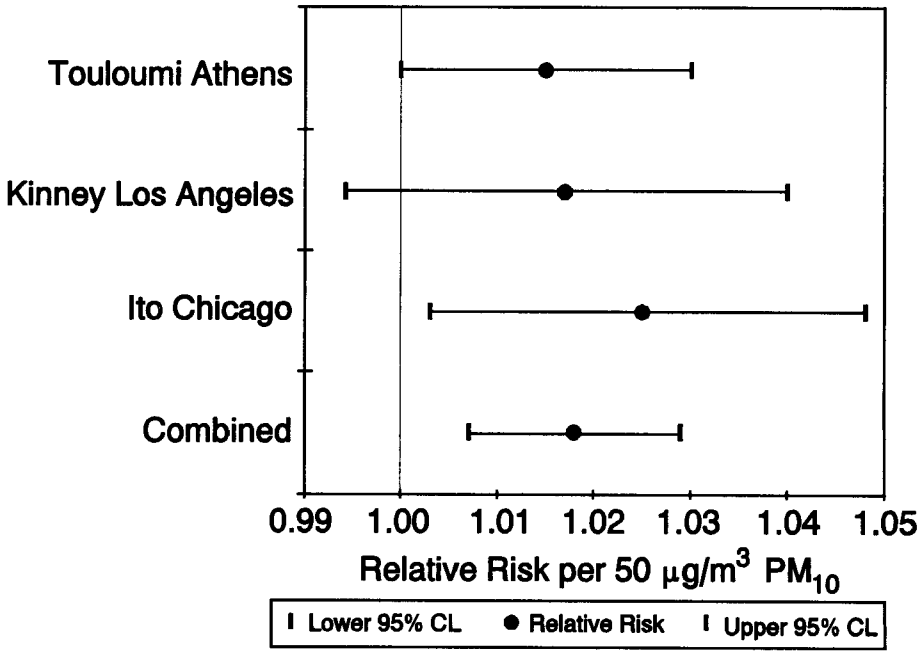

Figure 12-38. **Summary of studies used in a combined EPA meta-analysis of PM_{10}, effects on mortality, with other pollutants in the model.**

TABLE 12-25. COMBINED ESTIMATES OF RELATIVE RISK OF INCREASED MORTALITY FROM ACUTE EXPOSURE TO AIR POLLUTANTS

Pollutant	Increment	Model	Averaging Time	Relative Risk Estimate Per Increment	95 Percent Confidence Limits
PM_{10}	50 $\mu g/m^3$	No copollutant	0-1 days	1.031	1.025 to 1.038
PM_{10}	50 $\mu g/m^3$	No copollutant	3-5 days	1.064	1.047 to 1.082
TSP	100 $\mu g/m^3$	No SO_2		1.051	1.035 to 1.067
TSP	100 $\mu g/m^3$	No SO_2		1.050	1.029 to 1.072
PM_{10}	50 $\mu g/m^3$	+copollutants		1.018	1.007 to 1.029
TSP	100 $\mu g/m^3$	+SO_2		1.038	1.016 to 1.059
TSP	100 $\mu g/m^3$	+SO_2		1.030	1.008 to 1.053

[1]Including Schwartz Steubenville study.
[2]Including Moolgavkar Steubenville study.

depends on PM_{10} averaging times, with a 3% increase for averages of current and preceding day PM_{10} and 6% effect for 3 to 5 day moving averages.

These analyses suggest that there is an identifiable effect of PM exposure on increases in acute mortality, even when characterized by TSP, a relatively insensitive index of respirable particle concentration. The role of SO_2 as a possible proxy for fine particle exposure remains to be clarified. It is also not possible to overlook the potential confounding effects of other pollutants such as O_3 and NO_2.

12.6.5.3 Discussion

In general, there appears to be a range of acute health responses to air pollution exposure as characterized by some PM indicator. Dockery and Pope (1992) have stated that "It is ... presumptuous to assign these adverse health effects solely to the mass concentration of particulates. ... Many health effects of particles are thought to reflect the combined action of the diverse components of the pollutant mix." Since pollutant mixes and exposed populations differ from one location to another, it is more probable that there are real differences among different studies.

Several approaches to estimating a combined PM effect as a weighted average of study-specific effects may be considered: (1) regard each effect size estimate as a measurement in

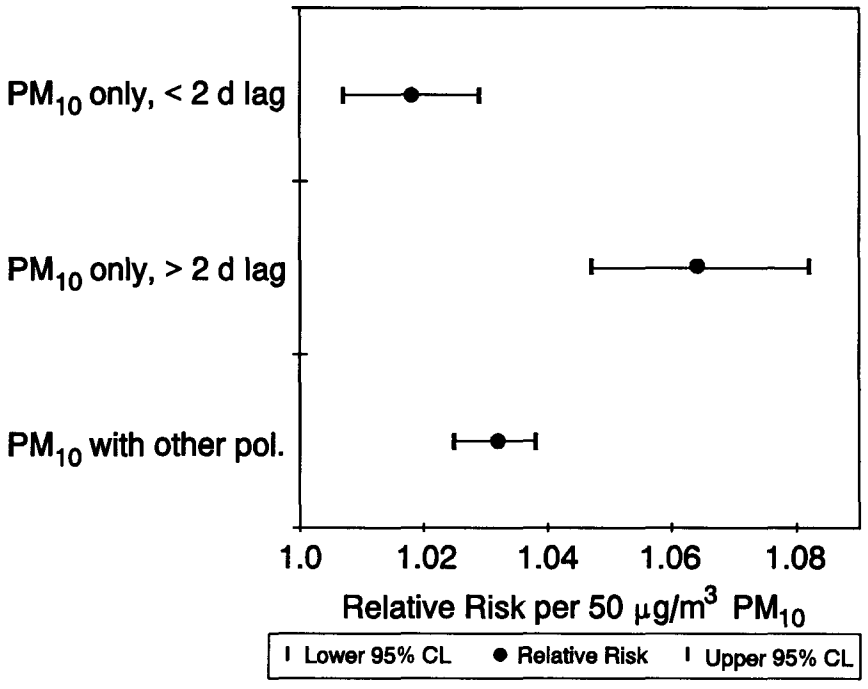

Figure 12-39. Summary of PM_{10} effects on mortality.

an ecological study and adjust for differences in effect size among cities as a function of differences in climate, mixture of other air pollutants, and differences in demographic characteristics; (2) carry out multiple comparisons of effect size estimates and group together those estimates that are not significantly different; (3) perform combined analyses in which the PM effect size parameter(s) are constrained to be equal in different data sets.

With the first approach (1), it may be possible to model the differences in PM effect size estimates by multiple regression on known quantitative differences in climate, copollutant mix, and population. This would require a "meta-regression" in which some assumptions would need to be made about the relationship between PM effect size and the inter-study variables that distinguish different cities, adding yet another layer of uncertainty about model specification. It would not be feasible to carry out this analysis unless there were a large enough number of studies, since multiple linear regression models do not perform well unless there are several times as many data values (effect size estimates from different studies) as there are variables that are used for adjustment.

With approach (2), each effect size estimate for which there was an attached standard error estimate would be compared with each other effect size estimate, as if each effect size

estimate was a separate group mean in an analysis of variance. The effect size estimates would then be grouped into clusters in which the cluster members (studies) were not statistically different from each other, although some methods allow for the possibility of partially overlapping clusters. A variety of multiple comparison procedures are available, using either methods based on normally distributed data or more robust methods (e.g., Tamhane and Hochberg, 1987). Some comparisons of a multiple hypothesis testing approach with a metaanalysis approach are described by Westfall and Young (1993), who prefer computer-intensive resampling methods such as bootstrap estimation or permutation testing that may not be feasible unless raw data were available. Conventional multiple testing methods can be done without raw data when standard error estimates are available, and may be especially suitable when there are only a few effect size estimates.

With alternative approach (3), it is essential that raw data be available. It is unlikely that raw data for all studies of any specified health outcome could be assembled within a short period of time, and even then it would likely take months to conduct such an analysis adequately.

The formal metaanalytic methods used to combine effect size estimates for acute mortality (Schwartz, 1994c) or for a variety of health outcomes (Dockery and Pope, 1994) could possibly be improved by including more information when weighing the studies, as we have suggested above. There are still many unresolved questions about how the synthesis of PM health effects data from different studies should be carried out.

12.7 SUMMARY AND CONCLUSIONS

The time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution can cause increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels, extending to 24 h concentrations below 150 $\mu g/m^3$ (the level of the present U.S. air quality standards). Furthermore, these new PM studies are consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. One of the more important findings is that longer averaging times (3 to 5 day moving averages) predicted larger and more significant effects on total, respiratory, or cardiovascular mortality in many

studies than did PM concentrations on the present or preceding day. Overall, the PM_{10} relative risk estimates derived from the most recent PM_{10} total mortality studies suggest a 24-h average 50 $\mu g/m^3$ PM_{10} acute exposure effect of the order of RR = 1.025 to 1.05 in the general population, with higher relative risks indicated for the elderly sub-population and for those with pre-existing respiratory conditions, both of which represent sub-populations especially at risk to the mortality implications of acute exposures to air pollution, including PM. Results are very similar over a range of specifications of statistical models used in the analyses, and are not artifacts of the methods by which the date were analyzed.

There is an indication among these various analyses that children may be more susceptible to the mortality effects of air pollution exposure than the population in general, but it is difficult, given the limited and somewhat conflicting results available at this time, to ascribe any such association to PM pollution in particular. This is an area where further research is clearly needed to broaden the base upon which to assess the potential for PM to increase mortality among children.

Hospitalization data can provide a measure of the morbidity status of a community during a specified time frame. Hospitalization data specific for respiratory illness diagnosis or more specifically for COPD and pneumonia give a measure of the respiratory status. Such studies provide an outcome measure that relates to mortality studies for total and specified respiratory measures. Tables 12-9 through 12-12 summarize these studies. These studies associate hospitalization data with measure of PM. Some of the same factors and concerns related to the mortality studies are an issue for these studies also.

Both COPD and Pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. There is a possible suggestion of a relationship to heart disease, but the evidence is very inconclusive. The admission studies of respiratory disease show a similar effect. The hospitalization studies in general use very similar analysis methodologies and the majority of the papers are written by a single author. Overall, these studies are indicative of health outcome related to PM. They are also supportive of the mortality studies, especially with the more specific diagnosis relationships.

Schwartz (1995c) reviewed the hospital admission and mortality studies of particulate matter and ozone. The hospitalization results were based on the studies of Thurston et al,

(1992), Schwartz, 1994a, Burnett et al, 1994, Schwartz et al, 1995, Schwartz, 1994b, Sunyer et al, 1993, Schwartz, 1994c, and Burnett et al, 1995. Summary tables for all respiratory admissions showed relative risks ranging from 1.10 to 1.20 per 100 $\mu g/m^3$ PM_{10} (or equivalently, 1.05 to 1.10 per 50 $\mu g/m^3$ PM_{10}). Summary tables for COPD admissions showed relative risks ranging from 1.15 to 1.57 per 100 $\mu g/m^3$ PM_{10} (or equivalently, 1.07 to 1.25 per 50 $\mu g/m^3$ PM_{10}). Schwartz (1995c) argues that because there is no significant heterogeneity in the relative risks across studies that

> "This suggests that confounding by other pollutants or weather is not the source of these associations, since the coincident weather patterns and levels of other pollutants varied greatly across the studies. In particular, studies in the western United States (Spokane, Tacoma) had very low levels of sulfur dioxide, and much less humidity than [sic] in the eastern United States locations."

However, tests for homogeneity are known to have very little power against specific alternatives, and so this conclusion may not be appropriate. Analyses of individual studies have identified situations in which the effects of confounding are minimal as discussed in Section 12.6.2.

The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates that were for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor for hospitalization usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may appropriately be associated with concurrent admission, while others may require several days for development to end in an admission. The exposure-response lag periods is not yet well examined.

Acute respiratory illness include several different endpoints, but the majority of authors reported results on at least two of (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (See Table 12-13). The results for upper respiratory illness are very inconsistent: two studies estimate a relative risk near 1.00 whereas four others obtain estimates between 1.14 and 1.55. These relative risks are all estimated for an increase of 50

$\mu g/m^3$ in PM_{10} or its equivalent. The relative risks for lower respiratory illness are spread between 1.01 and 2.03, but all are positive. The relative risks for cough include two below 1.0 and go as high as 1.51. All of these are suggestive of an effect. Whereas the hospital admission studies were all done in a similar manner and resulted in very similar results, these studies are done with very different designs and give very inconsistent results.

The acute pulmonary function studies are suggestive of a short term effect resulting from particulate pollution. Peak flow rates in children show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent (See Table 12-14).

Long-term exposure to air pollution was studied by use of cross-sectional studies, comparing rates of mortality or morbidity at a point in time against differences in annual average pollutant concentrations. Most older studies were population-based cross-section studies. These studies used outcome rates for entire cities or SMSA's. Several recent prospective cohort-based cross-sectional studies allow use of subject-specific information about other health risk factors, such as cigarette smoking or occupational exposure; and subject-specific outcome measures. The relative risk shows some sensitivity to model specification. For models of 1980 mortality from all natural causes, the RR from separate OLS regression models using TSP, PM_{15}, $PM_{2.5}$ or SO_4 as PM indicators all showed a positive test but statistically, non-significant effect. The PM_{15} RR is 1.036 at PM_{15} = 50 $\mu g/m^3$ (95% confidence interval 0.98 to 1.10), whereas a log-linear model for the same 62 SMSA found a larger and statistically significant RR for TSP of 1.066 (95% confidence interval 1.006 to 1.13 at TSP = 100 $\mu g/m^3$). The relative risk of major cardiovascular disease (CVD) for sulfate inhaled particles was 1.19 at SO_4 = 15 $\mu g/m_3$ (interval 1.03 to 1.35) when adjusted for one set of demographic coraviates, but smaller and not significant after adjustment with a larger set of covariates. The relative risk of COPD for TSP at TSP = 100 $\mu g/m^3$ or for non-sulfur TSP was highly significant, 1.50 and 1.43 with confidence intervals (1.22, 1.83) and (1.20, 1.71), respectively.

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the numbers of independent variables

considered, including the air pollutants. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the specific pollutants associated with mortality varied. However, all of these studies found at least some association between air pollution and mortality on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. The finding of significant associations with metals (Lipfert, 1978, 1984, 1993) and with cement plant particles (Bobak and Leon, 1992) suggests that many different types of particles may be involved. Analyses by age and cause of death were limited; the most consistent associations were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP (but not SO_4^{2-}).

Table 12-19 summarizes the three newer prospective studies considered here. The California and Six-City studies suffer from small sample sizes and inadequate degrees of freedom, which partially offsets the specificity gained by considering individuals instead of population groups. All of them may have neglected some important risk factors. The two early studies not shown in this table were largely inconclusive and the studies of California nonsmokers by Abbey et al. (1991, 1994) that had the best cumulative exposure estimates found no significant mortality effects of previous air pollution exposure. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality, but it is unfortunate that the ACS study did not consider a wider range of pollutants so as to also confirm the lack of importance for other pollutants. In addition, the timing of the critical exposures remains an open question. It is also important that a range of pollutants be considered in both chronic and acute studies, since it is possible that acute effects may be exhibited by one pollutant and chronic effects by another.

The RR estimates for total mortality are large and highly significant in the Six-Cities study. With their 95 percent confidence intervals, the RR for 50 $\mu g/m^3$ PM_{15} is 1.42 (1.16, 2.01), the RR for 25 $\mu g/m^3$ $PM_{2.5}$ is 1.31 (1.11, 1.68), and the RR for 15 $\mu g/m^3$ SO_4 is 1.46 (1.16, 2.16). The estimates for total mortality in the ACS study are much smaller, but also much more precise, 1.17 for 25 $\mu g/m^3$ $PM_{2.5}$ (RR 1.09, 1.26), and 1.10 for 15 $\mu g/m^3$ SO_4 (RR 1.06, 1.16). Both studies used Cox regression models and were adjusted for rather similar sets of individual covariates. In each case, however, caution must be applied in use

of the stated quantitative risk estimates, given that the life-long cumulative exposures of the study cohorts (especially in the dirtiest cities) included much higher PM exposures than those indexed by the more current PM measurements used to estimate the chronic PM exposures of the study cohorts. Thus, lower risk estimates very likely apply.

Cross-sectional studies may find a significant association between mortality and a specific air pollutant for any of several reasons:

- The association may reflect a non-zero integral of the acute effects of that pollutant over the period of study.

- The association may reflect a chronic effect from previous long-term exposures.

- The association may have resulted from confounding, either with another pollutant, with the characteristics of the sources that produced that pollutant (occupational hazards or exposures), or with human elements spatially associated with pollution sources such as differential migration of the healthy, less desirable housing near sources, or other socioeconomic factors.

The studies reviewed above probably all reflect some varying combinations of these possibilities. It is possible that a given regression coefficient may reflect the acute effects of one pollutant and the collinear portion of the chronic effects of another, for example. Convincing evidence of causal associations requires demonstration of specific disease-pollution combinations that are physiologically plausible. Supporting evidence may be obtained by showing that the statistical relationship improves when more reliable exposure data are used in the analysis.

Some of the prospective studies demonstrated that including additional pollutant exposures in a statistical model (cigarette smoke, occupational exposure) not reflected in the outdoor measurements lead to a stronger statistical mortality relationship with the outdoor measurements. This suggests two possibilities (there may be others):

- The indoor and outdoor exposures may reinforce each other and thus must have similar physiological effects. This may provide some clues as to the most likely of several collinear outdoor pollutants. The responses could be either chronic or acute.

- The indoor or occupational exposures may have created a disease state (independent of the outdoor exposures) that makes the individual more susceptible to outdoor pollution effects. This hypothesis suggests that the outdoor effects in the prospective studies are acute, since it is unlikely that

normally healthy people will experience acute effects at the air pollution levels now seen in U.S. cities.

Distinguishing between these two scenarios will likely require additional research, probably including temporal studies of long-term changes in air quality in different places.

At this time, the long-term studies provide support for the existence of short-term increase in mortality which are not subsequently canceled by decreases below normal rates. However, they do not exclude the existence of chronic effects. They provide no convincing evidence as to the specific pollutant(s) involved, and they do not rule out the existence of pollutant thresholds.

Three studies based on a similar type of questionnaire but done by two different groups of researchers, provide data on chronic respiratory disease and PM. All three studies suggest a chronic effect of particulate matter on respiratory disease, but the studies suffer from the usual difficulty of cross sectional studies. The effect of particulate matter is based on variations in exposure which are determined by the different number of locations. In the first two studies there were six locations and in the second there were four. The results seen were consistent with a particulate matter gradient, but it is impossible to separate out the effect of particulate matter and any other factors or pollutants which have the same gradient (See Table 12-21).

The chronic pulmonary function studies are less numerous than the acute studies (Table 12-22). The one study with good monitoring showed no effect from particulate pollution. Cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus the lack of statistical significance cannot be taken as proof of no effect.

Historical and present-day evidence suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 $\mu g/m^3$ as H_2SO_4, or roughly 8,000 nmoles/m_3 H_+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2. In addition, Thurston

et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels ($\leq$ 30 $\mu g/m^3$ as H_2SO_4, or $\leq$ approximately 600 nmoles/m_3 H_+), though these associations could not be separated from those for BS or SO_2. The only attempts to-date to associate present-day levels of acidic aerosols with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993b, respectively) were unable to do so, but there may not have been a sufficiently long series of H^+ data to detect H^+ associations. There is a critical need for present day replications of the London mortality-acid aerosol studies to be conducted, however, in order to determine if the London wintertime associations (which occurred in reduction-type atmospheres) are pertinent to present-day U.S. conditions, in which acid aerosol peaks occur primarily in the summer months (in oxidation-type atmospheres).

Taken as a whole, several analyses are suggestive of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Without nationwide measurements of airborne acidity, however, it is difficult to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. Thurston et al. (1992) and Thurston et al. (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM10 (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes ($H^+ \geq 10$ $\mu g/m^3$ as H_2SO_4, or $\approx$200 nmoles/m_3 H^+), which occur roughly 2 to 3 times per year in eastern North America. These studies provide evidence that present-day strongly acidic aerosols may represent a portion of PM which is

particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms except at H^+ above 110 moles/m_3 (Dockery et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991). Recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of chronic H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1993a) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.7, 95% CI: 1.1 to 2.4). It was also found in the 24-Cities study that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1993). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children. However, given the usually high correlation between acidic PM and PM in general, it is difficult to identify these effects solely with the acid portion of PM.

There is some uncertainty about human exposure to acid aerosols. Even though ambient acid aerosols may easily penetrate into inside air, household sources of ammonia may cause rapid reduction of interior acidity, so that total exposure to acidic particles may be proportionately smaller than exposure to non-acidic particles. However, even a relatively brief exposure to ambient acid aerosols outside the house could conceivably have detectable biological effects. This could explain a role for acidity effects in children, but may be less adequate to explain PM effects in adults who may spend even less time outdoors than children.

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APPENDIX 12A

EFFECTS OF WEATHER AND CLIMATE ON HUMAN MORTALITY AND THEIR ROLES AS CONFOUNDING FACTORS FOR AIR POLLUTION

Interrelationships Between Weather, PM, and Mortality

A number of studies have concluded that both extreme weather and high pollution adversely affect mortality. While a majority of this research has examined the independent effect of these stresses on mortality, few studies have successfully separated weather-induced from pollution-induced mortality. This has been especially true in the evaluation of acute mortality. There have been some efforts to evaluate these differential impacts (e.g., Ramlow and Kuller, 1990; Shumway et al., 1988; Schwartz and Dockery, 1992a; 1992b).

Some authors have conducted weather/pollution/mortality evaluations in Steubenville, OH; Philadelphia, PA; London, England; Birmingham, AL; and Utah County, UT as well as other locales (Table 12B-1). In all of these investigations, they have reported significant associations between human mortality and PM, and in some cases, the relationship extends to levels well below the current National Ambient Air Quality Standard. In several, they have also alluded to a weather-mortality relationship. For Steubenville, a positive non-linear relationship between both temperature and dew point temperature and mortality was detected. When dummy variables were used to denote hot days, humid days, and hot/humid days, the hot/humid days were a significant predictor of mortality. When seasonal variations were controlled for in their Poisson regression models however, neither temperature nor dew point proved to be significant predictors of mortality (Schwartz and Dockery, 1992b). In a study of British Smoke in London, Schwartz and Marcus (1990) controlled for temperature and humidity and improved the model results significantly over the results of a model with no meteorological variables.

More recent studies indicate that controls for weather may probably not been adequate to determine true meteorological impacts in the evaluations cited above (Kalkstein et al., in press). Many PM/mortality studies utilize rank-ordered temperatures, squared temperature and dewpoint values, moving averages of temperature, and mean temperatures for groupings of days (refer back to Table 12-2 in main chapter text for further details), which may not provide the detail to detect true weather/mortality relationships. In addition, it is probably not feasible to assume that cities within a wide range of climates demonstrate similar weather/PM impacts on mortality, and there are possibly some regional similarities in response which have not been adequately explored. In a reanalysis of Philadelphia mortality/PM relationships, Schwartz (1994) took a more direct approach to examine the

possibility of confounding weather impacts. The reanalysis utilized Hastie and Tibshirani's (1990) "Generalized Additive Model" to detect and control for nonlinearities in the dependence of daily mortality on weather; nevertheless, this study uncovered findings similar to the original Philadelphia study. In addition, Moolgavkar (1995) assert that the role of weather was improperly evaluated within the Steubenville study, and suggest a more sophisticated evaluation of meteorology in future PM/mortality analyses.

To further control for weather, Schwartz (1994) stated that the similar responses to air pollution in the mild weather of Philadelphia (based on a mean daily temperature of 57 °F) and cold weather of London reduce the confounding role of weather. In addition, Schwartz (1994) notes that similarity in temperature and humidity on high and low air pollution days (when different mortality response are noted), "... also would seem to eliminate weather as a potential confounder." However, it is possible that these studies do not remove the total confounding influence of weather, especially because of their dependence on mean temperatures and other meteorological surrogate which may not truly reflect weather variation.

There have been other studies which have attempted to assess the differential impact of PM and weather on acute mortality. For example, Ostro (1993) summarized studies which show strong associations between exposures to PM_{10} and total daily mortality for many urban areas in the United States, Europe, and Canada. In addition, he notes that results are remarkably consistent across regions. However, the impact of weather as a confounding influence is implicitly considered rather unimportant. Ito et al. (1993) showed that daily mortality in London was significantly associated with aerosol acidity levels and British Smoke. Weather played a lesser role, and Ito's work confirms results obtained by others who have evaluated London's mortality/PM/weather relationship (Schwartz and Marcus, 1990; Thurston et al., 1989; Mazumdar et al., 1982). However, it should be noted that London's marine climate is rather benign when compared to many large American cities, as thermal extremes are unusual.

Some studies for cities exhibiting higher climate variation yielded somewhat different results. Wyzga (1978) used the Coefficient of Haze (COH) as a surrogate measure of PM concentration, and determined that high COH values are associated with increased mortality in Philadelphia. However, he recognized the potential impact of extreme weather

as well, and noted that heat waves may also be responsible for large numbers of extra deaths. In a recent study by Wyzga in which weather was treated in a more sophisticated manner (Wyzga and Lipfert, in press), the impact of ozone concentrations and weather on acute mortality were evaluated and results were compared to TSP. The authors conclude that a determination of ozone and TSP impacts is most difficult because of the influence of confounders, particularly weather. In addition, use of different explanatory models yields disparate results, with pollution impacts ranging, "...from essentially no effect to response similar to that associated with a 10 °F increase in ambient temperature" (Wyzga and Lipfert, in press). This evaluation appeared to uncover a synergistic relationship between weather and pollution, as days with maximum temperatures exceeding 85 °F contributed most to the associations between TSP and mortality. Several other studies have uncovered synergistic relationships, and some of these consider pollution to be of secondary importance to weather in affecting acute mortality. Ramlow and Kuller (1990) found that daily mortality was most closely associated with the daily average temperature of the previous day rather than any pollution measure in Allegheny County, Pennsylvania. In a study which attempts to determine synergistic relationships between weather and pollution on mortality in Los Angeles, Shumway et al. (1988) determined that mortality is, "...an additive nonlinear function of temperature and pollution, whereas there may be significant interactions present, especially when low or high temperatures are combined with high pollution levels." The authors found that model-predicted average mortality values increased at both temperature extremes when particulate levels were held constant. Two evaluations in the Netherlands found temperature extremes in summer and winter to be primary determinants in mortality variation. Kunst et al. (1993) and Mackenbach et al. (1993) determined that the relationship between temperature and mortality is linear, producing a V-shaped temperature curve, with minimum mortality rates observed between 10 to 15 °C. The Kunst evaluation determined that summer acute mortality is not influenced by variations in air pollution concentration.

Although weather seems to induce mortality increases when temperatures are either very warm or very cold, the impact of weather as a confounder varies seasonally. For example, the impact of weather on acute mortality in winter is much more difficult to evaluate, and thermal relationships are decidedly weaker (WHO/WMO/UNEP, in press). Thus, although the temperature/mortality relationship might follow the V-shaped curve

Weather/Mortality Relationship

Both heat and cold-related climate stresses appear to have a significant impact on human mortality, but the impacts appear to vary spatially and temporally. Most research on weather/mortality relationships concentrate on summer temperatures, when significant spikes in daily mortality totals are apparent on certain hot days (Figures 12A-1 and 12A-2). Studies of winter weather/mortality relationships have greater uncertainty, and although winter death totals average about 10 to 15% higher than summer, the daily variance in mortality attributable to weather is considerably smaller (National Center for Health Statistics, 1978).

Most summer weather/mortality analyses concentrate on temperature, which is demonstrated to have the greatest impact of all meteorological variables. In fact, the notion of a "temperature threshold" is quite common in a number of studies, and in many cities it is apparent that elevated mortality occurs only during the 10 to 15% of all summer days which exhibit temperatures above the threshold (Smith and Tirpak, 1989; Table 12A-2). The magnitude of the threshold temperature appears to be related to the frequency of occurrence of high temperatures among these cities. For example, the temperature exceeds 96 °F in St. Louis with approximately the same frequency that it exceeds 90 °F in Detroit, values which represent threshold temperatures for these cities. This strongly suggests that the notion of a "heat wave" is relative on an interregional scale, and may depend upon the distribution of temperatures above the threshold. Most climate/health research considers the impact of temperature as absolute, and little attempt is made to consider the differential impact of heat or cold on an interregional scale (Schneider, in press).

Physiological Factors That May Be Sensitive To Meteorology

Several studies have noted that mortality can be further exacerbated by other meteorological factors such as wind and humidity (Kalkstein and Davis, 1989; Kunst et al., 1993). The combination of these elements with temperature produces an "apparent temperature", which is the perceived thermal load to the human body (Steadman, 1984). Healthy persons have efficient heat regulatory mechanisms which cope with increases in apparent temperature up to the threshold condition. When exposed to heat, the body can increase radiant, convective, and evaporative heat loss by methods such as vasodilation (enlargement of the blood vessels) and perspiration (Horowitz and Samueloff, 1987;

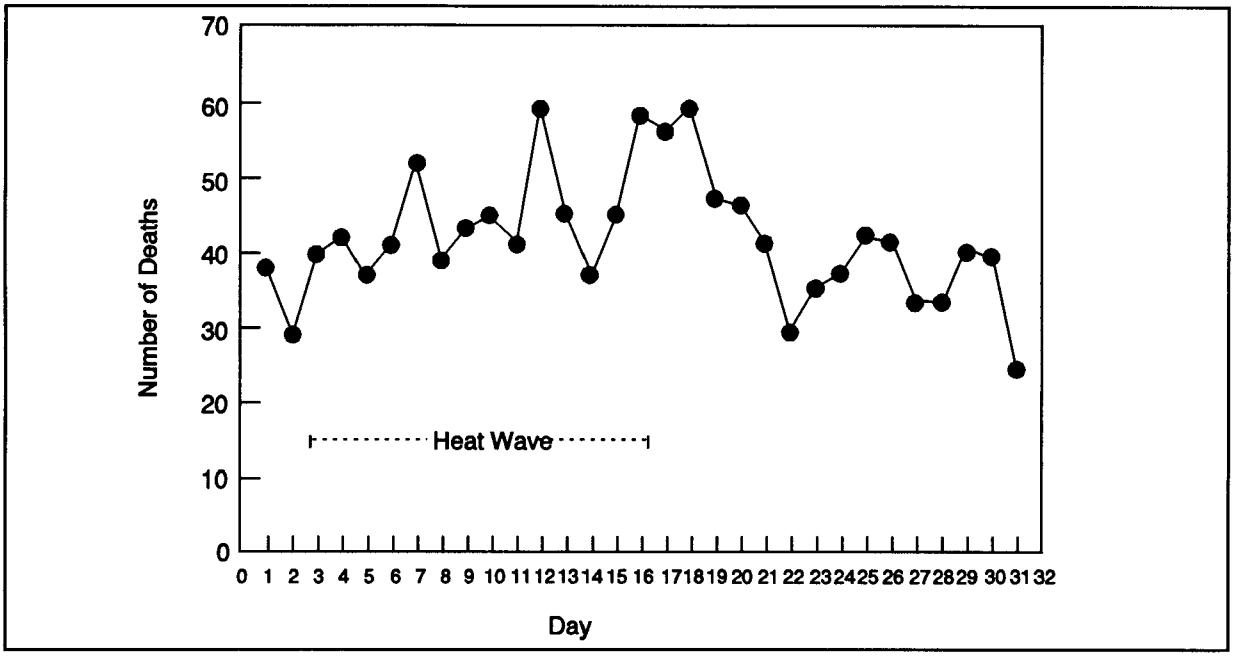

Figure 12A-1. Daily Mortality: Allegheny County, PA, July, 1988.

Source: Ramlow and Kuller (1990).

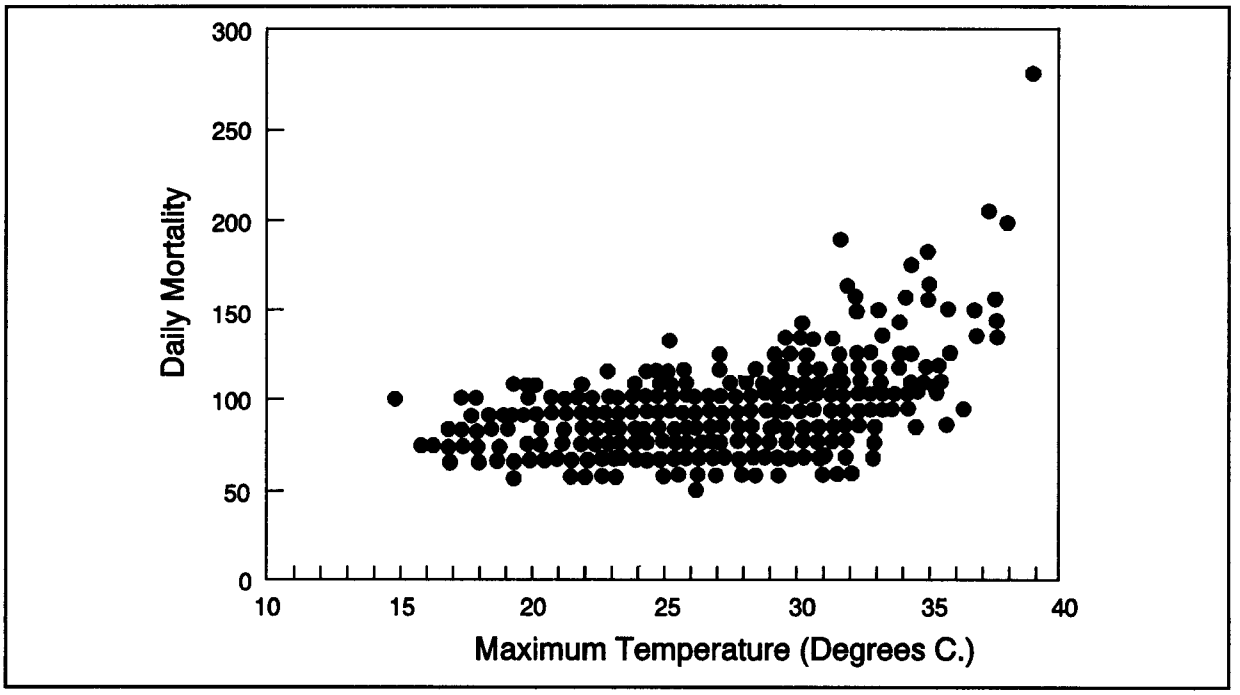

Figure 12A-2. Relations between summer maximum temperature and daily mortality in New York.

Source: Kalkstein (1993).

TABLE 12A-1. SUMMER THRESHOLD TEMPERATURES FOR SELECTED U.S. CITIES

City	Threshold Temperature (°F)	City	Threshold Temperature (°F)
Atlanta	94	Minneapolis	93
Chicago	91	New Orleans	[a]
Cincinnati	92	New York	92
Dallas	103	Oklahoma City	[a]
Detroit	90	Philadelphia	92
Kansas City	99	St. Louis	96
Los Angeles	81	San Francisco	84
Memphis	99		

[a]No threshold temperature detected.

Source: Smith and Tirpak (1989).

Diamond, 1991). In addition, acclimatization to oppressive conditions can occur within several days with continuing exposure (Kilbourne, 1992).

Heat shock proteins, which the body synthesizes when its internal temperature rises, represent one form of physiological acclimatization to heat (Born et al., 1990). A slight increase in internal temperature can induce heat shock protein production and thus, "...protect...cells against subsequent, otherwise lethal sudden temperature increase..." (Elliot, 1992). However, there are obvious indications that the body cannot cope with oppressive conditions indefinitely. Total deaths increase substantially when apparent temperatures exceed threshold values, especially for several consecutive days (Kalkstein and Smoyer, 1993).

In some cases, hot, dry weather can also induce increases in acute mortality. The desiccating impact of hot, dry conditions increases evaporation opportunity from the body, creating hyperthermal conditions which may result in death (Lowry, 1988; Jendritzky, 1991). High winds could potentially increase evaporation opportunity even further, but most weather/mortality studies surprisingly show little evidence of an important wind effect on human mortality during summer (e.g., Kunst et al., 1993). In one study where nighttime winds are inversely related to mortality, it was suggested that air flow in residences is thus

inhibited, creating oppressive conditions which pose a higher health risk (Kalkstein and Davis, 1989).

Many causes of death appear to increase when offensive weather is present. Although the most direct impact of heat stress on the human body is manifested as heat exhaustion or heatstroke, these causes represent only a small proportion of total mortality increases during offensive weather (Larsen, 1990a,b). For example, deaths from cardiovascular, cerebrovascular, respiratory, and immune system disorders appear to increase dramatically during stressful weather conditions. In southwestern Germany, cardiac infarction, nonrheumatic myocardiac diseases, vascular diseases of the brain, respiratory diseases, and bronchitis were isolated as the most important heat-related causes of death (Jendritzky and Bucher, 1993). A recent study in the Netherlands suggested that respiratory disorders account for the largest proportion of heat related deaths, followed by cardiovascular diseases (Kunst et al., 1993).

Differential temporal responses between heat related mortality and offensive weather are noted. The lag time between offensive weather and subsequent peaks in mortality is very short during summer. Most studies have identified a lag period of no longer than one day, and in some cases, the mortality increase occurs on the same day as the offensive weather (Jones et al., 1982; White and Hertz-Picciotto, 1985; Kalkstein, 1991; Kunst et al., 1993). In addition, most studies have noted that heat related mortality declines as the summer season progresses (Kalkstein and Davis, 1989; WMO/WHO/UNEP, in press). There are two possible explanations for this phenomenon: humans acclimatize to heat very quickly, even within a single season (Rotton, 1983), or many susceptible people die during early season heat waves, leaving less of a susceptible pool for later heat waves (Kalkstein, 1993). There is stronger evidence to support the latter contention. It appears that a proportion of people who die during heat waves would have died shortly afterward regardless of the weather. If such "mortality displacement" is taking place, it is probable that mortality totals shortly after a severe heat episode would be below the long term baseline (Figure 12A-3). This, in fact appears to be the case, and in an examination of several heat waves in New York City and St. Louis, daily mortality after the heat episode remained significantly below the baseline (Kalkstein, 1993). For New York and St. Louis, it was estimated that approximately 40% and 19%, respectively, of extra deaths during heat episodes represented mortality

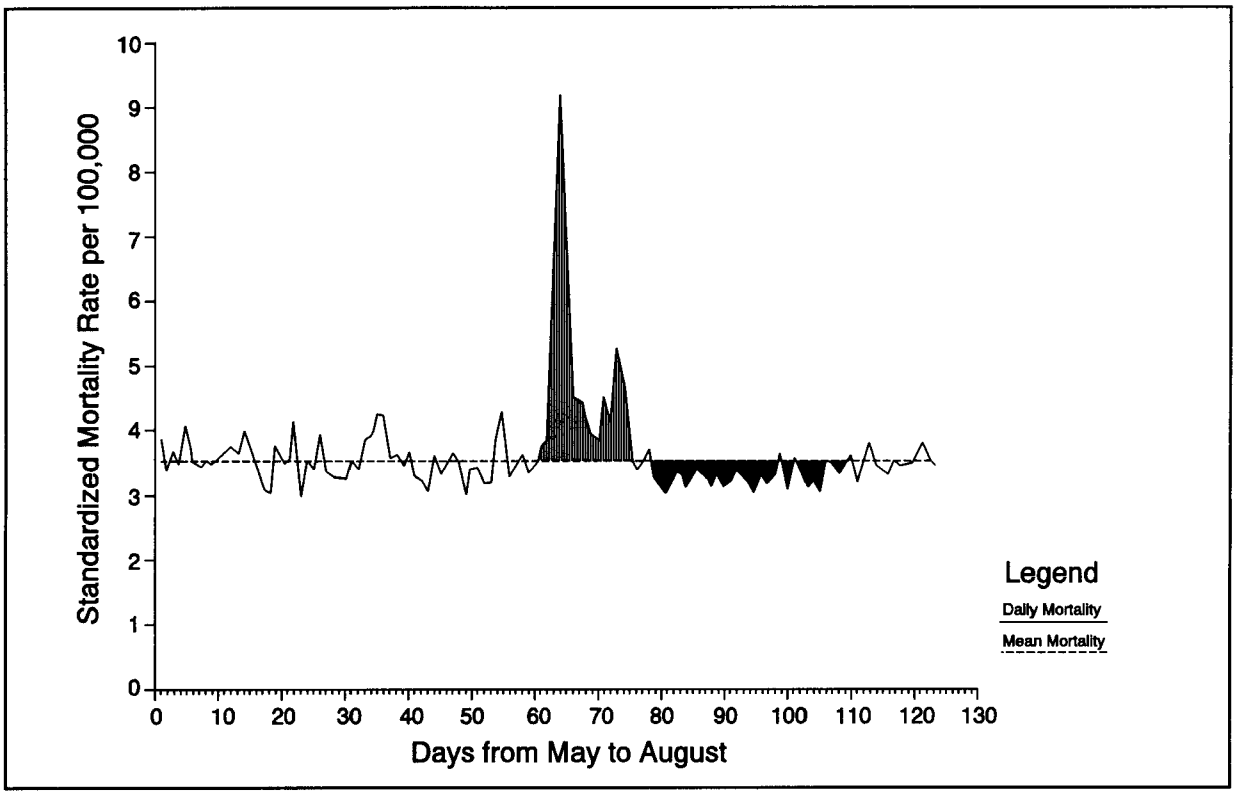

Figure 12A-3. Daily summer mortality for a New York heat wave, 1966. Darker shading represents heat related mortality; lighter shading represents diminished mortality attributed to "mortality displacement".

Source: Kalkstein, 1993.

displacement (Scheraga and Sussman, in press). Similar increases may not occur at all sites, however.

There is some evidence that the impact of weather on mortality is relative in winter as well, but there is considerable uncertainty about causal mechanisms. The strongest winter relationships are found in the northeastern, southeastern, and midwestern sections of the country, where the requisite damp, inclement weather is most common (Kalkstein and Davis, 1989; Larsen, 1990a). The weakest relationships are found in the southwestern U.S. and more arid sections of the country. The coldest areas do not tend to show the greatest winter impacts (Frost and Auliciems, 1993). One study suggests that poor populations in the Southeast are particularly at risk to cold temperatures due to relative economic disadvantages which render their dwellings less suitable to handle cold weather (Larsen, 1990a). However,

winter weather related mortality is largely attributed to indirect causes, such as infectious diseases (i.e., flu, etc.)

Cold season mortality attributed to weather is considerably more complex to establish. For example, the existence of a threshold is more difficult to discern in winter, and the impact of thermal factors appears to be less than in summer (Kalkstein and Davis, 1989). In addition, the causes of death related to weather are very different between the two seasons. Although cardiovascular disease appears important in both seasons (Auliciems and Frost, 1989), influenza, pneumonia, and increased mortality from a variety of accidents are of greater significance in winter (U.S. Department of Commerce, 1985).

Weather related mortality in winter does not tend to increase systematically as the temperatures drop. Several studies indicate that for cold weather locales such as Montreal and Minneapolis, mortality increases with decreasing temperature up to a certain point, but at very cold temperatures, mortality tends to decrease (Kalkstein, 1988; Auliciems and Frost, 1989; Frost and Auliciems, 1993). In less extreme climates, such as the Netherlands and Brisbane, Australia, mortality rates rise linearly with decreasing temperature (Kunst et al., 1993; Frost and Auliciems, 1993). Thus, in temperate environments, people appear unaccustomed to extreme cold, and react negatively. However, in cold climates, it is possible that behavioral responses, such as cold avoidance, appear to become the dominant thermoregulatory processes at very cold temperatures.

There is evidence that stormy, rather than very cold, weather is responsible for the greatest mortality in winter. Overcast and windy days with precipitation (especially snow) appear to be associated with the highest mortality totals in many mid-latitude locales (Rogot and Padgett, 1976; Glass and Zack, 1979; Baker Blocker, 1982; Kalkstein and Davis, 1989; Auliciems and Frost, 1989). Most of these evaluations suggest that acute myocardial infarction related to overexertion is the primary cause of death during inclement weather. In a 1978 blizzard in Rhode Island, emergency room admissions for myocardial infarction rose markedly three days after the storm, and mortality from ischemic heart disease showed a large increase for a five-day period after the storm (Faiche and Rose, 1979). One study even notes that relatively mild temperatures, when snow is wet, represents the most dangerous situation for the shoveller (Auliciems and Frost, 1989).

It is also suggested that storminess in winter increases mortality by confining people indoors for considerable amounts of time, permitting transmission of infectious diseases such as influenza and other microbial or viral infections (Richards and Marriott, 1974; WMO/WHO/UNEP, in press). Thus, lag times between offensive weather and subsequent related mortality in winter are much longer than in summer, with estimates of three to over eight days (Kalkstein, 1988; Larsen, 1990a; Kunst et al., 1993). Causes for this lag are unclear. Interestingly, the intraseasonal decreases in mortality found in summer do not seem to exist in winter (WMO/WHO/UNEP, in press).

Social/Demographic Factors

As might be expected, the elderly, people with pre-existing health problems, low-income groups, and urban residents are most at risk because of relatively low tolerance to heat and cold (Kilbourne, 1989). There is also some evidence that the very young (less than one year old) represent a high-risk category (Kalkstein and Davis, 1989). Elevated heat related mortality among the elderly may be due to reduced perspiration efficiency, as well as an inability to adapt to rapidly changing weather conditions (Kilbourne, 1989; Ramlow and Kuller, 1990). In addition, many medications taken by the elderly and people with health problems can increase the risk of heatstroke and other direct weather-related causes (Kilbourne et al., 1982).

One very important potential confounder for heat-related mortality is air conditioning. There is no doubt that the number of homes with air conditioning has increased rapidly over the past 30 years. In St. Louis, estimates indicated that 40% of the homes had air conditioning in 1965, and this number increased to 91% by 1992 (Stern et al., 1993).

The impact of weather on heat and cold related mortality shows considerable spatial variation. In summer, populations in the northeastern, midwestern, and Pacific regions of the U.S. show the greatest sensitivity to weather (Kalkstein and Davis, 1989; Larsen, 1990a,b). These areas are noted for great variability in summer temperatures, with intense heat waves imbedded within periods of relatively benign summer weather. The regions with the weakest summer weather/mortality responses are the southeastern, continental south, and southwestern portions of the country. These areas are noted for consistently hot weather throughout the summer, with lower variability in temperatures than regions to the north.

These disparities support the viewpoint that people respond to weather in relative, rather than absolute, fashion. In areas where extremely hot weather occurs irregularly, the weather/mortality response is significant, but in regions where heat is consistent and commonplace, the relationships are considerably weaker.

Other studies have uncovered similar findings. An evaluation of two Chinese cities, one in a subtropical climate (Guangzhou) and the other in a more temperate climate (Shanghai), uncovered similar results (Tan, 1992). The daily death rate in Shanghai exceeded that in Guangzhou by about 50% during days with temperatures above the threshold maximum temperature defined in the paper. An evaluation of ten cities in Canada yielded similar results (WMO/WHO/UNEP, in press). Three cities with infrequent but intense heat waves in summer (Toronto, Montreal, and Ottawa) demonstrated strong weather/mortality relationships. However, there appears to be a northerly extent to this impact, and Canadian maritime cities, such as Vancouver and St. Johns, demonstrated no relationship, even during the warmest days. It appears that temperatures in the maritime locales never become warm enough to elicit a heat/mortality response.

Thus, in developed countries, the greatest summer responses are noted in climates with high variability in temperatures, and with heat sufficient enough to create physiological stress. However, this may not be the case in developing countries. An evaluation of seasonal heat related mortality in Cairo, Egypt indicates a linear increase in deaths as maximum temperatures increase, although the response was less than that found in cooler Shanghai (Intergovernmental Panel on Climate Change [IPCC], in press). With the lack of air conditioning and other amenities, very hot or tropical cities in the developing world present an environment where behavioral avoidance is virtually impossible, rendering the impact of heat more extreme than in developed country counterparts.

These results suggest that physiological and behavioral acclimatization may occur with exposure to sustained periods of high temperatures. Long-term acclimatization is apparent in tropical and subtropical climates subjected to continuous hot weather (Diamond, 1991). Short-term acclimatization is possible in mid-latitudes as well with exposure to extended periods of hot weather, leading to reduced heat related mortality toward the end of the summer (Marmor, 1975; Rotton, 1983). However, mortality displacement may play a role in this reduction as well.

Acclimatization to a perpetually hot climate may occur during childhood and may be linked to activation of a greater percentage of sweat glands than would occur in an individual raised in a more moderate climate (Diamond, 1991). However, visitors from mid-latitude climates who are unaccustomed to extremely hot conditions can acclimatize to hot weather within a few days of exposure. Studies indicate that such individuals show an increased ability to sweat, and they sweat sooner than those not exposed to continual heat (Candas, 1987; Diamond, 1991).

Some research has found that low-income groups are more susceptible to heat related mortality (Jones et al., 1982), and a number of socio-economic issues have been evaluated to determine their possible influence on mortality. The most complete of these is a determination of the impact of poverty on mortality in four U.S. cities (Atlanta, New Orleans, New York, St. Louis; Smoyer, 1993). The results suggest that poverty does play a role in rendering segments of the population more sensitive to heat related mortality. With the exception of New York, the non-poor do not exhibit significantly higher heat related mortality. Poverty appears to be an especially strong factor in St. Louis, and to a lesser degree, in New Orleans. Neither poor nor non-poor groups responded negatively to weather in Atlanta. A particularly interesting response was noted in New York City, where both poor and non-poor populations appear highly susceptible to heat related mortality. In addition, these groups appear not to be susceptible within the surrounding less urban counties. This suggests that in New York the "urban heat island" impact is considerably stronger than any socio-economic factor in affecting heat-related mortality.

The Smoyer study also detected an age-related factor; the elderly poor seem particularly vulnerable to heat related mortality. In addition, those areas with the highest population density, lowest percentage of detached housing, and highest percentage of housing constructed before 1939 contained the most susceptible populations (Smoyer, 1993). Another evaluation which attempted to correlate heat related mortality with various socio-economic characteristics for 15 U.S. cities generally concurred with the Smoyer findings (Chestnut et al., 1993). In addition, cities with a large percentage of labor in manufacturing, a higher proportion of houses with incomplete plumbing, and with low percentages of population with at least a high school education also exhibited increased sensitivity to heat related mortality. It is possible that these socio-economic characteristics are not causal mechanisms, but are

instead coincidentally associated with older eastern and midwestern cities whose climatic characteristics render them more vulnerable to high heat related mortality totals. However, considering some of the poor amenities associated with substandard urban housing, such as reduced ventilation, increased heat load, lack of vegetation or shade, and high population densities, it is likely that some of these socio-economic factors play a role in exacerbating the heat/mortality problem (Lowry, 1988; Meyer, 1991; Smoyer, 1993).

Race appears to play a minimal direct role, although blacks appear more vulnerable to weather related mortality (Kalkstein and Davis, 1989). Physiological distinctions among the races seem to have little impact, but non-whites may be particularly vulnerable as they are concentrated within urban areas where behavioral avoidance is less possible. There is some evidence that improper or inadequate home heating or insulation during occasional cold waves in the South may render non-whites more vulnerable to cold related mortality there (Rango, 1984). For this reason, the Centers for Disease Control have noted that non-white elderly men constitute the highest risk group, especially if adequate housing is not available (Centers for Disease Control, 1982).

Long-term comparisons of heat related mortality as air conditioning has become more prevalent have yielded conflicting results. Several studies have not found significant decreases in mortality over the past several decades as use has increased (Ellis and Nelson, 1978; Larsen, 1990a). It has been suggested that exposure to air conditioning may decrease the body's ability to acclimatize, rendering air conditioning more harmful than good (Ellis, 1972). However, two more recent studies have determined that air conditioning plays some role in lessening heat related mortality (Rogot et al., 1992; Kalkstein, 1993). One study estimated that in New York, over 3,500 deaths were avoided during the 25 years of summers between 1964 and 1988 because of the mitigating impact of air conditioning. This represents a saving of over 21% of heat related deaths which would have occurred attributable to weather without the benefit of air conditioning (Kalkstein, 1993). In locations where air conditioning is prevalent even among less affluent residents, such as in certain U.S. cities, there may be reduced effects of both weather and PM.

Estimates of mortality attributed to weather have been attempted for a number of cities throughout the world (Table 12A-2; IPCC, in press). For some cities, the number of heat related deaths in an average summer exceeds 200. Under certain extreme circumstances,

TABLE 12A-2. ESTIMATES OF PRESENT-DAY HEAT RELATED MORTALITY DURING AN AVERAGE SUMMER

City	Mortality	City	Mortality
Atlanta	18	New York	320
Chicago	173	Oklahoma City	0
Cincinnati	42	Philadelphia	145
Dallas	19	St. Louis	113
Detroit	118	San Francisco	27
Kansas City	31	CANADA - Montreal	69
Los Angeles	84	CANADA - Toronto	19
Memphis	20	CHINA - Shanghai	418
Minneapolis	46	EGYPT - Cairo	281
New Orleans	0		

Source: IPCC (in press).

annual summer mortality can be much higher. For example, during a 10 year evaluation for Shanghai, the number of heat related deaths estimated for the hottest summer was 1,140 (Tan, 1992). Most, but not all, of these deaths were among the elderly. For the 15 U.S. cities listed in Table 12A-2, about 80% of the heat related deaths were individuals of 65 and older (Kalkstein, 1988). Other similar evaluations confirm that the majority of deaths were among elderly individuals (e.g. Ramlow and Kuller, 1990). Although estimates for winter mortality have been developed, these are considerably less reliable than those for summer. Most winter estimates for excess mortality attributable to weather are considerably lower than summer despite the generally higher winter total mortality, and one source puts them at approximately 20% of summer values (Kalkstein, 1988). However, it is difficult to assess the role of weather in contributing to outbreaks of droplet-borne diseases such as influenza. If mortality from these causes is included, winter values could be inflated considerably.

Controlling for Weather in PM/Mortality Analyses: The Use of Synoptic Climatological Methods

A number of procedures have been utilized to control for weather in PM/mortality studies, and although the variety has been great, they generally suffer from common shortcomings. First, many depend on arbitrary decisions to remove extreme weather events from the dataset. The definition of extreme weather to include, for example, days above

90 °F may be proper for a city in the north, but not for a locale further south. Thus, these arbitrary delineations consider weather as an absolute, rather than a relative, factor affecting human health. It is therefore possible that some stressful weather days are not identified, contaminating a PM/mortality dataset which is considered controlled for weather. Second, the use of weather "dummy variables" to control for meteorology within PM/mortality analyses categorizes weather within groupings which may not duplicate meteorological reality. Kalkstein et al. (1991, 1994) propose that the meteorology of a locale is defined by discrete, identifiable situations, which represent frequency modes for combinations of weather elements. Meteorological delineation that recognize the existence of such modes can be used to control for weather within this context. Third, the use of mean weather elements (e.g., mean daily temperature) does not permit a proper evaluation of, or control for, daily weather extremes. Finally, most all consideration of weather in PM/mortality studies are thermal (temperature), and, less frequently, moisture (humidity) dependent. This creates a potential weather control problem, as certain meteorological phenomena, such as stormy situations associated with mid-latitude cyclones, are not associated with thermal extremes, yet may be very important contributors to acute mortality (Kalkstein et al., 1994). These are rarely controlled for in PM/mortality studies, as they cannot be identified on the basis of temperature and humidity.

A completely different approach is that adjustment for weather-related variables is needed only insofar as it provides a basis for removing potential confounding of excess mortality with PM and other air pollutants, and that any empirical adjustment for weather is adequate. One of the most completely empirical methods for adjusting daily time series data for covariates is by use of nonparametric functions, such as LOESS smoothers, generalized splines, or generalized additive models (GAM), as demonstrated in (Schwartz, 1994 defgh, 1995a,b; Schwartz and MOrris, 1995). These are empirically satisfactory and may provide a better fit to data than synoptic categories, but at the loss of a basis for defining weather "episodes" as a characterization of duration of exposure.

Application of synoptic climatological procedures to control for weather has the potential to compensate for these difficulties and add further insight by defining an entire set of meteorological conditions which lead to increases in mortality. Many U.S. cities possess a single "offensive" summer air mass associated with unusually high mortality (e.g.,

Philadelphia, Table 12A-3). This "moist tropical" air mass in Philadelphia, possessing the highest maximum and minimum temperatures, was also associated with the greatest standard deviation in mortality of all air masses evaluated. Thus, although many days within the offensive air mass were associated with high mortality totals, a number of days showed little mortality increase. The greatest daily mortality totals during moist tropical air mass incursions occurred as part of a lengthy string of consecutive days of the air mass, and when minimum temperatures were particularly high. This type of information is vital when controlling for weather in PM/mortality analysis.

Offensive air masses which lead to mortality totals significantly higher than the long-term baseline have been identified for a number of U.S. cities (Table 12A-4). In most cases moist tropical air masses were deemed offensive (especially in the East), but the very oppressive "dry tropical" air mass was often associated with the greatest increases in mortality, especially in New York, St. Louis, Philadelphia, and in southwestern cities (Scheraga and Sussman, in press). In some cases, daily mortality totals are over 50% above the baseline (WHO/WMO/UNEP, in press). The air mass analyses support the notion that acute mortality increases only after a meteorological threshold is exceeded. This threshold is not only temperature dependent; it represents an overall meteorological situation which is highly stressful. It is noteworthy that most cities demonstrate only one or two offensive air masses which possesses meteorological characteristics exceeding this threshold.

In a PM study where stressful weather days are removed from the data base, synoptic categorization provides an efficient means to remove such days with greater security that very few meteorologically offensive days are contaminating the remaining dataset. In studies where weather is stratified based on certain meteorological elements, synoptic categorization allows for a meteorologically realistic control, and may be preferable to the use of arbitrary dummy variables when identifying meteorological conditions with an elevated mortality risk.

TABLE 12A-3. MEANS AND STANDARD DEVIATION FOR SUMMER AIR MASSES IN PHILADELPHIA

Air Mass Category Number	Total Mortality					Elderly Mortality			
	Mean 3 PM Temperature	Mean Mortality[a]	Standard Deviation	% of Top 50 Mortality[b]	% Top 50 % Frequency[c]	Mean Mortality	Standard Deviation	% of Top 50 Mortality	% Top 50 % Frequency
1	77.0	-4.11	12.87	2.00	0.14	-0.91	9.99	0.00	0.00
2[d]	89.0	8.89	16.14	46.00	3.77	6.72	12.58	46.0	3.79
3	82.4	1.63	12.82	14.00	1.27	1.59	10.76	14.00	1.28
4	79.0	-4.43	10.19	0.00	0.00	-2.82	9.33	2.00	0.23
5	82.6	-2.57	11.14	4.00	0.45	-1.36	11.10	4.00	0.45
6	85.0	3.92	16.83	14.00	1.99	3.84	13.77	10.00	1.42
7	80.6	0.70	11.82	2.00	0.14	0.52	10.41	4.00	0.67
8	85.5	2.47	12.49	8.00	1.08	2.70	9.88	10.00	1.33
9	74.7	-4.49	12.53	0.00	0.00	-2.56	10.39	2.00	0.31
10	83.6	0.13	11.80	6.00	1.07	1.28	10.86	4.00	0.67

[a]Values are evaluated against a baseline of 0.
[b]Represents the percentage of top 50 mortality days within a particular synoptic category.
[c]Ratio of percentage of top 50 days within the synoptic category over the seasonal frequency of the category. A number greater than one indicates that a larger proportion of days in the synoptic category are among the top 50 mortality days than might be expected based on the frequency of the category.
[d]"Offensive" category.

Source: Kalkstein (1993).

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TABLE 12A-4. DAILY EXCESSIVE MORTALITY (SUMMER SEASON) DURING OFFENSIVE AIR MASSES

City	Offensive Air Mass	Mortality Above Baseline[a]	City	Offensive Air Mass	Mortality Above Baseline[a]
Birmingham	MT	+2	Kansas City	DT	+5
Phoenix	MT	+1		MT*	+3
Los Angeles	MT	+9	St.Louis	DT	+15
	DM	+3		MT*	+2
Riverside	DT	+2	Newark	DT	+6
San Francisco	DT	+9		MT*	+4
Hartford	MT	+3	Buffalo	MT*	+3
Tampa	MM	+1	Nassau, NY	DT	+6
	MT*	+3		MT*	+5
Atlanta	DP	+4	New York	DT	+49
	MT*	+3		MT*	+30
Chicago	DT	+9	Cincinnati	MT*	+2
	MT*	+14	Columbus	MT*	+3
Indianapolis	MT*	+3	Portland	DT	+5
Louisville	MT*	+2	Philadelphia	DT	+32
Boston	MT*	+8		MT*	+10
Baltimore	MT*	+5	Providence	MT*	+7
Detroit	DT	+10	Memphis	DT	+3
	MT	+8		MT*	+1
Minneapolis	DT	+4	Dallas-Ft.Worth	DT	+3
	MT*	+6			
			Houston	DT	+8
			San Antonio	DT	+1

[a]Mean daily deaths above the long-term baseline.
Air Mass Abbreviations: MT = Moist Tropical; DM = Dry Temperate; DT = Dry Tropical; MM = Moist Temperate; DP = Dry Polar. Asterisks denote a particularly offensive subset of MT.

1

13. INTEGRATIVE SYNTHESIS: KEY POINTS REGARDING PM EXPOSURE, DOSIMETRY, AND HEALTH RISKS

13.1 INTRODUCTION

This chapter concisely characterizes the hazard identification and exposure-dose-response components of the risk assessment, integrating the key information and conclusions from preceding chapters into a coherent framework upon which to base interpretations concerning human health risks posed by ambient or near-ambient levels of particulate matter (PM) in the United States. Certain issues of direct relevance to standard setting are not explicitly addressed in this document, but are instead analyzed in the Staff Paper prepared by the Office of Air Quality Planning and Standards (OAQPS) as part of its regulatory analyses. Such analyses include: (1) discussion of what constitutes an "adverse effect" relative to developing the primary and secondary NAAQS; (2) exposure analyses and assessment of consequent risk; and (3) discussion of factors to be considered in determining an adequate margin of safety. Another issue directly pertinent to standard setting is identification of populations at risk, which is basically a selection by EPA of the subpopulation(s) to be protected by promulgation of a given standard. This issue is addressed only partially in this criteria document. For example, information is presented on factors, such as preexisting disease, that may biologically predispose individuals and subpopulations to adverse effects from exposures to PM. The identification of a population at risk, however, also requires information above and beyond data on biological predisposition, such as information on levels of exposure, activity patterns, and personal habits. Such information is included in the Staff Paper.

While more details are presented in the earlier chapters, this chapter characterizes key uncertainties involved in the data and limitations on the conclusions that can be drawn from them. Additionally, a new discussion expanding and placing into perspective key information and conclusions is provided. Toward this end, the chapter is organized into several sections, each of which covers one or more major components of an overall exposure-dose-response description: (1) chemical and size characteristics of ambient PM; (2) ambient levels of PM

and related exposure aspects; (3) dosimetry of inhaled particles in the respiratory tract; (4) qualitative and quantitative characterization of key health effects of PM; (5) characterization of potential health effects of chemical components of ambient PM (e.g., acid aerosols); (6) hypotheses concerning the biological bases for observed health effects; (7) identification of population groups potentially at enhanced risk for health effects associated with ambient PM exposure; and (8) implications of quantitative exposure-effects relationships for special risk groups.

13.2 CHEMISTRY AND PHYSICS OF ATMOSPHERIC PARTICLES

"Particulate matter" is a generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) dispersed in the ambient atmosphere over a wide range of sizes. The chemical and physical properties of PM vary greatly with time, region of the United States, meteorology, and source category, thus complicating the assessment of healths and welfare effects.

Atmosphere particles originate from a variety of sources (such as combustion-generated, photochemically produced, wind-blown dust, and plant products). Particle diameters range from < 10 nm to > 100 μm. Particles are ubiquitous in the atmosphere and can be biogenic or anthropogenic in origin. A complete description of the atmospheric aerosol would include an accounting of the chemical composition, morphology and size of each particle, and the relative abundance of each particle type as a function of particle size. However, most often the physical and chemical characteristics of particles are measured separately. The physical characteristics of aerosols are described by size distributions that are determined by physical measures. Chemical composition is determined by analysis of collected samples.

13.2.1 Size Characteristics

As discussed earlier in Chapters 3 and 4, the definition of fine and coarse particles is an operational one based on the observations by numerous investigators, beginning in the early 1970's, that mass size distribution measurements, when appropriately plotted, usually yielded bimodal distributions with a minimum between 0.7 and 3.0 μm diameter (Whitby,

1978; Wilson, 1995). An idealized distribution, showing the normally observed division of ambient aerosols into fine and coarse particles, is presented in Figure 13-1. (Aerosol refers to a suspension of solid or liquid particles in air. However, aerosol is sometimes used to refer to only the condensed phase portion when it is desired to emphasize that the discussion refers specifically to particles small enough to be suspended in air.) There is some overlap of fine and coarse particles in the intermodal region between 1 and 3 μm.

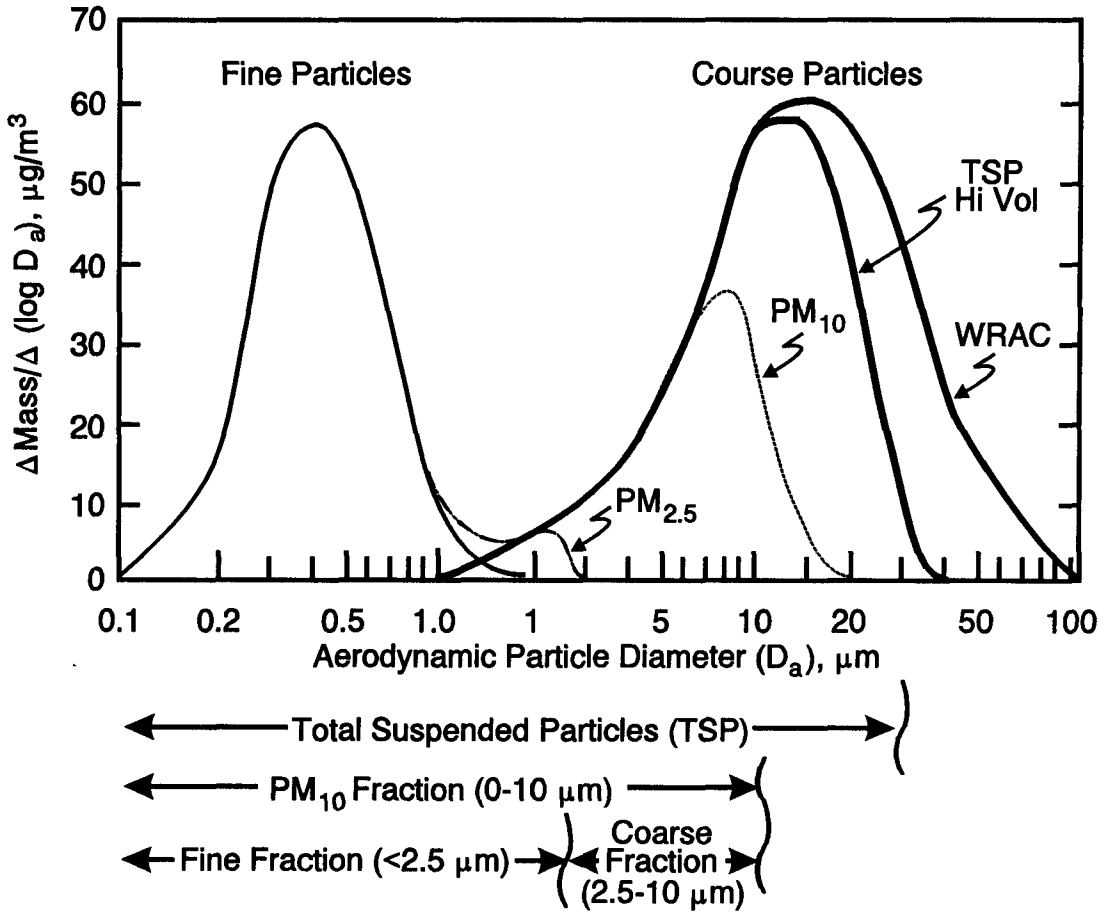

Figure 13-1. Sampling fractions for an idealized ambient particulate mass distribution.

It is also possible to define portions of the distribution by sampler design or by an upper or an upper and lower 50% cut-point. For example TSP or Total Suspended Particulate Matter is defined by the design of the High Volume Sampler (hivol) which

collects all of the fine particles but only a portion of the coarse particles. The upper cut-off size of the hivol depends on the wind speed and direction. Heroic measures, such as were undertaken with the Wide Area Aerosol Classifier (WRAC), are required to collect the entire coarse mode (Lundgren and Burton, 1995).

In order to avoid the lack of definition of the hivol's upper size cut-off and to focus regulatory concern on those particles small enough to enter the lower respiratory tract, the form of the PM National Ambient Air Quality Standard (NAAQS) was changed in 1987 from TSP, as measured by the hivol, to PM10 (USEPA, 1987). PM10 samplers collect all of the fine particles and a portion of the coarse particles. The upper cut-point is defined as having a 50 % collection efficiency at 10 ± 0.5 μm diameter. The slope of the collection efficiency curve is defined in the Federal Register, Part 53. There are also samplers with upper cut-points of 2.5 and 1.0 μm. The dichotomous sampler splits the sampled particles into a smaller and larger fraction.

In an analysis reported in 1979, EPA scientists recognized the need to measure fine and coarse particles separately (Miller et al., 1979). Based on the availability of a dichotomous sampler with a separation size of 2.5 μm, they recommended 2.5 μm as the cut-point between fine and coarse particles. Except for collection in clouds, fog, or at a relative humidity very close to 100%, the PM2.5 sample will contain all of the fine particles. However, especially in dry areas or during dry conditions, it may also contain a small but significant fraction of the coarse particles (Wilson, 1995).

As more experimental evidence and theoretical understanding developed, it was recognized that fine particles could be best understood as being composed of a nuclei mode and an accumulation mode (Whitby, 1978). The nuclei mode can be seen as a completely separate mode only under special conditions such as the oxidation of SO_2 to sulfuric acid in otherwise particle-free air or in the vicinity of sources of hot gases in which normally condensed species have been vaporized. A size distribution measurement, made in automobile traffic at the General Motors Proving Grounds, which demonstrates such a separation, is shown in Figure 13-2 (Wilson et al., 1977). The background air, measured before and after simulating freeway traffic on the proving ground track, indicated that all of the nuclei mode and a small fraction of the coarse mode were generated by the traffic, but that the accumulation mode and most of the coarse mode were more regional in nature.

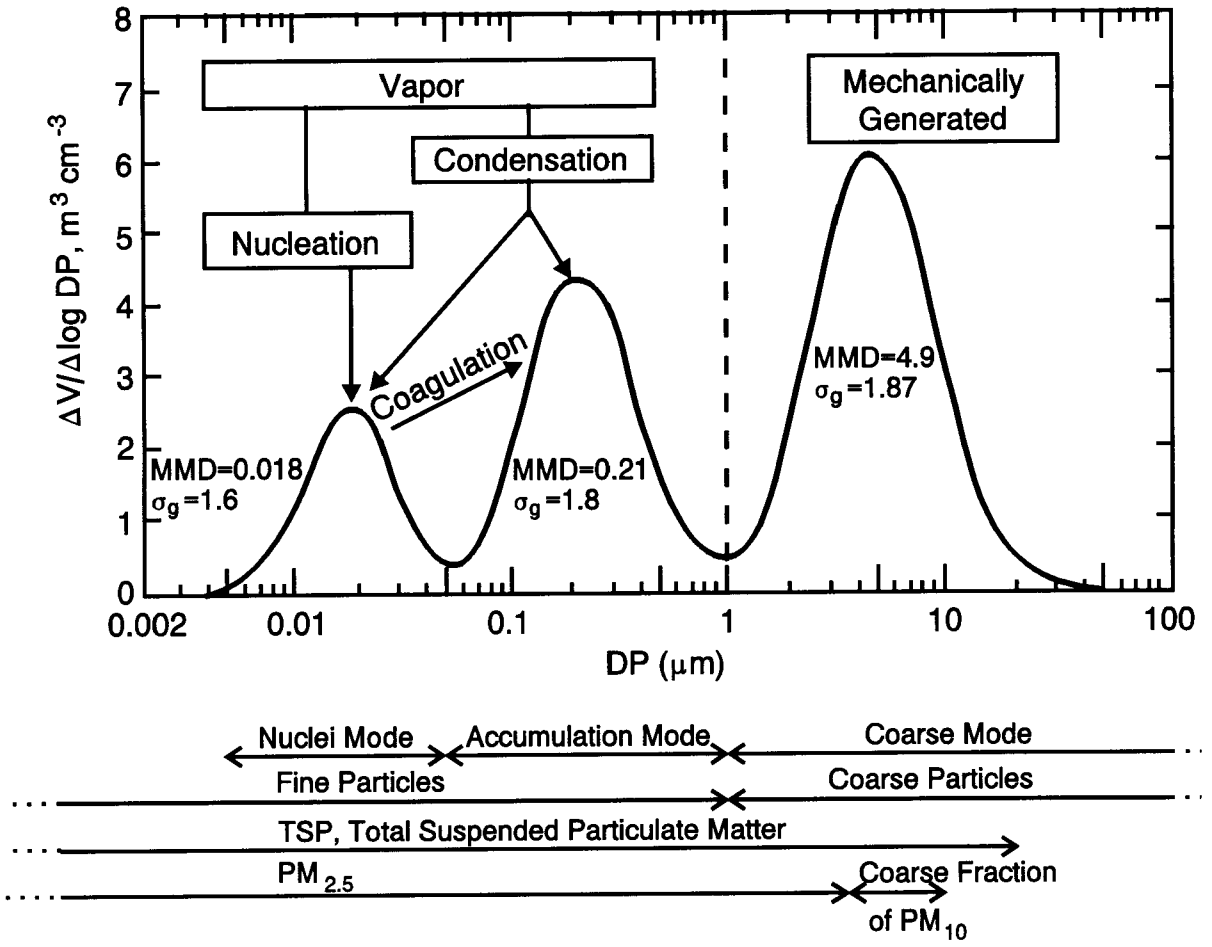

Figure 13-2. Measured mass size distribution showing particles in nuclei and accumulation modes of fine particles. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).

Source: Wilson et al. (1977).

Such studies have led to a better understanding of the formation mechanisms for fine and coarse particles. In simplest terms, coarse particles are formed by breaking up bigger particles into smaller particles. The coarse particle mode is sometimes called the dispersion, mechanically-generated or comminution mode. However, as particles become smaller and smaller, more and more energy is required to break them into smaller units. This establishes a lower limit of approximately 1 μm for coarse particles (Friedlander, 1977).

Fine particles are usually formed from gases. The processes of nucleation and growth are shown in Figure 13-2. Nucleation involves the formation of very small particles from gases. Low vapor pressure substances are generated in the gas phase by high temperature

vaporization or by chemical reaction in the atmosphere. Growth of particles in the nuclei mode occurs by two processes; coagulation, in which two small particles combine to form a larger particle, and condensation, in which gas or vapor molecules condense onto existing particles. The rate of coagulation depends on particle number and particle velocity; the rate of condensation depends on surface area. These parameters decrease rapidly as the particle size approaches 1 μm. As a result, particles normally do not grow by these processes to diameters above 1 μm. Since particles tend to "accumulate" in the size range from 0.1 to 1 μm, this size range is called the accumulation mode.

Secondary fine particles are formed by the atmospheric conversion of gases into particles. In one mechanism a gas is converted into the gaseous form of a material with a low vapor pressure. One example is the oxidation of SO_2 (sulfur dioxide) to H_2SO_4 (sulfuric acid) which forms fine particles by coagulation. In a second mechanism, a gas is converted into a second gas which can react further to form a low vapor pressure substance. An example is the oxidation of NO_2 (nitrogen dioxide) to HNO_3 (nitric acid) which can react with NH_3 (ammonia) to form fine particles of NH_4NO_3 (ammonium nitrate). Acid gases in the atmosphere, such as SO_2 and HNO_3, may also react with coarse particles (such as $CaCO_3$ from soil, construction or demolition or NaCl from sea spray or road salt) to form salts. These would still be considered coarse particles. Metals vaporized in high temperature processes such as smelting and organic material vaporized in cooking, which coagulate or condense without chemical reaction, form primary fine particles.

In addition to anthropogenic particles, resulting from human activities, fine PM also contains particles of natural origin, i.e. atmospheric reaction products of gases such as terpenes emitted by plants. Thus, the organic component of fine particles contains both natural and anthropogenic material and both primary and secondary material. Combustion products from the burning of gasoline and diesel fuel also give rise to fine particles. However, the combustion of coal and heavy fuel oil yields both fine particles, from material that is vaporized during combustion, and coarse particles, i.e. flyash, from non-combustible material.

In recent years it has been realized that during periods of fog or near 100 % relative humidity certain types of particles can grow by absorption of water and reach diameters of up to five times their dry size. Particle size distributions which include particles subjected to

such conditions sometimes show an accumulation mode which is split into a condensation or dry mode and a droplet or wet mode. This process is discussed in Section 3.7 of Chapter 3.

The nuclei or ultrafine mode, with particles from a few nm to 100 nm, has become of interest lately because of its suggested biological activity in the lower respiratory tract (see Sections 13.4, 13.6, and 13.7). Ultrafine particles always contribute most of the atmospheric aerosol by particle number (90 to 99%). Such particles, however, rapidly coagulate into the accumulation mode so they make a significant contribution to mass only under conditions in which they are rapidly generated, such as in vehicular traffic.

Available data on the measurement of atmospheric coarse particles indicate that the majority of the mass is usually associated with particles of 2 to 100 μm diameters, is lognormally distributed with a mass mean diameter (MMD) of 10 to 30 μm and a geometric standard deviation near 2. Fine particles generally have the majority of their mass in the 0.1 to 1.0 μm diameter and a geometric standard deviation of < 2.

There is generally a clear separation of atmospheric aerosol into two mass fractions-a fine and coarse mode with a minimum in the 1 to 3 μm range. This idealized "bimodal" ambient mass size distribution consist of both dispersed (coarse) and condensed (fine) particles. The total mass, mass mean diameter and the mass fraction in the two modes varies from location to location and from day-to-day, while the shape of the mass/size distribution remains rather constant.

13.2.2 Chemical Characterization of PM_{10} Particles

Many measurements indicate that the chemical composition of coarse and fine particles are distinct, as are the processes that affect their formation and removal (Figure 13-2). Coarse particles are typically generated by mechanical processes such as grinding, wind, and erosion and consist of substances such as soil dust, sea spray, plant fragments, tire wear particles, and emissions from rock-crushing operations. The data consistently show that crustal elements such as iron, silicon, and calcium are concentrated in the coarse fraction. The major sources of coarse particles are windblown dust from soil, unpaved roads, piles of material containing coarse dust, etc. and dust reentrained by turbulent air generated by traffic on paved or unpaved roads. Coarse particles are also generated by demolition of buildings and evaporation of sea spray. Pollen, mold spores, and parts of plants and insects are also

found in the coarse particle size range. The composition of the coarse particle minerals is similar to the composition of the earth's crust, with major components being calcite and silicon with major ingredients of iron and aluminum (Dodd et al., 1991).

Fine particle chemical composition differs greatly from that of soil and ocean derived coarse particles and erosion. The major components of fine particles are sulfate, nitrate, organic and elemental carbon, ammonium ion and a variety of trace elements. Metals and organic carbon can be found in both size fractions.

Fine particle mass is frequently dominated by sulfates. Sulfates and associated water can represent 75 to 80% of fine mass. Organic and elemental carbon can account for 15 to 20% of the mass. Sulfuric acid and its neutralization products with ammonia constitute a major anthropogenic contribution to fine particle aerosol.

Several atmospheric aerosol species, such as ammonium nitrate and certain organic compounds, are semivolatile and are found in both gas and particle phases. The gas-particle distributions of semivolatile organic compounds depend on composition, vapor pressure, total particulate surface area, and atmospheric temperature. Diurnal temperature fluctuations can cause dynamic changes in gas-particle partitioning on a time scale of a few hours. This process can lead to alteration of the chemical composition of atmospheric aerosols during sampling, storage, or analysis by loss of volatile components. Water is an important constituent of atmospheric particles. Hygroscopic or deliquescent particles can absorb water in increasing amounts as the relative humidity increases. Some but not all of this particle-bound-water can be lost when the sample is exposed to drier air.

The carbonaceous fraction of ambient PM consist of both elemental (EC) and organic carbon (OC). Wood-burning fireplaces are a major source of both EC and OC. Diesels are major sources of EC, also called black carbon. In areas where wood burning is significant, more particulate elemental carbon is expected in winter than summer. Most other EC is attributable to diesel motor vehicle sources. The concentration of EC varies significantly, depending on the location and the season. Elemental carbon concentration in rural and remote areas usually vary from 0.2 to 2.0 $\mu g/m^3$ and from 1.5 to 20 $\mu g/m^3$ in urban areas, with average EC concentration around 1.3 and 3.8 $\mu g/m^3$ for U.S. rural and urban sites, respectfully. The distribution of EC emitted by automobiles is unimodal with 85% of the

mass in particles smaller than 0.12 μm D_{ae}. The ambient distribution of EC is bimodal, with peaks in the 0.05 to 0.12 μm and 0.5 to 1.0 μm size ranges.

The organic component of the ambient aerosol both in polluted and remote areas is a complex mixture of hundreds of organic compounds. The concentration of OC is around 3.5 $\mu g/m^3$ in rural locations and 5 to 20 $\mu g/m^3$ in polluted atmospheres. Organic carbon can represent about 24% of the PM_{10} mass, with 30% being $PM_{2.5}$ mass.

Primary carbonaceous (OC) particles are produced by combustion, chemical, geological, and natural sources. Important sources in Los Angeles, CA included meat cooking (21.2%), paved road dust (15.9%), fireplaces (14%) and noncatalyst equipped automobiles (11.6%). Secondary organic aerosol material is formed in the atmosphere by the condensation of low vapor pressure products of the oxidation of organic gases on the already existing particles. Partial oxidation products of aromatics such as toluene contribute as much as 60% of the secondary organic aerosol. Organic compounds accumulate mainly in the submicrometer aerosol size range.

Trace elements that are found predominantly in the fine particle size distribution are Na, Cs, Cl, Br, Cu, Zn, As, Ag, Cd, In, Sn, W, and Pb. Greater than 75% of their mass is associated with particles of diameter less than 2 μm. Metals which are found in both fine and coarse modes are V, Cr, Mn, Fe, Co, and Se, while elements found primarily within large particle distributions are Ca, Al, Ti, Sc, and La. Table 13-1 shows the concentration ranges of some elements found in U.S. ambient air. Potential sources of trace metals found in fine airborne particles are primarily anthropogenic and include combustion of coal and oil, wood burning, waste inceneration, smelters, and metal mining production.

Fine particles emitted from oil and coal combustion are enriched with metals. Vegetative burning, which includes residential wood combustion and forest fires, is a source for release of trace elements into the atmosphere. Potassium is a characteristic trace element present in fine particles from wood burning. Vanadium can be related to oil burning. Over 90% of the mass from geological material is in the coarse particle size fraction, while the combustion-related source categories contained $\approx$90% of the mass in the $PM_{2.5}$ fraction.

Available data indicate that about 50% of aerosol nitrate and 20% of aerosol sulfate is associated with the coarse fraction of PM_{10} particles in marine-influenced environments (John et al., 1990). Wolff (1984) found coarse particle nitrate to be 18 to 90% and coarse sulfate

TABLE 13-1. CONCENTRATION RANGES OF VARIOUS ELEMENTS ASSOCIATED WITH PARTICULATE MATTER IN THE UNITED STATES ATMOSPHERE (ng/m^3)

Elements	Remote	Rural	Urban (USA)
As	0.007 to 1.9	1.0 to 28	2 to 2320
Cd	0.003 to 1.1	0.4 to 1000	0.2 to 7000
Ni	0.01 to 60	0.6 to 78	1 to 328
Pb	0.007 to 64	2 to 1700	30 to 96270
V	0.001 to 14	2.7 to 97	0.4 to 1460
Zn	0.03 to 460	11 to 403	15 to 8328
Co	0.001 to 0.9	0.08 to 10.1	0.2 to 83
Cr	0.005 to 11.2	1.1 to 44	2.2 to 124
Cu	0.029 to 12	3 to 280	3 to 5140
Fe	0.62 to 4160	55 to 14530	130 to 13800
Hg	0.005 to 1.3	0.05 to 160	0.58 to 458
Mn	0.01 to 16.7	3.7 to 99	4 to 488
Se	0.0056 to 0.19	0.01 to 3.0	0.2 to 30
Sb	0.0008 to 1.19	0.6 to 7	0.5 to 171

Source: Schroeder et al., 1987.

to be 3 to 23% of the total mass of aerosol at five different continental locations. Milford and Davidson (1987), summarizing the size distribution data for sulfates and nitrates, noted that the sulfate and nitrate had a major mass peak less than 2 μm, with a signficant secondary mass peak in the PM_{10}-coarse fraction size range (2.5 to 10 μm).

Chow et al. (1994) simultaneously measured $PM_{2.5}$ and PM_{10} particles at nine sites in the Los Angeles Basin during the summer and fall of 1987. PM_{10}-coarse fraction mass was about one-fourth of the $PM_{2.5}$ mass in the fall and one-half in the summer; the ratio was similar for most sites. Sodium, aluminum, silicon, calcium, and iron were abundant only in the coarse particle fraction. Nitrate was equally divided between coarse and fine particles. The ratio of PM_{10}-coarse fraction sulfate to fine particle sulfate was 5% in the summer and 20% in the fall.

Sweet and Vermette (1993) concluded that the PM_{10} mass is about 50% higher in urban areas than rural. The average concentration of most trace elements were 3 to 10 times higher in urban areas, with peaks 100 times higher. Crustal material (e.g., Ca, Si, Al, Fe)

had their major concentration in the PM_{10} coarse particle fraction, while anthropogenic material (i.e., Cu, Zn, Pb) had bimodal distribution, with 20 to 50% of total mass in the PM_{10} coarse particle fraction in both urban and rural areas. Fugitive emission sources (contaminated soil, road dust, steel and coal dust) accounted for nearly all of the anthropogenic coarse particle material.

A secondary mass peak contained within the PM_{10} coarse fraction size range occurs for sulfate, nitrate, and anthropogenic trace metals. The sulfate and nitrate peaks are probably due to chemical reactions on the surface of coarse particles. Urban areas must be considered as major sources for anthropogenic trace metals present in the PM_{10}-coarse fraction because urban concentrations of trace metals exceed rural area concentration by 5 to 10 times. PM_{10}-coarse fraction particles should not be lumped together with all coarse particles into a single category because the chemical composition of particles >10 μm is different (e.g., several types of pollens).

In addition to the above distinctions, there are many other differences between fine and coarse mode particles, as are summarized in Table 13-2.

13.3 UNITED STATES PM CONCENTRATIONS AND EXPOSURE CONSIDERATIONS

As discussed in Chapter 6, the nonurban (IMPROVE/Nescaum) and urban (AIRs) networks may be used to examine different patterns for PM concentrations in various regions of the U.S. and to compare urban and non-urban concentrations. Of particular interest is the observation of an urban excess of PM which varies both spatially and temporally.

Nationally, the fine fraction at non-urban sites ranges between 0.4 and 0.8 μm. The highest fine fraction is recorded east of the Mississippi River where 75% of the non-urban mass is in particles < 2.5 $\mu g/m^3$ in size. Thus fine particles dominate the non-urban aerosol concentration east of the Mississippi River. The mass of the fine fraction also exceeds the mass of the coarse fraction at the non-urban northwestern sites. The fine fraction is lowest in the southwestern United States ($< 50\%$) particularly in the Spring (Quarter 2). Thus the non-urban southwestern PM is dominated by coarse mass.

TABLE 13-2. COMPARISON OF FINE VERSUS COARSE MODE PARTICLES

	Fine	Coarse
Formed from:	Gases	Large solids/droplets
Formed by:	Chemical reaction Nucleation Condensation Coagulation Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding etc.) Evaporation of sprays Suspension of dusts
Composed of:	Sulfate, $SO_4^=$ Nitrate, NO_3^- Ammonium, NH_4^+ Hydrogen ion, H^+ Elemental carbon, C Organic compounds PNA Metals, Pb, Cd, V Ni, Cu, Zn Particle-bound water Biogenic organics	Resuspended dusts Soil dust, street dust Coal and oil fly ash Metal oxides of Si, Al, Mg, Ti, Fe $CaCO_3$, NaCl, sea salt Pollen, mold spores Plant parts
Solubility:	Largely soluble, hygroscopic and deliquescent	Largely insoluble and non-hygroscopic
Sources:	Combustion of coal, oil, gasoline, diesel, wood Atmospheric transformation products of NO_x, SO_2, and organics including biogenic organics, e.g., terpenes High temperature processes, smelters, steel mills, etc.	Resuspension of soil tracked onto roads and streets Suspension from disturbed soil, e.g., farming, mining Resuspension of industrial dusts Construction, coal and oil combustion, ocean spray
Lifetimes:	Days	Hours
Travel Distance:	100's of km	10's of km

In the non-urban East, the fine aerosol is dominated by sulfur aerosol types (sulfate and ammonium ion, and associated water) and organics, which together constitute about 80% of the fine particulate mass. Over the northwest, organics dominate the non-urban fine particle mass, especially during the winter season. In the southwest, fine soil is a major component, accounting for 25 to 30% of the non-urban fine mass. Non-urban sulfate, in the eastern United States, exceeds the concentration over the mountainous western states by factors of five or more. Fine non-urban particle nitrates are most prevalent over California, exceeding 4 $\mu g/m^3$ at most sites. Organic carbon non-urban concentrations are higher over California and northwestern sites, as well as eastern United States sites.

The eastern United States is covered by a widespread contiguous $PM_{2.5}$ non-urban concentration that ranges from 10 $\mu g/m^3$ in winter (Quarter 1) to 17 $\mu g/m^3$ in summer (Quarter 3). The lowest non-urban $PM_{2.5}$ concentrations are measured over the central mountainous western states. The low concentrations are about 3 $\mu g/m^3$, while the summer values are around 6 $\mu g/m^3$. Somewhat elevated $PM_{2.5}$ concentrations are observed over the southwestern border adjacent to Mexico as well as in California and the Pacific northwest.

The spatial pattern for non-urban PM_{10} concentrations is similar to the $PM_{2.5}$, however, the PM_{10} concentration exceeds the $PM_{2.5}$ by up to a factor of two, depending on region and season. Eastern non-urban PM_{10} concentrations range between 12 $\mu g/m^3$ in Quarter 1 and 25 $\mu g/m^3$ in Quarter 3. The lowest non-urban PM_{10} concentrations are measured over the central mountain states (5 $\mu g/m^3$ in Quarter 1). Higher PM_{10} non-urban concentrations between 10 to 20 $\mu g/m^3$ are measured over the southwestern United States, as well as over the Pacific states from California to the northwest.

The highest AIRs $PM_{2.5}$ concentrations are reported over eastern urban industrial centers, such as Philadelphia and Pittsburgh, where concentrations around 50 $\mu g/m^3$ exceed those of non-urban counterparts by a factor of 2 to 3. The excess urban $PM_{2.5}$ concentrations are confined to the immediately vicinity of urban centers. The $PM_{2.5}$ concentrations at remote New England, over the southeastern United States, and over the upper Midwest are within about 50% for AIRs $PM_{2.5}$ and Improve/Nescaum $PM_{2.5}$. This indicates that over the eastern United States, a regionally homogenous background of $PM_{2.5}$ concentration exists that has smooth spatial gradients. Superimposed on the smooth residual patterns are local hot-spots (within a few miles of urban industrial centers) with 2 or 3 times

excess concentrations. The eastern United States $PM_{2.5}$ is composed largely of secondary sulfate, nitrate, and organic aerosols that are produced several days after the emission of their gaseous precursors.

The reported AIRs $PM_{2.5}$ concentrations over the Pacific States are generally higher and average 20 to 50 $\mu g/m^3$. This is 5 to 10 times higher than comparison concentrations from the Improve NESCAUM $PM_{2.5}$ data set. The dramatic difference is due to urban-industrial-agricultural centers verses remote national parks and wilderness areas.

Urban PM_{10} data from the AIRs network are summarized in Table 13-3. The annual means for all regions show a decline from 1985 to 1993. The variability within the region is much greater in the west than southeast and midwest. The eastern U.S. has summer urban-peaks, while the west has fall and winter-peaks. The fine fraction is more predominate in the east than the southwest or upper midwest. Thus, there are distinctive differences by region for PM_{10} size fractions by mass.

The highest eastern United States urban PM_{10} concentrations are recorded in Quarter 3. The peak concentrations are over the Ohio River Valley, stretching from Pittsburgh to West Virginia, southern Indiana and St. Louis. In this region, the urban PM_{10} concentration over the industrialized midwest exceeds 40 $\mu g/m^3$. Additional hot-spots with $>$ 40 $\mu g/m^3$ are recorded in Birmingham, AL, Atlanta, GA, Nashville, TN, Philadelphia, PA, and Chicago, IL. The summertime PM_{10} urban concentrations in New England and upstate Michigan are $<$ 20 $\mu g/m^3$. The spatial variability of urban PM_{10} over the eastern United States is derived primarily from the varying emissions density of primary aerosols and precursors of secondary aerosols.

The eastern PM_{10} seasonality is rather pronounced, with winter concentrations December through March of 24 $\mu g/m^3$ and July through August peaks of 35 $\mu g/m^3$. Fine and coarse urban particles have different seasonal dynamics in the East. Fine particle mass is bimodal, with a major peak in July and a smaller winter peak in January. The coarse particle concentration shows a single broad peak over the warm season April through October. Sixty percent at PM_{10} is in the sub 2.5 μm size range.

The mountainous states, west of the Rockies, show high urban PM_{10} concentrations ($>$ 50 $\mu g/m^3$) at localized hot-spots during the cold season including Salt Lake City, LA basin San Jonquan Valley, and site in Wyoming, Oregon and Washington. The seasonality

TABLE 13-3. CHARACTERIZATION OF URBAN PM_{10} DATA FROM AIRS NETWORK BY REGION FOR THE UNITED STATES

Region	PM_{10} ($\mu g/m^3$) 1993	1985	SD[a]	Seasonality	Seasonal Variation %	$PM_{2.5}/PM_{10}$	Influences
Northeast	22	36	30%	Summer Peak July	20%[b]	62%	Canadian and Gulf airmasses, local sources, long range transport
Southeast	24	32	17%	Summer High July, August	37%	58%	Flat, poor regional ventilation
Industrial Midwest	25	38	28%	High June, August Low November, February	37%	59%	Winter cold Canadian airmasses. Summer moist Gulf Coast masses
Upper Midwest	25	31	19%	Slightly Lower Levels December/January	19%	38%	Agricultural Heartland windblown dust influence
Southwest	26	52	45%	April-June Peak October-November Peak August-September Dip		37%	low precipitation, coarse particle dominant, dust contribution to PM_{10}
Northwest	25	50	45%	Peak December Low March-May	36%	59%	Meteorology highly variable
Southern California	32	45	40%	Peak November Low March	27%	50%	Air flow from Pacific, dry summer, low in remote Basin wide elevation

[a]Standard deviation among monitoring stations within regions.
[b]Seasonal range expressed as percent.

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of urban $PM_{2.5}$ west of the Rockies is strongly peaked in December (40 $\mu g/m^3$) — about a factor of four higher than the summertime values. The coarse urban fraction shows a broad peak during late summer, July through October.

The eastern United States has summer urban peaks, while the west has fall and winter urban peaks. The fine fraction is 60% of PM_{10} in the east and 50% in the west. Fine particles dominate during the Winter season in the Western United States.

The urban PM_{10} concentrations exhibit marked differences in the shape of their distribution functions around the mean values. The day-to-day variations of urban PM_{10} concentration in Knoxville, TN are about 40% of the mean value of 35 $\mu g/m^3$, while Missoula, MT shows a coefficient at variation of 60% of the mean of 34 $\mu g/m^3$. During the winter season, the coefficient of variation is even higher. Thus, Missoula has a significantly higher short-term variation.

The highest logarithmic standard deviation in concentrations is recorded over the northeast and northwest states, during the cold season. Regionally, the logarithmic standard deviation in the north-northwest is about 2.0, with pockets of high winter variability such as Salt Lake City, Utah and Missoula, MT. In southern states, the summertime logarithmic standard deviation is below 1.5, indicating a more uniform summertime PM_{10} level, while the northern states are more epidsodic.

Tables 13-4a and 13-4b provide representative examples of current PM_{10} levels observed in selected U.S. SMSAs for 1993.

Among key issues addressed in Chapter 7 were (1) the relative contributions of ambient air PM exposures to total human exposure to particles (also including those derived from indoor sources) and (2) the extent to which ambient air monitoring sites might serve as reasonable indices (or proxy's) of variations in personal exposures of individuals evaluated in community-level epidemiologic studies of PM health effects. Suffice it to say here that widely varying percentages of total human exposure to particles can be attributed to those from ambient sources, depending upon a number of factors (penetration of outdoor particles to indoor space, presence/absence of indoor combustion sources, presence/absence of smokers in home or place of work, etc.). Probably of most importance are findings that, whereas very few coarse-mode ambient particles (> 2.5 μm) penetrate into closed indoor air spaces generally, substantial percentages of fine-mode particles (< 2.5 $\mu g/m^3$) indoors are

TABLE 13-4a. PM_{10} LEVELS BY ANNUAL AVERAGE FOR SELECTED U.S. SMSAs FOR 1993

Metropolitan Statistical Area	1990 Population	PM_{10} WTD AM[1] ($\mu g/m^3$)	PM_{10} 2nd Max[2] ($\mu g/m^3$)	O_3 (ppm)[3]
Santa Fe, NM	117,043	15	35	---
Amarillo, TX	187,547	16	29	-
Santa Rosa, CA	388,222	18	52	---
Springfield, MD	239,971	18	39	---
Casper, WY	61,226	18	41	---
Danbury, CT	187,867	19	46	0.14
Glens Falls, NY	118,539	19	44	---
Titusville Area, FL	398,978	19	57	---
New London Area, CT/RI	266,819	19	41	0.13
Bridgeport, CT	443,722	21	50	0.17
Fort Lauderdale, FL	1,255,480	21	71	---
Asheville, NC	174,821	22	58	---
Montgomery, AL	292,517	23	48	---
Honolulu, HI	836,231	24	58	---
Oakland, CA	2,082,914	26	71	0.13
Charleston, SC	506,875	26	58	---
San Francisco, CA	1,603,678	29	72	---
Dallas, TX	2,553,362	30	74	0.14
Louisville, KY	952,662	33	73	0.14
Baltimore, MD	2,382,172	35	70	0.15
Birmingham, AL	907,810	36	85	0.13
Mobile, AL	476,923	38	71	---
Orange County, CA	2,410,556	38	80	0.17
Phoenix, AZ	2,122,101	44	92	0.13
New York, NY	8,546,846	47	86	---

[1]Weighted Annual Mean
[2]Highest Second Maximum 24-hour Concentration
[3]Highest O_3 Second Daily Maximum 1-hour Concentration

TABLE 13-4b. SELECTED U.S. PM_{10} LEVELS BY 2ND MAX PM_{10} FOR 1993

Metropolitan Statistical Area	1990 Population	PM_{10} 2nd Max[2] ($\mu g/m^3$)	PM_{10} WTD AM[1] ($\mu g/m^3$)	Note
St. Louis, MO	2,444,099	101	44	O_3[3] 0.13
Los Angeles, CA	8,863,164	102	47	O_3 - 0.25, CO[4]-14
San Diego, CA	2,498,016	105	34	O_3 0.16
El Paso, TX	591,610	106	37	O_3 0.14, CO-11
Medford, OR	146,389	106	41	---
Seattle, WA	1,972,961	119	35	---
Gary, IN	604,526	122	34	---
Flint, MI	430,459	127	24	---
Bakerville, CA	543,477	128	54	O_3 0.16
Fresno, CA	667,490	131	53	O_3 0.14
Denver, CO	1,622,980	142	41	---
Chicago, IL	6,069,974	147	47	---
Eugene, OR	282,912	151	28	---
Salt Lake City, UT	1,072,227	156	42	---
Spokane, WA	361,364	166	46	CO 12
Pittsburgh, PA	2,056,705	167	38	SO_2[5] 0.155
Riverside, CA	2,588,793	172	73	O_3 0.23
Steubenville, OH	142,523	177	40	SO_2 0.244
New Haven, CT	638,220	178	52	O_3 0.15
Provo, UT	263,590	209	40	CO 10
Philadelphia, PA	4,856,881	531	34	O_3 0.14

[1]Weighted Annual Mean
[2]Highest Second Maximum 24-hour Concentration
[3]Highest O_3 Second Daily Maximum 1-hour Concentration
[4]Highest CO Second Maximum Non-overcapping 8-hour Concentration
[5]Highest SO_2 Second Maximum 24-hour Concentration

often found to originate from outdoor ambient air (e.g., > 60% in certain circumstances). Those include, for example, high percentages of sulfates derived from outdoor air and at times metals and other typical ambient air fine-mode particle constituents.

Chapter 7 also provides analyses of relationships between human exposures to airborne particles indexed by personal monitors versus either ambient or indoor fixed monitors. Several earlier studies appeared to indicate very poor associations between personal PM exposure (measured by personal monitors) and either ambient or indoor PM concentrations measured by fixed monitor sites, with correlations for the former (ambient) being near zero and those for the latter (indoor) being somewhat better but not high. More recent studies, however, have begun to demonstrate higher correlations between personal monitoring results and both indoor and outdoor fixed monitoring site data. Of particular importance is the finding that, although individual exposures may not be well correlated with ambient PM concentrations measured at representative fixed ambient monitoring site(s), the mean personal exposure of people in a community in fact tends to be correlated to the ambient concentration. Basically, in terms of community air pollution, a properly sited ambient PM measurement is reasonably related to the mean personal PM exposure of the community, although it will not be good a indicator of any single individuals' daily PM exposure. The important consideration here is that the ambient monitor(s) be properly sited. This would have to be evaluated study by study, which can be difficult or impossible if data has not been reported in the published epidemiologic studies. There must be limits to the acceptability to using a monitor for daily PM level changes, both in terms of distance from the population and terrain between population and monitoring site.

13.4 DOSIMETRY OF INHALED PARTICLES IN THE RESPIRATORY TRACT

Inhaled particles are deposited in the respiratory tract by several mechanisms: impaction, sedimentation, interception, diffusion, and electrostatic precipitation. Ventilation rates differ for various activity patterns in humans, for different ages, and among species. These ventilation differences coupled with differences in upper respiratory tract structure and in size, branching pattern, and structure of the lower respiratory tract among species and

between healthy versus diseased states result in significantly different patterns of airflow that in turn affect particle deposition in the respiratory tract regions. For a given aerosol, the two most important parameters determining deposition are the mass mean aerodynamic diameter (MMAD) and the distribution of particles about that mean (σ_g). Subsequent clearance of a deposited dose is dependent on the initial site of deposition, physicochemcial properties of the particles (e.g., dissolution half-time), and on time since deposition.

An accurate description of the exposure-dose-response relationship for PM should account, to the extent possible, for these mechanistic determinants of particle disposition (deposition, absorption, distribution, metabolism, and elimination). Mathematical dosimetry models that incorporate descriptions of disposition of chemicals have been useful in describing relationships between exposure concentration and target tissue dose, particularly as applied to describing these relationship for exposure-dose-response assessment. Deposited dose may be an appropriate metric for acute effects (e.g., mortality) especially if the particles exert their primary action on the surface contacted. An alternative to consider is deposited dose rate normalized to respiratory tract surface area because insoluble particles deposit and clear along the surface of the respiratory tract. Depending on the availability of morphometric information, other normalizing factors such as numbers of alveoli or macrophages, could be explored. Chronic effects may be better described by retained dose estimates, which represent the difference between deposition of particles and clearance.

The deposited dose and retained dose estimates calculated for typical ambient aerosols and laboratory animal data show anticipated differences due to the influence of particle diameter (d_{ae}) and distribution (σ_g), minute ventilation, and species-specific morphometry. Figure 13-3 shows the fractional deposition in the tracheobronchial (TB) region for various species and "normal augmenter" and "mouth breather" adult male humans for essentially monodisperse ($\sigma_g = 1.3$) or polydisperse ($\sigma_g = 2.4$) aerosols of various particle diameters.

Species differences in inhalability versus humans are marked, with larger diameter aerosols having minimal deposition in laboratory animals. This may explain why some animal studies with larger particles (e.g., 2 to 3 μm) require high concentrations to elicit any effects. For the smaller particles, deposition fractions in the laboratory animals species are actually higher than those in humans. This emphasizes the need to explore dose metrics based on particle number because concentrations of particles in this region are very small by

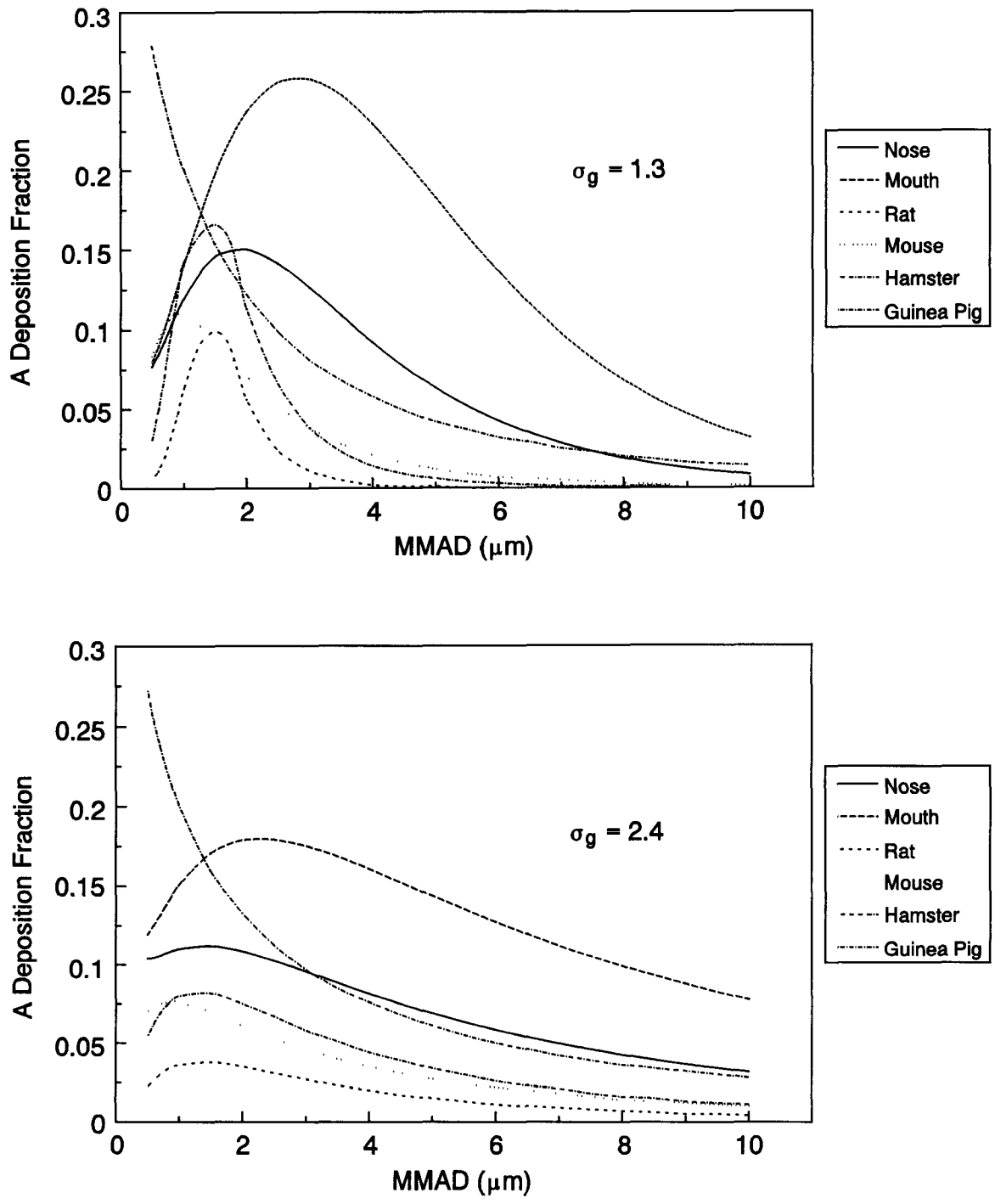

Figure 13-3. Predicted tracheobronchial deposition fractions versus MMAD of inhaled monodispersed (σ_g = 1.3) and polydisperse (σ_g = 2.4) aerosols (top and bottom panels, respectively).

mass but extremely high by number. Deposition in the alveolar region is also significant for the smaller diameter aerosols. Figures 13-4 and 13-5 show the retained dose (μg/g lung tissue) in the alveolar region for a small particle diameter and relatively monodisperse aerosol (0.5 μm MMAD, σ_g = 1.3) and a larger particle diameter and more polydisperse aerosol (2.55 μm MMAD, σ_g = 2.4), assuming two different dissolution-absorption half-times of 10 days and 1,000 days. These retained fractions are different than for deposited alveolar dose. Further, not only is the relationship between species different between the two aerosols, but within each aerosol the relationship changes depending on the assumed dissolution-absorption half-time. For the smaller diameter and monodisperse aerosol, the rat and hamster are consistently lower than humans in retained alveolar particle burden than are humans. For the larger diameter and polydisperse aerosol, rats and hamsters are more similar to humans for soluble particles (dissolution-absorption half-time of 10 days) versus the more insoluble.

Accounting for differences in dosimetry can change the relationship of apparent effect levels among species. The predictions to follow are based on several assumptions and models described in Chapter 10. A major assumption is that the concentrations involved are below those that cause particle overloading or alter clearance rates through chemical-specific toxicity. For example, if deposited dose is normalized to regional surface area, the same exposure concentration of a 0.5 μm MMAD and σ_g aerosol causing a TB effect in a rat versus guinea pig would be adjusted by 9.39 and 0.79, respectively, to calculate the human equivalent concentration (HEC). Based on the HEC values alone and not accounting for tissue sensitivity, the guinea pig would thus appear to be more sensitive than the rat when the HEC is calculated on this deposited dose metric. An alveolar dose based on retained burdens and assuming a soluble aerosol (dissolution-absorption halt-time of 10 days) would result in an HEC for this same aerosol (0.5 μm MMAD, σ_g = 1.3) of 0.22 and 7.84 for the rat and guinea pig, respectively. For a relatively insoluble aerosol (dissolution-absorption half-time of 1,000 days) with the same MMAD and σ_g, the HEC would be 0.49 and 2.76 for the rat and guinea pig, respectively. To illustrate, if a 0.5 μm MMAD aerosol with a σ_g of 1.3 caused an acute effect in the tracheobronchial region of rat at an exposure concentration of 100 $\mu g/m^3$, it would be predicted that 939 $\mu g/m^3$ would result in a similar tracheobronchial deposited dose and thereby a similar effect in humans, if species sensitivity to a given dose

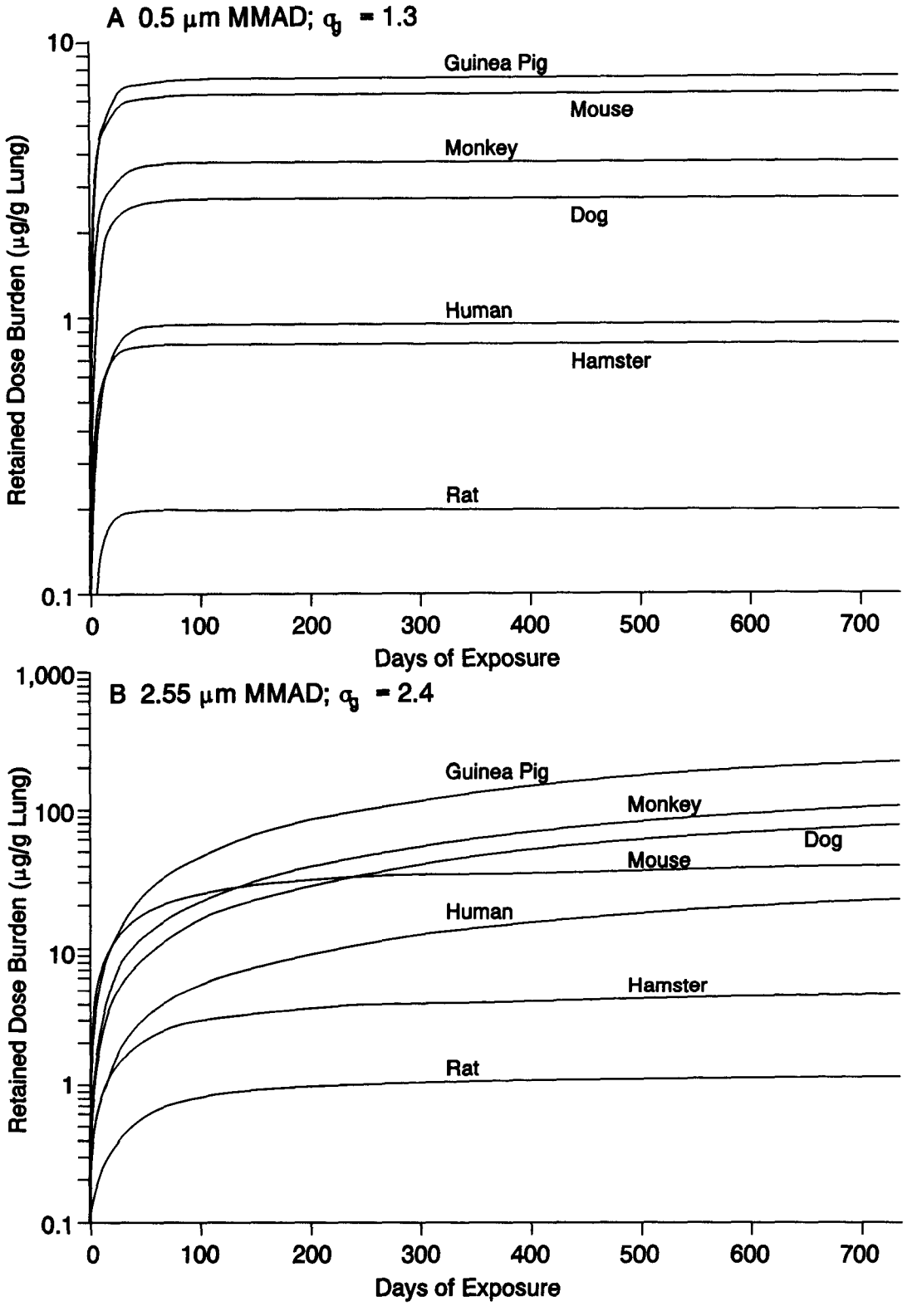

Figure 13-4. Predicted alveolar retained dose burden for 0.5 μm MMAD monodisperse (σ_g = 1.3) aerosol (top panel A) and 2.55 μm MMAD polydisperse (σ_g = 2.4) aerosol (bottom panel B), assuming a dissolution-absorption half-time of 10 days.

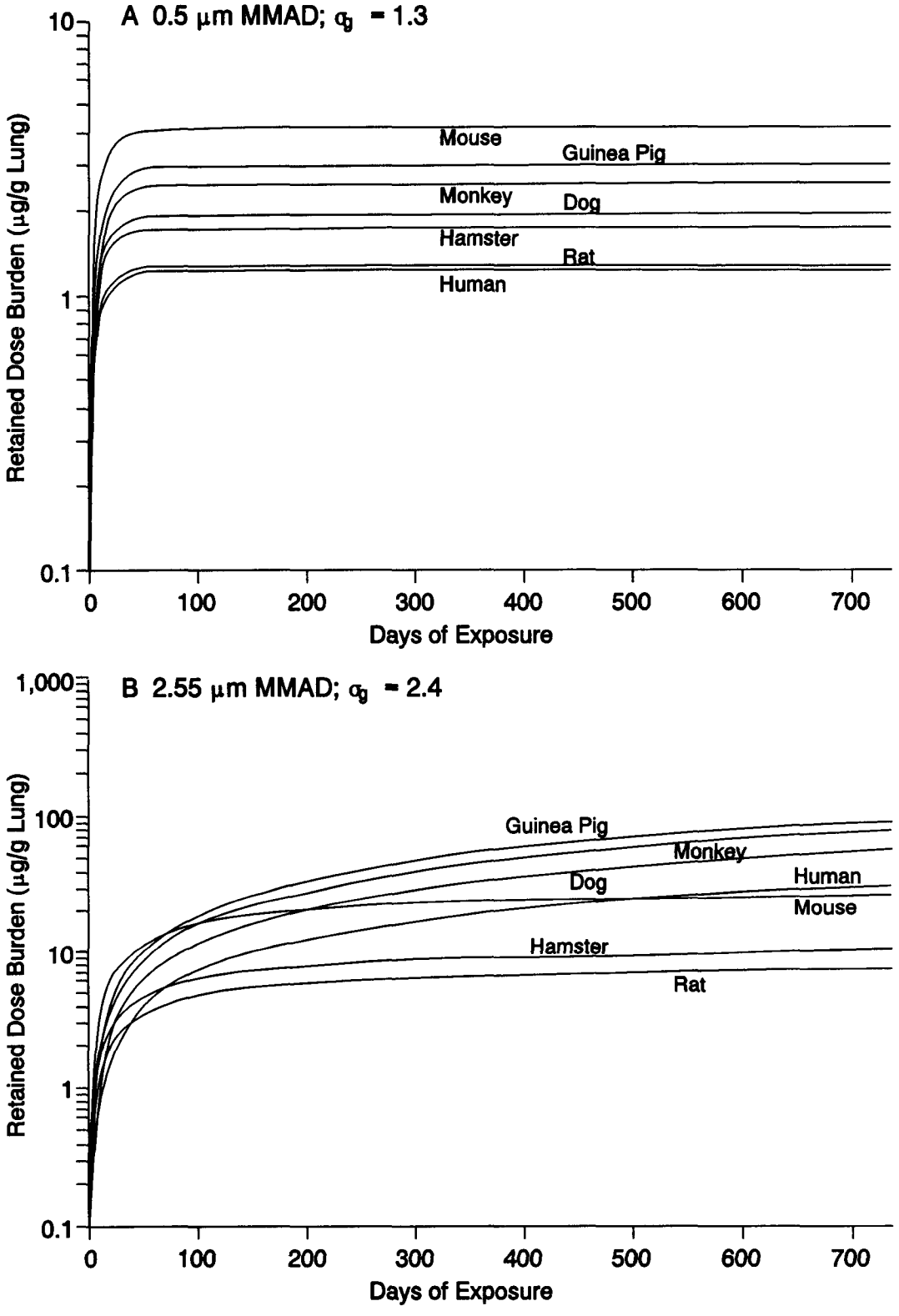

Figure 13-5. Predicted alveolar retained dose burden for 0.5 μm MMAD monodisperse (σ_g = 1.3) aerosol (top panel A) and 2.55 μm MMAD polydisperse (σ_g = 2.4) aerosol (bottom panel B), assuming a dissolution-absorption half-time of 1,000 days.

were equal. For chronic exposures when retained dose has a greater influence, an alveolar effect in a rat exposed to a 0.5 μm MMAD aerosol with a σ_g of 1.3 at an exposure concentration of 100 $\mu g/m^3$ would be predicted to be equivalent to a human exposed to 22 $\mu g/m^3$, assuming a dissolution-absorption half-time of 10 days and equivalent species sensitivity to retained dose.

These results clearly emphasize the need to adjust for interspecies differences in physiologic factors such as inhalability, deposition, and clearance mechanisms as well as for physicochemical characteristics of the aerosol, such as particle diameter, distribution, and solubility. Although not modeled in these exercises, hygroscopicity of aerosols is also anticipated to affect estimates of particle deposition and subsequent clearance.

The effects of particle diameter, distribution, and possibly hygroscopicity were also evident in the simulations of deposition for three ambient aerosols in "normal augmenter" and "mouth breather" adult males. As expected from experimental studies, mouth breathing alters deposition fractions in the tracheobronchial and alveolar regions compared to nasal breathing. More detailed analysis presented in Chapter 10 also showed differences in regional deposition fractions between activity patterns and across modes of the real-world trimodal aerosols. The differences shown in these simulations for deposition between normal augmenter and mouth breather adult males and among different activity patterns highlights the influence of ventilation rate and morphometry. This, in turn, points to the importance of characterizing the differences between the genders and the impact of age on deposition. The International Commission on Radiological Protection (ICRP) model has predicted differences between children of 1 year and adults across particle diameters ranging from the diffusion to aerodynamic range of approximately 2.5-fold in the tracheobronchial region and 2-fold in the alveolar region (ICRP66, 1994). Given the complexity of the deposition patterns by age, selecting any one example is an oversimplification at this time. For example, the ICRP has predicted that at about 0.2 μm MMAD, infants have greater deposition than adults, but at 2 μm MMAD, adults have greater deposition than infants.

Differences in ventilation and morphometry for diseased states can also be anticipated. There is a mismatch of ventilation and perfusion in lung diseases such as asthma, emphysema, and COPD (Bates et al., 1971, Bates, 1989). In more severe stages of these diseases, a small portion of the lung volume recieves most of the tidal breathing volume. In

emphysema, approximately one-fourth of the lung receives three-fourths of the tidal volume (Bates et al., 1971). These changes in ventilation and volume will result in some portions of the lower respiratory tract receiving a greatly increased particle burden compared to others. For example, Miller et al. (1995) predicted that a compromised human lung would have a greater number of particles (0.1 μm d_{ae}) deposited per alveolus and per macrophage. Larger particles (5 μm d_{ae}) were predicted to have greater deposition per alveolus, per macrophage, per surface area, and per ventilatory unit in the compromised human lung simulation. Also, Anderson et al. (1990) have shown that the deposition of ultrafine particles in patients with COPD is greater than that in healthy people.

13.5 KEY HEALTH EFFECTS OF PARTICULATE MATTER

This section concisely discusses key findings from PM_{10} and $PM_{2.5}$ studies that examine mortality and morbidity associated with ambient short- and long-term exposure.

13.5.1 Short-Term PM Exposure Mortality Studies

The 1982 criteria document (U.S. Environmental Protection Agency, 1982) concluded that the most clearly defined effects on mortality arising from exposure to PM have been sudden increases in the number of deaths occurring, on a day-to-day basis, during episodes of high pollution. The most notable of these occurred in the Meuse Valley in 1930, in Donora in 1948, and in London in 1952. During the December, 1952 epidsode between 3,000 and 4,000 excess deaths were attributable to air pollution, with the greatest increase in death from chronic lung disease and heart disease (United Kingdom Ministry of Health, 1954). In addition, the death rate increased most dramatically in those older than 45 years of age. Additional episodes with associated increases in mortality occurred in London during various winters from 1948 to 1962. Collectively, studies of these and other early episodes left little doubt that airborne particulate matter contributed to mortality associated with very high concentrations of urban aerosol mixes dominated by combustion products (e.g., from burning coal) and/or their transformation products (e.g., H_2SO_4).

Besides evaluating mortality associated with major episodes, the 1982 criteria document (U.S. Environmental Protection Agency, 1982) also focused on studies of more

moderate day-to-day variations in mortality within large cities in relation to PM pollution. Various methodological problems were identified in most of the studies, precluding quantitative conclusions regarding exposure-response relationships of importance for deriving air quality standards. Among the main problems noted were inadequate measurement or control for potentially confounding variables and inadequate quantification of exposure to airborne particles and other associated pollutants (e.g., sulfates or acid aerosols). Despite such problems, the U.S. Environmental Protection Agency (1982) document concluded that the then available studies collectively indicated that mortality was clearly and substantially increased when airborne particle 24-h concentrations exceeded 1,000 $\mu g/m^3$ (as measured by the Black Smoke, or BS, method) in conjunction with elevations of sulfur dioxide (SO_2) levels in excess of 1,000 $\mu g/m^3$ (with the elderly or others with severe preexisting cardiovascular or respiratory disease mainly being affected). As for evaluation of risks of mortality at lower exposure levels, the U.S. Environmental Protection Agency (1982) concluded that studies conducted in London by Martin and Bradley (1960) and Martin (1964) yielded useful, credible bases by which to derive conclusions concerning quantitative exposure-response relationships.

The 1986 addendum to the 1982 criteria document (U.S. Environmental Protection Agency, 1986) also considered several additional acute exposure mortality studies of London, England during the 1958-1959 through 1971-1972 winter periods conducted by Mazumdar et al. (1982), Ostro (1984), Shumway et al. (1983), and by EPA (later published in Schwartz and Marcus, 1990). After reviewing these various data analyses, and taking into account the previously reviewed London results and the above noted methodological considerations, the following conclusions were drawn (U.S. Environmental Protection Agency, 1986):

(1) Markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1,000 $\mu g/m^3$, especially during episodes when such pollutant elevations occurred for several consecutive days;

(2) During such episodes, coincident high humidity or fog was also likely important, possibly by providing conditions leading to formation of sulfuric acid (H_2SO_4) or other acidic aerosols;

(3) Increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1,000 $\mu g/m^3$, for SO_2 most clearly at concentrations in excess of $\approx$700 $\mu g/m^3$; and

(4) Convincing evidence indicates that relatively small, but statistically significant, increases in the risk of mortality exist at BS (but not SO_2) levels below 500 $\mu g/m^3$, with no indications of any specific threshold level having been demonstrated at lower concentrations of BS (e.g., at ≤ 150 $\mu g/m^3$). However, precise quantitative specification of the lower PM levels associated with mortality is not possible, nor can one rule out potential contributions of other possible confounding variables at these low PM levels.

In setting the current U.S. PM standards, the BS levels noted above were taken as indexing particles roughly in the same size range as inhalable particles reaching tracheobronchial or alveolar regions of the respiratory tract; and the U.S. 24 h primary NAAQS was set as 150 $\mu g/m^3$ PM_{10}.

The decade or so since the 1986 criteria document (U.S. Environmental Protection Agency, 1986) has been an active period for the reporting of time series analyses of associations between human mortality and acute exposures to PM at concentrations at or below the lower end of the range indexed by the above studies of London mortality or the level of the current U.S. 24-h standard. Some utilized TSP or other measures (e.g., COH, BS, etc.) as an indices of PM exposure, but during the last few years, the analyses have mainly focused on PM_{10} as a measure of PM. This is because sufficient routine PM_{10} ambient measurement data became available for such statistical analyses to be conducted in a wide variety of locales.

With regard to the results of the new time-series analyses, numerous investigators have reported very small, but statistically significant associations between increased relative risk for mortality and various indices of PM (e.g., BS, COH, TSP, PM_{10}, $PM_{2.5}$, etc.) for many different cities in the United States and in other countries, as well. The elderly (>65 yr old), particularly those with preexisting cardiopulmonary disease, were found to have distinctly higher risks than younger age groups. The small relative risk estimates for PM were consistently reduced when other likely important (potentially confounding) factors were also controlled for in the models, with the PM association still usually remaining statistically significant, although typically accounting for much less of the variance in mortality than did temperature or combinations of variables used to index contributions of weather-related factors to human mortality. Thus, qualitatively, the newly emerging database appears to provide indications that polluted atmospheres containing relatively low concentrations of

particles may contribute (along with other factors) to a very small increase in relative risk for human mortality, especially in the elderly with preexisting cardiopulmonary diseases.

However, it is important to note that differences in opinion exist within the scientific community with regard to: (a) how adequately other likely important confounding factors (including weather and copollutants) and/or other seasonal factors were controlled for across the various newly available analyses; and (b) the interpretation of the meaning or implications of reported associations between increased relative risk estimates and indices of ambient PM concentrations. For example, introduction of one or more other commonly-present ambient air pollutants (e.g., SO_2, O_3, CO, NO_x) into models of PM effects generally reduces the estimated PM effect, often by as much as 50% and, at times, to statistically non-significant levels. In a few studies, however, the size of the PM effect remained essentially the same or increased slightly upon introduction of other copollutants into the model. Similarly, analyses of PM-mortality effects by season (winter, spring, summer, fall), as done in only a few studies, have found varying patterns of PM-mortality effects being significant in one or another season(s) but not all, with specific effective seasons differing from one locale to another. The copollutant and seasonality analyses results, in particular, have led to considerable debate in the scientific community, typified on the one hand by (a) skepticism about the size and the "realness" of reported low-level PM effects and, on the other hand, (b) countervailing views asserting that the effect of PM (or any other weakly contributing factor) on mortality can be made to "disappear" by overspecification of applicable models (i.e., by introduction of sufficient other, possibly extraneous, variables into the models or by more detailed breakdown of data, e.g., by season, that may reduce the power to detect a PM effect).

No clear resolution of this debate or "consensus" opinion in the scientific community has yet crystallized, but some agreement appears to be emerging that the results for models containing only PM and no other copollutants may provide upper bound estimates for effects of ambient particle-containing mixes of pollutants, whereas results derived from analyses including other copollutants and extensive controls for weather, seasonality, and/or other likely important contributing factors should be viewed as lower-bound estimates of PM effects (which may be 50% or more lower than the upper bound or even include zero). The next several sections discuss key points regarding the derivation of quantitative estimates of

PM-related mortality and morbidity effects, taking into account the types of uncertainties and scientific debate just noted.

13.5.1.1 PM_{10} Relative Risk Analyses

This section discusses key findings from studies conducted since the PM criteria document addendum (U.S. Environmental Protection Agency, 1986) that have employed PM_{10} in their analyses of the human mortality effects of acute exposures to PM, as discussed in more detail in Chapter 12. Some studies considered daily mortality in the entire population (i.e., all ages) and some by cause; some also considered subpopulations (e.g, the elderly).

Two earlier published summaries of the PM literature converted all results to a PM_{10}-equivalence basis and provided quantitative intercomparisons (Ostro, 1992; Dockery and Pope, 1994). Other such summaries have been conducted using TSP as the reference PM metric (Schwartz, 1991; Schwartz, 1994a), and considered many of the same studies included in the two PM_{10}-equivalent summaries. The results presented in such summaries suggest about a 1 percent change in acute total mortality for a 10 $\mu g/m^3$ change in PM_{10}, but the estimates range from 0.3 to 1.6% (i.e., a factor of 5). While most of the 95% confidence intervals (CIs) of these estimates overlap, CIs of the highest and lowest estimates do not overlap, indicating significant differences between these estimates. Note that the effects indicated for a 10 $\mu g/m^3$ PM_{10} change cannot be reliably converted to other PM increments (e.g., 50 or 100 $\mu g/m^3$ PM_{10}), as differences in model specification (e.g., linear versus log models) will cause them to differ in their conversions to other particle concentration levels. The reasons for the approximately five-fold effect estimate difference noted among studies are not obvious from the information provided by these references, but one factor does appear to be the PM exposure averaging time, as estimates using multiple day PM_{10} averages are all seen to be 1% or higher. This is not unexpected, given that any lagged effects from prior days of PM_{10} exposure will be added to the effects estimate when a multi-day average is employed, increasing the estimated effect on a per $\mu g/m^3$ basis.

It is also important to note that other air pollutants were generally not addressed in deriving the coefficients reported by the above summaries. Differences among coefficients are to be expected, given that the composition (and, potentially toxicity) of the PM, as well

as the demographic characteristics in each city, can be expected to differ. Moreover, the conversions from other PM metrics to PM_{10} must necessarily introduce additional uncertainty. However, though not all of these results may therefore be the most appropriate available for quantifying a PM_{10} effect, they do consistently indicate that there is an association between acute exposure to ambient air mixes containing PM and increased daily mortality. Moreover, the by-cause results also reported in the summaries indicate that PM effect estimates are greater for respiratory causes, which lends support to the biological plausibility of the noted PM associations.

In an effort to more clearly quantify daily PM_{10}-total acute mortality associations, Table 13-5 summarizes the total mortality relative risks (RR) of a 50 $\mu g/m^3$ increase in PM_{10} estimated from nine studies reviewed in Chapter 12, which employed PM_{10} data in their analysis of total mortality data (or which had on-site PM_{10} reference data to convert other PM metrics with more certainty). The studies listed were selected for this analysis mainly because they can most readily be intercompared and provide direct data related to PM_{10} levels. The RR's calculated were based upon a 50 $\mu g/m^3$ increase above the mean PM_{10} 24-h concentration, which is approximately the order of magnitude of the typical difference between the mean and maximum in these cities. This is noted because in non-linear models such as were often employed in the studies discussed in Chapter 12, the RR estimate associated with a given $\mu g/m^3$ PM_{10} increase will vary depending upon the baseline concentration to which it is added.

From results presented in Chapter 12, it is apparent that these studies generally have yielded at least marginally significant PM_{10} coefficients, but the resultant excess risk estimates differ by a factor of five across these studies (from 1.5% to 8.5% per 50 $\mu g/m^3$). The mean and maximum PM_{10} concentration data are noted for each study. If the PM_{10} coefficient decreased as the mean level of PM_{10} decreased, then confounding as a function of varying PM level would be suggested. However, the data presented indicate that the variability in coefficients is not a function of PM_{10} level, as sites with high or low PM_{10} concentrations can report either high or low RR's. In Chapter 12, the statistical methodology characteristics of each study were concisely summarized, in order to determine if any factors are important to help explain the variability observed from study to study in the PM_{10} RR estimate. As noted earlier, the RR estimate for acute mortality associated with

TABLE 13-5. COMPARISON OF RELATIVE RISK (RR) ESTIMATES FOR TOTAL MORTALITY FROM 50 $\mu g/m^3$ CHANGE IN PM_{10}, USING STUDIES WHERE PM_{10} WAS MEASURED OR WAS CALIBRATED FOR THE SITE

Study	Reference	PM_{10} ($\mu g/m^3$)		Other Pollutants In Model	Lag Times, d	RR per 50 $\mu g/m^3$	95 Percent Confidence Interval
		Mean	Maximum				
Utah Valley, UT	Pope et al.(1992)	47	297	None	≤ 4 d	1.08	(1.05, 1.11)
				None, Winter	≤ 4 d	1.085	(1.03, 1.14)
				None, Summer	≤ 4 d	1.11	(0.92, 1.35)
				Max O_3, Summer	≤ 4 d	1.19	(0.96, 1.47)
				Avg O_3, Summer	≤ 4 d	1.14	(0.92, 1.41)
St. Louis, MO	Dockery et al. (1992)	28	97	None	≤ 3 d	1.08	(1.005, 1.15)
				O_3	≤ 3 d	1.06	(0.98, 1.15)
Kingston, TN	Dockery et al. (1992)	30	67	None	≤ 3 d	1.085	(0.94, 1.25)
				O_3	≤ 3 d	1.09	(0.94, 1.26)
Birmingham, AL	Schwartz (1993)	48	163	None	≤ 3 d	1.05	(1.01, 1.10)
Athens, Greece	Touloumi et al. (1994)	78	306	None	1 d	1.034	(1.025, 1.044)
				SO_2, CO	1 d	1.015	(1.00, 1.03)
Toronto, ON Canada	Özkaynak et al. (1994)	40	96	None	0 d	1.025	(1.015, 1.034)
Los Angeles, CA	Kinney et al. (1995)	58	177	None	1 d	1.025	(1.00, 1.055)
				O_3, CO	1 d	1.017	(0.99, 1.036)
Chicago, IL	Ito et al. (1995)	38	128	O_3, CO	≤ 3 d	1.025	(1.005, 1.05)
Santiago, Chile	Ostro et al. (1995a)	115	367	None	1 d	1.04	(1.005, 1.06)
				None	≤ 4 d	1.07	(1.04, 1.10)
				None, Poisson	1 d	1.022[1]	(1.003, 1.042)
				SO_2, Poisson	1 d	1.026[1]	(1.005, 1.047)
				NO_2, Poisson	1 d	1.043[1]	(1.020, 1.066)
				O_3, Poisson	1 d	1.026[1]	(1.005, 1.047)
Chicago, IL	Styer et al. (1995)	37	365	None	3 d	1.04	(1.00, 1.08)

[1]Calculated on a basis of 50 $\mu g/m^3$ increase from 50 to 100 $\mu g/m^3$.

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short-term exposure to PM_{10} is usually larger when other pollutants have not been simultaneously considered in the model. Those studies which considered PM_{10} both alone and with other pollutants in the model often yielded smaller, and usually more marginally significant, PM_{10} relative risks when other pollutants were also considered. This influence ranges from roughly a 20 to 50 percent reduction in the estimate of excess risk associated with PM_{10} (e.g., in Athens, Greece, the PM_{10} RR declines from 1.07 to 1.03 per 100 $\mu g/m^3$ when other pollutants are considered). Such a reduction is to be expected when co-linear variables are added.

Older studies using BS or TSP often found a degree of correlation between SO_2 and the PM indicator that reduced the apparent PM effect and attenuated its statistical significance (Schwartz and Marcus, 1990; Schwartz and Dockery, 1992a,b; Moolgavkar et al., 1995a,b). However, studies using a variety of PM indicators at cities were SO_2 levels were so low as to have little likelihood of SO_2 being a significant confounder of a PM effect (Fairley et al., 1991, for Santa Clara County; Pope et al., 1992, for Utah County) found quantitatively similar significant PM effects. While there is some possibility that summertime PM effects may be partially confounded with those of other pollutants (e.g., O_3) derived from motor vehicle fuel combustion or transformation products (Pope, 1994; Ostro et al., 1995; Moolgavker et al., 1995a,b; Dockery, 1994), winter effects of PM are clearly detectable when O_3 levels are much lower (Moolgavkar et al., 1995b; Pope, 1994; Schwartz, 1995b). If PM effects on mortality were so completely confounded with those co-pollutants so as to be undetectable, then one would need to invoke many different confounders in different studies of communities. While this explanation is not impossible, it appears highly unlikely, but cannot be precluded altogether since PM may derive from different sources in these studies, have varying size and chemical composition from one locale to another, and therefore may have different characteristics that affect health outcomes such as mortality.

Another factor which clearly affected the PM_{10} RR was the PM_{10} averaging period. Most of the studies which utilized multi-day averages of PM_{10} in their regressions (i.e., Utah Valley; St. Louis; eastern TN; Santiago; Chicago; and Birmingham) are among the higher RR estimate studies. As discussed above, this would be expected. However, the increase indicated for these studies is not proportional to the averaging time. Indeed, in sub-analyses included by Pope et al (1992), the PM_{10} mortality risk is indicated to be roughly doubled by

using a five day average versus a single day concentration, while sub-analyses presented by Ostro et al. (1995) for Santiago also indicate approximately a doubling in the PM_{10} RR when a 3 day average is considered (i.e., from RR = 1.04 for a single day PM_{10} value to RR = 1.07 for a 3d average PM_{10} value). This may be due to the fact that, since autocorrelation exists in the PM_{10} concentrations from day to day, the single day concentration is "picking up" some of the effect of multi-day pollution episodes, even though they are not explicitly modeled. These results suggest that a multi-day rather than a single-day average PM_{10} concentration may provide a more relevant index to gauge the effects of short-term PM exposures occurring over several consecutive days.

Table 13-5 shows that the total acute mortality relative risk estimate associated with a 50 $\mu g/m^3$ increase in the one-day 24-h average PM_{10} can range from 1.015 to 1.085, depending upon the site (i.e., the PM_{10} composition and population demographics) and also upon whether PM_{10} is modeled as the sole index of air pollution or not. Relative Risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the PM_{10} RR with multiple pollutants in the model range from 1.015 to 1.025. As noted earlier, the former range might be viewed as approximating an upper bound of the best estimate, as any mortality effects of co-varying pollutants are likely to be "picked up" by the PM_{10} index. On the other hand, the latter multiple pollutant model range might be viewed as approximating a lower bound of the best estimate, as the inclusion of highly correlated covariates may weaken the PM_{10} estimate. Both estimates should be considered in assessing the potential effects of PM_{10}. Overall, consistently positive PM-mortality associations are seen throughout these analyses, despite the use of a variety of modeling approaches, and after controlling for major confounders such as season, weather, and co-pollutants, with the 24-h average 50 $\mu g/m^3$ PM_{10} total mortality effect estimate most likely falling in approximately the RR = 1.025 to 1.05 range (representing an expected 2.5 to 5.0% increase in risk of death over daily background mortality rates for which a 50 $\mu g/m^3$ increment in ambient PM_{10} concentration could be a contributing factor).

It is logical to assume that the bulk of the total mortality effects suggested by these studies are among the elderly. During the historic London, 1952 pollution episode the greatest increase in the mortality rate was among older citizens and those having respiratory diseases. An analysis by Schwartz (1994c) of mortality in Philadelphia, PA during 1973

through 1980 comparing mortality during the 5% highest versus the 5% lowest TSP days found the greatest increase in risk of death in those aged 65 to 74 and those >74 year of age (mortality risk ratios = 1.09 and 1.12, respectively, between high and low TSP days). Also, in their time series analyses of Philadelphia daily mortality during this period, Schwartz and Dockery (1992) found a TSP-mortality coefficient which was significantly higher (β = 0.000910 $\pm$ 0.000161) for persons older than 65 years of age than they found for the younger population (β = 0.000271 $\pm$ 0.000206). These coefficients indicated an effect size for the elderly which was roughly three times that for the younger population (10% versus 3%, respectively, for a 100 $\mu g/m^3$ increase in TSP). In addition, two recent PM_{10} analyses have directly considered the question of PM_{10}-mortality associations among the elderly population ($\geq$ 65 years of age), and these provide further relevant insights into this question.

The first of these two analyses which directly considered the elderly when looking at PM_{10}-mortality associations was conducted by Saldiva and Bohm (1994) during May 1990 through April 1991 in Sao Paulo. Multiple regression models, including models with all pollutants considered simultaneously, consistently attributed the association found with mortality among the elderly to PM_{10}. The PM_{10} relative risk reported in this study (RR = 1.13 for a 100 $\mu g/m^3$ increase) is higher than noted above for total mortality studies addressing multiple pollutants (100 $\mu g/m^3$ RR $\approx$ 1.03 to 1.05), supporting past observations that the elderly represent a population especially sensitive to the health effects of air pollution. A second recent study directly examined the association between PM_{10} and mortality in the elderly population in Santiago, Chile (Ostro, 1995). In the overall population, the PM_{10} 100 $\mu g/m^3$ RR estimate was 1.08, but in the population aged 65 and greater, the PM_{10} RR of a 100 $\mu g/m^3$ increase in PM_{10} rose to an estimate of RR = 1.11 in the same model specification. Thus, these directly comparable estimates (i.e., using the same model specification and population) suggest that the elderly experience roughly a 40 percent higher excess risk from exposure to PM air pollution than the overall population.

Overall, considering the historical pollution episode evidence and the results of recent PM_{10}-mortality analyses evaluating elderly populations, it seems evident that elderly adults represent a population especially at risk for mortality implications of acute exposure to air pollution, including PM.

Relatively few studies have directly examined the PM-mortality association in children. It is difficult, given the limited and somewhat conflicting results available at this time, to ascribe any such association to low-level PM pollution in particular. This is an area where further research is clearly needed to broaden the base upon which to assess the potential for PM to increase mortality among children.

Throughout the results and discussions presented above and in more detail in Chapter 12 regarding the effects of acute PM exposure on human mortality, a consistent trend was for the effect estimates to be higher for the respiratory mortality category. This lends support to the biological plausibility of a PM air pollution effect, as the breathing of toxic particles would be expected to most directly affect the respiratory tract, and these results are consistent with this expectation. For example, the respiratory mortality relative risk estimates discussed in detail in Chapter 12 are all higher than the risks for the population as a whole. Of particular interest is to compare the relative risk values for each study that made most direct and appropriate comparisons. In the Santa Clara study (Fairley, 1990), the PM-respiratory mortality RR was 4.3 times as large as for deaths as a whole (i.e., 3.5/0.8). For Philadelphia, (Schwartz and Dockery, 1992a), the PM (TSP)-respiratory mortality RR was 2.7 times as large as for total mortality (i.e., 3.3/1.2). In the Utah Valley study (Pope et al., 1992), the PM_{10}-respiratory mortality RR was 2.5 times as large as for deaths as a whole (i.e., 3.7/1.5). In the Birmingham, AL study (Schwartz, 1994), the respiratory mortality RR of PM_{10} was 1.5 times as large as for deaths as a whole (i.e., 1.5/1.0). More recently, the Santiago, Chile PM_{10} study by Ostro et al. (1995) reported excess respiratory mortality RR of PM_{10} to be 1.8 times as large as for deaths as a whole (comparing 1.15/1.08 RR per 100 $\mu g/m^3$). Thus, in these studies, the PM RR for respiratory diseases is indicated to range from 50 to over 400% higher for respiratory disease categories than for all causes of death, indicating that increases in respiratory deaths are a major contributor to the overall PM-mortality associations noted previously. Moreover, since evidence suggests that an acute pollution episode is most likely be inducing its primary effects by stressing already compromised individuals (rather than, for example, inducing chronic respiratory disease from a single air pollution exposure episode), the above results indicate that persons with pre-existing respiratory disease represent a population especially at risk to the mortality implications of acute exposures to air pollution, including PM.

In overall summary, the time-series mortality studies reviewed in this and past PM criteria documents provide reasonably strong evidence that increases in daily human mortality are associated with short-term exposures to air pollution mixes containing elevated PM levels. Recent studies provide indications that small increases in such risk occur in association with air pollution indexed by moderate increases of PM_{10} (~ 50 $\mu g/m^3$) above routine ambient levels averaging around 50 to 100 $\mu g/m^3$. Overall, the PM_{10} relative risk estimates derived from the most recent PM_{10} total mortality studies suggest an acute exposure effect on the order of RR = 1.025 to 1.05 in the general population for increases in ambient air pollution indexed by a 24-h average 50 $\mu g/m^3$ PM_{10} increment, with higher (30-40%) relative risks indicated for the elderly sub-population and for those with pre-existing respiratory conditions.

13.5.1.2 Fine Particles/Acid Aerosols Relative Risks

As noted earlier in this document (Chapters 11 and 12) some epidemiologic and experimental toxicology data point toward fine particles as a class or certain constituents (e.g., acidic aerosols) as possibly being key contributors to observed PM-mortality and/or PM-morbidity associations. Only a few epidemiologic studies provide direct comparisons between various PM indices, including fine particle and acidity measurements.

For example, Dockery et al. (1992) investigated the relationship between multiple air pollutants to include $PM_{2.5}$, and total daily mortality during a one year period in St. Louis, MO and Kingston/Harrirman, TN and surrounding counties, as discussed in Chapter 12. The distribution of mortality, and air pollution between September 1, 1985 and August 31, 1986 are presented for St. Louis and Eastern Tennessee in Table 13-6.

In Poisson regressions controlling for weather and season (Table 13-7), previous day's PM_{10} was the only significant predictor of daily mortality (ß = 0.00175 $\pm$ 0.00067), but the association dropped off at 3 days (ß = 0.00042 $\pm$ 0.00063). The size-fractionated PM data were examined to determine whether this association could be attributed to either the fine ($PM_{2.5}$, aerodynamic diameter $d_a < 2.5$ μm) or the coarse (2.5 $\mu m < d_a < 10$ μm) component of the PM_{10} mass. The fine fraction ($PM_{2.5}$) was positively associated with mortality (ß = 0.00171 $\pm$ 0.00096, P = 0.075). Coarse particles were also positively

TABLE 13-6. MEAN VALUES OF VARIABLES RELATED TO DAILY MORTALITY IN ST. LOUIS AND EASTERN TENNESSEE

Variable	St. Louis			Eastern Tennessee		
	N[a]	Mean ± SD[b]	Range[c]	N	Mean ± SD	Range
Mortality						
Deaths/day	365	56.0 ± 8.2	31-81	365	15.5 ± 4.2	5-29
Particulate pollution						
PM_{10} ($\mu g/m^3$)	311	27.6 ± 14.9	1-97	330	30.0 ± 12.1	4-67
$PM_{2.5}$ ($\mu g/m^3$)	312	17.7 ± 10.0	1-75	331	21.0 ± 9.4	4-58
SO_4 ($\mu g/m^3$)	311	8.0 ± 5.1	0-38	330	8.7 ± 5.0	1-27
H^+ (nmole/m^3)	220	9.7 ± 12.0	0-88	232	36.1 ± 39.6	0-90

[a]Number of days of measurements.
[b]Standard deviation.
[c]Minimum-maximum.

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TABLE 13-7. COMPARISON OF UNIVARIATE REGRESSIONS WITH POLLUTION ON PREVIOUS DAY CONTROLLING FOR WEATHER AND SEASON VARIABLES

Pollutant	St. Louis			Eastern Tennessee		
	ß	(SE)	*t*	ß	(SE)	*t*
PM_{10} ($\mu g/m^3$)	0.00150	(0.00069)	2.17	0.00160	(0.00149)	1.07
$PM_{2.5}$ ($\mu g/m^3$)	0.00171	(0.00096)	1.78	0.00228	(0.00186)	1.23
SO_4^{-2} ($\mu g/m^3$)	0.00608	(0.00577)	1.05	0.008	(0.012)	0.67
H^+ (nmole/m^3)	0.00086	(0.00118)	0.73	0.00017	(0.00055)	0.31

associated (ß = 0.00247 ± 0.00129, P = 0.056). Neither fine nor coarse particles showed a stronger association than the other when considered simultaneously.

Both daily SO_4 and H^+ concentrations were significantly correlated with PM_{10} (Pearson correlations 0.52 and 0.76, respectively). Sulfate (SO_4^{2-}) as measured by the sulfur fraction of PM_{10} (β = 0.00608 ± 0.00577) and H^+ (ß = 0.00086 ± 0.00118) were positively, but not significantly, associated with daily mortality. Among the other particulate elemental concentrations, those correlated with PM_{10} concentrations were also associated with mortality. In particular, aluminum, calcium, chromium, iron, and silica all had correlations with PM_{10} of 0.5 or higher and had positive associations with mortality. Neither SO_2 nor NO_2 nor O_3 was significantly associated ($P > 0.30$) with total mortality.

13.5.2 Long-Term $PM_{10}/PM_{2.5}$ Exposure Mortality Studies

13.5.2.1 Population-Based Cross Sectional Mortality Studies

Ecological cross-sectional studies employing averages across various geopolitical units (cities, SMSAs, etc.) present data that examines the relation between mortality and PM levels. These community-based studies seeks to define the (average) community characteristics that are associated with its overall average health status, in this case annual mortality rate. Ozkaynak and Thurston (1987) analyzed 1980 total mortality in 98 SMSAs, using data on PM_{15} and $PM_{2.5}$ from the EPA inhalable particle (IP) monitoring network for 38 of these locations. Ozkaynak and Thurston ranked the importance of the various pollutants mainly by relative statistical significance in separate regressions. They concluded that the results were "suggestive" of an effect of particles on mortality decreasing with particle size; although in the basic model only SO_4^{2-} was significant. In some of the other models, $PM_{2.5}$ was also significant and PM_{15}, nearly so. However, if the effects are judged by elasticities rather than significance levels, SO_4^{2-}, $PM_{2.5}$, and PM_{15} would be judged as equivalent, with TSP ranking somewhat lower. Ozkaynak and Thurston (1987) also used source apportionment techniques to estimate that particles from coal combustion and from the metals industry appeared to be the most important. The coefficients and significance levels obtained for TSP by Ozkaynak and Thurston may be the result of the TSP data they used, which were based on a single monitoring station in each SMSA and thus are unlikely to be fully representative of population exposures. Thus, alternative interpretations of these

findings are certainly possible. In addition, because smoking, diet, and other socioeconomic or lifestyle variables were not considered in the regression model, the pollution coefficients may have been biased. Finally, this study did not specifically address the question of acute vs. chronic responses by exploring lagged pollution variables.

Data from up to 149 metropolitan areas (mostly SMSAs) were analyzed in a study of the relationships between community air pollution and "excess" mortality due to various causes for the year 1980 (Lipfert, 1993). Several socioeconomic models were used in cross-section multiple regression analyses to account for non- pollution effects. Two different sources of (measured) air quality data were utilized: data from the EPA AIRS database (TSP, SO_4^{-2}, Mn, and ozone) and data from the inhalable particulate (IP; PM_{15}) network; the latter data (PM_{15},$PM_{2.5}$ and $SO_4^{=}$ from the IP filters) were only available for 63 locations. All particulate data were averaged across all the monitoring stations available for each SMSA; the TSP data were restricted to the year 1980 and were based on an average of about 10 sites per SMSA. Using these models, statistically significant associations were found between TSP and mortality due to non-external causes with the log-linear models evaluated, but not with a linear model. Sulfates, manganese, inhalable particles (PM_{15}), and fine particles ($PM_{2.5}$) were not significantly ($P < 0.05$) associated with mortality with any of the parsimonious models, although $PM_{2.5}$ and manganese were close with linear models ($p=0.07$) and significance may have been affected by the use of smaller data sets. This study showed that $PM_{2.5}$ was the "strongest" particulate variable with linear models, but that TSP performed better in log-linear models. This study supported the previous findings of associations between TSP and premature mortality and also the hypothesis that improving the accuracy of pollutant exposure data tends to increase statistical significance.

13.5.2.2 Prospective Mortality Studies

Prospective studies consider data on the relative survival rates of individuals, as affected by age, sex, race, smoking habits, and certain other individual risk factors. This type of analysis has a substantial advantage over the population-based studies, because the identification of the actual decedents allows stratification according to important risk factors such as smoking. However, since none of the prospective cohort studies had data on personal exposures to air pollution, these studies are also "ecological."

The newer prospective studies (Abbey et al., 1991; Dockery et al., 1993; and Pope et al., 1995), are of most interest. Abbey et al. (1991a) describes a prospective study of about 6,000 white, non-hispanic, nonsmoking, long-term California residents who were followed for 6 to 10 years, beginning in 1976. The study was designed to test the use of cumulative exposure data as an explanatory factor for disease incidence and chronic effects. Pollutant species were limited to TSP and ozone in this paper; oxidant concentrations were used in the early part of the monitoring record. In a follow-up analysis, Abbey et al. (1995) considered exposures to SO_4^{2-}, PM_{10} (estimated from site-specific regressions on TSP), $PM_{2.5}$ (estimated from visibility), and visibility per se (extinction coefficient). No significant associations with nonexternal mortality were reported, and only high levels of TSP or PM_{10} were associated with symptoms of asthma, chronic bronchitis or emphysema. The finding of Abbey et al. (1991a) of no association between long-term cumulative exposure to TSP or O_3 and all natural-cause mortality may be interpreted as showing the absence of chronic responses after 10 years but not necessarily the absence of (integrated) acute responses, since coincident air pollution exposures were not considered.

Dockery et al. (1993) analyzed survival probabilities among 8,111 adults who were first recruited in the mid-1970s in six cities in the eastern portion of the United States. The cities are: Portage, WI, a small town north of Madison; Topeka, KS; a geographically-defined section of St. Louis, MO; Steubenville, OH, an industrial community near the West Virginia-Pennsylvania border; Watertown, MA, a western suburb of Boston; and Kingston-Harriman, TN, two small towns southwest of Knoxville. This selection of locations thus comprises a transect across the Northeastern and Northcentral United States, from suburban Boston, through Appalachia, and into the upper Midwest. The adults were white and aged 25 to 74 at enrollment. The final cohorts numbered 1,400 to 1,800 persons in each city. Follow-up periods ranged from 14 to 16 years, during which from 13 to 22% of the enrollees died. Of the 1,430 death certificates, 98% were located, including those for persons who had moved away and died elsewhere. The bulk of the analysis was based on all-cause mortality. Individual characteristics of the members (and thus of the decedents) considered included smoking habits, an index of occupational exposure, body mass index, and completion of a high school education. The effects of air pollution were evaluated in two ways: by evaluating the relative risks of residence in each city relative to Portage (the city with the

lowest pollution levels for most indices), and by including the community-average air quality levels directly in the models.

Based on statewide mortality data, substantial differences in survival rates would be expected across this transect of the Northeastern U.S. and were in fact observed. The long-term average mortality rate in Steubenville was 16.2 deaths per 1,000 person-years; in Topeka, it was 9.7, yielding a 67% variation in the range of annual average (crude) relative risk across the six cities. After individual adjustment for age, smoking status, education, and body-mass index, the range in average relative risk was reduced to 26%.

Dockery et al. (1993) report that "mortality was more strongly associated with the levels of fine, inhalable, and sulfate particles" than with the other pollutants, which they attributed primarily to factors of particle size. They provided relative risk estimates and confidence limits based on the differences between air quality in Steubenville and in Portage for these three pollutants.

Table 13-8 shows only small differences among many pollutants, including SO_2 and NO_2, owing in part to the strong collinearity present. Note that TSP and the coarse particle variables created by subtracting PM_{15} from TSP and $PM_{2.5}$ from PM_{15} were not significant, suggesting that particles larger than about 15 um in aerodynamic diameter may be less important; this outcome may reflect in part greater spatial variability within the communities for these measures. The non sulfate portion of $PM_{2.5}$ had the tightest confidence limits (SO_4^{2-} was multiplied by 1.2 before subtraction, assuming an average composition of NH_4HSO_4). Note also that the estimated 1970 TSP variable performed better than the TSP data used by Dockery et al. (ca. 1982). However, all of the differences in relative risks and their confidence limits could have occurred due to chance, given the availability of only 6 observations. No relationship was found for aerosol acidity (H^+), but only limited data were available.

The authors of this study appear to have made the most of the available individual data on some of the most important mortality risk factors. They were quite cautious in their conclusions, stating only that the results suggest that fine-particulate air pollution "contributes to excess mortality in certain U.S. cities." There are several other important outcomes:

- None of the population subgroups examined appeared to be significantly more sensitive to air pollution than any other.

TABLE 13-8. ESTIMATED RELATIVE RISKS IN SIX U.S. CITIES ASSOCIATED WITH A RANGE OF AIR POLLUTANTS

Species	Regr. Coeff.	Standard Error	Range	Rel. Risk	95% CIs (n=6)
PM_{15}	0.0085	(0.0026)	28.3	1.27	(1.04-1.56)
$PM_{2.5}$	0.0127	(0.0034)	18.6	1.27	(1.06-1.51)
SO_4^{2-}	0.0297	(0.0081)	8.5	1.29	(1.06-1.56)
TSP	0.0037	(0.0014)	55.8	1.22	(0.99-1.53)
TSP-PM_{15}	0.0042	(0.0032)	27.5	1.12	(0.88-1.43)
PM_{15}-$PM_{2.5}$	0.0178	(0.0098)	9.7	1.19	(0.91-1.55)
$PM_{2.5}$-SO_4^{2-}	0.0255	(0.0029)	8.4	1.24	(1.16-1.32)
PM_{15}-SO_4^{2-}	0.0121	(0.0034)	18.1	1.24	(1.05-1.48)
SO_2	0.0093	(0.0032)	19.8	1.20	(1.01-1.43)
NO_2	0.0126	(0.0046)	15.8	1.22	(1.00-1.49)
1970 TSP	0.0014	(0.00044)	154.0	1.25	(1.03-1.50)

Source: Dockery et al. (1993)

- The implied regression coefficients are much larger (about an order of magnitude) than those found in either type of population-based study. This could be interpreted as evidence that the chronic effects of air pollution far exceed the acute effects, or that not all of the spatial confounding has been controlled. Use of linear models for non-linear effects (body-mass index) and failure to control for alcohol consumption, diet, exercise and migration may have contributed to the relatively large effects indicated for air pollution.

- If the responses to air pollution truly are chronic in nature, it is logical to expect that cumulative exposure would be the preferred metric (Abbey et al., 1991). Pollution levels 10 years before this study began were much higher in Steubenville and St. Louis, as indexed by TSP from routine monitoring networks. Estimates of previous levels of fine particles are more difficult, but atmospheric visibility data suggest that previous levels may have been higher in winter, but not necessarily in summer. These uncertainties make it difficult to accept quantitative regression results based solely on coincident monitoring data. For example, annual average TSP in 1965 in Steubenville was about three times the value used by Dockery et al. (1993).

Because it seems unlikely that any of the perceived shortcomings of this study could have resulted in bias sufficient to reduce the risk estimates to levels less than those found in acute mortality studies, the study of Dockery et al. (1993) appears to provide support for the hypothesis that the results of long-term air pollution studies must also reflect the presence of acute effects on mortality as integrated over the long term, as suggested by Evans et al. (1984a). It may also be concluded that support has been shown for the existence of chronic effects; these two possibilities are not mutually exclusive. However, these conclusions must be qualified by the realization that not all of the relevant socioeconomic factors may have been properly controlled in this study.

Pope et al. (1995) analyzed 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS). The Cox proportional hazards model was used to define individual risk factors for age, sex, race, smoking (including passive smoke exposure), occupational exposure, alcohol consumption, education, and body-mass index. The deaths, about 39,000 in all, were assigned to geographic locations using the 3-digit zip codes listed at enrollment into the ACS study in 1982. Relative risks were then computed for 151 metropolitan areas defined by these zip codes and were compared to the corresponding air quality data, ca. 1980. The sources of air quality data used were the EPA AIRS system for sulfates, as obtained from high-volume sampler filters for 1980, and the Inhalable Particulate Network for fine particles ($PM_{2.5}$). The latter data were obtained from dichotomous samplers during 1979-81. Causes of death considered included all causes, cardiopulmonary causes (ICD-9 401-440, 460-519), lung cancer (ICD-9 162), and all other causes.

This study took great care to control for those potential confounding factors for which data were available. Several different measures of active smoking were considered, as was the time exposed to passive smoke. The occupational exposure variable was specific to any of: asbestos, chemicals/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel exhaust, or formaldehyde. The education variable was an indicator for having less than a high-school education. Risk factors not considered by Pope et al. include income, employment status, dietary factors, drinking water hardness and physical activity levels, all of which have been shown to affect longevity (Sorlie and Rogot, 1990; Belloc, 1973; Pocock et al., 1980). In addition, they did not discuss the possible influences of other air pollutants.

The ACS cohort is by no means a random sample of the U.S. population; it is 94% white and better educated than the general public, with a lower percentage of smokers than in the Six City Study. The (crude) death rate during the 7.25 years of follow-up was just under 1% per year, which is about 20% lower than expected for the white population of the U.S. in 1985, at the average age reported by Pope et al. In contrast, the corresponding rates for the Six- Cities study (Dockery et al., 1993) discussed above tended to be higher than the U.S. average.

The adjusted total mortality risk ratios for the ACS study (computed for the range of the pollution variables) were 1.15 (95% CL = 1.09 to 1.22) for sulfates and 1.17 (95% CL = 1.09 to 1.26) for $PM_{2.5}$. When expressed as log-linear regression coefficients, these values were quite similar for both pollution measures: 0.0070 (0.0014) per $\mu g/m^3$ for SO_4^{2-} and 0.0064 (0.0015) for $PM_{2.5}$, suggesting that particle chemistry may be relatively unimportant as an independent risk factor (it is possible that the SO_4^{2-} results have been biased high by the presence of filter artifacts). Pope et al. found that the pollution coefficients were reduced by 10 to 15% when variables for climate extremes were added to the model.

The results of the long-term prospective cohort studies are shown in Table 13-9. The results of the American Cancer Society prospective study were qualitatively consistent with those of the Six City study with regard to their findings for sulfates and fine particles; but relative standard errors were smaller, as expected because of the substantially larger database. However, no other pollutants were investigated in the ACS analysis, so that no further progress was made in attempting to identify the "responsible" pollutants. In addition, the ACS regression coefficients were about 1/4 to 1/2 of the corresponding Six City values and were much closer to the corresponding values obtained in various acute mortality studies. Thus it is not clear to what extent chronic effects (as opposed to integrated acute effects) are indicated by these results and to what extent the limited air quality data base used was responsible for this outcome.

The California and Six-City studies suffer from small sample sizes and inadequate degrees of freedom, which partially offset the specificity gained by considering individuals instead of population groups. All of them may have neglected some important risk factors. The studies of California nonsmokers by Abbey et al. (1991, 1994) that had the best

TABLE 13-9. PROSPECTIVE COHORT MORTALITY STUDIES

Source	Health Outcome	Population	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Total Deaths	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at SO_4 = 15, PM_{15} = 50, $PM_{2.5}$ = 25	RR. Confidence Interval	Elasticity
Abbey et al. (1991)	Total mortality from disease	Calif. 7th Day Adventist	1977-82 Defined by air monitoring sites	24 h TSP > 200	102	25-175 (annual avg)	NA	845	Cox proportional hazards	10 yrs	none	age, sex, race, smoking, education, airway disease	0.99 TSP[1]	(0.87-1.13)[1]	NS[2]
Dockery et al. (1993) p. 1758	Total mortality	White adult volunteers in 6 U.S. cities[3]	1974-91	PM_{15} $PM_{2.5}$ SO_4	29.9 18 7.6	18-47 11-30 5-13	1	1429	Cox proportional hazards	none	none	age, sex, smoking, education, body mass, occup. exposure hypertension[4], diabetes[4]	1.42 PM_{15} 1.31 $PM_{2.5}$ 1.46 SO_4	(1.16-2.01) (1.11-1.68) (1.16-2.16)	0.25 0.22 0.23
Pope et al. (1995) Table 2	Total mortality	American Cancer Society, adult volunteers in U.S.	1982-89 $PM_{2.5}$ 50 cities SO_4 151 cities	$PM_{2.5}$ SO_4	18.2 11[5]	9-34 4-24	1 1	20,765 38,963	Cox proportional hazard	none	none	age, sex, race, smoking, education, body mass, occup. exposure, alcohol consumption, passive smoking, climate*	1.17 $PM_{2.5}$ 1.10 SO_4	(1.09-1.26) (1.06-1.16)	0.117 0.077

[1]For 1,000 h/yr > 200 $\mu g/m^3$.
[2]NS = *non significant, confidence limits not shown.*
[3]Portage, WI; Topeka, KS; Watertown, MA; Harrisman-Kingston, TN; Steubenville, OH.
[4]Used in other regression analyses not shown in this table.
[5]Value may be affected by filter artifacts.

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cumulative exposure estimates found no significant mortality effects of previous air pollution exposure. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality. At this time, the long-term studies provide support for the existance of short-term PM-related mortality increases which are not subsequently offset by decreases below normal rates. However, they do not exclude the possible existence of additional chronic exposure effects, nor do they provide convincing evidence as to the specific pollutant(s) involved, and they do not rule out the possible existence of pollutant thresholds.

13.5.3 Morbidity Outcomes Associated With PM Exposure

Dockery and Pope (1994) reviewed the effects of PM on respiratory mortality and morbidity. The authors considered five primary health endpoints: mortality, hospital usage, asthma attacks, respiratory symptoms and lung funtion. In order to include as many studies as possible, they converted both British smoke and TSP measurements to PM_{10}. Results from each study were converted to an estimated percent change in the health endpoint per 10 $\mu g/m^3$ PM_{10}. These converted results were then combined across studies of similar endpoints using the standard inverse variance weighted method (fixed effects model). The authors concluded that there was a coherence of effects across the endpoints, with most endpoints showing a one to three percent change per 10 $\mu g/m^3$ PM_{10}. Pulmonary function showed a smaller change of 0.15 percent for FEV and 0.08 percent for PEFR. These smaller percent changes are to be expected because there is much less variation in pulmonary function measurements than in the other measures. The limitations of the methodological considerations as they pertain to quantitative assessment of the individual studies were discussed earlier in Chapter 12. Dockery and Pope (1994) also noted such limitations in their review.

The primary difficulties in combining studies can be summarized as follows. Most studies used several endpoints and it is not clear that results for all of the different endpoints were reported. Most studies used different lag times or moving averages for the pollutants, and in some cases reported only those which gave positive results. For those studies which did report results for similar endpoints, many were analyzed with different statistical models. The short-term studies must take into account serial correlation, and this was done in a

variety of ways in those studies which did adjust for it. For these reasons, key findings from most of the studies will be described rather than combined formally.

13.5.3.1 Short-Term PM Exposure Hospital Admission Studies

Hospitalization data can provide a measure of the morbidity status of a community during a specified time frame. Hospitalization data specific for respiratory illness diagnosis or more specifically for COPD and pneumonia give a measure of the respiratory status. Such studies provide an outcome measure that relates to mortality studies for total and specified respiratory measures. Tables 13-10 through 13-13 summarize these studies. These studies associate hospitalization data with various measures of PM. Some of the same factors and concerns related to the mortality studies are an issue for these studies also.

Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. There is a possible suggestion of a relationship to heart disease, but the evidence is very inconclusive. The admission studies of respiratory disease show a similar effect. The hospitalization studies in general use very similar analytic methodologies and the majority of the papers are written by a single author. Overall, these hospitalization studies are indicative of health outcomes related to PM. They are also supportive of the mortality studies, especially with the more specific diagnosis relationships.

13.5.3.2 Short and Long-Term Exposure Respiratory Disease Studies

Respiratory illness and the factors determining its occurrence and severity are important public health concerns. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common (Samet et al., 1983; Samet and Utell, 1990). Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage (Glezen, 1989; Samet et al., 1983; Gold et al., 1989). The occurrence of lower respiratory morbidity in early childhood may be associated with impaired lung function and growth that appears to persist through adolescence. Denny and Clyde (1986) stated that infections, reactive airways, and inhaled pollutants (mostly cigarette smoke) are the most important risk factors in the development of chronic lung disease. Thus, factors such as the

TABLE 13-10. HOSPITAL ADMISSIONS STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Burnett et al. (1994) All ages in Ontario, Canada, 1983-1988	9 monitoring stations measuring sulfate	sulfate means ranged from 3.1 to 8.2 $\mu g/m^3$	108	Lin. regress. on filtered data, 1-d lag best	Ozone	Temperature	none	1.03 (1.02, 1.04)
Thurston et al. (1994) All ages in Ontario, Canada, July and August, 1986-1988	3 monitoring stations measuring sulfate, TSP, and PM_{10}	mean sulfate ranged 38 to 124 (nmole/m^3), PM_{10} 30 to 39 $\mu g/m^3$, TSP 62 to 87 $\mu g/m^3$	14.4	Linear regression on filtered data, 0-d lag best	Ozone, H+, SO_2, NO_2	Temperature	none	PM_{10} 1.09 (0.96, 1.22)
							ozone	PM_{10} 1.01 (0.87, 1.15)
Thurston et al. (1992) All ages in Buffalo, Albany, New York City, July and August, 1988-1989	3 monitoring stations (one per city) measuring sulfate, H+	(values not given)	Buffalo, 24 Albany, 12, New York, 137	Linear regression on filtered data	Ozone, H+	Temperature	ozone	(not given for PM measures)
Schwartz (in press) Elderly in New Haven, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 41, 10% tile = 19, 90% tile = 67	8.1	Poisson log-linear regression, 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 29; 10% tile = 16; 90% tile = 45; SO_2 (ppb): mean = 30; 10% tile = 9; 90% tile = 61	Temperature and dew point adjusted for in the moving average	none	1.06 (1.00, 1.13)
							SO_2 (2 day lag)	1.07 (1.01, 1.14)
Schwartz (in press) Elderly in Tacoma, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 37, 10% tile = 14, 90% tile = 67	4.2	Poisson log-lin. regress. 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 25; 10% tile = 13; 90% tile = 36; SO_2 (ppb): mean = 17; 10% tile = 6; 90% tile = 28	Temperature and dew point adjusted for in the moving average	none	1.10 (1.03, 1.17)
							SO_2 (2 day lag)	1.11 (1.02, 1.20)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 13-11. HOSPITAL ADMISSIONS STUDIES FOR COPD

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Sunyer et al. (1993) Adults in Barcelona, 1985-1989	15 monitoring stations measuring black smoke	winter 33% tile = 49, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	12	Autoregressive linear regression analysis, 0-d lag best	Sulfur dioxide, winter 33%tile = 49$\mu g/m^3$, 67%tile = 77, summer 33%tile = 36, 67%tile = 55	min temp, dummies for day of week and year	none	winter: 1.15 (1.09,1.21) summer: 1.05 (0.98,1.12)
							SO_2	winter: 1.05 (1.01,1.09) summer: 1.01 (0.97,1.05)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% tile = 18, 90% tile = 58	2.2	Autoregressive Poisson model, 1-d lag best	Ozone, mean = 26 ppb, 10%tile = 11, 90%tile = 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.25 (1.10,1.44)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19. 90% tile = 77	2.2	Autoregressive Poisson model, 0-d lag best	Ozone, mean = 25 ppb, 10%tile = 14, 90%tile = 37	7 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.13 (1.04,1.22)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} monitoring stations, data available for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	5.8	Poisson auto-regressive model using GEE, 0-d lag best	Ozone, mean = 21 ppb, 10%tile = 7, 90%tile = 36	Dummy vars. for temp, month, lin. & quad. time trend	ozone	1.11 (1.04, 1.17)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

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TABLE 13-12. HOSPITAL ADMISSIONS STUDIES FOR PNEUMONIA

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10%tile = 18, 90% tile = 58	6.0	Autoregressive Poisson mod., 1-d lag best	Ozone: mean 26 ppb; 10% tile 11; 90% tile 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.08 (1.01,1.15)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19. 90% tile = 77	5.9	Autoregressive Poisson mod., 0-d lag best	Ozone: mean 25 ppb; 10% tile 14; 90% tile 37	7 cat. of temp. & dew pt., month, year, lin. & quad. time trend	none	1.09 (1.03, 1.15)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson auto-regress. mod. using GEE, 0-d lag best	Ozone: mean 21 ppb; 10% tile 7; 90% tile 36	Dummy variables for temp, month, lin. & quad. time trend	ozone	1.06 (1.02, 1.10)

TABLE 13-13. HOSPITAL ADMISSIONS STUDIES FOR HEART DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz and Morris (in press) Elderly in Detroit 1986-1989 Ischemic Heart Disease	2 to 11 PM_{10} monitoring stations, data available for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	44.1	Poisson auto-regressive model using GEE, 0-d lag best	SO_2, mean = 25 ppb, 10% tile = 11, 90% tile = 44 CO, mean 2.4 ppm, 10% tile 1.2, 90% tile = 3.8	Dummy vars. for temp, month, lin. & quad. time trend	none	1.06 (1.02, 1.10)
							ozone, CO, SO_2	1.06 (1.02, 1.10)
Burnett et al. (in press) All ages in Ontario, Canada, 1983-1988 Cardiac disease admission	22 sulfate monitoring stations	station means ranged from 3.0 to 7.7 in the summer and 2.0 and 4.7 in the winter	14.4	Linear regression on a 19 day linear filter, 1-d lag best	Ozone averaged 36 ppb	Temperature included in separate analyses by summer and winter	none	1.04 (1.03, 1.06)
							ozone	1.04 (1.03, 1.05)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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presence of PM (which increases the risk for respiratory symptoms and related respiratory morbidity) are important because of associated public health concern with regard to both the immediate symptoms produced and the longer term potential for increases in the development of chronic lung disease.

Acute Respiratory Disease Studies

Acute respiratory disease studies include several different endpoints, but the majority of authors reported results on at least two of: (1) upper respiratory illness; (2) lower respiratory illness; or (3) cough (See Table 13-14). These relative risks are all estimated for an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The results for upper respiratory illness are very inconsistent: two studies estimate a relative risk near 1.00 whereas four others obtain estimates between 1.14 and 1.55. The relative risks for lower respiratory illness are spread between 1.01 and 2.03, but all are positive. The relative risks for cough include two below 1.0 and go as high as 1.51. All of these are suggestive of an effect. Whereas the hospital admission studies were all done in a similar manner and resulted in very similar results, these studies are done with very different designs and give very inconsistent results.

Chronic Respiratory Disease Studies

The three studies are based on a similar type of questionnaire but were done by two different groups of researchers. All three studies suggest a chronic effect of particulate matter on respiratory disease, but the studies suffer from the usual difficulty of cross sectional studies. The effect of particulate matter is based on variations in exposure which are determined by the different number of locations. In the first two studies there were six locations and in the second there were four. The results seen were consistent with a particulate matter gradient, but it is impossible to separate out the effect of particulate matter and any other factors or pollutants which have the same gradient (See Table 13-15).

13.5.3.3 Short and Long-Term Exposure Pulmonary Function Studies

Pulmonary function studies are part of a comprehensive investigation of the possible effects of any air pollutant. Measurements can be made in the field, they are noninvasive, and their reproductibility has been well documented. Guidelines for reference values and

TABLE 13-14. ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1994) 300 elementary school children in Six-Cities in U.S., 1984-1988	PM_{10} monitoring in each city	median 30 $\mu g/m^3$ 10th percentile = 13, 90th percentile = 53	3.1	Autoregressive logistic regression using GEE	Ozone, NO_2, SO_2	Temperature	none SO_2 ozone	1.51 (1.12, 2.05) 1.39 (0.98, 1.96) 1.49 (1.10, 2.01)
Pope et al. (1991), students in the Utah Valley, winter 1989-1990	PM_{10} monitoring stations at 3 sites	mean = 46 $\mu g/m^3$, range = 11 to 195	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and ozone. Values were well below the standard	Variables for temperature and time trend	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.28 (1.06, 1.56)
Pope et al. (1991), asthmatic children in the Utah Valley, winter 1989-1990	PM_{10} monitoring stations at 3 sites	mean = 46 $\mu g/m^3$, range = 11 to 195	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and ozone. Values were well below the standard	Variables for low temperature and time trend	none	Upper resp. 0.99 (0.81, 1.22) Lower resp. 1.01 (0.81, 1.27)
Pope and Dockery (1992), symptomatic children in the Utah Valley, winter 1990-1991	PM_{10} monitoring stations at 2 sites	mean = 76 $\mu g/m^3$, range = 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temperature	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.27 (1.08, 1.49) Cough 1.29 (1.12, 1.48)

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TABLE 13-14 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Pope and Dockery (1992), asymptomatic children in the Utah Valley, winter 1990-1991	PM_{10} monitoring stations at 2 sites	mean = 76 $\mu g/m^3$, range = 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temperature	none	Upper resp. 0.99 (0.78, 1.26) Lower resp. 1.13 (0.91, 1.39) Cough 1.18 (1.00, 1.40)
Hoek and Brunekreef (1993), respiratory disease in school children aged 7 to 12 in Wageningen, Netherlands, winter 1990-1991	Two to 4 monitoring stations measured PM_{10}	max = 110 $\mu g/m^3$	(not given)	Autoregressive logistic regression using GEE	Max SO_2 = 105 $\mu g/m^3$, max NO_2 = 127 $\mu g/m^3$	Variable for ambient temperature and day of study	none	Upper resp. 1.14 (1.00, 1.29) Lower resp. 1.06 (0.86, 1.32) Cough 0.98 (0.86, 1.11)
Schwartz et al. (1991) Study of acute respiratory illness in children in 5 German communities, 1983-1985	Two to 4 monitoring stations in each area measured TSP	medians ranged from 17 to 56 $\mu g/m^3$, 10% tiles from 5 to 34, 90% tiles from 41 to 118	0.5 to 2.9	Autoregressive Poisson regression using GEE	median SO_2 levels ranged from 9 to 48 $\mu g/m^3$, median NO_2 levels ranged from 14 to 5 $\mu g/m^3$	Most significant terms of day of week, time trend, and weather (terms not listed)	none (TSP was not significant when NO_2 added to model)	1.26 (1.12, 1.42)

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TABLE 13-14 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1994) Study of respiratory symptoms in 6 U.S. cities, 1984-1988	Daily monitoring of PM_{10}, $PM_{2.5}$ at each city	median PM_{10} = 30 $\mu g/m^3$, 10% tile = 13, 90% tile = 53 median $PM_{2.5}$ = 18 $\mu g/m^3$, 10% tile = 7, 90% tile = 37	(not given)	Autoregressive logistic regression using GEE	SO_2, median = 4 ppb, 10% tile = 1, 90% tile = 18 NO_2, median = 13 ppb, 10% tile 5, 90% tile = 24, ozone	temperature, day of week, city or residence	all two pollutant models were fitted with minimal effect on PM	Cough (PM_{10} lag 1) 1.51 (1.12, 2.05) Upper resp. (PM_{10} lag 2) 1.39 (0.97, 2.01) Lower resp. (PM_{10} lag 1) 2.03 (1.36, 3.04)
Braun-Fahrländer et al. (1992) Study of preschool children in four areas of Switzerland	Daily monitoring of TSP	(not given)	4.4	Logistic regression	SO_2, NO_2, and ozone levels not given	city, risk strata, season, temperature	none	Upper resp. 1.55 (1.10, 2.24)
Roemer et al. (1993) Study of children with chronic respiratory symptoms in Wageningen, The Netherlands	Daily monitoring of PM_{10}	6 days above 110 $\mu g/m^3$	.094 incidence rate	Autoregressive logistic regression	SO_2 and NO_2 means not given	(not given)	none	Cough (not given, probably less than one)
Dusseldorf et al. (1994) Study of adults near a steel mill in The Netherlands	Daily monitoring of PM_{10}, iron, sodium, silicon, and manganese	mean PM_{10} = 54 $\mu g/m^3$, range = 4 to 137)	(not given)	Logistic regression	Geometric mean iron = 501 ng/m^3, manganese = 17 ng/m^3, silicon = 208 ng/m^3	(not given)	none	Cough 1.14 (0.98, 1.33)

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TABLE 13-14 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Ave. Rate per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Other pollutants in model	Result* (Confidence Interval)
Ostro et al. (1991) Study of adult asthmatics in Denver, Colorado November 1987 to February 1988	Two monitors provided daily measurements of $PM_{2.5}$	22 $\mu g/m^3$, range = 0.5 to 73	15 (out of 108)	Autoregressive logistic regression	nitric acid, sulfates, nitrates, SO_2, and H^+	day of survey, day of week, gas stove, minimum temperature	none	Cough 1.09 (0.57, 2.10)
Ostro et al. (1993) Study of non-smoking adults in Southern California	Apparently one site (Azusa). PM measurements included sulfate fraction and COHS	mean sulfate = 8 $\mu g/m^3$, range = 2 to 37 mean COHS = 12 per 100 ft, range = 4 to 26	4.2/person for lower, 10.2/person, upper	Logistic regression	ozone, mean = 7 pphm, range = 1 to 28	temperature, rain humidity	none	Sulfates: Upper resp. 0.91 (0.73, 1.15) Lower resp. 1.48 (1.14, 1.91)

* Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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TABLE 13-15. CHRONIC RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Overall Symptom Rate	Model Type & Lag Structure	Other pollutants measured	Other Covariates	Other pollutants in model	Result* (Confidence Interval)
Ware et al. (1984) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1974-1977	Daily monitoring of TSP, SO_2, NO_2, and ozone at each city	City TSP means ranged from 39 to 114 $\mu g/m^3$	Cough, .08, Bronchitis .08, Lower resp. .19	Logistic regression	SO_2, NO_2, and ozone	age, gender, parental education, maternal smoking	none	Cough 2.75 (1.92, 3.94) Bronchitis 2.80 (1.17, 7.03) Lower resp. 2.14 (1.06, 4.31)
Dockery et al. (1989) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1980-1981	Daily monitoring of PM_{15}, sulfate fraction at each city	City PM_{15} means ranged from 20 to 59 $\mu g/m^3$	Cough, .02 to .09, Bronchitis .04 to .10, Lower resp. .07 to .16	Logistic regression	SO_2, NO_2, and ozone	age, gender, maternal smoking	none	Cough 5.39 (1.00, 28.6) Bronchitis 3.26 (1.13, 10.28) Lower resp. 2.93 (0.75, 11.60)
Chapman et al. (1985) Study of persistent cough and phlegm (bronchitis) in adults in four communities in Utah. Survey done in 1976	Daily monitoring of TSP, and sulfate fraction at each city	Previous 5 year TSP ranged from 11 to 115 $\mu g/m^3$	.02 to .05 by city	Logistic regression	SO_2, NO_2	smoking	none	Mothers 1.75 (1.21, 2.54) Fathers 1.94 (1.16, 3.25)
Neas et al. (1994) Study of children aged 7 to 11 from six cites in U.S. Survey done 1983-1986.	$PM_{2.5}$	Not given	Not given	Logistic regression	NO_2	household smoking, gas stove, age, gender	none none none	Cough 1.08 (0.76, 1.53) Bronchitis 1.32 (0.98, 1.79) Lower resp. 1.23 (0.98, 1.55)

* Estimates calculated from data tables assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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interpretative strategies of lung function tests have been prepared (American Thoracic Society, 1991). Various factors are important determinants of lung functions.

Lung function in children has been related to genetic factors that exert their greatest influence through general stature as measured by height and age. Growth patterns in children differ by gender. Lung function declines with age among adults (Dockery et al., 1988). The study of the growth of pulmonary function and generalized growth models consider factors of how growth is statistically dependent on the initial measures of function, and how it is related to respiratory illness in childhood. The effects of active smoking and passive smoking (Lebowitz and Holberg et al., 1987) are also considered. Epidemiological studies relating particulate matter to decrements in pulmonary function represent a potentially important health effect.

The acute pulmonary function studies are suggestive of a short term effect resulting from particulate pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent (See Table 13-16).

The chronic pulmonary function studies are less numerous than the acute studies (Table 13-16). The one study with good monitoring showed no effect from particulate pollution. Cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus the lack of statistical significance cannot be taken as proof of no effect.

13.5.3.4 Comparison of the Effect of PM_{10} to $PM_{2.5}$ on Respiratory Disease and Pulmonary Function

The most direct comparison of the effect of PM_{10} to $PM_{2.5}$ results when studies include both exposure measures in their analyses. This occurred in the Six City study (Schwartz et al. 1994), the Tuscon study (Quackenboss et al., 1991) and the Uniontown study (Neas et al., 1995). None of these studies could directly show that one of these measures was a significantly better predictor than the other. The Schwartz et al. (1994) study suggested that PM_{10} was a better predictor of respiratory disease. The Quackenboss et al. (1991) study

TABLE 13-16. ACUTE AND CHRONIC PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Dockery et al. (1982) School age children in Steubenville, OH, measured at three times between 1978 and 1980	Single station measuring TSP	up to 455 $\mu g/m^3$	individual regression analyses for each child, coefficients pooled across time	SO_2	average temperature	TSP	FVC: 8.1 ml $FEV_{0.75}$: 1.8 ml Note: decreases were statistically significant
Dassen et al. (1986) School age children in The Netherlands, measured in November, 1984 and January, 1985	Six station network measuring TSP, RSP (PM_{10})	TSP and RSP both exceeded 200 $\mu g/m^3$	multiple linear regression	SO_2	technician, appliance, presence of colds	RSP	slopes not given but FVC, FEV_1, and PEFR were significantly reduced during episodes
Quackenboss et al. (1991) Asthmatic children aged 6 to 15 years in Tuscon, AZ, measured in May and November, 1988	Individual monitoring of homes of $PM_{2.5}$, PM_{10}		Random effects linear model	NO_2	temperature, wind speed, dew point	$PM_{2.5}$	PEFR: 375 ml/s Note: these are diurnal rather than daily changes
Pope et al. (1991) Study of asthmatic children in the Utah Valley	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 11 to 195 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	low temperature	PM_{10}	PEFR: 55 ml/s (24, 86)
Pope and Dockery (1992) Study of non-asthmatic symptomatic and asymptomatic children in the Utah Valley	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 11 to 195 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	low temperature	PM_{10}	Symptomatic PEFR 30 ml/s (10, 50) Asympto-matic PEFR 21 ml/s (4, 38)

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TABLE 13-16 (cont'd). ACUTE AND CHRONIC PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Koenig et al. (1993) Study of asthmatic and non-asthmatic elementary school children in Seattle, WA in 1989 and 1990	$PM_{2.5}$ calibrated from light scattering	$PM_{2.5}$ ranged from 5 to 45 $\mu g/m^3$	Random effects linear regression	none	height, temperature	$PM_{2.5}$	Asthmatics FEV_1 42 ml (12, 73) FVC 45 ml (20, 70) Non-asthmatics FEV_1 4 ml (-7, 15) FVC -8 ml (-20, 3)
Hoek and Brunekreef (1993) Study of children aged 7 to 12 in Wageningen, Netherlands	Single site measure black smoke. PM_{10} was measured during episodes	range of PM_{10} was 30 to 144 $\mu g/m^3$	SAS procedure AUTOREG	SO_2, NO_2	day of study	PM_{10}	PEFR 41 ml/s (-8, 90)
Roemer et al. (1993) Study of children with chronic respiratory symptoms in The Netherlands	Single site measure black smoke. PM_{10} was measured using an Anderson dichot	range of PM_{10} was 30 to 144 $\mu g/m^3$	multiple linear regression analysis	SO_2, NO_2	none	PM_{10}	PEFR 34 ml/s (9, 59)
Pope and Kanner (1993) Study of adults in the Utah Valley from 1987 to 1989	PM_{10} was collected daily from the north Salt Lake site	PM_{10} daily mean = 55 $\mu g/m^3$, ranged from 1 to 181 $\mu g/m^3$	Linear regression on difference in PFT as a function of PM_{10}	Limited monitoring of SO_2, NO_2, and ozone	low temperature	$PM_{2.5}$	FEV_1 29 ml (7, 51) FVC 15 ml (-15, 45)
Neas et al. (1994) Study of lung function in children in 6 cities in the U.S. Data collected from 1983-1988.	Daily monitoring of $PM_{2.5}$, sulfate fraction at each city	not given	Linear regression using logarithm of PFT value	SO_2, NO_2, and ozone	city, gender parental education, history of asthma, age, height, weight	$PM_{2.5}$	FVC and FEV_1 not changed. Values could not be converted to mls.

* Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} on 100 $\mu g/m^3$ increase in TSP.

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suggested that $PM_{2.5}$ was a better predictor of lung function change. The Neas et al. (1995) study used only the $PM_{2.5}$ values in their analysis, but this may have been due to the fact that the PM_{10} values were not available as 12 h averages whereas the other pollutants were.

There were at least three other studies that used $PM_{2.5}$ as a measure of particulate exposure. The Ostro et al. (1991) study of respiratory disease in Denver found an effect that was in the middle of the range of effects found by the PM_{10} studies. The Koenig et al. (1993) study of lung function found a slightly larger effect for asthmatics and slightly smaller effect for non-asthmatics when compared with the PM_{10} studies. Finally, the Neas et al. (1994) Six City study of lung function did not give parameter estimates which could be compared directly with the other studies.

Based on the above information, there is currently no obvious way by which to clearly distinguish morbidity effects of PM_{10} versus $PM_{2.5}$. Even the suggestive evidence leaves the scales in a balanced position.

13.5.4 Coherence of Epidemiologic Findings

Factors involved in evaluating both the data and the entire group of epidemiological studies, include the strength of association, the consistence of the association, as evidenced by its repeated observation by different persons, in different places, circumstances and time, and the consistency with other known facts (Bates, 1992). One can look for interrelationships between different health indices to provide a stronger and more consistent synthesis of available information. The various findings that support a picture of coherence would provide a stronger case with quantitative studies as opposed to qualitative studies. Other studies may be inappropriate to use in such a discussion, the quality of the study should be considered. Bates (1992) states that the difficulty with discussing any index of internal coherence is that this requires a series of judgements on the reliability of the individual findings and observations. The outcome of a coherence discussion then is a qualitative presentation in the end, not quantitative. Thus, coherence cannot be formally measured.

Bates (1992) also noted that the strength of different health indexes are important as are difficulties in assessing exposure. Bates (1992) also suggests three areas to look for

coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) between epidemiological, controlled human and animal data.

Coherence by its nature considers biological relationships of exposure to health outcome. The biologic mechanism underlying an acute pulmonary function test reduction in children is most likely not part of the acute basis for a change in the mortality rate of a population exposed in an older group of individuals. In looking for coherence one should compare outcomes that look at similar time frames—daily hospitalizations compared to daily mortality rather than monthly hospitalizations. Overall the data indicates that PM has a relationship with a continuum of health outcomes, but the studies may not establish a coherence between them. The underlying mechanisms may be different.

The principal health outcome for which coherence is desirable is mortality, the death rate in a population. This can be considered within the endpoint and/or in other endpoints. Of the various morbidity outcomes studied and discussed in the earlier part of the chapter, hospitalization studies reviewed in the chapter support this notion. The mortality studies suggest that these specific causes provide stronger relationships (i.e., larger RR estimates) than total mortality. The outcome potentially most related is hospital admission for respiratory or cardiovascular causes in the older age group (i.e., > 65 years old). In a qualitative sense, the increased mortality found in that age group should also be paralled by increased hospital admissions.

Partial coherence is established by those studies in which increased incidence of different health outcomes associated with PM are found in the same population, as is the case for the following examples, based on currently published studies:

- Detroit: Mortality mainly in elderly populations, hospital admissions for respiratory causes and for cardiovascular causes in the elderly;
- Birmingham: Mortality mainly in the elderly, hospital admissions for the elderly;
- Philadelphia: Mortality and hospital admissions for pneumonia in the elderly;
- Utah Valley: Mortality and hospital admissions for respiratory causes in adults.

Also, pulmonary function, respiratory symptoms, and medication use in asthmatic subjects of all ages; hospital admissions for respiratory symptoms, pulmonary function, respiratory symptoms, and medication use in healthy school children, pulmonary function in

symptomatic and asymptomatic children; and elementary school absences in children were found to be associatied with PM exposures in Utah Valley. A similar study found a PM effect on pulmonary function in smokers with COPD in Salt Lake Valley. The Utah Valley population was largely non-smoking, so smoking was not likely to be a source of confounding.

While these multiple outcomes did not occur in strictly identical subgroups of each population, there was probably a sufficient degree of overlap to indicate that PM was a significant predictor of a wide range of health outcomes within a specific community. The symptoms serious enough to warrant hospitalization and the major part of the excess mortality occurred in the elderly sub-group of the population. However, a significant decrement in pulmonary function and increased incidence of symptoms associated with daily increases in PM occurred in children in Utah Valley, along with a "quality of life" effect measured by lost school days. Thus, there is evidence for increased risk of health effects related to PM exposure ranging in seriousness from asymptomatic pulmonary function decrements, to respiratory symptoms and cardiopulmonary symptoms sufficiently serious to warrant hospitalization, and to excess mortality from respiratory and cardiovascular causes, especially in those older than 65 years of age.

Children may also be at increased risk of pulmonary function changes and increased incidence of symptoms associated with PM exposure. While we have arrayed these health outcomes in order of increasing severity, there is as yet little indication that there is a progression of effects in any single individual associated with increasing exposure to PM. The "exposure-response" relationship that is derived in most studies must be understood as characterizing population risk from population exposure. Additional studies are needed to define the relationship(s) among individual exposure to PM and other stress factors, individual risk, and individual progression among disease states. Differences in PM dosimetry in the developing, aged, or diseased respiratory tract may also contribute to increased susceptability.

The coherence of the various health effects in humans could be established more conclusively from epidemiology studies if there were better evidence. We cannot prove that the people that suffered respiratory symptoms in response to PM exposure were among the same people who suffered pulmonary function decrements from PM exposure in the past,

that those who were admitted to hospital for respiratory or cardiopulmonary causes in response to PM exposure were among those who had suffered respiratory symptoms or pulmonary function decrements from earlier PM exposures, nor that those who died from PM exposure were among those who had earlier shown other health endpoints associated with PM exposures. Such information could, in principle, be extracted from longitudinal data bases such as those collected by health care providers; however, although some such efforts are now being considered, the preferred design for such a study is a prospective design rather than a retrospective design. If and when these studies are completed, they could be useful in future PM health assessments.

13.6 HEALTH EFFECTS OF AMBIENT PM CONSTITUENTS

There are literally hundreds of ambient PM consituents, having varying degrees of health effects information. The key constituents (defined as those individual compounds likely to constitute > 1 ng/m^3 in ambient U.S. urban air) include several heavy metals (e.g., cadmium, manganese, chromium, aluminum, lead, etc.), asbestos, silica, carbon particles, nitrates, sulfates, and acid aerosols. Other constituents of interest include transition metals (e.g., iron) and ultrafine particles. Of all of these materials, only a few have a direct relevance to PM as a criteria pollutant. For example, acid aerosols are a generic subclass of PM and are summarized here. The others are of indirect interest insofar as they can elucidate and extend the epidemiologic findings. For example, because heavy metals are regulated as hazardous air pollutants (i.e., they are not criteria pollutants, except for lead), their data base is mainly of value here to help illustrate the great importance of particulate chemistry to health outcome. Transition metals and ultrafines may be important mechanisms for lung morbidity and mortality observed in epidemiologic studies. These issues are discussed in more depth later, in an attempt to present hypotheses for the biological plausibility of the epidemiologic findings for PM exposure.

The carcinogencity of diesel (and carbon) particles and particle-bound organics was summarized in Chapter 11. Diesel emissions are regulated separately (mobile source provisions of the Clean Air Act), and many of the organics of concern on PM are regulated as hazardous air pollutants. Therefore, they do not have much direct relevance *per se* for

deriving criteria for PM standards. Nevertheless, they do have an indirect relevance. The diesel and carbon studies assist in interpreting other animal toxicity studies by showing that: (1) high concentrations of particles can cause unrealistic phenomena (particle overloading) that can produce health outcomes not likely to occur at typical non-episodic ambient PM concentrations; and that (2) the carbon core of the diesel particle may be significantly more responsible than adsorbed organics for its carcinogenic properties. Data on particle-bound organics illustrate that PM can act as a physical carrier of other pollutants, including carcinogenic compounds. However, quantitative relationships between (a) results of animal studies of organic extracts of particles concentrated from ambient air and (b) potential human carcinogencity associated with ambient or near-ambient exposures to such particles remain to be defined.

Because of the above factors, this section focuses mainly on the health effects of acid aerosols as the one specific PM constituent class having the most extensive data most clearly pointing toward likely contributions to reported ambient PM-mortality/morbidity effects. The bulk of the recent data base of controlled exposure studies on PM involves sulfur oxide particles, primarily H_2SO_4, and the available evidence indicates that the observed responses to these are likely due to H^+ rather than to SO_4^{-2}. Acidic sulfates exert their action throughout the respiratory tract, with the response and location of effect dependent upon particle size and mass and number concentration. The other constituents discussed in Chapter 11 are alluded to later in this integrated synthesis chapter as they pertain to the biological plausibility of the epidemiologic results.

13.6.1 Mortality Effects of Acid Aerosols

Few epidmiological studies have examined mortality data for an association with ambient particulate strong acid aerosol (H^+) exposures. The scarcity of the analyses is due to the absence of adequate ambient acid measurement techniques in the past, and to the lack of routine acid aerosol monitoring in more recent years. Some studies now exist which suggest that human health effects may be associated with expsoures to ambient acid aerosols, both: (1) as derived from reexamination of older, historically important data on air pollution episode events in North America and Europe and (2) as can be deduced from limited recent epidemiology studies carried out in the U.S., Canada, and Europe.

Historical and present-day evidence suggests that strongly acidic PM can be associated with both acute and chronic human health effects. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicates that extremely elevated daily acid aerosol concentrations (on the order of 400 $\mu g/m^3$ as H_2SO_4, or roughly 8,000 nmoles/m^3 H^+) may be associated with excess acute human mortality when present as a copollutant with elevated concentrations of PM and SO_2. In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels ($\leq$ 30 $\mu g/m^3$ as H_2SO_4, or $\leq$ approximately 600 nmoles/m^3 H^+), although these associations could not be separated from those for BS or SO_2. The only attempts to date to associate present-day levels of acidic aerosols with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993b, respectively) were unable to do so, but weaknesses in these analyses (in particular, too limited H^+ data for the analysis) may have made associations undetectable. At very high concentrations that do not occur in the ambient air, mortality in laboratory animals can occur following acute exposure, due primarily to laryngeal or bronchoconstriction; larger particles are more effective in this regard than are smaller ones.

13.6.2 Respiratory Illness Effects of Acid Aerosols

Historical and present-day evidence suggests that there can be both acute and chronic effects of strongly acidic PM on human health. Increased hospital admissions for respiratory causes were documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. Thurston et al. (1992) and Thurston et al. (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major copollutant, O_3, in the regression model. In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes ($H^+ \geq 10$ $\mu g/m^3$ as H_2SO_4, or $\approx$200 nmoles/m^3 H^+), which occur roughly 2 to 3 times per year in eastern North America. These studies provide evidence that present-day strongly acidic aerosols

may represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms studies of healthy children indicate the potential for acute acidic PM effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms except at H^+ above 110 nmoles/m^3 (Dockery et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al. 1991).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of chronic H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1993a) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.7, 95% CI: 1.1 to 2.4). It was also found in the 24-Cities study that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1993). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children.

The respiratory tract has an array of defense mechanisms to kill, detoxify, and physically remove inhaled material, and these defenses may be altered by exposure to H_2SO_4 at levels $<1{,}000$ $\mu g/m^3$. Acid aerosols alter mucociliary clearance in human and laboratory animals, with effects dependent on exposure concentration and the region of the lung being studied. For example 1- to 2-h resting exposures of humans to 100 $\mu g/m^3$ accelerate clearance in large bronchi, but slows clearance in smaller more peripheral airways.

Clearance in asthmatics is also affected, but the results are not clearly interpretable. Long-term exposure also affects mucociliary clearance in animals. For example, in rabbits exposed intermittently for 125 $\mu g/m^3$ H_2SO_4 for 1 year, clearance was accelerated during exposure but was depressed 6 months after exposure ceased. These responses are complex and are accompanied by histological and chemical changes in mucus and epithelial secretory cells. Defenses, such as resistance to bacterial infection, may be altered by acute exposure to concentrations of H_2SO_4 around 1,000 $\mu g/m^3$.

Severe morphologic alterations in the respiratory tracts of animals occur at high acid levels. At low levels and with chronic exposure, the main response seems to be hypertrophy and/or hyperplasia of mucus secretory cells in the epithelium; these alterations may extend to the small bronchi and bronchioles, where secretory cells are normally rare or absent.

Limited data also suggest that exposure to acid aerosols may affect the phagocytic functioning of alveolar macrophages; the lowest level examined to date is 500 $\mu g/m^3$ H_2SO_4. Alveolar region particle clearance is accelerated by repeated H_2SO_4 exposures to as low as 250 $\mu g/m^3$; higher levels retard clearance. Acute exposure of rabbits to lower concentrations (e.g., 75 $\mu g/m^3$ H_2SO_4) can affect other alveolar macrophage functions.

13.6.3 Pulmonary Function Effects of Acid Aerosols

Both acute and chronic exposure of laboratory animals to H_2SO_4 at levels well below lethal ones will produce functional changes in the respiratory tract. The pathological significance of some of these are greater than for others. Acute exposure will alter pulmonary function, largely due to bronchoconstrictive action. However, attempts to produce changes in airway resistance in healthy animals at levels below 1 mg/m^3 have been largely unsuccessful, except when the guinea pig has been used. The lowest effective level of H_2SO_4 producing bronchoconstriction to date in the guinea pig is 100 $\mu g/m^3$ (1-h exposure). In general, smaller size droplets are more effective in altering pulmonary function, especially at low concentrations. Yet even in the guinea pig, there are inconsistencies in the type of response exhibited towards acid aerosols. Chronic exposure to H_2SO_4 is also associated with alterations in pulmonary function (e.g., changes in the distribution of ventilation and in respiratory rate in monkeys). But, in these cases, effective concentrations are $\geq$500 $\mu g/m^3$. Hyperresponsive airways have been induced with repeated

exposures to 250 $\mu g/m^3$ H_2SO_4 in rabbits, and have been suggested to occur following single exposures at 75 $\mu g/m^3$.

Ten human clinical studies since 1988 have confirmed previous findings that healthy subjects do not experience decrements in lung function following single exposures to H_2SO_4 at levels up to 2,000 $\mu g/m^3$ for 1 h, even with exercise and use of acidic gargles to minimize neutralization by oral ammonia. Mild lower respiratory symptoms occur at exposure concentrations in the mg/m^3 range, particularly with larger particle sizes.

There is no clearly established exposure-response relationship across studies. Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but reported effective concentrations differ widely among studies. Adolescent asthmatics may be more sensitive than adult asthmatics, and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels (e.g., less than 100 $\mu g/m^3$). Although the reasons for the inconsistency among studies remain largely unclear, individual variability in sensitivity and subject selection may be an important factors. Even in studies reporting an overall absence of effects on lung function, occasional asthmatic subjects appear to demonstrate clinically important effects. Two studies from different laboratories have suggested that responsiveness to acid aerosols may correlate with the degree of baseline airway hyperresponsiveness. However, based on very limited studies, the elderly and individuals with chronic obstructive pulmonary disease do not appear to be particularly more susceptible to the effects of acid aerosols on lung function than healthy adults.

Two recent studies have examined the effects of exposure to both H_2SO_4 and ozone on lung function in healthy and asthmatic subjects. Both studies found evidence that 100 $\mu g/m^3$ H_2SO_4 may potentiate the response to ozone, in contrast with previous studies. Recent summer camp (and schoolchildren) studies of lung function have also indicated a significant association between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al, 1995).

In view of uncertainties about differences between high acid concentrations needed to produce effects in animal studies and low concentrations found in the human environment, the epidemiologic evidence does not establish a clear role for acid aerosols as a primary agent contributing to ambient PM exposure effects on pulmonary function.

13.7 BIOLOGICAL PLAUSIBILITY: POTENTIAL MECHANISMS OF ACTION

13.7.1 Introduction

Epidemiologic studies have suggested that ambient particulate exposure may be associated with increased mortality and morbidity at PM concentrations below those previously thought to affect human health (Chapter 12). However, the biological plausibility of a causal relationship between low concentrations of PM and daily mortality and morbidity rates is neither intuitively obvious nor expected based on experimental studies of the toxicity of inhaled particles. As indicated in Chapter 11, chronic toxicity from poorly soluble particles has been observed based on the slow accumulation of large lung burdens of particles, not due to small daily fluctuations of one or another of the specific PM constituents discussed in that chapter. Two possible exceptions can be noted. Acute toxicity from inhaled particles has been demonstrated with acidic particles, but only at much higher particle concentrations than those observed in the recent epidemiology studies reporting an association between low-level PM concentrations and morbidity/mortality. Acute toxicity resulting in death has also been reported in rats inhaling singlet ultrafine particles (<0.05 μm) formed in the pyrolysis of perfluorinated compounds at concentrations of 60 to 200 $\mu g/m^3$, (Oberdörster et al., 1995; Warheit et al., 1990), but the significance of these findings for ambient human exposures is yet to be determined.

To approach the difficult problem of determining if the association between low-level PM concentrations and daily morbidity and mortality is biologically plausible, one must consider: the chemical and physical characteristics of the particles in the inhaled atmospheres; the characteristics of the morbidity/mortality observed and the affected population; as well as potential mechanisms that might link the two. Several salient considerations related to the evaluation of biological plausibility of the epidemiology findings are discussed below.

13.7.2 Characteristics of Observed Morbidity and Mortality

If daily mortality rates are increased in association with elevated ambient particulate concentrations, what are the people dying of? Schwartz (1994) addressed this question by comparing causes of death in Philadelphia on high pollution days (average = 141 $\mu g/m^3$)

with causes of deaths on lower pollution days (average = 47 $\mu g/m^3$). On the high pollution days there was a higher relative increase in deaths due to chronic obstructive pulmonary disease (COPD) (RR = 1.25), pneumonia (RR = 1.13), cardiovascular disease (RR = 1.09) and stroke (RR = 1.15). There was also an increase in reports of respiratory factors being contributing causes in the deaths and a higher relative age of those dying. The patterns of causes of death and age of those dying were found to be similar to the patterns observed in the London smog deaths of 1952.

Other studies on associations of morbidity with particulate pollution noted small decreases (2 to 2.5%) in pulmonary function (FVC or FEV_1) in smokers on high pollution days (100 $\mu g/m^3$; Salt Lake City; Pope and Kanner, 1993) and in nonsmokers (>60 $\mu g/m^3$; NHANES I data, Chestnut et al., 1991). An increased number of asthma attacks among working age adults was correlated with increases in particulate pollution over a 3-year period (average particle level = 76 $\mu g/m^3$) in Helsinki (Pönkä, 1991). Thus, the characteristics of health effects on high particle pollution days are mainly cardiopulmonary in nature and are the types of effects that can be considered plausibly related to airborne toxicants.

It is also of interest to consider the health status of the people affected. People with previously existing health conditions (such as COPD, asthma, or other chronic debilitating conditions) are logically likely to be more susceptible to effects from exposure to particulate pollutants than would be healthy persons. Such a situation might result in an increased daily mortality rate on days with higher PM_{10}, followed by a decreased daily mortality rate so that the average mortality rate over a longer time period would not be affected.

Data on the relative effect of particle exposures in persons with pre-existing pulmonary disease compared to healthy persons do not yield a clear picture. Pope and Kanner (1993) reported an approximate 2% decline in FEV_1 in smokers with mild to moderate COPD during an increased concentration in PM_{10} of 100 $\mu g/m^3$ in Salt Lake City. However, persons with severe COPD (average FEV_1 equal to 50% of predicted) had no further reduction in pulmonary function upon acute (2 h) exposure to 90 $\mu g/m^3$ H_2SO_4 in clinical studies (Morrow et al., 1994). Exercising asthmatics experienced mild bronchoconstriction following the same exposures. In a separate study, exercising adolescent asthmatics exposed to 68 $\mu g/m^3$ H_2SO_4 experienced reduced pulmonary function (average of 6% decrease in FEV_1) (Koenig et al., 1989), but in another study, exercising asthmatics did not respond to

exposures to as high as 130 $\mu g/m^3$ H_2SO_4 (Avol et al., 1990). Using an elastase-induced rat model of emphysema, Mauderly et al. (1990) found that exposure to diesel exhaust, which contains aggregates of ultrafine soot particles, resulted in less particle deposition in the lungs of emphysematous rats than in normal rats, thus sparing the emphysematous rats the health effects induced by the soot particles in normal animals.

13.7.3 Influence of Particle Size, Chemical Composition, and Respiratory Tract Deposition/Clearance

The PM_{10} standard is the only U.S. national ambient air quality standard that is not chemical-specific. The chemical composition of a particle will greatly affect its toxicity and, if possible, should be considered in determining if the observed associations between atmospheric PM concentrations and increases in morbidity/mortality are causal. For example, alpha-quartz particles are more toxic than TiO_2 particles (Driscoll and Maurer, 1991); and acid sulfate aerosols are more likely to cause acute health effects than are neutral sulfate aerosols (Fine et al., 1987).

Size is also important in defining the toxicity of particles. Recent studies indicate that ultrafine particles (<20 nm) are much more toxic than larger inhalable particles (Oberdörster et al., 1992; Driscoll and Maurer, 1991). The ultrafine particles have a greater number and surface area per unit mass than fine or coarse particles, which may account, in part, for their greater toxicity. Fine particles tend to have a different chemical composition than larger particles, because their source is often combustion processes. A study of the chemical composition of $PM_{2.5}$ particles versus PM_{10} particles in Los Angeles indicated that nitrates, sulfates, ammonium and organic and elemental carbon were the most abundant species in the $PM_{2.5}$ fraction, while the coarser particles contained soil-related species, such as aluminum, silicon, calcium, and iron (Chow et al., 1994). Chemical composition of PM_{10} is discussed in Chapter 3 and summarized earlier in this chapter (Section 13.2).

In a few epidemiology studies, the investigators attempted to determine what size and/or chemical form of particles had the strongest association with health effects. For example, in the Harvard 6-cities study (Dockery et al., 1993), the excess chronic mortality was most strongly associated with the ambient fine particles, including sulfates. However, in a study of daily air pollution in St. Louis and eastern Tennessee by Dockery et al. (1992),

the strongest association of particulate pollution with daily mortality rates was PM_{10}, with progressively weaker associations with $PM_{2.5}$, sulfate, and aerosol acidity. This is the opposite of what one would expect if aerosol acidity were the main cause of increased mortality, as has been suggested (Lippmann, 1989). The Six Cities study investigators state, however, that the low daily death counts, the short study period, and the large geographic areas considered in the St. Louis/Eastern Tennessee study limited the statistical power of the study, and they could not conclude that the acidity of the aerosol was not associated with mortality.

If the chemical and physical forms of the PM are important in determining the health effects induced by PM, one would expect different concentration-response curves to be observed in different epidemiology studies, depending on the type of aerosol present in the atmosphere. Spurny (1993) in his analysis of studies conducted in the south-western part of Germany found differences in concentrations, composition, and cell-toxic effects among urban, residential, and remote areas. The different slopes of the concentration-response curves for the different cities could be due to several factors, including differences in physicochemical properties and resultant potency of the PM in the different cities.

It is also worth noting that considerations of dosimetry could potentially provide insight on plausible mechanisms or alter the exposure-dose-response relationships evaluated. To date, most analyses have used the exposure concentration ($\mu g/m^3$) of particles. Because deposition of particles in the respiratory tract are determined by particle diameter and distribution, calculation of the RR estimates based on various internal dose metrics (e.g., deposited dose (mass) rate per tracheobronchial or alveolar surface area or deposited particle number rate per surface area), could alter some of these relationships. Different dose metrics may be more appropriate to characterize acute effects (e.g., mortality) versus chronic effects (e.g., morbidity). Certainly dosimetry can provide insight on the variability of inhaled dose due to differences in airway morphometry and ventilation rates among species, age, genders, and disease status of the respiratory tract. For example, it has been shown that patients with COPD have increased deposited particle burdens when compared to healthy subjects (Anderson et al., 1992). To the extent that particle composition alters the particle diameter and distribution of a given aerosol, dosimetry will also be effected. Solubility of an aerosol influences clearance rates and subsequent retained dose estimates. The potential for

dosimetry to influence the exposure-dose-relationship should be considered to the extent that mathematical modeling andd norphometric data allow.

13.7.4 Potential Mechanisms of Causality Between Low Levels of Particulate Pollution and Health Effects

Pathophysiologic mechanisms by which various specific PM constituents can cause health effects are discussed in detail in Chapter 11. Here, the focus is on mechanisms by which airborne particles are known to cause health effects and the extent to which such mechanisms provide plausible evidence or explanations for the reported epidemiologic findings of increases in morbidity and daily mortality rates at low PM concentrations. For purposes of this discussion, health effects of particle inhalation are discussed below in terms of: clinical considerations, acute lung injury, chronic pulmonary toxicity from accumulation of particles in the lung, effects on pulmonary function, effects on pulmonary defense mechanisms, and pathophysicologic mechanisms. Also considered in this section is the potential for interactive mechanisms among air pollutants that might influence the health effects induced by airborne particles. This is an area in which there is little information; most studies have been directed toward determining the toxicity of single compounds.

Clinical Considerations

Potential mechanisms which might help explain the phenomenon of particle related mortality have been considered by Frampton and Utell (1995). These mechanisms include: (1) "premature" death, that is the hastening of death for individuals already near death (i.e., hastening of an already certain death by hours or days); (2) increased susceptibility to infectious disease; and (3) exacerbation of chronic underlying cardiac or pulmonary disease.

Particulate pollution could contribute to daily mortality rates by affecting those at greatest risk of dying, i.e., those individuals for whom death is already very imminent. Acute exposure to moderately elevated concentrations which might only be a minor irritant to healthy people could be the "last straw" that tips over the precariously balanced physiology of a dying patient. Other studies suggest that the full effect of particles on mortality cannot be explained solely by acute PM exposure death-bed effects (Frampton and Utell, 1995), i.e.,

some studies also indicate an effect on annual mortality rates which cannot be explained simply by the hastening of death for individuals already near death.

Particle exposure could also increase susceptibility to respiratory infection with bacteria or viruses, leading to an increased incidence of (and death from) pneumonia in susceptable members of the population. However, pneumonia rarely results in death within 24 h of onset; serious infections of the lower respiratory tract generally develop and evolve over weeks, and would not explain effects on daily mortality. If pollutant exposure increased susceptibility to infectious disease, it should be possible to detect differences in the incidence of such diseases in communities with low vs. high particle concentrations. Emergency room visits and hospitalizations for pneumonia caused by the relevant agent should also be measurably higher on days with elevated ambient particle concentrations. However, no such relationship has been observed, and laboratory animal data to support such a mechanism are weak.

Particulate air pollution might also aggravate the severity of underlying chronic lung disease. This mechanism could explain increases in daily mortality (through effects on those near death from their disease) and longitudinal increases in mortality (if individuals with chronic airways disease experienced more frequent or severe exacerbation of their disease, or more rapid loss of function as a result of particulate exposure).

What chronic disease processes are most likely to be affected by inhaled particulate matter? To explain the daily mortality statistics, there must be common conditions that contribute significantly to overall mortality from respiratory causes. The most likely candidates are the chronic airways diseases, particularly chronic obstructive pulmonary disease (COPD). This group of diseases encompasses both emphysema and chronic bronchitis, however, information on death certificates does not allow differentiation between these diagnoses. The pathophysiology includes chronic inflammation of the distal airways as well as destruction of the lung parenchyma. There is loss of supportive elastic tissue, so that the airways collapse more easily during expiration, obstructing outflow of air. Processes that enhance airway inflammation or edema, increase smooth muscle contraction in the conducting airways, or slow mucociliary clearance could adversely affect gas exchange and host defenses. Moreover, the uneven ventilation-perfusion matching characteristics of this disease, with dependence on fewer functioning airways and alveoli for gas exchange, means

inhaled particles may be directed to the few remaining functioning lung units in higher concentration than in normal lungs (Bates, 1992)

Particulate pollutants have been associated with increases in cardiovascular mortality both in the major air pollution episodes and in the more recent time-series analyses. Bates (1992) has postulated three ways in which pollutants could affect cardiovascular mortality statistics. These include: (1) acute airways disease misdiagnosed as pulmonary edema; (2) increased lung permeability, leading to pulmonary edema in people with underlying heart disease and increased left atrial pressure and (3) acute bronchiolitis or pneumonia induced by air pollutants precipitating congestive heart failure in those with pre-existing heart disease. Moreover, the pathophysiology of many lung diseases is closely intertwined with cardiac function. For example, one postulated cause of the increasing mortality rate in asthma is overuse of adrenergic agonist medications leading to fatal cardiac arrhythmias. Many individuals with COPD also have cardiovascular disease caused by smoking, aging, or pulmonary hypertension accompanying COPD. Terminal events in patients with end-stage COPD are often cardiac complications, and may therefore be misclassified as cardiovascular deaths. Hypoxemia associated with abnormal gas exchange can precipitate cardiac arrhythmias and sudden death.

Acute Lung Injury

The acute toxicity of particles in the respiratory tract has been the topic of numerous studies to determine the potential pulmonary toxicity of dusts, particularly those of concern in industrial processes. Toxic particles that deposit in the lung can induce an inflammatory response that, if it persists, may lead to pulmonary fibrosis and impaired pulmonary function. The response of the respiratory tract to such particles includes the release of numerous cytokines from alveolar macrophages and epithelial lining cells that promote healing and repair or, if healing does not occur because of the persistence of toxic particles, may promote development of fibrosis. Although such acute responses are well known, they typically only occur after several days or weeks of exposure to airborne particle concentrations many fold higher than those that have been shown to be associated with increased mortality and morbidity in epidemiology studies. Recently, however, it has been observed in experimental animal studies that certain types of particles are acutely toxic to the

lung at low exposure concentrations. A half-hour exposure of rats to freshly generated ultrafine polytetrafluoroethylene particles at a concentration of 64 $\mu g/m^3$ resulted in severe pulmonary inflammation and death (Oberdörster et al, 1995). Warheit et al. (1990) also found that fresh ultrafine aerosols resulted in mortality in rats by causing severe lung injury. The significance for environmental exposures of the highly toxic fresh aerosols formed from pyrolysis of perfluorinated materials is unknown at this time, because of the rapid loss of toxicity of the aerosols with time and the lack of information on the concentration of those specific aerosols in the ambient atmosphere. Although it is known that combustion processes emit ultrafine aerosols into the environment (Cantrell and Whitby, 1978), it is not clear how much ultrafine particulate matter is present as the product of pyrolysis of perfluorinated compounds. Nor is there much information on typical ambient concentrations of other ultrafine particles (e.g., metals from high temperature smelting) or their persistance as ultrafines in urban aerosol mixes.

Toxicity Resulting from Accumulation of Particles in the Lung

The accumulation of large lung burdens of poorly soluble particles can lead to decreased clearance of subsequently inhaled particles and an enhanced rate of accumulation of particles in the lung (Morrow, 1992). Large lung burdens of particles of even relatively low inherent toxicity have been shown to induce lung cancer in animal models such as the rat (Mauderly et al., 1994). But how much prior exposure to particles is required to accumulate enough particles to impair clearance of subsequently inhaled particles? Rats exposed to 350 $\mu g/m^3$ diesel soot (aggregated ultrafine carbon particles) for 24 months did not accumulate enough particles to induce pulmonary inflammation (as measured by both histopathology and analysis of lung lavage fluid) or to impair particle clearance, but rats exposed to 3500 $\mu g/m^3$ for the same length of time did. Rats that inhaled carbon black particles at an 8-h time-weighted concentration of 10,000 $\mu g/m^3$ 5 days a week for 12 weeks also accumulated enough particles to induce an inflammatory response by 6 weeks (Henderson et al., 1992).

In general, the toxicity resulting from accumulation of large burdens of particles in the lung does not likely provide a plausible biological basis for reported associations between acute exposures to low level PM concentrations (ca, 30 to 200 $\mu g/m^3$) of inhalable particles (PM_{10}) and daily mortality/morbidity rates. One possible exception that stands out as a

relatively sizeable segment of the general population would be smokers or former smokers among the elderly. In such individuals, particle overload from 40 to 60 years of directly inhaled tobacco smoke particles could make them more vulnerable to the impacts of relatively small additional acute increments in their lung particle burdens, as would the preexisting chronic cardiorespiratory diseases caused by smoking.

A second possible exception might be elderly persons who experienced notable past exposures over many years to very high ambient or workplace PM concentrations, as would be the case for individuals who resided or worked in heavily industrialized cities before effective occupational and air pollution control measures were introduced in the 1950s to 1970s to reduce such exposures. For example, in the Harvard 6-cities study, an association was found between daily mortality rates and PM levels across a few rural communities, lightly industrialized cities, and some heavily industrialized cities. Because the ranking of the cities in terms of air-pollution levels did not change during the study period, it is not possible to distinguish completely between effects due to past historical exposures and those due to recent exposures. Therefore, the elevation in daily mortality rates in industrialized cities such as Steubenville compared to less industrialized cities (such as Topeka or Portage) may be in part based on accumulated past exposures to higher particle levels and consequently larger lung particle burdens in the former.

Impaired Respiratory Function

Very few of the specific PM constituents discussed in Chapter 11 have acute exposure effects on respiratory function, except possibly at very high concentrations (in the $\mu g/m^3$ range). One possible exception is acid aerosols, which appear to have acute effects on pulmonary function among some sensitive individuals at levels below 1,000 $\mu g/m^3$. Exposures to acid particles are known to induce hyperreactive airways and in some cases, bronchoconstriction, but at concentrations in the mg/m^3 range, well above peak U.S. ambient acidity levels of 50 to 75 $\mu g/m^3$. In healthy humans, inhalation of 1,000 $\mu g/m^3$ H_2SO_4 aerosol for 3 h did not cause any influx of inflammatory cells into the lung based on analysis of lung lavage fluid obtained 18 h after the exposures (Frampton et al., 1992). However, mild bronchoconstriction has been reported after brief exposures to as low as 68 $\mu g/m^3$ H_2SO_4 in exercising adolescent asthmatics and 90 $\mu g/m^3$ in excersing adult asthmatics

(Morrow et al., 1994); (Koenig et al., 1989), although this has not always been observed (Avol, et al., 1990). Also of interest is the finding that hyperresponsive airways developed after exposure of healthy rabbits to as little as 75 $\mu g/m^3$ H_2SO_4 for 3 h (El-Fawal and Schlesinger, 1994). Additional studies have also found that acid-coated particles were more potent than the acid or particles alone. Therefore, under some circumstances, one possible mechanism for increased mortality among some elderly persons with a debilitating disease (asthma) on days with moderately high PM pollution might be that acid aerosols place a stress on their cardiopulmonary system, leading to death.

Impaired Pulmonary Defense Mechanisms

The ability of particulate exposures to reduce pulmonary defense mechanisms has been documented for aerosols of H_2SO_4 and trace metals. Trace metals have been shown to be cytotoxic to alveolar macrophages (AMs) and immunosuppressive, but only at much higher concentrations than encountered in ambient atmospheres (Zelikoff et al., 1993). Sulfuric acid aerosols have also been shown to alter resistance to bacterial infection in mice after acute exposures to 1,000 $\mu g/m^3$; repeated exposures to 100 $\mu g/m^3$ reduced mucociliary transport rates in animals. Even these levels of H_2SO_4 are much higher than have been reported in atmospheres of cities evaluated in the recent epidemiology studies. Also, one would expect effects from impaired pulmonary defense mechanisms to develop over an extended period of continuing exposure, not within a few days.

Synergistic Effects

An area for which there is little information is the potential interactive effects of mixtures of air pollutants and/or with other factors (e.g., aging). The potential significance of mixtures is illustrated by the studies of Amdur and Chen (1989), in which a repeated daily 3-h exposure for 5 days of guinea pigs to 20 $\mu g/m^3$ of H_2SO_4 coated on metal particles resulted in decrements in lung volume and pulmonary diffusing capacity and elevations of lung weight/body weight ratio, protein, and number of neutrophils in pulmonary lavage fluid. For example, A 1-h exposure to 20 $\mu g/m^3$ H_2SO_4 coated on metallic particles increased bronchial reactivity in guinea pigs; a 10-fold higher concentration of H_2SO_4 alone was required to produce the same response (Chen et al., 1992b). However, such synergistic

effects were not observed by Anderson et al. (1992), who studied the effects on 15 healthy and 15 asthmatic volunteers of 1-hr exposures to 100 $\mu g/m^3$ H_2SO_4 (0.5 μm) or 250 $\mu g/m^3$ carbon black (0.5 μm) separately or with the H_2SO_4 coated on the particles. The exposures did not result in changes in symptoms or pulmonary function, except for an equivocal response in one person.

The population segment most susceptible to elevations in ambient PM are the elderly (> 65 years old) with preexisting respiratory disease. Aging, in the absence of pathology, is an extremely complex biological phenomenon and is described as being a multifactorial process composed of both genetic and environmental components (Cristofalo et al., 1994). While the physiological characteristics of the healthy older population is an area of active research, significant decrements in key physiological parameters including lung volumes, FEV_1, flow velocity/volume curves, resting cardiac output, and cardiac output reserve with age have been reported (Kenney, 1989). However, there is controversy concerning decrements in physiological function associated with the aging process alone as well as with accompanying disease processes or with other environmental stressors. Moreover, there is little information on the extent to which an older population might be more susceptible to the effects of ambient particulate pollution (Cooper et al., 1991). It is possible that the elderly are more susceptible to ambient particles because of numerous changes in the body's protective mechanisms and protracted exposures to particles over a life time. This could allow time for latent effects from earlier life time exposures to manifest themselves, and for potential cumulative effects to emerge. Virtually nothing is known of the possibilities for interaction among toxicants over a long life time or the possibilities for interaction between medications and ambient pollutants.

Pathophysiologic mechanisms

The respiratory system may be compromised and become less efficient in older people or as a result of disease, and inhaled particles could, conceivably, further compromise their respiratory function. Because small increases in environmental particle concentrations would not be lethal to most people, the effect must result from initiating or promoting a lethal failing of a critical function, such as ventilation, gas exchange, pulmonary circulation, or

cardiorespiratory control in subjects brought to the limits of tolerance by preexisting conditions (Mauderly, 1995).

Inhaled particles or their pathophysiological reaction products could further impair ventilation in the chronically ill individual by further reducing airway caliber. For example, particles may activate airway smooth muscle, constricting airways, or may influence various airway secretions which could add to and thicken the mucous blanket. Inhaled particles or their pathophysiological reaction products could decrease the diffusing capacity of the lungs by decreasing the area of the respiratory membrane available for diffusion, by increasing diffusion distances across the respiratory membrane, and/or by causing abnormal ventilation-perfusion ratios in some parts of the lung. Particles or their products could also act at the level of the pulmonary vasculature to elicit changes in pulmonary vasculature resistance, which could further alter ventilation-perfusion abnormalities in people with respiratory disease. Furthermore, particles could conceivably alter respiratory and cardiovascular control by affecting local control mechanisms located in the endothelial cells or other sites. This could produce changes in peripheral and central control mechanisms and directly affect the respiratory and cardiovascular control centers. Little evidence is currently available that directly addresses the above speculative possibilities.

13.7.6 Biological Plausibility Conclusions

Having considered the characteristics of the particulate exposure atmospheres and the types of morbidity and mortality associated with the polluted atmospheres, what can be concluded about the biological plausibility of the epidemiological results? The types of morbidity and mortality reported to be associated with increased ambient particle concentrations are consistent with the types of health effects that one might expect from exposures to high levels of PM. Therefore, the type of response seems plausible, if one accepts the temporal relationships modeled in the epidemiological studies. The analyses found associations with 1-day or multi-day (usually 3 to 5 day) lags. The concentrations of particulate matter reported to be associated with such health responses, however, are much lower than would be expected based on animal and human clinical studies of responses to single particulate pollutants. This is true even when one considers that there is evidence that the people who make up the excess mortality population may be susceptible subpopulations.

Moreover, it is not clear what portion of the inhalable particulate matter constitutes the delivered dose that is associated with the observed morbidity or mortality. There are suggestions from both animal toxicology data and epidemiology data that ultrafine acid aerosols may be of greater health significance than the rest of the particulate mass. Finally, the potential for interactive effects between PM of different types and PM and other air pollutants is not known.

Thus, although there are several hypotheses as outlined above, little clear or convincing evidence is available at this time to support the biological plausibility of a causal relationship for the reported epidemiologic associations between low ambient concentrations of PM and daily mortality and morbidity rates.

13.8 IDENTIFICATION OF POPULATION GROUPS POTENTIALLY SUSCEPTIBLE TO HEALTH EFFECTS FROM PM EXPOSURE

Certain groups within the population may be more susceptible to the effects of PM exposure, including persons with preexisting respiratory disease, children, and the elderly. The reasons for paying special attention to these groups is that (1) they may be affected by lower levels of PM than other subpopulations and (2) the impact of an effect of given magnitude may be greater. Some potential causes of heightened susceptibility are better understood than others. Subpopulations that already have reduced ventilatory reserves (e.g., the elderly and persons with asthma, emphysema, and chronic bronchitis) would be expected to be more impacted than other groups by a given decrement in pulmonary function. For example, a healthy young person may not even notice a small percentage change in pulmonary function, but a person whose activities are already limited by reduced lung function may not have the reserve to compensate for the same percentage change.

Based on Chapter 12 discussions, it is clear that the bulk of the total mortality effects suggested by the epidemiology studies discussed earlier are among the elderly. During the historic London, 1952 pollution episode the greatest increase in the mortality rate was among older citizens and those having respiratory diseases. An analysis by Schwartz (1994c) of mortality in Philadelphia, PA found the greatest increase in risk of death in those aged 65 to 74 and those >74 year of age (mortality risk ratios = 1.09 and 1.12, respectively, between

high and low TSP days). Other studies also suggest that the elderly experience a higher excess risk from exposure to PM air pollution than the population overall.

Other potentially susceptible groups include patients with COPD, such as emphysema and chronic bronchitis. Some of these patients have airway hyperresponsiveness to physical and chemical stimuli. A major concern with COPD patients is the absence of an adequate ventilatory reserve, a susceptibility factor described above. In addition, altered distribution of respiratory tract ventilation in COPD may lead to a greater delivery of PM to the segment of the lung that is well ventilated, thus resulting in a greater regional tissue dose. Also, PM exposure may alter already impaired defense mechanisms, making this population potentially more susceptible to respiratory infection. It is estimated (U.S. Department of Health and Human Services, 1990; Collins, 1988) that 14 million persons ($\approx$6%) suffer from COPD in the United States. Bronchial mucous transport clearance may be impaired in people with chronic bronchitis, asthma, and in association with various acute infections. Rates of alveolar region clearance appear to be reduced in humans with chronic obstructive lung disease.

Throughout the results and discussions presented above and in Chapter 12 regarding the effects of acute PM exposure on human mortality, a consistent trend was for the effect estimates to be higher for the respiratory mortality category. This lends support to the biological plausibility of a PM air pollution effect, as the breathing of toxic particles would be expected to most directly affect the respiratory tract, and these results are consistent with this expectation. For example, the estimates of relative risk for PM-induced mortality due to respiratory causes discussed in Chapter 12 are all higher than the risks for the population as a whole and for other causes. More specifically, the PM RR for respiratory diseases ranged from 50 to more than 400% higher for respiratory disease categories than for all causes of death, indicating that increases in respiratory deaths are a key major contributor to the overall PM-mortality associations noted previously. PM relative risk estimates for cardiovascular causes were also notably elevated. Moreover, since evidence suggests that an acute pollution episode is most likely be inducing its primary effects by stressing already compromised individuals (rather than, for example, inducing chronic respiratory disease from a single air pollution exposure episode), the above results indicate that persons (especially the

elderly) with pre-existing cardiovascular or respiratory disease constitute a population segment especially at risk for mortality implications of acute ambient PM exposures.

Apropos to the identification of individuals with pre-existing respiratory and cardiovascular diseases as being at special risk for ambient PM exposure effects, it is important to highlight smoking as a key etiological agent for such diseases. The U.S. Environmental Protection Agency (1992) report on environmental tobacco smoke indicates that smoking is the major cause of chronic obstructive pulmonary disease (COPD), which includes emphysema, and is thought to be responsible for approximately 61,000 COPD deaths yearly, i.e., about 82% of U.S. COPD deaths (U.S. DHHS, 1989). Tobacco use is also a major risk factor for cardiovascular diseases, the leading cause of death in the United States. It is estimated that each year 156,000 heart disease deaths and 26,000 deaths from stroke are attributable to smoking (CDC, 1991). Smoking is also a risk factor for various respiratory infections, such as influenza, bronchitis, and pneumonia. An estimated 20,000 influenza and pneumonia deaths per year are attributable to smoking (CDC, 1991).

The U.S. Environmental Protection Agency report also indicates that in children, ETS exposure is causally associated with an increased risk of lower respiratory tract infections such as bronchitis and pneumonia. It is estimated that 150,000 to 300,000 cases annually in infants and young children up to 18 months of age are attributable to ETS. ETS exposure is also causally associated with additional episodes and increased severity of symptoms in children with asthma. It is estimated that 200,000 to 1,000,000 asthmatic children have their condition worsened by exposure to ETS. ETS is also a risk factor for new cases of asthma in children who have not previously displayed symptoms (U.S. Environmental Protection Agency).

Lastly, the EPA report also indicates that environmental tobacco smoke (ETS) is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers (U.S. Environmental Protection Agency, 1992).

Overall, then, the most susceptible population segment that can be most clearly identified as being at likely increased risk for low-level ambient PM exposure-induced mortality or morbidity are elderly individuals with pre-existing cardiovascular respiratory diseases, the majority of which are likely either current or former smokers. Smoking may also be a key ancillary contributor to any low-level PM exposure-induced exacerbation of

respiratory infections among other adults and children and to any increased cancer mortality attributable to chronic ambient PM exposures.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels. Although the reasons for the inconsistency among studies remain largely unclear, subject selection may be an important factor. Even in studies reporting an overall absence of effects on lung function, occasional asthmatic subjects appear to demonstrate clinically important effects. Studies from different laboratories suggest that responsiveness to acid aerosols may correlate with degree of baseline airway hyperresponsiveness. On the other hand, based on very limited studies, elderly and individuals with chronic obstructive pulmonary disease do not appear to be particularly susceptible to the effects of acid aerosols on lung function.

Alveolar deposition at different flow rates was lower (26% versus 48% thoracic deposition) in subjects after induced bronchoconstriction. In asthmatics, thoracic deposition of particles was higher than healthy subjects (83% versus 73% of total deposition). Trachial/bronchial deposition was also found to be higher in asthmatics. The results are similar to those found in subjects with obstructive lung disease. The buffering capacity of mucus may be altered in persons with compromised lungs. For example, sputum from asthmatics had a lower pH than that from normals and a reduced buffering capacity, and so may represent a population segment especially sensitive to inhaled acidic particles.

The National Institutes of Health (1991) estimates that approximately 10 million persons in the United States have asthma. In the general population, asthma prevalence rates increased by 29% from 1980 to 1987. For those under 20 years old, asthma rates increased from approximately 35 to 50 per 1,000 persons, a 45% increase. The airways of asthmatics may be hyperresponsive to a variety of inhaled materials, including pollens, cold-dry air, allergens, and air pollutants. The potential addition of an PM-induced increase in airway response to the already heightened responsiveness to other substances raises the possibility of exacerbation of this pulmonary disease by PM.

13.9 IMPLICATIONS OF RELATIVE RISK ESTIMATES

Preceding sections of this Chapter concluded that the newly emerging epidemiologic data base on PM-mortality/morbidity effects provides reasonably consistent results indicative of increased risk of mortality and morbidity effects being associated with exposures of the general population to ambient air pollutant mixes containing PM concentrations currently found in many U.S. urban areas. This includes effects associated with ambient air exposures to pollutant mixes having 24-h PM_{10} concentrations falling in the range of 30 $\mu g/m^3$ to 200 $\mu g/m^3$, including evidence suggestive of effects below 150 $\mu g/m^3$ (the level of the current 24-h U.S. PM_{10} NAAQS).

It was also noted in Chapter 12 that the relative risk (RR) estimates for both the mortality and morbidity effects associated with short-term (ca. 24-h or a few days) exposures to ambient PM are very small compared to RR values typically viewed in epidemiologic literature as providing strong evidence for a likely causative association. Section 13.5.4 further noted the relatively limited evidence directly demonstrating coherence between the mortality and morbidity effects findings from epidemiologic studies, with the most compelling evidence for coherence now being findings of both increased hospital admissions (for cardiopulmonary endpoints) and increased mortality in relation to increments in 24-h PM concentrations in the same population group (the elderly) within several U.S. urban areas (Detroit, Birmingham, Philadelphia) and the Utah Valley. However, only very limited evidence for the biological plausibility of acute low-level PM exposure effects at the above-stated PM_{10} concentration range now appears to exist to support several hypotheses discussed in Section 13.7 with regard to possible mechanisms of action. A key point emerging from the plausibility discussion (Section 13.7) and the ensuing Section (13.8) was the identification of elderly individuals (65 yr. old) with preexisting chronic cardiovascular and respiratory disease conditions (the majority of whom are likely current or former smokers) as being the most susceptible general population segment most clearly at special risk for mortality and morbidity effects associated with exposures to ambient air mixes containing moderately elevated PM concentrations.

The meaning or interpretation of quantitative estimates of PM-related effects (i.e., relative risk estimates) discussed earlier as having been generated by the newly available PM epidemiology studies remains a subject of controversy, with divided opinions still existing in

the scientific community as noted earlier in this chapter. Thus, in attempting to interpret such risk estimates, several caveats should be kept in mind. First, caveats analogous to those made in point (4) at the top of page 13-29 for key conclusions drawn from the last previous PM criteria review still apply. That is, although new evidence has emerged which points toward very small, but statistically significant increases in risk of human mortality and morbidity effects being associated with exposures to ambient air mixes containing moderately elevated PM (with no evident thresholds being identified in the studied range of PM concentrations), precise quantitative specification of relative contributions of such low-level concentrations of ambient PM to reported mortality and morbidity effects is not possible at this time. Nor can one now separate out with confidence potential relative contributions to the reported PM effects of several other likely important confounding or interacting variables.

With regard to the latter, it is as of yet very difficult, for example, to sort out with confidence relative contributions of weather versus PM per se. It is clear that temperature extremes (very hot or very cold days in relation to typical ranges of temperature for any given locale) have notable effects on variations in daily mortality, with temperature or other combinations of variables indexing weather impacts usually being found to be significant predictors of daily human mortality in modeling of PM effects and to account for distinctly larger proportions of the variance in daily mortality than do indices of PM pollution. On the other hand, in most of the newer PM studies, small elevations in relative risk attributable to PM still remained even after control for temperature extremes and/or other weather indices; and PM effects were found to be significant in several analyses (e.g., for London) restricted to days not involving wide variations in temperature that would constitute geographic-specific extremes. It is also not yet clear to what extent any given relative risk estimate derived from any of the newer analyses represent actual risk due to an increase in ambient PM or to what extent the elevations in risk attributed to modeled PM indices more broadly represent increased mortality or morbidity risks due to human exposure to the overall pollutant mix in the particular airshed evaluated (including not only the ambient PM aerosols present but other copollutants, such as SO_2, CO, O_3, NO_x or non-particulate organic air toxics).

Other caveats bear on the issue of how generalizable the reported PM relative risk estimates are. It is not yet possible to determine the extent to which the risk estimates for

PM mortality or morbidity effects are generalizable to other geographic areas or are highly site-specific, i.e., narrowly applicable to the specific cities from which they were derived or, at least, most credibly confined for use in projecting any estimates of likely PM risk to other airsheds with fairly similar ambient aerosol mixes in terms of particle size distribution and chemical composition. Thus, it is not clear, for example, how credible the use of PM-related relative risk estimates derived from Philadelphia, St. Louis, or other midwestern or eastern U.S. conurbanations (or foreign cities such as Sao Paulo, Santiago, or Athens) with high percentages of particles from combustion processes might be in attempting to estimate PM-related risks for other cities, e.g., in the western U.S., with much greater proportions of crustal materials in the ambient air pollutant mix. Use of presently available PM-related risk estimates to attempt to quantify potential PM-related risks across various seasons in locales where widely varying seasonal mixes of particles of different sizes/chemical composition may also be of dubious scientific credibility at this time.

Another issue of much interest and debate has been that of "threshold" for the estimated PM effects derived from the newly available analyses. As noted above and discussed in Chapter 12, no evident thresholds have yet been demonstrated for reported PM-related mortality or morbidity effects, based on the presently available published analyses. On the other hand, as also discussed in Chapter 12, only very limited efforts have been made to date to undertake statistical analyses by which to more definitively address the issue; and serious doubt exists as to whether any thresholds, if they do exist, even in the range of the observed data (i.e., roughly from 30 to 200 $\mu g/m^3$ PM_{10}) can be demonstrated, given notable statistical power limitations associated with necessary breaking down of data into more refined intervals as part of any threshold "search". Nor is there now any scientifically credible basis by which to make a "no-threshold" argument in support of extrapolating currently available PM relative risk estimates to ambient PM concentrations below the range of observed data used in the reported analyses. This is especially true in view of the lack of any well demonstrated evidence for one or another hypothesized potential mechanisms of action that might plausibly explain the elevated risk of mortality or morbidity at the very low PM concentrations implied by the results of the newly available epidemiology studies.

It is also clear from the available analyses that the occurrence of any increased risk of mortality or morbidity due to short-term moderate elevations in PM (either alone or in

concert with other copollutants) likely represents the outcome of a combination of risk factors culminating in relatively rare health events (as clarified further by the ensuing quantitative discussion below). By far the greatest risk is posed for the elderly over 65 years old and especially those with preexisting cardiopulmonary diseases, with very distinctively lower risk estimates having been derived for younger individuals and those without chronic respiratory or cardiovascular diseases. Thus, in order for notable health effects to occur in association with short-term exposures to ambient PM (and/or copollutants), it appears that other predisposing conditions and/or contributing risk factors must be present, as well. That is, low-level ambient PM exposures alone do not typically appear to be sufficient per se to induce increased morbidity or mortality, but may contribute to such health outcomes under conditions when one or more other contributing risk factors also converge. Thus, for example, short-term low-level exposures to ambient PM at concentrations in the ranges evaluated in most of the newer epidemiology studies are extremely unlikely alone to cause lung function decrements or respiratory symptoms of much note (except possibly for some highly sensitive asthmatic patients), based on currently available epidemiologic and controlled human exposure study results. Nor are such exposures likely to markedly reduce or impair respiratory tract defenses (e.g., alveolar macrophage numbers or function, retrociliary clearance mechanisms, lung immune response, etc.) sufficiently so as to cause increased susceptibility to respiratory infections, based on available experimental toxicology findings. On the other hand, once a respiratory infection were to occur due to other causes, then it is conceivable that added stress due to low-level PM exposure in terms of small further decrements in pulmonary function or exacerbation of respiratory symptoms could lead to worsening of the acute illness and, possibly, the need for medical attention and/or hospital admission in some cases.

Still additional converging risk factors appear to be necessary for exposures to ambient air pollution mixes containing low concentrations of typical outdoor urban aerosols to contribute to increased mortality. By far the most important are the cooccurrence of advanced age ($>$ 65 yr old) and already compromised cardiopulmonary function. In older individuals with preexisting COPD, emphysema, chronic heart disease, etc. resulting from other predisposing risk factors (e.g., long-term earlier high-level particle exposures from smoking or past occupational or ambient PM exposures before effective control measures

were introduced), it appears conceivable that additional stress from low-level ambient PM exposures might cause further complications that might lead to terminal consequences in some cases. Several possibilities were discussed earlier as having been hypothesized, e.g., increased air flow to and consequent greater particle deposition/retention in remaining functioning areas of the compromised lung, possible tipping over by small additional particle burdens of already saturated lung defenses due to particle overloads from past long-term high level particle exposures, and/or the induction of cascading inflammatory or other immune responses (due to particularly toxic specific PM consultants, e.g., possibly certain transition metals) that overwhelm remaining lung reserves and oxygen exchange mechanisms. However, at this time, no clearly convincing scientific evidence has yet been reported by which to either compellingly substantiate or refute such hypothesized possibilities. Thus, considerable uncertainties still exist with regard to what the relative risk estimates from the newly available epidemiologic studies may imply.

In evaluating the potential public health significance of the relative risk increases for mortality or morbidity effects reported in the newer PM epidemiology studies, much recent interest has focussed on use of such relative risk estimates to generate projections of numbers of excess deaths or morbidity events likely to be associated with ambient PM exposures at concentrations currently found in the United States or other countries. Given the above-noted caveats and uncertainties pertaining both to the derivation of the relative risk estimates and their interpretation, there are substantial reasons to caution against attempting such calculations at this time and to have major reservations about accepting any such projections as credible quantitative estimates of additional deaths or morbidity events likely to actually occur with current or future exposures in the United States or elsewhere. At best, such projections might be associated with exposures to PM-containing ambient air mixes in cities with closely similar particle size/chemical composition characteristics and population demographics to those cities from which the relative risk estimates were derived. It is currently questionable as to whether widely generalizable, broadly applicable projections can be made based on some single "best estimate" of PM-related relative risk and, also, whether such projections can be credibly aggregated across PM exposure variations during different seasons and/or across geographic locales with widely disparate mixes of PM aerosols and/or other copollutants.

Despite the above caveats and reservations, however it may be useful to provide illustrative examples of possible quantitative implications of relative risk estimates of the type generated by the recent PM epidemiology analyses. Table 13-5 earlier showed that total acute mortality relative risk estimates associated with exposure to ambient air pollution having a 50 $\mu g/m^3$ increase in one-day 24-h average PM_{10} can range from 1.015 to 1.085, depending upon the site (i.e., the PM_{10} composition and population demographics) and also upon whether PM_{10} is modeled as the sole index of air pollution or not. Relative Risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the PM_{10} RR with multiple pollutants in the model range from 1.015 to 0.025. The former range, as noted earlier, might be viewed as approximating an upper bound of the best estimate, as any mortality effects of co-varying pollutants may be "picked up" by the PM_{10} index, whereas the latter multiple pollutant model range might be viewed as approximating a lower bound of the best estimate, as the inclusion of highly correlated covariates might weaken the PM_{10} estimate. Thus, "typical" total mortality effect estimates (per 50 $\mu g/m^3$ PM_{10} increase) most likely fall within an approximate RR = 1.025 to 1.06 range, based on the various coefficients reported in the published studies. The formal EPA meta-analyses results discussed in Chapter 12 yielded a best estimate of 1.031 with 95% confidence intervals (CI) of 1.025 to 1.038 for PM_{10} studies using models that include 0-1 day lags but no copollutants. For those analyses with longer lag times (3-5 days) and no copollutants in the models, the EPA meta-analyses yielded a best estimate of 1.064 (CI = 1.047 to 1.082). Thus, the very small increased risks of about 3.1 to 6.4% over baseline mortality levels (per 50 $\mu g/m^3$ increase in 24-h PM_{10} concentration in the 30 to 200 $\mu g/m^3$ range) derived from the EPA meta-analyses probably represent currently best available upper bound estimates for reported PM_{10}-related total mortality effects. Lower bound estimates, from analyses that included other copollutants in the models for acute PM-mortality effects, could be as much as 50% lower than the above upper bound estimates or, possibly, even include zero (i.e., represent no increased risk) especially during some seasons in different locales.

To help place these findings into a context by which to better understand the potential implications of such relative risk estimates, Table 13-17 summarizes important information by which to project potential increases in excess mortality in a city of one million people that

might be associated with exposure to ambient air mixes in which an increment in 24-h PM_{10} exposure of 50 $\mu g/m^3$ may be a contributing factor. First it is important to note that the typical general population baseline or background risk of death on any given day in the U.S. is only about 23.6 in a million (23.6×10^{-6}) or 23.6 deaths per day in a city of 1 million people. If the 24-h PM_{10} concentration increased by 50 $\mu g/m^3$ on a given day (e.g., from a usual level of about 50 $\mu g/m^3$ to around 100 $\mu g/m^3$) then risk for mortality in the total general population would be expected to increase by about 3.0 to 6.0% over baseline, i.e., to increase from 23.6 in a million to about 24 or 25 in a million as an upper bound estimate. In other words, exposure to the ambient mix of pollutants indexed by the 50 $\mu g/m^3$ increase in 24-h PM_{10} levels might contribute to as much as an additional 0.7 to 1.5 deaths per million people exposed, as shown in the Table 13-17 far right column.

Of the 23.6 baseline deaths per day expected in a city of 1 million, about 17 would be attributable to elderly individuals (aged 65 or over), who only constitute about 12.6% of the 1991 U.S. population but for whom the background risk of dying on a given day is much higher than for the total general population. For such individuals, the upper bound estimate for increased numbers of excess deaths possibly contributed to by the 50 $\mu g/m^3$ PM_{10} increase would be projected to be approximately 1.0 (more than half of the higher estimate for total mortality among the entire population), assuming that the specific city has a typical demographic distribution of percentages of people in different age brackets. In other cities or locations with notably higher elderly populations (e.g., some retirement communities or cities left with higher percentages of the elderly possibly due to outmigration of younger people), then the overall risk and expected deaths per day would be higher. Conversely, in other locations with much younger than average populations and lower percentages of elderly residents, the risk and expected numbers of PM-related excess deaths would be lower.

If the increment in PM_{10} concentration continued to average about 50 $\mu g/m$ above routine ambient levels for 3-5 days in the given city of 1.0 million people, then relative risk estimates derived from PM_{10}-mortality models using 3-5 d lags might more appropriately apply. Then, the expected number of deaths to which the 3-5 day 50 $\mu g/m^3$ PM elevation might be projected to contribute could range up to about 1.5 deaths per day among the total general population per 1 million people exposed; or up to about 4.5 to 7.5 deaths during the

TABLE 13-17. ESTIMATED EXCESS MORTALITY PER DAY IN A POPULATION OF ONE MILLION FOR WHICH AN INCREASE OF 50 $\mu g/m^3$ PM_{10} (24-h) COULD BE A CONTRIBUTING FACTOR

Health Outcome	Age Group	Population Baseline Annual Mortality	Population Baseline Daily Mortality	PM_{10} Lag Time	Upper Bound Excess Risk Per PM_{10} 50 $\mu g/m^3$	Possible Number of PM-Related Deaths/Day
Total Mortality	All	8,603[1]	23.6	< 2d	0.03[2]	0.7
	65+	6,201[3]	17.0	2d	0.06[4]	1.0
Total Mortality	All	8,603	23.6	3-5d	0.06[2]	1.5
Respiratory Mortality	All	676[1]	1.85	3-5d	0.19[5]	0.3
Cardiovascular Mortality	All	3,635	10.0	3-5d	0.09[5]	0.9

[1]From Monthly Vital Statistics Report for 1991 (U.S. CD 1993).
[2]From EPA meta-analyses, Table 12-25; all models without co-pollutants
[3]Elderly as 12.6% of 1991 U.S. population
[4]From Saldiva and Bohn (1994) and Ostro et al. (1995), variance-weighted average (TWA); Section 12.3.1.3
[5]From Pope, et al. (1991), Schwartz (1993) for Utah Valley and Birmingham TWA, Table 12-4

TABLE 13-18. ESTIMATED NUMBER OF DEATHS PER DAY IN CITIES OF 10,000 to 10 MILLION[1] FOR WHICH AN INCREASE OF 50 $\mu g/m^3$ PM_{10} COULD BE A CONTRIBUTING FACTOR

	Expected Number of PM-Related Excess Deaths Per Day				
Population of City	Whole Pop. All Causes < 2d Lag	65+ Pop. All Causes < 2d Lag	Whole Pop. All Causes 3-5 Day Lag	Whole Pop. Respiratory 3-5 Day Lag	Whole Pop. Cardiovascular 3-5 Day Lag
10 Million	~4 - 7	~5 - 10	~7 - 15	~2 - 3	~5 - 9
5 Million	~2 - 4	~2.5 - 5	~4 - 8	~1 - 2	~2 - 5
1 Million	~0.4 - 0.7	~0.5 - 1	~0.8 - 1.5	~0.2 - 0.3	~0.5 - 1.0
500,000	~0.2 - 0.4	~0.3 - 0.5	~0.4 - 0.8	~0.1 - 0.15	~0.2 - 0.5
100,000	~0.05	~0.07	~0.01	~0.03	~0.07
50,000	~0.03	~0.04	~0.05	~0.02	~0.04
10,000	~0.005	~0.01	~0.01	~0.002	~0.008

[1]Upper end of range for each city size calculated from upper bound estimates in Table 13-17 for population of 1 million. Lower end of range derived as lower bound estimate roughly 50% less than the upper bound, as per text.

full 3-5 days of elevated PM_{10}. Of the 1.50 excess death per day attributed to the 3-5 day 50 $\mu g/m^3$-increment in PM_{10} 24-h concentrations, an estimated 0.34 would likely be due to respiratory causes and about 0.91 to cardiovascular causes. Obviously, both the increased deaths due to respiratory and cardiovascular causes would mainly occur in elderly persons having preexisting chronic respiratory or cardiovascular disease conditions. Note that small numerical inconsistencies in Table 13-17 and in succeeding tables on morbidity arise from the fact that the excess risk estimates are based on different studies in a number of different populations, with different baseline death or hospital admissions rates.

Table 13-18 simply takes the information from the far right column of Table 13-17 on upper bound estimates of the number of possible PM-contributory deaths per day (for the total population, for the elderly 65+, and for respiratory and cardiovascular causes), and depicts ranges of lower and upper bound estimates for comparable numbers of estimated possible deaths per day contributed to by exposure to ambient air pollution mixes containing 50 $\mu g/m^3$ increments in PM_{10} concentrations in cities ranging from 10 thousand to 10 million in size. Table 13-18 is extremely informative in showing that no appreciable risk for mortality is expected to occur with exposure to such ambient air mixes for cities less than 1 million population, even if the PM_{10} elevation lasts for 3-5 days or occurs several times a year; nor is there much appreciable risk for the elderly in smaller population cities, unless perhaps a particular city with less than 1 million population has an extraordinarily high percentage of elderly residents. This applies even for days when 100 $\mu g/m^3$-increments in PM_{10} might occur for 3-5 days in a row. Even for cities of 1 million population, the projected upper bound risk may be of dubious public health significance unless 50-100 $\mu g/m^3$ PM_{10} elevations were to occur numerous times per year, especially in view of such tiny increased risk likely mainly being posed for elderly individuals with preexisting cardiopulmonary disease conditions that predominantly arise from voluntary smoking. Any risk of excess mortality associated with short-term, acute exposures to ambient air pollutant mixes having 50-100$\mu g/m^3$ increments in 24-h PM_{10} levels would most likely be projected as possibly causing meaningful numbers of excess deaths mainly as such exposures occur for large segments of the elderly population (age 65+ yrs) with preexisting cardiopulmonary diseases in rather large cities exceeding 1-2 million population. The level of public concern, however, even in such cases may be tempered by the likelihood that a majority of those at

special risk are most probably current or former smokers, given the predominant role attributed (U.S. EPA, 1992) to smoking in the etiology of preexisting cardiopulmonary diseases that distinguish those identified as being at greater risk.

There is some limited direct evidence for an interaction between smoking status and excess mortality attributable to PM exposure. Based on the Six Cities Study, Dockery, et. al. (1993) reported an increased RR for $PM_{2.5}$ between the least polluted city (Portage) and the most polluted city (Steubenville) that is substantially (albeit not significantly) higher in individuals who are current or former smokers, compared to never-smokers. This is shown in Table 13-19. Prospective studies that have individual data on smoking status probably offer the best opportunity for detecting differential effects of smoking status on PM-related mortality and morbidity for use in future criteria assessments.

TABLE 13-19. ASSOCIATION BETWEEN CIGARETTE SMOKING STATUS AND EXCESS MORTALITY RISK FROM AIR POLLUTION IN THE SIX CITIES STUDY

	Relative Risk for Worst $PM_{2.5}$ City (Steubenville) Versus Lowest Best $PM_{2.5}$ City (Portage)					
Smoking Status	M+F	(95% CI)	M	(95% CI)	F	(95% CI)
Never Smoker	1.19	(0.90,1.57)	1.29	(0.80,2.09)	1.15	(0.82,1.62)
Former Smoker	1.35	(1.02,1.77)	1.31	(0.96,1.80)	1.48	(0.82,2.66)
Current Smoker	1.32	(1.04,1.68)	1.42	(1.05,1.92)	1.23	(0.83,1.83)

[1]Based on Table 3 from Dockery, et. al (1993)

The prematurity of the excess deaths is also a matter of considerable importance, but there is as yet little firm evidence from acute mortality studies by which to judge whether PM-related excess deaths generally represent highly comprised elderly individuals dying a few days or weeks sooner than they would have otherwise versus several months or years of prematurity of death for some.

Morbidity effects demonstrated as likely being associated with short-term exposures to ambient U.S. PM exposures include increased hospital admissions for respiratory and cardiovascular disease conditions, increased respiratory symptoms (including exacerbation of asthma), and small pulmonary function decrements (e.g., 2-3% decreases in FEV_1 or FVC).

Probably of most immediate public health concern are the hospital admissions, which are also more readily quantifiable and understandable as an index of obviously serious health impacts. Table 13-20 summarizes key types of information by which one might attempt to project increments might contribute per of 1 million people exposed. Table 13-20 can be interpreted in an analogous fashion to Table 13-17. Note from Table 13-20 that the typical number of PM_{10}-related hospital admissions for cardiovascular causes would be projected to be only about 2.5 times as high as the number of potential deaths during the same event, and the number of respiratory admissions about 6 times as high as the possible number of deaths from respiratory causes shown in Table 13-17. However, many deaths from cardiovascular or respiratory causes occur without a prior hospital admission. There is, nonetheless, a reasonable numeric consistency between the rough estimates of potential hospital admissions or discharges and possible total deaths contributed to by exposure in a community to PM-containing ambient-air mixes.

Table 13-21 then scales expected daily hospital admissions potentially associated with exposures to ambient air mixes having a 50 $\mu g/m^3$ increase in PM_{10} (24-h) for towns and cities with populations of 10 thousand to 10 million (analogous to what was done earlier in Table 13-18, based on Table 13-17 calculations). However, in this case, both tables 13-20 and 13-21 provide only upper bound estimates for hospital admissions based on available analyses, which did not include copollutants in the models. Essentially the same types of statements as made with regard to the very small increases in excess risk depicted in Tables 13-18 and 13-19 for mortality also generally apply here for hospital admissions, except to note somewhat larger projected numbers for possible hospital admission cases for which the ambient PM exposure might be a contributing factor.

Overall, based on the foregoing discussions, there appears to exits credible evidence for a likely very small, but real PM effect on human health in some susceptible subpopulations (including contributing along with other risk factors to premature deaths among the elderly with preexisting cardiopulmonary diseases) at PM_{10} 24-h concentrations in the range of 30 to 200 $\mu g/m^3$. However, the biological mechanisms by which such effects occur are as yet not well understood and remain to be delineated, as is the case for clearer characterization and interpretation of relative risk estimates for PM-related effects and their appropriate use in projecting potential public health impacts.

TABLE 13-20. ESTIMATED HOSPITAL ADMISSIONS PER DAY IN A POPULATION OF ONE MILLION FOR WHICH AN INCREASE OF 50 $\mu g/m^3$ (24-h) PM_{10} COULD BE A CONTRIBUTING FACTOR

First Listed Diagnosis	Age Group	Population Baseline Annual Discharges	Population Baseline Daily Hospital Discharges	Excess Risk per PM_{10} 50 $\mu g/m^3$ (Lag $\leq$1 d)	Possible Number of PM-Related Hosp. Admissions Per Day
All conditions	All	124,110[1]	340.0	--	--
	65+	42,845[2]	117.4	--	--
Respiratory Conditions (all)	All	12,180[1]	33.4	0.06[3]	2.0
	65+	5,101[1]	14.0	0.08[3]	1.1
Pneumonia	All	4,340[1]	11.9	--	--
	65+	2,335[2]	6.4		
				0.08[4]	0.5
COPD	All	3,337[7]	9.1	0.15[5]	1.4
	65+	2,560[7]	7.0	0.16[3]	1.1
Heart Disease	All	12,310	58.4	0.04[6]	2.3
	65+	13,502	37.0	0.06[6]	2.2

[1]From Table 12-7
[2]From Table 12-7, assuming 12.6% age 65+
[3]From Table 12-9, average
[4]From Table 12-11, average
[5]From Table 12-10, average
[6]From Table 12-12
[7]From 1992 detailed Tables; excludes asthma (ICD9 493-493.9)

TABLE 13-21. ESTIMATED NUMBERS OF HOSPITAL ADMISSIONS FOR RESPIRATORY AND CARDIOVASCULAR CAUSES PER DAY IN CITIES OF 10,000 to 10 MILLION FOR WHICH AN INCREASE OF 50 $\mu g/m^3$ PM_{10} (24-h) COULD BE A CONTRIBUTING FACTOR

	All Respiratory Conditions		Pneumonia		COPD		Heart Disease	
Population of City	Whole Pop.	65+ Pop.	Whole Pop.	65+ Pop.	Whole Pop.	65+ Pop.	Whole Pop.	65+ Pop.
10 Million	20.0	11.0	--	5.0	14.0	11.0	23.0	22.0
5 Million	10.0	5.5	--	2.5	7.0	5.5	11.5	11.0
1 Million	2.0	1.1	--	0.5	1.4	1.1	2.3	2.2
500,000	1.0	0.55	--	0.25	0.7	0.55	1.15	1.1
100,000	0.2	0.11	--	0.05	0.14	0.11	0.23	0.22
50,000	0.1	0.05	--	0.02	0.07	0.05	0.12	0.11
10,000	0.02	0.01	--	0.01	0.02	0.01	0.02	0.02

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