CHAPTER 2

Health Context for Management of Particulate Matter

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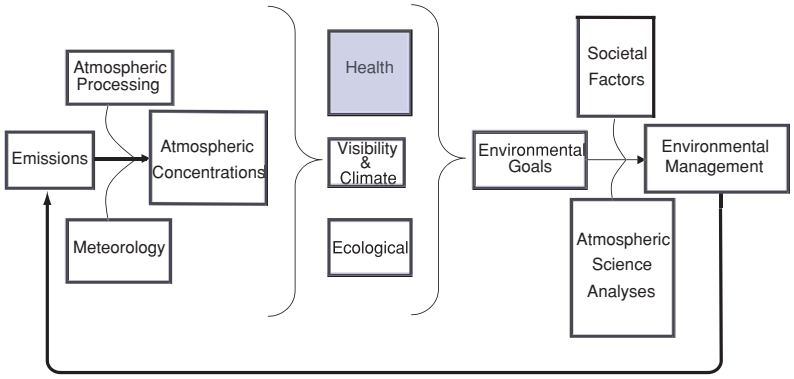

2.1 OVERVIEW

This chapter's objective is to provide a health context for this Assessment which, as noted in Chapter 1, focuses on atmospheric-science considerations related to the management of airborne PM. PM, unspecified as to chemical composition, is of major concern for producing health effects and, thus, subject to government regulation in many countries including Canada, Mexico, and the United States. There is a considerable and growing body of evidence showing an association between increases in adverse health effects, especially of the cardiac and respiratory systems, and elevated levels of PM in air. This evidence has served as a driver for promulgation of new standards and guidance for PM and the development of related control strategies.

The intent of this chapter is to provide the reader with an awareness of the critical interfaces between the atmospheric sciences and health sciences, and to identify opportunities for improved interactions and flow of information between the communities in both directions (opportunities appear in italic text). This awareness should facilitate the development of new information to be considered in future reviews of the health effects of PM and in the development of effective and efficient control strategies to minimize human health impacts of PM pollution.

The chapter builds on the overall framework (Figure 1.1) used for this Assessment by utilizing an expanded conceptual framework that links sources of air pollution to human-health responses (Figure 2.1). This paradigm is similar to that proposed for research on PM by the NRC (1998), shown in Figure 1.4.

The subsequent material in this chapter provides 1) a historical perspective on health and air pollution, 2) a review of exposure assessment and dosimetry, 3) sources of information for understanding the health effects of PM, emphasizing epidemiological approaches, 4) a review of key epidemiological findings, 5) consideration of supporting toxicological evidence, and 6) a summary of policy-relevant findings and opportunities for advancing the science in this field.

Specific studies are cited to provide key information and illustrate important concepts. However, this chapter is not intended to be a comprehensive review of the substantial literature available on the health effects of PM and its co-pollutants. The reader interested in more detailed and comprehensive coverage of PM health effects will find several recent publications useful (California EPA, 2002; CEPA/FPAC, 1999, 2002; Gehr and Heyder, 2000; Holgate et al., 1999; McClellan, 1999, 2002; Molina and Molina, 2002; NRC, 1998, 1999, 2001, 2002 and 2004; Phalen, 2002; U.S. EPA, 1996a, 1996b; 2003a, 2003b; Wilson and Spengler, 1996).

2.2 HISTORICAL PERSPECTIVE

The history of airborne materials impacting on health has been reviewed (Brimblecombe, 1999). Air-pollution problems were recognized very early in many industrial areas, but probably nowhere was the problem as apparent as in London. The high levels of pollution combined with the city's notorious fog created a serious problem and the term "smog"–from contraction of smoke and fog.

In the late 1800s and early 1900s, a series of incidents drew attention to air pollution as a serious health issue. The first observations were on acute air-pollution episodes, periods in which there was a short-term increase in ambient pollution greater than would normally be expected as part of day-to-day variation (Anderson, 1999). In December 1930, stable atmospheric conditions in the Meuse Valley in Belgium resulted in pollution causing 60 deaths and illnesses of hundreds of people. In October 1948, particularly calm and stable meteorology in Donora, Pennsylvania, resulted in severe air pollution and increased morbidity and mortality from respiratory effects. A serious pollution event with serious health impacts occurred in Pozo Rico, Mexico in 1950. In December 1952, smog in London resulted in about 4,000 deaths, principally among the infirm, the old, or those with respiratory disease. Another major smog episode in London in December 1962 resulted in 340 deaths.

The post-World War II era brought changes that impacted air quality. The primary fuel for railroad locomotives shifted from coal to diesel oil. Many businesses shifted from the use of coal to oil. The use of gasoline-powered passenger vehicles began to grow exponentially. Trucks became a major mode of long-distance transport of goods and there was a shift from gasoline to diesel engines for heavy-duty applications. Additionally at this time, large generating stations, using coal as a fuel, were built to meet the demand for electrical power. Tall stacks soon came in vogue as a means of releasing emissions above the inversion layer and enhancing dispersion.

In the 1960s, studies were reported indicating that ambient air pollution had effects beyond those associated with acute pollution episodes. Martin (1964) reported that overall annual mortality, as opposed to acute episodic mortality, in the Greater London area was significantly related to smoke levels. Holland and Reid (1965) conducted a cross-sectional study of lung function of postal workers in London compared to that of others in country towns with lower pollution levels. The socioeconomic level of the workers was the same and smoking intensity could be characterized. There was a clear decrement in function for the London workers compared to provincial workers.

It is informative to consider briefly the historical evolution of the metrics used in studies of air pollution and, especially, the role of PM. In the earliest episodes in the late 1800s, a typical metric was the frequency of "fog" or "stinking-fog" days. The latter were days of especially high pollution with the associated odor of sulfurous compounds. For episodes occurring in the mid-1900s, the air-pollution metrics were "Black Smoke" (measured by the reflectance method) and SO_2. The reported values were extraordinarily high as illustrated by the 1952 London episode. For it, mean maximum levels of Black Smoke were 1600 $\mu g/m^3$ with a single maximum value of 4460 $\mu g/m^3$ and for SO_2 a mean maximum level of 700 $\mu g/m^3$ and a single maximum of 1340 $\mu g/m^3$. Other studies in the mid-1900s, for example of the 1953 New York City episode, related at least in part to forest fires, reported smoke levels measured as coefficients of haze (Greenberg et al., 1962a,b).

A report of the 1975 Pittsburgh episode used Total Suspended Particulates (TSP) as an air-pollution metric (with a maximum value of 700 $\mu g/m^3$) along with SO_2 (130 ppb) (Stebbings et al., 1976). The first report from Steubenville for studies of air-pollution episodes conducted in 1978 and 1979 reported TSP values of 422 and 271 $\mu g/m^3$ and SO_2 of 281 and 455 $\mu g/m^3$ (Dockery et al., 1982).

The first National Ambient Air-Quality Standard (NAAQS) for PM in the United States was set in 1971 (Federal Register, 1971), based on a Department of Health Education and Welfare criteria document (U.S. HEW, 1969). It used TSP as an indicator and relied heavily on the acute pollution episode data from England with extrapolation from Black Smoke measurements.

In the l950s and 1960s, concern for the health effects of airborne radioactive material and the availability of radioactive tracer technology served as a stimulus to the development of a large body of literature on the relationship between particle size and respiratory tract deposition (ICRP, 1994; NCRP, 1997). These data served to focus attention on particles of a size that were most readily inhaled. It was during this period the concept of aerodynamic size emerged and

new instruments were developed for size-selective monitoring including monitors for PM_{15}, PM_{10}, $PM_{2.5}$ and PM_1.

The evolution of PM metrics continued as new studies were conducted on the health effects of both acute and chronic exposure. One of the first acute-exposure epidemiological studies using PM_{10} as an air-pollutant metric was conducted in 1985-86 (Dockery et al., 1992). Sulfate was reported as an air-pollutant metric in a study by Bates and Sizto (1987). Johnson et al. (1990) reported a study of lung function in children that used $PM_{2.5}$ as an exposure metric in addition to TSP and PM_{10}.

A review of the chronic exposure studies also reveals a similar shift in the PM metric. Lave and Seskin (1970), in their classic population-based study of mortality that considered U.S. Standard Metropolitan Statistical Areas, reported an association of mortality with TSP and $SO_4^=$. Miller et al. (1979), in a landmark paper, discussed the rationale for moving to size-selective mass-based standards. This included the merits of using PM_{15}, PM_{10}, $PM_{2.5}$ and PM_1 metrics. The use of PM_{10} as an air-pollutant metric in chronic exposure studies began to appear in papers in the late 1980s. For example, Özkaynak and Thurston (1987) reported on a population-based mortality study that used PM_{10}. Dockery et al. (1993) reported on mortality in the Six Cities cohort-based study, and Dockery et al. (1989) reported on symptoms and disease in children in the Six Cities Study. Interestingly, these latter studies used both PM_{15} or PM_{10} and $PM_{2.5}$ as metrics.

In 1987, the indicator for the U.S. NAAQS was changed from TSP to PM_{10}. The PM_{10} metric was considered to be more health protective than TSP because it was directed at particles that had a higher probability of being inhaled and deposited in the thorax. The 1987 PM_{10} standard was based largely on the acute pollution-episode data (Federal Register, 1987). Numerous epidemiological studies using PM_{10} as an indicator began appearing in the late 1980s. Use of the PM_{15} and PM_1 metrics was discontinued and only limited data were collected on the $PM_{2.5}$ metric after PM_{10} was established as the regulated indicator.

In 1997, the United States announced a new NAAQS for PM that retained the PM_{10} indicator and, most significantly, introduced a new $PM_{2.5}$ indicator (Federal Register, 1997). A national $PM_{2.5}$ monitoring plan was initiated in 1998 to meet a statutory requirement for three years of ambient data prior to determining attainment status and the need for implementation plans. With hundreds of sites going in across the nation, a wealth of new $PM_{2.5}$ information has begun to flow. In the late 1990s, an increasing number of papers began to appear using the $PM_{2.5}$ metric, a reflection of the addition of $PM_{2.5}$ as an indicator for the NAAQS and the availability of monitoring data. Canada established a Canada Wide Standard for $PM_{2.5}$ in 2000.

Following promulgation of the revised PM NAAQS in 1997, numerous petitions for legal review concerning a number of issues were filed. Consideration of the details of the legal actions by the U.S. Court of Appeals and the U.S. Supreme Court are beyond the scope of this chapter. However, several outcomes are worthy of note. First, the Court reaffirmed prior rulings holding that in setting the NAAQS, U.S. EPA is not permitted to consider the cost of implementing the standards; EPA can consider costs in establishing the schedule for implementing the standards. Second, the Court concluded that PM_{10} is a poorly matched indicator for coarse particulate pollution. The Court vacated the 1997 revised PM_{10} standard, resulting in the 1987 PM_{10} standards remaining in effect.

The U.S. EPA has interpreted the Court's ruling as precluding the promulgation of further revisions to the PM_{10} NAAQS. Alternatively, in the most recent Criteria Document (CD) and Staff Paper (SP) for particulate matter, EPA has laid the groundwork for proposing a coarse-particle $PM_{10-2.5}$ NAAQS to complement the fine-particle $PM_{2.5}$ NAAQS. The $PM_{10-2.5}$ indicator refers to particles with a mean aerodynamic diameter greater than 2.5 μm but less than or equal to 10 μm. At the time this Chapter was prepared, a Federal Reference Method for $PM_{10-2.5}$ had not yet been developed. The majority of measurements of $PM_{10-2.5}$ and related studies of health effects have been based on differences between concurrent measurements of PM_{10} and $PM_{2.5}$.

From the foregoing, it is apparent that the inputs of both atmospheric scientists, making measurements of air quality, and health scientists, evaluating health responses, have been required for the conduct of epidemiological studies. It is also apparent that epidemiological studies of associations between increased levels of adverse health responses and air pollution can be conducted only using the air-pollutant metrics that have been measured. Hence there has been a progression, from monitoring data and then epidemiological evaluations to using "stinking fog" days to Black Smoke and coefficients of haze to TSP to PM_{10} to $PM_{2.5}$. The latter metrics in the series are reflective of the metrics used in federal standards or guidance and, hence, in regulatory-compliance monitoring. The epidemiological studies have also considered pollutants other than PM for which measurements were available. This typically has included the other regulated criteria pollutants such as ozone, SO_2, NO_x, and CO. As will be discussed later, the opportunity is now at hand to select and evaluate in both toxicological and epidemiological studies PM metrics other than those that are reflective of current regulations. These studies will be designed to test whether these new metrics are more closely linked to adverse health effects than the existing PM indicators and, thus, warrant consideration in developing new regulations and control strategies for PM.

2.3 EXPOSURE ASSESSMENT

Major advances have been made in exposure assessment in recent years. This topic has been reviewed by Özkaynak (1999), the U.S. National Research Council (1991), and the U.S. EPA (1992).

A number of options exist for assessing exposure for use in the conduct of epidemiological studies (Textbox 2.1). These various indices can be placed into perspective by considering the schematic rendering of the relationship between ambient (outdoor) and indoor concentrations of pollutants and biologically effective dose as shown in Figure 2.1. In considering this figure, it is important to recognize that pollutants from outdoor sources can penetrate indoors and, thus, are a major source of indoor concentrations of pollutants including PM, especially in buildings that use outside air directly for heating or cooling. The vast majority of epidemiological studies of air pollution, including those of PM, have been conducted using outdoor fixed-location monitors to provide pollutant composition and concentration profiles for use as exposure metrics (see Figure 2.1).

The Total Exposure Assessment Methodology (TEAM) and National Human Exposure Assessment Study (NHEXAS) were human-exposure assessment field studies that provided a foundation for building models of human exposure to CO, VOCs, and PM (Özkaynak et al., 1996; Wallace, 2000). The relationship between personal exposure and ambient concentrations has been found to vary with the pollutant, climate, building practices, and personal activities. The validity of using ambient PM_{10} measurements as a surrogate for PM_{10} personal exposures was demonstrated for one location and a short period of observation by Clayton et al. (1993). This work is summarized in Figure 2.2. In this figure data are presented relating total personal exposure, personal exposure to ambient PM and personal exposure to non-ambient (i.e., indoor origin) PM to ambient concentrations. As may be noted (panel c) the personal exposure to non-ambient PM was not correlated with ambient PM as would be expected. On the other hand, personal exposure to ambient PM was very closely correlated with ambient PM concentrations (panel b). This is a reflection of both the high penetration of ambient PM_{10} in dwellings resulting in exposure indoors and the individual's exposure to ambient PM_{10} outdoors. Total personal exposure to total PM (panel a) was correlated with ambient PM concentrations. However, as expected the correlation was not as good as seen in panel b because of the influence of PM of non-ambient (indoor) origin. It should be noted that these data were collected during September in Riverside, CA, a locale with a very mild climate and unique PM composition. In Riverside, many homes open directly to the outdoors in September, creating significant opportunities for air exchange, compared with many other North American locations. Thus, caution should be exercised in extrapolating these findings to other areas.

Textbox 2.1. Indirect Methods of Assessing Exposure

Source of Information	Type of Information
Source strength	Emission rate (mass per time), traffic density
Geographical information	Distance of the place of residence from the source
Dispersion models	Spatiotemporal concentration distributions from modeling of emission rates, meteorology, air chemistry, geography
Ambient (Outdoor) monitoring	Ambient concentration for defined period
Outdoor-indoor penetration	Modeling from outdoor concentration, building and ventilation characteristics
Indoor monitoring	Indoor concentration for defined period
Questionnaires and interviews	Source strength, distance from the source, time-activity
Personal exposure	Concentration over time modeled from concentrations of pollutants in microenvironments and time-activity patterns
Personal monitoring	Continuous or cumulative concentrations measured over time
Human samples	Concentration of biomarkers of exposure in human tissues and hair
Toxicological models	Concentration and dose of pollutants in target organs modeling from concentration, breathing rate, and metabolism

[Modified from Samet and Jaakkola (1999)]

The NRC Committee on Research Priorities for Airborne Particulate Matter identified personal exposure studies of PM as deserving of high priority. In their 2001 report, the Committee (NRC, 2001) identified 15 studies as being underway on the outdoor-personal exposure topic. Special attention was being given to studying potential susceptible populations including the elderly, children, asthmatic children and adults, chronic obstructive pulmonary disease (COPD) patients, patients with myocardial infarcts and their spouses, and non-smoking healthy adults in different cities across the United States. Examples of such studies are the work of Rojas-Bracho et al. (2000) with individuals with COPD and of Sarnat et al. (2000) of senior citizens. *Further progress in understanding total personal exposure including the relationship between PM and various constituents, such as carbonaceous species in the ambient and indoor environments, will require continued collaboration between atmospheric scientists, health scientists and specialists in the field of exposure assessment.* This kind of research is just beginning to involve detailed characterization of PM constituents, an area that will continue to benefit from the input of atmospheric scientists.

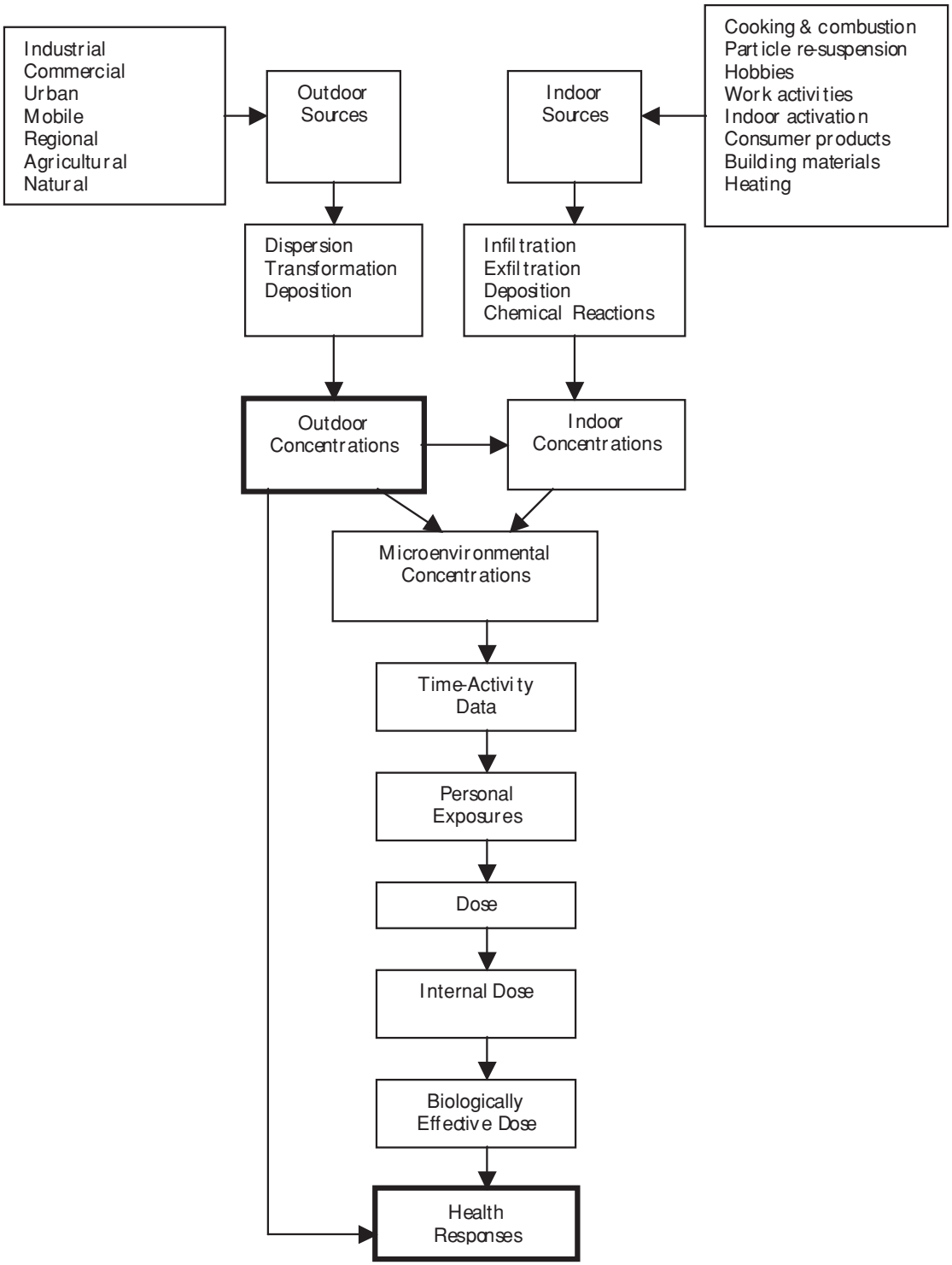

Figure 2.1. Schematic rendering of relationship among outdoor and indoor sources, personal exposure, biologically effective dose, and health responses (Adapted from Özkaynak, 1999).

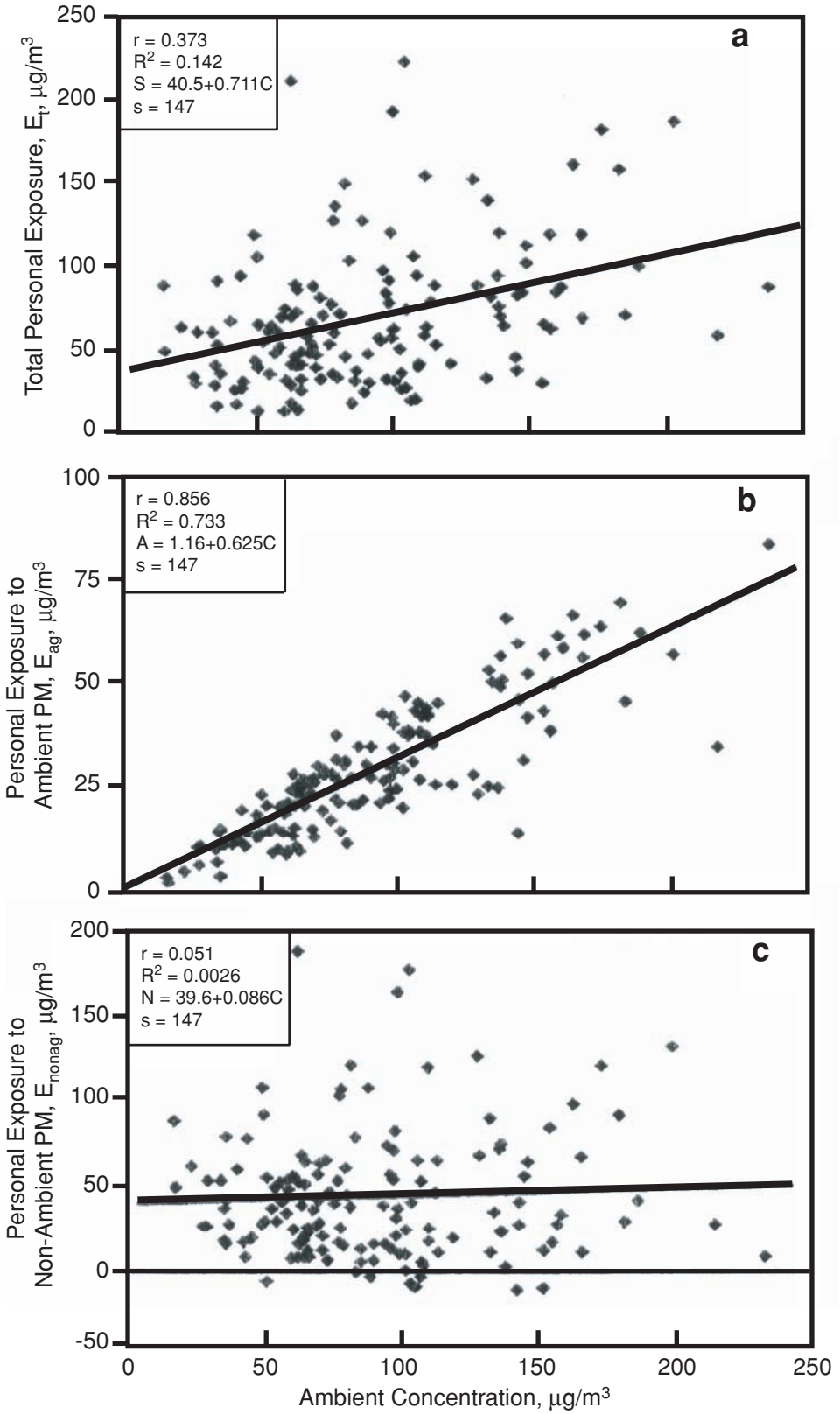

Figure 2.2. Regression analysis of daytime personal exposure to PM_{10} (Clayton et al., 1993).

In considering the relationship between various measures of exposure and internal dose from PM, it is important to consider the very important influence particle size has on the deposition of inhaled PM (Figure 2.3). Excellent summaries of these data are available (ICRP, 1994; NCRP, 1997; Miller, 1999; Schlesinger, 1995). The particle-deposition efficiencies shown in Figure 2.3 have been corrected to account for inhalability. Inhalability is the sampling efficiency of the nose and mouth for particles (Phalen et al., 1986). For 10 μm particles, inhalability is about 77 percent and for $PM_{2.5}$, inhalability is greater than 90 percent (Vincent, 1999). Particle size is plotted as aerodynamic diameter in the figure. Different, size-dependent ranges of aerodynamic behavior exist. The deposition of larger particles is influenced mainly by inertial forces and gravitational settling, while deposition of particles less than about 0.5 μm diameter is influenced by Brownian diffusion. Particle size influences both the fractional total deposition in the respiratory tract as well as the distribution of PM in subunits of the respiratory tract. Consideration of deposition data of this kind as well as the size distribution of ambient PM was a major factor leading to the establishment of PM_{10} and $PM_{2.5}$ as indicator metrics for PM standards.

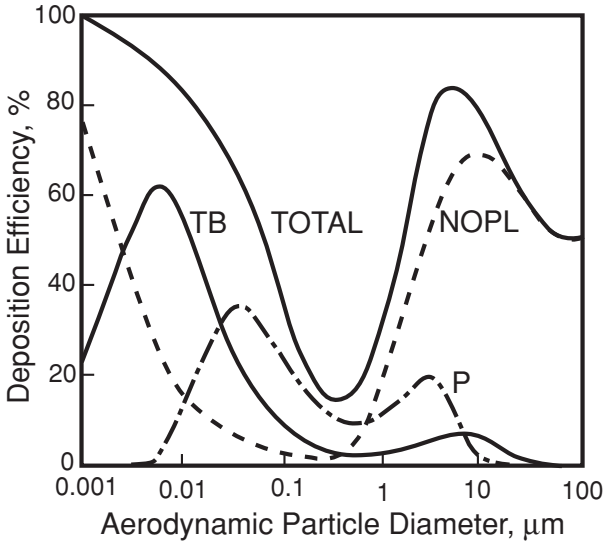

Figure 2.3. Particle deposition in the major regions of the human respiratory tract during normal respiration corrected for size-dependent inhalability. (NOPL, naso-oro-pharyngo-laryngeal) region; TB, tracheobronchial region; and P, pulmonary region). Developed from the National Council on Radiation Protection Model (NCRP, 1997) by Phalen (2002).

For any given particle size, some portion of the particles of that size will deposit in each of the three primary regions of the respiratory tract: naso-oro-pharyngo-laryngeal, tracheobronchial, and pulmonary. This is also the case when deposition is integrated for all particle sizes within a $PM_{2.5}$ or PM_{10} sample. Any given sample only represents a measure of what is in the air and is not necessarily reflective of any individual's exposure. For example, even if the ambient air were characterized with $PM_{2.5}$ and $PM_{10\text{-}2.5}$ samples, there may be substantial material present greater than 10 μm in size that has not been sampled and has the potential for being inhaled and deposited in the naso-oro-pharyngo-laryngeal region and, to a lesser extent, in the tracheobronchial region and influencing the development of disease.

Once particles are deposited, the real size, surface area, and chemical composition become major factors determining the clearance of PM from the respiratory tract, and the converse - retention. The clearance of relatively insoluble PM in pure forms (such as aluminosilicate, titanium dioxide, and black carbon) from the different regions of the respiratory tract is generally quite well understood (Wolff, 1996; Snipes, 1995; Miller, 1999). Unfortunately, only limited data are available on the clearance and retention patterns of specific chemical constituents of ambient PM. A lack of such data has been a factor impeding progress in understanding the various mechanisms by which PM and specific PM constituents may cause health effects. *Progress in understanding the disposition in the human body, and in laboratory animal species, of various key constituents of ambient PM can undoubtedly be aided by closer collaboration between atmospheric scientists and health scientists.*

2.4 SOURCES OF INFORMATION ON HEALTH RESPONSES TO AIR POLLUTION

Information on health responses to air pollution, including PM, are obtained from multiple sources: epidemiological studies, controlled exposure studies of human subjects, investigations using laboratory

animals and research conducted in vitro with cells and tissues.

2.4.1 Epidemiological Approaches

Epidemiology comprises the scientific methods used to study the occurrence of disease in human populations, including description of the occurrence of disease and identification of the causes of disease such as air pollution. Detailed coverage of epidemiological approaches to studying air pollution is provided in recent reviews by Samet and Jaakkola (1999) and Pope and Dockery (1999). Epidemiological studies are of special value because they involve the study of people in their natural setting and exposures that occur in the course of everyday life. Their results can document increased occurrence of adverse effects of air pollution, describe the relationship between exposure and response, and characterize effects on susceptible groups within the population, e.g., persons with cardiorespiratory disease.

In general, epidemiological studies are carried out to 1) to determine if air pollution or a source of air pollution poses a hazard to human health, 2) to characterize the relationship between the level of exposure and the response, and 3) to examine responses of potentially sensitive groups to pollutant exposures. These objectives relate directly to the information needs of policy makers as they address key questions: 1) Does a particular pollutant pose a hazard to human health?, 2) What are the levels of risk at specific exposure levels? and 3) Which groups need special consideration because of their susceptibility? Epidemiological studies may also provide information to assist the policy makers in deciding on control strategies (What is the anticipated health impact of reductions in a particular pollutant or reduction of emissions from a given source?) and whether a particular control strategy has had impact (Are there reductions in health impacts related to control measures?).

The fundamental focus of epidemiological studies of air pollution and health as schematically depicted in Figure 2.4 is to evaluate the association between various health metrics (upper portion of figure) and various air-quality metrics (lower portion of figure). A glossary of some of the key terms used in the field of epidemiology is provided in Textbox 2.2. A listing of some of the indirect methods of assessing exposure was provided earlier in Textbox 2.1 and some of the common health metrics are provided in Textbox 2.3. The terms acute (i.e., of short duration) and chronic (i.e., of long duration) may be used in describing both exposure and health responses. Acute or short exposures usually give rise to acute effects. For example, an immediate symptom of cardiac or respiratory effects is death. However, these acute effects may be observed in individuals with chronic disease arising from a range of factors. Chronic, or long-duration exposure, perhaps over a lifetime, may

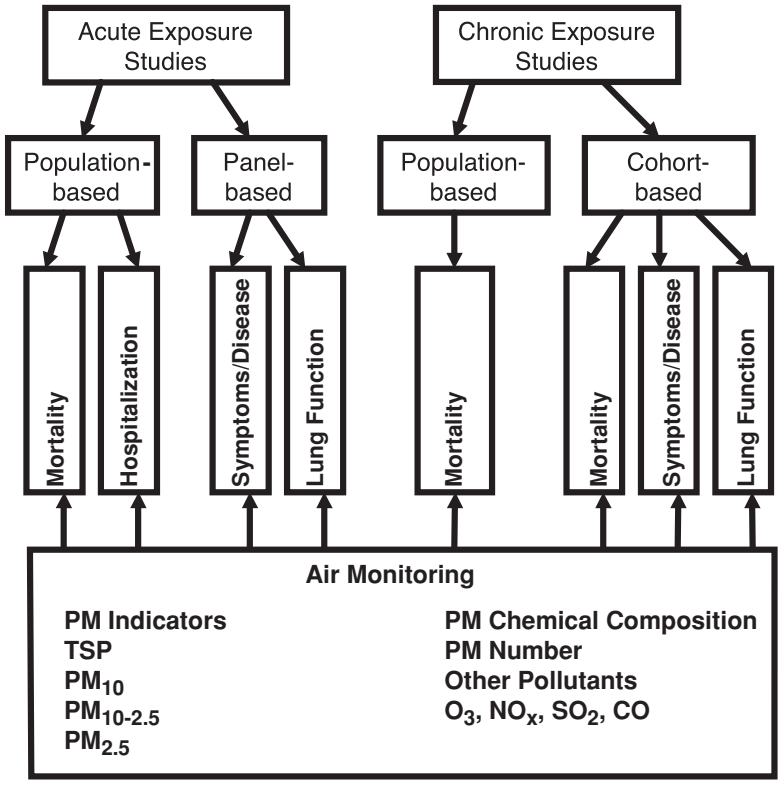

Figure 2.4. Schematic rendering of basic design for epidemiological studies (Adapted from Pope and Dockery, 1999).

Textbox 2.2. Glossary of Epidemiological Terms

Association	Non-random occurrence of disease in relation to exposure
Bias	Error in the measurements of an exposure's effect
Case-Control Study	An analytical design involving selection of diseased cases and non-diseased controls followed by assessment of prior exposures
Trial	An analytical design involving random assignment of exposure to two or more subject groups
Panel or Cohort Study	An analytical design involving selection of exposed and non-exposed subjects with subsequent follow-up for development of disease
Confounding	Bias resulting from the contamination of an exposure's effect by that of another risk factor
Cross-Sectional Study	Subjects are identified and exposure and disease status determined at one point in time
Incidence Rate	Ratio of number of new cases to population at risk during a specified time period
Misclassification	Bias from error in determining exposure or disease status
Mortality Rate	Ratio of number of deaths to population at risk during a specified time period
Prevalence	Proportion of population with disease at a particular time
Selection Bias	Bias resulting from the technique used to select a study's subjects

[From Samet and Jaakkola (1999)]

give rise to bouts of acute symptoms of disease or more typically diseases that develop and are manifested over long time periods.

The listing (Textbox 2.3) of health metrics focuses on the respiratory system because it is both the portal of entry for air pollutants and is frequently impacted by the inhaled materials. In considering these outcomes, it is important to recognize that they are not specific or unique in their relationship to either air pollution in general or to specific pollutant indicators such as PM. Indeed, cardiac and respiratory diseases are caused or aggravated by many factors and are among the most common ailments as will be detailed below. In epidemiological investigations, the models used are typically additive or relative-risk models with the results expressed as increased risk relative to the baseline morbidity or mortality associated with a given increment of exposure to a particular pollutant. As will be discussed later, the ambient air-pollution effect detected may represent a small percentage increase over the background level of disease. Thus, the effects of ambient PM are reflected as a statistical

increase in morbidity and mortality in populations rather than as effects that can be identified in specific individuals.

It has been known for a long time that the health effects of inhaled pollutants are not restricted to the respiratory tract, but that inhaled materials can impact non-respiratory organs. Examples are 1) inhaled lead affecting both the hematopoietic and nervous systems, 2) carbon monoxide affecting the central nervous system, the oxygen-carrying capacity of blood and the heart, and 3) inhaled chemicals like benzene causing leukemia. Only very recently has an association been demonstrated between exposure to PM and heart disease including death (Utell et al., 2002).

The total burden of respiratory and cardiac disease in most countries including Canada, Mexico, and the United States is substantial. This can be illustrated using data from the United States. In 1997, there were 3,475,000 hospital discharges for respiratory disease (Lawrence and Hall, 1999). Of these, 38 percent were for pneumonia, 14 percent for asthma,13 percent for chronic bronchitis, 8 percent for acute bronchitis, and others not specified. There were 195,943 deaths recorded as caused by respiratory disease (Hoyert et al., 1999). Of these, 44 percent resulted from acute infections, 10 percent were for emphysema and bronchitis, 2.8 percent for asthma, and 42 percent from unspecified COPD. In 1997, there were 4,188,000 hospital discharges with heart diseases listed as the first diagnosis (Lawrence and Hall, 1999). Of these, 50 percent were for ischemic heart disease, 18 percent for myocardial infarction or heart attack, 23 percent for congestive heart failure, and 15 percent for cardiac dysrhythmias. In 1997, there were 726,974 deaths from heart disease (Hoyert et al., 1999). From consideration of these values, it is apparent that there is a large background of respiratory and cardiac disease arising from multiple risk factors, which makes it difficult to detect small signals of increased disease attributed to PM. Because these diseases are very common it is also apparent that even a very small percentage increase attributed to PM will represent a substantial number of cases.

Textbox 2.3. Health Outcome Measures in Studies of Air Pollution

General
- Overall mortality
- Morbidity index

Cardiac and Respiratory
- Acute and chronic symptoms
- Acute infections
- Chronic cardiac respiratory diseases
- Degree of non-specific airways responsiveness
- Reduced level of lung function
- Increased rate of lung function decline
- Decreased rate of lung function growth
- Altered cardiac functio
- Exacerbation of a chronic cardiac or respiratory disease
- Hospitalization for a chronic cardiac or respiratory disease
- Lung cancer
- Death secondary to a cardiac or respiratory disease

Neuropsychological
- Reduced performance on neurobehavioral testing
- Neuropsychological syndrome
- Neuropsychological disease

[Modified from Samet and Jaakkola (1999)]

The study designs of epidemiological investigations of air pollution can be grouped in several ways. In Figure 2.4, the focus is first on acute versus chronic exposure and second on the unit of observation: populations or individuals. Studies based on groups are referred to as ecological studies. Population studies may compare 1) indicators of adverse health effects across geographic areas with different pollutant levels, and 2) temporal associations between pollutant levels and measures of health outcome for a single or multiple communities. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS; Samet, et al., 2000a, 2000b; HEI, 2000a, 2000b) is an excellent example of a retrospective time-series study of 90 communities in the United States.

Study designs that have individuals as a unit of observation are of three types: 1) cross-sectional studies, 2) cohort studies, and 3) case-control studies (see Textbox 2.2 for details). Of the designs having individuals as the unit of observation and analysis, the cross-sectional study is generally the most economical and feasible approach. Although the effect of ambient pollution may be studied on individuals, data are ultimately aggregated and statistical comparisons made on a group or subpopulation basis. It has not been possible to attribute the health status of any given individual to PM or other pollutants except in a statistical sense. Cross-sectional studies are often used to compare the health status of residents of more versus less polluted communities. The effects of exposure may be biased, for example, by the tendency of more susceptible persons to reduce their exposure by leaving the polluted community.

In a cohort study, exposures of individuals are assessed directly or indirectly and they are followed for the development of the outcomes of interest, for example, the occurrence of symptoms of disease or changes in lung function. Cohort studies may be prospective if the disease of interest will occur in the future, or retrospective if they have already taken place when the study is initiated. The Six Cities Study (Ferris et al., 1979) is an excellent example of a prospective cohort study that included from the beginning substantial involvement from atmospheric scientists. More than 8000 subjects were enrolled in 1974 through 1976 in six cities selected for a range of air-quality conditions and then followed with periodic measurements of lung function, respiratory symptoms, and other health indices, and simultaneous monitoring of air pollution. The cohort design has the advantage of direct estimation of disease rates and the opportunity to prospectively accumulate comprehensive exposure data including changes in exposure over time.

Panel studies represent a special type of short-term cohort study. The subjects, often individuals considered to be of greater susceptibility such as patients with COPD or heart disease, are enrolled and both health outcomes and exposure monitored intensively. Hence usually only a modest number of individuals can be studied, especially if an attempt is made to characterize (directly or indirectly) individual exposures.

The case-control study approach compares exposures of persons having the outcome of interest with those of controls, providing a measure of association between exposure and disease. This design has been widely used for studying lung cancer. It represents an optimum approach for studying uncommon diseases. It has been used infrequently for studying non-malignant respiratory diseases which are common, as was discussed earlier, and air pollution.

The successful conduct of epidemiological investigations is dependent upon the quality of both health-outcome data and exposure data. Shortcomings in health-outcome data cannot be made up for by giving increased emphasis to the exposure data or vice versa. All studies of environmental air pollution inevitably involve multiple pollutants. The atmosphere is a complex mixture of gases and PM that varies both spatially and temporally in chemical composition and in the size distribution of the particulate phase. While the focus in any given study may be on some specific PM indicator such as $PM_{2.5}$, it is necessary to consider the effects of other air pollutants, including other PM indicators, that may also adversely impact health. *Long-term monitoring data on PM mass concentrations, PM composition, gas-phase precursors of secondary particulate species, and gas-phase copollutants in multiple communities will provide the best opportunity for evaluation of associations with health data.*

It is also critical that other variables that can influence health be considered. This includes factors such as age, climate and temperature, socio-economic status, educational level, occupation, and lifestyle factors such as smoking. And finally, it is important to consider the total body of epidemiological and related evidence. This is especially the case when attempting to assess whether the statistical associations observed are causal. This issue has been addressed by Hill (1965) and Rothman (1986) in proposing criteria to move beyond statistical associations to consider whether a causal association has been demonstrated (Textbox 2.4).

Textbox 2.4. Criteria for Assessing Causality of Associations

Strength of association	Strong associations considered to be more likely causal than weak associations
Consistency	Repeated observation of the association in different studies strengthens the likelihood of causality
Specificity	A cause is associated with a single effect
Temporality	Exposure precedes effect
Biological gradient	An exposure-response relationship is present
Plausibility	The association should be consistent with relevant biologic data

[From Hill (1965) and Rothman (1986).]

2.4.2 Controlled-Exposure Studies with Human Subjects

Studies with human subjects exposed to well-characterized test atmospheres provide an opportunity to obtain detailed information on the disposition of inhaled PM and clinical responses. The basic approaches to the conduct of such studies have been described by Frampton and Utell (1999), Frampton et al. (2000), and Utell et al. (2002). All such studies must be carried out under defined protocols that have been reviewed and approved by an Institutional Review Board to ensure conformance with all the applicable standards for human experimentation. The subjects in such studies are defined as to their health status and may be normal individuals or potentially sensitive individuals such as those with asthma or COPD. Ethical considerations dictate that the subjects not be the most ill or feeble individuals in a particular diagnostic category. Most controlled-exposure studies of air pollutants have been conducted with well-defined atmospheres of single pollutants such as radio-labeled particles, ozone, H_2SO_4, NO_2, or carbon black. The studies with inhaled radio-labeled particles and subsequent measurements of deposition and retention have provided a sound understanding of the influence of particle size on the disposition of particles (ICRP, 1994; NCRP, 1997).

Chemical composition is not considered in current North American PM standards. This poses a difficult problem in deciding what is an appropriate material for use in clinical studies. Specific PM constituents such as H_2SO_4 droplets and carbon black have been studied. In addition, in recent years technology has been developed to expose both laboratory animals and human subjects to concentrated ambient PM (Sioutas et al., 1995). Such studies have an advantage in that investigators are studying real-world PM; however, they must accept whatever the composition of PM is in the ambient air at the time of the study.

A broad array of measurements can be made to assess changes in the clinical condition of the subjects related to the test exposure. This has typically included measurements of pulmonary function and in some recent studies an assessment of various parameters related to cardiac function (Frampton and Utell, 1999; Utell et al., 2002). Advances have been occurring at a phenomenal rate in the understanding of both normal biology and disease at the molecular level. The human genome is on the verge of being fully characterized and increased attention is being given to characterizing related proteins (the proteome) and how normal metabolism occurs as well as the handling of introduced materials (metaboleome). Many of these advances are now being used to study the effects of inhaled particles and other pollutants in controlled-exposure studies with human subjects. Some of these approaches ultimately may be adapted for use in large-scale population studies. This may include the development of new biomarkers of exposure, susceptibility, and health effects. A key consideration in such work will be the validation of a growing list of candidate biomarkers such that they can be used

with confidence to define the point at which responses should be equated to adverse health effects that warrant preventive measures (ATS, 2000).

An obvious strength of clinical studies is that they involve human subjects, and thus the data generated are clearly of interest in setting standards to protect human health. Key limitations are the small number of subjects that can be studied, short periods of exposure and observation, the need to extrapolate from simple aerosols to complex ambient PM and from high concentrations of simple aerosols or concentrated ambient PM to the lower PM concentrations typical of ambient air. The conduct of controlled studies with human subjects requires the use of specialized equipment and facilities, capabilities that exist in only a few institutions around the world. *Atmospheric scientists, as active collaborators in controlled-exposure studies with human subjects and laboratory animals, can assist in producing and characterizing test atmospheres that will assist in testing various mechanistic hypotheses.*

2.4.3 Laboratory Animal Studies

Laboratory animal studies with controlled exposures typically play a central role in characterizing the hazardous properties of various substances including ambient PM. Approaches to the conduct of such studies have been reviewed (Valentine and Kennedy, 2001; McClellan and Henderson, 1995). In the absence of adequate human data, laboratory animal data may be used not only to describe hazard but may also play a crucial role in characterizing the exposure-response relationship for the substance. In the case of PM, laboratory animal studies share many of the limitations described earlier for controlled-exposure studies with human subjects. In addition, there is the issue of extrapolating from another species to humans. In the case of inhaled materials this extrapolation issue is complicated by differences in the dimensions of the respiratory tract of laboratory animals and humans and the impact of these differences on the deposition of inhaled PM. Fortunately, there is a large body of literature on the deposition and clearance of inhaled particles in the principal laboratory animal species for comparison to data on humans (Schlesinger, 1995; Miller, 1999; Snipes, 1995; Wolff, 1996). As with human studies, a serious limitation relates to the need for specialized equipment and facilities to conduct inhalation studies, capabilities that exist in only a few institutions around the world. If alternative approaches such as intratracheal instillation are used to introduce material into the respiratory tract, there is an additional challenge of extrapolating from non-physiological approaches of delivering PM to the inhalation route of interest.

Laboratory animal studies have been conducted using simple atmospheres containing well-defined PM such as carbon black or titanium dioxide. In addition, some studies have been done with complex atmospheres such as diluted vehicle exhaust. Other studies have been done using concentrated ambient particulate matter using the new particle concentrator technology (Clarke, et al., 2000; Godleski et al., 2000).

A strength of laboratory animal studies is the extent to which different species and strains can be used to take advantage of particular characteristics matched to an experimental need. In recent years this has included animals that have been genetically manipulated to either enhance or suppress certain biological characteristics. Recognizing the extent to which many of the uncertainties related to PM effects relate to responses of susceptible individuals, researchers have made on-going efforts to develop and use animal models that mimic some of the characteristics of humans considered to be especially susceptible to PM. Several different animal models have been developed for pulmonary and cardiac diseases including consideration of asthma and aging (Cantor, 1989; Bice et al., 2000; Mauderly, 2000; and Muggenburg et al., 2000). An obvious advantage of laboratory animal studies is the ability to carry out experimental manipulations that might not be feasible with human subjects.

2.4.4 Tissue and Cell Studies

A wide range of in vitro experiments can be conducted with tissues and cells obtained from both laboratory animals and human subjects. In some cases, cultured cells from established cell lines can be used allowing experiments to be performed under carefully replicated conditions to test the influence of multiple experimental variables. *Atmospheric*

scientists can aid in the design and use of novel systems to deliver PM with specific characteristics to cell populations in ways that will enhance extrapolation from the in vitro situation to the in vivo.

As will be discussed later, controlled-exposure studies with human subjects, laboratory animals and cells provide valuable tools for evaluating and prioritizing the multiple hypotheses that have been advanced to explain the mechanisms of action of PM. *Atmospheric scientists can play a valuable collaborative role in helping health scientists understand the dynamic nature of ambient PM size and chemical composition and identify parameters for investigation in biological studies.*

2.5 EPIDEMIOLOGICAL FINDINGS

2.5.1 Acute Exposure

The designs for acute exposure studies and chronic exposure studies shown in Figure 2.4 will be used as a basis for discussion of the current status of our knowledge of health effects associated with PM exposure.

Numerous acute exposure, population-based mortality studies have been conducted as reviewed by Pope and Dockery (1999), CEPA/FPAC (1999), Anderson (1999), California EPA (2002) and the U.S. EPA (1996a,b, 2001; 2002). In recent years the population-based studies have been extended to evaluation of hospitalization and related health-care endpoints. These studies have been conducted most frequently using administrative morbidity and mortality data bases collected for other purposes and air-quality monitoring data collected for regulatory compliance purposes. The earliest and most methodologically simple studies focused on acute pollution episodes. They were simple because of the substantial effect compared to background mortality. A summary of the findings from acute exposure studies using PM_{10} as a metric developed by Pope and Dockery (1999) from a review of the literature is shown in Figure 2.5. All of the changes shown are expressed as percent change relative to the background rate of the morbidity or mortality indicator. These authors have cautioned that these are not precise estimates because of the difficulty of comparing across studies using different measures of pollution, differently defined health endpoints, and different models. However, the data are illustrative of the relative magnitude of epidemiological associations.

In the 1970s, investigators began to use formal time-series analyses to explore potential associations between daily mortality and air pollution at relatively low levels. Time-series studies have the advantage of using mortality and air-pollution data over much

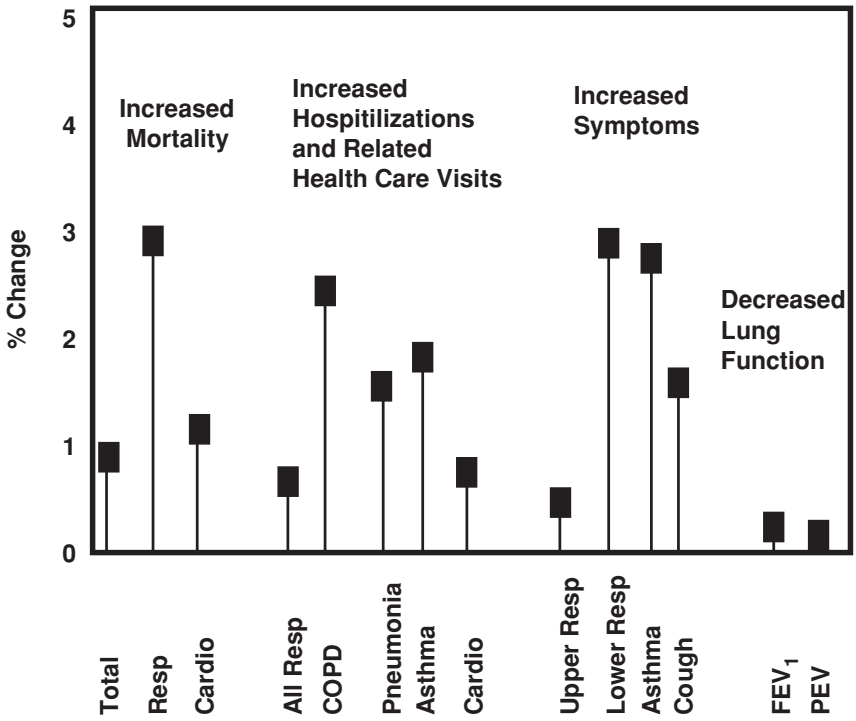

Figure 2.5. Stylized summary of acute exposure studies, percent change in health endpoint per 10 μg/m³ increase in PM_{10} (adapted from Pope and Dockery, 1999)

longer time periods than the few days of a single, acute pollution episode. This approach increased the statistical power of the studies by increasing the number of adverse outcomes (deaths usually identified by cause) and the number of monitored days. In time-series studies, each population essentially serves as its own control, i.e., it is assumed that various risk factors such as smoking, employment, and socio-economic status are not changing day to day.

In the early 1990s, investigators began to conduct time-series analyses using Poisson regression modeling. Many of the studies used the Generalized Additive Models (GAM) described by Hastie and Tibshirani (1990). These studies took advantage of computerized records of daily mortality, air pollution (typically the criteria pollutants), season, barometric pressure, temperature, and other weather metrics. Inclusion of other pollutants in the model generally reduced the estimated PM effect. Population-based socio-economic data were also available. Data on factors other than air pollutants are important because the relative risk associated with changes in these various confounders may be significant as well and need to be addressed in the course of estimating air-pollution risks. New statistical software became available in the 1990s for Poisson regression analysis of count data permitting statistical analysis of daily counts of death even for relatively small metropolitan areas.

Some of the time-series studies provided for classification of mortality by cause. PM had the largest effects on deaths related to respiratory and cardiovascular disease and, because the number of cardiovascular deaths were greater than the number of respiratory deaths, the majority of the effect was attributable to the former. Typically, the relative risk of mortality increased with increasing PM concentrations in a near-linear fashion. A lag between air pollution and mortality was usually observed, suggesting that mortality lagged 1 to 5 days following an increase in air pollution, though a few studies have suggested periods of slightly elevated risk for a period of up to several weeks. Because PM measurements were not always made using the same metrics, conversions were made by assuming that PM_{10} = 0.55 x TSP; PM_{10} = Coefficient of Haze/0.55; and PM_{10} = Black Smoke.

The most substantial time-series study conducted to date, NMMAPS, was carried out by investigators at Johns Hopkins University (Samet et al., 2000a, 2000b; HEI 2000a, 2000b). The study examined the association between mortality and air pollution for 90 U.S. cities over the period 1987 to 1994 using the GAM feature of S-PLUS, a statistical software package. The investigators originally reported a pooled estimate of a 0.41 percent increase (1.0041 times the baseline mortality) per 10 $\mu g/m^3$ increase in PM_{10} with a posterior standard error of 0.05 when the standard GAM convergence criteria were used. As an aside, the statistical association was based on PM_{10} rather than $PM_{2.5}$ because $PM_{2.5}$ data were not available. *In the future, as information becomes available on $PM_{2.5}$ and other PM indicators such as the carbonaceous fraction and inorganic elements from the speciation studies, it will be appropriate to extend the NMMAPS kind of analyses.*

The NMMAPS' investigators reported in 2002 that the standard convergence criteria in S-PLUS were not sufficient; the result was an overestimation of the effect of PM pollution and an underestimation of the variance for a given city (Dominici et al., 2002). Using substantially more restrictive convergence criteria, the investigators found the pooled estimate of the effect on mortality decreased to 0.27 percent (1.0027 times the baseline mortality) per 10 $\mu g/m^3$ increase in PM_{10}, again with a standard error of 0.05. The investigators also observed that using the more restrictive convergence criteria, the within-city variance increased compared to when the standard convergence criteria were used. The underestimation of the within-city variance may be balanced by the overestimation of between-city variance without impacting the total variance (Daniels et al., 2002). The existence of between-city differences may be reflective of pollution differences between the cities including PM composition. *The opportunity exists for atmospheric and health scientists to collaborate on the search for variations in health impacts that may relate to differences in PM characteristics.*

Ramsey et al. (2003) have also examined the analytical methods in detail and indicated that the standard errors of the measures of association were systematically underestimated, with the potential to increase the apparent level of statistical significance. This occurred in part because of a large correlation

between nonlinear functions included in the GAM analyses. The reader interested in obtaining a better understanding of issues involved in software reliability in performing these types of analyses is referred to the papers of McCullough (1998, 1999).

Samet et al. (2003) have also evaluated the use of Generalized Linear Models (GLM) with natural cubic splines for confounder adjustment (Daniels et al., 2002). They found a pooled estimate of 0.21 percent (1.0021 times the baseline mortality) per 10 $\mu g/m^3$ increase in PM_{10}. Samet and colleagues have cautioned against selecting any particular model as correct, and urged researchers to explore the sensitivity of their findings to model selection.

The recent findings of issues related to model selection and statistical criteria are clearly not restricted to the NMMAP study. The findings have triggered re-evaluation of a number of key time-series studies conducted during the last decade. Because of the importance of the time-series studies in the review of the NAAQS for PM, arrangements were made for the Health Effects Institute to convene a special panel to peer review the re-evaluated time-series analyses. The report of the panel (HEI, 2003a) includes sections on each of the studies re-evaluated, such as the NMMAP study (HEI, 2003b), so this information could be considered in the Criteria Document (U.S. EPA, 2003a) and Staff Paper (U.S. EPA, 2003b) currently being prepared. In addition to considering the individual studies the special HEI panel provided a commentary on the strengths and weaknesses of the time-series methodology. An important conclusion was that difficulties remain in the handling of confounding by weather, which have important implications for the resulting estimated concentration-response coefficients for PM indicators and other air pollutants.

Pope and Dockery (1999), based on their review of the literature, provided a schematic summary of effects estimates of acute exposure to PM_{10} (Figure 2.5). They suggested that each 10 $\mu g/m^3$ increase in PM was associated with a 0.8 percent (1.008 times the baseline mortality) increase in daily mortality. This estimate, as well as those for other endpoints, may need to be revised depending on the outcome of the re-analysis of key time-series studies. Pope and Dockery (1999) noted that the associations for respiratory mortality were substantially larger, and those for cardiovascular mortality were larger than those for total mortality. Increases in PM_{10} exposure were also associated with increased hospitalizations and increased health-care visits for respiratory and, to a lesser extent, cardiovascular disease. Associations were also observed for lower respiratory symptoms, exacerbation of asthma and coughing and, to a lesser degree, upper respiratory symptoms and small declines in lung function.

While the results in Figure 2.5 are for PM_{10}, generally similar effects have been observed for $PM_{2.5}$. However, the percent change is usually larger per µg of $PM_{2.5}$ than per µg of PM_{10} reflecting the greater apparent potency of the $PM_{2.5}$ fraction. Limited data are available on the $PM_{10-2.5}$ metric. There are health effects attributed to this fraction although the findings are generally not as consistent as for $PM_{2.5}$. These inconsistencies may in part be a reflection of the sampling methods and calculation of $PM_{10-2.5}$ by subtracting $PM_{2.5}$ values from PM_{10} values. That $PM_{10-2.5}$ causes health effects is not surprising recognizing that a substantial portion of any material in this size fraction deposits in the naso-oro-pharyngeo-laryngeal region and, to a lesser extent, in the tracheobronchial and pulmonary regions. *As improved techniques are developed for quantifying the $PM_{10-2.5}$ fraction, it will be important to conduct additional epidemiological studies with the aim of better characterizing the concentration – response relationships for both the $PM_{10-2.5}$ and $PM_{2.5}$ fractions as well as for specific chemical constituents in the two fractions.*

Some attempts have been made to evaluate association between particular sources of pollution and health outcomes. Such studies offer a direct bridge between pollution sources, ambient air quality and apparent population health effects. One controversial attempt of this kind used air-quality modeling (Chapter 8) to estimate ambient PM concentrations from certain sources, then estimated potential morbidity and mortality in exposed populations (Levy et al., 2000). In another study, Laden et al. (2000) took advantage of the extensive air-monitoring data collected in the Six Cities Study to use factor-analysis methods, as noted in Chapter 7, to identify through chemical tracers different classes of sources. They identified combustion PM

from mobile sources (Pb tracer) and coal-fired power plants (Se tracer) and crustal PM (Si tracer) and related these to mortality. An increased level of crustal $PM_{2.5}$ was not associated with increased mortality. However, they observed for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ from mobile sources a 3.4 percent (Confidence Interval [C.I.] 1.7-5.2 percent) increase in mortality (1.034 times the baseline mortality). For an equivalent increase in $PM_{2.5}$ from coal combustion they observed a 1.1 percent (C.I. 0.3-2.0 percent) increase in daily mortality (1.011 times the baseline mortality).

A key to this study was an extensive data base on the size and chemical composition of PM and the ability to establish linkages to major sources of PM. The Laden et al. (2000) study aggregated the results of the six cities; however, it did not sufficiently examine the nature of sources of PM city by city. In particular, there are ambiguities associated with interpretation of data from one city, Boston, relating to a residual oil combustion source near the monitoring site, and the presence of Se in both coal and residual oil (Grahame and Hidy, 2003). While these studies point to the important future role of integration of source and ambient air characterization with health effects, they also indicate that each of the components needs to be analyzed with the most current detailed information available. Additional studies of this type involving close collaboration between atmospheric scientists and health scientists will help advance the understanding of PM and the role of particular kinds of sources of PM and influencing health. *The improvement of national emission inventories will greatly facilitate the conduct and interpretation of studies attempting to link sources, ambient concentrations, and health effects.*

2.5.2 Chronic Exposures

Acute exposure studies linked to indices of acute morbidity or mortality provide little information about how air pollution affects longer-term morbidity or mortality rates, how much life is shortened, or the potential role of air pollution in the process of inducing chronic disease. Chronic exposure studies as shown schematically in Figure 2.4 evaluate the effects of ambient exposure that persists for long periods of time as well as the cumulative effects of repeated acute exposure episodes. Chronic exposure has been reviewed by Pope and Dockery (1999), CEPA/FPAC (1999), California EPA (2002) and the U.S. EPA (1996a,b; 2001; 2002).

The two most comprehensive cohort-based studies of mortality are the Six Cities Study and the American Cancer Society Cohort. The Six Cities Study involved a 14-16 year follow-up of 8000 adults living in six communities selected to provide a gradient in several indices of air pollution (Ferris et al., 1979; Dockery et al., 1993). Extensive effort was made to characterize ambient air, including the use of TSP, PM_{10}, $PM_{2.5}$ and $SO_4^=$ as PM indicators. The original American Cancer Society (ACS) study (Pope et al., 1995) included 500,000 persons followed from 1982-1989 living in 151 metropolitan areas across the United States with $SO_4^=$ measurements (measured in 1986) and 240,000 individuals living in 50 metropolitan areas with $PM_{2.5}$ measurements (for 1979-1983). Both studies were based on prospective-cohort health and individual risk-factor data and could control for individual differences in age, gender, race, cigarette smoking and other risk factors. Strengths of the Six Cities Study relate to its balanced study design (approximately the same number of subjects in each community) and the planned prospective collection of air-pollution data. A primary limitation was the limited number of subjects (8000) in a limited area (six communities in mid- to northeastern United States). A strength of the ACS study was the larger number of subjects (up to 500,000) from communities across the United States. A limitation was that individuals self-enrolled, and there was a lack of provision for prospective collection of air-pollution data and, thus, the need to rely on air-pollution data collected primarily for regulatory compliance and other purposes.

Key results from the two studies are shown in Table 2.1. In the Six Cities Study, excess mortality associated with $PM_{2.5}$ was 26 percent greater for the most polluted city compared to the least polluted city. In the ACS study, the excess mortality was 15 percent and 17 percent greater for the most polluted compared to the least polluted area based on $SO_4^=$ and $PM_{2.5}$, respectively, as indicators. It is informative to consider the data for cigarette smokers in the two studies. In both studies, smokers, not unexpectedly, showed a substantial increase in all-cause mortality

Table 2.1. Comparison of Mortality Risk Ratios (and 95 percent C.I.) for Smoking and Air Pollution from the Six Cities and ACS Prospective Cohort Studies. (from Pope and Dockery, 1999)

Cause of Death	Current Smoker [a]		Particulate Air Pollution (Most vs least polluted city)		
	Six Cities	ACS	Six Cities ($PM_{2.5}$)	ACS ($PM_{2.5}$)	ACS (SO_4)
All	2.00 (1.51-2.65)	2.07 (1.75-2.43)	1.26 (1.08-1.47)	1.17 (1.09-1.26)	1.15 (1.09-1.22)
Cardiopulmonary	2.30 (1.56-3.41)	2.28 (1.79-2.91)	1.37 (1.11-1.68)	1.31 (1.17-1.46)	1.26 (1.16-1.37)
Lung Cancer	8.00 (2.97-21.6)	9.73 (5.96-15.9)	1.37 (0.81-2.31)	1.03 (0.80-1.33)	1.36 (1.11-1.66)
All Others	1.46 (0.89-2.39)	1.54 (1.19-1.99)	1.01 (0.79-1.30)	1.07 (0.92-1.24)	1.01 (0.92-1.11)

[a] Risk ratios for current cigarette smokers with approximately 25 pack-years (about average at enrollment for both studies) compared with never smokers.

(about 2.0 times that for never smokers) and cardiopulmonary mortality (about 2.30 times that for never smokers) and a very substantial excess risk for lung cancer (more than 8.0 times that of never smokers). The magnitude of the cigarette-smoking effects emphasizes the importance of accurate ascertainment of smoking history and status in all cohort studies so this risk factor can be adequately controlled for in the overall analysis. The Six Cities Study design also had provision for evaluation of respiratory disease and lung function. Other studies have also evaluated these parameters for an association with PM exposure.

Pope and Dockery (1999), based on their review of the literature, have provided a schematic summary of the effect of chronic exposure to $PM_{2.5}$ (Figure 2.6). They have emphasized that these are representative values and are not intended to be definitive point estimates. They elected to use $PM_{2.5}$ as the metric because it was the primary PM measurement in the most recent and most rigorous chronic studies. They noted that in these studies, and especially the mortality studies, $PM_{2.5}$ was more closely associated with the health outcomes than PM_{10} or TSP.

Several points should be kept in mind when comparing the results of the acute (Figure 2.5) versus chronic (Figure 2.6) exposure studies. As already noted, the acute exposure results are expressed per 10 $\mu g/m^3$ of PM_{10} while the chronic exposure results are per 5 $\mu g/m^3$. $PM_{2.5}$ frequently represents about 50 percent of the PM_{10} fraction, an observation that can be kept in mind in comparing the magnitude of the effects in the two figures. In addition, it should be recognized that the chronic effects are not merely a summing of the effects of a series of acute exposure episodes. It should also be kept in mind that the graphs are plots of relative risk, i.e., the percentage change in baseline occurrence associated with increases in ambient PM. In the absence of specific knowledge of the background or baseline rates it is not possible to calculate the absolute level of added risk and make comparisons on that basis.

Both the Six Cities and ACS data sets have been subjected to a new analysis (Krewski et al., 2000). This effort generally confirmed the original analyses and conclusions despite identifying some issues of data quality and completeness in both studies. The Krewski et al. (2000) analysis did find that when the

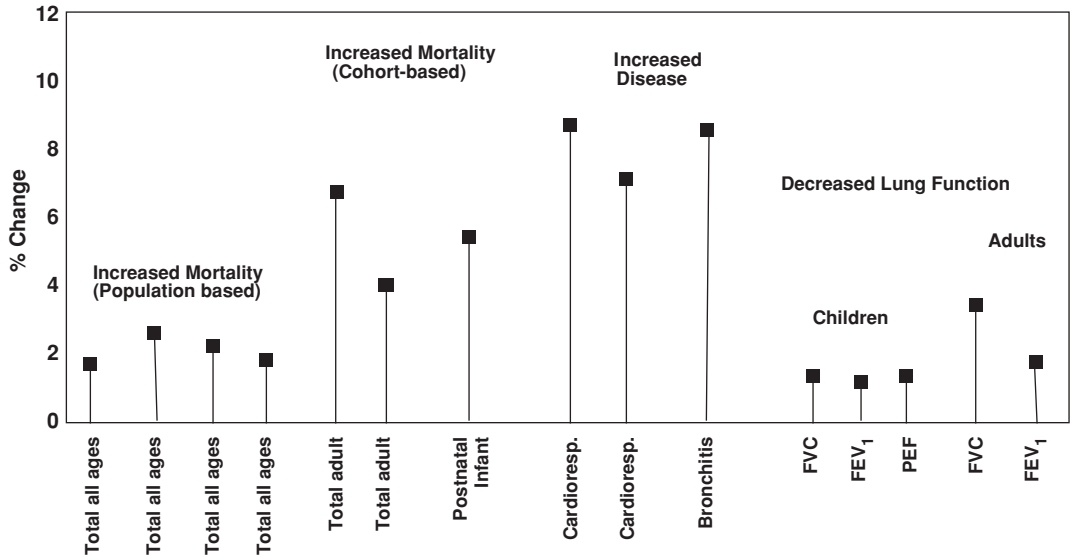

Figure 2.6. Stylized summary of chronic exposure studies, percent change in health endpoint per 5 μg/m^3 change in $PM_{2.5}$. Duplicative values are based on the results from different studies. (Adapted from Pope and Dockery, 1999).

general decline in $PM_{2.5}$ over the observation period was included as a time-dependent variable, the association between $PM_{2.5}$ and all-cause mortality reduced the relative risk to 1.22 (C.I. 1.03-1.45). The importance of independent confirmation of the basic validity of the original findings should not be underestimated in view of the central role of the results of these studies in the establishment of PM standards.

The ACS study has recently been updated using data on vital status and cause of death through December 31, 1998 (Pope et al., 2002). The new analysis also included additional air-monitoring data, most notably $PM_{2.5}$ data for 116 metropolitan areas for 1999-2000 (mean of 14.0 μg/m^3 compared to 21.1 μg/m^3 for 61 areas in 1979-1983), PM_{10} data for 102 areas for 1982-1998 (mean 28.8 μg/m^3) and TSP data for 150 areas for 1982-1998 (mean 56.7 μg/m^3). Each 10 μg/m^3 increase in $PM_{2.5}$ was associated with approximately a 4 percent, 6 percent, and 8 percent increased risk of all-cause, cardiopulmonary and lung-cancer mortality, respectively (1.04, 1.06, and 1.08 times the baseline respectively). Measures of the coarse-particle fraction and TSP were not consistently associated with mortality. As expected, the estimated relative risks for an average current smoker were equal to 2.58, 2.89 and 14.80 times that of a never smoker for all-cause, cardiopulmonary, and lung cancer mortality, respectively, values that were higher than that of the earlier analysis for the aging cohort (Table 2.1).

A critical issue in interpreting the results of both the Six Cities and the ACS data sets is the period of exposure that yielded the health results observed. Air quality has improved substantially over the lifetime of the individuals who have died during the studies. The specific levels of ambient PM and other air pollutants are not known for most of the earlier time the individuals lived. The air-quality data available are only present for relatively recent time periods and these are the data used to develop the denominators in the reported exposure concentration-response coefficients, as for example in Table 2.1. If early life exposures were higher and contributed to the observed PM-associated mortality, then the coefficients based on recent air-quality measurements are biased on the high side by some unknown amount.

A consistent finding from both the acute- and chronic-exposure epidemiological findings is that the PM effects are most substantial in susceptible sub-populations. These include individuals with pre-existing diseases of the respiratory and cardiac systems and children and the elderly.

A key issue in evaluating any hazardous material contained in PM is the nature of the ambient concentration – personal exposure – response relationship. Of particular interest is the threshold (if a threshold indeed exists) and shape of the concentration-response function. A detailed coverage of these topics is beyond the scope of this chapter. In most studies that have identified these issues, clear evidence of a threshold has not been evident and the added level of adverse health outcomes appeared to increase monotonically in a near-linear manner with increasing PM concentration (Pope, 2000; Daniels et al., 2000). It is not known if the evidence on absence of thresholds and linearity drawn from the time-series studies will change when the re-analyses are completed. These are issues being evaluated now.

It has been noted by others critiquing this topic (NRC, 2002) that the statistical power to assess the shape of ambient concentration-response functions is weakest at the lower and upper ends of the observed concentration ranges. Further, since the number of communities studied are limited, the ability to formally test for the absence or existence of a no-effects threshold is limited. In addition, even if thresholds exist, they may not be the same for all endpoints and all regions of the continent. It should be noted that in some large-scale studies such as NMMAP (Samet et al., 2000; Samet et al., 2003), there was variability in the PM_{10} response among the cities with some cities not exhibiting a statistically significant increase in the relative risk for PM_{10} exposure. This may be interpreted as representing differences in PM potency or concentrations or as evidence of a variation in PM_{10} composition or evidence of a practical threshold.

It is appropriate to consider both the strengths and weaknesses of epidemiological studies, as they supply the most critical data for setting health-based standards and developing controlled strategies. A major strength of the epidemiological studies is that they involve people carrying out their normal everyday activities and breathing ambient air both outdoors and within dwellings, work places, and vehicles. The epidemiological investigations are largely based on measurements of ambient air. Such measurements may have a variable degree of coherence with personal exposure, though work to date indicates that ambient measures do suffice in characterizing personal exposure to ambient PM. Public policy and pollution-control strategies typically, and necessarily, focus on ambient air.

Pope and Dockery (1999) have identified four limitations of epidemiological studies. These are worthy of consideration because in some cases coordinated activities between atmospheric scientists and health scientists can serve to minimize the limitations. *First,* they note that epidemiology provides little information about biological mechanisms. While this is true in a broad sense, epidemiological studies using panels of individuals numbering in the tens to perhaps hundreds of people can provide valuable insights into the mechanisms of action of air pollutants. This is especially the case if both detailed measurements of air quality and various health indicators are made.

Second, interpretation of epidemiological studies is frequently handicapped by a lack of understanding of the coherence between ambient measurements and personal exposure. However, most work to date indicates that ambient measures do suffice in characterizing personal exposure to PM. Again, coordinated efforts between atmospheric scientists, exposure-assessment specialists, and health scientists are already improving the level of understanding in this area.

Third, a basic limitation of epidemiological studies is the difficulty of disentangling independent effects or potential interactions between highly correlated risk factors. Many of these issues are beyond the field of atmospheric science, e.g., ascertainment of smoking status, socio-economic status, and educational level. However, many of the factors such as weather and barometric pressure are of concern to the atmospheric-science community. One key issue that does intersect the atmospheric-science community relates to the need for information on co-pollutants such as particulates and gaseous precursors, (e.g., ozone, SO_2, NO_x, CO) and other measures yet to be identified. Atmospheric scientists are knowledgeable of the dynamic nature of the atmosphere and its constituents. *The insights of atmospheric scientists will be helpful in planning and conducting the sophisticated analyses of air monitoring and health data necessary to identify*

small signals of the biological effects of pollution amongst the many other causal factors for the same diseases. Comprehensive plans for both data collection and analysis are needed to maximize the return on substantial investments.

Fourth, Pope and Dockery (1999) noted that a basic limitation of epidemiological studies is the inability to fully explore the relative health impacts of various constituents of particulate air pollution. This is an area in which atmospheric scientists can have substantial impact by working with health scientists. In a coordinated multi-disciplinary effort they can identify key atmospheric constituents, for example, 1) specific chemical constituents such as the carbonaceous content or specific classes of chemicals, i.e., organics or metals by particle size fraction, or 2) physical parameters such as surface area or particle number that warrant detailed study. This information would provide guidance for adopting sampling strategies that could yield measurements of air constituents on both spatial and temporal scales matched to health data. As is readily apparent from consideration of the relative risks attributed to the various size-based PM indicators, there is a need in cross-sectional cohort investigations to study simultaneously many communities and populations measured in the tens to hundreds of thousands of individuals over extended periods of time.

The air-quality measurement needs in epidemiological studies are quite different than those of a typical "atmospheric science" field campaign conducted for short periods of time. However, future epidemiological studies can build on the experience gained from short-term intense campaigns with emphasis given in the larger- and long-term epidemiological studies to obtaining air-monitoring data at multiple sites in a highly efficient and effective manner. The nature of future studies can be anticipated by considering two past landmark studies: the ACS study and the NMMAPS.

One landmark study is the ACS study (Pope et al., 2002). In the most recent report, analyses were reported for up to 500,000 individuals for which mortality could be ascertained for a 16-year period (1982-1998) and fine-particle data were available using $PM_{2.5}$ for 1979-1983 and 1999-2000 and $SO_4^=$ data were available for 1980-1981 and 1990. The study would have been strengthened if fine-particle measurements had been available for all 16 years and if additional speciation data had been available.

A second landmark study is the NMMAPS time-series study (Samet et al., 2000; Samet et al., 2003) of 90 cities for the period 1987 to 1994 using PM_{10} measurements. The EPA Staff Paper (U.S. EPA, 2003b) analyzed the findings reported for the NMMAPS and found an association between the study size and stability of the risk coefficients. It appeared that in excess of 10,000 events (deaths per day times the number of monitored days) were necessary to obtain stable estimates of risk.

While any given epidemiological study may be addressing hypotheses related to PM, it is important to recognize that people are breathing "one atmosphere," which includes all particulate and gaseous constituents. Thus, it is of major importance to have reliable data on the gaseous pollutants as well as on PM. *Most of all, it is important to recognize that advancing scientific knowledge of the health effects of air pollution, and especially the role of PM and specific constituents, will require moving beyond dependence on "regulatory-compliance" based air-monitoring data with its emphasis on currently regulated pollutant indicators.*

2.6 INTERVENTION STUDIES

An accountability framework that will enable measurement of progress toward the goal of protecting public health is needed. Unfortunately, risk-management actions are often difficult to assess for their utility in actually reducing the health impact of interest. For most environmental actions, reduction in the pollutant of interest is often as far as one can go in discerning the benefit of control actions when direct measurement of changes in the adverse effects in the population is not possible. In the absence of direct evidence the benefits must be extrapolated from knowledge of changes in the concentration of PM and other pollutants and knowledge of the potency of the pollutant indicators gained from other studies. In the United States, a Committee of the National Research Council has recently provided a useful critique of methods used in estimating the

public health benefits of air-pollution regulations (NRC, 2002).

However, for some PM air-pollution situations it has been possible to directly measure the health benefits of specific risk-management actions. Administrative databases (such as mortality and hospital admission records) have been used to examine the influence of day-to-day (and longer) increases in air pollution. This raises the possibility of using similar techniques to examine declines of PM indicators and any concomitant changes in health status for several endpoints.

Precipitous declines in air pollution, usually elicited by regulatory initiatives, offer an opportunity to observe changes in underlying risk at rates much higher than one would normally observe in PM epidemiological studies. Several such regulatory mechanisms have been instituted with sufficient subsequent time elapsed to examine the influence of resultant air-pollution changes on mortality and other health effects. Two of the most notable cases are the banning of coal use in Dublin, Ireland in 1990, and the switch to low-sulfur fuels in Hong Kong in the same year.

Clancy et al. (2002) examined the periods leading up to and following the ban on coal sales in Dublin, and compared non-trauma, cardiovascular, and respiratory death rates for the two periods. From an air-quality impact perspective, this intervention resulted in a decline of Black Smoke by approximately 50 percent, while SO_2 declined by about 30 percent. For all three measures of mortality, statistically significant declines in the expected death rate occurred.

Several researchers have examined aspects of health indicator response to a reduction of sulfur content of fuels (gasoline and fuel oil) in 1990 in Hong Kong. Sulfur dioxide and PM measures all declined significantly in the period following the application of this regulation. Wong et al. (1998, 1999) examined respiratory symptoms in women and children in high- and low-pollution neighborhoods, finding statistically significant declines in the endpoints measured. Similarly, Hedley et al. (2002) used this air-quality scenario to examine the impact of the sulfur reduction on mortality rates for the following five-year period. The authors stratified deaths by age and specific cause of death, finding statistically significant declines in most categories.

One of the earliest studies of the influence of an "intervention" on air-quality and health responses was the study of Pope (1989) on the impact of a closure of a steel mill. Pope demonstrated that closure of the steel mill directly impacted air quality and that there were associated changes in health indices. Laboratory studies using particulate matter collected on filters demonstrated a coherence between laboratory findings of pulmonary toxicity and epidemiological observations (Dye et al., 2001). The laboratory studies pointed to a role for metal compounds mediating the toxic effects.

Another model of utility to investigate potential health benefits is exemplified in the work of Avol et al. (2001) in the twelve-community Children's Health Study. As part of this larger study, the investigators examined the impact of moving to communities of higher or lower air pollution. As a group, subjects who had moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with a higher PM_{10} showed decreased growth in lung function.

While all the above studies may have limitations of one kind or another, the design and results indicate that observing the impact of air-quality interventions is both possible and useful. Whether the result of regulatory intervention or a physical change in location of individuals, these studies were able to observe health benefits using available techniques. It should be possible to apply such techniques to other situations of this type, as well as to air-quality regimes where decline is significant but more gradual. Expanding these types of studies to a wider range of interventions and resultant air-quality impacts would serve to broaden our understanding of the population response to air pollution as well as provide a retrospective evaluation of proposed regulatory and other actions.

However, the difficulty of conducting such studies should not be underestimated as is apparent from consideration of the results of NMMAPS. For the 88 cities in the contiguous United States, statistically significant effects of PM_{10} were observed in some

individual cities but not in other cities. In about a third of the cities the apparent added risk from ambient PM_{10} was either negative or zero. This and other evidence of inter-city and inter-regional differences needs to be carefully investigated. The magnitude of the pooled estimate of 0.27 percent increase (1.0027 times the baseline mortality) per 10 $\mu g/m^3$ in PM_{10} illustrates the statistical challenge of demonstrating the effects of changes in PM.

2.7 TOXICOLOGICAL EVIDENCE

Extensive research has been initiated, especially during the last decade, to provide information on the biological mechanisms of action of PM and specific constituents. This research has been directed toward two key questions: 1) What are the potential mechanisms by which PM causes health effects? and 2) What specific component or components in ambient PM cause health effects? Information on the first question is important in providing support (or lack of support) for biological plausibility to explain the statistical associations observed in epidemiological studies. Information on the second question also addresses the causality issue (Textbox 2.4) and, in addition, may potentially provide valuable guidance for the development of pollution-control strategies if specific PM constituents or their precursors and their sources can be targeted.

To help guide research on the mechanisms linking ambient PM exposure and adverse health outcomes, Mauderly et al. (1998) compiled a list of hypotheses that have been advanced by multiple investigators (Textbox 2.5). All of these hypotheses have been addressed to varying degrees by recent research, with the greatest use made of animal studies with controlled exposure to various agents. Of necessity, many of these studies have used short-duration exposures and relatively high concentrations of the particular agent in an attempt to identify effects and mechanisms of action. In addition to the animal studies, a limited number of studies have been initiated with small panels of human subjects exposed under controlled conditions to defined test materials such as carbon black. In some cases, subjects have been exposed to test aerosols of concentrated ambient PM.

The research performed to date is best viewed as being of an exploratory hypothesis-generating nature, yielding valuable background information for future systematic investigations. Some of the key findings have been reviewed by MacNee and Donaldson (1999); Frampton et al. (2000); Utell et al. (2002); NRC (2003); Lippmann et al. (2003); Green and Armstrong (2003); and Walberg (2003). The results to date of the laboratory-animal and human studies have not been able to unequivocally determine the particle characteristics or toxicological mechanisms by which ambient PM affects the respiratory and cardiac systems. Thus, all of the suggested hypotheses in Textbox 2.5 remain viable and are deserving of additional research to test their validity. The studies conducted to date have been very useful in identifying a series of inter-related pathways by which inhaled PM can impact the occurrence of cardiac and respiratory effects. It is quite likely that some of the pathways may be affected by particles of a particular size and/or chemical composition while other pathways may not be affected by those particles but be affected by particles of other sizes or with other chemical constituents. With mechanistic pathways identified, it will be possible to plan and conduct studies using aerosols with particles that vary in size and composition to obtain direct comparisons of the relative effects of the different PM components. *The conduct of comparative studies will require collaboration between aerosol scientists and health scientists to develop appropriate techniques for the production, characterization and delivery of the specialized test aerosols with known particle-size distributions and size-resolved chemical composition.*

Laboratory experimentation with either animals or human subjects exposed under controlled conditions with PM concentrations typically higher than found in the ambient environment, can aid in establishing the plausibility of the various hypotheses. However, ultimately it will be desirable to obtain human data from epidemiological investigations that monitor the putative agents and compare health effects with the various PM indicators over ranges of concentrations typically found in the environment. For specific PM constituents, the test of the hypotheses will be similar to the situation for PM_{10} versus $PM_{2.5}$ – i.e., testing whether the putative toxicant has a greater potency (effect per unit mass) than $PM_{2.5}$ or PM_{10}.

Textbox 2.5. Hypothetical Interaction Between PM and Human Physiological or Toxic Responses

Hypothesis of PM Characteristic and Human Health Response	Rationale for Hypothesis
Particle Mass Concentration – Non-chemically specific mass cardiopulmonary loading response associated with a complex chemical mixture of wide range of particle size.	Based on evidence derived from a variety of epidemiological studies in North America and elsewhere. PM mass is contributed largely by particles over 0.1 μm.
Particle Size/Surface Area —Response to fine particles with major surface area for adsorption of chemical species and subsequent desorption in lower lungs.	The surface area per unit particle size has a multi-modal distribution analogous to the mass distribution. Since particles are non-spherical, methods need to be adopted that can measure at least total surface area directly noting that the actual surface for adsorption may vary with condensed material. Surface area is contributed to largely by particles of 0.1 to 0.3 μm.
Ultrafine PM – Animal experiments suggest that some particles less than 0.1 μm diameter may have a strong physiological effect on the respiratory system.	Ultrafine particles in the air are generally believed to be highly transient in character. They may derive directly from source emissions or from atmospheric chemical reactions. Estimating human exposure is problematic. Ultrafine particles (of the order of 0.01 μm) dominate particle number count.
Metals or Metal Compounds– Certain metals like V, Cu, Fe, Zn, and Ni have cytotoxic or inflammatory properties. These may catalyze biochemical reactions that result in an adverse respiratory response.	The human reaction to combined metal and acidic components such as H_2SO_4 has been hypothesized to be potentially important for PM since the 1960s, but remains unconfirmed.
Acids— Acidic particles have been shown to have toxic properties in some animal studies based on hydrogen ion delivered to respiratory surfaces.	Linkages to acid anions such as $SO_4^=$ and NO_3^- have not been unequivocally demonstrated in epidemiological or laboratory studies on humans. Organic acids may be a factor that requires sustained investigation.
Organic Compounds – There are a large number of organic compounds found in PM, some of which are known to be mutagenic or carcinogenic.	The carbonaceous fraction is recognized to be the least well characterized of the components of PM. The organic material found in the air ranges from paraffinic or olefinic compounds of varying molecular weight to highly oxygenated or nitrated material. Only 10 to 20 percent of OC is attributed to specific organic compounds with existing methods.
Biogenic Particles – A variety of particles originate from biogenic sources, including spores, fungi, bacteria and viruses.	The phrase "biogenic particles" refers to those formed biogenically, as opposed to those arising from reactions of organic vapors of biogenic origin. The physiological or toxic interactions of individual biogenic particles and pollutant material are unknown.
Sulfate and Nitrate Salts– These compounds are believed to be mainly ammonium salts in PM.	The direct linkage between sulfate and nitrate salts and adverse human health effects remains uncertain. Sulfate concentrations and hospital admissions are clearly linked in S. Ontario.
Peroxides– The presence of peroxides in particles and their toxic properties provide a hypothetical pathway to health effects.	The presence of highly oxidative species related to photochemical processes is well known in atmospheric chemistry. Their significance in producing human-health responses has not been extensively investigated.
Soot – Soot particles (or elemental carbon) potentially can stimulate a toxic response in themselves or carry adsorbed material that can initiate a response.	Soot in the air can be modified significantly by inorganic gas, water or organic vapor adsorption. Different extents of their interactions may have different effects on both.
Co-pollutant Interactions– Some epidemiological and/or laboratory exposure studies have suggested that a synergistic response may take place when PM and gases such as SO_2, NO_2, O_3 or CO are present.	In most places air contains multiple pollutants that vary in concentration over time and space, and vary in their potency for producing adverse health effects. Epidemiological studies show a distribution of risk among gaseous and particle aspects of the air pollution mix. The lack of clarify and consistency may be due to the variability of copollutant interactions.

(After Mauderly et al., 1998)

Collaboration is needed between health scientists and atmospheric scientists in designing and conducting epidemiological studies and associated long-term monitoring programs for key atmospheric constituents that are hypothesized to be associated with adverse health effects. The size of the populations studied and the duration of the studies can be informed by considering the findings in recent epidemiological studies as was discussed earlier. Past experience has clearly demonstrated the value of doing studies in multiple cities and making observations on very large populations over extended periods of time.

2.8 POLICY-RELEVANT FINDINGS AND FUTURE OPPORTUNITIES

There is a considerable and growing body of evidence showing an association between adverse health effects, especially of the cardiac and respiratory systems, and exposure to elevated ambient levels of PM.

The total personal PM exposure of individuals, which includes their ambient (outdoor) and indoor environments, is related to the PM content of ambient air. The ambient-air concentrations of PM, and other air pollutants, have been extensively studied as potentially controllable variables that influence total personal exposure and, thus, human health.

Epidemiological studies of large populations have shown statistically significant increases in various indices of adverse health outcomes over the background incidence and increased levels of ambient PM. The adverse health outcomes observed in these studies are commonly (though not exclusively) cardiac and respiratory in nature. Such diseases are also very common in the general population and even a small percentage increase in background incidence translates into a significant number of additional cases.

Increases in adverse health outcomes have been observed for both short- and long-term exposures to PM. The increases in adverse health outcomes have been observed for a range of ambient particulate matter indicators including TSP, PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$. A higher potency has typically been observed for $PM_{2.5}$ compared to other PM indicators consistent with the concept that smaller particles penetrate further down the respiratory tract. Nonetheless, the epidemiological literature does demonstrate some level of association with the larger particles, which deposit more readily in the upper respiratory tract.

Certain population subgroups appear to have heightened susceptibility to PM, such as those with pre-existing cardiac and respiratory disease (seen frequently in smokers), asthmatics, and the elderly. Increases in adverse health effects appear to occur without a threshold in the ambient concentration-health response relationships and appear to increase in a near-linear fashion from the baseline incidence of health effects with increasing PM concentrations. Some evidence suggests that there may be regional differences in the potency of various PM indicators, possibly a reflection of regional differences in the composition of PM. Additionally, some evidence exists linking increases in adverse health outcomes and specific sources of PM.

There is also some evidence of improved health associated with reductions in PM exposure. Such studies have been both opportunistic in nature, taking advantage of significant reductions in PM pollution over short time periods to examine mortality and other adverse health endpoints, or have been designed to follow groups as their exposure to air pollution has changed. These studies, while requiring careful interpretation, offer the opportunity to examine the benefits of specific air-quality interventions, as well as the opportunity to compare the benefits of specific changes in the air-pollution mix. Pursuit of these situations in a strategic and proactive manner offers the potential for gaining insights into the benefits of control activities.

A number of hypotheses have been advanced to explain how various chemical and physical parameters of PM may interact with the body to provide mechanistic explanations for the various health outcomes. These hypotheses are being evaluated in toxicological studies using laboratory animals and controlled exposure of human subjects. However, to date none of these hypotheses have been proven or eliminated from consideration. Continuing tests of these hypotheses will require collaboration

between atmospheric scientists and health scientists in order to identify and characterize the hypothesized PM constituent or parameters, the PM indicators usually monitored, and other pollutants, and to relate these to health effects in multiple communities over decades. Such collaboration will enhance efforts in the fields of toxicology, clinical effects, and in both short-term and long-term epidemiological investigations. *Further progress in understanding health effects of current levels of ambient PM and various constituents depends on achieving a high level of collaboration between health scientists and atmospheric scientists, to obtain detailed characterization of PM and copollutants in multiple communities over decades to match with health data*.

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