

**Health Effects Associated with Exposure to
Ambient Air Pollution**

Draft Background Paper for Discussion

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1.0 Introduction

The NERAM Colloquium Series on Health and Air Quality (2001-2006) was initiated to provide an opportunity for scientists, regulators, air quality managers, public health organizations, and representatives of the business community to examine the current state of science underlying the development of air quality objectives, to identify gaps and uncertainties in the science, and to make recommendations for research and policy directions to support air quality management strategies.

The objective of the 2003 NERAM/AirNet Conference on Strategies for Clean Air and Health, the third meeting in the Colloquium Series, is to provide an integrated review of best available information in four main areas supporting policy development: i) health effects of air pollution ii) air quality modeling iii) policy tools and inputs and iv) policy options. Background papers on each of the four topics are designed to provide delegates from a variety of disciplines with a common information base for consideration during the conference deliberations. This paper provides an overview of the current state of science addressing the impacts of air pollution on human health.

In January 1998, the U.S. National Research Committee (NRC) on Research Priorities for Airborne Particulate Matter was convened at the request of Congress following the promulgation of new National Ambient Air Quality Standards (NAAQS) for PM_{2.5}. Realizing the potentially vast implications of these standards and unaddressed uncertainties in the scientific evidence supporting the standards, Congress requested the committee on the premise that new research evidence would lead to greater confidence in the basis for the new particulate matter NAAQS and provide guidance on emission control strategies that would most protect public health. The Committee’s first report, *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio* (NRC, 1998) set out a conceptual framework for addressing the health effects of airborne particulate matter (Figure 1) and identified the ten most critical research needs linked to key policy-related scientific uncertainties.

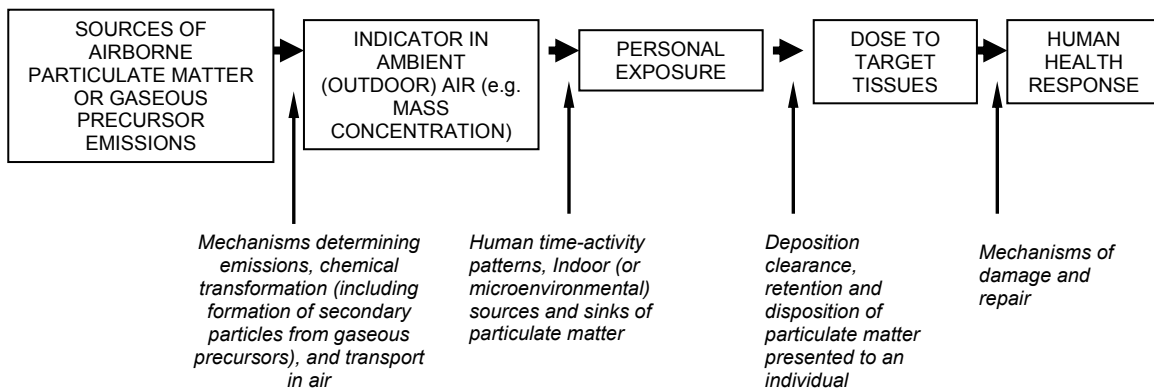


Figure 1: NRC 5 Stage Framework for Integrating Particulate Matter Research (NRC, 1998)

The 5 main components of the framework are as follows (NRC, 1998):

Sources—Outdoor sources of particulate matter (or gaseous precursors) that can adversely affect public health include motor vehicles; fossil-fueled electric power plants; industrial facilities; agricultural practices, consumer products; other human sources; and natural processes, such as forest fires or wind erosion. This element of the framework includes factors determining the release characteristics, dispersal, and transport of emissions that lead to atmospheric contamination.

Ambient Indicators—The mass concentration or other measures of indicators such as PM₁₀ or PM_{2.5} in ambient air. Data for the indicators are collected at fixed outdoor monitoring sites to determine regulatory attainment of the NAAQS, or in some health studies, to represent particulate-matter exposure in a given area.

Exposure—The concentration of particulate-matter indicator actually coming into contact with an individual over a specified period. Actual exposure to humans is determined by ambient air concentrations, contributions from indoor sources, and human time-activity patterns. The relevant point of contact is the breathing zone of the individual.

Dose—The amount and specific types of toxicants deposited in various parts of the respiratory tract and other sites within the body over a specified period. The dose of specific toxicants received by an individual is affected by factors such as retention and clearance of PM (or specific constituents of PM) from target tissues in the lung and respiratory tract. The dose delivered to specific tissues might result in injury and altered performance of repair mechanisms.

Response—Changes in specific human health parameters attributable to tissue doses resulting from inhaled particulate matter. These biological responses can be expressed in terms of molecular or cellular changes in the lung or other tissues, overall tissue damage, or ultimately, clinical signs of toxicity, such as illness or premature death.

Applying the Framework and criteria such as scientific value, value for decisionmaking, and feasibility and timing, the Committee identified the following 10 highest priority research topics (not in order of priority or timing).

Research Topic 1. Outdoor Measures Versus Actual Human Exposures

What are the quantitative relationships between concentrations of particulate matter and gaseous copollutants measured at stationary outdoor air-monitoring sites and the contributions of these concentrations to actual personal exposures, especially for subpopulations and individuals?

Research Topic 2. Exposures of Susceptible Subpopulations to Toxic Particulate-Matter Components

What are the exposures to biologically important constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Research Topic 3. Characterization of Emission Sources

What are the size distribution, chemical composition, and mass-emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary particle formation through atmospheric chemical reactions?

Research Topic 4. Air-Quality Model Development and Testing

What are the linkages between emissions sources and ambient concentrations of the biologically important components of particulate matter?

Research Topic 5. Assessment of Hazardous Particulate Matter Components

What is the role of physicochemical characteristics of particulate matter in eliciting health effects?

Research Topic 6. Dosimetry: Deposition and Fate of Particles in the Respiratory Tract

What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Research Topic 7. Combined Effects of Particulate Matter and Gaseous Co-Pollutants (Toxicological and Epidemiological Studies)

How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?

Research Topic 8. Susceptible Subpopulations

What subpopulations are at increased risk of adverse health outcomes from particulate matter?

Research Topic 9. Mechanisms of Injury

What are the underlying mechanisms (local pulmonary and systemic) that can explain the epidemiological findings of mortality/morbidity associated with exposure to ambient particulate matter?

Research Topic 10. Analysis and Measurement

To what extent does the choice of statistical methods in the analysis of data from epidemiological studies influence estimates of health risks from exposures to particulate matter? Can existing methods be improved? What is the effect of measurement error and misclassification on estimates of the association between air pollution and health?

The NRC study serves as a comprehensive framework for reviewing the current state of scientific evidence underlying the linkage between exposure to air pollution and human health effects and for examining progress towards addressing critical research needs for air quality policy development. Two reports have subsequently been released (National Research Council, 1999; National Research Council, 2001). These reports provided some redirection of the initial research agenda, expanding the work to be done on emissions characterization and modeling, and also charting the initial progress. The Committee is currently finalizing its fourth and final report, gauging progress on the research agenda.

Chapter 2 will discuss the findings of North American and European studies according to the NRC priority research topics. Chapter 3 will synthesize the findings according to key questions underlying air quality policy decisions. Chapter 4 will conclude the report with a discussion of the implications of the findings for the development future air quality management strategies.

2.0 Evidence of Adverse Health Effects: Addressing NRC Research Priorities

Current concern for airborne particulate matter and health dates to the early 1990s when a series of papers was published linking daily mortality counts to levels of particulate matter on the same or recent days. These findings were unexpected, as mortality was considered to be a crude and insensitive outcome for assessing the health effects of air pollution, and levels of particulate matter had sharply declined from several decades earlier, when excess mortality had been clearly documented at times of high air pollution. Concern was heightened by the 1993 report from the Harvard Six Cities study (Dockery et al. 1993) which associated longer-term exposure to air pollution with mortality, implying that the findings of the daily time-series studies did not reflect only a brief life shortening (i.e., “harvesting” or “mortality displacement”). The findings of the Harvard study were replicated in a 1995 report from the American Cancer Society’s nationwide study involving about one-half million Americans (Pope et al. 1995).

Initially, there was substantial skepticism around these reports and alternative explanations to a causal association of particulate matter with adverse health effects were raised including methodologic problems in the study designs and analytical methods and uncontrolled confounding by the effects of other factors, particularly weather. As particulate matter always exists as one component of a complex pollution mixture, the certainty with which effects could be attributed to particulate matter, versus other mixture components or to the mixture itself, was also questioned. Researchers were also not

confident about the mechanisms that might underlie the effects observed at contemporary ambient levels of particulate matter.

Consequently, substantial research was initiated about a decade ago to reduce these critical uncertainties and to strengthen the evidence base for control of the health effects of particulate matter. A research agenda for this purpose was set out in early 1998 by the Committee on Research Priorities for Airborne Particulate Matter of the US National Research Council (NRC, 1998). That Committee offered a systematic framework for identifying key uncertainties and for targeting research to reduce these uncertainties. In a multi-year research portfolio, the Committee set out ten topics that were to be addressed in a sequenced fashion. As this manuscript was prepared, the Committee's fourth report, coming approximately five years after its first was yet to be published. That report will provide a review of research over the five years from 1998, the time of the first report, to 2003, when the last report was prepared.

In this document, we offer a general review of progress in the decade since the early 1990s, drawing on general knowledge of this area as well as several key synthesis documents (the US Environmental Protection Agency's draft Criteria document and Staff Paper; reviews prepared by WHO Euro, and the peer-reviewed literature). We note that there is now a greater consensus as to the role of airborne particles in causing adverse health effects; in fact, debate has shifted away from whether there is an effect of particulate matter to questions as to aspects of particles that determine toxicity and to the sources of those particles that are most injurious to health.

In several areas, substantial progress has been made over the last decade. Substantial research has been carried out on personal exposures to particulate matter and the contribution of particles from outdoor sources to total personal exposure, an area of investigation corresponding to Topic 1 of the National Research Council's Committee. Studies have been carried out in the United States and in Europe that have involved personal monitoring of various population groups of interest in order to characterize the contribution of outdoor particles to personal exposure, and particularly to variation in person exposure over time. This research was initiated, in part, to better understand the implications of using ambient monitors for population-level studies of particles and health, and also to considering exposure-based control strategies. The monitored populations have included children, healthy adults, and adults in groups within the population considered to be at risk for health effect of air pollution, including persons with chronic obstructive coronary heart disease and pulmonary heart disease. These studies have documented that particles in outdoor air penetrate indoors and make substantial contributions to day-to-day variation in total personal exposure, a critical finding with regard to interpreting the time-series studies. This work has not yet addressed personal exposures to particles in relationship to specific characteristics of the particles, based on size or chemistry; most have involved monitoring for PM_{2.5}.

Progress has been made in other areas, although without the relatively definitive overall gains that have been made for the topic of personal exposure. Work to advance understanding of mechanisms of toxicity continues to provide multiple leads, perhaps

unified by the finding that particles incite inflammation and release of oxygen radicals with the potential for injury at sites of deposition. Particles also activate inflammatory cascades that may have local and systemic actions. Mechanisms by which inhaled particles could affect organs distant from the site of deposition are of particular interest, given the many studies now showing adverse effects of particles on the heart.

With regard to public health protection, identifying susceptible groups within the overall population is of particular interest. These groups may be susceptible on the basis of an underlying condition, particularly chronic heart and lung diseases, and vulnerable to exacerbation of these diseases. If these groups are to be protected, we need to characterize the exposure-response relationships for these adverse effects. Some information on dose-response relationships has been obtained by “clinical studies” (controlled exposures of human volunteers) to concentrated ambient particles (CAPS). The results have been variable across the centers where this work has been done, with some but not all studies showing evidence of adverse effects.

New methods have also been developed for research on particles, both for toxicologic and epidemiologic studies. The particle concentrator offers a useful tool for carrying out both animal and human studies. A principal limitation is that particles can be concentrated only in a single location; some groups are using portable concentrators so that studies can be carried out in locales of particular interest. Epidemiological approaches have also evolved. The single-city time series study of a morbidity or mortality indicator has largely been replaced by multi-city studies, which are more informative because they gain information from both within-city temporal comparisons and across-city geographic comparisons. Examples of these approaches include the Air Pollution and Health: A European Approach (APHEA) studies and the National Morbidity Mortality and Air Pollution Study (NMMAPS) carried out in the United States. Additionally, the methodologic issues of “harvesting” and measurement error have been considered and their implications for interpreting the time-series studies addressed to some extent. Several analytic approaches have been described that provide some discrimination between harvesting and an effect of air pollution on the short to medium-term (one to two months). Several new cohort studies are in progress that are intended as efficient approaches to further characterizing the long-term effects of air pollution on mortality. For example, the group at Johns Hopkins is using the U.S. Medicare system to address short-and long-term effects of air pollution.

Over the last several years, new methodologic issues were raised in regard to the time-series approach. A problem was found in the application of the GAM function in S-plus to analyses of air pollution time-series data. The convergence criteria that were set by default were insufficiently strict for air pollution data and incomplete convergence introduced an upward bias in the results of a number of critical studies. Reanalyses have now been carried out for some of the most significant of these studies, including APHEA and NMMAPS. Overall, the risk estimates tended to decline with reanalysis. Additional, more subtle methodologic issues were also described related to the adequacy of control for confounding and the sensitivity of findings to the particular statistical model chosen.

While these issues have minor quantitative implications, they have little consequence for interpretation of the general body of time-series studies of air pollution and health.

Some other critical topics on the research agenda for particulate matter and health remain largely unaddressed. The characteristics of particles that may figure in their toxicity have yet to be adequately characterized. Research in this area is complicated by the diversity of sources of particles and the resulting spectrum of characteristics. Additionally, different characteristics may be relevant to different health outcomes. The matrix defined by particle characteristics and health outcomes has yet to be satisfactorily explored. There has also been only limited research on combined effects of particles with other pollutants.

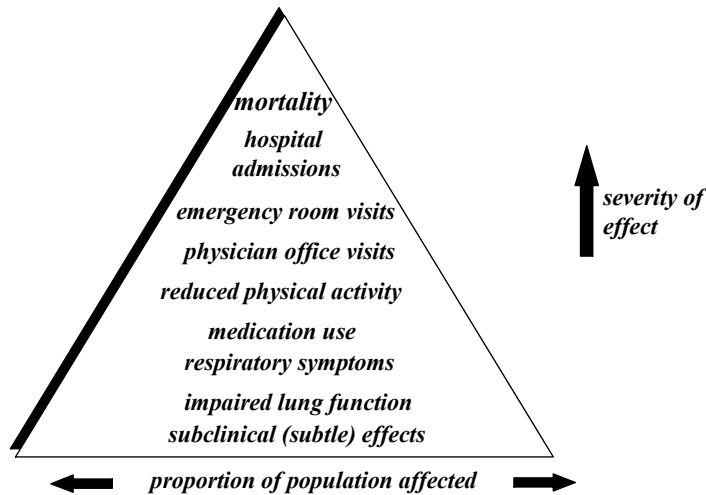
3.0 Population Health Effects of Particulate Air Pollution

The World Health Organization (2002) has identified ambient air pollution as a high priority in its Global Burden of Disease initiative, and estimated that air pollution is responsible for 1.4% of all death (Cohen et al., 2003). In this section, we examine the population health impacts of air pollution, including both mortality and morbidity. Characterizing the population health risks of ambient air pollution is critical to the development of risk management policies and strategies as discussed in section 4. Our discussion focuses on the following questions.

3.1 What are the Adverse Health Effects of Particulate Air Pollution?

Epidemiological and toxicological studies have demonstrated that particulate air pollution is associated with a range of adverse health outcomes, ranging from mortality to subclinical respiratory symptoms (Figure 2).

Figure 2. Air Pollution Health Effects Pyramid



Associations between mortality and particulate air pollution have established primarily on the basis time series and cohort studies. Time series studies are used to correlate daily fluctuations in ambient air pollution levels with daily mortality rates, and have consistently demonstrated increased mortality on or shortly following days with increased ambient particulate levels in urban centres worldwide. The most convincing data of this type derives from combined analyses of data from multiple urban areas, including 90 of the largest U.S. cities (Dominici et al., 2003), as well as 25 European (Katsouyanni et al., 2003), and 10 Canadian (Burnett et al., 2001) cities. An ongoing analysis of data from the U.S., Europe, and Canada (Katsouyanni et al., 2002) will provide the most complete compilation and assessment of time series data on particulate air pollution and mortality to date.

Because air pollution is a complex mixture of particulate and other co-pollutants, it is important to consider the relative contributions of all pollutants to pollution-related mortality. Burnett et al. (2001a) found gaseous co-pollutants to be associated with increased mortality, with ozone, carbon dioxide, sulfur dioxide, and nitrogen dioxide all accounting for an appreciable proportion of excess mortality associated with short-term exposure to ambient air pollutants. Stieb et al. (2002) conducted a meta-analysis of published excess mortality rate ratios from time series studies, and found significant increases in risk for both particulate and gaseous co-pollutants.

Urban air also contains a number of toxic substances such as benzene (Krewski et al., 2000) that require consideration. Burnett et al. (2001) have shown that trace elements including zinc, nickel and iron are associated with increased mortality in time series studies based on data from 10 Canadian cities. Although air toxics are not the primary focus of this article, the National Research Council (2001) has developed methodologies for assessing the risk of short-term exposures to highly hazardous substances for periods ranging from 10 minutes to 8 hours, and has developed exposure guidelines for three levels of adverse effect: irritation, disabling effects, and lethality (National Research Council, 2000, 2002, 2003).

The analysis of time series data of this type requires careful consideration of seasonal trends in the data, as well as adjustment for important covariates such as climate and gaseous co-pollutants (Burnett & Krewski, 1995). Although Dominici et al. (2003) and Ramsay et al. (2003a) have recently shown that time series analysis can lead to overestimation of risk as well as overstatement of the precision of risk estimates due to convergence problems in the generalized additive model, correction of this problem using more stringent convergence criteria confirms that mortality is associated with short-term fluctuations in particulate air pollution (HEI, 2003a). Case-crossover analyses can also be applied to time series data (Lin et al., 2003a). Although these analyses avoid the need to consider secular trends in the data, case-crossover and time series generally lead to similar conclusions (Fung et al., 2003b).

Although time series analyses provide important information about the effects of short term exposure on mortality, they are unable to identify effects with a lag period longer than about two weeks (Dominici et al., 2000). The effects of long-term exposure to

particulate air pollution can be identified through cohort mortality studies Dockery et al. (1995) reported an increase in overall and cardiorespiratory mortality in six cities in the midwest and northeast U.S. in relation to PM_{2.5} concentrations monitored from the mid 1970s through to 1989. Pope et al. (1995) reported similar findings by following a group of over 550,000 subjects established by the American Cancer Society in over 150 large U.S. cities from 1982 to 1989. Further follow-up of this cohort through to 1998 confirmed the original findings, and provided evidence of an increased risk of lung cancer mortality due to PM_{2.5} (Pope et al., 2002). Additional analyses of this cohort, with follow-up through to 2000, are underway (Krewski et al., 2003b). Abbey et al. (1999) are continuing the Adventist Smog and Health (ASHMOG) cohort study of 6,338 nonsmoking California Seventh-day Adventists to further assess the relationship between mortality and long term exposure to particles and other air pollutants.

These cohort mortality studies have demonstrated consistent associations between long-term exposure to particulate matter and mortality, and have played a pivotal role in the establishment of quality objectives for PM_{2.5} in the U.S. (Greenbaum et al., 2001). Krewski et al. (2000, 2003) showed that long-term exposure to sulfur dioxide was also associated with mortality in their re-analysis of the ACS cohort with follow-up through to 1989, originally examined by Pope et al. (1995). Although SO₂ demonstrated more robust associations with mortality than did PM_{2.5} in this comprehensive re-analysis, a plausible biological pathway by which SO₂ might lead to increased mortality has not been identified (Dockery et al., 2003). In contrast, PM_{2.5} is now thought to lead to increased cardiovascular mortality as a consequence of accelerated atherosclerosis (Pope et al., 2003), possibly mediated by the induction of endothelins and cytokines.

The time series and cohort studies conducted to date indicate that both short-term and long-term exposures to particulate matter can lead to increased mortality in the general population. The possibility that short-term exposures may primarily affect frail individuals with pre-existing co-morbidities has been investigated by Zeger et al. (1999). This initial work and subsequent investigations by Dominici et al. (2000), Zanobetti et al. (2000), Schwartz (2000), and Fung et al. (2003a) indicate that the so-called harvesting hypothesis cannot fully explain all of the excess mortality associated with short-term exposures to particulate air pollution.

These results indicate that both short-term and long-term exposures to particulate air pollution have been associated with increased mortality. Whereas the cohort studies conducted to date have revealed excess relative risks on the order of 15-30% for long-term exposure to 18 µg/m³ PM_{2.5}, short-term exposures generally lead to excess relative risks of 5% or less. New methods for the joint analysis of time-series and cohort studies are being developed that will help to determine the relative contributions of short-term and long-term exposures to the burden of mortality associated with exposure to particulate air pollution.

There is now convincing and consistent evidence that particulate matter, and other forms of ambient air pollution, can exacerbate events leading to increased instances of cardio-respiratory morbidity. As with the particle-mortality association, the most compelling

results stem from research and analyses of multiple urban centres, and include the 16 cities across Canada representing 12.6 million people (Burnett et al., 1997a), as well as 8 cities from across Europe (Atkinson et al., 2001; Le Tertre et al., 2002), and 8 urban counties in the U.S. (Schwartz, 1999). Most air pollution-morbidity studies adopt time-series approaches and variation occurs mainly in terms of location, characteristics of population under investigation, and by health outcome.

Exposures to particulate air pollution have been shown to increase the number of hospital admissions for a range of cardio-respiratory diagnoses and events (Peters et al., 2000). Particles have been implicated as an explanation for an increase in cardio-respiratory admissions for 168 acute care hospitals in Ontario, Canada (Burnett et al., 1995), for cardiopulmonary admissions in Los Angeles (Linn et al., 2000), for acute respiratory admissions (Ofstedal et al., 2003), and for admissions diagnosed as respiratory, cardiac, and both cerebral and peripheral vascular diseases (Burnett et al., 1999).

A number of studies have also investigated the contribution of particulates and gaseous forms of air pollution to both acute and chronic morbidity-related health effects. Kunzli et al. (2000) found that air pollution accounted for more than 25,000 new cases of chronic bronchitis (adults), more than 290,000 episodes of bronchitis (children), more than 0.5 million asthma attacks, and more than 16 million person-days of restricted activities in Austria, France, and Switzerland. Particulate air pollution has been linked to a decline in airway hyperresponsiveness among children in more polluted areas (Jang et al., 2003). Gent et al. (2003) found that acute episodes of asthma for children using maintenance medications are linked to pollutant levels far below EPA standards. In another study, a decline in lung function was positively associated with a six-month period of high ozone and particle concentrations (Calderon-Garciduenas et al., 2003). Air pollution has also been positively associated with decreased lung function in elementary school children (Koenig et al., 1993). Stieb et al. (2002) found a 22% increase in the number of disability days associated with a change in particulate concentration equal to the interquartile range.

There is also compelling evidence that morbidity from particulate and gaseous air pollution is found more often among particularly susceptible populations. Recent work on the potential mechanisms of action of particulate air pollution point to pathways also influenced by diabetes; diabetics have double the risk of particulate-related cardiovascular admissions when compared to non-diabetics (Zanobetti and Schwartz, 2002). A discussion of plausible mechanisms that could be responsible for attenuating the effect of air pollution on cardiovascular morbidity has been discussed elsewhere (Utell et al., 2002). Age is also a strong predictor of susceptibility. Many studies have concluded that young children and the elderly are more at risk for respiratory and cardiopulmonary disease associated with exposure to air pollution (Burnett et al., 1997b; Anderson et al., 2003; Sunyer et al., 2003; Yang et al., 2003a). Recent research suggest health impacts of air pollution in early stages of human development (Burnett et al., 2001). In one study, low ambient air pollution concentrations were associated with adverse pregnancy outcomes including low birth weight, preterm birth, and intrauterine growth retardation (Liu et al., 2003). In another study, particles were found to be positively associated with first hospitalizations due to respiratory disease in early childhood (Yang et al., 2003b).

Level of socioeconomic status has been shown to modify the effect of ambient air pollution associated with asthma hospitalizations for males and females (Lin et al., 2003a).

The use of alternative research designs to the usual time-series approaches has yielded similar results and strengthens the case for air pollution and morbidity associations. Lin et al. (2002) used both case-crossover and time-series analyses to assess the associations between particulate matter and asthma hospitalization among children 6-12 years of age. Both approaches yielded similar positive associations between coarse particles and hospitalization. A subsequent study by the same team used the case-crossover design to find a differential effect of gaseous air pollution on the same cohort. A significant effect of carbon monoxide and sulphur dioxide was found for boys and girls respectively, while the effect of nitrogen dioxide was positively associated with asthma hospitalization for both sexes (Lin et al., 2003b). Karakatsani et al. (2003) performed a case-control study nested in a defined cohort to investigate the association between long-term exposure to ambient air pollution and the development of chronic bronchitis, emphysema, and COPD.

4.0 Where Do We Go From Here: Policy Directions

The preceding discussion of the current state-of-the-science on air pollution and health provides a basis for examining policy options for air pollution control. Specifically, we address the following policy related questions.

4.1 What are the health risks at current ambient levels and how are they distributed in the population?

Epidemiologic studies have been able to identify a wide range of adverse health effects in the general population associated with current ambient air pollution levels, ranging from mortality to subtle subclinical effects (Figure 2). These population based studies are notable in their consistency, and are supported by both toxicological and clinical research (National Research Council, 2002). Overall, the World Health Organization (2001) estimates that ambient air pollution may be responsible for some 5% of all deaths occurring annually. Particulate and gaseous pollution is strongly associated with cardiorespiratory outcomes, in terms of both morbidity and mortality.

Evidence to date has demonstrated associations between ambient air pollution and adverse health outcome across all segments of the population, including potentially susceptible subgroups such as children and the elderly (Wang et al., 2003). Although it has been postulated that air pollution may lead to increased mortality primarily affecting frail individuals with pre-existing co-morbidities, retrospective time series studies have been unable to clearly identify specific co-morbidities that significantly modify pollution-mortality associations (Goldberg et al., 2003). Empirical studies also indicate that pollution related mortality is not confined to individuals with pre-existing health conditions that may render them susceptible to air pollution exposure (Dominici et al., 2000; Fung et al., 2003). Socio-economic status (SES) has been shown to modify the association between both long-term (Krewski et al., 2003) and short-term (Villeneuve et

al., 2003) exposure to particulate air pollution, with risk increasing with decreasing SES. However, since SES may be a marker for a complex set of lifestyle and other factors, the implications of this observed effect modification by SES are unclear at this time.

4.2 Which pollutants contribute most to population health effects?

Given a sufficiently strong evidence base, pollutant control strategies might be directed towards those sources contributing the greatest burden of risk to health. To establish the needed evidence base, researchers need to address the health effects of the overall air pollution mixture and then to decompose those effects into the source contributions, linking sources to pollutants to health effects. This is a difficult topic that would require an ambitious research agenda.

At present, regulators address a suite of major pollutants, including generally particulate matter, ozone, carbon monoxide, nitrogen dioxide and sulfur dioxide. This strategy has long been in place and partially reflects the view that each of these pollutants conveys risk to human health. However, there is a mix of primary pollutants (particles, carbon monoxide, sulfur dioxide, and nitrogen dioxide) and of secondary pollutants (particulate matter and ozone). Additionally, sulfur dioxide and nitrogen dioxide contribute to the formation of secondary particles and nitrogen dioxide is critical in the formation of ozone. Given these interrelationships and the not surprising correlations among concentrations of these pollutants, separating their effects may prove difficult. The emphasis on identifying toxicity-determining characteristics of particulate matter is even more challenging, as particulate matter itself is a mixture having multiple sources.

4.3 Can we identify the most important pollutants requiring mitigation?

Air pollution is a complex mixture of a number of individual pollutants, including particulates, gases, bioaerosols, and toxic substances. The concentrations of criteria pollutants such as particulate matter, ozone, sulfur dioxide, carbon monoxide, and nitrous oxides, tend to be highly correlated with each other, making it difficult to identify the effects of individual pollutants in observational studies. Estimates of the population health burden of short-term exposure to individual pollutants suggest that both particulate and gaseous co-pollutants contribute significantly to morbidity in the general population (Burnett et al., 2000). Detailed analyses of the ACS cohort have shown mortality to be associated with both fine particulate matter and sulfur dioxide, with SO₂ being somewhat more robust against adjustment for co-pollutant exposure than PM_{2.5} (Pope et al., 2002; Krewski et al., 2003). Since a plausible biological pathway exists for mortality associated with exposure to particulate matter, but not for sulfur dioxide, it is possible that SO₂ is a marker for exposure to another pollutant such as sulfate particles.

At present, the weight of evidence suggests that particulate air pollution is an important component of the complex mixture to air pollutants to which we are exposed (Greenbaum, 2003). PM_{2.5}, which can penetrate deeper into the airways than coarser particles, has been the focus of intensive investigation, and has been consistently associated with morbidity and mortality in the general population. Recent evidence has

suggested a mechanistic pathway based on accelerated atherosclerosis for particulate induced cardiorespiratory conditions.

Current evidence also suggests a role for gaseous co-pollutants in the etiology of pollution-related morbidity and mortality. However, present evidence precludes a clear demarcation of the relative contribution of particulate and gaseous pollutants to the population health burden of ambient air pollution.

4.4 How effective would source control be in terms of reducing exposures to multiple pollutants?

The HEI Accountability working group (HEI, 2003) notes that while the link between a new regulation and resulting changes in emissions is the most straightforward component of the chain of accountability, its assessment has a number of possible complications.¹ Changes in ambient concentration resulting from specific emission reduction policies may be difficult to detect in routinely collected data on ambient air quality. A number of factors influence changes in ambient concentrations including the relative contribution of the regulated source to total emissions of the pollutant in question, concurrent changes in emissions of the same pollutant by other sources, and variation in meteorologic influences on atmospheric transport and chemical transformation. The link from ambient air quality to exposures and doses in the population are influenced by time-activity patterns, penetration of outdoor pollutants indoors and chemical transformations. In general, tools available to characterize the effects of regulatory action on pollutant emissions and air quality are better developed than tools for assessing the relation between ambient pollutant concentrations and exposures and doses received by the population.

Tracking the effect of changing emissions on air quality can be relative straightforward for some primary pollutants, such as lead. The decline of atmospheric lead concentrations and blood lead levels following the phase out of leaded gasoline provides an example illustrating the close linkage between source control and reduced exposures. Tracking changes in secondary pollutants (e.g. ozone and fine particles) is more complex. For example, changes in vehicle emissions cannot be readily linked to ozone concentrations in urban areas, as concentrations are determined by multiple factors beyond emissions of ozone precursors. Models provide a means to quantify the complex chemical and meteorological interactions that relate precursor emissions to production of secondary pollutants and play a central role in air quality management for PM_{2.5} and ozone.² The HEI monograph notes that surprisingly little effort has been devoted to assessing how accurately models predict changes observed after implementation of specific emission policies. The expansion of speciation monitoring in the United States will provide improved tools for tracking ambient effects of changes in emissions and judging the validity of modeled projects and the effectiveness of corresponding control programs. To further assess the benefits of specific emission control policies, the monograph

¹ The material in this section is drawn from HEI (2003b) Chapter 3 “From Regulatory Action to Exposure and Dose”.

² See Reid et al. (2003) further discussion of air quality models as a policy tool.

recommends that carefully designed small scale exposure studies of specific subpopulations be conducted to complement a large US personal exposure study, the National Health and Nutritional Examination Survey (NHANES), which recently assessed personal exposures to and blood levels of VOCs among a stratified random sample of 1000 US adults.

4.5 *Should efforts be focused on the control of individual pollutants or should broader source control strategies focusing on air pollution mixtures be implemented?*

The scientific basis for deciding among these (or other options) lies in answering Question 4.2 above with sufficient certainty. In part, focusing on particulate matter and ozone, whose concentrations are determined by a broad range of sources, may be an effective approach to controlling air pollution generally. Carbon monoxide has specific cardiac effects and emissions of carbon monoxide from motor vehicles have been drastically curtailed, illustrating the efficacy of targeted source control strategies when warranted by scientific evidence. For most countries and specific locales, we also lack the emissions inventory information that would be needed to target source control strategies and our tools for modeling the contributions of specific sources to concentrations and exposures are inadequate. At this juncture, we offer the opinion that the scientific evidence does not yet warrant a deviation from current approaches.

4.6 *How have health risks declined with declining levels of air pollution?*

Ambient air pollution levels have been generally declining over the last 20 years. Although this reduction in exposure to air pollution may be expected to lead to reduced health risk, it is difficult to directly demonstrate concomitant reductions in mortality and morbidity in the general population because of the modest reductions in ambient pollution levels and the relatively small attributable risk associated with air pollution. Recent time series studies have consistently identified associations between air pollution and both mortality and morbidity, indicating that even current low levels of pollution are associated with adverse health outcomes. Cohort studies involving follow-up over extended periods afford an opportunity to assess changes in risk with changes in ambient air pollution levels. In the Harvard six cities study conducted by Dockery et al. (1993), prospectively monitored pollution levels exhibited a notable decline between the early 1970s and the late 1980s. Villeneuve et al. (2002) attempted to characterize the relationship between temporal changes in PM_{2.5} levels and mortality in this study: it was found that the relative risk of pollution related mortality did not depend on when exposure occurred in relation to death, possibly because of the limited variation in the rate of decline in ambient pollution levels in these six cities. Follow up of the ACS cohort through to 1989 (Pope et al., 1995) and 1998 (Pope et al., 2002) suggested a decrease in the relative risk of mortality associated with PM_{2.5}; however, it is not clear if this reduction in relative risk is due to lower pollution levels or increase exposure misclassification due increased population mobility in the extended follow-up.

4.7 *What is the current evidence of benefits related to air pollution mitigation?*

With increasing economic costs of control measures to achieve further improvements in air quality in North America and western Europe, policy makers and other stakeholders are seeking evidence of public health improvements resulting from past efforts to reduce air pollution.

The Health Effects Institute's recent monograph "*Assessing Health Impact of Air Quality Regulations Concepts and Methods for Accountability Research*" (HEI, 2003b)³ states that carefully constructed evidence about the extent to which control measures have improved health is still lacking and proposes a framework and methods for accountability research. The challenges in assessing the health impact of air quality regulations are considerable. Diverse approaches are required to evaluate the impact of national, regional and local level interventions that take effect at various time frames. PM and photochemical oxidants are complex mixtures with multiple sources. Isolating the health effective component of various pollutant specific control measures is difficult. Large regulatory initiatives such as the US Clean Air Act may require long time frames before reductions in pollutant emissions translate into reduced incidence of mortality and morbidity from cardiovascular and respiratory diseases. The longer the time between implementation of a policy and manifestation of changes in disease incidence, the greater the possibility that other behavioral and environmental factors may influence risk.

Estimating benefits and costs

In developing clean air policies, governments have used risk estimates from epidemiologic studies to estimate avoided health impacts associated with various air quality scenarios (EPA 1997, 1999, Canada Wide Standards Development Committee for Particulate Matter and Ozone, 1999). These health impact estimates are expressed in monetary terms based on economic valuation literature and compared with various baseline scenarios and the costs of emission controls to achieve various ambient air quality levels. In its retrospective and prospective analysis of the Clean Air Act, EPA relied primarily on the long-term American Cancer Society cohort study by Pope and colleges (1995) to estimate adult mortality associated with elevated PM. The retrospective analysis showed that aggregate monetized benefits (\$22,171 billion 1990 dollars) are estimated to exceed costs (\$523 billion 1990 dollars) by more than an order of magnitude for the first twenty years of the Clean Air Act (1970 to 1990). More than four-fifths of these estimated benefits are derived from avoided mortality at \$4.6 million per life. The decline in PM concentrations during the first 20 years of the Clean Air Act is associated with the majority of mortality benefits. The phase out of lead in gasoline also contributed to reduced mortality during this period. In the prospective analysis, from 1990 to 2010, total monetized benefits also exceeded costs although the ratio of benefits to costs was lower than for 1970 to 1990. Subsequent disaggregated analyses suggest major differences in net benefit across titles of the Clean Air Act. Most analyses show

³ The material in this section is drawn from the HEI Monograph. (HEI, 2003b).

that the new PM_{2.5} NAAQS is likely to have a better cost-benefit ratio than the new ambient ozone standards.⁴

In the United Kingdom, the Committee on Medical Effects of Air Pollution (COMEAP) estimated the total life-years gained by the 2001 population of England and Wales if the annual average PM_{2.5} concentrations were 1 µg/m³ lower than that occurring in 2000. The estimates span a 20 fold range of potential gain in life expectancy from 0.2 to 4.1 million life-years (UK Department of Health, 2001).

Several quasi-experimental, observational studies have evaluated the health benefits associated with emission reductions. These studies include those conducted in Dublin, Ireland (Clancy et al. 2002) and Hong Kong (Hedley et al. 2002) in which new air quality regulations implemented in relatively short times had a major impact on emissions, and studies in which point-source industrial emissions decreased dramatically (Pope, 1989).

Focused air pollution regulations

The impact on mortality six years following a 1990 ban on the use of coal for domestic heating in Dublin was estimated. Following the ban, concentrations of black smoke and sulfur dioxide fell 35.6% and 11.3% respectively. Age standardized mortality from natural causes declined by 5.7%. The declines were more substantial for people less than 60 years of age (7.9%), for mortality due to respiratory causes (1.5%) and cardiovascular causes (10.3%) as opposed to other causes (1.7%) and in winter. The estimates were adjusted for weather, influenza epidemic and secular changes in countrywide mortality. The impact was qualitatively similar but quantitatively larger than what one would have predicted from existing European studies of air pollution and mortality (Katsouyanni et al. 1997).

In 1990, the sulfur content of fuel oil in Hong Kong for power generation and road transport was reduced to 0.5% or less by weight. This change was implemented over a single weekend. Ambient levels of both SO₂ and SO₄ were compared with indices of respiratory health in children living in two areas of Hong Kong that differed markedly in levels of ambient air pollution. After the reduction in fuel sulphur content, ambient levels of both SO₂ and SO₄ fell markedly in the more polluted area (80% and 38% respectively) but major changes were not observed in the less polluted areas. The improvement in air quality was associated with larger declines in respiratory symptoms among primary-school children in the more-polluted area than in the less-polluted area (Peters et al. 1996). The regulations were also associated with declines (2.1%, 2.0% and 3.9%) in the upward trend of annual average natural cause, cardiovascular and respiratory disease mortality, respectively, compared to the previous 5 years. Annual rates of mortality due to other causes were not markedly affected. Reductions in mortality were more pronounced in the most highly polluted areas. Hedley et al. (2002) estimated that the regulation resulted in gains in average life expectancy per year of exposure to the lower levels of air pollution: 20 days for women, 41 days for men.

⁴ See background paper by Rabl et al. (2003) for further discussion of cost-benefit analysis of air quality policies

Natural experiments

A widely cited example is the closing of the Provo, Utah steel mill for one year in 1996 (Pope, 1989). Pope et al. studied mortality and morbidity associated with changes in particle concentrations and characteristics before, during and after the year in which the plant was not operating. The mill contributed approximately 50% of the Valley's respirable PM. PM concentrations during winters when the steel mill was open were nearly double those when it was closed. Elevated PM levels were associated with increase hospitalizations for pneumonia, asthma, bronchitis and pleurisy. Hospital admissions of children due to respiratory disease were two to three times higher during the years the mill was open. More recent toxicologic analyses of extracts collected from filters used to monitor PM levels in the Utah Valley show that the extracts caused increases in oxidant generation, airway inflammation, cytokine release and other indicators of lung injury. These effects were larger for particles collected when the steel mill was operating than when it was closed. The monograph notes that such studies however will never stand alone as accountability assessments as other factors could confound the observed effect. Also the observed reduction of PM concentration may have little relevance to the magnitude of concentration reductions that would result from intentional regulatory efforts to improve air quality.

4.8 *What measures of risk should be used in the estimation of public health benefits of air pollution controls?*

A critical step in estimating the benefits of proposed air pollution policies is the appropriate selection of adverse health outcomes and concentration response functions describing the quantitative association between ambient air pollution levels and the corresponding health effects. The findings of epidemiological studies provide the scientific basis for these decisions. Because of the importance of estimates of health benefits in decision-making and concerns about the methods used by EPA, the U.S. Senate directed EPA to request that the National Research Council (NRC) evaluate methods used to derive health benefits estimates and make recommendations on best practices for these assessments. The NRC Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations (NRC, 2002) undertook a review of EPA health benefits analyses conducted for rule making on PM and ozone standard setting, Tier 2 motor vehicle emissions standards and gasoline control requirements, heavy duty engine and vehicle standard and highway diesel fuel sulfur control requirements, and the 1990 Clean Air Act Amendments. The Committee considered the structure of the analyses and methodological issues regarding exposure assessment, the selection of health outcomes and the concentration response function, the analysis of uncertainty and the presentation of the methods and results.

The Committee identified the following issues regarding the selection and definition of mortality and morbidity outcomes:

- Clinically diagnosed illnesses, such as chronic bronchitis and asthma attacks are typically evaluated in benefits analyses. These outcomes cover a wide range of severity levels and time courses. For example, chronic bronchitis can range from a chronic cough to a severe chronic airway obstruction that requires long-term care. EPA needs to investigate and improve the methods used to reconcile differences between the severity of disease described in air pollution epidemiology and that commonly used to develop estimate of background disease prevalence and incidence.
- Mortality estimates tend to dominate the overall health benefits estimates when a dollar value is assigned to them. Data on morbidity is less comprehensive and needs to be improved, especially if the value assigned to mortality decreases and morbidity outcomes begin to play a more dominant role in the benefits analyses.
- A key assumption is that there is a causal association between types of air pollution and adverse health outcomes. The Committee identified two general issues pertaining to confounding that contribute to uncertainty in the interpretation of studies on air pollution health effects. First, air pollutants often have a common source and are subject to similar atmospheric dispersion processes. Concentrations of pollutants tend to be correlated, and their independent effects are often difficult to disentangle using multi-pollutant models. PM is a heterogeneous mixture, and the component responsible for observed effects has not been determined. The second issue is the possibility that some unknown factor that has not been controlled for explains the association between ambient concentrations in air pollution and risk of health effects. EPA recommended that the evidence of causality be summarized to justify the inclusion or exclusion of health outcomes and to assess the uncertainty associated with the assumption of causality.

In its critique of selection of epidemiological studies selected by EPA for use in its benefits analyses the Committee offered the following assessment and recommendations:

- The selection of the American Cancer Society (ACS) cohort study (Pope et al., 1995) for the evaluation of PM-related premature mortality was reasonable as cohort studies provide a more complete assessment of health effects than time series studies because they include long-term cumulative effects of air pollution. Cohort studies also provide data to estimate the number of life-years lost in a population, not just the number of lives lost, thus allowing for several valuation methods to be used.
- EPA used U.S. studies to provide data to estimate health benefits. Data for many health outcomes in the U.S. studies are restricted to a specific age group. For example, the data for hospital admissions apply to persons 65 years or older, primarily because the data come from Medicare databases. EPA should use the findings of recent studies conducted outside the U.S. that provide information on health outcomes with broader age ranges and on outcomes not currently evaluated, such as levels of use of the primary care system. The Committee encourages EPA to estimate and report benefits by age, sex and other demographic factors when possible.

- The Committee recommended that EPA thoroughly review the selection of the best estimate for long-term effects of air pollution on mortality given the reanalyses of the ACS study and Harvard six cities study (Krewski et al. 2000), the recent extended analysis of the original ACS study (Pope et al., 2002), the availability of a third cohort study (Abbey et al., 1999; McDonnell et al. 2000), and the publication of the first European cohort study (Hoek et al., 2002). The Committee recommended that EPA consider derivation of a weighted-mean estimate from the cohort studies following review of the entire database. The inclusion or exclusion of studies and the weighting scheme should be justified and clearly explained.
- EPA used time series studies to derive benefits estimates of selected morbidity outcomes for its primary analyses. The Committee concluded that consideration of these studies is appropriate to estimate acute effects from short term exposure, however a thorough investigation of problems associated with the use of S-plus statistical software to fit generalized additive models (GAM) to the data (HEI, 2003) is required to determine the effect on the coefficients used in the benefits estimates.
- To evaluation short term effects of air pollution, EPA should use concentration-response functions from studies that integrate over several days or weeks the exposure period and the time period of the event, rather than those that restrict these time periods to 1 or 2 days.

The Committee emphasized the large amount of uncertainty inherent in health benefit analyses that is rooted in incomplete scientific knowledge and concluded its report with recommendations to improve the transparency of assumptions and the estimation and communication of uncertainty.

- Health benefits analyses should reflect the plausibility and uncertainty of the concentration response function, such as imprecision of exposure and response measures, potential confounding factors, and extrapolation from the study population to the target population. EPA should strive to present the results of its health benefits analyses in ways that avoid conveying an unwarranted degree of certainty, including placing less emphasis on single numbers and more emphasis on ranges.
- EPA should document clearly the rationale for its selection of studies and concentration-response coefficients as these choices require judgment on the part of the analyst.
- EPA should evaluate threshold assumptions in a consistent and transparent framework using several alternative assumptions in the formal uncertainty analysis.

4.9 What scientific evidence is needed for development of location specific standards?

At present, air pollution control strategies are based largely on national ambient air quality objectives, taking into account both health implications of pollution exposure and

the cost of pollution mitigation (Raizenne, 2003). As we work towards the long-term goal of reducing ambient air pollution, there may be opportunities for more cost-effective pollution mitigation actions in some areas as compared to others. The development of location specific air pollution standards and guidelines requires local air pollution monitoring data, as well as information on mitigation options and costs in those areas. This information may be used to design cost-effective location specific air pollution control programs that will contribute to national and international air pollution control objectives.

4.10 What scientific evidence is lacking to guide air pollution control strategies?

Progress in refining policy directions for air quality risk management will require additional scientific information in a number of areas (Maynard, 2003). Maynard et al. (2003) noted that research is needed on indicators of population health impacts, individual exposure and outcome studies, identification of sensitive subpopulations, effects of individual pollutants on population health, comparative risk assessment, characterization of uncertainty in risk estimates, effectiveness of policy interventions, predictions of the benefits; targeted interventions, and effective stakeholder engagement in risk management decisions.

Here, we focus on the following four overarching issues related to the NRC's framework for integrating particulate matter research.

i) assessing the toxicity of components of ambient air pollution

Further research is needed to identify the toxic components of the complex mixture of ambient air pollutants to which we are exposed, particularly to clarify the role of particulate and gaseous co-pollutants. Observational studies are limited by joint exposure to multiple pollutants, although a national study with sufficient variation in the composition of the pollutant mix may afford an opportunity to disentangle the effects of multiple pollutant exposures. Toxicological studies can be used to systematically study the effects of individual pollutants, joint exposures, and interactions among pollutants using factorial experimental designs. Controlled clinical studies may also be used to investigate these same effects at low exposure levels, following research ethics board guidelines.

Specific studies are also needed to better define the characteristics of particulate air pollution that mediate particle toxicity. Particle size appears to be correlated with toxicity, with smaller particles that can penetrate deeper into the airways demonstrating stronger associations with adverse health outcomes. In addition to particle mass and number, the role of toxic substances and biologically active agents affixed to particles also require further investigation. A deeper understanding of the toxic constituents of particulate air pollution will provide a firmer basis for the design of air quality standards and guidelines for particulate air pollution.

ii) effects of long-term exposure

Virtually all of the current evidence on the effects of long-term exposure to particulate and gaseous co-pollutants derives from three large cohorts: the Harvard six cities cohort (Dockery et al., 1993), the American Cancer Society cohort (Pope et al., 1995, 2002), and the Seventh Day Adventist cohort (Abby et al., 1999). While providing consistent evidence of effects of an association between particulate air pollution and mortality, these cohorts are subject to certain limitations relating to exposure misclassification (due to the use of fixed site ambient monitors for exposure assessment) and adequacy of adjustment for important covariates such as socioeconomic status and co-morbidity. Of these three studies, only the Harvard six cities study was originally designed to examine the health risks of long-term exposure to ambient air pollution. All three studies focus primarily on mortality rather than morbidity; none of these three studies focuses on children.

Although further follow-up of all three cohorts will provide additional information on the adverse health outcomes associated with long-term exposure to particulate and gaseous pollutants, a prospective cohort study with more detailed exposure information would afford an opportunity to better characterize the population health impacts of ambient air pollution (Brunekreef, 2003; White & Suh, 2003). With regular monitoring of study subjects, a prospective study of this type could provide detailed information on morbidity associated with long-term exposure to air pollution, as well as mortality. Such a study could be linked to the ongoing supersites air quality monitoring program, which provides the most detailed information on ambient air quality collected to date. Personal exposure monitoring for some subjects would also help to provide more refined measures of exposure (Chang et al., 2003). Linking such an initiative to the proposed longitudinal study of children's health and the environment would afford an opportunity to examine health effects in a potentially susceptible population subgroup (Wigle, 2003).

iii) mechanisms of cardiovascular and respiratory mortality

Cardiovascular and respiratory mortality represent health outcomes that have been consistently associated with exposure to ambient air pollution. An important consideration in assessing the weight of evidence on the health effects of air pollution is a plausible mechanistic pathway by which pollutants may exert their adverse effects. In recent years, a cohesive biological picture of particulate toxicity has begun to emerge, with accelerated atherosclerosis representing a plausible pathway for both morbidity and mortality. Further research is needed to clarify these initial results, along with parallel work on mechanistic pathways that may apply to gaseous co-pollutants. Collectively, this information will help to identify the toxic components of the complex mixture of air pollutants to which we are exposed.

iv) one atmosphere approach

Regulators are faced a number of challenges in setting air quality objectives for individual pollutants. Uncertainties in source apportionment make it difficult to predict the impact of specific emissions controls on air quality. With the high degree of collinearity among criteria air pollutants, consideration might be given to air pollution control strategies that focus on the atmosphere as a whole, rather than emphasizing one pollutant over another. Such a “one atmosphere” approach would emphasize reduction in air pollution in general, with the expectation of achieving significant reductions in the concentrations of individual pollutants in ambient air. The adoption of this approach would reduce the need for more detailed scientific information on the adverse health effects of individual pollutants, but would require a greater commitment to the control of air pollution in general.

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