The Particulate Air Pollution Controversy

A Case Study and Lessons Learned

by
Robert F. Phalen

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Dedicated to Kathy, Bob, Steve, Michelle, and Joseph

CONTENTS

PREFACE

Small invisible particles in the urban air, especially those produced by human activities, have recently stimulated intense scrutiny, debate, regulation, and legal proceedings. The stakes are high, both with respect to health impacts and economic costs, and the methods used previously to resolve similar issues are no longer adequate. Everyone on earth inhales thousands to millions of particles in each breath, so if urban particulate air pollution—particulate matter (PM)—is significantly hazardous, the negative impact on health could be staggering. Yet the activities that generate PM, such as farming, manufacturing, mining, transportation, and generating electricity, are themselves essential to human health and welfare. Scientists, regulators, legislators, activists, judges, lawyers, journalists, and representatives of the business community are actively involved in addressing the question of what should be done. This complex issue presents opportunities for critically assessing the relevant knowledge and for adopting more rigorous approaches to this and similar problems.

What is the PM controversy, and why is it a good case study for how science and public policy might better interface? The PM controversy is the sum of the frequently heated debates related to the potential health risks from urban PM. The debates in the scientific, political, legal, and public arenas have placed pressure on scientists and regulators to generate better data and to consider creative solutions to reduce the impact of PM on human health. The pressure has been intensified by the clash between economic and regulatory interests. Because science and technology work slowly in relation to the speed at which regulations proceed, there is a need for new ideas and approaches. It is unlikely that any single book can provide an adequate treatment of the PM controversy. Therefore, the emphasis here is on science—what is understood, what is not known, the responses to uncertainties, and the lessons learned. When it is relevant, nonscientific topics are discussed, albeit superficially. Other treatments of aspects of this topic, in addition to the U.S. Environmental Protection Agency Criteria Documents, have been published (Chow and Ono, 1992; Gehr and Heyder, 2000; Holgate et al., 1999; Lee and Phalen, 1996; Lipfert, 1994; NRC, 1998, 1999, 2001; Phalen and Bell, 1999; Vostal, 1998; Wilson and Spengler, 1996).

This book is concise and simply written in an attempt to make it useful to nonspecialists. Although I have tried to be fair in exploring various aspects of the controversy, as a research scientist, my bias is to be skeptical, especially of new information before it has withstood the tests of time and challenge. I am indebted to the following people who have provided suggestions, technical assistance, and critical reviews: Susan Akhavan, Dean Baker, Edward Calabrese, Maria Costantini, Nancy Eng, Alan Hansen, Michael Kleinman, Morton Lippmann, Michael Oldham, Michael Perkins, Leslie Redpath, and Peter Valberg.

The book is organized into 10 chapters, which may be read in any order. Chapter 1 describes the evidence implicating PM-associated air pollution as a threat to human health. Chapter 2 presents a historical perspective, including recent events related to the PM controversy. Chapter 3 explores the challenges that have been directed at the reliance on recent epidemiology studies on PM. Chapter 4 provides information on the nature of urban PM-associated air pollution, its relevant properties, its sources, and how it distributes in the air. Chapter 5 covers the entry of particulate air pollutants into the respiratory tract and some aspects of what happens to inhaled particles that are deposited in the body. Chapter 6 presents controlled studies that contribute to understanding the potential health effects of PM. Chapter 7 summarizes the research that needs to be done and thus highlights gaps in knowledge. Chapter 8 explores the potential risks and other consequences that arise when PM-associated pollutants are controlled. Chapter 9 presents challenges to common assumptions about environmental air pollutants. Chapter 10, the final chapter, draws conclusions from the foregoing and presents new challenges to scientists, regulators, politicians, and the public. Approximately 200 key references are cited throughout this book to aid further research by the reader. This book is also intended to provoke exploration and thought in hopes that better decisions will be made in the future on this and similar issues related to public health.

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CHAPTER 1
Harmful Effects of Particulate Air Pollution

1.1. RELEVANCE TO THE PARTICULATE MATTER (PM) CONTROVERSY

Regulators and scientists are struggling to understand the human health effects of low levels of modern urban particulate air pollution (particulate matter, PM). Because the continuing regulation of particulate matter has significant economic implications, an emotional controversy, the "*PM* controversy," has evolved. The evidence for harmful effects at realistic urban air concentrations predominantly comes from epidemiology studies. These studies emerged as a result of observations made during and after a few notable air pollution disasters. These early disasters stimulated efforts that led to improved air quality and ushered in a number of more sophisticated investigations. In the late 1980s and early 1990s, newer epidemiology methods found health effect associations with very low levels of particulate air pollution measures. The collection of epidemiology studies is the scientific basis for the continuing concern over the health effects of PM. This chapter traces the evolution of these studies and their implications.

1.2. BREATHING AND AIR QUALITY

In an average resting adult, a tidal volume of about 500 ml is inhaled and exhaled every 4 seconds. During heavy exercise, the ventilation is increased by about 10-fold to 60 liters per minute. At rest, an adult inhales about 10,000 liters daily, which over a 75-year lifespan amounts to about 250 million liters of air, which is enough to fill a modern sports arena. A newborn child inhales about 0.9 L/min at rest. Smaller individuals actually breathe more air per unit of body mass than do larger individuals (Guyton, 1947; Phalen et al., 1988).

Perfectly clean air, which cannot be found in nature, is about 76% nitrogen gas by weight, 23% oxygen (a very reactive gas), 1% argon, 0.03% carbon dioxide, plus smaller quantities of other gases, such as helium and neon. Also, most air will contain water vapor, as much as 25 grams per cubic meter at room temperature when the relative humidity is 100%.

Real ambient air, on the other hand, contains particles and vapors that come from natural and anthropogenic sources. Although what is thought of as clean air contains tens of thousands of suspended particles per liter, people are not usually aware of them. Similarly, normal air will have varying concentrations of hundreds of vapors, produced by natural sources as well as human activities. For the majority of people, breathing the air over a lifetime does not produce any significant disease

or distress. At autopsy, the total content of mineral particulate matter in the human lung is about 0.1 grams (Kalliomaki et al., 1989), a small percentage of the total inhaled.

Air contaminants can be classified in several ways. One classification segregates air contaminants into the broad categories of infectious agents, allergens, chemical irritants, and chemical toxicants (biologic and nonbiologic). Another classification segregates air contaminants into particles, gases, and vapors (like gases, vapors are free molecules in the air, but they are normally liquids under the prevailing temperature and pressure). For regulatory purposes, air contaminants are often classified as anthropogenic (human generated), natural, or secondary (produced by chemical reactions in the atmosphere).

To understand the health-related effects of air pollutants, definitions of their concentrations in air are needed. For particles, concentrations are expressed in terms of some particle property such as mass per unit volume of air (e.g., mg of particulate mass per m^3 of air) or by the number of particles present (e.g., million particles per m^3 of air). For gases and vapors, three types of concentration units are commonly used. The volume ratio, parts volume of air (e.g., 1 part per million), the partial pressure exerted by the gas (e.g., 1 mm Hg pressure out of the 760 mm Hg total air pressure) and as for particles, the mass in a given volume of air (e.g., mg per m^3 of air). Each of these ways of expressing concentrations of pollutants is in common scientific use, and when enough is known about a given contaminant (particle size, molecular weight, specific gravity, total air pressure, etc.), one can convert among the units.

Convenient conversion factors, for gases and vapors at 24°C (75°F) from mg/m^3 to ppm, and for spherical particles from number of particles/m^3 of air to mg/m^3, are given below.

$$\text{ppm (gas in air)} = (24.45)\,(\text{mg/m}^3)\ /\ \text{MW} \tag{1.1}$$

$$\text{mg/m}^3\ \text{(particles in air)} = (524)\,(N)\,(D^3)\,(\rho_p) \tag{1.2}$$

MW is the gram molecular weight, N is the number per m^3, D is the particle diameter in cm, and ρ_p is the particle's material density in gm/cm^3. Equation 1.2 assumes that the particles are perfect spheres and that they do not have internal voids. In practice, particle aerodynamic diameter, which corrects for shape and density, is used by modern scientists and regulators.

How contaminated must air be before it is considered to be impure? This question cannot be answered, as it depends on a number of factors including who is breathing the air, for how long, at what exercise level, and the specific contaminants under consideration. Therefore, modern air standards differ for occupational settings, outdoor settings, domicile settings, etc. Even when an air standard has been accepted as adequately protective of human health, some individuals may develop aversions to its odor, an allergic response, or some unexplained sensitivity. Therefore, air standards often represent compromises that are practical, achievable, and protective for the vast majority. As technological processes evolve, as the economy improves (so that controls can be afforded), and as medical knowledge advances, air standards tend to become more stringent.

1.3. EARLY INDICATIONS OF HEALTH EFFECTS OF URBAN AIR POLLUTANTS

1.3.1. Emergence of Quantification of Particulate Matter

Historical accounts of air pollutant exposures in cities and workplaces prior to the mid-1900s typically were not accompanied by quantitative air concentration data. One can read about the "unbearable . . . stench" in twelfth-century London, the "horrid smoake" of fifteenth-century London (Wilson, 1996), and the "air pollution disaster" in Belgium's Meuse Valley in 1930 (Clayton, 1978). Similarly, Drinker and Hatch (1936) describe the particle levels in the workplace in terms of dustfall (the amount of material falling into a bucket on the floor) or millions of particles per cubic foot (using limited optical particle counting methods). Even today, the British Smoke (BS) method for measuring particulate air pollution is used. In this method, air is drawn through a filter, and the color shade of the filter compared to painted standard surfaces, making true mass estimates difficult.

In the United States, filter-weighing methods (the high-volume TSP, total suspended particulate) increased in use since the mid-1950s until supplemented by finer mass fractions (EPA, 1982, 1996). It is fair to say that the relevant measures of contaminants in the air that relate to human health effects have not been perfected. Future developments in devising proper air-concentration measures will most likely integrate knowledge of internal dosimetry, toxicology, and atmospheric chemistry.

The late 1950s and early 1960s marked the period in which relatively reproducible measurements of particulate concentrations began to accompany epidemiological studies of human health effects of air pollutants. Several useful summaries of this early epidemiological data can be found, but the air-quality criteria documents, published by the U.S. EPA, are among the most complete and authoritative (EPA, 1982, 1996). A useful reference on the early state of knowledge on the health effects of airborne particles is a publication by the National Academy of Sciences entitled *Airborne Particles* (Committee on Medical and Biologic Effects of Environmental Pollutants, 1977). Several competent editors and authors have also reviewed the health effects literature on particulate air pollution. Included in this category are: *Air Pollution*, Volume 2, *The Effects of Air Pollution* (Stern, 1977); *Environmental Toxicants* (Lippmann, 2000); *Air Pollution and Community Health: A Critical Review and Data Sourcebook* (Lipfert, 1994); *Particles in Our Air: Concentrations and Health Effects* (Wilson and Spengler, 1996); and *Air Pollution and Health* (Holgate et al., 1999).

1.3.2. The Three Great Air Pollution Disasters

There is considerable consensus on the effects of very high concentrations of environmental air pollutants as occurred in the "great air pollution disasters." Although different authors include more or fewer episodes in the "disasters" category, three incidents shaped scientific thinking and public policy. These incidents, which occurred from 1930 to 1952, had several extraordinary factors in common: heavy emissions of air pollutants, prolonged near-stagnant air conditions, low air temperatures, and fog. The first incident, in December 1930, affected several

communities in a 20 to 24 km stretch of the valley of the Meuse River in eastern Belgium. The valley is about 2½ km wide and 100 m deep, and it was heavily industrialized, having several electrical power plants and heavy industries (Table 1.1) as well as other pollutant sources. The six-day episode began December 1, with dropping temperatures, fog, and very low wind speeds. More than 60 excess deaths occurred, accompanied by many cases of cough, shortness of breath, and irritation (Stern, 1977; Clayton, 1978; Lipfert, 1994; Wilson and Spengler, 1996). Deaths were mostly in, but not limited to, those who were elderly and had preexisting heart and lung diseases. As no air-concentration measurements were made at the time, speculation and modeling had been used to identify SO_2 and acid-droplets as the probable causal agents. Even with estimates for SO_2 as high as 1 to 10 ppm in the air, there is suspicion that a secondary pollutant or a mixture produced unusually toxic air pollution (Table 1.2).

Table 1.1 Air pollution sources present in the Meuse River Valley in 1930 (Clayton and Clayton, 1978, p. 596).

A.	**Heavy industry**	B.	**Others**
	Four very large steel plants		Railroads
	Three large metallurgical factories		Coal heating of homes
	Six glass works		Automobiles and trucks
	Three zinc plants		
	Four electric power generating plants		
	Five coking operations		
	One sulfuric acid plant		
	One fertilizer plant		

Table 1.2 Some of the air pollutants believed to have been elevated during the Meuse River Valley episode (Clayton and Clayton, 1978, p. 397).

A.	**Gases and vapors**	B.	**Particles**
	Sulfur dioxide		Hydrochloric acid
	Carbon monoxide		Sulfuric acid
	Nitric acid		Soot
	Formaldehyde		Cement dust
	Nitric oxide		Lime dust
	Hydrocarbon vapors		Metals
			Silica

The second incident occurred October 25 to 31, 1948, in Donora (and nearby Webster), an industrial community of about 14,000 (1,000 in Webster) in southwestern Pennsylvania. Donora is located at a bend of the Monongahela River (which cuts a valley 120 m deep) surrounded by high ground. The area was heavily industrialized (Table 1.3), and essentially all private and commercial establishments used soft coal as the only fuel (Ashe, 1952). The episode began with a persistent fog and stagnant wind conditions. The weather conditions during the episode were described as "unique in intensity as far back as history is available" (Ashe, 1952). Over the next few days the fog became odorous (a smell of SO_2), and visibility was low enough (~15 m) that traffic essentially stopped. Temperatures were cool but not unusually cold. Either 18 or 20 deaths have been attributed to the episode, when about one or two were expected during the period (Lipfert, 1994). There is dispute over the number that become ill, but about 40% of the population was probably affected. There is also uncertainty over animal deaths, but chickens, along with other farm animals, seemed to be particularly vulnerable (Lipfert, 1994). Older persons (over 50 years) with existing cardiopulmonary diseases were hit hardest. Cough, dyspnea, and eye and respiratory irritations were seen. As in the Belgian episode, no air monitoring was in place, but later estimates place the possible SO_2 level as high as 5.5 mg/m^3 (2 ppm), and the total suspended particulates (TSP) could have been as high as 30 mg/m^3 (Stern, 1977; Lipfert, 1994; Wilson and Spengler, 1996). Other air contaminants that were probably present in significant amounts include sulfuric acid, carbon monoxide, oxides of nitrogen, carbon, iron oxide, zinc oxide, and several other metals. A subsequent Public Health Service study concluded that a combination of pollutants would have been required to produce such severe health effects (Shrenk et al., 1949).

Table 1.3 Air pollution sources present in or near Donora, PA, in October 1948 (Clayton and Clayton, 1978, p. 596).

Four steel plants
One zinc plant
One sulfuric acid plant
One glass company
One electric power plant
One railroad
Steamship operations
Use of soft coal for fuel

The most severe of the great air pollution disasters occurred December 5 to 8, 1952, in London, England, which lies in the broad valley of the Thames River. The intense, nearly stagnant fog, produced by a low-temperature inversion at about 100 m altitude led to a rapid buildup of a sooty, apparently acidic smog that was so

intense that London traffic was impeded and pedestrians became lost (Lipfert, 1994). The number of deaths attributable to the smog is uncertain, as a concurrent influenza epidemic and the effects of temperature and high humidity were confounding factors (Holland et al., 1979). However, the British Ministry of Health (MOH) reported over 4,000 excess deaths, and most estimates attribute 3,000 or more deaths to the episode (Stern, 1977; Clayton, 1978). Two age groups were most strongly affected—those 45 years or older and infants under 1 year of age. Preexisting illness, especially of the heart and lungs, was a major risk factor for mortality in 80% of the victims. MOH reported the following: "The fog was, in fact, a precipitating agent operating on a susceptible group of patients whose life expectation, judging from their preexisting diseases, must even in the absence fog, have been short" (Clayton, 1978, p. 600). Causes of death were listed as bronchitis, pneumonia, and heart disease. Illnesses tended to occur on the third and fourth days of the episode, hospital admissions for respiratory and heart conditions were elevated, and the common symptoms were consistent with respiratory-tract irritation. This was apparently the first documented air pollution disaster for which air sampling data, before, during, and after the event, were available. In the weeks prior to the episode, particulate levels averaged 0.5 mg/m^3, and SO_2 levels averaged 0.15 ppm. During the episode, 48-hour averaged particle levels reached 4.5 mg/m^3, and SO_2 levels reached 1.3 ppm (Clayton, 1978). The particle levels are based on the British Smoke Shade methodology, so they may underestimate the actual levels. The air pollution also acutely damaged and soiled metal surfaces, cloth, and skin, and from the effects on such surfaces, the air pollution was apparently very acidic (Lipfert, 1994). The source of the air contaminants was certainly soft-coal combustion, which was widely used for domestic heating. The British Clean Air Act of 1956 subsequently limited the use of such coal for heating homes. As in the other great air pollution disasters, some unmeasured toxic agent or a combination of pollutants was believed to have produced the health effects (Ashe, 1952). According to Lipfert (1994), the London excess mortality ratio was 2.6, but Wilson and Spengler (1996) put the death rate at five times normal.

Much has been written on the lessons learned from these and other air pollution episodes, but the following conclusions seem warranted. First, severe air pollution episodes are capable of producing excess morbidity and mortality. Second, deaths lag the beginning of the episode by a few days, usually two or more. Third, those who have preexisting heart and lung diseases, especially older adults, are the most severely affected. Fourth, exceptionally unfavorable meterologic conditions, including zero or very low wind speeds, a severe air inversion, and high humidity and/or low temperature, were present. Fifth, combinations of pollutants, including some that were not measured, were believed to have caused the illnesses and deaths. These episodes, summarized in Table 1.4, sparked intense activity in the public health community, and regulatory actions as well as a large number of studies were subsequently initiated.

Table 1.4 Summary of the great air pollution disasters.

Location, Date, Locale	Duration in Days	Day of Deaths	Fold Increase in Death Rate	Suspected Agents
Belgium, Dec. 1930, Meuse River Valley	7	5–6	10	SO_2, CO, acids, fluoride, metals, unknown secondary pollutants, synergistic factors
Donora, PA Oct. 1948, Monongahela River Valley	7	3	10	SO_2, CO, acids, metals, dusts, NO_x, secondary pollutants, synergistic factors
London, Dec. 1952, Thames River Valley	5	3	2–5	SO_2, acid aerosol, soot, hydrocarbons, secondary pollutants, synergistic factors

1.3.3. Early Epidemiology Studies

Although there were numerous epidemiology studies in the immediate period following the 1952 London episode that examined associations between air pollution and measures of health (mortality, pulmonary function, pulmonary symptoms, school absences, hospital admissions, etc), it is difficult to apply their conclusions today for a variety of reasons. Air pollution levels were generally high, and the measures were crude, including air-filter soiling and filter weighing (TSP). It is not easy to make reliable comparisons with modern measures (Roemer and van Wijnen, 2001). Each of these methods is affected by changes in air chemistry (which affects stain intensity on a filter) and by changes in the particle size

distribution. The TSP monitors in use had inlets that accepted variable fractions of large particles (25 to 50 μm aerodynamic diameter), so wind and relative humidity variations influenced the results. Studies in this period frequently suffered from the use of "central" (often in the center of a city) monitors to estimate exposures of broadly dispersed populations, and poor control for smoking, occupational exposures, socioeconomic factors, weather, influenza, and other potential confounders. However, progress was made because criticism of the methodology led to steady improvements in the studies.

In studies conducted after the "disasters", high concentrations (750 to 1,000 plus $\mu g/m^3$) of smoke particles and SO_2 were associated with mortality and other adverse health effects in normals, and somewhat lower levels appeared to effect sensitive people (Martin, 1964; McCarroll and Bradley, 1966; Lunn et al., 1967; Lave and Seskin, 1970, 1977; Lebowitz et al., 1972; Samet et al., 1981). Lave and Seskin's studies (1970, 1977) were among the first serious attempts to examine the long-term effects of air pollution on mortality in several cities. These investigators concluded that mortality rates were associated with air pollution measures, that fine particles and sulfates were the strongest indicators, and that mortality rates increased about 3% for each 10 $\mu g/m^3$ of particulate mass in the air. But these studies were criticized due to confounding (non-air pollution) differences in cities and poor definition of actual exposures of the studied populations (Lipfert, 1994). The studies by Lunn et al. of young children concluded that in Sheffield, England, respiratory illnesses in very young children were associated with long-term exposure to SO_2 and British Smoke. Martin (1964) derived excess mortality factors of 0.013% per $\mu g/m^3$ of smoke and 0.016% per $\mu g/m^3$ of SO_2, but the adequacy of the London sampling stations used for characterizing exposure has been questioned despite the fact that these unit mortality factors were consistent with the 1952 London experience (Lipfert, 1994). City effects on health were reported in the landmark Harvard Six Cities Studies, which utilized extensive air sampling, pulmonary function measurements, questionnaires, and sophisticated analytical methodology (Dockery et al., 1989, 1993). The Six Cities Studies were also significant in that the importance of indoor air pollutant exposures was demonstrated (Samet et al., 1988).

The forementioned, and other studies, supported the conclusions drawn from the great air pollution disasters. Major episodes, especially those with significant levels of sulfur compounds, were associated with adverse health effects in susceptible populations. As for the great episodes, it was not possible to disentangle the effects of individual pollutants, and unmeasured components in the air could not be ruled out as having equal, or greater, effects than the measured ones. These studies also raised new questions. Are there thresholds in concentrations of air pollutants below which no significant effects occur? How important is particle size as a factor in the toxicity of air pollution? Could healthy young people (other than infants) be adversely affected by air pollution? Could air pollution produce new cases of chronic disease? Would improvements in air quality lead to measurable improvements in health? Even today, when the air quality is significantly improved throughout much of the world, most of these questions are still debated.

The studies during this postdisaster period would lead to another era in particulate air pollution research with an increased awareness of several important factors, including the following:

- The crude air monitoring techniques used for establishing compliance with air standards were of marginal use for health-effect studies.
- Characterization of population exposures would be a major challenge for future studies.
- Significant sophistication was needed in the design of epidemiology studies, especially for dealing with confounders.
- Epidemiological studies alone would not be able to identify causal agents with sufficient accuracy to allow efficient, targeted control strategies.

1.3.4. Modern Epidemiology Studies

As air pollution levels declined in the United States over the past several decades, epidemiological investigations underwent considerable sophistication. Higher-quality aerometric data has been incorporated, and greater attention has been paid to confounders. Additionally, and most important, the statistical techniques used by modern epidemiologists have seen considerable evolution. When the U.S. EPA published its review and analysis of epidemiology studies in the 1996 criteria document (EPA, 1996), a set of questions was used to address the utility of epidemiological studies. These questions related to (1) the quality of air pollutant measures used; (2) the definition and selection of study populations; (3) the reliability of the health measures used; (4) the appropriateness of the statistical analyses; (5) the control of confounding factors; and (6) the consistency, coherence, and plausibility of the findings. The studies themselves were grouped by the EPA into four categories: (1) acute effects; (2) prospective studies in which health measures were followed; (3) long-term, cross-sectional studies comparing distinct populations at a point in time after exposure; and (4) synthesis (including meta analysis) studies. Each of these types of studies has distinct strengths and weaknesses. For discussions of these strengths and weaknesses, the reader is referred to several works (Friedman, 1994; Lipfert, 1994; EPA, 1996; Pope, 2000b).

The modern epidemiology studies used techniques that were very effective in detecting subtle associations between measures of particulate air pollution and measures of adverse health effects. The result was that associations were found that implied that levels of pollutants far lower, in fact well below accepted air-quality criteria, were possibly adversely affecting human health on a wide scale. These studies stimulated substantial scientific controversy and even questions about whether it would be possible to achieve air standards below which no adverse effects could be detected.

The modern epidemiology study findings have been succinctly summarized in review papers by the leading epidemiologists (Pope et al., 1995; Pope and Dockery, 1996; Pope, 2000a, 2000b). Several studies have found associations between short-term changes in particulate air pollution and acute mortality (cardiovascular and respiratory related) and acute morbidity (hospital admissions, emergency room visits, exacerbation of asthma, respiratory symptoms, lung function measures, restricted activity days in workers, and school absences). For the most part, these studies associated ill effects with increases in PM_{10} (mass of particles smaller than 10 μm aerodynamic diameter) over previous levels. The change was

typically calculated as the difference between the PM_{10} on the date in question and the average PM_{10} of the previous one to four days (Li and Roth, 1995). Table 1.5 summarizes the initial estimates of epidemiological associations in relation to an increase (or increment) in PM_{10} of 10 $\mu g/m^3$ over a recent daily average value. Although the associated effects per 10 $\mu g/m^3$ PM_{10} increment are small, when multiplied by the millions of persons exposed (virtually everyone in U.S. cities), thousands of deaths and other adverse effects have been postulated. These types of associations for acute effects have been seen in dozens of cities worldwide.

Table 1.5 Summary of typical epidemiologic associations between percentages of increases in adverse effects and increments of PM_{10} (from Pope et al., 1995) (LRT = lower respiratory tract, URT = upper respiratory tract).

- Mortality up for each 10 $\mu g/m^3$ PM_{10} increment:

Total	1%
Respiratory	3%

- Hospital admissions and visits up for each 10 $\mu g/m^3$ PM_{10} increment:

Respiratory	1%
Asthmatics	3%

- Other associations for each 10 $\mu g/m^3$ PM_{10} increment:

Asthma attacks	+3.0%
Cough	+2.5%
LRT symptoms	+3.0%
URT symptoms	+0.7%
Lung function	-0.1%

Chronic exposures to low levels of particulate air pollutants were also associated with adverse effects in the modern studies (Pope et al., 1995). In the aforementioned Six Cities Study, over 8,000 adults were followed for 14 to 16 years in six U.S. cities in which TSP, PM_{10}, $PM_{2.5}$ (particles under 2.5 μm in diameter), H^+ (acidity), and sulfates were monitored. Across these cities, increased cardiopulmonary mortality was associated with particulate air pollution (Dockery et al., 1993). In a similar eight-year study involving about 500,000 adults in 151 U.S. metropolitan areas, an association was observed between mortality (from all causes) and sulfate and $PM_{2.5}$ (Pope et al., 1995). This study drew data from the American Cancer Society (ACS) Prevention Study.

The importance of these studies lies primarily in their consistency; that is, similar associations were seen linking health effects to particulate measures in a

large number of cities. Also, the modern associations appear to be showing effects that are similar to those of the great air pollution disasters. The weaknesses include the use of increments in particle mass (which are different than actual levels) and the very sophisticated mathematical models that were used to account for confounding factors (gaseous pollutants, weather variables, etc.) (Moolgavkar et al., 1995; Li and Roth, 1995). Subsequent reanalysis of the acute effects seen in Philadelphia, commissioned by the Health Effects Institute (HEI, 1997), verified the statistical validity of the associations, but at significantly lower relative risk levels than were originally reported. The HEI analysis concluded that "Given the limitations discussed above, it is not possible to establish the extent to which particulate air pollution by itself is responsible for the widely observed association between mortality and particulate air pollution in Philadelphia, but we can conclude that it appears to play a role" (from the HEI Statement in HEI, 1997).

1.4. LESSONS LEARNED

The early air pollution disasters and the epidemiology studies that followed have taught many lessons. Major episodes of urban air pollution are capable of producing significant numbers of deaths and illnesses in susceptible people over a relatively short period of time. The adverse effects, seen within a few days into an episode, are difficult to attribute to any specific pollutant, but heavy industrialization and the widespread use of "dirty" fuels are known to be problematic. The problem of identifying specific culprit pollutants has become even more difficult as the air in cities has become less polluted, yet associations between several measures and ill effects are still consistently observed. The methods used in epidemiological investigations have evolved rapidly, and the sensitivity of such methods challenges researchers to understand the potential effects of tiny perturbations in air quality. There is a clear need to involve the techniques of modern human clinical investigations and sensitive laboratory animal studies to interpret the epidemiologic associations. It is also clear that the proper measures of urban air pollution have still not been discovered. This is especially true in the case of increments in, as opposed to levels of, pollutants showing associations with adverse effects. The picture is unclear as to which pollutants might be harming whom and by which mechanisms of injury. This lack of clarity stimulates controversy and frustrates drawing firm conclusions regarding appropriate pollution controls.

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CHAPTER 2
Historical Overview

2.1. RELEVANCE TO THE PM CONTROVERSY

Today there is great concern in many segments of the public, regulatory, and scientific communities over the health effects of low levels of urban particulate air pollution (particulate matter, PM), which has been estimated to claim between 15,000 and 60,000 lives yearly in the United States alone. Some believe that the threat is overstated or even trivial and that further regulation of urban PM is premature or even harmful to public health. Others press for immediate and strong regulatory actions to drive urban PM levels down well below current concentrations. It is useful to explore in a broad manner how the concerns over particulate air pollution might have developed and why PM generates such strong interest. As this is being written, hundreds of millions of dollars are committed to research and litigation related to PM. What the future holds is unpredictable. The key issues will not be settled soon, and the long-term impacts of this controversy on both science and regulation are significant. This chapter addresses two topics—how fears of air pollution may have developed and how regulation of particulate air pollution has evolved.

2.2. THE BIOLOGY PROBLEM

Mammalian biology predisposes humans to fear air pollutants for many reasons. The need for oxygen is one of our greatest physiological urgencies, being similar to the need to escape physical pain. Oxygen deprivation for more than about 15 seconds produces anxiety, and after 3 minutes death is near. Each breath can be a significant event when it is not easy and satisfying. Additionally, the respiratory system is both complex and vulnerable to injury.

The average resting adult inspires 15 breaths per minute, with each breath having a volume of about 500 cc. Thus, in a day, the air intake is about 10,000 liters. This is a huge volume compared to the daily intakes of 1 to 2 liters of food and of water. Air is rapidly brought into contact with about 70 m^2 of the thinnest and most delicate membranes of the body – the alveolar walls. The alveoli are thus exposed continuously to the normal gaseous components in air (nitrogen, oxygen, water vapor, and trace gases) plus any contaminants present.

Each breath also contains about 1 million or more tiny solid and liquid particles. Many are potentially infectious (bacteria, fungi, and viruses), and others are capable of chemically damaging the respiratory system. This threat is balanced by specialized cell populations in the lungs that engulf, remove, and destroy

infectious entities and many chemical toxicants. Other cells divide and replace damaged tissues. When the insults to the respiratory tract exceed its defensive capabilities, disease will result.

The deep lung is sheltered by the oral and nasal cavities, pharynges, and thousands of branching tubular bronchi and bronchioles. These airways have a relatively thick liquid mucus layer and sensory systems and muscles that regulate their opening sizes. When irritants or allergens land on the mucus, the sensory apparatus can trigger a variety of responses. These responses include altering the breathing rate, changing the thickness of the mucus coating, and producing involuntary bronchial muscle contraction. When these defensive reactions are strong, the results can be alarming, including difficulty in drawing a breath, choking on excess mucus, uncontrollable coughing, and sustained bronchoconstriction.

The upper respiratory tract is also home to the olfactory apparatus, which cannot be overlooked when considering air pollutants. The sense of smell is exquisitely sensitive and involves regions in the brain that produce both conscious and unconscious reactions. The brain has two main functions – to get us what we want and to keep us out of trouble. One ancient function of our sense of smell is to detect threats, such as the proximity of a predator. Odors that are unfamiliar or disagreeable can trigger aversion or even fear.

2.3. PHYSICAL FACTORS

Air pollutants are ever-present and varied. Natural and anthropogenic phenomena in our environment and our individual actions produce gaseous and particulate air pollutants. Living things shed dead cells and other biological debris; microbes and plants produce spores and pollen; liquids produce droplets due to splashing and bubbling; and wind picks up particles from dry surfaces. Combustion and industrial processes add to the air contaminant load. Reactions among air contaminants produce an ever-changing contaminant mixture. At any given time, hundreds to thousands of different pollutants are suspended in the ambient air. When the pollutant concentrations or toxicities exceed our level of adaptation, a distress condition can result.

Air is an excellent vehicle to efficiently transport and deliver contaminants to the respiratory system. Air is a viscous fluid microscopically, which means that tiny particulate air pollutants can remain suspended in it for long periods – several hours or more. The viscous air entrains small particles, which in turn enter the respiratory system during inhalation. In short, the ocean of air in which we live is an effective medium for bringing pollutants into our bodies.

2.4. TOXICOLOGY: THE SCIENCE OF POISONS

Nature produces an astounding array of plant and animal toxins to fend off competing species, predators, and parasites and to subdue prey. Similarly, humans have created poisons for controlling pests and for eliminating other people. Technology, both primitive and modern, has also produced substances that cause poisonings. Poisonous substances have been in the environment longer than humans

have, and they are continuously evolving as a result of changing natural and anthropogenic factors.

Toxicology developed to deal with recognizing and controlling chemical poisons. Toxicology addresses natural and anthropogenic toxicants, the organs that are affected, and the mechanisms by which toxicants harm the body. Inhalation toxicology is concerned with airborne toxicants, both natural and anthropogenic, irrespective of which organs or organ systems might be adversely affected. Like other branches of toxicology, inhalation toxicology is not balanced; only adverse effects are tallied and potentially beneficial effects are not considered. This lack of balance can lead to a magnification of the negative attributes of substances. Any substance, including an air pollutant, when subjected to a toxicological examination will be found to be harmful; the probability of actual harm in realistic circumstances, along with potential beneficial effects of exposure, are often left out of the picture. Thus, the nature of inhalation toxicology often serves to magnify the level of risk associated with air pollutants – especially in the minds of those not well versed in the health sciences.

2.5. AIR POLLUTION FROM ANTIQUITY

The earth's atmosphere has seen continual change, both before and after the assent of humans. In reviewing the history of air pollution, Leslie Chambers (1976) pointed out that the first catastrophic air contaminant was probably oxygen. Early life would not have depended on oxygen, which was probably nonexistent in the free state prior to photosynthesis. Therefore, the increase in concentration of gaseous oxygen was likely a catastrophe for early life forms. Yet this highly reactive gas permitted the rise of oxygen-metabolizing organisms including ourselves.

During the prehistoric period, natural phenomena such as fires, dust storms, products of decay, and emissions from biological sources would have posed challenges to the health of people. Early human activities associated with obtaining food, clothing, and shelter modified air quality in the vicinity of early family or tribal groups. The domestication of fire in the old Stone Age (prior to 50,000 B.C.) and its use inside primitive dwellings would have produced a significant change in air quality. In the middle Stone Age (30,000 to 10,000 B.C.), a factor that would have increased exposure to air pollutants was the transition from nomadic to permanent and more crowded communities. The new Stone Age (10,000 B.C. and later) saw greater concentrations of population and the development of village activities such as mining, manufacturing, farming, and herding. These activities would have led to changes in air pollutants, both with respect to types and concentrations. The first modern civilizations were also impacted by poor air quality. Studies of tissues from 5,000-year-old Egyptian mummies show the existence of pneumoconiosis (lung disease produced by dust), carbonaceous deposits, and possibly invasive nasal/sinus cancers due to the inhalation of organic carcinogens (Lippmann and Schlesinger, 1979; Brimblecombe, 1999). This evidence also points to the early impact of dusty trades and the adverse effects of chronic exposures, which were facilitated by increased lifespans.

The evolution of fuel and the technology for using it had a significant impact on humans' ability to maintain health. Wood, a primary energy source of

early civilizations, left a record of blackened surfaces on the walls of dwellings. Early written records of respiratory deaths focused on suffocation and poisonous gases, indicating that wood smoke was not widely perceived as a health threat (Chambers, 1976). Smelting and other early industrial activities were later recognized as causes of respiratory illnesses (Lippmann and Schlesinger, 1979). The depletion of wood reserves and the discovery of coal as an energy source changed the nature of air pollution in the human environment.

Coal usage was associated with the rise of industrialization and the presence of a more odorous and irritating combustion product (largely due to coal's sulfur content). Written records from England document the impact of coal combustion on the development of air pollution regulations. Apparently the discomfort of nobility during the reigns of Edward I (1272–1307), Edward II (1307–1327), Richard II (1377–1399), and Henry V (1413–1422) led to official actions against the free use of coal (Chambers, 1976; Lippmann and Schlesinger, 1979). These actions moved from a mere protest against the use of "sea coal" to the torture of a man for creating "pestilential odor," taxation on coal use, and eventually the establishment of a commission to oversee the importation of coal (Chambers, 1976). The problem may have been temporarily abated by effective chimneys in the 1500s, but the introduction of the steam engine exacerbated the issue and apparently led to stronger regulation (Brimblecombe, 1999).

In 1661, John Evelyn (scientist and cofounder of the Royal Society) published *Fumifugium; or the Inconvenience of the Aer and Smoke of London Dissipated; Together with Some Remedies Humbly Proposed* under the command of Charles II (Chambers, 1976). This document included a scholarly discussion of the sources of pollutants, their effects, and proposed controls (Lippmann and Schlesinger, 1979). Evelyn's work set the stage for systematic investigations and rational controls on urban air pollution such as the British Alkali Works Regulation Act of 1863, which led to the use of high stacks to limit ground levels of acidity (Lipfert, 1994).

By the beginning of the nineteenth century, public pressure prompted the formation of official committees and eventually official inspectors and regulations to control coal-burning emissions (Chambers, 1976). This development was reinforced by the London air pollution episode of 1952, which prompted studies of the effects of air contaminants on populations (Bates, 1999). Meanwhile, the discovery of oil in Pennsylvania and its wide use as a fuel changed the nature of urban air pollution. The lower sulfur content of oil compared to that of coal produced a new type of smog. This form of air pollution, known as *photochemical smog*, contained ozone and other oxidants that were documented as producing lung damage in laboratory studies. Studies by A.J. Haagen-Smit showed that smog was formed by the action of ultraviolet light on hydrocarbons and nitrogen dioxide (Chambers, 1976).

2.6. GAS WARFARE AND AIR POLLUTION DISASTERS

Although the military use of fire, smoke, and suffocating gases predates modern times, the use of poison gas in World War I convincingly demonstrated the lethality of airborne toxicants (Wachtel, 1941; Withers and Lees, 1987). The French are credited with the first, though unsuccessful, use of grenades containing ethyl

bromacetate (a strong mucous membrane irritant) in 1914. The following year, the Germans released nearly 200 tons of chlorine (also a strong irritant) from cylinders at Ypres, Belgium, which produced about 15,000 casualties, stimulating the development of effective gas masks. Mustard gas (β, β dichlorodiethylsulfide), a highly lethal irritant when inhaled or deposited on the skin, was successfully used by the Germans in 1917. This agent was the highest toxic casualty producer, although other gaseous agents were used by both sides in World War I. The war's gas casualties may have exceeded 1 million (Wachtel, 1941). Such military uses served to instill a public fear of poisonous clouds, setting the stage for the great air pollution disasters that were documented decades later.

The first of the three great air pollution disasters occurred in Belgium's Meuse River Valley in 1930. In December, a thick, cold, stagnant fog that trapped industrial air contaminants was blamed for thousands of illnesses and 60 deaths. A second disaster, in October 1948, occurred in Donora, Pennsylvania, a heavily industrialized town in the Monongahela River Valley. A damp inversion and buildup of air pollutants in the fog was blamed for causing illness in over 40% of the population of 14,000 and increasing the normal death toll from 2 to 20 during the period. The third episode involved a five-day foggy inversion in industrial London in December 1952. In the London episode, 4,000 excess deaths were attributed to the polluted air. These three episodes, and to a lesser extent others, firmly established the dangers associated with domestic and industrial air emissions.

2.7. A REGULATORY HISTORY

Regulation of air pollutants tended to be sporadic prior to the twentieth century. Descriptions of philosophies and important events can be found in a variety of sources (Chambers, 1976; Lippmann and Schlesinger, 1979; Stern, 1982; Lipfert, 1994; Brimblecombe, 1999; Holgate et al., 1999; and Costa, 2001). In the twentieth century, air-quality regulations became commonplace in Western nations. In Britain, the Clean Air Act of 1956, which initially focused on control of air pollution from domestic heating, was extended to industry in 1968 (Lipfert, 1994). In 1971, the Canadian Clean Air Act established national regulatory authority, and the 1988 Canadian Environmental Protection Act defined 44 substances that had the potential for harming human health. In the United States, some cities, counties, and states adopted air pollution ordinances and laws prior to federal involvement. A bill was passed in 1955 authorizing the Public Health Service (of the U.S. Department of Health, Education, and Welfare) to conduct research on air pollution. Additional legislation in the United States was initiated with the Clean Air Act of 1970, in which the newly established U.S. Environmental Protection Agency (EPA) was authorized to set National Ambient Air Quality Standards (NAAQS), both primary (for protecting human health) and secondary (for other effects) (Grant et al., 1999). The NAAQS are currently focused on six pollutants that are considered to present dangers to human health or welfare: ozone, carbon monoxide, particulate matter, sulfur dioxide, nitrogen dioxide, and lead. In setting primary NAAQS, the cost and feasibility of attainment were excluded by law, and a five-year cycle of review of the standards was mandated. The responsibility for devising plans to meet the NAAQS was left to the individual states, subject to EPA review. Subsequent amendments to

the Clean Air Act added stratospheric ozone-depleting substances, acid rain, and 189 hazardous air pollutants (HAPs).

2.8. MODERN EPIDEMIOLOGY

A number of epidemiologic studies published circa 1990 using advanced analytical methods had a profound effect on the NAAQS review of particulate matter (EPA, 1996). These studies, which used large data sets for health effects and monitored air pollutants, fell into three broad categories: acute studies that related health effects in large populations to pollutant levels (or changes in levels) occurring over a period of one to a few days, prospective cohort studies that related air monitoring to health outcomes in a large number of individuals followed over a long period (usually years), and cross-sectional studies that compared measured pollutants to the health status of populations with different long-term exposures. It was recognized that each type of study had strengths and limitations and that epidemiology studies alone were not capable of establishing cause-and-effect relationships. The Six Cities Study (prospective cohort) focused on the death rates of 8,000 adults living in six cities in eastern portions of the United States (Dockery et al., 1993). Averaged community air monitoring data for several indices of air pollution (including total particle mass, inhalable particle mass, fine and coarse particle mass, sulfuric acid, sulfate, SO_2, NO_2, and O_3) were examined separately and correlated with the risk of dying in each city compared to Portage, Wisconsin (the city with the least air pollution). Death rates were corrected for population differences in age, gender, smoking, education, and body mass, but not for occupation, diet, income, or physical activity. Several air-quality measures, including fine, total, inhalable and sulfate particle mass, were significantly associated with decreased lifespan. Figure 2.1 shows the results for total and fine particle mass.

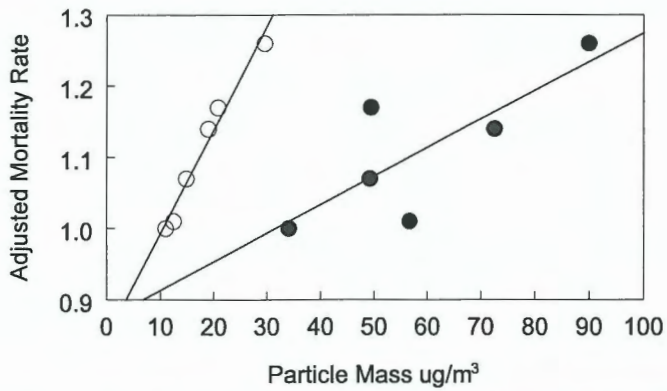

Figure 2.1 Sample results from the Harvard Six Cities Study in which the mortality rate relative to Portage are plotted vs. two measured air pollutants. Fine particles and total particles are represented by open and solid circles, respectively.

The acute effects studies compared changes in particulate mass over the previous few days' average to changes in health measures, including hospital admissions, respiratory and cardiac symptoms and deaths, and pulmonary function. These studies were summarized by Pope et al. (1995) for 10 cities. Since each population was evaluated over a short period, confounders such as age, gender, education, income, smoking, and health status were not factors; the major methodologic challenge involved correcting the results for confounding variables such as weather and unmeasured copollutants, which were known to affect the health outcomes and which were related to the measured pollutant levels. The initial results, summarized in Table 2.1 (Pope et al., 1995), indicated that several adverse health outcomes were associated with remarkably small increases (over the previous days' levels) in particulate mass. These data were subjected to challenges and reanalyses (HEI, 1995, 1997, 2002). The magnitudes of the health-effect findings were subsequently decreased compared to those in Table 2.1, but their statistical significance remained. Thus, both long-term and acute health effects were associated with particulate air pollutant levels below the then current NAAQS.

Table 2.1 Epidemiologic associations for increments in daily particulate mass and adverse health outcomes (Pope et al., 1995).

	For Each Increment of 10 μg PM_{10}/m^3 Air
Total mortality	Up 1%
Respiratory mortality	Up 3%
Hospital visits	
Respiratory	Up 1%
Asthmatics	Up 3%
Asthma attacks	Up 3%
Lung function	Down 0.1%

2.9. RECENT EVENTS

2.9.1. New PM Regulations in the United States

Primarily as a result of its analysis of epidemiologic data on PM, the U.S. EPA issued new primary (health-based) NAAQS in July 1997. The EPA was under pressure to work quickly as a 1995 ruling by a U.S. District Court (in response to a lawsuit filed by the American Lung Association) ordered the agency to promulgate revised PM and ozone standards by January 1997. The new standards (Table 2.2) for all practical purposes retained the previous limits for PM_{10} (particles 10μm or less in aerodynamic diameter) and created new limits for another class of particles, $PM_{2.5}$ (particles 2.5μm or less in aerodynamic diameter). The standards were based

on two previously invoked averaging times, 24 hours and 1 year, to protect the public from short-term (acute) effects and long-term (chronic) effects, respectively. The logic behind the particle size range for the new $PM_{2.5}$ standards was that smaller particles had both differences in chemistry and health effects compared to the larger PM_{10} size range.

The process used by the U.S. EPA in establishing the new standards is, and was, quite elaborate (Grant et al., 1999). First, a "criteria document" (CD) including a review of the published scientific data on chemistry, sampling, sources, environmental concentrations, human exposures, dosimetry, toxicology, and epidemiology was prepared with the aid of non-EPA experts. The 1996 PM criteria document is about 3,000 pages long. After the CD was critiqued and revised, the EPA technical staff interpreted the report and prepared a "staff paper" containing recommended revisions to the NAAQS for the EPA administrator. The CD and staff paper were then reviewed by a Congress-mandated group of technical experts, the Clean Air Scientific Advisory Committee (CASAC). After its review, the CASAC prepared comments that were transmitted to the EPA administrator through a series of letters. EPA staff then prepared a revised staff paper. The CASAC accepted the revisions and issued a "closure" letter to the EPA administrator. In this case, the chairperson of CASAC, Dr. George Wolff (a principal scientist for General Motors Corporation) stated that "the CASAC Panel succumbed to the pressures exerted by the accelerated schedule and reluctantly came to closure on the CD" (Wolff, 1996). The EPA administrator, the Honorable Carol Browner, issued Advance Notice of the proposed NAAQS in June 1996 and solicited public comment; over 50,000 comments were received. The final standards were promulgated 13 months later, but they were soon after legally challenged.

Table 2.2 Primary NAAQS for particulate matter issued in July 1997 by the U.S. EPA. The standards are mass-based in that μg of particles per m^3 of air is the regulated metric. The old 24-hour PM_{10} standard, which allowed one exceedance per year, was changed to require the 99th percentile concentration to be within the target value. The $PM_{2.5}$ standards were based on meeting a 98th percentile value for 24 hours and a three-year arithmetic mean for the annual value.

Criteria Pollutant	24-Hour Standard ($\mu g/m^3$)	Annual Standard ($\mu g/m^3$)
PM_{10}	150	50
$PM_{2.5}$	65	15

2.9.2. Legal Actions

Although it was not a unique development, a number of legal actions were initiated in response to PM research and regulation. Various parties sued to (1) gain

access to pertinent scientific research data, (2) overturn the new PM (and ozone) regulations, and (3) eliminate the authority of the U.S. EPA to establish legally enforceable air standards. Logical arguments and counterarguments were made on each side of these issues.

The issue of access to scientific data involves opposing interests. The first interest is that of access control by scientific investigators to data that they have created. Such data are valuable in that they can be used to develop future research proposals to maintain lines of investigation. Making databases available to others can lead to decreased competitiveness and the loss of key personnel. The opposing interest applies to data that are used for setting standards. It can be argued that the public interest is best served by making all such research data a matter of public record. Any investigator can then perform a reanalysis and publish their results, which may support or challenge the original study. Scientists themselves are divided on the issue of open access to data sets and even the methods used for data analysis. In an attempt to balance these opposing interests, Cohen and Hahn (1999) proposed several recommendations relating to access to scientific data. Among these were allowing public access to data that have an economic impact of at least $100 million; allowing access to data acquired under new, but not prior, federal grants; and establishing an agency that would replicate findings of studies that have a significant impact on regulations. In 1999, an amendment was made to Circular A-110, which provides standards for the administration of federal grants in the United States. The amendment makes data relating to published findings, which were used to develop "agency action that has the force and effect of law," available on request under the Freedom of Information Act. The amendment was not retroactive, and certain types of information (e.g., trade secrets and personal information on research subjects) were protected from disclosure. Whether or not this solution to the problem of public access to scientific data is a final one remains to be seen.

An attempt to overturn the new NAAQS for PM (and ozone) came in the form of a suit filed with the U.S. Court of Appeals for the District of Columbia Circuit (*American Trucking Association v. EPA*). The American Trucking Association was joined in the suit by the U.S. Chamber of Commerce, other business interests, and the states of Michigan, Ohio, and West Virginia. The suit claimed that the U.S. EPA had exceeded its authority by failing to take into account the costs of the new rules and that it had failed to adequately defend their selection of the specific PM criteria. The three-judge court ruled two to one in May 1999 that the U.S. EPA had failed to articulate an "intelligible principle" for selecting the NAAQS and declared the new air standards were void (Langworthy and Goldberg, 2000). However, the court supported the EPA's stance that it could not take into account the costs associated with implementing the NAAQS when setting the standards. In June 1999, the EPA petitioned the District of Columbia Circuit Court to rehear the case. The court declined, and in January 2000, the EPA (and the American Lung Association, the Commonwealth of Massachusetts, and the state of New Jersey) petitioned the U.S. Supreme Court to overturn the lower court's decision. The Supreme Court was also asked to rule on whether the EPA had the authority to establish legally binding air (and other) regulations. In February 2001, the U.S. Supreme Court issued a unanimous decision. Siding with the EPA, the court concluded that the agency was legally barred from taking compliance costs into account and that the EPA had acted within its discretionary scope in establishing the

NAAQS. It is unlikely that similar legal action challenging the EPA's authority will be pursued in the foreseeable future.

To strengthen the role of science in environmental regulation, the U.S. Congress held a series of hearings in the late 1990s. Congress directed the EPA to seek the assistance of the National Academy of Sciences in defining a research program that would aid the establishment of future PM NAAQS. The Committee on Research Priorities for Airborne Particulate Matter of the National Research Council, chaired by Dr. Jonathan Samet, defined the needed research and evaluated its progress (NRC, 1998, 1999, 2001).

2.9.3. Media Coverage

In 1993, the lay and scientific print media in the United States published numerous articles proclaiming the lethality of urban particulate air pollution – even at levels previously deemed to be safe. Figure 2.2 reproduces some of the headlines. About three years later, the coverage shifted to the controversial nature of the new standards for PM (Figure 2.3). In 2000, the press coverage focused largely on legal proceedings related to the new PM standards.

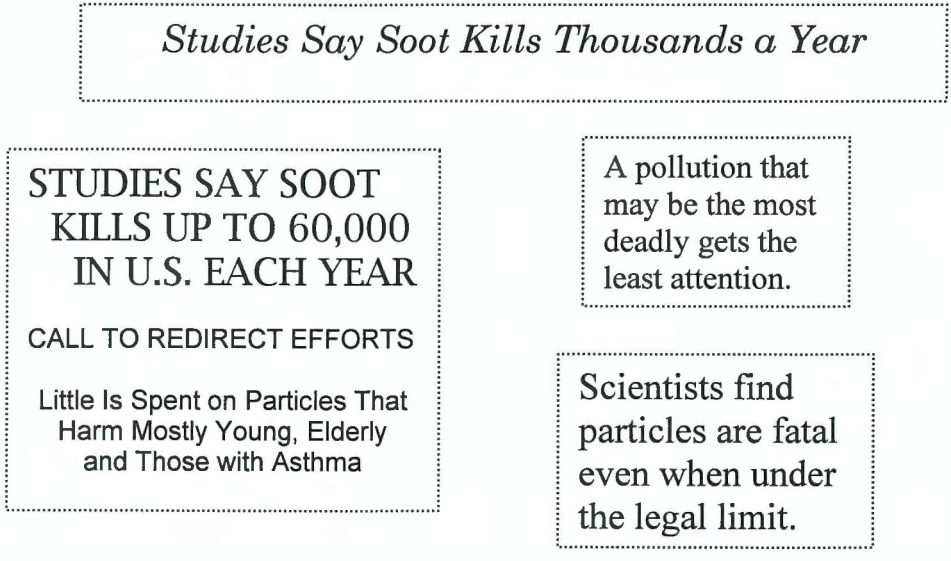

Figure 2.2 Press headlines in 1993 from *Time, Science, Scientific American,* the *New York Times* and the *Los Angeles Times.*

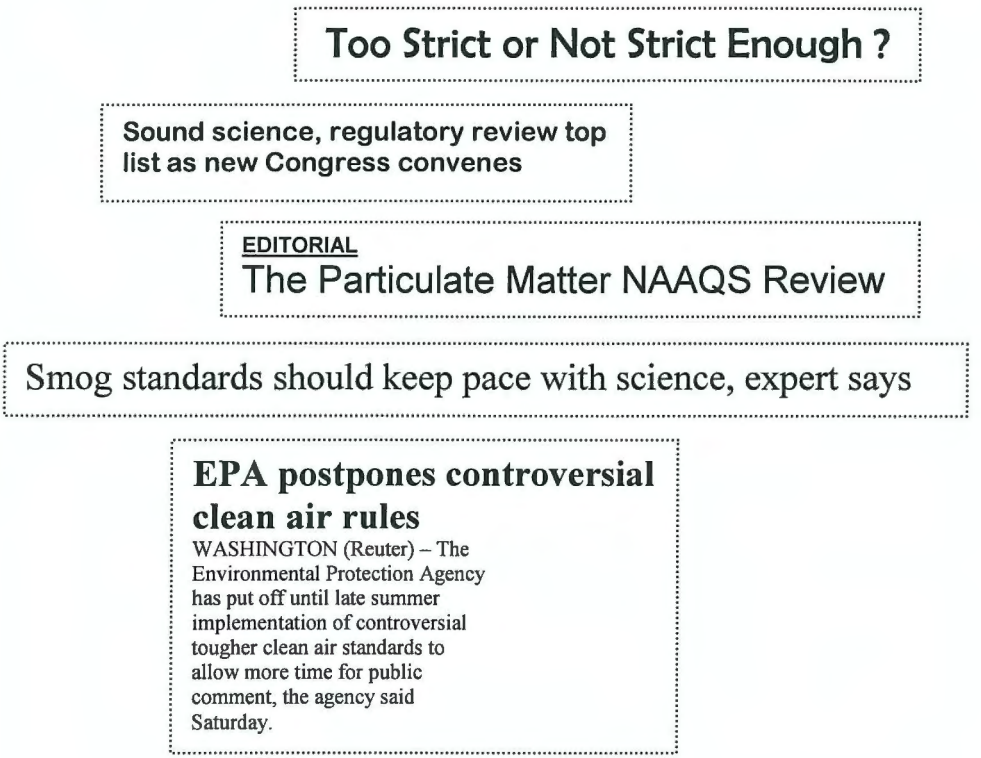

Figure 2.3 By 1996, the focus in the press had shifted to the controversy. These headlines are from the *Los Angeles Times*, *Journal of the Air and Waste Management Association*, *Environmental Science and Technology*, *Environmental Management,* and *CNN Interactive News*.

2.10. LESSONS LEARNED

By considering the long history, including prehistory, of particulate air pollution, a variety of observations can be made. The issue of health impacts of particulate air pollution is not likely to disappear in the foreseeable future. The requirements for breathing large volumes of air, the relative delicacy of the respiratory system, and the fact that virtually all human activities generate particulate pollutants support this prediction.

In the past, it was possible to have confidence in simple regulatory strategies to reduce risks, largely because alternate technologies were available and exposures were substantial. Today, with the risks to an average individual small, new controls and new technologies are not guaranteed to reduce them. In addition, reducing the level of one pollutant can increase the levels of others, so analyses of remedial actions have become exceedingly complex. Regulatory actions are now

more complicated and more contentious. The situation is problematic because of the increased number of stakeholders who have an impact on regulation. The modern regulator must deal not only with the science but also with public perception, various advocacy groups, the media, and the courts. It is essential that the processes by which data are analyzed and complex factors are weighed be rigorous enough to satisfy the diverse stakeholders. It will be difficult to find a replacement for the simple principle of reducing harm to negligible levels by promulgating ever stricter air-quality standards. Regulators will be forced to adopt more sophisticated strategies for establishing standards and to clearly explain their analyses. Until new widely accepted principles for regulation are found, litigation can be expected, along with periods of chaos in industry because of the time and expense required to change successful practices.

The relevant sciences must improve their tools so that the full complexity of organism-environment interactions can be examined. The practice in toxicology of documenting only the harmful aspects of an exposure is no longer sufficient. Toxicologists are challenged to better understand the effects of low doses, effects of changes in pollutant levels (as opposed to just levels), and unusual or infrequent adverse responses. The relationship between acute and long-term health impacts must also be examined. New research projects must be designed to evaluate long-term effects. Long-range planning for the introduction of new technologies is needed because of the time required for research and development and the evaluation of potential adverse consequences. Risk assessors must also place more effort in identifying the potential adverse effects of tightening standards.

Another important lesson is that research must be coordinated across disciplines and the results better integrated. Epidemiology findings must be supported by laboratory research that can establish cause-and-effect relationships. The disciplines of atmospheric science, exposure assessment, and biostatistics must also contribute. In this regard, the analyses and recommendations of the National Research Council (NRC, 1998, 1999, 2001) appear to be an excellent first step.

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CHAPTER 3
Interpreting the PM Epidemiology

3.1. RELEVANCE TO THE PM CONTROVERSY

The epidemiologic associations published in the late 1980s and early 1990s linking adverse health effects to small increments over previous levels of particulate air pollution (particulate matter, PM) stimulated considerable controversy. The associations were unexpected and were obtained using complex novel methods. The epidemiologic findings introduced the possibility that minute levels of particulate air pollutants have serious effects on human health and that major unprecedented changes in our culture could be required to eliminate these effects. On the other hand, major changes in industry and lifestyle have unpredictable effects on health and no one could guarantee that the collateral damage would be an acceptable tradeoff. Another problem was that such low levels of anthropogenic particulate air pollutants had not been very active in toxicology or human clinical studies. Therefore, challenge and scrutiny of the epidemiologic associations were expected. Shortly after the new associations were given press coverage, scientists gathered to understand, examine, defend, and challenge the studies ("Proceedings", 1995). Table 3.1 lists some of the challenges raised. The main concern appeared to be that the epidemiology would be acted on without an appreciation of its limitations.

3.2. THE EPIDEMIOLOGIC ASSOCIATIONS

Although major air pollution episodes were known to increase short-term mortality and morbidity rates, reports published in and shortly after 1989 indicated similar effects in cities having low levels of PM. The studies were varied, covering acute and chronic effects associated with exposure to particulate air pollution. The magnitude and complexity of this research is evidenced by the U.S. EPA's 500-plus page summary and analysis (EPA, 1996). The acute effects studies of PM_{10} (mass of particles under 10 μm diameter) produced unprecedented results. When increments in particle mass (over the running average of previous particle mass levels) were correlated with lagged (one to five days) mortality and morbidity, small statistically significant associations were seen. The associations were observed in many cities worldwide, irregardless of the actual levels of particle mass. Tiny increments over virtually any running average of particle mass were associated with acute adverse health effects. These new epidemiology findings have been summarized along with a review of more than two dozen reviews of the findings (Pope, 2000). Nearly all reviews of the acute epidemiology studies concluded that the studies were consistent and that evidence existed of probable effects of PM on health. All of the reviews acknowledged that there were remaining uncertainties (Pope, 2000). The

Table 3.1 Some initial challenges to the associations of small increments in particulate air pollution (mainly PM_{10}) and human mortality and morbidity. From the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity ("Proceedings", 1995).

Challenge	Rationale
Absence of clinical plausibility	Neither clinical nor toxicological studies had uncovered effects at such low levels.
The deaths may be in hospitals and homes	The most vulnerable are likely to be the least represented by outdoor area samplers.
PM_{10} could be a surrogate for the real culprits	Although particulate mass was monitored, it seemed to be an unlikely cause. Further control of PM mass may not improve health.
Season and weather are large confounders	Temperature swings and other weather events produce adverse health effects as well as changes in air pollution.

uncertainties and concerns listed in the reviews included lack of information on biological mechanisms, limited information on personal exposures, difficulties in disentangling effects of any single air pollutant in the mix of pollutants, and lack of specificity as to whether or not particle mass is a surrogate for some other particle-related factor such as size, number, or composition (Pope, 2000). Although such concerns reflect general limitations of epidemiologic studies (Hill, 1965; Friedman, 1994; Taubes, 1995), the fact that the adverse health outcomes were almost exclusively cardiopulmonary related (as were seen in the great air pollution disasters) appeared to support the validity of the associations (Pope, 2000). These modern epidemiology studies were relied on by the EPA in revising standards for particulate matter (EPA, 1996).

3.3. PHILOSOPHICAL CHALLENGES

There are philosophical reasons that the epidemiologic associations were debated. Should epidemiologic data, without the traditional corroboration from toxicological or clinical studies, be accepted as a sufficient basis for regulatory action (tightening the particulate air pollution standards in this case)? Historically, control action has usually been taken when three types of studies—epidemiologic, toxicologic, and clinical—have been in hand and consistent. If an exception is made for particulate air pollution, why not make exceptions all of the time? If such a philosophy is adopted, how will spurious (no real cause and effect) or trivial (having

negligible health impact) relationships be filtered out of the regulatory process? Should substantial changes be made in industry (which supplies food, electrical power and other goods and services), lifestyle, and other accepted aspects of life on the basis of epidemiologic associations alone?

Another philosophical question is raised by acting on such associations. The question relates to the isolation of specific adverse effects without factoring in nonadverse effects. This is akin to looking at one side of a coin, with the estimated harm associated with PM on one side and the benefits associated with activities that generate PM on the other side. If the minimization of harm is important, can that be done by basing control strategies for risk factors solely on PM's direct adverse effects? If that were done for eating solid foods, which leads to the choking deaths of many Americans yearly (nearly 100 children are treated at Children's Hospital in Pittsburg, PA, annually for foreign body ingestion or aspiration [Rimell et al., 1995]), regulators might be expected to outlaw solid food in the American diet. Should all physical exercise be outlawed because it leads to premature deaths in the elderly and ill, as well as accidental injury and death in the healthy? In most areas of life, actions are taken not on isolated facts, but instead with consideration of the total consequences of an action. This philosophy of taking all consequences (beneficial and harmful) into account should be rigorously applied to environmental regulations.

3.4. CHALLENGES BASED ON THE SIZE OF THE ASSOCIATIONS

By any measure, the associations linking particles to adverse effects imply relative risks that are small. Initial estimates had put relative risks of mortality or morbidity on the order of 1.01 to 1.03 for each 10 $\mu g/m^3$ increment of particulate mass, and more recent refinements led to smaller risk estimates. An analysis of 90 U.S. cities placed the relative mortality risk of 10 $\mu g/m^3$ increments in PM_{10} at 1.005 (Samet et al., 2000). Although the risks may include very serious effects, including deaths, hospital admissions, and worsening of conditions such as asthma and bronchitis, the probability of such risks is small in relation to that of other risks that are routinely accepted (Cohen and Lee, 1979; Cohen, 1991). For perspective purposes, Table 3.2 provides examples of risks related to factors such as residence, occupation, and lifestyle. In the table, risk is expressed in terms of loss of life expectancy. The reasons that many risks are accepted include personal freedom, cultural tradition, and offsetting benefits, such as prosperity and survival.

Traditionally, epidemiologic associations that infer relative risks that are less than two or three (doubling or tripling the risk) have been regarded as weak enough to suspect that the associations are spurious (Taubes, 1995). Some other risk factor that is linked to the measured one may be the real cause. Yet there are many reasons why small epidemiologic associations receive attention. First, they may be reflecting a real cause-and-effect relationship. Second, the press seems to be eager to report a risk without seriously challenging whether it is spurious or trivial, let alone whether it has withstood scientific challenge. In fact, reports in the press subject the public to what is increasingly seen as an "epidemic of anxiety" (coined by Lewis Thomas as quoted in Taubes, 1995). The actions of the press, as explained by Taubes, is due in part to an overconfidence in the power of observational epidemiologic studies to provide information that accurately depicts reality. Thus,

the press may be more guilty of not adequately understanding the fallibility of science and the challenge required before facts are established than they are of deliberately misinforming the public. Another reason that positive epidemiologic associations receive attention relates to the reluctance on the part of many scientists to publish negative results. Those who conduct studies know that new funding, given the intense competition for grants, can rarely be acquired to follow up negative results. Thus, the motivation to publish negative findings is usually low. Finally, positive associations are of interest because they imply that reductions in risks are possible. If the associations between exposure to an agent and adverse health effects are real and significant, then action, in the form of voluntary or regulatory controls, may lead to a better future. The problem is that most PM exposures are also linked to some benefits, which erode when controls are imposed.

Table 3.2 The effect of various factors on average human lifespan (compared to 63 years for a worldwide average). (data are from varied sources as published by Cohen and Lee, 1979, and Cohen , 1991).

Factor	**Effect on Lifespan**
Residence	
Gambia	26 years lost
United States	12 years added
Japan	14 years added
Moving to Missouri from California	2.5 years lost
Occupation / Education	
U.S. president (assassination)	5.1 years lost
Firefighter	3.5 years lost
Coal miner	3.2 years lost
Educator	3.1 years added
Primary school dropout	2.2 years lost
College degree	2.2 years added
Lifestyle / Environment	
Alcoholic	11 years lost
Unmarried male	9.6 years lost
Male, relative to female (USA)	7.7 years lost
Living in poverty (USA)	6.9 years lost
Unmarried female	4.4 years lost
Cigarette smoker (average for male and female)	3.5 years lost
35% overweight (average for male and female)	2.6 years lost
Driving small instead of large car (USA)	70 days lost
One pound overweight	34 days lost
Air pollution (USA Average)	23 days lost
Natural radiation exposure (USA)	8 days lost

3.5. ECOLOGIC STUDY ISSUES

Ecologic studies focus on groups as a whole, as opposed to individuals. When groups of individuals are used in studies that produce statistical associations, special problems arise. Friedman (1994) states that when a positive association is found, "five basic questions will usually require immediate attention." First, is the association a chance occurrence? Second, could bias have produced the association? Third, is the association due to confounding variables? Fourth, within the group, to whom does the association actually apply? Fifth, is a cause-and-effect relationship producing the association? Each of Dr. Friedman's questions is applicable to ecologic studies.

3.5.1. Chance Findings

Good statistical techniques can address the problem of chance findings. This is usually done by establishing confidence limits around a result. Confidence limits, such as the 95% confidence interval, place an understandable uncertainty around a finding. For a relative risk, if this interval does not include 1 (no change in risk), then there is probably no more than a 5% chance that the risk is a statistical fluke. But even here, if enough analyses are done, there is a good chance that many will produce mutually supportive positive associations, even though the association is a chance occurrence. This is a potential problem if negative findings are not reported as frequently as are positive findings. Also, some reported epidemiologic studies were positive for some particulate measures, say PM_{10}, but others positive only for total PM or other measures. Some studies were positive for the increase in a specific PM measure over a previous three-day average, but others for an increment above a five-day average. Also, some reported studies were positive for a given measure of effect, and others a different effect. So although many studies passed a confidence-interval evaluation, each study was somewhat different from the others, raising the possibility that statistical chance may have been more important than is apparent. This problem must be addressed by the use of standardized methods. The Health Effects Institute (HEI) of Boston, MA, has taken a leadership role in analyzing the epidemiologic findings on particulate air pollution in a manner that controls for such problems (e.g., Samet et al., 2000). The continuing series of HEI reports (HEI, 2001) should be followed by those interested in this problem.

3.5.2. Bias

Bias has many forms; selection bias, information bias, and confounding bias are usually considered in epidemiology (Marsh, 1992, Friedman, 1994). In some cases, bias is more likely to obscure an effect than to produce an artifactual one. Yet bias due to confounding (bias due to factors that differ between groups that are being compared) can produce false positive associations. Confounding bias is perhaps the most difficult to correct for. Confounding bias occurs, for example, when an unmeasured risk factor is a true risk factor for the adverse health outcome, and it is associated with the measured factor. For particulate exposures several such potential confounding factors have been identified. Significant changes in particle levels accompany changes in seasons, days of the week, weather variables, fuel

quality, fuel usage, changes in nonparticulate pollutants, and changes in human activity patterns (Valberg and Watson, 1998). In addition, the chemistry of high-particle air pollution episodes differ from the normal air chemistry (Larson and Cass, 1989; Tsai and Cheng, 1999; Tuch et al., 1997; and Woo et al., 2001). Lipfert (1994) discusses these and other factors related to uncertainties in particulate exposure associations. Additional research must be conducted to understand the impact of these several forms of bias on the epidemiologic associations between particulate exposure and adverse human health measures.

3.5.3. Particulate Mass as a Surrogate

It is likely that particle mass per se is not producing the observed health effects. With respect to particulate air pollution and human health, an unmeasured factor related to both the mass of particles in the air and to health could lead to the observed associations. Possible confounders include an unmeasured air pollutant (such as reactive metals, gases/vapors, allergens and combinations of contaminants), particle count, meteorological factors that modify particulate levels, and behavioral factors that increase air pollution and adverse health outcomes. Another potential confounder is that changes (over previous days levels) in a causal factor, as opposed to actual levels of the factor, are producing the observed associations (Vedal, 1997). In some cases, refinement in epidemiology studies can lead to control of such confounders. For stubborn confounders, human clinical or toxicology studies are needed. In any case, the likelihood that unmeasured factors are important makes it difficult to have confidence that abatement measures that control particulate mass will have a significant impact on health.

3.5.4. To Whom Do the Associations Apply?

The question of to whom in a group an observed association applies is an important one. Friedman (1994) gives an example of the hypothetical finding of a positive association between coronary artery disease and hand-grip strength. He poses that a significant association would be found showing that those with stronger grip would also have more severe arteriosclerosis. This association could be caused by including both men and women in the study, as women have less strength and less coronary artery disease than do men. But to whom does the association apply? In this thought experiment, the association would not occur for just women nor just for men. This example is provided to show how the principle operates. Yet it is important to identify the individuals in the study groups for whom the associations between particle exposures and adverse effects apply.

With respect to particulate air pollution, the issue is difficult, as perhaps only one in several hundred thousand individuals are seriously affected by small increments in pollutant levels. With respect to the excess mortality produced by a single small episode, about one in a million are victims. It has been suggested that people this sensitive have exceptional risk factors and are unlikely to be outdoors where the air pollution monitors are located. It is difficult to design studies that identify such rare individuals and their exposures, but until such studies are done, it is difficult to have confidence that these people will be protected by control efforts (Hauck, 1998; Charnley and Goldstein, 1998).

3.5.5. Cause and Effect

When does one accept an association as causal – that is, representing a true cause-and-effect relationship? This difficult issue has stimulated considerable and lively debate among those involved in the particulate air pollution controversy.

Establishing a cause-and-effect relationship is a complex task. It turns out that usually the best that can be done is to provide evidence for the likelihood that such a relationship exists. The task is particularly difficult in epidemiology because the suspected cause cannot be easily manipulated in ways that are possible in controlled laboratory investigations. Bradford Hill proposed a list of nine criteria for evaluating the likelihood that a statistical association is a causal one: (1) strength of the association, (2) consistency of the association, (3) specificity of the association, (4) temporality, in that the cause comes before the effect, (5) dose-response relationship, (6) biological plausibility, (7) coherence, (8) experimental manipulation of the cause leads to expected changes in the response, and (9) analogy with other accepted cause-and-effect relationships (Hill, 1965). Just how well do the epidemiologic associations between current levels of particulate air pollution and adverse health effects in humans fulfill these criteria? Lipfert (1994) uses Hill's criteria and argues that the majority of these criteria have been met. But there are significant failures relating to strength (the association is small), specificity (specific pollutants have not been identified), and biological plausibility (the physiological steps from exposure to death are only guesses at this time). Perhaps the most extensive challenge of the cause-and-effect assumption for the epidemiologic associations for fine particles was presented by John Gamble (1998). A challenge to Gamble's paper, and his response, was published in *Environmental Health Perspectives* (Vol. 107, pp. A392–A394, 1999). There is a case for requiring external validation of the epidemiologic associations, as by controlled laboratory studies in humans, laboratory animals, and in-vitro models. This external validation is a major focus of the research that has been recommended by several scientific bodies as described in Chapter 7.

3.6. LESSONS LEARNED

Epidemiologic associations are excellent beginnings to understanding an issue that involves public health. Yet epidemiology has its limitations, which must always be borne in mind. Epidemiology can serve as an initiator of new questions that are relevant to public health. Epidemiologic associations produce diverse reactions, as some people seem willing to make a leap of faith and begin actions to control a potential risk, while others require more information. When the relative risks involved are large, it is usually easy to follow-up with controlled toxicology and clinical research to assign cause and effect relationships. However, associations that imply small relative risks present substantial difficulties due to uncertainties about who is affected, by what agent(s) and by what mechanism(s). Rare events are difficult to study. The questions raised can be expected to require a massive and lengthy research effort before a cause-and-effect relationship can be established. Until such follow-up research is performed, it will be difficult to have confidence in

risk-reduction strategies. Yet some will press hard for new regulations, without waiting for the scientific process to work.

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CHAPTER 4
The Nature of Urban Particulate Matter

4.1. RELEVANCE TO THE PM CONTROVERSY

In order to understand the potential health effects of urban particulate air pollution (particulate matter, PM), it is essential to develop a working knowledge of its sources, compositions, and size distributions. Trends in PM concentrations over the last few decades and differences in the nature of PM from one region to another are also relevant topics.

4.2. DEFINING PM

Particulate air pollution is a complex aerosol that is not easy to define. Like all aerosols, it is a two-component system consisting of finely divided condensed matter and a gaseous suspending medium. Upper and lower limits on the particle sizes in aerosols have been established. For the upper size limit, an aerodynamic equivalent diameter (the diameter of a water droplet having the same settling velocity in still air as the particle in question) of 100 μm is used because particles of this size or greater do not remain suspended in the air for any appreciable time (Table 4.1). For the lower size limit, 0.001 μm is a reasonable cutoff, as smaller diameter particles contain only a few atoms of material, and they form and evaporate in the air. In addition, extremely small particles rapidly diffuse and attach to other particles, which moves them into larger-size categories. Table 4.1 shows that diffusion dominates the movement of small particles in the air.

Aerosols change their characteristics as they age and as environmental conditions change. An aging aerosol may undergo evaporation, coagulation (the sticking together of particles that collide), and compositional changes produced by reactions. Some aerosols grow significantly when inhaled into warm humid air or change after they are sampled onto a filter (where evaporation and chemical reactions may occur). Specifying the size and chemical composition of PM is not always easy.

For convenience, subscripts are used to indicate an upper diameter limit in a given particle mass fraction. PM_{10} and $PM_{2.5}$ represent mass fractions consisting of particles under 10 μm and 2.5 μm aerodynamic diameter, respectively.

Table 4.1 Settling velocities (V_s) in still air and the time required to settle 2 meters (T_s) as a function of aerosol particle diameter for unit density (1 g/cm^3) spheres. Also shown are Brownian diffusion speeds (V_d) and the times required for the particles to diffuse an average of 2 meters (T_d) from a starting position.

Diameter (μm)	V_s (cm/s)	T_s	V_d (cm/s)	T_d
0.001	0.0000007	10 years	0.3	11 minutes
0.01	0.000007	11 months	0.02	3 hours
0.1	0.00009	27 days	0.004	14 hours
1.0	0.004	16 hours	0.0007	3 days
10.0	0.3	11 minutes	0.0002	12 days
100	25	8 seconds	0.00007	1 month

4.3. SOURCES, TRANSPORT, AND COMPOSITION OF PM

4.3.1. Sources of PM

The three major sources of PM are natural, anthropogenic, and secondary. Natural sources of PM include wind-generated dusts, fogs and sea sprays, fires and volcanoes, pollen production by plants, spore production by fungi, and a number of microbial processes. Anthropogenic sources of PM are usually classified as (1) mobile (including cars, trucks, planes, ships, trains, and construction or farm equipment) or (2) stationary (including electric power plants, factories, mines, farms, dairies, homes, and waste-disposal sites). Secondary PM is produced by reactions in the air, including the transformation of gases or vapors into liquids or solids. The reacting gases and vapors may have come from either natural or anthropogenic sources or both (in which case the sources cannot always be identified). Table 4.2 lists the main sources and annual emissions for PM_{10} and precursor gases.

Table 4.2 Major sources of ambient PM in the United States in 1993, including primary particle sources and sources of precursor gases (sulfur and nitrogen oxides) and volatile organic compounds (VOCs) (EPA, 1996).

Source	Thousands of Tons/Year			
	PM_{10}	SOx	NOx	VOCs
Fuel combustion				
Utilities	270	15,836	7,782	36
Industrial	219	2,830	3,176	271
Other sources	723	600	732	341
Industrial processes	553	1,862	905	3,091
Solvent utilization	305	43	90	10,381
On-road vehicles	197	438	7,437	6,094
Off-road vehicles	395	278	2,996	2,207
Fugitive dust				
Roads	22,568			
Construction/mining	11,368			
Agriculture	7,236			
Fires/other combustion	1,026			
Natural sources	628			
Miscellaneous	0	11	296	893
Total	45,488	21,898	23,414	23,314

Because people spend considerable time in indoor environments, sources of pollutants in buildings must also be considered. Essentially any human activity, including sleeping, will be associated with the generation of PM. In bed, body movement will generate aerosols consisting of bedding fibers, skin flakes, and other resuspended dusts. Other activities such as dressing, grooming, cooking, cleaning, walking, talking, gardening, exercising, painting, sawing, etc., will generate a characteristic cloud of PM in the person's breathing zone (Morandi et al., 1988; Thatcher and Layton, 1995). This "personal cloud" is measured by air samplers placed on the person. Personal clouds are poorly defined for essentially all human activities, but when measured, they have at times represented a significant or even dominant portion of the person's exposure (Sexton et al., 1984; Spengler et al., 1985). In situations where outdoor PM levels are particularly high, personal exposures can be lower than outdoor concentrations (Lioy et al., 1990).

4.3.2. Transport and Modeling of PM

Downwind from large sources, such as highly industrialized and heavily populated regions, PM concentrations can be elevated over distances of hundreds of kilometers. Large particles, especially those with aerodynamic diameters greater than about 5 μm, can be expected to fall out of the air within a few kilometers of

their source. Fine particles, especially those below 1 μm in diameter, are more likely to travel longer distances. Particles that are formed by chemical reactions that convert gases or vapors to liquids or solids can be expected to have relatively uniform concentrations within a region and to freely penetrate into indoor environments.

Complex "source" and "receptor" models address the transport of PM and PM precursors through the environment. Particle sedimentation and diffusion rates, airflow patterns, penetration into and out of indoor environments, and chemical and physical transformations, all interact and must all be considered. Such models are particularly important for estimating exposures to fine ($PM_{2.5}$) and ultrafine particles (under 0.1 μm diameter) because substantial particle fractions in these size regimes are formed during transport. Numerical methods, used in source modeling, require meteorological data (air velocities, turbulence, temperatures, pressures, and humidities), geographic features, emission rates, and physical-chemical reaction rates. Output from the models includes the concentrations of chemical species at various locations and times (Meng et al., 1998; Seigneur et al., 1999). Receptor models use ambient PM concentration data as input and calculate the types and emission strengths of sources that would produce the observed concentrations at locations of interest. In a review of source and receptor modeling (Seigneur et al., 1999), the authors concluded that source models needed improvements for modeling organic aerosol formation, the formation of sulfates and nitrates in the presence of fog and clouds, and for modeling plumes from large localized sources. Both source and receptor models need improvements with respect to standardization and validation. It appears that the basic framework exists for source and receptor modeling for use in making decisions on how to control PM to meet National Ambient Air Quality Standards (NAAQS), but current models are not yet capable of providing definitive data. This is a problem because strategies directed toward meeting the NAAQS are dependent on accurate predictions. The reader is referred to more complete sources of information on PM modeling but is cautioned that simple generalizations are elusive (EPA, 1996; Friedlander, 1977; Lippmann and Schlesinger, 1979; McMurry and Wilson, 1982; Spengler and Wilson, 1996).

4.3.3. Composition of PM

Numerous sources and chemical processes cause the composition of PM to be complex. Some simplification is possible when composition is considered in relation to particle size (Table 4.3). From the point of view of urban PM, the coarse size range (2.5 μm to 10 μm aerodynamic diameter) is usually dominated by soil particles, desiccated cellular debris, spores, and pollen, while the fine size range of urban PM (<2.5 μm) is usually dominated by combustion products. Ultrafine particles (diameters less than 0.1 μm) are found in large numbers in the air but have negligible mass in relation to the less numerous larger particles. Ultrafine particles are produced mainly by combustion and contain organic carbon, refractory metals (added to or naturally present in fuels) and vapor condensation products (Hughes et al., 1998).

Table 4.3 Typical composition and sources of urban PM. For simplification, three classes—coarse, fine, and ultrafine particle diameter ranges—are presented, with the understanding that urban PM is frequently more than trimodal.

Coarse Particles (2.5 μm to 10 μm in diameter)

Minerals – from soil, road dust, and industrial dusts
Metals – from soil and combustion of coal and oil
Organic carbon – from tire rubber and asphalt road wear
Bioaerosols – from animals, complex plants, fungi, and bacteria
Aqueous droplets – from fogs and water spray
Associated gases – ammonia, SO_2, H_2S, and CO_2

Fine Particles (smaller than 2.5 μm in diameter)

Minerals – from soil, road dust, and industrial processes
Metals – from coal/oil combustion, wear of machinery, and industrial processes (smelting, welding, etc.)
Carbonaceous – from wildfires, burning solid fuels and waste, cooking, engine exhaust, tire wear, and liquid fuel combustion
Sulfates and nitrates – from volcanoes, oceans, and oxidation of SO_2 and NO_x emitted by fires and engine exhaust (many of these particles are acidic)
Ammonium compounds – from reactions of ammonia (produced by animals, sewage, fertilizers, and engine exhaust)
Bioaerosols – primarily from viruses and bacteria
Associated gases – formaldehyde, SO_2, NO_x, O_3, and CO

Ultrafine Particles (smaller than 0.1 μm in diameter)

Metals – from incombustible constituents of fuels
Organics – from condensation of volatile emissions from complex plants, microbes, and fuel combustion.
Carbon – from fuel combustion
Miscellaneous – from gas-to-particle conversion reactions

Low-temperature processes (below 100°C) generate relatively large particles and evolve gases and vapors that are stable at such temperatures. Examples of low-temperature processes and their products include wind erosion and resuspension resulting in 2 to 50 μm diameter airborne soil dusts; wave action and bubble bursting in the ocean resulting in sea spray droplets and sea salt aerosols of 1 to 100 μm; fog formation resulting in water droplets that are 20 to 80 μm in diameter; farming, mining, demolition, and construction operations that produce

dusts of 10 to 100 μm or larger in diameter; mechanical operations such as sawing, grinding, and dispersing powders that produce particles in the diameter range of a few μm and larger; and spraying operations that produce droplets of a few μm to 50 μm in diameter. Microbial, insect, and plant life produce spores, danders, and pollens that range in diameter from about 1 μm to about 80 μm. Low-temperature processes produce gases and vapors including water vapor, ammonia, hydrogen sulfide, and a large variety of organic vapors. In addition, some low-temperature processes, such as the radioactive decay of natural radon and the disturbance of asbestos-containing materials, produce finer particles (0.01 to about 5 μm aerodynamic diameter).

High-temperature processes (about 600°C or greater) vaporize and combust many substances and thus can produce much smaller particles as well as a large variety of vapors and gases. Burning oil, coal, wood, paper, agricultural waste, and tobacco generates primary particles that are usually under 1 μm in diameter, as well as carbon monoxide, sulfur oxides, oxides of nitrogen, and countless organic vapors. Similarly, volcanic action generates large and small particles as well as sulfur-containing smokes. Other high-temperature processes, including welding and cooking, produce fine particles and a variety of gases and vapors.

4.4. INDOOR VS. OUTDOOR PM

The average person spends the majority of their time in indoor environments where air contaminant levels can be substantial. Samet and Spengler (1991) summarized the situation as follows:

> Most indoor living or working environments have air pollutant sources. Even people and pets can be sources of fibers, particles, organic vapors, and microbiologic material. Additional pollution comes from heating and cooking, combustion sources, emissions from tobacco, abrasion of surfaces, outgasing of vapors, intrusion of soil gases, and a plethora of biological sources; thus, it should not be surprising to find indoor environments that are substantially more polluted than nearby outdoor air. High concentrations of pollution in indoor settings can, at times, dominate short- and long-term exposures and may be associated with discomfort, irritation, illness, and even death.

Associations between outdoor PM levels and human health effects are complicated by indoor exposures in several ways. First, outdoor pollutants enter buildings and contribute to indoor exposures; the rate of intrusion is greater for smaller particles and for less reactive chemicals than for those that react with surfaces (such as ozone) and during seasons when buildings are better ventilated (Leaderer et al., 1999; Abt et al., 2000). Also, some factors that modify outdoor pollutant levels, such as the use of heating and air-conditioning systems, modify the characteristics and levels of indoor pollutants. Valberg and Watson (1998) have explored alternative, albeit untested, hypotheses for linking outdoor PM with human health effects. These authors argue that three pathways, in addition to direct

exposure to outdoor PM, should be considered (1) direct effects of weather conditions on health, (2) human behavior patterns that produce excess mortality and morbidity that are coincidentally linked to outdoor PM levels, and (3) weather and behavior patterns linked with outdoor PM that change exposures to indoor pollutants. As an example of the third pathway, the authors point out that indoor wood-burning increases both indoor and outdoor PM levels.

The relative contributions of indoor sources to PM exposures depend on the characteristics of the indoor environment. When certain sources are present, such as tobacco smokers, standing water, unvented stoves, insect infestations, and wood-burning equipment, air quality can be dominated by these pollutant-generators. Also, the rate of intrusion of outdoor air and the combined effect of small sources of pollutants may have a profound effect on indoor air quality. Indoor air quality and the potential health effects of indoor pollutants is a large subject, and readers are referred to several sources of information (Samet and Spengler, 1991; Gammage and Berven, 1996; Committee on Indoor Pollutants, 1981; World Health Organization, 1990; and EPA, 1991).

4.5. PARTICLE SIZE DISTRIBUTIONS

4.5.1. Size-Distribution Basics

In the urban atmosphere and in indoor air, suspended particles will have varied sizes, shapes, densities, and compositions. To simplify and describe aerosols, size distributions are used. A size distribution describes the probability of encountering a given value of some property of interest as a function of particle diameter. Many properties of particles are of interest when considering health effects, but the most useful are (1) number, or how many particles are present in a given size range; (2) surface, or what the total surface area of the condensed material in a size range is; (3) mass, or how much particulate mass is in a certain size interval; and (4) composition, or how much of a given chemical resides in a given particle-size interval. Number, surface, mass, and composition have each been associated with adverse health effects (Peters et al., 1997; Brunekreef, 2000; Samet, 2000). Also, any one aerosol can have different size distributions based on count, surface, mass, or composition, and different health effects may be correlated with different size distributions. For example, chronic effects may correlate with the distribution of silica, while acute irritancy may best correlate with either the count or the fine mass distribution.

Distributions are characterized by numerical descriptors that express central tendency and dispersion (such as a mean and standard deviation). If all of the particles in an aerosol are the same size, shape and density (i.e., monodisperse), then the mean size, mode (most commonly present size), and the median (size for which half of the particles are larger) will be the same, and the standard deviation will equal zero. If the distribution is symmetric about a peak at the middle, then the mean, mode, and median will be equal, and the standard deviation will be larger than zero; the larger the standard deviation, the broader the range of sizes present.

Real-world aerosols seldom have symmetric size distributions, which complicates the situation. Real aerosols can usually be described by a set of

distributions skewed toward larger sizes. The most common mathematical function used for each distribution is the lognormal distribution. In a lognormal distribution, the logarithms of the diameters will be symmetrically (or normally) distributed as shown in Figure 4.1A. The geometric standard deviation is used to describe dispersion. (If you are an aerosol physicist, this makes perfect sense; otherwise don't worry about it.) The take-home message is that such size distributions are described by different characteristic diameters, such as the count mode, or mass median diameter as shown in Figure 4.1B. Also, if the geometric standard deviation is larger than 1.2, the aerosol is no longer monodisperse; it is polydisperse.

4.5.2. Urban PM

Urban PM is multimodal with respect to size, and at least three lognormal distributions are usually required to represent the particle count or mass as a function of particle diameter. When the chemical composition is considered, many modes or peaks can be identified at various particle diameters (Noble and Prather, 1996). The three-mode model, proposed by Kenneth Whitby and William Wilson in the 1970s for sulfur-containing aerosols (Whitby, 1978; Wilson, 1978), is still used for describing urban PM and calculating inhaled doses (EPA, 1996; Snipes et al., 1996). Figure 4.2 shows a hypothetical scheme that gives rise to the trimodal atmospheric aerosol. However, the actual number, relative sizes, and positions of aerosol modes depend on the place, time, species measured, and even the particular sampling instruments used for analyses. Furthermore, if the number distribution is measured, the great majority of particles (up to 99%) are usually found in the mode smaller than 0.1 μm in diameter, but if the mass distribution is measured, the majority of the mass will usually be in particles larger than a few μm in diameter.

4.6. EPISODES

Episodes of air pollution are periods of higher than usual concentrations that may last for hours or several days. Episodes occur when pollutant-creation rates significantly exceed dissipation rates, thereby causing concentrations to build. Pollutants are created by primary emission phenomena, formation in the atmosphere by reactions, and intrusion from outside the area. The rate of pollutant creation in an area will depend on the numbers and emission strengths of sources, the humidity, temperature, solar energy input, and the movement of air. Thus, conditions such as traffic congestion, heavy industrial operations, temperature extremes, heavy sunshine, and fires can greatly increase the air pollutant-creation rate. Dissipation rates for pollutants are decreased by air stagnation, fog formation, and low inversions. Inversions, or more precisely, temperature inversions, prevent the rise of air pollutants away from the earth's surface. Some geographical regions are more susceptible to having decreased air pollutant dissipation rates. Such areas include river valleys and areas with frequent wind stagnation and/or temperature inversions. Areas bounded by mountainous terrain are susceptible to air pollutant buildup, especially during inversions.

Major episodes occur when emission rates are high and very poor meteorological conditions are present. Small episodes occur when conditions are

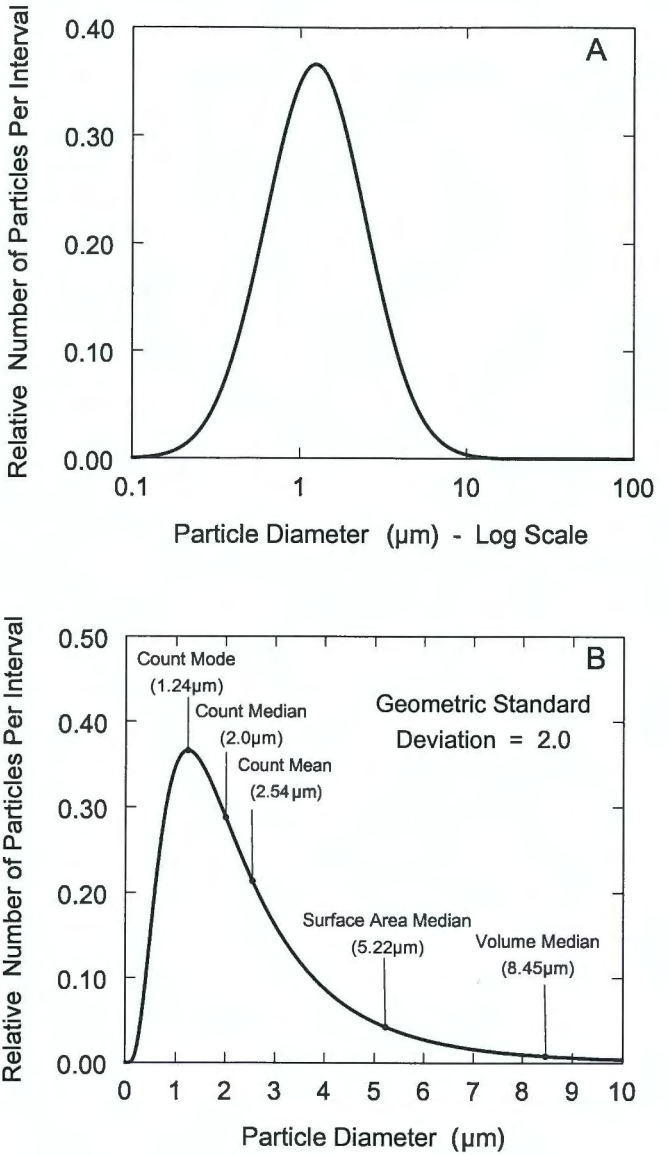

Figure 4.1 Lognormal distributions with a count median diameter of 2 µm and a geometric standard deviation of 2. A: Normalized with the diameter on a logarithmic scale. B: The same distribution on a linear scale, which produces a skewed curve.

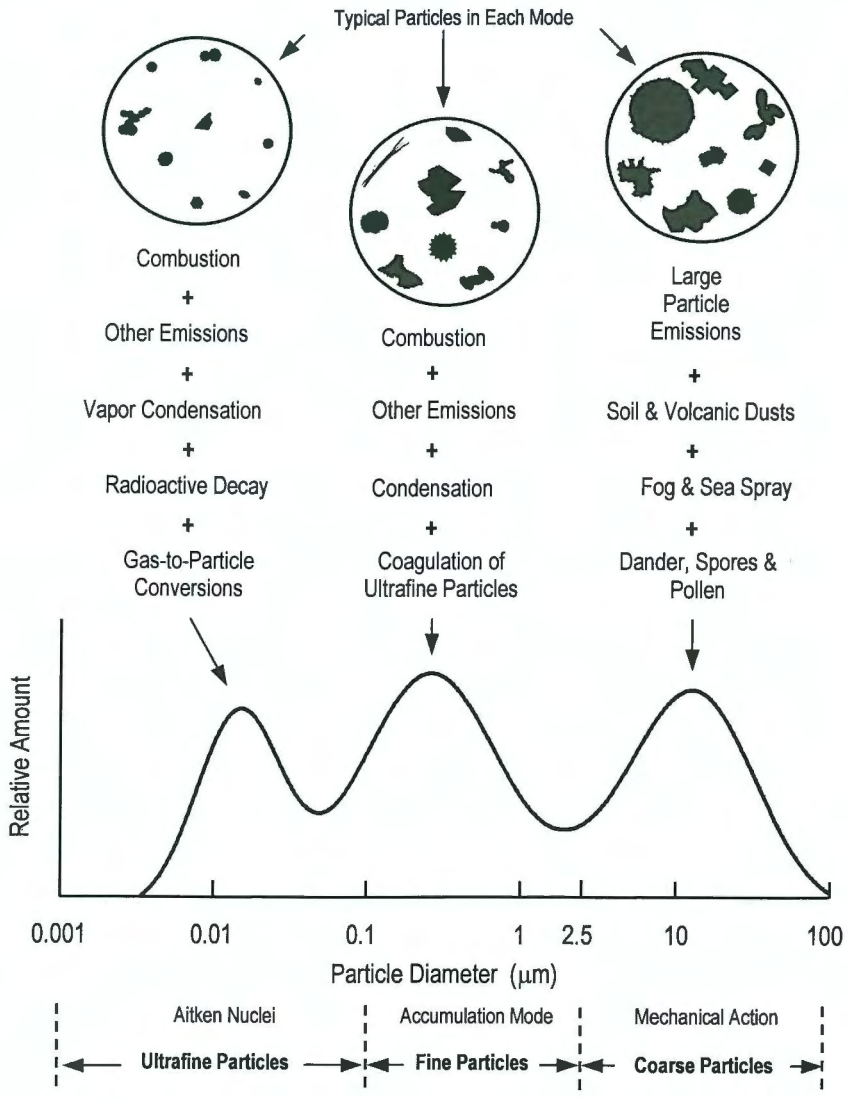

Figure 4.2 Conceptual depiction of the complex atmospheric aerosol including proposed sources and typical shapes of particles in each mode. Actual urban aerosols are more complex than this depiction in that different and additional modes are present if specific chemical species are represented.

less severe. Brief periods of increased pollution tend to occur within the diurnal cycle in many locations. High-traffic periods in the morning and late afternoon tend to produce elevated air pollutant concentrations for a few hours. Additionally, apparently random variations in pollutant levels occur in essentially any locale. Episodes, both large and small, have been correlated with changes in measures in human health (see Chapters 1 and 2).

The problem of understanding the health effects of air pollution episodes is confounded by a lack of knowledge of how episodes differ from other periods with respect to the chemical mix of pollutants present. In addition to general elevations in total pollutant levels, episodes may have unique combinations or ratios of pollutants. During episodes in an urban region in Taiwan, increases were seen in fine-particle nitrate and organics, and a decrease was seen in coarse-particle elemental carbon (Tsai and Cheng, 1999). Also, the peak diameter in the mass distribution dropped from 3.2 to 5.6 μm to 0.56 to 1.0 μm, indicating that traffic was a major contributor. Data from five California cities indicate that episodes can be highly variable chemically at a given location (Larson and Cass, 1989). For example, during days with high PM levels at Pasadena, Lennox and Azusa, fine particle sulfates were both higher and lower than normal. Also, during a winter in Erfurt, Germany, particle mass and number were poorly correlated (Tuch et al., 1997). This suggests that using particle mass as a marker of air quality could be a problem if particle count is important toxicologically. Ultrafine particle episodes in Atlanta, Georgia, were associated with several factors, including night time, high solar radiation, and the morning rush hour (Woo et al., 2001). New research is required to better understand the characteristics of PM episodes.

4.7. LONG-TERM TRENDS IN PM POLLUTION

A potential complication for regulating urban PM on the basis of epidemiological associations arises from the changing nature of air pollution from year to year. The epidemiological studies are typically published years after the actual exposures. Steady decreases in emissions due to technological advances have improved air quality in many regions. Vehicles have advanced from having average precontrolled emission values of over 100 grams/mile of hydrocarbons, carbon monoxide, and nitrogen oxides, to a modern level of about 4 grams/mile for the same substances (Klimisch, 1998). Stationary sources have made less dramatic improvements in their emissions, but significant strides have been made over the past 40 years (EPA, 1995). Lipfert (1998) reviewed and analyzed PM sampling data in U.S. cities over the last 50 years and found a decreasing trend of 2% to 8% per year for total particulate, PM_{10}, and $PM_{2.5}$ fractions. Such improvements have occurred in spite of increases in population, vehicles, air-conditioners, etc.

The U.S. EPA has quantified the decreases in PM_{10} levels in the United States in recent years (EPA, 1996). For sites that had monitoring stations for the seven-year period of 1988 to 1994, PM_{10} concentrations decreased an average of 20%. For the eastern Unites States, the decrease was 18% and for the western U.S., it was 28%. If background PM_{10} levels are subtracted from the measurements, the reductions over the period were 30% for the eastern half of the United States, and 33% for the west.

4.8. REGIONAL DIFFERENCES IN PM

Each locale is unique with respect to its mix of sources of PM and its geography and meteorology. Three major regions have been identified in the United States. These regions are Eastern, characterized by the use of oil and coal for electrical power along with frequent generally high relative humidity conditions; Western, characterized by the use of natural gas, hydroelectric and solar electric power, significant sunshine, and prevailing low humidity; and Northeastern, characterized by the greater use of wood burning for heating in the winter time. As expected, the three regions have very different types of PM and associated copollutant gases. In the East, sulfur-containing compounds, such as sulfur dioxide and sulfates (along with acidity), are commonly encountered. In the West, wind-blown dust is frequently elevated, as are the photochemical reaction products, ozone, oxides of nitrogen, and secondary organic compounds. In the Northwest, smoke levels are frequently elevated. Data on the characteristics of $PM_{2.5}$ in various regions of the United States clearly show that regional differences in aerosol composition are striking (Tolocka et al., 2001). These differences make it difficult to define national air-quality standards that are optimal for each region.

4.9. MAJOR UNCERTAINTIES

Considerable uncertainty exists regarding the variable spatial, temporal, and chemical nature of PM and its associated copollutants. Just how much of this uncertainty must be resolved to support rational environmental quality criteria is not known because the possible culprits for producing human health effects at low levels are still unknown.

Personal exposure data are needed for those individuals most at risk. The seriously ill, the aged, and the very young are presumed to be most susceptible to the effects of PM exposure. The most seriously compromised may spend more of their time indoors than do healthy individuals. Therefore, indoor environments, such as hospital wards, nursing homes, and bedrooms, will require more study of the prevailing air contaminants. For such studies, biological aerosols along with inorganic substances must be characterized, as these aerosols can have significant allergenicity and infectivity.

The uncertainties related to linking specific sources to levels of PM in the human breathing zones are significant. This is especially true when the complexities of transport and chemical reactions are considered. A variation on this problem relates to understanding how control of a specific pollutant source might modify personal exposures to key pollutants. It is known that some sources, such as those that produce ammonia, serve to decrease the airborne levels of acids. Similarily, control of one size range of emitted particles can result in the emission of larger numbers of particles in other size ranges (switching fuels or engine designs are examples). These uncertainties must be resolved before confidence can be placed in decisions that control emissions from processes that supply food, energy, raw materials, manufactured goods, and transportation.

Some basic uncertainties relate to sampling and characterizing PM exposures. How much detail is needed with respect to chemical speciation? Can the total acidity substitute for an elaboration of each of the acid species present? Similarly, how many forms of metals, allergens, organic vapors, sulfur, and nitrogen species must be separately measured? There is uncertainty relating to the environmental conditions required for relevant sampling, as samples taken at room temperature and humidity will give results that differ from samples acquired at the temperature and humidity in the respiratory tract. Also, the degree to which environmental humidity and temperature modify the toxicity of inhaled PM is poorly understood, so aerosol characterizations that are used to correlate with health effects should be accompanied by environmental data.

It is not clear that exposures averaged over several hours or days are more important than are instantaneous exposures (Michaels, 1998). The most sensitive associations with health effects seem to involve increments (or episodes) above previous levels. Is the important factor simply a change in the levels, or is it that episodes differ chemically from the previous pollutants?

4.10. LESSONS LEARNED

An impressive array of instruments and procedures exist for measuring PM and associated pollutants in great detail. But until atmospheric chemists know what should be measured, they are faced with an impossible task, as everything cannot be measured in ultimate detail. It is clear that analytical efforts must be guided by adverse health effects as disclosed by developments in epidemiology and toxicology. The specialties relating to health and to atmospheric chemistry are intertwined, and progress can be made only by cooperation and collaboration across the respective specialties.

Generalizable research, which provides information common to many circumstances, and an understanding of basic phenomena will be more important than specific measurements that relate only to one time and place. Models that predict exposures in unstudied circumstances will be critical to answering the major questions regarding PM exposures and health. It is evident that the exposure of populations to PM is a complex phenomenon, and each chemical component may need to be treated uniquely. Much research is needed to understand how specific control measures will affect the exposure of human populations.

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CHAPTER 5
The Fates of Inhaled Particles

5.1. RELEVANCE TO THE PM CONTROVERSY

For inhaled particles, *dosimetry* relates to quantifying the deposition of inhaled substances on respiratory tract surfaces and their subsequent clearance or movement within the body. There are several reasons why dosimetry considerations are important. To identify subpopulations sensitive to urban particulate matter (PM) exposures, it is helpful to be able to predict inhaled particle doses for individuals. Proper environmental measurements and pollutant-control strategies depend on an understanding of the critical doses to target tissues. It is also necessary to calculate doses in laboratory animal studies so that they may be properly interpreted in relation to human exposures. Proper interpretation does not always imply performing an extrapolation, as is the case for studies of mechanisms and the relative toxicities of particulate materials. The doses of interest fall into several categories. First is the *total particle deposition dose* or the total amount that initially deposits in the respiratory tract. *Regional deposition doses* are of importance, as they define the amounts of particulate material that deposit in specific anatomical regions; the nose, tracheobronchial tree, and alveolar zones are often separately considered. If one takes the clearance of deposited particles into account, *time-integrated doses* may be calculated for target tissues. Various chemical components of deposited particles may dissolve and have independent fates in the body, so dissolution and bioavailability considerations are important. The importance that the U.S. EPA placed on dosimetry is evidenced by an extensive review of dosimetry research in PM criteria documents (EPA, 1996, 2002). Similarly, the National Research Council placed considerable importance on dosimetry in defining the national research agenda on PM (NRC, 1998, 1999, 2001).

5.2. WHAT PARTICLES ARE ACTUALLY INHALED?

Until studies were performed in Germany and Great Britain using life-sized mannequins in wind tunnels, little consideration was given to the efficiency with which airborne particles are inhaled into the human nose and mouth (Ogden and Birkett, 1977; Vincent and Mark, 1982). These studies established the importance of *inhalability*, which is the sampling efficiency of the entrance airways (nose and mouth) for particles (Phalen et al., 1986; Soderholm, 1989). The wind-tunnel studies showed a strong dependence of aerosol particle inhalability on several factors, including particle size, wind speed, and orientation of the subject's face to the wind direction. The American Conference of Governmental Industrial Hygienists' inhalability convention, defined over all averaged wind angles (0 to 360°) and low

wind speeds, is shown in Figure 5.1. When the wind speed is zero, the inhalability of large particles will be lower than shown in the figure (Breysse and Swift, 1990). The inhalability of particles with aerodynamic diameters (corrected for particle density and shape) larger than 100 μm is unknown. Modification of the adult inhalability factors to include children is probably not necessary, as the differences between children and adults are small (Phalen et al., 1992). However, children inhale more air per unit body mass, like all smaller mammals, which increases the inhaled particle mass deposition rate as body mass decreases (Phalen et al., 1992). Significantly, wind speed is a major modifying factor for inhalability; and since children are more likely than adults to spend time outdoors, wind speed must also be considered for children breathing urban PM (Vincent, 1999b).

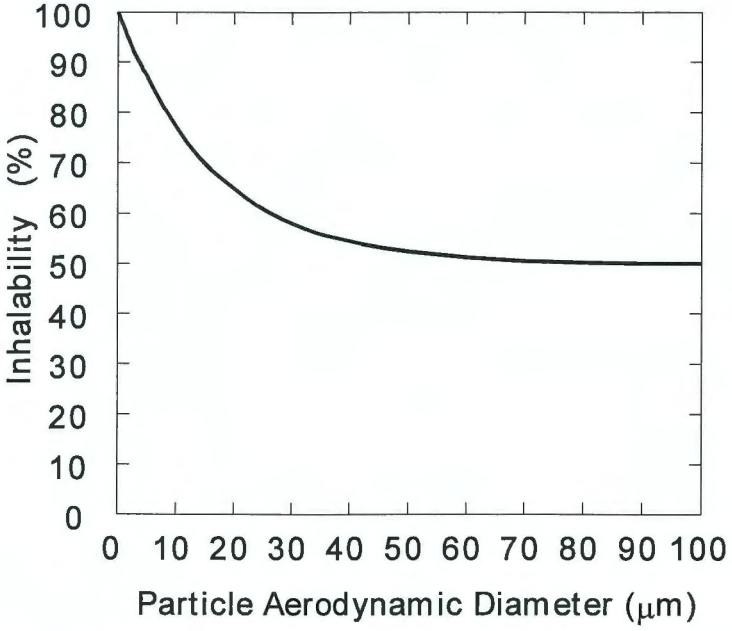

Figure 5.1 Aerosol inhalability, which is the wind speed and orientation averaged efficiency with which the human head samples aerosol particles from the ambient air (ACGIH®, 2001).

For urban PM, the relevant particle sizes for health effects are assumed to all fall below 10 μm aerodynamic equivalent diameter. For 10 μm particles, inhalability is about 77%, and for $PM_{2.5}$ (aerodynamic diameter <2.5μm), the inhalability is greater than 90% (ACGIH®, 2001; Vincent, 1999b).

5.3. WHERE INHALED PARTICLES DEPOSIT

5.3.1. Anatomical Conventions

The human respiratory tract may be broken into a few distinct regions (Table 5.1). Within these regions are similar tissues (similar cellular components), similar particle deposition and clearance mechanisms, and similar disease states. Such a compartmental scheme dates to the 1966 International Commission on Radiological Protection (ICRP) Task Group on Lung Modeling chaired by Paul Morrow (Morrow et al., 1966); the original regions are still used with some refinements (ICRP, 1994; NCRP, 1997).

Table 5.1 Regions of the human respiratory tract used for analyzing particle inhalation (Morrow et al., 1966; ACGIH®, 1985; ICRP, 1994; NCRP,1997).

Region	Anatomic Structures	ACGIH®	ICRP	NCRP
Head airways	• Nose • Mouth • Nasopharynx • Oropharynx • Larynx	Head airways region (HAR)	Extrathoracic region (ET)	Naso-oro-pharyngo-laryngeal region (NOPL)
Tracheo-bronchial tree	• Trachea • Bronchi • Bronchioles (to terminal bronchioles)	Tracheo-bronchial region (TBR)	Bronchial region (BB) and bronchiolar region (bb)	Tracheo-bronchial region (TB)
Gas exchange	• Respiratory bronchioles • Alveolar ducts • Alveolar sacs • Alveoli	Gas exchange region (GER)	Alveolar interstitial region (AI)	Pulmonary region (P)

5.3.2. Aerosol Considerations

To understand particle deposition in the respiratory tract, some elementary particle physics must be appreciated. The mechanisms by which airborne particles deposit on respiratory tract surfaces are multiple and include inertial impaction, diffusion, gravitationally induced sedimentation, electrostatic attraction, and

interception (for particles, such as long fibers that don't easily pass through the airspaces). When any particle departs the airflow because of these mechanisms and touches an airway wall, it is assumed that it will stick to the surface and deposit. Most mathematical particle deposition models consider only the first three deposition mechanisms, impaction, diffusion, and sedimentation, making modeling straightforward using a computer (Yeh et al., 1976). The other mechanisms (electrostatic and interception) are needed only in special circumstances. Since most urban PM can be assumed not to carry high levels of charge (ions in the air reduce charges to Boltzmann equilibrium), and since fibers are usually not present in the air in significant numbers, the focus on three mechanisms is usually sufficient for health-risk considerations. However, the influence of charge on deposition of fibers and ultrafine urban particles may be significant (Cohen et al., 1996).

Particles in the air have a variety of shapes and densities (material density, not number density), so a means of dealing with the effect of this variation is required for modeling inhaled doses. A convention developed by aerosol physicists uses an equivalent aerodynamic diameter for each type of particle. The equivalent aerodynamic diameter for any particle is simply the geometrical diameter of a smooth spherical particle that has a density of 1 g/cm^3 and the same settling speed in still air, under standard conditions, as the particle in question. For nonspherical particles, the aerodynamic diameter must usually be determined through experimentation. For spherical particles, the aerodynamic diameter (D_{ae}) is equal to the geometrical diameter (D) times the square root of the particle's density:

$$D_{ae} = D \cdot (\rho_p)^{1/2} \tag{5.1}$$

It is also important to consider the distribution of aerodynamic diameters in an aerosol. In real-world situations, airborne particles exist in a range of sizes; that is, they will not all have a single aerodynamic diameter. For aerosols, the distribution of sizes cannot be described by a bell-shaped (normal) distribution function. The distribution will be skewed (and usually lognormal) because of energy limitations; less energy is generally required to form larger particles than smaller ones. Consider the energy required to chop a large object into smaller pieces. The finer the division, the more the energy that must be expended until at some point there is not enough energy available to create new surfaces by dividing the material into finer portions. This is a simplified explanation, but the fact is that the distributions of sizes of real-world aerosols will be skewed toward larger particles, and such distributions can be described by lognormal functions for all practical purposes. For a lognormal distribution of particles, the logarithms of the diameters are normally distributed as described in the previous chapter. Real-world aerosols have many sources, thus a lognormal distribution will be present for each separate generation mechanism that produces particles.

5.3.3. The MMAD

Since the mass of any potentially harmful substance is usually an important property, inhalation toxicologists often refer to the mass median aerodynamic diameter (MMAD) when calculating doses. The MMAD is the aerodynamic diameter of a particle in the total aerosol distribution that divides the mass in half;

half of the aerosol particle mass is in aerodynamically larger particles, and half is in smaller particles. The MMAD is used in dose calculations because there is a cancellation (more or less) of errors for the doses from the smaller and the larger halves of the particle distribution; if one half is overestimated, it is hoped that the other half is underestimated by an equal amount. However, toxicity might not always be proportional to the mass of a toxicant. If particle count is the key toxic factor, then MMAD is not very useful as a dose indicator.

5.3.4. Particle Deposition and Particle Size

Figure 5.2 shows the expected particle deposition efficiencies in the main regions of the respiratory tract (using NCRP compartments) for an adult engaged in low-level physical activity. The curves in 5.2A are not corrected for inhalability, as are those in 5.2B. One sees that nearly all sizes of particles will deposit in all regions of the respiratory tract, but the probability of deposition varies considerably with particle size. These deposition curves will vary with the state of physical activity, breathing parameters and body size, as well as differences in the anatomy of individuals. It is important to realize that the curves in Figure 5.2 are unique to the specific assumptions used by the NCRP. The model of the ICRP produces similar but not identical particle-size-dependent deposition curves (Yeh et al., 1996). When a population of individuals is being considered, these curves, at best, pertain only to the average individual. Bennett (2000) discusses dosimetry in relation to potentially susceptible subpopulations exposed to PM.

5.3.5. Species Differences

Given the significant variability in aerosol deposition efficiency among people, one expects even greater dissimilarities among different species. Such differences are important because much of the knowledge concerning the health effects of air contaminants comes from inhalation studies using laboratory animals. In laboratory animals, serious adverse effects can be studied and cause-and-effect relationships established by manipulating the exposure. Many animal studies are performed to elucidate mechanisms of toxicity, and in these cases, dosimetry is useful to make sure that known (and realistic) quantities of pollutant are delivered to the tissues of interest. In mechanistic studies, dosimetric extrapolation to humans is not mandatory, as it is usually sufficient to determine that the same mechanisms can (or cannot) occur in people. Other types of studies, such as dose-response investigations, are used to link specific air concentrations of pollutants to the level of harm. For these studies, an extrapolation to humans is needed to derive the air concentrations that would produce unacceptable harm to human populations (Jarabek, 1995).

Although each species appears to possess unique particle-size-dependent deposition curves and unique clearance rates, several animal models have been well studied, making extrapolation of data from them to humans possible. The best understood laboratory animal models with respect to inhaled particles are rats and dogs. Data exist on mice, hamsters, monkeys, guinea pigs, rabbits, ferrets, donkeys, and a few other animals as well (Phalen, 1984; Schlesinger, 1985; Raabe et al., 1988; Snipes, 1989; Oldham et al., 1994). Software for calculating particle deposition in

each lung lobe and the upper airways of rats and humans is available (at low cost) from the Dutch National Institute of Public Health and the Environment Library (P.O. Box 1, 3720 BA Bilthoven, The Netherlands). The software is called MPPDep, for Multiple Path Particle Deposition Model (Subramaniam et al., 1999).

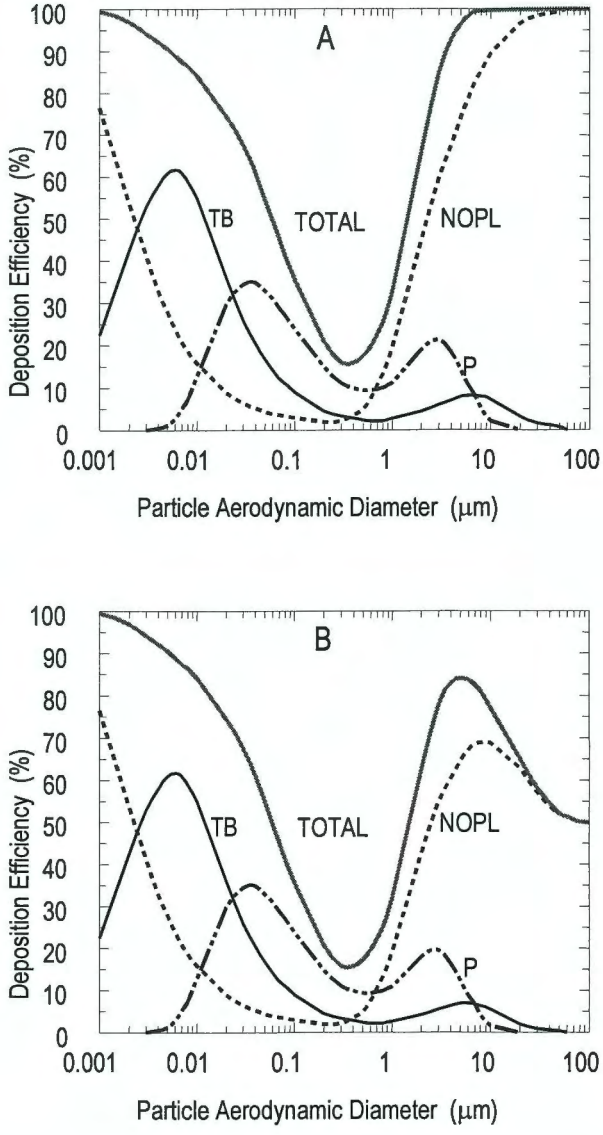

Figure 5.2 A. Particle deposition in the major regions of the human respiratory tract during normal respiration (NCRP, 1997). B. Particle deposition efficiencies from Figure 5.2A multiplied by the size-dependent inhalability.

5.4. PARTICLE CLEARANCE

After a particle deposits on an airway wall, it can have a variety of fates. It may rapidly dissolve in the airway-coating fluid and then be partitioned among the fluid volumes consisting of surfactant, mucus, lymph, blood, and intercellular and extracellular fluids. Once dissolved, the material is usually transported away from the respiratory tract, but it may also bind to nearby fixed-tissue elements such as collagen or components of resident cells. Particles that do not dissolve rapidly in the chemical environments of the respiratory tract have fates that are strongly influenced by the original site of deposition and also by the particle size. Such particles are called insoluble, but in reality they only have slow dissolution rates in relation to mechanical clearance rates. Given enough time, even "insoluble" materials can be expected to dissolve in the environment of the respiratory tract.

The anterior 1 cm of the nose is relatively dry like the skin, and particles are cleared from that region by extrinsic (or physical) mechanisms: wiping, picking, blowing, and sneezing. The rest of the nose (except the olfactory portion) and the pharynxes (air passages behind the nose and mouth) are covered with mucus and "beating" ciliated cells. Particles deposited on healthy ciliated mucosa are transported to the back of the throat where they are swallowed. One exception is ultrafine particles; they apparently can be transported across the overlying mucus layer down into the interstitial spaces where they may remain for extended periods. Another exception relates to infections, which denude the surface of cells, leading to mucus stasis (and removal by coughing) and the long-term retention of insoluble particles. Little is known about the clearance of particles deposited on olfactory tissue or in the sinus cavities.

The larynx, trachea, bronchi, and bronchioles are also covered with cilia and with mucus that is driven toward the throat and swallowed. The fates of insoluble particles in this region will be similar to those for the nose. There is good evidence that some of the smaller particles penetrate the mucus layer, move into the bronchial epithelium, and clear very slowly (Patrick and Stirling, 1977; Stahlhofen et al., 1990; Kreyling and Scheuch, 2000). Another important question arises relating to ultrafine (diameter < 0.1 μm) insoluble particles; such particles may migrate intact and accumulate in other organs (Ferin and Oberdörster, 1992; Oberdörster, 1994). An important potential target organ for the accumulation of insoluble particles is the heart. In the Harvard Six Cities Study, increased deaths due to cardiopulmonary diseases were associated with increased levels of fine particles (Dockery et al., 1993), and cardiac abnormalities have been reported in dogs exposed to concentrated air pollutants (Godleski et al., 1997). For most insoluble particles mucociliary clearance is efficient, and it limits their persistence in the healthy tracheobronchial region to a day or so. Again, infection can disrupt particle clearance, in which case a persistent cough may become the only effective clearance mechanism for deposited particles. Coughing clears small airways inefficiently, so a rapid series of several coughs is often seen for many weeks after the infection is gone and epithelial repair is taking place (Mossberg, 1980).

In the alveolarized regions of the respiratory tract, the clearance of insoluble particles is exceptionally complex (Morrow, 1973; Kreyling and Scheuch, 2000). Alveoli are not covered with mucus and have no ciliated cells. Clearance of some particles deposited in this region may take years in humans. The major

clearance mechanisms are solubilization (Mercer, 1967), engulfment and transport by phagocytic macrophage cells (Stöber et al., 1990), movement into the lymph system followed by transport to lymph nodes, and possibly movement to the mucus-coated airways where they are transported to the throat for swallowing.

If the respiratory tract is healthy, the clearance of insoluble particles will generally be multiphasic, with a faster clearance of those particles deposited on mucus-coated regions and a much slower clearance of those deposited in alveoli. Figure 5.3 shows typical particle clearance curves for insoluble particles in normal (healthy) humans and clearance curves for several species.

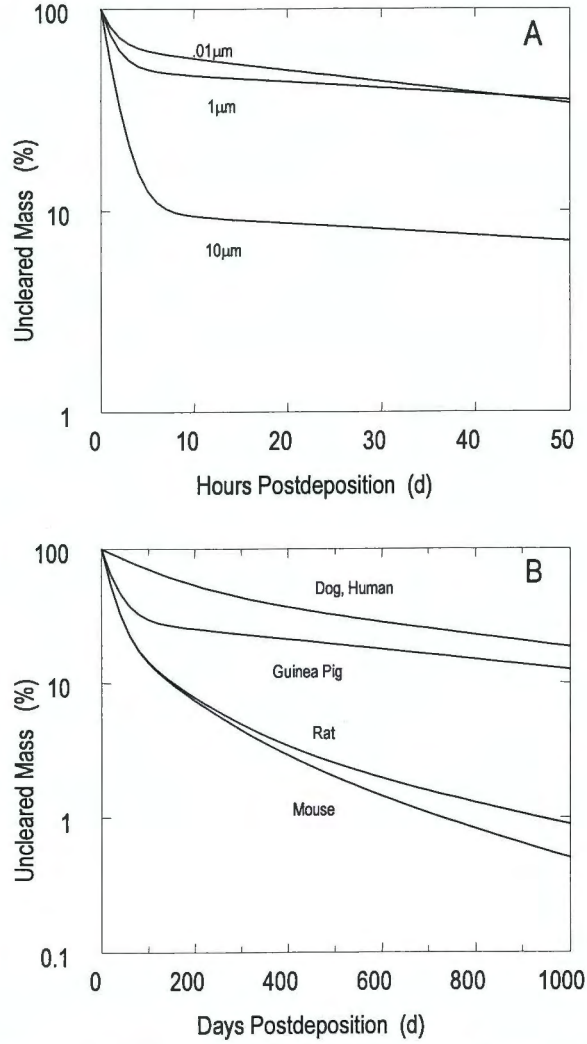

Figure 5.3 Clearance curves for (A) insoluble particles inhaled by humans and (B) curves for 1 to 3 μm diameter particles for dogs, humans, guinea pigs, mice, and rats. (Wolff, 1996; ICRP, 1994).

5.5. INDIVIDUAL DIFFERENCES

Just as there are large individual differences in observable physiological phenomena (e.g., strength, speed, endurance, and coordination), there are similar differences in internal functions, including blood pressure, metabolism, and particle deposition and clearance. Some differences are due to normal variations in anatomy and physiology, while others are due to the presence of diseases. The normal variations in particle deposition efficiencies and deposition sites are surprisingly large, as is seen in Figure 5.4 for the nasal deposition of inhaled aerosols. Differences in particle clearance rates are also variable from one person to another and even within a single individual at different times. So when estimating doses for human populations, the dose for an average person may be exceeded by 10-fold or more in some members of the population (Cuddihy et al., 1979). Pavia et al. (1980) have summarized the effects of several factors including some common diseases on particle clearance rates. The more important factors that alter clearance include chronic disease from cigarette smoking, lung damage from inhalation of highly toxic aerosols, asthma, influenza, pneumonia, and cystic fibrosis.

For urban PM, the deposition efficiencies and sites, as well as the rates of clearance, can be expected to have wide variations in human populations. Dose estimates from computational models provide only approximate values for any given individual. Using accepted deposition models and assumed urban particle-size distributions, Snipes et al. (1996) calculated expected PM deposition doses for personal exposures of normal healthy people. These calculations demonstrate how particle-size distributions and biological factors together define the doses of particles in humans. One finding was that when the cities of Phoenix, AZ, and Philadelphia, PA, were separately modeled, larger particles dominated the doses to the alveolar region in Phoenix but not in Philadelphia.

5.6. MAJOR UNCERTAINTIES

Although much is known regarding inhaled particle deposition and clearance, significant uncertainties that bear on the effects of inhaled PM remain. The normal variations in particle deposition and clearance have not been well explored, let alone the health consequences to individuals. Thus, in their recommendations for research, the National Research Council (NRC, 1998) called for the acquisition of data relating to modeling the fates of inhaled particles, especially in suspected susceptible subpopulations. The required studies included those that (1) define respiratory tract anatomy in children, the elderly, and diseased people; (2) provide deposition data as influenced by particle size, hygroscopicity (exhibiting growth in humid environments), and breathing rates; (3) develop, refine, and validate mathematical models for doses in various groups of people; and (4) enhance understanding of particle clearance efficiencies and mechanisms and how they may differ among individuals in the general population. The second NRC report (NRC, 1999) added extrapolation modeling for laboratory animals as a research priority.

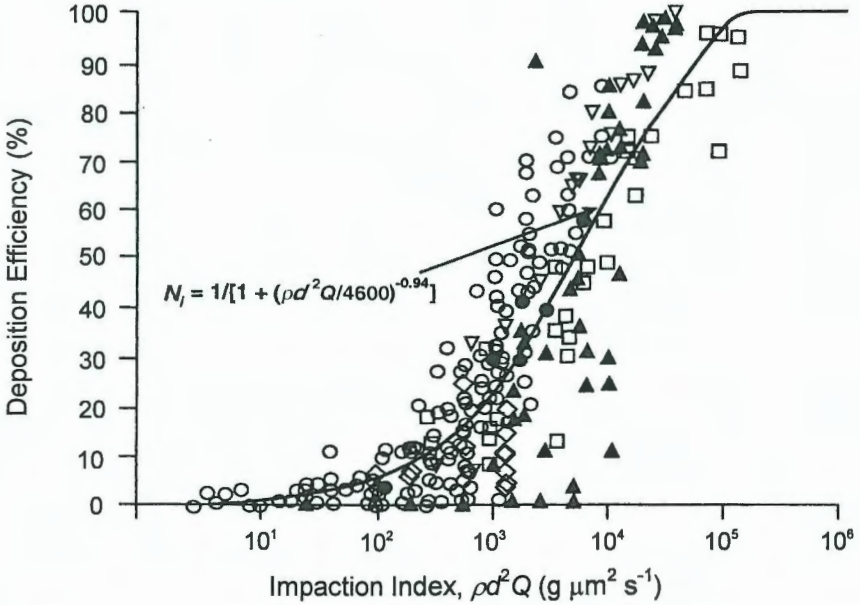

Figure 5.4 Aerosol deposition, and its variability in the nasal region of human volunteers as a function of an impaction parameter (NCRP, 1997; Landahl et al., 1951; Pattle, 1961; Lippmann , 1970, 1977; Hounam et al., 1971; Giacomelli-Maltoni et al., 1972; Martin and Jacobi, 1972; Heyder and Rudolf, 1977).

There are other significant uncertainties related to particle deposition and clearance. The actual property of PM ideal for dosimetry calculations is not known; particle mass, number, surface, and reactivity are among the possibilities. The amounts of specified agents required to alter clearance rates or to trigger a disease process are not well understood. Is the chronic deposition of particles necessary for maintaining normal clearance? What are the short-term and long-term adaptations of the clearance mechanisms to particle exposures? What do common medications do to particle deposition and clearance? Another area in which more research is needed relates to the fates of inhaled ultrafine particles. Because such particles have tiny masses, they are difficult to trace in the body. But ultrafine particles are numerous in urban air, and they may be able to enter tissues of the respiratory tract relatively freely (Oberdörster et al., 1995; Vincent, 1999a). Until these and other questions are resolved by researchers, it will be difficult to accurately estimate the health risks of populations exposed to urban PM.

5.7. LESSONS LEARNED

It is clear that dosimetry considerations are important for interpreting human epidemiological studies, human clinical investigations, and laboratory animal research on the dose-response relationships and mechanisms of action for inhaled

particles. The existing database is strong for understanding events in adult human males and in the most common animal models. In fact, some of the existing mathematical models are more sophisticated than is needed, given the uncertainties in knowledge regarding the compositions and concentrations of urban PM. However, as more is learned about the pollutants themselves, the models can be expected to be modified and become more useful.

Serious deficiencies must be addressed regarding the deposition and clearance of inhaled particles. Normal variability is known to be sufficiently great to modify risks, but the knowledge that exists today does not permit a solid assessment of this variability or its consequences regarding individuals. Not enough is known regarding the effects of disease on the fates of inhaled particles, which is a serious problem because individuals with severe cardiopulmonary disease are presumed to be at higher risk for adverse effects from breathing of air pollutants.

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CHAPTER 6
The Toxicology of Particulate Material

6.1. RELEVANCE TO THE PM CONTROVERSY

Toxicology, "the science of poisons," involves controlled studies in cell and tissue cultures, laboratory animals, and human volunteers in an effort to understand the effects of xenobiotics (foreign chemicals) on living systems. Toxicology plays several roles in the particulate air pollution (particulate matter, PM) issue. First, toxicology is important for determining whether the epidemiological associations relating PM to human health are causal. The suspected agents can be administered in graded amounts, or withdrawn totally; so observed effects can be confidently ascribed to specific components, or combinations. Dose-response phenomena can be investigated to determine at what levels effects occur, and how successively larger doses modify responses. Similarly, investigations can determine whether repeated exposures lead to sensitization or adaptation, or both. Sensitive populations are potentially identifiable, provided the proper models are used. Finally, toxicology studies are needed to identify the mechanism(s) of action that might be involved in the adverse human responses to PM. Toxicology has several limitations. The "real world" can never be examined in its full complexity in the laboratory. The substances studied by inhalation toxicologists are usually based on analysis of the atmosphere, and transient or exotic chemicals may not have been detected. Exposing laboratory animals or human volunteers to actual smog can overcome some of the problems, but such exposures will be specific as to time and place, thus limiting their generalizability. Also, the models studied by toxicologists may not include some important sensitive human populations. Yet toxicology is an essential partner to epidemiology in identifying, understanding, and controlling health hazards from chemical substances.

6.2. METHODS OF STUDY

Toxicology studies can be classified by the complexity of the biological system on which they focus. Thus, toxicologists may examine chemical reactions, subcellular structures, cells, tissues, organs, organ systems, whole laboratory animals, and humans. The earlier in this sequence, the more "basic" the study, and the more difficult it is to apply the findings to public health. Toxicology draws on many sciences, including chemistry, biology, physiology, and medicine.

Modern toxicology studies are relatively complex. Basic considerations include identification of the problem to be investigated, the model(s) to be used, the chemicals and their physical forms, and the route(s) of administration and amounts to be used. Of major importance are the endpoints (biological response

measurements), the duration of the exposures, and the time period for which the evaluations will continue. Data evaluation and interpretation of the results are not always straightforward, as toxicologists tend to make numerous measurements, which complicate statistical testing. Often they limit their examinations to one or a few organs. Some changes in the measurements are difficult to interpret, as they may be adaptive, harmful or both. (A rise in blood pressure is an adaptive response that could also be harmful).

Inhalation toxicology is concerned with the adverse effects of inhaled substances. The effects may be on any organ or tissue in the body, although the pulmonary effects are usually dominant. Inhalation is a unique route in comparison to other forms of exposure, although useful results are also obtained after instilling substances into the lung. When substances are inhaled, their physicochemical properties are important in determining where and how efficiently they will deposit in the respiratory system. For particles, aerodynamic sizes, densities, electrical charges, and shapes will determine where they deposit; for gases, molecular weights, reactivities, and solubilities in aqueous media are important. Particle-size selection can be difficult because of species differences in the efficiencies of deposition of various sizes of particles. Inhalation studies have been the subject of several general references (Leong, 1981; Phalen, 1984, 1997; Dungworth et al., 1988; Gardner et al., 1993; McClellan and Henderson, 1995; Salem, 1987; and Jenkins et al., 1994).

Clinical studies of inhaled air contaminants that use human volunteers are critical for confirming the results of laboratory animal studies and for testing hypotheses generated in epidemiology investigations (Utell and Frampton, 2000). Such studies are directly relevant for establishing air-quality standards. The volunteers may be healthy or ill, resting or exercising, and young, mature, or elderly. The main limitations include restrictions due to safety considerations and the exclusion of the seriously ill or very young for ethical reasons. Human exposures are usually brief because, unlike laboratory animals, they cannot be kept in the laboratory for prolonged periods. Laboratory animal studies and human clinical studies are complementary, as the limitations of one are the strengths of the other.

6.3. HYPOTHESES FOR PM TOXICITY

6.3.1. Mechanisms of Injury

Table 6.1 lists some of the mechanisms by which PM can impair health, along with the subpopulations that may be especially vulnerable. Although most of these mechanisms are capable of producing lung failure, some involve the heart. For a mechanism to be important, it must be capable of causing partial or total failure of a major organ, or exacerbating an existing disease. The dynamic processes of living systems involve continual adjustments to environmental variations, including variations in air quality. Thus, some changes in physiological functions or anatomy are transient and do not pose a general threat to health. Determining whether a particular response is a health threat or merely a protective or adaptive response is often a matter of judgment as well as a source of controversy. It must be understood that some individuals are so fragile that virtually any biological change, including adaptive responses, can be life threatening. For example, exposure to moderate

Table 6.1 Proposed mechanisms by which inhaled particles might produce injury along with the target organs affected and presumed vulnerable subpopulations.

Mechanism of Injury	Target Organs	Vulnerable Subpopulations
Inflammation	Lung	Asthmatics, bronchitics
Increased permeability	Lung, heart	Asthmatics, cardiac patients
Edema	Lung, heart	Persons with advanced cardiac or lung diseases
Bronchoconstriction	Lung	Asthmatics
Impaired defenses/ infections	Lung, other	Young children, bronchitics, immunocompromised
Blood vessel injury/ blood coagulation	Heart, lung	Persons with advanced cardiac or lung diseases
Excess mucus	Lung	Asthmatics, bronchitics
Neurogenic	Heart	Persons with cardiac diseases

altitude, mild exercise, or psychological stress can be hazardous for people with advanced cardiopulmonary disease.

6.3.2. Particle Characteristics

Several physical and chemical characteristics of PM have been proposed as being responsible for producing the adverse health effects that have been reported by epidemiologists. These characteristics are listed in Table 6.2, along with the mechanisms of injury associated with each and the sources of the particles that might produce injury. This list is not exhaustive, but it represents some of the major types of particles that toxicologists are currently examining. Any, and all, of these particle characteristics could explain the epidemiologic associations, but the key uncertainty is whether they are present in sufficient quantities in the breathing zones of susceptible individuals to produce illness or death.

Table 6.2 Characteristics of PM that have been proposed as producing adverse health effects in humans, along with the mechanisms of injury and potential sources of the particles.

Characteristic	Mechanism	Particle Sources
Ultrafine size	Increased airway permeability, inflammation	Combustion, high-temperature processes, reactive gases and vapors
Silica content	Inflammation, macrophage injury, cell killing	Soil, sandblasting, ore recovery
Acidity	Mucus secretion, impaired mucus clearance, bronchoconstriction	Combustion of sulfur containing fuels, internal combustion engines
Biogenic Aerosols	Bronchoconstriction, inflammation, infection	Plants, animals, fungi, bacteria, viruses
Metals and highly Reactive species	Inflammation, cell killing	Fuel combustion, industrial processes, soil, photochemistry
Oxidative properties	Cell damage	Combustion products, industrial processes, soil, photochemistry
Mixtures	Various	Various

6.3.3. Other Explanations

In addition to PM, other pathways related to PM have been suggested as causing the epidemiologic associations between health and PM measures (Valberg and Watson, 1998). Some pathways are listed in Table 6.3, along with potentially susceptible populations. All of these factors, plus all of the aforementioned PM characteristics, will have some effects on health. The key question relates to the strength of the effects, which may range from negligible to severe.

Table 6.3 Nonparticle pathways (explanations) for producing associations between adverse health and PM measures along with potentially susceptible subpopulations.

Pathway	Potentially Susceptible
Meteorology	Persons with advanced lung and heart disease
Elevated indoor exposures related to PM episodes	Asthmatics, bronchitics, emphysemics, young children, elderly, immunocompromised, cardiac patients
Gaseous pollutants (CO, SO_2, NO_x, volatile organics)	Cardiac patients, asthmatics, others with advanced lung disease
Panic or fear of air pollution	Cardiac patients, asthmatics, other groups with fragile health

6.4. CLINICAL PLAUSIBILITY

An important issue related to establishing a cause-and-effect relationship between urban PM and adverse health effects involves the concept of clinical plausibility. The word *clinical*, derived from the Greek *klinikos* (pertaining to a bed), relates to the direct observation of patients. A similar concept, biological plausibility, relates to the direct observation of changes in the status of an organism. It has been argued that epidemiological associations, especially when the association is not particularly strong (less than a doubling of the probability of an outcome), do not permit the assumption of causality unless medical (or biological) plausibility is also established. A problem arises when one must define exactly what is needed to establish clinical plausibility.

Substantial differences of opinion exist regarding the evidence required for establishing a causal link between PM exposure and injury. At one extreme, strong proof, similar to a proof in geometry, is required. Given some solid assumptions drawn from chemistry and physiology, one might establish an unbroken chain of events (such as pollutant deposition, early response, secondary reactions, organ failure, etc.), at the end of which death or debility is virtually certain. Such proofs do exist for many illnesses and poisonings, and when this is the case, intervention (at least in principle) is straightforward. At the other extreme, plausibility might simply mean that there is an absence of proof of absurdity. Intense smog episodes kill people, so why would not smaller ones? A substantial fraction of the research needs

discussed in Chapter 7, especially those in the toxicology category, relate to plausibility questions.

If the economic costs related to curtailing PM were negligible, then the strength of the medical evidence required might not be so important. But controlling PM has impacts with respect to the provision of food, raw materials, finished goods, electricity, transportation, and shelter and implications to employment and income. Therefore, since tradeoffs that impact health are involved in PM control, proof of a causal link and the identification of the specific causal agent(s) become very important. Toxicology research, including human clinical studies, will need to clearly demonstrate how the suspect agent produce morbidity and mortality. Once the link is certain, efficient controls or other protective actions for the affected individuals can be agreed on.

6.5. NEW RESEARCH APPROACHES

The necessity for establishing clinical plausibility has generated a significant challenge to toxicologists. The reason for this is that the enormous database on inhaled particles does not indicate that tiny levels are capable of producing significant acute harm, except for allergens, pathogens, or hypothetical supertoxic agents. Such supertoxic agents are not known, as even chemical warfare agents such as phosgene, mustard gas, lewisite, soman, and sarin require tens of micrograms to kill normal people. Virulent microorganisms that produce severe disease states are an exception in that microgram levels can seriously injure and kill; although the time to illness or death is usually more than the one to three days that is attributed to PM episodes.

Because of the lack of a ready explanation for how as low a concentration as 10 $\mu g/m^3$ of PM might be lethal, toxicologists have intensified the development and use of new models. These models have included studying fresh concentrated air pollutants (CAPs) and the use of very old and very ill laboratory animals.

6.5.1. Concentrated Air Pollutants

The development of devices that delivered significant quantities of CAPs to animal exposure systems led to new types of toxicology studies. Among the first reports of such a study was a paper presented at the Second Colloquium on Particulate Air Pollution and Human Health held in Park City, UT, in May 1996 (Godleski et al., 1996). The major objective of the study by Dr. John Godleski and colleagues at the Harvard School of Public Health in Boston, MA, was to examine the biologic plausibility that inhaled PM exposures would produce deaths in ill populations. The animals, laboratory rats, had a severe bronchitis (with lung inflammation, airway hyperresponsiveness, and increased deposition of inhaled particles) that was produced by preexposure to 250 ppm SO_2 five hours per day, five days per week for six weeks. The study exposures were to Boston air that had been concentrated by about 30-fold. The Harvard Ambient Particle Concentrator (Sioutas et al., 1995) took outdoor air and stripped away particles smaller than 0.1 μm and larger than 2.5 μm, leaving the intermediate sizes concentrated in an air stream. Four groups of animals were examined: bronchitic rats exposed to CAPs six hours

per day for three consecutive days; bronchitic rats exposed to filtered laboratory air six hours per day for three consecutive days; and two groups of healthy rats similarly exposed to CAPs or filtered air using the same exposure protocol. Endpoints were spontaneous deaths, autopsy, analysis of lavaged lung cells, and histopathologic examination of lung tissues. The results were striking; only the CAP-exposed bronchitic group had significant mortality (37% died), with no deaths in the bronchitic-filtered air group. Also, the bronchitic animals (including those not dying) exposed to CAPs showed evidence of increased bronchoconstriction and increased inflammatory cells in lung lavages. This study produced considerable interest because real air pollutants had been used, and significant deaths were observed. The particle concentrations in the CAP chambers ranged from 190 to 317 $\mu g/m^3$, which is high for modern cities, but the average volume median particle diameters ranged from 0.3 to 0.5 μm, which is realistic.

Following these initial rodent studies, the group performed exposures to Boston CAPs using dogs. Such studies in larger animals are essential following such a spectacular result in rodents because the architecture of the rodent lung is very simple compared to that of larger mammals. Thus, the dog is more likely to respond in a humanlike manner than the rat. The dog exposures focused on changes in electrocardiograms (ECGs), with an emphasis on measuring the variability in electrical signals that control the rhythmic contractions of the heart. Again, the CAP exposures were reported as producing significant changes in comparison to exposures to filtered air. These studies were reported in an invited presentation at the Annual American Association for Aerosol Research Conference in Cincinnati, OH, in June 1998 (Godleski, 1998). The studies by John Godleski inspired other investigators to develop air pollution concentrators and to initiate similar studies (Sioutas et al., 1995; Gordon et al., 1999).

6.5.2. Compromised Animal Models

The suspected PM-sensitive human subpopulations include very young children, the elderly, and individuals with serious cardiopulmonary diseases such as asthma, bronchitis, emphysema, and congestive heart failure. In contrast, nearly all of the laboratory animal models used in environmental studies involve animals that are free of cardiopulmonary diseases. In the past, the sensitivity of animal models to the effects of particle inhalation has been achieved by selecting sensitive species (e.g., the guinea pig for bronchoconstriction), using sensitive endpoints (e.g., histopathology, particle clearance, and biochemical and cell-function measures), preconditioning to purified air, and using large numbers of subjects to detect small changes in structure or function. Although compromised animal models have been used in studies of human diseases for many decades (Phalen, 1984; Cantor, 1989), such older models and newer ones are gaining popularity (Conn et al., 2000; Bice et al., 2000; Mauderly, 2000; Muggenburg et al., 2000). Table 6.4 shows some ongoing research in this area.

Among the models of interest are those that represent elderly individuals, asthmatics, and bronchitics. Some of these models have indicated increased sensitivity to the effects of inhaled PM. Dr. Cheryl Killingsworth and colleagues at the Harvard School of Public Health in Boston, MA, studied the effects of inhaled resuspended oil-fuel fly ash particles using rats that were pretreated with a single

subcutaneous injection of monocrotaline. Monocrotaline injection produces an acute, progressive inflammation of the lung with associated high blood pressure and

Table 6.4 Some new research on the effects of inhaled PM on compromised-animal models (adapted from NRC, 1998).

Project Title (some are approximate)	Investigator	Institution
"Use of Compromised Animal Models to Evaluate the Susceptibility to Inhaled PM"	J. Mauderly	Lovelace Respiratory Research Institute, Albuquerque, NM
"Effects of Exposure to Fine and Ultrafine . . . Particles in Young, Adult, and Old Rats"	M. Kleinman, and K. Pinkerton	U.C. Irvine, Irvine, CA; U.C. Davis, Davis, CA
"Particulate Matter Effects on Animal Models of Asthma"	S. Gavett	U.S. EPA, Research Triangle Park, NC
"Chronic Obstructive Pulmonary Disease: What Can a Rat Model Tell Us?"	U. Kodavanti	U.S. EPA, Research Triangle Park, NC
"Adverse Health Effects of Ambient PM in Compromised Animal Models"	T. Gordon	New York University Medical Center, Tuxedo, NY
"Ultrafine Particles . . . : Mechanisms and Correlation with Age and Disease"	G. Oberdörster	University of Rochester, Rochester, NY
"Mechanisms of Morbidity/ Mortality Due to Air (Pollutant) Particles"	J. Godleski	Harvard School of Public Health, Boston, MA
"Studies on the Causality of PM . . . in Animals with Asthma, Heart Failure and Pulmonary Hypertension"	F. Cassee and L. van Bree	National Institute of Public Health and Environment, Bilthoven, the Netherlands

right heart enlargement (Killingsworth et al., 1996). The fuel fly ash particle concentration was about 600 $\mu g/m^3$, the particle median aerodynamic diameter was 2 μm, and the exposures were six hours per day for three days. Deaths (42%) were seen in the fly ash-exposed group, but not in exposed control (saline injected) groups, during exposure. The authors concluded that the induced inflammation enhanced the inflammatory effects of the fly-ash particle exposure, producing the deaths. In this study, the fly ash level was very high and also contained several metals, including iron, aluminum, vanadium, nickel, and magnesium. Increased levels of an inflammatory-related protein (MIP-2) were seen in both lung and heart tissues of monocrotaline-treated rats, which led the investigators to suspect that some of the deaths may have been related to effects on the heart. Dr. Michael Kleinman, at the University of California, Irvine, conducted nose-only exposures to ammonium bisulfate and carbon particles, with and without ozone, using aged rats (24 months approximate age). Many pollutant combinations were inhaled, but the most effective in producing changes (i.e., cell death and altered collagen levels) were atmospheres that contained both ozone and ammonium bisulfate (Kleinman et al., 1996).

The above studies were only the first of many that explored the use of the compromised animals in particulate air pollution research.

6.6. MAJOR UNCERTAINTIES

The major uncertainties facing toxicologists relate to key questions raised by the epidemiology associations. First, what in urban air are the likely chemical and/or physical agents driving the epidemiological associations? Many possibilities exist, including that one or more multicomponent combinations or unmeasured substances are super toxic. Second, who are the affected individuals? The major emphasis is currently on cardiopulmonary patients and the elderly, but other possibilities exist including persons with conditions such as sleep apnea or allergies, those with nutritional or immunological deficiencies, those compromised by medications or acute infections, and genetically predisposed groups. Third, how might the mortality or morbidity be effected? Possibilities include direct effects on the respiratory system, direct and indirect effects on the heart, and other effects including alterations in the central nervous system or immune functions.

Another uncertainty involves extrapolation of laboratory studies to human populations. At some point, the hypotheses developed using laboratory animals would ideally be tested in humans. Such tests are difficult both technically and ethically because complex exposures and compromised subjects are likely to be required. Risks faced by human subjects must be minimized. Slowly escalating the exposure levels, while maintaining close medical surveillance during and after the study, are the major means of protecting the subjects.

Another uncertainty associated with toxicology studies of PM is that toxicology usually examines only harm and not benefit. For example, if particle inhalation is also necessary for maintaining normal effective respiratory-tract defenses, the focus only on adverse effects could eventually lead to over control of environmental PM to the extent that the health of the public as a whole is degraded. This problem is not unique to PM concerns, but it is also an emerging issue in infectious disease resistance as well: microbiologists have questioned the trend

toward avoiding contact with microbes in water, food, and air. The concern relating to microbes, that immunity or other defenses may be lost, may also relate to nonbiogenic air pollutants.

6.7. LESSONS LEARNED

The main lesson learned from examining the role of toxicology in understanding the PM epidemiology is nothing new: a new issue requires new research and the development of new approaches. The models used by toxicologists must be modified to answer new questions. The new models must be more realistic in order to apply to real-world exposures (which involve complex pollutants, many cofactors, and highly varied human populations). The new models must also be medically relevant to apply to the actual etiologies involved in human disease production, disease exacerbation, and mortality.

Additional lessons have been learned regarding the need for toxicology research to be part of a multidisciplinary effort. The move toward more relevant exposures requires that toxicologists collaborate with epidemiologists, atmospheric scientists, chemists, and aerosol scientists. Also, the need for toxicology studies to be relevant to human disease patterns requires an affiliation with medically trained scientists. It is not surprising that some of the most creative and relevant animal toxicology is practiced by veterinarians and physicians. Important studies are being conducted by investigators trained in veterinary medicine, such as Drs. Gunter Oberdörster of the University of Rochester, Jack Harkema of Michigan State University, and Joe Mauderly of the Lovelace Respiratory Research Institute. Certainly medical training is essential to the relevant human clinical studies, such as those being conducted by Drs. Mark Utell and Mark Frampton (University of Rochester), Henry Gong (University of Southern California), and others.

A final lesson extracted from examining toxicology research on PM is that low-dose, large population issues will require a change in the thinking of toxicologists. This topic is treated in a special issue of *Critical Reviews in Toxicology* (Volume 31, Issues 4 and 5, 2001). Only documenting adverse acute effects, to the exclusion of long-term effects or the potential benefits of PM-related exposures, leads to a distorted picture of the implications to public health.

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Chapter 7
Research Needs

7.1. RELEVANCE TO THE PM CONTROVERSY

The possibility that significant health effects might be occurring in populations breathing particulate material (PM) at levels below accepted air-quality standards stimulated scientific debates. These debates identified numerous gaps in the relevant scientific databases. Accordingly, the realization that many relevant questions could not be answered led to efforts to define and prioritize the needed research. Several parties, including scientists attending PM Colloquia, the U.S. EPA, the National Research Council of the National Academy of Sciences, the Health Effects Institute, and the EPA's Clean Air Scientific Advisory Committee, have identified the high-priority needs for further research. The following sections describe some of these efforts and the results produced. In addition, these planning efforts serve as models by which scientists, regulators, and funding agencies might logically address other important scientific issues in the future.

7.2. COLLOQUIA ON PARTICULATE AIR POLLUTION

7.2.1. First Colloquium (January 1994, Irvine, CA)

This colloquium was perhaps the first to assemble a large diverse group of researchers, regulators, and others interested in the issues raised by epidemiological studies that associated small increments in PM with adverse acute effects on human health. The 200 attendees were asked to submit suggestions for research after each session of scientific presentations. The scientific sessions, featuring talks by leading researchers, covered four topics: epidemiologic findings; epidemiologic methods; mechanisms of toxicity; and sources, levels, and characterization of particulate air pollutants. Written suggested research projects were gathered at the end of each session. These suggestions (over 100 total) encapsulated the perceived needs for research by a diverse group that had received an update on the relevant issues. The research suggestions were sorted, condensed, and published (Phalen and McClellan, 1995), but a brief summary is given here. Given the uncertainties relating to PM effects and the differences of opinion among colloquium attendees, the suggestions were surprisingly coherent and largely noncontroversial.

Defining exposures to air pollutants was perceived as a topic requiring new research as the specific individuals who might be affected and the relevant sources were unknown. Monitoring of actual exposures was necessary at more sites (both indoor and outdoor), more frequently, and using improved methods to define particle size distributions and levels of stable and transient chemical species. Personal

exposures using monitors mounted on people, rather than at central locations, were also needed because area monitors did not accurately reflect pollutants in the breathing zones of individuals. Data on individual exposures were needed for future epidemiological investigations. Inhalation doses needed to be better defined in terms of how much of each chemical species was expected to deposit in the various anatomical regions of the respiratory tract in various types of individuals, especially those in high-risk groups (infants, the chronically ill, and the elderly). Such information would help to pinpoint potentially important groups in future epidemiological and toxicological investigations. The number of cities studied needed to be expanded, especially to include those that were very polluted, very clean, or had recently had major declines in PM. Such data would both sharpen conclusions from epidemiological studies and assess the benefits of pollution control efforts. New long-term epidemiological studies were considered necessary, especially if better chemical exposures and dose estimates for individuals could be included. There was also a perceived need to quantify the average loss of life expectancy (estimates ranged from a few days to several years) associated with air-pollution-related deaths and to develop and establish risk models that could be used to predict the benefits associated with various abatement strategies. It was realized that new reductions in pollutant levels would be costly, so cleanup strategies would require substantial justification.

With respect to epidemiological methods, research was needed to improve epidemiological models so that when personal exposures where obtained they would be properly taken into account, and the effects of exposure measurement errors on epidemiologic results would be quantified. Also, it was recommended that central databases (both synthetic and real) be established and made widely available, so that results and conclusions of past studies could be checked, and new methods and hypotheses could be examined. The effects of weather variables, and exposure to mixtures of pollutants were also seen as requiring further research because extreme weather conditions and potentially synergistic mixtures could have major effects on health.

Toxicology research was needed to develop and use new animal models of diseased humans, to better understand the limits of applicability of existing models, and to greatly expand the numbers and types of pollutants that could be studied. It was realized that current animal models (typically disease free) were unresponsive to small concentrations of the chemically simple particulate air pollutants (such as nitrates, sulfates, carbon, and soil). Some specific suggestions called for greater study of ultrafine particles (diameters less than 0.1 μm), iron-containing particles, and aqueous particles, as well as a greater emphasis on macrophage cell populations, in-vitro methods, nonpulmonary effects, and pathologic effects on small airways. In effect, the commonly used toxicology methods were not sophisticated enough.

Research needs in the atmospheric sciences were identified in several areas including: development of better laboratory and field analysis and monitoring methods; better characterizations of certain environmental air pollution components (e.g., short-lived compounds, inorganic compounds, biological aerosols, other organics, aqueous droplets, and mixtures); better definitions of the chemical characteristics of air-pollution episodes at varied urban locations; and examination of the air-chemistry consequences associated with burning proposed "alternative" fuels

in vehicles. Again, the currently used methods were considered crude in light of the new questions raised by the epidemiologists.

7.2.2. Second Colloquium (May 1996, Park City, UT)

This colloquium, held just over two years after the first one, had a similarly diverse attendance but broader scientific coverage; sessions on particle deposition and clearance, exposure assessment, indoor exposures, and occupational exposures were added to the program. At this meeting, the research suggestions were submitted after all of the papers had been delivered rather than after each session. Again, the suggestions were analyzed and published (Phalen and Lee, 1998) so only a brief summary will be given here. A small separate workshop, chaired by Dr. Morton Lippmann, on long-term research needs was held just prior to the colloquium. The recommendations from this workshop, which supplement those below, were also published (Lippmann et al., 1998).

This time, the suggested research included most of the projects previously suggested plus some new ones. New collaborations were suggested—between economists and epidemiologists to shed light on cost-benefit issues and to establish relevant valuations of health, and between pathologists and epidemiologists to allow inclusion of autopsy data in investigations. Epidemiologists were encouraged to study the increasing asthma rates in light of improving outdoor air quality and to focus more on personal exposures and nonparticulate pollutants (that coexist with PM). Studies of retired workers exposed to high levels of particles while working were suggested to see if they had any induced sensitivity to environmental particles or increased disease rates after retirement.

Clinical studies were suggested to learn more about pollutant deposition and clearance in diseased humans and to look at the acute responses of suspected sensitive populations to well-defined inhalation exposures. Such clinical studies would be used as a bridge between epidemiological and toxicological investigations.

Toxicology study suggestions beyond those from the previous colloquium included: investigation of the roles of particle count and surface area in relation to mass in producing effects; use of concentrated ambient particles in inhalation experiments; and study of costressors (such as heat), long-term exposures, and the potential for sensitization to air pollutants. One goal was to reduce uncertainty regarding the proper measure of particulate air pollution, as mass alone was not seen as sufficient.

Research needs relating to sampling, analysis, and exposure assessment included studies of how indoor and outdoor pollution temporally correlate, chemical interactions among realistic combinations of air pollutants, and interactions of viable (infectious and allergenic) with nonviable air pollutants. It was believed that previous studies had neglected the true complexity of air pollution.

Several suggestions related to practical issues, on which efficient progress depends. These included fostering international cooperation, pooling resources from government, industry and other institutions, and setting up central resources (including important data) that would be available to researchers.

It became clear that this second effort at defining the needed research was superior to the first. Greater collaboration, greater study breadth, and greater

attention to practical issues were now encouraged. The core questions remained, but the means for answering them required significant improvement.

7.2.3. Third Colloquium (June 1999, Durham, NC)

The third colloquium focused on the research agenda proposed by the National Research Council (NRC, 1998, 1999, 2001). Over 170 papers were presented as posters, and the plenary sessions focused on specific health-related questions as follows:

- Session 1: What are we breathing, and how can it best be characterized? (Chair: Dr. Ronald Wyzga)
- Session 2: What properties of particulate matter are responsible for health effects? (Chair: Dr. Jonathan Samet)
- Session 3: What are the biological mechanisms underlying adverse health effects? (Chair: Dr. Kevin Driscoll)
- Session 4: What improvements in dosimetry and extrapolation modeling will provide for better evaluation of human health effects and risk assessment? (Chair: Dr. Robert Phalen)
- Session 5: Who is susceptible to particulate matter and why? (Chair: Dr. Mark Utell)
- Session 6: Integrative summary of the colloquium. (Chair: Dr. David Bates)

In addition to covering the main question/topic addressed in each session, attendees were not discouraged from raising new issues or posing challenges to the assumptions implicit in the views presented.

All of the posters' authors, invited speakers, and session chairs were encouraged to submit their material for publication in the proceedings (Phalen and Bell, 1999). Peer-reviewed papers were published in special issues of the journal *Inhalation Toxicology* (Vol. 12, Suppl. 1–2, 2000). The research needs identified were not substantially different from those previously indicated, but the questions asked were more focused. However, the relationships between acute and chronic responses to air pollutants were seen as requiring greater attention, as was the need to better understand which genetic and other factors might produce extreme susceptibility. It was acknowledged by several participants that the colloquia had had significant impact on their research programs. The formal gatherings of scientists with diverse interests offered stimulating research collaborations and a significant sophistication to many projects.

7.3. THE U.S. EPA IDENTIFIES RESEARCH NEEDS

The U.S. EPA allocates resources for analyzing gaps in the scientific data base and for planning the research required to serve their periodic reviews of criteria air pollutants. A 150-page EPA report issued in January 1998 laid out the needs for research on PM to support future National Ambient Air Quality Standards (NAAQS)

(EPA, 1998a). A second related report, based on a well-attended workshop, was issued about the same time (EPA, 1998b).

Because of its experience in setting NAAQS for PM and other criteria pollutants, the EPA was in a favorable position to identify uncertainties in the research database and to ascertain research needs. EPA staff, the Clean Air Scientific Advisory Committee (CASAC) to the EPA, the public, and scientists from academia, private research organizations, other governmental agencies, and the business community had opportunities to participate in the identification of research needs by the EPA. However, the EPA, out of necessity, limited its interest to identifying research seen as actually required for setting the NAAQS. The NAAQS are focused on a few, nonbiological, contaminants (ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, suspended particulate matter, sulfates, and lead).

For PM, the EPA first identified several important uncertainties that are similar to those already described (EPA, 1998a, 1998b). Then, the research needed to resolve the uncertainties was defined. Using this process, the following top six "highest priority" and next four "next level of priority" research topics were identified (EPA 1998a):

1. The effects of long-term exposure to PM;
2. Identification of susceptibility factors (who is harmed and why?);
3. The mechanisms that produce relevant biological responses;
4. The key biologically active components of PM;
5. The relationships between personal exposures and PM as measured by central outdoor monitors;
6. The shapes of "exposure-dose-response" relationships for important health outcomes;
7. Determination of background PM concentrations, as exist at rural sites;
8. The effectiveness of PM reductions in improving health;
9. Atmospheric modeling to assist in defining exposures in unmonitored regions; and
10. Improved source characterizations to aid toxicology research efforts and risk-management decisions.

In addition, the EPA stressed three "overarching concepts":

1. Interdisciplinary collaboration involving cooperation among atmospheric scientists, laboratory researchers, clinical scientists and epidemiologists;
2. Inclusive research on PM that considers the complex associated mix of gases and semivolatile pollutants and their physical and chemical interactions; and
3. International collaboration to take advantage of unique exposures and to promote harmonization of PM indicators that correlate with effects.

The EPA reports relating to PM research needs also included detailed descriptions of needs within specific areas or disciplines including "epidemiology," "toxicology and dosimetry," and "measurement, characterization, and exposure" (EPA, 1998a). Another aspect of the EPA documents included the names and affiliations of the people involved in preparing and critiquing the reports, as well as

descriptions of the rationale and processes employed. It is apparent that the EPA devoted considerable effort to recommending the research needed for establishing the NAAQS.

7.4. NATIONAL RESEARCH COUNCIL (NRC) RECOMMENDATIONS

7.4.1. The NRC Committee and Its Approach

Realizing that tightened regulations on particulate air pollutants would have potentially severe impacts on the economy, the U.S. Congress directed the administrator of the U.S. EPA to support an independent study of important research needs that could be *met before the next review* of the PM National Ambient Air Quality Standards (McClellan, 1998). Congress directed that the study be performed by the National Research Council (NRC). The NRC is the principal operating agency of the National Academy of Sciences (NAS) and the National Academy of Engineering (NAE). The NRC committee, composed of 20 prominent experts and chaired by Dr. Jonathan Samet, was charged with producing four reports between 1998 and 2002. Committee members represented diverse disciplines and viewpoints, and they were asked to serve as individuals rather than representatives of their organizations. Furthermore, they were not compensated, nor were they permitted to compete for the planned new research funding related to their recommendations. Congress also provided the EPA with $49.6 million in fiscal year 1998 for PM research linked to the NRC's recommendations, which represented about twice the amount requested by the EPA.

The first report of the NRC Committee, issued in January 1998, was titled *Research Priorities for Airborne Particulate Matter: I, Immediate Priorities and a Long-Range Research Portfolio* (NRC, 1998). In this report, the Committee established two basic philosophical foundations for the planning process. The first was a set of criteria for judging potential research priorities and projects. The criteria were scientific value, value for decision making in relation to NAAQS for PM, and feasibility and timing considerations. The second philosophical foundation was a fixed conceptual framework within which the recommendations were established. The use of such a framework, no matter how broad, would exclude consideration of some potentially valuable research activities. The framework had five main components (Figure 7.1). These components—sources, ambient indicators, exposure, dose, and response—along with the three criteria for establishing priorities were used to produce a list of the 10 highest-priority research topics.

7.4.2. Highest-Priority Research Topics of the NRC

The following highest-priority research topics of the NRC were not presented in order of priority or timing; timing was a separate issue that was treated elsewhere in the report.

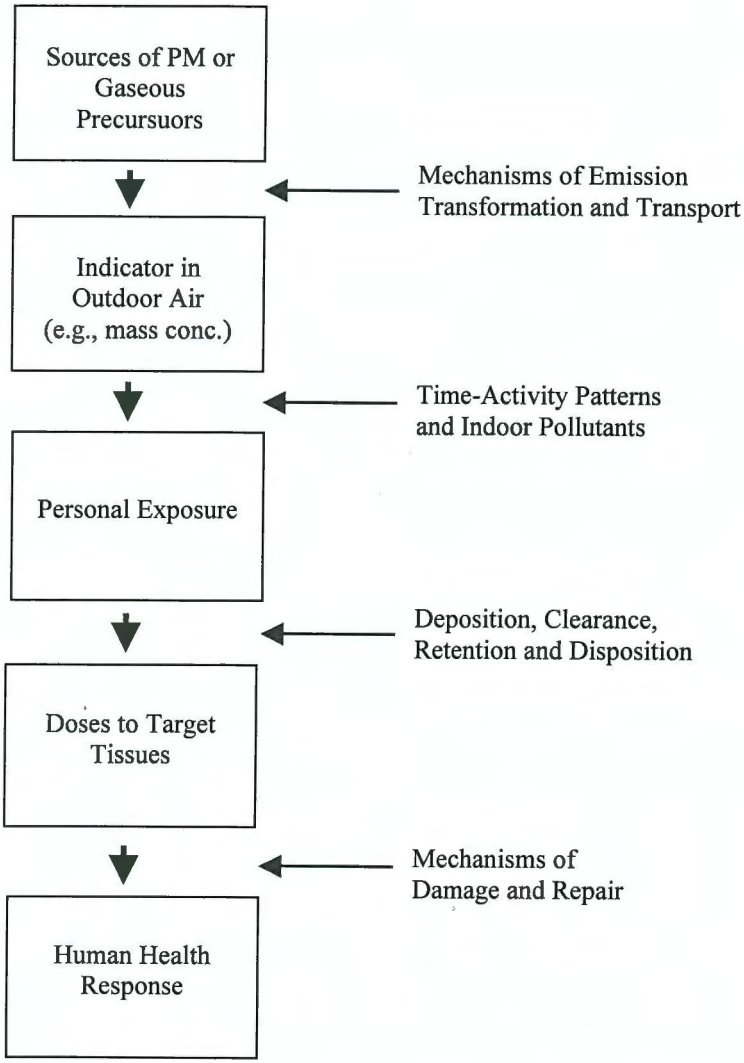

Figure 7.1 The five-component framework of the Committee on Research Priorities for Airborne Particulate Matter of the National Research Council (from NRC, 1998, Figure 3.1).

1. Investigations were needed on the quantitative relationships between measurements taken at centrally located stationary air monitors and the actual exposures in the breathing zones of individuals. An emphasis was placed on both particles and associated copollutant gases, indoor as well as outdoor exposures, human time-activity patterns, and potentially susceptible subpopulations. Possible susceptibles included children, the elderly, people with respiratory tract or cardiopulmonary diseases, and those with compromised immune systems.
2. Investigations were needed on exposures of susceptible populations to the most biologically important (regarding health) "constituents" and "specific characteristics" of PM. "Constituents" are chemical substances or mixtures, and "specific characteristics" include particle-size distributions, particle counts, physical associations among components and other nonchemical characteristics.
3. Development of advanced modeling and measurement tools that would accurately relate specific sources of pollutants to specific exposures of human populations or individuals was needed. Modeling the fates of emissions and their variability, as well as developing better personal and ambient monitors were included under this priority.
4. Application of advanced modeling and improved analytical methods to link the biologically important constituents and characteristics of PM to their sources was needed. This knowledge could lead to effective control methods.
5. Research, using toxicological and epidemiological methods, on the roles of physiochemical characteristics of PM in producing adverse health effects was needed. Under this priority, laboratory surrogates for ambient PM should be developed, relevant dose metrics (particle mass, surface area, number, reactivity, etc.) should be established, and the importance of particle size and chemistry investigated. Because the "most relevant route of exposure is inhalation," the inhalation route was recommended for use.
6. Investigations of the deposition patterns and fates of inhaled particles and their constituents, especially in presumed susceptible subpopulations, were needed. This priority included obtaining data on lung structure and breathing patterns, the effects of particle hygroscopicity on deposition, particle clearance mechanisms, and the bioavailability of particle-related constituents.
7. Investigations were needed, using toxicological and epidemiological methods, to disentangle the effects of PM from those of gaseous copollutants. This complex issue requires a variety of studies that include natural experiments (comparison of regions that are uniquely different) as well as controlled laboratory-animal and human-clinical investigations where simple combinations and more-complex mixtures of pollutants could be studied. This topic called for the epidemiologic research to focus on the influence of copollutants "on the association between chronic health effects and exposure to PM."

8. Identification of the human subpopulations that may be at increased risk of adverse health effects of exposure to PM was needed. Such studies include identifying susceptibility factors such as variations in deposition and clearance rates of pollutants, and the effects of age, gender, disease, coexposures, and other susceptibility factors. Once this information had been obtained through controlled human studies and studies in appropriate animal models, epidemiological studies should be conducted to validate the conclusions.
9. Investigation of the mechanisms of injury that might explain the epidemiological associations between PM measures and increased morbidity and mortality were needed. This required the use of laboratory animal models, including those for compromised people, in-vitro models, and clinical studies that included children, the elderly, smokers, and ill subjects.
10. Development and application of improved methods of statistical analysis of epidemiological data including the effects of measurement errors and misclassification errors on findings was needed. Included in this large category were issues relating to removing long-term trends (such as those due to season), filtering, autocorrelation, timing of exposure and responses, copollutant effects, shapes of exposure-response curves, possible false positives when using regression models, and the influences of errors related to inadequate exposure estimates and uncertainties for causes of deaths.

The NRC report was especially strong with respect to identifying uncertainties and putting forth a coherent research plan. The report included schedules, funding recommendations, and an inventory of ongoing research efforts. The identified research needs would stimulate increased funding, and a large worldwide research effort. Future reports refined the research agenda and evaluated the research progress on achieving the goals. The second NRC report (NRC, 1999) recommended relatively minor changes in the research agenda but noted that attempts at integration of the research were not yet adequate. In the third report (NRC, 2001), initial progress on the high-priority projects was assessed, and suggestions were made for improving the research activities as well as the integration process.

7.5. OTHER EFFORTS TO IDENTIFY RESEARCH NEEDS

7.5.1. The Clean Air Scientific Advisory Committee (CASAC)

The Clean Air Scientific Advisory Committee (CASAC) of the U.S. EPA's Science Advisory Board is a diverse group of non-EPA scientists that acts as an independent review committee for EPA criteria documents on air pollutants. CASAC not only evaluates the completeness and quality of the criteria documents, but it also identifies gaps in knowledge and provides comments to the EPA administrator on proposed revisions of air quality criteria (NAAQS).

With respect to the 1996 PM criteria document (EPA, 1996) and the revised standards based on that review, CASAC had difficulty in achieving "closure."

"Closure" is obtained when a CASAC consensus is achieved and transmitted to the EPA administrator. The closure letter, dated March 15, 1996, prepared by the CASAC chair, Dr. George Wolff, indicated general approval of the draft Criteria Document. However, the committee noted that the "understanding of the health effects of PM is far from complete," and several important uncertainties were identified (Wolff, 1996a, 1996b). These uncertainties included the following:

1. The influence of confounders that make causality uncertain;
2. The effects of PM measurement errors on the epidemiological findings;
3. The existence of alternative explanations for the PM-health associations;
4. The lack of understanding of toxicological mechanisms;
5. The lack of knowledge as to how much life-shortening might be produced by the deaths associated with PM pollution;
6. The effects of exposure misclassification on the epidemiological associations;
7. The uncertain shape of the dose-response function for PM pollution; and
8. The effect of the use of the different models in the various epidemiology studies.

In items 1 and 3 above, CASAC expressed some skepticism regarding causality and indicated that non-PM-exposure factors should be considered. Such factors include weather-related and gaseous pollutant factors as well as behavioral or psychogenic phenomena that occur with high PM days (Valberg and Watson, 1998).

7.5.2. The Health Effects Institute (HEI)

The Health Effects Institute (HEI) of Boston, MA, was established in 1980 to act as an independent and impartial source of information on the health effects of vehicle-related pollutants and to support needed research on such pollutants. The HEI is typically funded 50% by the U.S. EPA and 50% by motor vehicle manufacturers. In addition to supporting research projects on PM, the HEI holds meetings of research scientists in order to identify high-priority research needs related to its mission. Over the last few years the HEI has solicited timely research proposals related to the health effects of PM, including the following:

1. Identification of populations at risk and underlying mechanisms of effects that may explain the epidemiologic observations (HEI, 1994);
2. Reanalysis of key epidemiologic studies that have indicated associations between low levels of PM and human mortality and morbidity, including analyses to control for the confounding effects of weather and copollutants and to evaluate the robustness of the original findings to alternative analytic approaches (HEI, 1995; HEI 1997b);
3. Identification of the characteristics of ambient PM that may be toxicologically relevant by investigating which compounds associated with inhaled particles delivered to the lung are bioavailable and their fates and reactivities (HEI, 1996);
4. Characterization of exposure to PM and application of improved exposure estimates to epidemiologic analyses (HEI, 1998); and

5. Identification of pathophysiologic changes related to particle size and composition (through epidemiologic and human and laboratory animal controlled exposure studies) (HEI, 1998).

Successful applicants are expected by the HEI to submit a final report at the conclusion of their study. These reports are peer-reviewed and published by the HEI with an agency-prepared commentary to place the study into a broader scientific context, point out strengths and limitations, and discuss the implications of the findings for public health. Such reports become important contributions to the health-effects database because the studies are targeted to answer questions relevant to major issues. The planning and oversight processes used by the HEI, which includes advice from active researchers, is an important factor in the success of their reports. Notable among such reports were the reports of the results of the "Particle Epidemiology Evaluation Project," entitled *Particulate Air Pollution and Daily Mortality: Analysis of the Effects of Weather and Multiple Air Pollutants* (HEI, 1995, 1997a). These reports covered the replication of key epidemiology studies and an analysis of the confounding effects of weather and copollutants.

7.6. COMPARISON OF RESEARCH PLANNING EFFORTS

It is valuable to compare and contrast the various attempts to define the uncertainties and needed research related to PM and health. The efforts of the U.S. EPA and of the NRC were focused on data specifically required for the setting of NAAQS. Implicit in their recommendations were the assumptions that PM, as a criteria pollutant, produces adverse health effects and that an ambient level of PM could be found such that susceptible subpopulations would not suffer. These assumptions tended to preclude research on alternate explanations for the epidemiologic associations between ambient PM and health. Also, the roles of natural pollutants in producing the associations were not initially given serious consideration, except as such pollutants interacted with NAAQS pollutants. Furthermore, the economic costs of controlling criteria pollutants were excluded from consideration in establishing the NAAQS. However, economic costs also have adverse health consequences (due to unemployment and higher costs of food, clothing, electric power, shelter, transportation, and services).

In contrast, the identification of uncertainties and research needs at the PM colloquia, and by the CASAC, were not subject to any limitations or constraints. The colloquium participants specifically called for studies on natural pollutants and collaborative research between economists and epidemiologists to include consideration of a larger public health picture. CASAC also emphasized its interest in alternative explanations for the PM-health associations. Not everyone on the CASAC believed that anthropogenic pollutants alone should be pursued by PM researchers.

It is understood that the identification and planning of needed research was linked to directives imposed on the planners. Both the EPA and the NRC had mandates in this case that focused their consideration on the roles of anthropogenic air pollutants in producing adverse effects. Although the studies recommended by

these groups were well researched and detailed, they were necessarily limited in scope.

7.7. IMPORTANCE OF THE RESEARCH PLANNING PROCESS

One of the strengths of science is the often careful process by which research programs are planned. This process involves assembling worldwide leaders in research, especially those having relevant experience and/or specialized knowledge. Research planning meetings involve extensive preparation, debate and discussion, and usually written reports. In many cases, the participants help to prepare announcements soliciting proposals that will address the needed research. When funding is directly tied to the planning process, it is common for those participating in the process to be barred from receiving funding. Despite this penalty, scientists seldom turn down the opportunity to meet, to share, and to argue their ideas.

What does this rich planning process actually achieve? Many funding agencies are responsive to needs as identified by scientists, and their research budgets may be redirected as a consequence. Several U.S. federal agencies in addition to the EPA support PM health research, including the National Institute of Environmental Health Sciences (NIEHS), the National Institute for Occupational Safety and Health (NIOSH), the Centers for Disease Control and Prevention (CDC), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID). Nonfederal PM health research efforts in the U.S. are supported by the American Petroleum Institute (API), the California Air Resources Board (CARB), the Chemical Industry Institute of Toxicology (CIIT), the Coordinating Research Council (CRC), the Electric Power Research Institute (EPRI), and the Health Effects Institute (HEI). Each of these agencies engages in their own formal planning efforts relating to research priorities. A list of these and other agencies involved in PM research efforts compiled by Dr. Maria Costantini of the HEI and Dr. John Vandenberg of the U.S. EPA is found in Appendix E of an EPA report (EPA, 1998b) and Appendix B of an NRC report (NRC, 1998). In the NRC report, nearly 300 studies were listed. Taken together they effectively address the research needs that have been presented here.

The research planning process as described in this chapter played a role in facilitating increased U.S. federal budgets for basic research. In deliberations regarding a plan for doubling the federal spending for research over the next few years, Senator Bill First (R-TN) commented: "You have to make sure . . . efficiencies as well as priorities are there." Future expansion of U.S. federal funding may require that the National Academy of Sciences help to set priorities as well as establish measurable outcomes (Lawler, 1998). Thus, the NAS reports on research priorities for PM may serve as a model for planning, coordinating, and monitoring research in other fields of science that receive federal funding.

7.8. LESSONS LEARNED

The concern for the potential health effects of previously accepted levels of particulate air pollution presented some significant challenges. The "business as usual" approach had to be set aside by scientists, funding agencies, and regulators and new objectives defined. The challenge has been successfully met as a result of proper actions by several stakeholders. Scientists, regulators, and others gathered at colloquia to initiate identification of important unresolved issues. Funding agencies launched their own research planning activities, and governmental and private entities began to generate financial resources to support the research. The U.S. Congress acted by directing the EPA to guide the formation of an NRC committee on research priorities and to provide the substantial funds needed to pursue the priorities. A large coordinated research effort was defined and monitored by the NRC committee. It appears that this process has been effective, and future decisions related to regulating PM will benefit greatly. The lesson learned here is that diverse communities (scientists, regulators, interest groups, industries, and legislators) can act cooperatively and productively in response to a significant challenge.

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CHAPTER 8
What's at Stake?

8.1. RELEVANCE TO THE PM CONTROVERSY

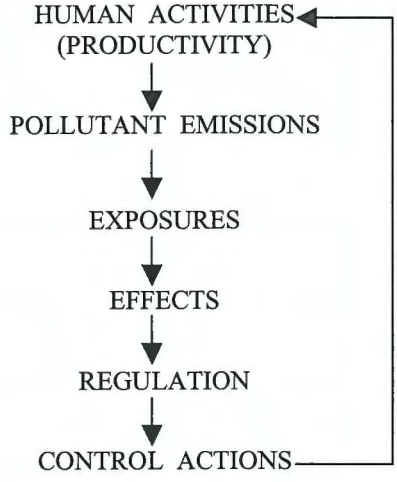
Why not eliminate all substances from the air, food, and water that could possibly produce harmful effects? This is impractical for several reasons. First, the required diversion of resources for identifying and implementing the necessary controls could not be borne by any society, no matter how wealthy. Second, this is impossible since all substances, including water, oxygen, and nutrients are capable of harming health (Table 8.1 illustrates the point). Third, the processes that contaminate the environment are frequently essential for sustaining health and life. Such processes include food production, extraction of raw materials, manufacturing, transportation of goods and people, generation of electricity, and the activities of all living things. Therefore, economic and health trade-offs are important considerations in setting contamination limits for the air, food and water (Graham and Wiener, 1995). Each pollutant control action produces adverse impacts along with the desired benefits. The relationship between regulatory controls and productivity is shown in simplified form in Figure 8.1.

Not long ago, the author testified before a board that was charged with deciding the budget for a local air pollution control agency. A representative from a dairy provided memorable testimony at the hearing. The dairy, a major supplier of milk for the community, described a dilemma related to dealing with solid wastes from their cattle. An official from a water regulatory agency asked them to stop making waste piles because of the seepage of nitrates into underground water. In response, the dairy began spreading the waste over the ground to facilitate the transport of ammonia into the air. Shortly after this process was instituted, an agent from the air regulatory agency visited and indicated that the air contamination was unacceptable. The agency wanted the waste piled up and covered to prevent air pollution. Because this method would be unacceptable to the water regulators, the dairy was forced to consider leaving the state. The adverse effect on public health from the loss of this dairy due to the diminished availability of fresh milk was obviously not within the responsibilities of either the air or water regulators – nor was an assessment of the resulting loss in wages, taxes paid by the dairy, and goods and services purchased by the dairy. In fact, the elimination of all dairies would be beneficial to local water and air quality, but the health tradeoff would nullify the benefits. This story is only one example of the often ignored adverse health effects of environmental regulations. The direct benefits of control (reduced risks from contaminants) are usually considered only in relation to the direct costs of control. In the case of the dairy, the costs considered—piling up versus spreading out the waste—were small. However, what was ignored (nutrition) was significant.

Table 8.1 Excerpts from material safety data sheets for NaCl.

Appearance and odor	White/gray, crystalline, odorless solid
Storage and precautions	Closed container, controlled room temperature, dry and well-ventilated area. Handle in approved fume hood or with adequate ventilation. Do not breathe dust. Do not get in eyes. Wash thoroughly after handling. Eye wash and safety equipment should be readily available.
Toxicity and health	Oral LD_{50} Rat 3,000 mg/kg. Possibly irritating to skin. Irritating to eyes. Causes stomach irritation. Aggravates cardiovascular conditions.
First aid	Inhalation: Remove to fresh air. Skin: Wash with soap and water thoroughly. Eyes: Immediately flush with water for 15 minutes. Ingestion: Keep warm and quiet, and get medical attention.
Spill procedures	Evacuate area of all unnecessary personnel. Wear suitable protective equipment. Contain the release. Take up and containerize for proper disposal.

Figure 8.1 The adverse effects of pollutant regulation on productivity can eventually be overcome.



When revised National Ambient Air Quality Standards for Particulate Air Pollution (PM NAAQS) were proposed in 1997, several groups and individuals responded to the U.S. EPA's invitation to provide comments. Although the response was enormous and impractical to fairly summarize, the issue of risk tradeoffs was addressed in a 7,000-word response by a group called "Citizens for a Sound Economy Foundation" (CSE, 1997). Among the concerns that CSE had was a failure to account for effects including human mortality and suffering related to increased costs of energy. They cited the known benefits of air conditioning in controlling indoor air pollution and preventing hyperthermic deaths during hot weather, and the lack of data on how the cost and availability of electricity impacted air conditioner use. CSE expressed similar concerns with respect to the adverse impacts on the cost of heating services and of many goods, including gasoline, on low-income groups. Specifics cited by CSE included a doubling of deaths in New York City following a 103°F day, and for persons who used air conditioning 50% to 80% lower death rates during heat waves. The group was also concerned over the effects of loss of jobs on human dignity and well-being, noting that small businesses were particularly vulnerable to closing as a result of being unable to comply with air-quality standards.

Because the adverse effects of air pollutants have been extensively studied and published, this chapter focuses on some of the potential problems related to their control.

8.2. THE SOURCES OF PM AND ASSOCIATED BENEFITS

8.2.1. Natural Processes

Countless natural phenomena that would occur even if humans did not exist produce air contaminants that cause adverse health effects in human populations. Among such phenomena are the action of wind on soil; the generation of aerosols and gases by bodies of surface water (oceans, lakes, rivers, and streams); the dispersion of pollens and volatile organic substances by higher plants; the generation of aerosols and gases by mammals, birds, insects, and other animals; and the dispersion of spores and other airborne substances by fungi, bacteria, and other simple organisms. Such airborne substances are essential to shaping a habitable planet, the water cycle, and the perpetuation of life. These sources could be controlled by covering the soil and bodies of water and the widespread use of defoliants and pesticides. Suppression of natural sources of air pollutants for the purpose of making the air less harmful to breathe would not only be a formidable task, but if achieved, it would bring about the extinction of life on the planet. It is clear that a goal of eliminating all harm can actually produce maximum harm. Thus, allowing some, even sometimes significant, harm from air pollutants is wise. In some locales, natural phenomena could and should be suppressed in the interest of human health. But widespread reductions of natural phenomena would have catastrophic consequences. A sensible approach for maximizing public health includes encouraging those individuals who are adversely affected by natural air pollutants to take individual actions. Such actions include selecting favorable places to live, applying pollutant controls in their immediate vicinity, avoiding unnecessary

contact with offending pollutants and taking medications as needed to prevent and/or control discomfort and disease.

8.2.2. Anthropogenic Activities

Human activities, like natural phenomena, generate air contaminants. Table 8.2 lists several examples along with the benefits associated with each of these particle sources. Like natural phenomena, such activities are necessary for sustaining life, so their relentless suppression will threaten public health.

Table 8.2 Sources of urban particulate air pollution and the associated benefits. The source categories are not mutually exclusive.

Sources	Emissions	Benefits
Farming and dairying	Dust, diesel exhaust, ammonia, sprays, biogenic aerosols	Without affordable food and milk, malnutrition and starvation become realities. Ammonia neutralizes air acidity.
Electric power generation	Fly ash, metal-containing aerosols, sulfur-containing particles, various gases and vapors (nuclear plants are essentially free of air pollutants).	Affordable and reliable electricity is needed for heating, air conditioning, food preservation, and other survival- and economic-related activities.
Diesel engine operation	Fine particles, gases, vapors	Cost-effective diesel engines are essential for the operation of heavy trucks, trains, ships, and farm, mining, and construction equipment. They are important to human health and prosperity.
Manufacturing	Coarse and fine particles, gases, vapors	Goods such as food, clothing, medications, and machinery are essential to survival.
Miscellaneous combustion	Fine and ultrafine particles, gases, vapors	Waste reduction, manufacturing, transportation, electric power generation, and other essential activities depend on fuel combustion.
Miscellaneous spraying	Fine particles, gases, vapors	Paints, pesticides, disinfectants, etc. are important for protecting valuable goods and controlling disease.

The basic human activities needed to sustain life include the production and distribution of food and potable water; the provision of shelter, lighting, heating, and in some locales, air conditioning; the manufacture and distribution of goods including clothing, personal care items, tools, utensils, and medications; and the provision of transportation and communication. In addition, human beings must perform activities that are recreational, cultural, and entertaining in order to thrive. Such activities modify the environment in ways that produce unavoidable health-related risks, including those associated with the production of air pollutants. In fact, the mere presence of human beings will contaminate the air to the extent that some risk will be borne by vulnerable subpopulations.

The benefits of limiting human activities must also be weighed against the practicality of such an action. Even when some activity is clearly identified as producing air pollutants that cause illness (all activities probably fall into this category), it is important to realize that modification of the activity may require significant time. The modification of farming, manufacturing and other processes can take many decades to achieve. For example, food production currently involves working the soil, controlling plant and animal diseases and destructive pests, harvesting; processing, refrigerating, packaging, transporting, and distributing. Centuries have been invested in instituting workable systems for making food available for consumption, and many decades will probably be required to substantially modify the existing processes. Identifying a problem can occur quickly, but fixing it may not. The separation of decision making for reducing risks from decision making related to ensuring adequate production of food or any other important commodity is a recipe for trouble.

8.3. CONSEQUENCES OF OVER- OR UNDERCONTROL OF PM

At this time the optimal levels of control and the timing of instituting additional controls of particulate air pollution in the interest of protecting human health are unknown. Thus, it is possible to either over control or under control the levels of particles in the air. The optimal level of control, which maximizes human welfare, would set levels such that the direct health benefits are closely balanced by the adverse consequences associated with the increased costs of important activities. It is worth noting that control costs generally rise steeply as the extent of control increases. The health benefits side of control of particulate air pollutants appear to be relatively easy to define, and they include decreased new cases of cardiopulmonary diseases and decreased exacerbation of existing diseases. Considerable effort has gone into defining this side of the equation, and various estimates are available regarding reduction in asthma attacks, and other ilnesses associated with a lowering of particulate pollutant levels (Hall et al., 1992). However, these estimates are mostly based on particulate mass, which does not distinguish which components, if not total mass, are actually responsible for the observed health effects. Further, the adverse consequences of particle controls have not been explored nearly as thoroughly. Estimates of the monetary costs for control devices and procedures have been made, but other consequences of control have not been addressed in a quantitative manner. Such consequences include the loss of important technologies, the increased cost of goods and services, and the loss of jobs, all of which will

adversely affect human health. As cleaner technologies are developed, and the cost of their introduction declines, the optimal level of particulate air pollution that is permitted can be expected to decrease, as long as such decreases are considered beneficial. Which brings us to a rarely considered consequence.

Lower air pollutant levels translate to quantifiable health benefits, but there may also be a limit to the benefits of clean air. At some point, decreased particulate pollutant levels can be expected to produce a population that has lost much of its defenses against inhaled materials. This situation could depress the ability of large numbers of people to withstand challenges produced by infectious airborne microorganisms, natural aeroallergens, smokes from unpreventable fires, and even relatively inert wind blown soil. In this scenario, lung disease rates and death rates could dramatically increase. As a possible example, the modern-day increase in the incidence of asthma in affluent countries has been attributed by some to diminished respiratory challenges to infants during the neonatal period (Shirakawa et al., 1997; von Mutius et al., 1994; Gergen and Weiss, 1992).

Another consideration arises as a result of the advent of rapid and widely available worldwide travel. People are traveling to locales that have very different pollutant levels, both chemical and microbial. It is becoming apparent that people from "clean" areas suffer in "dirty" areas, sometimes to the extent that they must leave. To prevent the differential adaptation of various communities, worldwide coordination of pollution-control strategies is desirable. Such coordination may involve slower implementation of controls in wealthy nations to allow poorer nations to keep up.

8.4. MAJOR UNCERTAINTIES

In addition to the lack of certainty about the actual health effects of inhaled low concentrations of particulate air pollution and the net benefits of more stringent control, there has been no serious assessment of the adverse effects on health caused by the impact of such controls on the cost and availability of goods and services. A formal approach to assessing the risk tradeoffs of actions designed to protect health and the environment has been described (Graham and Wiener, 1995). Quantification of the health-related impact of factors, such as curtailment of business activities and the decrease in availability of employment is a significant need. The question of how far the levels of air pollutants should be reduced, and how fast, is still open. Also, the trend of decreasing exposure to contaminants has an unknown impact on human defenses against the effects of exposure to uncontrollable contaminants.

8.5. LESSONS LEARNED

The major lesson here is that steps taken to control particulate air pollution will have impacts other than just the anticipated direct costs of controls and the estimated direct benefits to health. Estimating the indirect effects, including costs and availability of goods and services, and the effects on long-term health and the economy is a difficult task. Yet this task is essential if human health is to be served. In the past, the benefits associated with control of air pollutants have generally

outweighed the costs, both direct and indirect. Today, as air quality has improved, and the links between economic factors and health have become more apparent, the approach of mainly considering just the costs of meeting air quality standards should give way to a better approach. Although assessing the negative consequences of a pollution-control edict is more difficult than assessing the benefits, such a balanced assessment is required by modern circumstances.

The time required to change long-standing industrial and other processes must also be respected. In many cases, there are no feasible quick fixes for polluting processes. The time required to replace old technologies with newer ones depends on several factors, including the availability of funds, the existence of research programs, and the availability of trained researchers and technicians.

Finally, the assumption that modern industry is harming public health and must therefore be forced to comply with ever more stringent regulation is subject to challenge. Modern industrial goods and services are, in fact, major factors in protecting public health and providing prosperity.

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CHAPTER 9
Challenges to Dogma

9.1. RELEVANCE TO THE PM CONTROVERSY

Progress occurs by a combination of two processes—*incrementalism*, which involves the serial application of small improvements and *replacement*, which involves dropping the familiar altogether for something new. Science and public health have benefited from both processes, and both are clearly indispensable. Incrementalism is the more familiar and typically the more reliable process. Yet problems eventually arise that require replacing previous ideas and approaches.

The epidemiological associations indicating possible health risks from breathing small amounts of particulate air pollution are reproducible, but they seem to conflict with toxicological and clinical studies. This contrast invites one to question some of the assumptions relating to the health effects of air pollutants. Although many of our current assumptions are valid, the opportunity to challenge beliefs and introduce new ideas should not be passed up. If some of the accepted explicit or implicit assumptions can be replaced with more useful concepts, then that is what should happen. This chapter identifies some ideas that need to be critically examined.

9.2. CHALLENGING CURRENT DOGMA

There are many ways to define dogma, but the following definition suits the purposes of this chapter:

> Dogma (from the Greek, doekin – to seem)—A point of view or set of views assumed to be authoritative but without adequate grounds.

Scientists develop conceptual models that are increasingly more accurate descriptions of observable phenomena. Models and ideas that have long lives frequently assume the status of dogma. These models and ideas must eventually be replaced with better ones. As Professor Werner Stöber expressed it, "Science is error, error, error, less, less, less" (Stöber, 1998).

Assumptions about nature (in the present case, human health) are useful because they allow setting aside difficult fundamental questions that cannot be easily examined. But such assumptions limit the scope of inquiry and confine thought. Eventually progress leads to uncovering inconsistencies and then to the examination and overthrow of dogma. As an example, consider the principle of conservation of physical mass, which was long held in chemistry and physics. Professor Albert Einstein discovered that mass could be converted to energy and vice versa; the

conversion factor c (speed of light in a vacuum) is found in his famous $E = mc^2$ relationship. Although the conservation of mass, neglecting Einstein's mass-energy relationship, is valid to about 10^{-8} percent in ordinary chemical reactions, it fails to work for nuclear reactions. So the belief that mass can neither be created nor destroyed gave way to the principle of conservation of mass-energy. This important step led to revelations in understanding the universe, as well as practical applications related to medicine and nuclear power. The particulate air pollution controversy similarly affords an opportunity to identify and to challenge some of the assumptions that underlie thinking, research strategies, and the setting of standards for air pollutants. Among the assumptions that might be questioned are the following:

- An agent shown to be toxic at high doses is also harmful at low doses.
- When large populations face small per-person risks, the total risk is the product of the large number of people and the small risk per person.
- Any stress is harmful to health and must be minimized.
- Natural chemicals are inherently safer than anthropogenic chemicals.
- Contaminant concentrations can be controlled below levels that harm even sensitive individuals.
- Contaminants should be isolated and regulated one by one as a means of protecting health.
- The most recent science is the best science.

9.3. THE LOW-DOSE QUESTION

If a substance is harmful to health at high or moderate doses, will very low doses also be harmful? The lay public, and many health professionals, usually assume that the answer is yes—as some agents are toxic and should be eliminated from the environment, while others are safe. Such all-or-nothing logic has lead to large expenditures of energy and resources to eliminate negligible risks. Such thinking is applied to radiation, pesticides, food preservatives, and air pollutants. Risk estimates for low-dose exposures frequently involve extrapolations of the risks associated with large exposures down to the realm of tiny ones. Such extrapolations can be contrary to the basic principles of toxicology and biology (Abelson, 1994). Furthermore, there is evidence that exposure to small doses of toxic agents may even be essential to maintaining normal defenses.

Ionizing radiation serves as a good example of the fallacy of less-is-better thinking. In a review of human populations exposed to elevated but low doses of radiation, Professor Thomas Luckey concluded that exposures of up to 40 times the average ambient radiation background of 0.26 cGy/yr (260 mrad/yr) were beneficial to human health. Decreased cancer rates have been observed in several radiation-

exposed populations including radiation workers, bomb-test exposed fishermen, Taiwanese living in houses containing radioactively contaminated steel, low-dose exposed atomic bomb survivors, and Ural Mountain villagers that were evacuated after an explosion involving radioactive waste (Luckey, 1997). In all of these cases, cancer rates were below normal, and for one case the cancer rates in these populations have been only 3% of the expected rate – the 5,000 Taiwanese who received up to 2.3 cSv (2.3 rem) of gamma rays from cobalt contaminated steel. In fact, low-dose radiation has been associated with increased lifespan, immunity, growth rate, infection resistance, and decreased cancer and cardiovascular-related mortality. This apparent beneficial effect of radiation doses above the natural background is termed *radiation hormesis*. Radiation hormesis is believed to be caused by a variety of mechanisms including immune system stimulation (Liu et al., 1987), stimulation of cell growth, and increased rates of repair of damaged DNA. For more information on radiation hormesis, see the special issue of *Health Physics* (Vol. 52, No. 5, 1987) devoted to that topic.

Could the stimulating effects seen for low-dose radiation exposure also apply to chemicals such as pesticides and heavy metals? According to a variety of carefully controlled investigations, the answer may be yes (Calabrese et al., 1987; Calabrese and Baldwin, 1998, 2001). Chemical hormesis has been observed in a large variety of species, for a large number of endpoints, and for many classes of chemicals. Plants, microorganisms, insects, and mammals exhibit such effects. The chemicals for which hormesis has been observed are largely those that have been subjected to the most study. Metals (excluding those nutritionally required) top the list, with nearly 30% of the studies in which sufficient dose ranges were evaluated showing hormetic effects at low doses (Calabrese and Baldwin, 1998). In addition, antibiotics, herbicides, insecticides, hydrocarbons, and several other classes of chemicals have exhibited hormesis. In these cases, growth, survival, longevity, and reproduction have been used as endpoints that provide evidence for beneficial effects. Edward Calabrese and Linda Baldwin proposed that altered patterns of gene expression are responsible for the observations. They described two classes of such expression—"enhanced metabolic capacity for detoxification" and "more general protection against cellular damage." For additional reading, the reader is referred to the *BELLE Newsletter* (*Biological Effects of Low Level Exposures*, University of Massachusetts, School of Public Health, Amherst, MA 10003) and *Critical Reviews in Toxicology* (Vol. 31, Nos. 4–5, 2001).

The implications of the foregoing are of potential importance when considering acceptable environmental exposures. Exposure to small quantities of many toxic substances may be important for inducing and maintaining defenses against subsequent chemical challenges. On the other hand, loss of defenses will not necessarily be detrimental if there are no significant future exposures to deal with. If future significant exposures occur, then a loss of defenses can be problematic. In short, there may be a limit below which it is unwise to control particulate air pollution exposures even if some adverse effects may occur.

9.4. THE SMALL-UNIT RISK, LARGE POPULATION DILEMMA

9.4.1. The Problem

When large populations are exposed to tiny per-person risks, special problems arise that can lead to erroneous conclusions. This situation is known as the *low-dose, large-population dilemma*, where *low-dose* implies the existence of a statistically small level of risk for any one individual. The *large-population* can refer to thousands, millions, or even billions of people. The *dilemma* arises when one engages in mathematical exercises involving the products of very small and very large numbers in order to estimate the total harm. Numerous debates, including some related to exposure to urban air pollution, are related to this issue.

9.4.2. Examples

It is common for scientists and regulators to use the following process. First, a small exposure-associated risk—say one chance of death per 100,000 persons per year (10^{-5})—is estimated. Such a risk estimate might be obtained by extrapolating downward from data on high-dose exposures, or it could come from a small relative risk association from an epidemiological study. Second, the number of people potentially at risk is estimated, usually from census data. This figure could be all urban dwellers in the United States (about 200 million) or even the world's population (about 6 billion). Third, the two numbers are multiplied together, for example – 10^{-5} times 2×10^{8} – to get 2,000. This number is then the estimated annual death rate due to exposure to the agent in question. Because the thought of such a number of deaths is alarming, an immediate action to control the exposure may be seen as mandatory. But there are problems with this analysis. First, the risk estimate itself is likely to be very uncertain or even fictitious. Extrapolation from high-dose effects to very low-dose ones is questionable, as was discussed in the previous section. Also, if the small relative risk came from one or more epidemiologic studies, the measured (or estimated) exposure may not be the actual cause. The agent may co-vary with another true cause, or it may be the measured part of a multiagent combination that produces the adverse effect (Pope, 2000). A worse problem occurs when an assumption is made that reducing the exposure will, in fact, reduce the risk. Reducing the exposure may also have adverse consequences, such as increasing other exposures or causing the loss of use of an agent that is required for food production, manufacturing, transportation, electrical power generation, or other activity that supports health.

A variant of this scenario involves summing all of the exposures for the entire population and then determining how many people could be harmed (e.g., killed) by this total exposure. For example, say that the average per-person exposure dose to radioactivity from all routes related to nuclear power plants is 10^{-4}Sv (10 mrem/yr), a practically harmless exposure. If this dose is multiplied by a population of 300 million, the total collective dose is 3 million rem. If 600 rem is received by an individual (in whole-body x-rays) there is a near-certain probability of death. Therefore, 3 million rem is sufficient to kill 5 thousand people. The problem is that the exposure is thinly distributed, not concentrated in a few people. Thus, the tempting conclusion that 5,000 annual deaths occur is not valid. To further illustrate

the point, consider atmospheric oxygen, beneficial at a 21% concentration but potentially deadly (due to brain injury) if breathed at 100% at an atmospheric pressure of 1500 mm Hg for more than 12 hours (Guyton, 1991). If the collective-dose concept is valid for this toxic gas, then about 10% of the world's population should die daily, which is obviously absurd. Yet this type of logic is sometimes applied to less toxic agents than oxygen. This example could have involved diesel-engine exhaust, pesticide sprays, or many other agents.

9.4.3. Risk Tradeoffs

In addition to the problems associated with estimating the consequences of large populations exposed to small unit risks, there are potentially serious problems with pursuing strategies to reduce the exposures. When the risk is small, its reduction can easily be offset by other risks that are increased by control actions. Reducing exposures to any given agent may have a large number of consequences (both known and unknown), each of which may influence human health. As an example, consider a preservative or a pesticide that has a small extrapolated risk associated with exposures to residues in food. In this case, reducing use of the agent, can lead to loss of food production and quality, increases in insect populations, or substitution of other preservatives and pesticides that are less well studied. Unfortunately, an analysis of the totality of consequences of reducing exposures to substances that may carry small risks is seldom done. Yet if controls are effected, the totality of consequences will occur. Small risks may best be left alone unless an analysis that includes all reasonable tradeoffs is performed. The topic of risk tradeoffs is the subject of a pioneering book, *Risk vs. Risk: Tradeoffs in Protecting Health and The Environment* (Graham and Wiener, 1995), which should be examined by anyone interested in risk reduction.

9.5. STRESSORS AND HEALTH

9.5.1. What Are Stressors?

Biological stressors are agents that challenge the physiological status quo and produce perturbations in the internal environment of an organism. Biological responses triggered by stressors have implications to future fitness.

9.5.2. Physiological Responses to Stress

Complex organisms, including humans, respond to stress, and even the absence of stress. For example, increases in strength, maximum oxygen consumption, and cardiovascular fitness follow the stresses associated with regular strenuous muscular exercise. Similar beneficial responses occur with respect to increased bone density as a result of increased weight-bearing and increased oxygen carrying capacity of blood as a result of high-altitude stress. Also, the absence of regular exercise or weight-bearing stresses lead to muscle wasting, diminished pulmonary function, and decreases in bone strength. In sum, human beings are constantly remodeling in response to changes in the environment, and when such

changes are significant enough to be called stressors, the physiological changes frequently result in increased fitness. Also, minimizing stress can lead to a loss of fitness; the phrase "use it, or lose it" captures this concept nicely.

Less well understood are the effects of environmental contaminant exposures on fitness. If such exposures are decreased below some level, will the normal defenses to contaminants diminish? There is some evidence that this is so. In laboratory animals, it is well known that preconditioning in very clean environments often leads to decreased variability and increased susceptibility to the effects of subsequent exposure. It is common practice for investigators studying inhaled particles and gasses to provide housing conditions that are nearly free of airborne particles and contaminant gasses (Mautz and Kleinman, 1997). Such preconditioning is often necessary for the observation of responses to tested pollutants.

9.5.3. Adaptation

Preexposure of laboratory animals and human subjects to modest ozone levels provides protection against subsequent exposures to high (even otherwise lethal) concentrations of the gas (Hackney et al., 1977; Folinsbee et al., 1994; Linn et al., 1982). Such tolerance is seen within a few days of the initial exposure, and protection lasts for several days to perhaps a week or more. Daily exposures to ozone lead to initial increases and then a lack of responsiveness after two or three days. In addition, an acute exposure to ozone can also provide protection against subsequent exposures to other gases with similar mechanisms of action, such as nitrogen dioxide and hyperbaric oxygen. It should be understood that the protective effects of such exposures are temporary and are of known value only if a subsequent oxidant challenge must be met. One can also argue that adaptations to environmental contaminants have a long-term cost.

Adaptation to the harmful effects of particle inhalation has not been well examined, but there is an indication that it may occur. The recent acute human mortality and morbidity associations with increases in particulate air pollutant mass are seen when the daily particle levels are elevated above the previous day's running averages (Pope, 2000). The acute health effects are associated with *changes* in particle mass, not the actual *levels* of particle mass. One interpretation is that sensitive individuals may lose their adaptation to particles when levels are decreased for a few days. There is some preliminary laboratory support for short-term adaptation to inhaled ultrafine particles (polytetrafluoroethylene fumes). Preexposure of rats for 5 min/day for three days produced 100% protection from the inflammatory effects of a subsequent fume challenge (Oberdörster et al., 1997). The authors pointed out that messages encoding cytokines and antioxidant proteins were significantly increased in the adapted animals.

At this time, one may conclude that exposure to contaminants can produce both harm and increased resistance to subsequent exposures. Additional research is needed to explore when overall fitness is compromised by continual reductions in particulate air pollutants.

9.6. NATURAL VS. ANTHROPOGENIC POLLUTANTS

When dealing with the relative toxicity of substances, it is useful to focus on a specific effect. A dramatic effect is lethality, which may be represented by the dose of an agent (mg/kg body mass) required to produce near-term death in 50% of the subjects (LD_{50}). Instead of considering PM, where the dose is less well defined, it is useful to look at substances that are administered via injection into the blood or feeding (Table 9.1). It is clear that natural substances are among the most toxic known. Failure to recognize this fact can lead to significant numbers of deaths. Worldwide, about 1 billion cases of common infections occur; 4 million children die yearly from diarrhea and 1 million from neonatal tetanus, and in Africa about 1 million people die annually from malaria (Last, 1992). Natural causes of death pose a larger problem than does poisoning by anthropogenic chemicals. There is little justification for assuming that anthropogenic threats outweigh natural ones.

On the surface, it is easy to distinguish natural from anthropogenic air pollutants. The natural ones would be there even if people were not present, and the anthropogenic pollutants are the result of human activity. However, many chemicals that are found in the air have both natural and anthropogenic sources. Table 9.2 lists some common air contaminants, their sources, and the ratios of natural to anthropogenic emissions into the atmosphere. Human activities produce about 20% of the direct particulate emissions and about 1% of the gaseous emissions (many of which form secondary particles) of these substances. If natural sources of these substances are dominant, what is the reason for a regulatory focus on the anthropogenic sources? There are two reasons: the anthropogenic sources are easier to control and generally emitted near populated areas. But this focus on anthropogenic pollutants contributes to a fear of contaminants associated with human activities and a complacency concerning natural hazards.

Table 9.1. Approximate LD_{50} values (mg/kg) of some chemical agents. A = anthropogenic, N = natural (Klassen and Eaton, 1991).

Substance	LD_{50}	Relative Toxicity	Principal Source
Ethyl alcohol	10,000	1	A (beverages)
Sodium chloride	4,000	2.5	N (diet)
Morphine sulfate	900	11	A (medical)
Phenobarbital sodium	150	67	A (medical)
Picrotoxin	5	2,000	N(plant seeds)
Nicotine	1	10,000	N+A (tobacco)
Tetrodotoxin	0.1	100,000	N (puffer fish)
Botulinum toxin	0.00001	1,000,000,000	N (bacteria)

Table 9.2. Anthropogenic and natural sources of common air contaminants (from Lippmann and Schlesinger, 1979, and Stern, 1976).

Contaminant	Anthropogenic Sources	Natural Sources	Natural/Total
Primary particles	Farming, manufacturing, combustion	Soil, fires, sea salt, volcanoes	>10
Secondary particles	Combustion, manufacturing products	Plants, microbes, fires	4
Hydrogen sulfide	Manufacturing, sewage treatment	Decay, volcanoes	30
Sulfur dioxide	Coal and oil combustion	Volcanoes	Not known
Ammonia	Waste treatment	Decay	>200
Nitrogen oxides	Combustion	Decay, biological action	30
Hydrocarbons	Combustion, chemical processes	Biological processes	20
Carbon dioxide	Combustion	Decay, ocean release	70
Carbon monoxide	Combustion	Fires, ocean release, reactions	0.1

9.7. CAN THE MOST SENSITIVE BE PROTECTED?

The Executive Summary of the U.S. Environmental Protection Agency's "Air Quality Criteria for Particulate Matter" (EPA, 1996) begins with a summary of relevant sections of the Clean Air Act. It is seen in this summary that the EPA must set "primary National Ambient Air Quality Standards (NAAQS)" to "protect against adverse health effects of listed criteria pollutants among sensitive population groups,

with an adequate margin of safety." The current interpretation of this charge is to identify a very sensitive subpopulation, find a level of the pollutant under consideration that does not harm this group, and if there is any scientific uncertainty, apply a more stringent standard. This approach can be questioned. First, the uncertainty is significant when cutting-edge epidemiologic studies of large populations are being considered. Such studies typically cannot define who is most susceptible or what pollutants will harm them. Because epidemiological studies relate most directly to humans, their use in establishing NAAQS generates pressure to incorporate substantial safety factors. This can lead to standards that are difficult, if not impossible, to meet in the real word. Second, the most sensitive subpopulation can be so delicate—on the edge of morbidity and mortality—that a minor environmental perturbation can harm their health. Such perturbations include changes in temperature, barometric pressure, or increments in the level of an air contaminant. Protecting these sensitive individuals by controlling pollutant emissions may not be possible. This problem has been recognized in the occupational setting where some categories of workers are excluded from consideration when recommending exposure limits. In the "Introduction to the Chemical Substances" of the American Conference of Governmental Hygienists "2001 TLVs® and BEIs®" (ACGIH®, 2001), three groups are excluded from consideration in defining recommended air exposure limits:

- Those who due to "wide variation in individual susceptibility . . . may experience discomfort from (exposure to) some substances at concentrations at or below the threshold limit";

- A "smaller percentage" who may experience "aggravation of a preexisting condition"; and

- The "hypersusceptible" due to "genetic factors, age, personal habits (e.g., smoking, alcohol or other drugs), medications, or previous exposures."

In the workplace, it is understood that protecting everyone is not feasible, at least if productivity is to be maintained. Similarly, it may not be possible to protect hypersusceptible individuals from environmental exposures by controlling outdoor air quality. Some individuals cannot tolerate low levels of dusts, smokes, pollens, dander, and other contaminants. For such people, personal strategies must be used to guard their health, not nationwide ambient air standards. Protecting very sensitive people will often require the input of physicians and may include the following actions:

- Not exercising outdoors on certain days;

- Avoiding proximity to certain emission sources such as congested traffic; fires; farms during cultivation, harvesting, or pesticide application; active construction sites; and some industrial operations;

- Improving their general health status by avoiding poor personal habits and by following approved treatment regimens for their conditions;

- Using medications, both prophylactically, and in response to exacerbations of preexisting diseases; and

- Using air-conditioning and air-cleaning devices in their homes, and if extremely sensitive, using personal protective devices such as dust masks.

Although such advice may seem harsh, it is practical, and it may be one way to realistically serve public health.

9.8. IS ISOLATING INDIVIDUAL CONTAMINANTS LOGICAL?

Historically, contaminants have been considered individually when setting ambient air-quality standards. There are several realities that make the one-agent-at-a-time approach problematic. The air contaminants that have been designated as criteria pollutants comprise only a tiny fraction of those present, but they receive a great deal of attention. Criteria air pollutants have been detected at lower and lower levels due to the development of sophisticated monitoring instruments and analytical procedures. Toxicologists, who are trained to focus on adverse effects, have developed increasingly sensitive endpoints for studying these few criteria air pollutants. Thus, detectability of a chemical itself has become a cause for concern. Furthermore, air chemistry is so complex that driving the concentration of one pollutant down can (and often does) drive the concentrations of other pollutants up.

Populations have always been exposed to dynamic mixtures of substances in the air, so evaluation of mixtures is a rational approach to protecting health. It is clear that many air contaminants are products of the interaction of both natural and anthropogenic emissions. Current regulatory strategies focus on anthropogenic contaminants to the extent of virtually ignoring natural pollutants. Realistic regulations must consider the full complexity of the air, including natural contaminants and the products of interactions of natural and anthropogenic substances.

9.9. IS THE MOST RECENT SCIENCE TRUSTWORTHY?

Scientists understand that the cutting edge of science is controversial, full of poorly understood findings, and even subject to erroneous interpretation. New findings typically require decades of challenge before they are useable. Research findings are almost always more uncertain than they first appear, and scientists must fully explore new data before accepting them as trustworthy. This does not imply that science is not useful or important; it is invaluable, even irreplaceable. Without the accumulated body of scientific knowledge, humans would likely have average lifespans less than one-third of what they are today (Cohen, 1991).

So why must regulations reflect the latest scientific data when many scientists themselves do not believe that such information is ready for use? First, there is a problem with the public perception of scientific research. The public can see science as infallible, precise, and producing results that are free of all error. Also, when a scientific result is successfully challenged and overturned, it may be seen as an anomaly or junk science in the eyes of the public. Some see peer review as conveying the stamp of certainty and perhaps finality. Yet scientists see peer review as a process by which obviously flawed or poorly written reports are kept out of the literature. To scientists, peer review does not mean that the work is immune from later challenge. What is not clear is when new scientific information is ready for public or regulatory consumption. There is no good answer to this question, but when scientific controversy surrounds a finding, or even a large set of findings, then the findings are probably not ready for automatic assimilation into public decision-making processes.

9.10. LESSONS LEARNED

The main lesson learned from the foregoing is an old one; beliefs must be continually challenged to prevent them from becoming outdated. When applied to the particulate air pollution controversy, such challenge leads to questioning several assumptions that were useful in the past. Today, most people live in an air environment that is much less polluted than it has ever been; the large exposures that have significantly shortened lifespans have mostly disappeared. The virtual elimination of substantial urban concentrations of lead and other substances directly linked to specific diseases has improved public health. Modern exposures to smaller concentrations of substances are difficult to further control, let alone eliminate. Emissions enter into complex atmospheric reactions, and they are also associated with human productivity, so driving individual air-contaminant levels ever lower may not protect public health. In addition, small stressors can protect against unavoidable future challenges and may help maintain normal physiological defenses. Hypersusceptible individuals cannot be protected solely through environmental regulations; they may need to take personal actions on a case-by-case basis. Also, cutting-edge scientific findings must be allowed to settle and mature before they can support wise regulatory actions. Some of these lessons may improve the manner in which air contaminants are studied, controlled, and regulated in the future.

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CHAPTER 10
Conclusions and Recommendations

10.1. RELEVANCE TO THE PM CONTROVERSY

The evolving scientific knowledge relating to the health effects of urban particulate air pollution is both exciting and puzzling. To draw this case study to a conclusion, it is useful to highlight what is known, what is unknown, and what lessons have been learned.

10.2. WHAT IS KNOWN?

10.2.1. The Epidemiological Associations

Substantial levels of particulate matter (PM) are known to be capable of producing human mortality and morbidity. Associations between adverse acute health outcomes and small increments in PM measures have been repeatedly observed so they are not in doubt. However, they have raised more questions than they have answered. The recent associations are remarkably small yet statistically real. Sometimes total PM has produced associations, and sometimes PM_{10}, $PM_{2.5}$, or even submicrometer size particles gave stronger signals. Sometimes gaseous pollutants have been implicated as important for enhancing the PM effects, but not always. Acid-containing particles have at times produced significant associations with human health effects, but not always. The adverse health outcomes have generally included effects related to the respiratory tract and to the cardiovascular system, but again, different studies frequently point to different effects. Thus, the associations are reproducible and robust, but they have not been consistent enough to clearly establish causality or to implicate a key pollutant or some key combination of pollutants. In addition, the recent acute epidemiological associations involve increments over previous PM levels, rather than absolute levels of PM, implying that short-term biological adaptations may be important. These effects of increments are not classical dose-response phenomena.

10.2.2. The Complexity of PM Exposures

Particulate matter is an unusual pollutant. It is the only regulated national criteria air pollutant in the United States that is not specified with respect to chemical composition. Because the measures of PM are typically based on mass as determined gravimetrically, very small particles and their associated chemistries are not represented realistically in the monitoring process. The use of PM_{10} and $PM_{2.5}$ mass subfractions has been the primary means of dealing with particle-size

characteristics from a regulatory standpoint. Centrally located area monitoring is used to represent the exposures of large populations despite great temporal and spatial variability in both composition and size distribution. PM is always accompanied by copollutant gases and vapors. The compositions and concentrations of nonparticulate pollutants are also variable in space and time. The role(s) of such copollutants in harming health is (are) still not clear. It is probable that regulating particulate mass could lead to decreases, or increases, in risks to susceptible populations. One must conclude that the current focus on particle-mass fractions may not be adequate for the purposes of providing efficient or even appropriate health protection.

10.2.3. The Role of Toxicology

Epidemiological associations are a starting point in the process of identifying potentially harmful concentrations of agents. Thus far, toxicological studies have implicated several air pollutants as being potentially harmful to human populations. Such studies have shown that some chemical compositions, some particle-size ranges, and some combinations of particles and gaseous copollutants are more toxic than others. But the culprits that may be causing adverse health effects at very low concentrations in the air have not been identified. It is clear that toxicological studies will be essential for testing cause-and-effect relationships, but it is not clear that the existing toxicological protocols and models are up to this task. Therefore, additional toxicological investigations that can be applied to actual human exposures must be conducted. Similarly, clinical studies with human subjects have not yet identified a population that reflects the risks seen by epidemiologists. Not only must new research models be developed, but the total impacts of PM exposure on health—beneficial and adverse, long-term and short-term—must be more thoroughly examined.

10.2.4. The Needed Research

On many occasions, scientists and regulators have identified the needed research. In each case, the perceived needs are remarkably consistent. Funding increases have launched much of the needed research in epidemiology, toxicology, and atmospheric science. The research community has turned toward the research priorities identified by the National Research Council (NRC, 1998, 1999, 2001). What additional research will be indicated by the initial studies remains to be seen, but if past experience provides any foresight, one can expect that the first round of studies will not completely resolve the major issues.

10.3. WHAT IS UNKNOWN?

10.3.1. Who, What, and How?

Among the substantial uncertainties and questions regarding the linkage between PM_{10} or $PM_{2.5}$ and human health are the following:

- Who (what subpopulation(s)) is (are) actually harmed?
- What property of PM is harming them (mass, number, surface, metals, acids, reactive species, copollutants, etc.)?
- How are people harmed by low levels of PM, if indeed they are?

Until these important questions have been answered, it seems very unlikely that appropriate control measures can be taken that will protect potentially at-risk subpopulations. One possibility is that there is a single critical at-risk subpopulation that is being affected by a single air pollutant chemical. In this case, control of the adverse effects is relatively simple, at least in principle. In contrast, a large variety of people may be harmed by a large number of air pollutants. In this case, control will be expensive and complex with many tradeoffs.

10.3.2. The Metric

"The metric" is jargon for the appropriate measure of PM that, when reduced to some level in the air, will result in reducing risks to an acceptable level. This proper metric has yet to be identified for low levels of PM associated air contaminants. Over the past several decades, the metric has evolved from crude measures such as smoke shade, to total particulate mass, to PM_{10} alone, and to PM_{10} and $PM_{2.5}$ mass. For reasons already presented, mass-based metrics alone are unlikely to be adequate. Also, the metrics used thus far do not take into account the impacts of natural pollutants, including many allergens. Numerous improved metrics can be envisioned, but as of now, they are all speculative. The appropriate metric will no doubt need to include chemical and physical features of PM as well as associated gases. The temporal features of PM exposure may also need to be included in the regulatory process, due to adaptive and sensitization phenomena that modify biological responses.

10.3.3. Episode Chemistry

It seems reasonable that periods of elevated air-pollutant concentrations are more likely to produce adverse health effects than are "average" periods. Therefore, there is a need to clearly understand how episodes differ from normal periods with respect to the composition of the pollutants, as well as their concentrations. As of today, episode chemistry and how it varies with season and region is poorly understood. In addition, it is not known why episodes in different cities that have similar measured pollutant concentrations have different toxicities. Until more is known about episodes it will be hard to impose proper controls. Also, because air-pollutant chemistry is exceedingly complicated, the effects of controlling selected emission sources on the resultant air chemistry is not sufficiently understood. As of now, it is possible to envision a well-intended control strategy that results in a more toxic air pollution. Mass can be reduced at the expense of higher particle counts, and ammonia reduced at the expense of increased acidity. The unknowns related to air pollution episodes represent serious gaps in knowledge.

10.3.4. Personal Exposures

Too little is known about the PM-associated air pollutants as they exist in the immediate breathing zones for individuals. Since this personal exposure history ultimately produces effects, correlation of effects with data from area samplers is of limited value. In addition, the most relevant personal exposures are most certainly those for subpopulations that may be more susceptible to PM effects. Because such subpopulations have only been generally defined, personal exposure for several candidate groups is in need of study. Such groups include very vulnerable individuals among the elderly, the very young, and persons with preexisting pulmonary or cardiovascular diseases (or susceptibility to such diseases).

10.3.5. How Relevant Are Current Toxicology Models?

At this time, the relevance of the currently used laboratory toxicology models for predicting the effects of low-level exposures in potentially susceptible human subpopulations is in question. Clearly, mechanistic study information and information on the comparative toxicity of various PM components is useful. However, if certain compromised individuals are the critical populations that require additional protections, then toxicology models need to be validated for these groups. Recent advances, especially in using aged and diseased rodents, are steps forward. However, the relevance of these models to humans has not been established. Several obstacles must be overcome, including understanding the possibly unique dose distributions of inhaled particles in susceptible people, the problem that months or years of exposure may be required to sensitize people to PM components; the problem of dietary or medicinal interactions as important cofactors in response; and the problem that certain human diseases have no good laboratory animal counterparts. In addition, short- and long-term adaptive phenomena must be considered for animal models of human responses. Uncertainties in the area of toxicology models are both formidable and critical to overcome.

10.3.6. What Are the Effects of PM Control Measures?

Because the causal agent or agents (for producing increased mortality and morbidity) have not been identified, PM control strategies are largely based on historical precedent and best guesses. Studies are needed to examine the changes in health that are associated with past and current controls on PM-associated emission sources. Such studies are complicated by substantial changes in lifestyle and environmental quality that confound studies of the effects of PM-associated air pollution. The positive impacts of new controls are unknown, as are the negative health impacts of new controls.

10.3.7. How Serious Are the Tradeoffs?

All pollution-control actions will have effects other than those anticipated. When these effects are negative, they are called *risk tradeoffs* (Graham and Wiener, 1995). In some cases, new untested technologies may be forced to replace older and better understood ones. Controls will also generally produce changes in the costs and

availability of goods and services and in some cases the availability of employment. Some of the unintended effects of controlling PM-associated pollutants will adversely affect human health. Of necessity, past control strategies have been aimed only at reducing the health effects of some specified pollutants. Some analyses have attempted to compare the cost of controls with the savings produced by expected health benefits. However, the total impacts on human health from all consequences of future control strategies have not been assessed. This represents a serious current challenge.

10.3.8. How Different Is Modern Air Pollution from Previous Air Pollution?

Much of our knowledge on the potentially adverse effects of air pollutants was gained by studying people exposed 10 or more years ago. One suspects that changes in technology and lifestyle will have marked impacts on the nature of air pollution beyond documented decreased mass concentrations. Additives to, and new formulations of vehicular fuel, have resulted in changes in air chemistry that have not been well defined. Of necessity, air-quality regulations are based on old air chemistries, not current ones. The uncertainties in this area of knowledge are significant, and their investigation is of great importance.

10.4. WHAT NEEDS TO BE DONE?

10.4.1. By Researchers

The research community faces major challenges relating to the health effects of PM exposures. First, the tendency for researchers to stay within narrow disciplines must be changed. Toxicologists must become more knowledgeable about the nature of air pollutants, the epidemiological findings, and the complex fates of inhaled particles. Similar challenges face atmospheric chemists, epidemiologists, and other specialists; more communication across the disciplines is needed. Scientists who do not place their main research into the larger picture or who design studies that are not based on relevant knowledge from other disciplines are probably not going to have a significant impact on public health policy. Communication across disciplines is facilitated by conferences that focus on issues rather than disciplines.

Scientists must move more rapidly to develop better tools, as the old ones have become inadequate. Better real-time air monitors, especially those that are lightweight and inexpensive and can be worn by large numbers of people, are needed. Instruments that provide accurate particle-size segregation and analyses of particle count, surface area, and chemistry are also needed. Epidemiologists must persist in the introduction of new tools. But they should also clearly communicate the limitations and uncertainties associated with their findings. Clinicians must aid in finding potentially hypersusceptible individuals. Better laboratory animal models that mimic potentially at-risk humans must be developed and used by toxicologists. Tools that will allow for proper estimation of the total consequences of PM control strategies are also in need of development. The need to introduce better tools poses a serious challenge to scientists who have become comfortable with existing methods.

Scientists are also challenged to better communicate with regulators and the public. Regulators have the responsibility for protecting public health, and the public has the power to precipitate rapid change. Both of these groups struggle to understand the latest research, key on isolated findings or frightening possibilities, and then act decisively. Scientists must aid in the understanding of the dangers in accepting findings that have not withstood the test of time. Also, scientists must point out that research findings are often very limited in that many relevant events relating to the health of an organism are often ignored. As an example, epidemiology and toxicology studies on table salt show that this essential dietary component is also toxic. Yet restricting the population exposure to safe levels will in fact harm health. Scientists understand that their studies do not consider all of the relevant factors, but the public has no idea that this is the case.

10.4.2. By Regulators

Those charged with establishing clean-air regulations have an excellent record of identifying the major air pollutants, seeing that the required research is performed, and recommending safer air standards. Until now, the regulatory task has been relatively simple because of past high levels of emissions, the appearance of obvious health effects, and the historical lack of attention to abatement technologies. Today, the problem is different in that most of the controllable emission sources have been significantly reduced, the health effects are small and usually seen only in sophisticated modeling exercises, and many economically and technically feasible control strategies have been implemented. Even more challenging is the fact that the tradeoffs are no longer negligible and may be approaching the point where some controls may cause a net deterioration in human health and welfare.

The challenge to regulators is to reassess and replace the strategies that have worked in the past. New strategies must include more consideration of uncertainties in the evidence for harm at current levels of air pollution, improved analysis of the tradeoffs in cost of goods and loss of jobs, and recognition of the relatively long time scale required for new process and control technologies to emerge. This may require adopting a much slower pace for increasing the stringency of standards in the interest of public health. The bottom line is that more factors must be taken into account by regulators in the current era. In addition, regulators must be prepared to deal with the possibility that if pollutant levels are too low, the public may be at risk of losing some adaptive capabilities—capabilities that will be necessary when uncontrolled challenges are faced.

10.4.3. By Legislators

There is a general belief that legislation can solve the problem of adverse effects associated with exposures to environmental pollutants. Can a substance associated with adverse effects be banned or at least regulated to some low level such that it will cause absolutely no harm? The answer to this question appears to be no for several reasons. First, the substance may also be associated with sources that are essential to health, such as pesticides, vehicles, factories, electric power plants, farms, and construction sites. Essentially all human activities will modify the environment in ways that will adversely affect some people. When attempting to

balance the positive aspects of an environmental regulation with the negative aspects, it is easy to underestimate the negative consequences. Therefore, legislators must be challenged with giving up on an attempt to legislate away all harm and instead seek to minimize harm by taking into account all of the consequences of their legislative actions. With respect to environmental contaminants, it must be realized that it is impossible, and unwise, to eliminate them altogether. It is probably not feasible to even reduce such contaminants to levels below which some people will not be harmed. In this case, sensitive individuals may need to do what they have always done—i.e., protect themselves through individual actions. People with allergies to fungal spores or pollens have learned to recognize these air pollutants and avoid them. Just as it is not possible to legislate these natural air pollutants away, it may also not be possible to legislate anthropogenic pollutants away. Legislators must be more sophisticated in analyzing the complex issues associated with public health in relation to environmental contaminants.

10.4.4. By the Public

In the United States, as in much of the rest of the world, ultimate power resides with the people. The public must become much more savvy with respect to the complexities involved in protecting their health. It is unwise for the public to focus solely on isolated risks and then exert pressure on regulators and legislators to reduce that particular risk. All of the major consequences associated with reducing a specific risk must be taken into account. Also, the public must understand that laws and regulations simply cannot eliminate all risks. Each activity that produces goods and services will have some adverse effects. Each chemical substance that is necessary for maintaining health will also have some adverse effects. At a more fundamental level, even if the environment could be made sterile and contaminant-free, we might be worse off. We would most likely lose our ability to combat challenges, and disease rates could increase. Thus, the public is challenged to ask for the acquisition of new knowledge and for greater sophistication and wisdom from regulators who deal with public health. This will lead to regulatory decisions that wait for science to work and that take into account more factors. The benefits will come more slowly, but they will be more solid. This approach is better than that which demands quick fixes.

10.4.5. By Industry

There are clear lessons for industry in the particulate air pollution controversy. First, cleaner technologies must be developed to keep pace with the increasing pressure from legislators, regulators, advocacy groups, and the general public. This will necessitate better anticipatory planning because replacing an existing technology with a viable new one may take decades of research, testing, and implementation. The use of retrofit air cleaning devices is only a temporary solution, one that is increasingly more cumbersome. When new technologies are first envisioned, their air-polluting characteristics must be considered early on rather than later during development. In addition, the past trend of one industry shifting the regulatory focus toward "the other guys" is counterproductive. Today, everyone is under increasing pressure to come up with cleaner technologies, and the practice of

pointing out the sins of other industries only increases the pressure on everyone. Industry has two other challenges—to increase public education regarding the benefits of industrial activity and to support responsible and objective research relating to the assessment and control of the potential health effects of their pollutants. Industry has played an important and positive role in improving the public health. Food, goods, transportation, and electrical energy are all contributions of industry. These contributions must continue but in a more enlightened manner.

10.5. LESSONS LEARNED

10.5.1. Overview

This PM case study can teach a variety of lessons, all of which cannot be explored in this small volume. The following issues are selected because of their generalizability. These issues are at the core of the controversy, and until they are dealt with, one can expect the controversy to continue and to continue to divide the stakeholders.

10.5.2. Time Scales for Change

Science is good at producing useful knowledge largely because of the process of performing research, publishing the results, replicating the research, challenging the findings, and eventually rejecting or accepting the new knowledge. This process takes decades to work properly. A typical research study is performed over several years, and it may not appear in the scientific literature for two to three years after completion. The reason for this is that scientific papers usually require lengthy analyses prior to their writing, are subjected to anonymous peer reviews, undergo rewriting, are subjected to further review, and then are scheduled into the production cycle of journals. After a paper has been published, other scientists design and propose similar studies to funding agencies in hope of getting support. Usually two or more years are required for scientists to prepare a proposal, get a critique, and then resubmit a revised proposal that is funded. The process ensures that substantially flawed research is seldom done, but it adds time to the emergence of new knowledge. The new studies that are conducted may support or challenge the findings of the initial research, which usually initiates a third generation of research. With luck, the later studies eventually resolve one or more issues raised by the original research. However, ten or more years have passed before there is a general agreement that new knowledge has been added. Typically, this process also uncovers new unforeseen issues that elucidate fundamental ignorance. When this happens, the original questions may be suspended while more fundamental ones are examined. The process is excruciatingly slow, but no better method has been developed. This is the pace of science and the development of secure knowledge. The latest science may be the most exciting science, but it is not the best science.

Similarly, technological change is a slow process. A new technology must be based on a lengthy research and development process involving dozens of costly stages. At any stage, the new technology may develop complications that may lead to its abandonment. Promising technologies must be heavily funded before they can

become viable. Funding, building new facilities, and establishing efficient production lines may take several years. Successfully developed technologies must also be introduced, sold, and integrated into the society. This process also may require decades.

10.5.3. Public Health Is Complex

Public health depends first and foremost on the wide availability of affordable goods and services. Such goods and services must be available to the poor as well as to the wealthy. The costs of regulations are reflected in the prices of food, shelter, transportation, and energy. The tradeoff of the impact of a cleaner environment and the access to important goods and services must be borne in mind. Prosperity is a major requirement for having a healthy population, as prosperity leads to improvements in production methods, the development of cleaner processes, a stronger research community, and the means to correct problems generated in the past.

The battle among groups that support more stringent regulations and groups that oppose them is counterproductive. Resources are devoted to forcing and then overturning decisions made by regulators, legislators, and courts. Cooperation in maximizing the public good should replace the prevailing contentious activities.

Health is also complex in that cleaner may not always be better with respect to long-term health. What is good from some individuals may not be good for the larger population. Complex organisms adapt, sometimes rapidly, to decreased challenge by loss of resistance to challenge. Only if future challenges are essentially eliminated does loss of resistance then become beneficial. Public health policies must take into account the possible consequences of loss of resistance in the population.

10.6. THE CROSSROAD

Today, we are at an important crossroad with respect to the future of air-pollutant regulation. One road involves performing the needed research and making decisions on the basis of the science, with full consideration of the many tradeoffs associated with new regulations. The other road involves adopting regulations driven by politics and pressure groups. The first road is obviously the more beneficial one for protecting human health. However, it requires a more patient and reasoned approach that invests in research, allows time for the science to work, and then allows the time needed for technological change. The second approach promises uncontrolled, chaotic, and rapidly changing rules. A great deal is at stake. Will science and reason, or expediency, fear and ignorance be the determinants of public health decisions. To travel the better road, there must be a new era of cooperation and communication among scientists, regulators, legislators, advocacy groups, and the public.

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The Particulate Air Pollution Controversy
A Case Study and Lessons Learned

by **Robert F. Phalen**

Do current levels of particulate air pollutants claim thousands of thousands of lives yearly, or is the actual risk negligible? Scientists, regulators, legislators, producers, and portions of the lay public are all attempting to understand and respond to recent scientific findings that have significant consequences regarding public health, the economy and how hundreds of research programs are funded and guided.

This concise book presents the relevant scientific data, historical developments, unsolved problems, and new research opportunities related to particulate air pollution and human health. Included are chapters on the nature of particulate air pollution, fates and toxicity of inhaled particles, evidence of harmful effects of air pollution, events that led to the current controversy, interpretation of modern epidemiology studies, needed research, challenges to commonly accepted ideas about pollutants and health, and recommendations for scientists, regulators, legislators, the public and industry.

Modern technologies and rigorous efforts to control air emissions have produced significant improvements in air quality. Yet, modern city dwellers still inhale numerous tiny invisible particles in each breath. Epidemiologists have repeatedly found associations between small day-to-day increases in particulate pollutants and adverse health effects. But are the associations strong enough to establish a cause and effect relationship? In addition, are stringent new controls on the sources of particulate pollutants warranted? The processes that produce particulate air pollutants also sustain public health. Tighter air regulations impact these processes and others that are difficult to quickly change. A coordinated worldwide effort to provide the research required to answer the critical questions has been launched. It is important that this research effort be given time to unfold.

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