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Perspective

THE PARTICULATE AIR POLLUTION CONTROVERSY

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□ *Scientists, regulators, legislators, and segments of industry and the lay public are attempting to understand and respond to epidemiology findings of associations between measures of modern particulate air pollutants (PM) and adverse health outcomes in urban dwellers. The associations have been interpreted to imply that tens of thousands of Americans are killed annually by small daily increments in PM. These epidemiology studies and their interpretations have been challenged, although it is accepted that high concentrations of air pollutants have claimed many lives in the past. Although reproducible and statistically significant, the relative risks associated with modern PM are very small and confounded by many factors. Neither toxicology studies nor human clinical investigations have identified the components and/or characteristics of PM that might be causing the health-effect associations. Currently, a massive worldwide research effort is under way in an attempt to identify whom might be harmed and by what substances and mechanisms. Finding the answers is important, because control measures have the potential not only to be costly but also to limit the availability of goods and services that are important to public health.*

Keywords. *air pollution, PM, particles, EPA standards, aerosol, inhalation toxicology*

INTRODUCTION

Background on the Harmful Effects of Particulate Air Pollution

Scientists and regulators are struggling to understand the human health effects of low levels of urban particulate air pollution (particulate matter, PM). Because the regulation of PM has economic implications, the "*PM* controversy" has evolved. (For a more in-depth treatment, see Phalen, 2002.) The evidence for harmful effects at realistic concentrations predominantly comes from epidemiology studies using newer methods that discovered health-effect associations with very low levels of particulate air pollution measures.

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Perfectly clean air, which cannot be found in nature, is about 76% nitrogen gas (by weight), 23% oxygen, 1% argon, 0.03% carbon dioxide, plus smaller quantities of other gases, such as helium and neon. Also, air will contain as much as 25 g/m^3 of water vapor at room temperature. Ambient air contains hundreds of vapors and tens of thousands of suspended particles per liter. The contaminants can be classified in several ways but, for regulatory purposes, "anthropogenic" (human generated), "natural," and "secondary" (produced by chemical reactions in the atmosphere) are used.

How contaminated must air be before it is considered impure? The answer 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, and so on. Even when an air standard has been accepted as adequately protective of health, some individuals may develop aversions to its odor, allergic responses, or unexplained sensitivities. Therefore, air standards often represent compromises that are practical, achievable, and protective for most people. 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.

There is 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 had several factors in common: heavy emissions, prolonged near-stagnant air conditions, low temperatures, and fog. The first, in December 1930, affected communities in a valley of the Meuse River in eastern Belgium. The valley was industrialized, having several electrical power plants and heavy industries as well as other pollutant sources. The six-day episode began with dropping temperatures, fog, and very low wind speeds. More than 60 excess deaths occurred, accompanied by cases of cough, shortness of breath, and irritation (Stern, 1977; Clayton, 1978; Lipfert, 1994; Wilson and Spengler, 1996). Deaths occurred mostly in those who were elderly and had pre-existing heart and lung diseases. Speculation and modeling has identified SO_2 and acid droplets as the probable causal agents. The second incident occurred in October 1948 in Donora (and nearby Webster), an industrial community of about 14,000 (1,000 in Webster) in Pennsylvania at a bend of the Monongahela River surrounded by high ground. The area was heavily industrialized, and essentially all private and commercial establishments used soft coal for fuel (Ashe, 1952). The episode began with a persistent fog and stagnant wind conditions. Over the next few days the fog became odorous (a smell of SO_2), and visibility was low enough ($\sim$15 m) that traffic essentially stopped. Either 18 or 20 deaths have been attributed to the episode, when about one or two were expected during the period (Lipfert, 1994). Older persons (over 50 years) with existing cardiopulmonary diseases were most

affected. Cough, dyspnea, and eye and respiratory irritations were seen. As in the Belgian episode, no air monitoring was in place, but estimates place the possible SO_2 level as high as 5.5 mg/m^3 (2 ppm), and the total suspended particulates (TSP) as high as 30 mg/m^3 (Stern, 1977; Lipfert, 1994; Wilson and Spengler, 1996). Other 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). The most severe of the air pollution disasters occurred in December 1952 in London, England, which lies in the 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 traffic was impeded and pedestrians became lost (Lipfert, 1994). The number of deaths attributable to the smog is uncertain, because influenza and the effects of temperature and high humidity were possible confounding factors (Holland *et al.*, 1979). However, the British Ministry of Health reported over 4,000 excess deaths, and most estimates attribute 3,000 or more deaths to the episode (Stern, 1977; Clayton, 1978). Most strongly affected were those 45 years or older and infants under 1 year. Pre-existing illness, especially of the heart and lungs, was a risk factor for mortality in 80% of the victims. Causes of death were listed as bronchitis, pneumonia, and heart disease. 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 source of the air contaminants was 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 air pollution disasters, some unmeasured toxic agent or a combination of pollutants was believed to have produced the health effects (Ashe, 1952). Much has been written on these air pollution episodes, but several 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 pre-existing 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.

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 crude measures, including air-filter soiling and filter weighing (TSP), were affected by changes in air chemistry, particle size distribution, wind, and relative humidity. 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 confounders. However, progress was made because criticism of the methodology led to steady improvements in the studies.

As air pollution levels declined in the United States over the past several decades, epidemiological investigations underwent considerable sophistication. Higher-quality aerometric data have been incorporated, and greater attention has been paid to confounders. Additionally, the statistical techniques used by modern epidemiologists have seen considerable evolution. 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 (Pope *et al.*, 1995; Pope and Dockery, 1996; Pope, 2000a, 2000b). In summary, the studies 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 the previous day's levels. The increase was typically the difference between the PM_{10} on the date in question and the average of the previous 1 to 4 days (Li and Roth, 1995). Table 1 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. Subsequent analysis has

TABLE 1 Summary of Typical Initial Epidemiologic Associations Between Percentages of Increases in Adverse Effects and Increments of PM_{10} from Pope *et al.* (1995)

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%

LRT = lower respiratory tract, URT = upper respiratory tract (Phalen, 2002).

decreased these estimates by about 50%. 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 annual deaths and other adverse effects have been postulated. These types of associations for acute effects have been seen in dozens of cities worldwide.

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 Harvard 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 8-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 Prevention Study.

The strength of these studies lies primarily in their reproducibility; that is, similar associations were seen linking health effects to particulate measures in a large number of cities. The weaknesses include the small risk factors, the use of increments in particle mass (which are different than actual levels), and the sophisticated mathematical models that were used to account for confounding factors (gaseous pollutants, weather variables, etc.) (Li and Roth, 1995; Moolgavkar *et al.*, 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 "[g]iven 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). The picture is unclear as to which pollutants might be harming whom and by which mechanisms of injury.

Regulatory Actions

The U.S. Environmental Protection Agency (EPA) is 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, PM, sulfur dioxide, nitrogen dioxide, and lead. In setting primary NAAQS, the cost and feasibility of attainment are excluded by law, and a five-year cycle of review of the standards is mandated. Primarily as a result of its analysis of epidemiologic data on PM, the EPA issued new primary (health-based) NAAQS

TABLE 2 Primary NAAQS for Particulate Matter Issued in July 1997 by the EPA

Pollutant	24-Hour standard, $\mu g/m^3$	Annual standard, $\mu g/m^3$
PM_{10}	150	50
$PM_{2.5}$	65	15

The previous 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 (Phalen, 2002).

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) for all practical purposes retained the previous limits for PM_{10} and created new limits for another class of particles, $PM_{2.5}$ (particles 2.5 μm or less in aerodynamic diameter). The standards were based on two previously invoked averaging times, 24 h and 1 year, to protect the public from short-term (acute) effects and long-term (chronic) effects, respectively. The process used by the 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. 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 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 stated that "the CASAC Panel succumbed to the pressures exerted by the accelerated schedule and reluctantly came to closure on the CD" (Wolff, 1996a).

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 by the U.S. Chamber of Commerce, other business interests, and the states of Michigan, Ohio, and West Virginia. The suit claimed that the 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 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 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 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.

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 defined the needed research and evaluated its progress (NRC, 1998, 1999, 2001).

Interpreting the PM Epidemiology

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 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. Shortly after the new associations were given press coverage, scientists gathered to understand, examine, defend, and challenge the studies (Phalen and McClellan, 1995). Table 3 lists some of the challenges raised.

TABLE 3 Initial Challenges to the Associations of Small Increments in Particulate Air Pollution (Mainly PM_{10}) and Human Mortality and Morbidity (Phalen, 2002)

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 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.

In addition, the epidemiology has been reviewed repeatedly (Pope, 2000a). Nearly all reviews of the acute epidemiology studies concluded that the studies were consistent and that evidence existed of probable effects but that there were uncertainties. The uncertainties and concerns 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, 2000a).

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). 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). However, the press seems eager to report risks without seriously challenging whether they are spurious or trivial, let alone if they withstand 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).

When groups of individuals are used in studies that produce statistical associations, certain questions arise. 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? Confidence limits, such as the 95% confidence intervals, placed understandable uncertainties around the PM–health findings. Thus, the findings did not appear to be spurious. Confounding bias occurs 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 confounding factors have been identified. Significant changes in particle levels are associated with seasons, days of the week, weather, fuel quality, fuel usage, and changes in human activity patterns (Valberg and Watson, 1998). Possible confounders also include an unmeasured air pollutant (such as reactive metals, gases/vapors, allergens, and combinations of contaminants) and particle count. Another potential confounder is that changes (over previous day's levels) are a causal factor, as opposed to actual levels of the factor, and are producing the observed associations (Vedal, 1997). It is not clear that the significant potential confounders have been dealt with.

The question of to whom in a group an observed association applies is an important one. With respect to particulate air pollution, the issue is difficult,

because perhaps only one in several hundred thousand individuals is made ill by small increments in pollutant levels. With respect to the excess mortality produced by a single small episode, about one in a million might be a victim; just who these rare individuals are is still unknown.

Establishing a cause-and-effect relationship is particularly difficult in epidemiology because the suspected cause cannot be manipulated in ways that are possible in 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 leading 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 guesses at this time). Opinions are divided on the extent to which Hill's criteria are met.

When the relative risks involved are large, it is usually easy to have confidence in cause-and-effect relationships. However, associations that imply small relative risks present difficulties due to uncertainties about who is affected, by what causal factors, and by what mechanism(s). The questions raised regarding risks from small levels of PM can be expected to require a significant research effort before those who are skeptical will have confidence in risk-reduction strategies.

THE NATURE OF URBAN PARTICULATE MATTER

Particulate air pollution is a complex aerosol that is not easy to characterize or define. Like all aerosols, it is a two-component system consisting of finely divided condensed matter and a gaseous suspending medium. The major sources of urban PM are natural, anthropogenic, and secondary. Natural sources 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 will come from both natural and anthropogenic sources (in which case the sources cannot

TABLE 4 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, 1996a)

	Thousands of Tons/Year			
Source	PM_{10}	SO_X	NO_X	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

always be identified). Table 4 lists the main sources and annual emissions for PM_{10} and precursor gases.

Because people spend considerable time in enclosed environments, sources of pollutants in buildings must also be considered. Activities such as grooming, cooking, cleaning, gardening, painting, sawing, and so on will generate a characteristic cloud of PM in the person's breathing zone (Morandi *et al.*, 1988; Thatcher and Layton, 1995). 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).

From the point of view of urban PM, the coarse size range (2.5 to 10 μm aerodynamic diameter) is usually dominated by soil particles, desiccated cellular debris, spores, and pollen, whereas 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).

Urban PM is multimodal, and at least three size 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

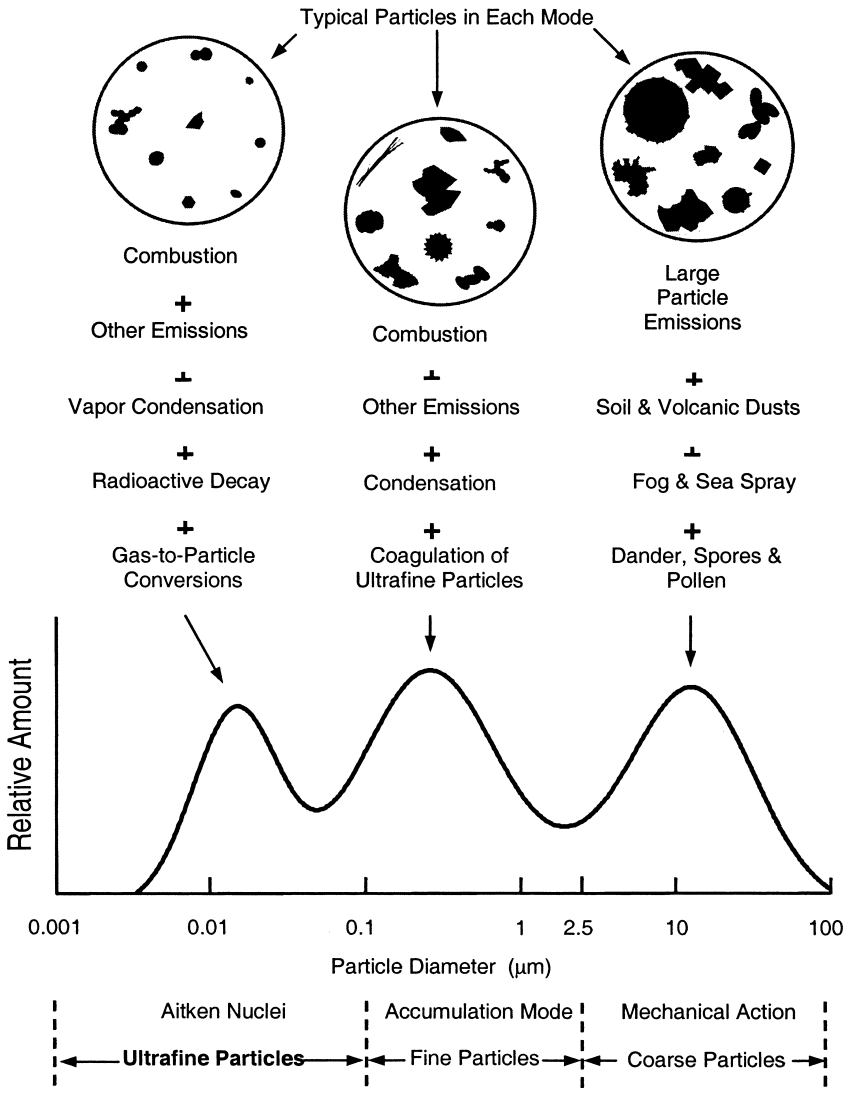

FIGURE 1 Conceptual depiction of the complex atmospheric aerosol including proposed sources and typical shapes of particles in each mode. Actual urban aerosols are more complex than this depiction in that different and additional modes are present if specific chemical species are represented (Phalen, 2002).

peaks can be identified at various particle diameters (Noble and Prather, 1996). The three-mode model, proposed in the 1970s for sulfur-containing aerosols (Whitby, 1978; Wilson, 1978), is still used for describing urban PM and calculating inhaled doses (EPA, 1996a; Snipes *et al.*, 1996). Figure 1 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.

A potential complication for regulating urban PM arises from the variable nature of air pollution in time and space. The epidemiological studies are typically published years after the actual exposures. Vehicles have advanced from having average precontrolled emission values of over 100 g/mile of hydrocarbons, carbon monoxide, and nitrogen oxides to a modern level of about 4 g/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 past 50 years and found a decreasing trend of 2 to 8% per year for total particulate, PM_{10}, and $PM_{2.5}$ fractions. The EPA has quantified the decreases in PM_{10} levels in the United States in recent years (EPA, 1996a). For sites that had monitoring stations for the seven-year period of 1988 to 1994, PM_{10} concentrations decreased an average of 20%. 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. 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 Northwestern, characterized by the greater use of wood burning for heating in the winter time. In the East, sulfur-containing compounds, such as sulfur dioxide and sulfates (along with acidity), are commonly elevated. 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 applicable to all regions.

THE FATES OF INHALED PARTICLES

The human respiratory tract may be broken into a few distinct regions (Table 5). 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 (Morrow *et al.*, 1966); the original regions are still used with some refinements (ICRP, 1994; NCRP, 1997).

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

TABLE 5 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	Head airways region	Extrathoracic region	Naso-oropharyngolaryngeal region
	Mouth			
	Nasopharynx			
	Oropharynx			
	Larynx			
Tracheobronchial tree	Trachea	Tracheobronchial region	Bronchial region and bronchiolar region	Tracheobronchial region
	Bronchi			
	Bronchioles (to terminal bronchioles)			
Gas exchange	Respiratory bronchioles	Gas exchange region	Alveolar interstitial region	Pulmonary region
	Alveolar ducts			
	Alveolar sacs			
	Alveoli			

particles, such as long fibers). When any particle departs the airflow because of these mechanisms and touches an airway wall, it is assumed that it will deposit. Figure 2 shows the expected particle deposition efficiencies in the main regions of the respiratory tract (using National Council on Radiation Protection and Measurements compartments) for an adult engaged in low-level physical activity. The curves in Figure 2A are not corrected for inhalability, as are those in Figure 2B. 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. When a population of individuals is being considered, these curves, at best, pertain only to the average individual.

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 (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 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. 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

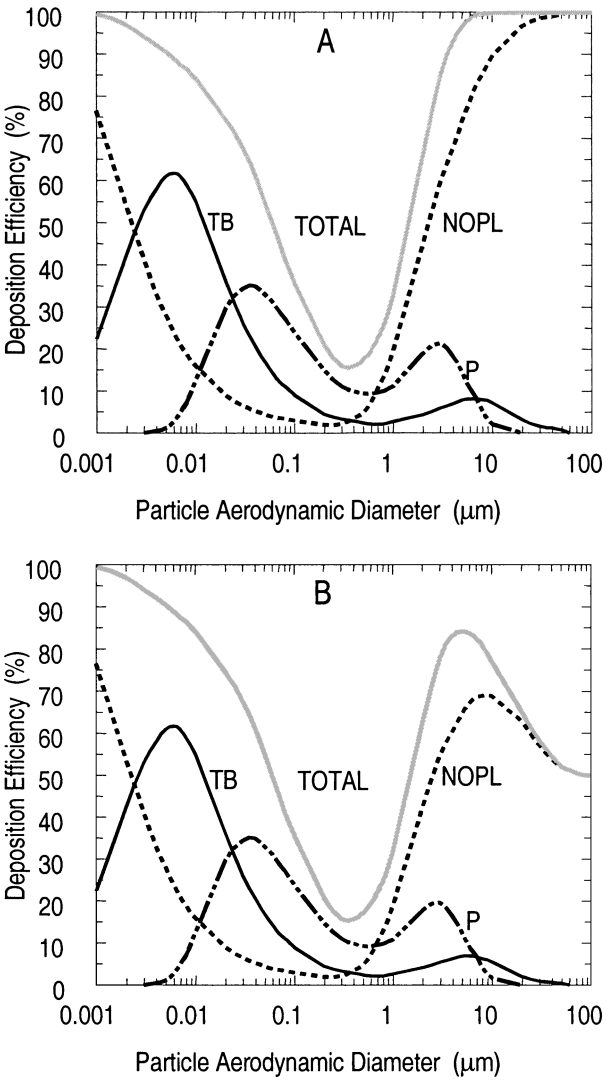

FIGURE 2 (A) Particle deposition in the major regions of the human respiratory tract during normal respiration (NCRP, 1997); (B) particle deposition efficiencies from A multiplied by the size-dependent inhalability.

slower clearance of those deposited in alveoli. 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. 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. Although much is known regarding inhaled particle deposition and clearance, significant uncertainties remain. The normal variations in particle deposition and clearance have not been well explored, let alone those for seriously ill 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 second NRC report (NRC, 1999) added extrapolation modeling for laboratory animals as a research priority.

There are other significant uncertainties related to particle deposition and clearance. The actual property of PM ideal for dosimetry calculations (the proper "metric") is not known; particle mass, number, surface, and reactivity are among the possibilities. The amounts of specified agents required to trigger a disease process are not well understood, along with the short-term and long-term adaptations to particle exposures. 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 monitor in the air or 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, 1999).

THE TOXICOLOGY OF PARTICULATE MATERIAL

Toxicology, "the science of poisons," includes controlled studies in cell and tissue cultures, laboratory animals, and human volunteers in an effort to understand the effects of xenobiotics on living systems. Inhalation toxicology is concerned with the adverse effects of inhaled substances, which may be on any organ or tissue in the body. Clinical studies of inhaled air contaminants that use human volunteers are critical for confirming the results of laboratory *in vitro* and animal studies and for testing hypotheses generated in epidemiology investigations (Utell and Frampton, 2000). Laboratory animal studies, human clinical studies, and epidemiology studies are complementary, because the limitations of one are the strengths of the other.

Table 6 lists some of the proposed toxicological mechanisms by which PM might impair health, along with the subpopulations that may be especially vulnerable. For a mechanism to be important, it must usually be capable of producing or exacerbating a disease, as some changes in physiological functions or anatomy do not pose a significant threat to health. It must be understood that some individuals are so fragile that virtually any biological change, including adaptive responses, can be life threatening.

Several physical and chemical characteristics of PM have been proposed as being responsible for producing the adverse health effects reported by epidemiologists (Table 7) along with the mechanisms of injury and sources

TABLE 6 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, other	Asthmatics, bronchitics
Increased permeability	Lung, heart	Asthmatics, cardiac patients
Edema	Lung, heart	Persons with advanced cardiac or lung diseases
Bronchoconstriction	Lung	Asthmatics
Impaired dfenses/ 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

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.

In addition to PM *per se*, other pathways related to PM have been suggested to cause the epidemiologic associations between health and PM measures (Valberg and Watson, 1998). Some pathways are listed in Table 8, along with potentially susceptible populations. All of these factors, plus all of the aforementioned PM characteristics, will have some effects on health.

New Research Approaches

The enormous toxicology database on inhaled particles does not indicate that tiny levels are capable of producing significant acute harm, except

TABLE 7 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 (Phalen, 2002)

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
Biogenics	Bronchoconstriction, inflammation, infection	Plants, animals, fungi, bacteria, viruses
Metals and reactive species	Inflammation, cell killing	Fuel combustion, industrial processes, soil, photochemistry
Oxidants	Cell damage	Combustion products, industrial processes, soil, photochemistry
Mixtures	Various	Various

TABLE 8 Nonparticle Pathways (Explanations) for Producing Associations Between Adverse Health and PM Measures Along with Potentially Susceptible Subpopulations (Phalen, 2002)

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, others with fragile health

for allergens, pathogens, or hypothetical supertoxic agents. Such supertoxic agents are not common, 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 associated with PM episodes.

Because of the lack of a ready explanation for how a concentration as low 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. A pioneering study was conducted by Dr. John Godleski and associates at the Harvard School of Public Health (Godleski *et al.*, 1996). The major objective of the study was to examine the biologic plausibility that inhaled PM exposures would produce deaths in ill populations. Godleski's laboratory rats had a severe bronchitis produced by pre-exposure to 250 ppm SO_2 for 6 weeks. The follow-up exposures were to Boston air that had been concentrated about 30-fold by the Harvard Ambient Particle Concentrator (Sioutas *et al.*, 1995), which 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 airstream. Four groups were examined: bronchitic rats exposed to CAPs 6 h per day for 3 consecutive days; bronchitic rats exposed to filtered laboratory air 6 h per day for 3 consecutive days; and two groups of healthy rats similarly exposed to CAPs or filtered air using the same exposure protocol. The results were striking; only the CAP-exposed bronchitic group had significant mortality (37% died), with no deaths in the bronchitic filtered-air group. 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 much higher than that seen in modern cities. Following these initial rodent studies, the group performed exposures to Boston CAPs using dogs. The dog exposures focused on changes in electrocardiograms, 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 (Godleski, 1998).

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 (Bice *et al.*, 2000; Conn *et al.*, 2000; Mauderly, 2000; Muggenburg *et al.*, 2000). Among the models of interest are those that represent elderly individuals, asthmatics, and bronchitics.

Other Toxicology Issues

Several challenges face toxicologists related 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? Second, who are the affected individuals? Third, how might the mortality or morbidity be produced? A limitation 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 overcontrol 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 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. Although most current PM toxicology studies involve acute exposures, low-dose, long-term, and large population issues will require a similar change in the thinking of toxicologists. To date, toxicologists have not been able to replicate the low-dose PM findings seen in epidemiologic studies.

RESEARCH NEEDS

Several parties, including scientists attending PM Colloquia, the EPA, the NRC of the National Academy of Sciences, the HEI, and the EPA's CASAC, have identified the high-priority needs for further research. The EPA allocates resources for analyzing gaps in the scientific database 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 NAAQS (EPA, 1998a). A second related report, based on a focused workshop, was issued about the same time (EPA, 1998b). The EPA first identified several important uncertainties; then the research needed to

resolve the uncertainties was defined. The following top ten 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 NRC's committee on PM, composed of 20 prominent experts and chaired by Dr. Jonathan Samet, was charged with producing four reports between 1998 and 2002. 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). The following highest-priority research topics of the NRC were not presented in order of priority.

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.
2. Investigations were needed on exposures of susceptible populations to the most biologically important "constituents" and "specific characteristics" of PM.
3. Development of advanced modeling and measurement tools that would accurately relate specific sources of pollutants to specific exposures was needed.

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 on the roles of physiochemical characteristics of PM in producing adverse health effects was needed. 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.
7. Investigations were needed, using toxicological and epidemiological methods, to disentangle the effects of PM from those of gaseous copollutants.
8. Identification of the human subpopulations that may be at increased risk of adverse health effects of exposure to PM was needed.
9. Investigation of the mechanisms of injury that might explain the epidemiological associations between PM measures and increased morbidity and mortality were needed.
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.

The NRC report was especially strong with respect to putting forth a coherent research plan. Future reports refined the research agenda and evaluated the research progress on achieving the goals.

The CASAC of the 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. With respect to the 1996 PM criteria document (EPA, 1996b) and the revised standards based on that review, CASAC had difficulty in achieving "closure." The committee noted that the "understanding of the health effects of PM is far from complete," and several important uncertainties were identified (Wolff, 1996b, c). 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, 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).

What does the research planning 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; the National Institute for Occupational Safety and Health; the Centers for Disease Control and Prevention; the National Heart, Lung and Blood Institute; and the National Institute of Allergy and Infectious Diseases. Nonfederal PM health research efforts in the United States are supported by the American Petroleum Institute, the California Air Resources Board, the Chemical Industry Institute of Toxicology, the Coordinating Research Council, the Electric Power Research Institute, and the HEI. 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 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.

WHAT'S AT STAKE?

Why not eliminate all substances from the air that could possibly produce harmful effects? First, the required diversion of resources could not be borne by any society, no matter how wealthy. Second, this is impossible because all substances, including oxygen, are capable of harming health. Third, the processes that contaminate the environment are frequently essential for sustaining health and life. Each pollutant control action produces adverse impacts along with benefits. When revised NAAQS for Particulate Air Pollution (PM NAAQS) were proposed in 1997, several groups and individuals responded to the EPA's invitation to provide comments. The issue of risk trade-offs was addressed in a 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. 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

TABLE 9 Sources of Urban Particulate Air Pollution and the Associated Benefits; The Source Categories Are Not Mutually Exclusive (Phalen, 2002)

Sources	Emissions	Benefits
Farming and dairying	Dust, diesel exhaust, ammonia, sprays, biogenic aerosols	Prevents malnutrition and starvation
Electric power generation	Fly ash, metal-containing aerosols, sulfur-containing particles, various gases and vapors (nuclear plants are essentially free of air pollutants)	Supplies electricity for heating, air conditioning, food preservation, and other survival- and economic-related activities
Diesel engine operation	Fine particles, gases, vapors	Diesel engines are essential for the operation of heavy trucks, trains, ships, and farm, mining, and construction equipment
Manufacturing	Coarse and fine particles, gases, vapors	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

and well-being, noting that small businesses were particularly vulnerable to closing as a result of being unable to comply with air-quality standards.

Human activities, like natural phenomena, generate air contaminants. Table 9 lists several examples along with the benefits associated with each of these particle sources. Such activities are necessary for sustaining life, and so their suppression may threaten public health. 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. Such activities produce unavoidable health-related risks, including those associated with the production of air pollutants. The current approach of separation of decision making for reducing risks from decision making related to ensuring adequate production of food or other important commodities and activities is a recipe for trouble.

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. The optimal control would set levels such that the direct health benefits are closely balanced by the adverse consequences associated with the increased costs of important activities. The health-benefits side of control of particulate air pollutants appears to be relatively easy to define, and it includes

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 illnesses associated with a lowering of particulate pollutant levels (Hall *et al.*, 1992). The adverse consequences of particle controls, which probably are felt most strongly by the disadvantaged, 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.

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 could depress the ability of people to withstand challenges produced by airborne microorganisms, aeroallergens, smokes from unpreventable fires, and even wind-blown soil. In this scenario, lung disease rates and death rates could increase. 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 (Gergen and Weiss, 1992; von Mutius *et al.*, 1994; Shirakawa *et al.*, 1997).

A formal approach to assessing the risk trade-offs of actions designed to protect health and the environment has been described (Graham and Wiener, 1995). 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. 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. 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.

CHALLENGES TO DOGMA

The particulate air pollution controversy affords an opportunity to challenge some of the assumptions that underlie 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.

The Low-Dose Question

The lay public and many health professionals assume that some agents are toxic and should be eliminated from the environment, whereas others are safe. Such all-or-nothing logic can lead to large expenditures 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, 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. This apparent beneficial effect 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.

Similarly, 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 beneficial 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. Calabrese and 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." The implications 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.

The Small-Unit Risk, Large-Population Dilemma

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 to estimate the total harm. First, the risk estimate itself is likely to be very uncertain or even fictitious. 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, 2000a).

Stressors and Health

Complex organisms, including humans, respond to stress or its absence. For example, increases in strength, maximum oxygen consumption, and cardiovascular fitness follow the stresses associated with strenuous muscular exercise. Also, the absence of weight-bearing stresses leads to muscle wasting and decreases in bone strength. Human beings are constantly remodeling in response to changes in the internal and external environments. The phrase "use it or lose it" captures the concept. The effects of environmental contaminant exposures on fitness are poorly understood. In laboratory animals, it is known that preconditioning in clean environments often leads to increased susceptibility to the effects of subsequent exposure. It is common practice for investigators studying inhaled particles and gases 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. Pre-exposure 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; Linn *et al.*, 1982; Folinsbee *et al.*, 1994). Such tolerance is seen within a few days of the initial exposure, and protection lasts for several days to perhaps a week or more. 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 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, 2000a). 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. Pre-exposure 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 under what conditions overall fitness might be compromised by continual reductions in particulate air pollutants.

Is Isolating Individual Contaminants Logical?

Historically, contaminants have been considered individually when setting ambient air-quality standards. There are several problems with this one-agent-at-a-time approach. The air contaminants that have been designated as criteria pollutants compose 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 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, and 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.

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. 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 final or immune from later challenge. What is not clear is when new scientific information is ready for public or regulatory consumption. 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.

CONCLUSIONS AND RECOMMENDATIONS

The State of Current Knowledge

Substantial levels of urban PM, as have occurred in the past, are known to be capable of producing human mortality and morbidity. Also, associations between adverse acute health outcomes and small increments in PM measures have been repeatedly observed. However, they have raised more questions than they have answered. 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 associations are reproducible, but they have not been consistent enough to establish causality or to implicate a key pollutant or some key combination of pollutants.

PM 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 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 co-pollutant gases and vapors. The roles of such co-pollutants in harming health are not clear. Thus, a focus on particle-mass fractions may not be adequate for providing appropriate health protection.

Epidemiological associations are a starting point in the process of identifying potentially harmful concentrations of agents. Toxicological studies have shown that some chemical compositions, some particle-size ranges, and some combinations of particles and gaseous co-pollutants 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. 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. The research community is guided by the research priorities identified by the NRC (1998, 1999, 2001). Funding increases have provided budgets to conduct much of the needed research in epidemiology, toxicology, and atmospheric science.

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 unlikely that appropriate control measures can be taken that will protect potentially at-risk subpopulations.

The "metric" is the appropriate measure of PM that, when regulated appropriately, 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. The appropriate metric will no doubt need to include chemical and physical features of PM as well as associated gases. In addition, it is not known why episodes in different cities that have similar measured pollutant concentrations have different toxicities. 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.

Too little is known about the PM-associated air pollutants as they exist in the immediate breathing zones for individuals. In addition, the most relevant personal exposures are those for subpopulations that may be especially

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 pre-existing pulmonary or cardiovascular diseases (or susceptibility to such diseases). 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. Recent advances, especially in using aged and diseased rodents, are steps forward. However, the relevance of these models to humans has not been established.

All pollution control actions will have effects other than those anticipated, including negative *risk trade-offs* (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. The total impacts on human health from all consequences of future control strategies have not been assessed.

Much of our knowledge of the potentially adverse effects of air pollutants was gained by studying the effects of exposures that occurred 10 or more years ago. Changes in technology and lifestyle have 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 older air chemistries, not current ones. The uncertainties in this area of knowledge are significant, and their investigation is important.

What Needs To Be Done?

The research community faces major challenges relating to the health effects of PM exposures. First, the tendency to stay within narrow disciplines must be changed. Toxicologists must become more knowledgeable about air chemistry, epidemiology, and the fates of inhaled particles. Similar challenges face atmospheric chemists, epidemiologists, and other specialists. Epidemiologists must persist in their 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. Economists that evaluate the effects of regulation must become more involved in the issues surrounding PM controls. Scientists are also challenged to better communicate with regulators and the public. Both of these groups struggle to understand the latest research, key on isolated findings or frightening possibilities, and then act decisively. Scientists

understand that their studies do not consider all of the relevant factors, but the public has no idea that this is the case.

Those charged with establishing clean-air regulations have a good record of identifying the major pollutants, encouraging the required research, and recommending safer air standards. Previously, the regulatory task was simpler because of high levels of emissions, obvious health effects, and the lack of attention to cleaner technologies. Today, the problem is different in that most of the serious emission sources have been significantly reduced, and the health effects are usually seen only as outcomes of sophisticated computational exercises. Even more challenging is the fact that the trade-offs are no longer negligible and may be approaching the point where some controls may cause a net deterioration in human health and welfare. New strategies must include more consideration of uncertainties and better evaluation of the evidence for harm at current levels of air pollution, improved analysis of the trade-offs 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.

There is a general belief that legislation can solve the problem of adverse effects associated with exposures to environmental pollutants. Can offending substances be banned or regulated to some low level such that they will cause 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 balancing the positive aspects of an environmental regulation with the negative aspects, it is easy to underestimate the negative consequences. Therefore, legislators are 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 significant consequences of their legislative actions. With respect to environmental contaminants, it must be realized that it is impossible, and perhaps 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. Legislators must be more sophisticated in analyzing the complex issues associated with public health in relation to environmental contaminants.

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 improper to focus solely on isolated risks and then exert pressure on regulators and legislators to reduce that particular risk. 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. Public health is served by good science, dedicated qualified civil servants, and patience.

There are also 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 anticipatory planning because replacing an existing technology may take decades of research, testing, and implementation. When new technologies are first envisioned, their air-polluting characteristics must be considered early on rather than later. Industry has two other challenges—to increase public education regarding the benefits of industrial activity and to support responsible and objective research relating to air pollutants. Industry has played an important and positive role in improving the public health. Food, goods, transportation, electrical energy, and jobs are all contributions of industry. These contributions must continue, but in a more enlightened manner.

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 trade-offs associated with new regulations. The other road involves adopting regulations driven by public fear, 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 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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