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What's Wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter ($PM_{2.5}$)?

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Associations between airborne concentrations of fine particulate matter ($PM_{2.5}$) and mortality rates have been investigated primarily by ecologic or semiecologic epidemiology studies. Many investigators and regulatory agencies have inferred that the weak, positive association often observed is causal, that it applies to all forms of airborne $PM_{2.5}$, and that current ambient levels of $PM_{2.5}$ require reduction. Before implementing stringent regulations of ambient $PM_{2.5}$, analysts should pause to consider whether the accumulated evidence is sufficient, and sufficiently detailed, to support the $PM_{2.5}$ National Ambient Air Quality Standard. We take two tacks. First, we analyze the toxicologic evidence, finding it inconsistent with the notion that current ambient concentrations of all forms of fine particulate matter should affect pulmonary, cardiac, or all-cause mortality rates. More generally, we note that the thousands of forms of $PM_{2.5}$ are remarkably diverse, yet the $PM_{2.5}$ NAAQS presumes them to be identical toxicologically, and presumes that reducing ambient concentrations of any form of $PM_{2.5}$ will improve public health. Second, we examine the epidemiologic evidence in light of two related examples of semiecologic associations, examples that both inform the PM–mortality association and have been called into question by individual-level data. Taken together, the toxicologic evidence and lessons learned from analogous epidemiologic associations should encourage further investigation of the association between particulate matter and mortality rates before additional regulation is implemented, and certainly before the association is characterized as causal and applicable to all $PM_{2.5}$.

***Key Words*: particulate matter ($PM_{2.5}$); air pollution; National Ambient Air Quality Standard (NAAQS); health effects; ecologic fallacy; epidemiology.**

INTRODUCTION

Many observational studies have reported weak, positive associations between rates of mortality in populations and moderate concentrations of fine particulate matter ($PM_{2.5}$)[2] measured in ambient air near those populations (see Lipfert and Wyzga, 1995; and Krewski *et al.*, 2000, for reviews). These observational studies include cross-sectional studies (Dockery *et al.*, 1993; Pope *et al.*, 1995), in which mortality in various metropolitan areas is associated with ambient concentrations of $PM_{2.5}$ in those areas, and time-series studies (Samet *et al.*, 2000), in which daily mortality[3] within a metropolitan area is associated with concurrent or lagged daily fluctuations in ambient $PM_{2.5}$ concentrations.

The U.S. Environmental Protection Agency (U.S. EPA, 1996, 1997, 2001) and others (Pope, 2000; Ware, 2000) have taken these associations to be causal, and U.S. EPA has proposed that $PM_{2.5}$ in ambient air be stringently regulated (U.S. EPA, 1997). In particular, the fine particulate matter National Ambient Air Quality Standard (NAAQS) mandates that $PM_{2.5}$ in ambient air not exceed 15 $\mu g/m^3$ as an annual average (calculated as the mean of 3 years of quarterly means of 24-h measurements) and 65 $\mu g/m^3$ as a 24-h standard (calculated as the 98th percentile of 24-h measurements). Although sufficient data on ambient $PM_{2.5}$ have yet to be amassed for portions of the country, indications from many metropolitan areas are that this $PM_{2.5}$ NAAQS will commonly be exceeded (Fitz-Simons *et al.*, 2000), so that emission sources of $PM_{2.5}$ and its precursors will require additional control. Cost estimates for such controls nationwide range from $8 to $150 billion annually (*http://www.rppi.org/es226.html*).

We and others (Lipfert and Wyzga, 1995; Phalen and McClellan, 1995; Moolgavkar and Luebeck, 1996;

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[2] $PM_{2.5}$ refers to all airborne solid or liquid particles with a mass mean aerodynamic diameter less than or equal to 2.5 μm.

[3] Some studies have also investigated various rates of morbidity, such as admissions to emergency rooms for respiratory problems, but the relevant mortality studies have been more numerous, are easier to compare, and form the central basis for the $PM_{2.5}$ NAAQS.

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Gamble, 1998; Phalen, 1998; Valberg and Watson, 1998; Lippmann and Schlesinger, 2000) are concerned about the scientific bases of this NAAQS, both in toxicology and in epidemiology. Many problematic assumptions have been made in crafting the $PM_{2.5}$ NAAQS. Among these are the assumptions that: (1) any and all forms of $PM_{2.5}$ in ambient air cause death, and do so with identical toxic potencies; (2) daily and annual, average, mass-based concentrations of total $PM_{2.5}$ in air are the best, relevant measures for public health; and (3) decreasing such concentrations of ambient $PM_{2.5}$ in any form will decrease rates of death in a reliably quantifiable fashion (Abt Associates Inc., 2000; Freeman, 2001; Levy and Spengler, 2002).

As discussed below, many toxicologic and controlled human studies indicate that current, low-level ambient concentrations of various common types of PM are nontoxic. These experimental studies thus suggest that the observational, population-based studies that have been interpreted as implicating all forms of ambient PM may be confounded. Of course, lack of coherence between toxicologic and epidemiologic observations does not per se indicate that the population-based associations are spurious. However, there are other problems with this epidemiologic literature. Many of the observational studies are ecologic or semiecologic (Gamble, 1999; Kunzli and Tager, 1999; Greenbaum *et al.*, 2001) in design, meaning that they depend on measurements of exposure made at the community level by stationary monitors of air quality, rather than at the level of individuals, whose actual exposures to PM are determined by a host of individual activities and locations, indoors and outdoors. As explained below, recent evidence suggests that these PM-mortality studies are plagued by the "ecologic fallacy," which is that associations derived from observations on populations may not apply to individuals.

Further, the relative risk estimates for death from all causes and for death from cardiopulmonary disease published in the most widely relied on observational studies (Pope *et al.*, 1995, and Dockery *et al.*, 1993, reassessed in Krewski *et al.*, 2000), though statistically significant, are very weak, with estimates quite close to 1.0. These relative risks are on the order of 1.05 to 1.14, respectively, for each 10-μg increase of $PM_{2.5}$ per cubic meter of ambient air. In other studies, the relative rates are indistinguishable from 1.0, and evenly weakly (but significantly) less than 1.0. For example, Lipfert *et al.* (2000), reporting on a large cross-sectional study, find a relative risk for mortality of 0.94 for a 10-μg of $PM_{2.5}$ per cubic meter of ambient air increase. And Moolgavkar (2000) found that ambient PM was not strongly or consistently associated with various measures of daily mortality in three metropolitan areas (Cook County, Los Angeles County, and Maricopa County), whereas ambient carbon monoxide showed reasonably consistent weak associations with mortality.

The epidemiologist Robins (2001) writes:

> I believe that, in an observational study, every two variables have an unmeasured common cause, and thus there is always some uncontrolled confounding .... As epidemiologists, we should always seek highly skeptical subject-matter experts to elaborate the alternative causal theories needed to help keep us from being fooled by noncausal associations.

In what follows, we hope to provide some informed skepticism on the associations between current levels of ambient PM and risk of death.

Before discussing some toxicologic and epidemiologic issues, we point out that positive associations from these studies, if causal, suggest that ambient PM is remarkably deadly. Consider the following simple comparison. Krewski *et al.* (2000) report that sulfate (often a major component of fine PM) in ambient air correlates with lung cancer mortality, and estimate a relative risk of lung cancer mortality of 1.33 (95% CI, 1.10–1.61) associated with a change in mean ambient particulate sulfate concentrations of 19.9 $\mu g/m^3$. Assuming a linear dose–response relationship, the concentration–response relationship can be used directly to calculate a lethal potency for sulfate as a presumed lung carcinogen. To estimate an individual's lifetime risk of death from inhaling a carcinogen, the lifetime-average concentration to which the individual is exposed is multiplied by the chemical's inhalation unit risk factor (URF), expressed in units of inverse concentration (e.g., $m^3/\mu g$). Thus, we can estimate from the data reported in Krewski *et al.* (2000) an inhalation URF for sulfate of 1.1×10^{-3} $m^3/\mu g$. Such a URF would mean that sulfate in ambient air is, for example, 1.7 times more potent a lung carcinogen than coke oven emissions (URF $= 6.2 \times 10^{-4}$ $m^3/\mu g$). How plausible is this?

TOXICOLOGIC CONCERNS

At the toxicologic level, we evaluate what is known of the underlying biology, chemistry, and pathophysiology to determine the likelihood that observational associations are causal. Taking this view, it is clear that high ambient levels of ozone, for example, harm the respiratory health of asthmatics. Ozone is a highly reactive chemical that one would expect to affect lung tissue and function. Experiments have borne out this expectation in every species of animal tested, including humans. Ozone clearly causes inflammation of the respiratory tract in a dose-dependent fashion. Controlled, environmental chamber studies with asthmatics and others have shown that ozone, at airborne concentrations comparable to or only slightly greater than ambient, causes irritative cough, substernal chest pain on inspiration, decreases in lung function, and increased bronchial reactivity (Mudway and Kelly, 2000).

In contrast, what are our mechanistic expectations for airborne PM? What do experimental exposure

studies reveal, both in rodents and in people? Given our understanding of the pathophysiology of cardiovascular disease and other important causes of death, how likely are low levels of ambient PM to play a causal role?

As noted above, implicit in the NAAQS for $PM_{2.5}$ is the notion that all forms of $PM_{2.5}$ in ambient air are qualitatively and quantitatively identical. This notion is quite incorrect. The term $PM_{2.5}$ (in the context of ambient air regulations) refers to *any* atmospheric material, solid or liquid, with an effective diameter equal to or smaller than 2.5 μm (as collected by Federal Reference Method samplers and measured, by weight, under specific temperature and humidity conditions). As such, $PM_{2.5}$ refers to thousands of different things, both natural and synthetic. Various forms of $PM_{2.5}$ differ with respect to: (1) size (with diameters ranging from a few nanometers to 2500 nm), shape, and surface characteristics; (2) water solubility and pulmonary persistence; (3) chemical composition, pH, and metal content; and (4) biologic and immunologic properties and potencies. Clearly, it makes no more sense to think about estimating "*the* health effects of $PM_{2.5}$ in ambient air" than it does to consider estimating "*the* health effects of gases in ambient air." In the latter case, no one would assume that ambient mass concentrations of oxygen, nitrogen, ozone, carbon monoxide, mercury, phosgene, and sarin were all identically toxic, just because they are all gases and so "can penetrate into the sensitive regions of the respiratory tract" (*http://www.epa.gov/oar/oaqps/regusmog/infpart.html*). Similarly, no one would claim that reducing oxygen in air by a certain amount would be as healthful as reducing phosgene in air by the same amount.

Moreover, not all ambient $PM_{2.5}$ is the direct or indirect result of pollution, since $PM_{2.5}$ includes thousands of species of viruses and bacteria, various molds and pollen fragments (from thousands of species of flowering plants), fragments of countless species of insects, and bits of different types of sand and soil. Clearly, even restricting the discussion to "natural $PM_{2.5}$," small amounts of some forms, such as smallpox virus, can be deadly; other forms, entirely benign.

Pollution-derived $PM_{2.5}$ is also a complicated mixture. Standard characterizations of ambient $PM_{2.5}$ consist principally of five or six classes of compounds: sulfates, nitrates, organic compounds, elemental carbon, crustal material (or minerals), and "other" (U.S. EPA, 1996). Such characterizations are, however, far too crude to signify much toxicologically. Obviously, members of the "organic compounds" class of $PM_{2.5}$ are quite diverse in their structures and expected toxicities. Even members of a category as seemingly simple as the first, sulfates, differ in important features. For example, most ambient sulfates (such as ammonium sulfate and sodium sulfate) are water-soluble, but a few (such as calcium sulfate) are not. The solubility or insolubility of aerosols and particles is expected to be a central determinant of toxicity, as it is for airborne fibers (McConnell, 2000). Remarkably, the $PM_{2.5}$ NAAQS makes no distinction between insoluble and soluble forms. Solubility aside, sulfate salts range widely in their effects on respiratory function and structure (reviewed in Amdur, 1986). Because of these differences, Amdur (1986) has noted, "an air quality standard based on 'suspended sulfate' without further characterization would be entirely inappropriate; the term is toxicologically meaningless."

Nonetheless, reduction of sulfates and nitrates in ambient air is likely to be a key strategy employed by regulators and others in attempting to comply with the $PM_{2.5}$ NAAQS. This is because together (as ammonium sulfate and ammonium nitrate) they make up some 40–50% of the mass of $PM_{2.5}$ in metropolitan areas (Van Loy *et al.*, 2000; NYSDEC, 2002), and because both derive almost entirely from the gas-to-aerosol conversion of gases that have been well characterized and that originate from a well-defined set of controllable sources—utility and industrial coal combustion for sulfates, and utility, industrial, and motor vehicle fuel combustion for nitrates (U.S. EPA, 1996). But toxicologically, we know of no evidence or reason to believe that reducing current airborne concentrations of simple sulfate and nitrate-based PM will decrease rates of death. If these forms at these levels are indeed harmless, then reducing the precursor gases in hopes of reducing human mortality from PM is senseless.[4]

Leading laboratory-based researchers working on PM differ with regard to the specific hypotheses they are investigating, but none labors under the impression that all forms of $PM_{2.5}$ are alike. Oberdörster and colleagues, for example (1995; Oberdörster, 1996, 2001), are evaluating the properties of specific forms of insoluble "ultrafine" particles, such as various forms of elemental carbon-based $PM_{0.1}$. They suggest that insoluble particle number concentrations (e.g., 10^{10} particles/m^3) may be more important than mass concentrations, and that specific surface characteristics of insoluble particles likely influence toxicity. Researchers at U.S. EPA, such as Dye, Ghio, Devlin, and colleagues (Dye *et al.*, 2001; Ghio and Devlin, 2001), are focusing on specific transition metals (such as vanadium and zinc) solubilized from ambient PM influenced by poorly controlled steel mill emissions. Researchers from Cal Tech, such as Dr. Miguel, the late Dr. Cass, and their colleagues (Miguel *et al.*, 1999), have quantified various immunologically active fractions of paved road dust-derived fine PM. These fractions include allergens from various molds, trees, grasses, cat and dog dander epithelium, and rubber latex. Still others working

[4] We are not, of course, referring to decrements in visibility, which sufficient concentrations of airborne sulfates and nitrates are well known to cause. We also do not address acid precipitation.

with the late Dr. Cass, such as Hannigan and colleagues (1996), focus on PM rich in specific sets of organic chemicals, such as polycyclic aromatic hydrocarbons (PAHs) and various mutagens.

In contrast, so far as we know, no experimenter is currently testing whether ambient or moderately elevated concentrations of relatively nonacidic, soluble sulfates or nitrates in particular harm health (even though these chemicals make up sizable mass fractions of ambient PM). This is because such hypotheses have been repeatedly tested, using both human volunteers and laboratory animals, and these constituents have been found to have little effect (see, for example, Avol *et al.*, 1979; Utell *et al.*, 1983; Aris *et al.*, 1991; reviewed in U.S. EPA, 1996). Some of these studies have provided data on the pulmonary responses of both normal human subjects and asthmatics to airborne PM. These chamber studies involved volunteers exposed to controlled concentrations of various types of airborne PM, such as carbon particles and sulfate aerosols. Some of the test protocols have included exercise, so as to increase rates of lung ventilation and increase effective dose. All of the chamber studies have been carried out at considerably greater-than-ambient concentrations of particulate. Overall, as might be expected, asthmatics have been found to be more sensitive to high levels of highly acidic aerosols than normal subjects, but neither asthmatics nor normal subjects have exhibited decrements in pulmonary function following exposure either to nonacidic or to only somewhat acidic airborne PM, or to moderate, though still much higher than ambient levels of strongly acidic PM.

Consider the experimental data generated in a double-blind, randomized study by Utell and colleagues (1983). These investigators exposed 17 asthmatic volunteers to 100, 450, or 1000 $\mu g/m^3$ sodium chloride, sulfuric acid aerosols, and three sulfate salt aerosols of differing acidities. Neutral and mildly acidic aerosols had no effect on airway responsiveness. Even at the highest level of exposure, aerosols of salt caused no significant change in lung function. The highly acidic aerosols, both sulfuric acid itself and the acidic salt, NH_4HSO_4, did provoke airway responses, and did so in a dose-dependent fashion. Thus, at 1000 $\mu g/m^3$, sulfuric acid aerosol and NH_4HSO_4 aerosol strongly affected airway conductance and flow rates; intermediate responses were seen at 450 $\mu g/m^3$; and no significant responses were seen at 100 $\mu g/m^3$. Thus, even though strongly acidic sulfates do induce bronchoconstriction, they do not appear to do so, even in asthmatics, at levels as low as 100 $\mu g/m^3$. Ambient air levels of sulfuric acid aerosol, in contrast, are typically below 5 $\mu g/m^3$ (Lioy and Waldman, 1989).

Results from studies in laboratory animals are similar. These studies enjoy advantages over human experiments, including that: (i) multiple animal species can be studied, and the most sensitive species identified; (ii) elevated concentrations not possible with human volunteers can be used; (iii) chronic, indeed lifetime, exposure is possible; (iv) young, aged, and diseased animals can be tested; and (v) comprehensive pathologic follow-up is possible.

Various species of laboratory animals have been exposed to various types of PM at levels manyfold greater than ambient air PM levels, with little in the way of adverse effects on lung tissues or function. Nitrates and sulfates in particular fail to alter pulmonary function at airborne levels smaller than about 4000 and 1000 $\mu g/m^3$, respectively (U.S. EPA, 1996). Experiments using other sorts of PM indicate that continuous lifetime exposure of laboratory rats, the most sensitive species for these studies, to concentrations of 100–200 $\mu g/m^3$ must be exceeded before potentially adverse changes appear (U.S. EPA, 1996; Stöber *et al.*, 1998).

The nontoxicity of even high-level concentrations of airborne sulfate is also suggested by its widespread use in medicine. Many bronchodilators used to treat asthma, such as albuterol, metaproterenol, and terbutaline, are supplied as the sulfate salts (*Physicians' Desk Reference*: Arky and Davidson, 1998). One puff from a standard inhaler containing albuterol sulfate, for example, supplies an asthmatic with some 20 μg of sulfate, delivered at a concentration of some 10,000 μg of sulfate per cubic meter of inspired air (assuming 2 liters of air per deep inspiration). Medicinal chemists, clinicians, and others do not believe this to cause harm, let alone to hasten death.

We noted above that some of the observational epidemiologic studies relate ambient sulfate to rates of lung cancer. Is there experimental evidence on this point? As far as we know, cancer bioassays of inhaled sulfate have not been performed, but chronic bioassays of ingested sulfate salts are numerous. Such tests have been performed using aluminum potassium sulfate, beryllium sulfate, sodium sulfate, vanadyl sulfate, and zirconium(IV) sulfate: none has indicated that sulfates are carcinogenic, even when administered at high doses for most of a lifetime (Gold and Zeiger, 1997).

Respiratory diseases and death, however important, are less prevalent than cardiovascular morbidity and mortality. Overall, deaths from heart disease rank first among all causes of death in the United States, occurring at a sixfold higher rate than deaths from chronic obstructive pulmonary disease, for example (*http://www.cdc.gov/nchs/fastats/lcod.htm*). Since some observational studies have linked ambient PM with cardiovascular death rates in populations, toxicologists have begun to investigate whether PM can be shown, in laboratory animals, to induce hematologic, cardiac, or other alterations potentially indicative of cardiovascular disease risk.

Gordon and colleagues (2000) studied the responses of compromised laboratory rodents—both monocrotaline-sensitized rats and of hamsters with genetic cardiomyopathy—to inhalation of concentrated ambient particles (CAP). Despite exposures to CAP of up to 900 $\mu g/m^3$, and despite using rodents with compromised cardiopulmonary function, cardiac and pulmonary changes due to CAP exposure could not be demonstrated at all in hamsters, and were only slightly, inconsistently, and transiently observed in rats. In other sets of experiments, Godleski *et al.* (2000) exposed normal and compromised (with experimental coronary occlusions) laboratory dogs to CAP on the order of 100–1000 $\mu g/m^3$. Relative to sham exposures, the CAP exposures induced electrocardiogram changes, notably in the compromised dogs, but changes induced in the normal dogs, at least, did not correlate with the concentrations of CAP to which they were exposed. Overall, laboratory results to date "do not resolve the biological plausibility of adverse health effects associated with ambient PM in epidemiologic studies" (Gordon *et al.*, 2000).

EPIDEMIOLOGIC CONCERNS

If typical concentrations and forms of ambient PM are harmless, why do the vast majority of relevant observational epidemiologic studies find weak, but positive, associations between ambient PM and death? Consider the problems for causal interpretation when exposures to fine particulate matter have been consistently measured at the community level, rather than at the individual level. First, consider two analogous situations in which community-level variables had been associated with all-cause mortality rates, but such associations have dissolved when individual level data became available. Both are examples of the ecologic fallacy, and should give pause to those who would characterize the relationship between PM and mortality as causal on the basis of the existing literature.

The first example concerns the relationship between socioeconomic status and all-cause mortality. Low socioeconomic status has long been associated with increased rates of mortality (Kitagawa and Hauser, 1973; Feinstein, 1993). More recently, not only a person's own socioeconomic status, but characteristics of the social environment have been correlated with all-cause mortality rates. Social environment, measured per force at the level of the community, has been associated with increased rates of all-cause mortality, even after adjusting for individual income level, education, race/ethnicity, perceived health status, smoking status, body mass index, and alcohol consumption (Yen and Kaplan, 2000). Disparities in the distribution of wealth within a community have also been observed to affect mortality rates (Ross *et al.*, 2000; Brodish *et al.*, 2000). In a recent review, Wagstaff and van Doorslaer (2000) examined various hypotheses to explain the association between measures of income inequality and population health. They concluded: (a) data from aggregate-level studies are largely insufficient to discriminate between competing hypotheses; (b) only individual-level studies have the potential to discriminate between most of the hypotheses; and (c) the individual-level studies provide strong support for the "absolute income hypothesis," no support for the "relative income hypothesis," and little or no support for the "income inequality hypothesis." Thus, examination of the association measured at the level of the individual, rather than at the level of the community, contradicts the ecologic literature associating all-cause mortality rates with disparities in wealth distribution.

The second example concerns a longstanding paradox in the health services literature, which is the consistently observed correlation between physicians per capita and all-cause mortality rates (Young and Lyson, 2001). In a more holistic analysis (Young, 2001) that included urban expansion and migration patterns, as well as physicians per capita, the original correlations between physicians per capita and mortality rates dissolved in two of the three data sets. The author concluded that the "conceptual and empirical analysis exposed the positive correlation [between physicians per capita and all cause mortality] as spurious."

How might these examples inform interpretations of the association between the concentration of ambient fine particulate matter and all-cause mortality rates? In at least two ways, we suggest.

First, the examples suggest that any ecologically measured variable that correlates with wealth should be expected to correlate also with all-cause mortality rates. Is the concentration of fine particulate matter such a variable? The data suggest that it is. Most convincing is the observed interaction between concentration of fine particulate matter and education reported in the HEI Re-analysis (Krewski *et al.*, 2000) of the Six Cities study (Dockery *et al.*, 1993) and the ACS study (Pope *et al.*, 1995). Summary Table 3 of the Re-analysis shows that the associations between concentration of fine particulate matter and all-cause or disease-specific mortality rates are consistently highest in those with less than a high school education, intermediate among those with a high school education, and null or even protective among those with more than a high school education.

Is there any biologic basis for this consistent observation? Perhaps, but we suggest instead that the interaction between education and PM lends support to the hypothesis that ambient PM concentration is a crude measure of disparities in socioeconomic status. That is, when examined within strata of an individual-level measure of socioeconomic status (education), the correlation persists only among the poor (who tend to be the less educated), which is the observation expected

if the fine particulate matter is just a marker for socioeconomic status, now observed only within strata of a better measure of socioeconomic status. Exactly this pattern has been observed for the comparison of wealth distributions (wide disparity versus narrow disparity), for which an effect on all-cause mortality rates "affects mainly the health of the poor" after controlling for individual-level variables (Wagstaff and van Doorslaer, 2000).

Second, the correlations between ecologic measures of socioeconomic status and physicians per capita with all-cause mortality rates in the particulate studies are opposite to the well-established ecologic correlations provided by the examples. Summary Table 5 of the HEI Re-analysis shows the relative risk of all-cause mortality in the sulfate cohort associated with ecologic covariates used in the sensitivity analysis of the ACS study. Population change (RR = 0.85), income (RR = 0.93), poverty (RR = 0.95), income disparity (RR = 0.88), education (RR = 0.91), and physicians per capita (RR = 0.95) all showed effects opposite those consistently observed in the abundant literature that is the basis for the two examples. How well can the ecologic correlation between concentrations of fine particulate and all-cause mortality be trusted when this data set cannot replicate established ecologic associations?

The primary cross-sectional study of interest here (the ACS study by Pope *et al.*, 1995; reanalyzed in Krewski *et al.*, 2000) suffers from another crucial problem. The problem is termed "spatial autocorrelation," and its demonstrable presence within the data from the ACS study cannot be overlooked. A fundamental assumption of the Cox proportional hazards models used to analyze the data is that the response of interest (here, a monotonic transform of mortality hazard) has a normal error distribution around the value predicted by the model. The residuals should not deviate systematically from a normal distribution. If there is a discernible pattern in the residuals, then the model is likely misspecified, with the possibilities of biases and incorrect estimates of random error. Such patterns are relatively common in cases where (as here) the exposure cannot be assigned randomly. A secondary assumption of the modeling is that the effects of such model misspecification are small. However, when model misspecification is identified, this secondary assumption should be examined to the extent possible.

In the study by Pope *et al.* (1995), there is indeed a discernible pattern in the residuals: all the residuals that come from spatially close observations tend to be more similar than would be expected by chance. It follows that a fundamental assumption of the core models relied on by EPA and others is demonstrably incorrect, and the possibilities for bias and misestimation of uncertainty should be examined. This problem of spatial correlations was described and evaluated to some extent in the HEI Re-analysis by Krewski and co-workers (2000), and reemphasized in a more recent analysis of sulfates by Burnett *et al.* (2001). Those evaluations show that:

a. The modeling assumptions about independence of observations used to obtain the mortality/$PM_{2.5}$ coefficients relied on by U.S. EPA are incorrect.

b. Failure to account for the incorrect assumptions results in estimates that are substantially biased.

c. The confidence intervals reported originally (both by Pope *et al.*, 1995, and Krewski *et al.*, 2000) are substantially too small.

The secondary assumption of the modeling, that the model misspecification has only a small effect on the results, is thus incorrect.

The spatial correlation problem cannot yet be resolved. Something is quite clearly lacking from the regression models, not to mention, more fundamentally, from the available data on which the models are based. Most models oversimplify, and because these observational models in particular are heuristic at best, there should be no surprise in their failure to include all relevant inputs. All the relevant inputs simply are not known. It should be emphasized that these conclusions can be reached even using evidence internal to the studies themselves. Additional biases may exist that are not detectable at all using the original study data.

The experience of other sciences with "statistical significance" estimates should also be borne in mind. Even in measurement of physical quantities (such as the speed of light), where all measurements are of well-defined quantities, the measurements are of high precision, all variables are under the experimenters' control, and there are extensive attempts to account for systematic error, it is invariably and demonstrably true that "statistical" uncertainty estimates substantially underestimate the errors.

Even well-controlled, observational studies may be confounded by overlooked, unmeasured variables. For example, a major epidemiologic study in Utah County by Pope (1989) indicated that ambient air PM_{10} from steel-making was associated with pediatric respiratory hospitalizations. Ambient PM in that county had a major stationary source, a steel mill, which operated in the early 1980s, then closed for 12 months in 1986–1987, then reopened. This open–closed–open cycle resulted in markedly lower levels of the county's ambient PM in the winter of 1986–1987 than in the winters immediately before and after. Pope (1989) found that children's rates of hospitalizations for respiratory problems were lower in the winter when the mill was closed, relative to the winters when the mill was open. The statistical correlations were clear and apparently unconfounded by other air pollutants and other factors measured. But what Pope (1989) did not measure was respiratory syncytial virus (RSV), and that virus has a major, directly biologic causative influence on the data. The prevalence of RSV

peaks each winter, but some winter peaks are smaller than others (Wright and Bieluch, 1993). As it happened, RSV activity was low in Utah County during the same winter when the mill was closed and PM levels were low. Lamm and colleagues (1994), trained in pediatrics and pathophysiology, uncovered this potentially confounding, viral cause for the observed variations in pediatric hospitalization rates. They concluded that the "statistical association between PM_{10} levels and respiratory hospitalizations of children that was estimated in the previous study [Pope, 1989] is actually a spurious correlation caused by the omission of an important covarying explanatory factor." Pope (1996) and others (Dye *et al.*, 2001) discount RSV, and believe that ambient PM in Utah County in the 1980s was a major determinant of morbidity. Of course, it might also have been the case that both RSV and metal-enriched PM played a role in respiratory disease noted in Utah County during this time. Perhaps, for example, steel mill-derived pollution increased children's susceptibilities to RSV infection.

OBSERVATIONAL STUDIES ON AMBIENT PM AND DAILY RATES OF MORTALITY

As noted above, daily, time-series studies (such as by Samet *et al.*, 2000; Schwartz, 1991) associate rates of deaths with small changes in ambient PM levels. Though such studies have certain methodologic advantages relative to the between-cities analyses, they have their own disadvantages too, including inability to have measured or controlled for various well-known, fluctuating triggers of myocardial infarctions and other important causes of death. The case-crossover design is ideally suited to measure the transient effects of an exposure, such as fine particle concentration, on an acute outcome, such as sudden cardiac arrest. It compares the concentration of PM to which a person was presumed to have been exposed at the time of his or her cardiac arrest to the concentration to which he or she was presumably exposed in a preceding time interval. Because the cases essentially act as their own controls, all confounders are controlled at an individual, rather than ecologic, level. In addition, although concentrations of pollutants are measured at central monitoring stations, the concentration comparisons are all within a city rather than across cities. Consider the following three case-crossover studies.

The first, Levy *et al.* (2001), tested the hypothesis that risk of cardiac arrest is a function of ambient pollution, measured several ways. The subjects were 362 cases of cardiac arrest in Seattle, between the years 1988 and 1994. The ambient data included measurements of $PM_{2.5}$, PM_{10}, SO_2, CO, O_3, and temperature. The results were weakly nonpositive; that is, central tendency estimates suggested that as ambient concentrations of PM increased, relative risk of cardiac arrest decreased. Several models and lag times were evaluated, with a typical result that for an increase of 19.3 μg PM_{10}/m^3, the relative risk of cardiac arrest was 0.87 (95% CI = 0.74–1.0).

A similar, case-crossover study was conducted by Peters *et al.* (2001), testing whether risk of myocardial infarction is associated with ambient PM. The subjects were 772 cases of myocardial infarction in Boston from 1995 to 1996. Air pollution data included measurements of $PM_{2.5}$, carbon black, SO_2, CO, and O_3. The results were weakly positive for PM. In particular, for an increase of 25 μg $PM_{2.5}/m^3$ 2 h prior, the relative risk of myocardial infraction was 1.5 (95% CI = 1.1–2.0); for an increase of 20 μg $PM_{2.5}/m^3$ 24 h prior, the relative risk of myocardial infarction was 1.7 (95% CI = 1.1–2.3).

Unfortunately, neither of these studies, however well designed, is particularly informative. That is because other, nonpollutant triggers of myocardial infarction were neither measured nor considered, and some of these might well covary with ambient PM. Transiently increased levels of PM in outdoor air are caused in part by an increase in activities, such as driving of cars and trucks and increased production at factories and other sources. Some of these activities likely correlate with physical and emotional stresses of various kinds, such as anger, which are themselves strongly associated with increased risk of heart attacks and other causes of death (Mittleman *et al.*, 1995; Willich *et al.*, 1993). In this regard, consider a third, case-crossover study.

Möller *et al.* (1999) hypothesized that the triggering of myocardial infarction is a function of anger. Their subjects were 699 cases of myocardial infarction in Stockholm, Sweden, from 1993 to 1994. Data on "hostile behavior" and physical symptoms in the days and hours prior to myocardial infarction were gathered through detailed, structured interviews, performed by nurses who were blind to the hypothesis. The results were strongly positive. In particular, during 1 h after an episode of anger, the relative risk of myocardial infarction was 15.7 (95% CI = 7.6–32.4). Clearly, if the daily and/or hourly fluctuations in traffic and other activities that increase ambient PM also increase anger, even slightly, the latter could confound associations between the former and myocardial infarction.

DISCUSSION AND CONCLUSIONS

Associations between various measures of air pollution in metropolitan areas and rates of morbidity and mortality in populations in those areas have been reported for decades (Stocks, 1959; Lave and Seskin, 1970, 1979; Wilson *et al.*, 1980; Pope *et al.*, 1995). Without question, sufficiently high levels of ambient air pollution cause morbidity and mortality. High levels of air pollution experienced in the Meuse Valley in 1930, in Donora in 1948, and in London in 1952 clearly caused disease and hastened death. But these smogs

were formed under unusual meteorologic conditions, and presented as complex mixtures of PM, SO_2, acid aerosols, and many less well characterized industrial pollutants (such as from a local zinc works in Donora), so that the specific causal roles of the individual air pollutants could not be discerned.

The central questions at issue now involve whether current, low-level, ambient concentrations of $PM_{2.5}$ per se are fatal. If so, such harm must be due to some specific fractions of $PM_{2.5}$, since the thousands of forms of $PM_{2.5}$ differ in myriad relevant ways. At present, no one knows what forms of ambient $PM_{2.5}$, if any, are fatal, so no one can know what forms should be reduced, let alone to what level.

If reducing ambient concentrations of PM could do no harm, few would care whether the scientific bases for reductions were clearly established. However, many of the sources of PM themselves confer public health benefits, such as home heating, refrigeration, and air conditioning. Changes meant to alleviate PM-associated risks will themselves pose different risks to public health.

Some might argue that it matters little whether we know what aspects of ambient $PM_{2.5}$, if any, affect mortality in many observational, population-based studies. Surely, they would argue, since ambient $PM_{2.5}$ generally correlates with rates of mortality, reducing any or all types of $PM_{2.5}$ must save lives.

This is incorrect, for at least two reasons. The first is that many methods of PM control serve to reduce mass concentrations of fine PM in ambient air but do not reduce, and sometimes increase, concentrations of ultrafine PM in air (Pitz *et al.*, 2001). To the extent that insoluble ultrafine PM may be hazardous (Oberdörster, 2001), such actions could hardly be considered to be health-protective. Similarly, if sulfate in ambient air is benign, but vanadium-enriched ultrafine PM in air is not, what good would reducing the former do, especially if it comes at the expense of increasing the latter?

The second reason is that if the PM–mortality association is confounded by factors that can vary with PM, but form no part of PM, then reducing ambient concentrations of PM without reducing the confounding causes will do no good. Some of these confounding causes may be other forms of pollution, measured and unmeasured, that covary with ambient PM. Other confounding causes may be nonpollutants, such as stress, anger, noise (Razdan and Sidhu, 2000), and other modifiers of morbidity and mortality. Surely we would do better by reducing confounding causes than by reducing things that merely correlate with those causes.

In the meantime, what should we do, both in regulation and in research? First, U.S. EPA might do well to follow the lead of the Dutch National Institute of Public Health and the Environment (RIVM in Bilthoven), an agency that recognizes the apparent, important differences among various forms of ambient PM. In particular, the Netherlands Aerosol Program (NAP, 2001) writes:

> More than one third of the PM_{10} in The Netherlands seems to be toxicologically inert at the current concentrations: water, sea salt, ammonium sulphate, ammonium nitrate and probably the non-crystalline crustal material too . . .. Decreasing the levels of inert components will not reduce the health risk of the population.

Though recognizing the need for ambient PM regulation, the Dutch also note (NAP, 2001):

> The causal factor for the PM associated health effects is still unknown. PM_{10}, $PM_{2.5}$ and other PM metrics as Black Smoke or a foreign metric as Coefficient of Haze all seem to be a proxy for the causal factor(s). Currently not one of the PM metrics seems to be significantly better at predicting health effects than any of the others. During this situation of uncertainty therefore one standard would suffice.

In this view, then, there is little rational basis for crafting a $PM_{2.5}$ standard separate from a PM_{10} standard, and there is no basis for regulating the apparently nontoxic portions of inhalable PM.

Even were one convinced of the current need for some form of a $PM_{2.5}$ standard, over and above a PM_{10} standard, one must recognize the arbitrariness of the limits set by U.S. EPA. There is little, genuine, data-based or risk-based justification for the specific values chosen by the Agency: one might as easily have set a $PM_{2.5}$ annual standard set at either 10 or 20 $\mu g/m^3$, rather than the 15 $\mu g/m^3$ chosen. Given the very large ratios of costs to likely benefits, we would favor the more lenient standard, compliance with which could still generate useful information about air quality (especially from the "Supersites" ambient monitoring research program and related efforts), and so allow the scientific community to zero in on actual, PM-associated causes (as opposed to markers) of disease and death. Generating useful, detailed information to characterize ambient $PM_{2.5}$ (and, perhaps, ambient $PM_{0.1}$) and its effects seems worthwhile; but attempting to reduce health risk and attain compliance by stringently regulating all forms of $PM_{2.5}$ as if they were equivalent does not.

Regardless of the specific values set at the federal level for the NAAQS, it is the individual states, in designing and implementing state implementation plans (SIPs), that decide in detail how to comply. Perhaps some of these state-based regulators will recognize the distinctions among the types and precursors of ambient PM, and so fashion their SIPs to reduce the potentially toxic, as opposed to apparently inert, particulate-associated pollutants. In other words, rather than working to further reduce ambient sulfates and nitrates, state regulators might focus on controlling emission sources of ambient PM composed of organic compounds and/or elemental carbon (which together account for some 40% of the mass of $PM_{2.5}$ in urban areas (Van Loy *et al.*, 2000; NYSDEC, 2002)).

As matters of epidemiologic and toxicologic research, at least two broad approaches seem worthwhile. First, epidemiologists should focus on case-crossover studies, rather than cross-sectional studies, since the latter type cannot adequately control for confounding by many personal and geographically associated causes of disease and death. Observational studies being conducted as part of The Aerosol Research and Inhalation Epidemiology Study (ARIES), for example, represent improvements over existing studies (Ron Wyzga, personal communication, 2002; Van Loy *et al.*, 2000; Klemm and Mason, 2000). As importantly, environmental epidemiologists need to collaborate with chronic disease epidemiologists, so that data on air pollution, mood, stress, physical activity, and other risk factors might be simultaneously gathered and evaluated when analyzing daily rates of death or incidents of myocardial infarction.

Since hypotheses regarding air pollution and chronic disease cannot be tested fully epidemiologically, toxicologic studies involving chronic exposures to laboratory animals must play a central role. Hypothesized links between cardiovascular disease and inhaled particulate matter may be especially important to study using animal models, though such models must be developed and chosen with care (Muggenburg *et al.*, 2000).

The results of better epidemiologic and toxicologic research might well suggest very different forms of regulation of ambient air quality. Regulations such as U.S. EPA's $PM_{2.5}$ NAAQS, based on insufficient knowledge, are especially susceptible to the law of unintended consequences. Airbags designed to save adult lives kill infants. Gasoline reformulated with MtBE to clean up air fouls groundwater. DDT used to prevent millions of cases of malaria thins the shells of eagle eggs. Everyone can think of examples in which technologic "fixes" of one problem have created other, unintended problems. It is not reactionary or unprogressive to call, as we do, for better, more focused research in the area of ambient PM and health effects. We suggest that the reality, the magnitude, and many other details of low-level PM-associated risks must be known with considerably more certainty, lest we end up doing more harm than good.

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REFERENCES

Abt Associates Inc. (2000). *The Particulate-Related Health Benefits of Reducing Power Plant Emissions*. Prepared for the Clean Air Task Force, Boston, MA.

Amdur, M. O. (1986). Air pollutants. In *Casarett and Doull's Toxicology*, 3rd ed. Macmillan, New York.

Aris, R., Christian, D., Sheppard, D., and Balmes, J. R. (1991). Lack of bronchoconstrictor response to sulfuric acid aerosols and fogs. *Am. Rev. Respir. Dis.* **143,** 744–750.

Arky, R., and Davidson, S. C. (1998). *Physicians' Desk Reference*, 52nd ed. Medical Economics, Montvale, NJ.

Avol, E. L., Jones, M. P., Bailey, R. M., Chang, N. M., Kleinman, M. T., Linn, W. S., Bell, K. A., and Hackney, J. D. (1979). Controlled exposures of human volunteers to sulfate aerosols: Health effects and aerosol characterization. *Am. Rev. Respir Dis.* **120,** 319–327.

Avol, E. L., Linn, W. S., Whynot, J. D., Anderson, K. R., Shamoo, D. A., Valencia, L. M., Little, D. E., and Hackney, J. D. (1988). Respiratory dose–response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. *Toxicol. Ind. Health* **4,** 173–184.

Avol, E. L., Linn, W. S., Shamoo, D. A., Anderson, K. R., Peng, R. C., and Hackney, J. D. (1990). Respiratory responses of young asthmatic volunteers in controlled exposures to sulfuric acid aerosol. *Am. Rev. Respir Dis.* **142,** 343–348.

Brodish, P. H., Massing, M., and Tyroler, H. A. (2000). Income inequality and all-cause mortality in the 100 counties of North Carolina. *South. Med. J.* **93,** 386–391.

Burnett, R., M., R., Jerrett, M., Goldberg, M.S., Cakmak, S., Pope, C.A., III, and Krewski, D. (2001). The spatial association between community air pollution and mortality: A new method of analyzing correlated geographic cohort data. *Environ. Health Perspect.* **109**(Suppl. 3), 375–380.

Dockery, D. W., Pope, C. A., III, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., Ferris, B. G., Jr., and Speizer, F. E. (1993). An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* **329,** 1753–1759.

Dye, J. A., Lehmann, J. R., McGee, J. K., Winsett, D. W., Ledbetter, A. D., Everitt, J. I., Ghio, A. J., and Costa, D. L. (2001). Acute pulmonary poxicity of particulate matter filter extracts in rats: Coherence with epidemiologic studies in Utah Valley Residents. *EHP Suppl.* **109,** 395–404.

Fang, J., Madhavan, S., Bosworth, W., and Alderman, M. H. (1998). Residential segregation and mortality in New York City. *Social Sci. Med.* **47,** 469–476.

Feinstein, J. S. (1993). The relationship between socioeconomic status and health: A review of the literature. *Milbank Q.* **71,** 279–321.

Feng, D. L., and Tofler, G. H. (1995). Diurnal physiologic processes and circadian variation of acute myocardial infarction. *J. Cardiovasc. Risk* **2,** 494–498.

Fitz-Simons, T. S., Mathias, M., and Rizzo, M. (2000). *Analyses of 1999 PM Data for the PM NAAQS Review*. Office of Air Quality Planning and Standards, U.S. EPA, Washington, DC; see also http://www.epa.gov/oar/oaqps/pm25/analyses.html.

Frank, R., and Tankersley, C. (2002). Air pollution and daily mortality: A hypothesis concerning the role of impaired homeostasis. *Environ. Health Perspect.* **110,** 61–65.

Freeman, A. M., III (2001). *An Analysis of the Pataki Power Plant Proposal vs. Full Environmental Comparability Using the New York Externalities Cost Model*. Bowdoin College, Brunswick, ME.

Gamble, J. F. (1998). $PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause–effect or statistical associations? *Environ. Health Perspect.* **106,** 535–549.

Gamble, J. (1999). Reply to Kunzli and Tager regarding causality in $PM_{2.5}$ cohort studies. *Environ. Health Perspect.* **107,** A393–A394.

Ghio, A. J., and Devlin, R. B. (2001). Inflammatory lung injury after bronchial instillation of air pollution particles. *Am. J. Respir. Crit. Care Med.* **164,** 704–708.

Godleski, J. J., Verrier, R. L., Koutrakis, P., Catalano, P., Coull, B., Reinisch, U., Lovett, E. G., Lawrence, J., Murthy, G. G., Wolfson,

J. M., Clarke, R. W., Nearing, B. D., and Killingsworth, C. (2000). Mechanisms of morbidity and mortality from exposure to ambient air particles. *Res. Rep. Health Eff. Inst.* **91,** 5–88.

Gold, L. S., and Zeiger, E. (Eds.) (1997). *Handbook of Carcinogenic Potency and Genotoxicity Databases*. CRC Press, Boca Raton, FL.

Gordon, T., Nadziejko, C., Chen, L. C., and Schlesinger, R. (2000). *Effects of Concentrated Ambient Particles in Rats and Hamsters: An Exploratory Study*. HEI Research Report No. 93.

Greenbaum, D. S., Bachmann, J. D., Krewski, D., Samet, J. M., White, R., and Wyzga, R. E. (2001). Particulate air pollution standards and morbidity and mortality: case study. *Am. J. Epidemiol.* **154,** S78–S90.

Hajat, S., Haines, A., Atkinson, R. W., Bremner, S. A., Anderson, H. R., and Emberlin, J. (2001). Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. *Am. J. Epidemiol.* **153,** 704–714.

Hannigan, M. P., Cass, G. R., Lafleur, A. L., Busby, W. F., Jr., and Thilly, W. G. (1996). Seasonal and spatial variation of the bacterial mutagenicity of fine organic aerosol in Southern California. *Environ. Health Perspect.* **104,** 428–436.

Kitagawa, E. M., and Hauser, P. M. (1973). *Differential Mortality in the United States*. Harvard Univ. Press, Cambridge, MA.

Klemm, R. J., and Mason, R. M., Jr. (2000). Aerosol Research and Inhalation Epidemiological Study (ARIES): Air quality and daily mortality statistical modeling–interim results. *J. Air Waste Manage. Assoc.* **50,** 1433–1439.

Koren, H. S. (1995). Associations between criteria air pollutants and asthma. *Environ. Health Perspect.* **103,** 235–242.

Krewski, D., Burnett, R. T., Goldberg, M. S., Hoover, K., Siemiatycki, J., Jerrett, M., Abrahamowicz, M., White, W. H., *et al.* (2000). *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality*. Health Effects Institute, Cambridge, MA.

Kulle, T. J., Kerr, H. D., Farrell, B. P., Sauder, L. R., and Bermel, M. S. (1982). Pulmonary function and bronchial reactivity in human subjects with exposure to ozone and respirable sulfuric acid aerosol. *Am. Rev. Respir. Dis.* **126,** 996–1000.

Kulle, T. J., Sauder, L. R., Hebel, J. R., Miller, W. R., Green, D. J., and Shanty, E. (1986). Pulmonary effects of sulfur dioxide and respirable carbon aerosol. *Environ. Res.* **41,** 239–250.

Kunzli, N., and Tager, I. B. (1999). Comments on "$PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause–effect or statistical associates?" *Environ. Health Perspect.* **107,** A392–A393.

Laden, F., Neas, L. M., Dockery, D. W., and Schwartz, J. (2000). Association of fine particulate matter for different sources with daily mortality in six U.S. cities. *Environ. Health Perspect.* **108,** 941–947.

Lamm, S. H., Hall, T. A., Engel, A., Rueter, F. H., and White, L. D. (1994). PM_{10} particulates: Are they the major determinant of pediatric respiratory admissions in Utah County, Utah? (1985–1989)? *Ann. Occup. Hyg.* **38,** 969–972.

Lave, L. B., and Seskin, E. P. (1970). Air pollution and human health. *Science* **169,** 723–733.

Lave, L. B., and Seskin, E. P. (1979). Epidemiology, causality, and public policy. *Am. Scientist* **67,** 178–186.

Levy, D., Sheppard, L., Checkoway, H., Kaufman, J., Lumley, T., Koenig, J., and Siscovick, D. (2001). A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* **12,** 193–199.

Levy, J. I., and Spengler, D. (2002). Modeling the benefit of power plant emission controls in Massachusetts. *J. Air Waste Manage. Assoc.* **52,** 5–18.

Lipfert, F. W., and Wyzga, R. E. (1995). Air pollution and mortality: Issues and uncertainties. *J. Air Waste Manage. Assoc.* **45,** 949–966.

Lipfert, F. W., Perry, H. M., Jr., Miller, J. P., Baty, J. D., Wyzga, R. E., and Carmody, S. E. (2000). The Washington University–EPRI Veteran's Cohort Mortality Study: Preliminary results. *Inhal. Toxicol.* **12,** 41–73.

Lioy, P. J., and Waldman, J. M. (1989). Acidic sulfate aerosols: Characterization and exposure. *Environ. Health Perspect.* **79,** 15–34.

Lippmann, M., and Schlesinger, R. B. (2000). Toxicological bases for the setting of health-related air pollution standards. *Annu. Rev. Pub. Health* **21,** 309–333.

McConnell, E. E. (2000). A science-based paradigm for the classification of synthetic vitreous fibers. *Regul. Toxicol. Pharmacol.* **32,** 14–21.

Menon, P. K., Stankus, R. P., Rando, R. J., Salvaggio, J. E., and Lehrer, S. B. (1991). Asthmatic responses to passive cigarette smoke: Persistence of reactivity and effects of medications. *J. Allergy Clin. Immunol.* **88,** 861–869.

Menon, P., Rando, R. J., Stankus, R. P., Salvaggio, J. E., and Lehrer, S. B. (1992). Passive cigarette smoke-challenge studies: Increase in bronchial hyperreactivity. *J. Allergy Clin. Immunol.* **89,** 560–566.

Miguel, A. G., Cass, G. R., Glovsky, M. M., and Weiss, J. (1999). Allergens in paved road dust and airborne particles. *Environ. Sci. Technol.* **33,** 4159–4168.

Mittleman, M. A. Maclure, M., Sherwood, J. B., Mulry, R. P., Tofler, G. H., Jacobs, S. C., Friedman, R., Benson, H., and Muller, J. E. (1995). Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. *Circulation* **92,** 1720–1725.

Möller, J., Hallqvist, J., Diderichsen, F., Theorell, T., Reuterwall, C., and Ahlbom, A. (1999). Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program (SHEEP). *Psychosom. Med.* **61,** 842–849.

Moolgavkar, S. H. (2000). Air pollution and daily mortality in three U.S. counties. *Environ. Health Perspect.* **108,** 777–784.

Moolgavkar, S. H., and Luebeck, E. G. (1996). A critical review of the evidence on particulate air pollution and mortality. *Epidemiology* **7,** 420–428.

Mudway, I. S., and Kelly, F. J. (2000). Ozone and the lung: A sensitive issue. *Mol. Aspects Med.* **21,** 1–48.

Muggenburg, B. A., Tilley, L., and Green, F. H. (2000). Animal models of cardiac disease: Potential usefulness for studying health effects of inhaled particles. *Inhal. Toxicol.* **12,** 901–925.

Netherlands Aerosol Program (NAP) (2001). *Discussion Document on Health Risks of Particulate Matter in Ambient Air*, final draft. RIVM, Bilthoven. N.Y. State Department of Environmental Conservation (NYSDEC). (2002). *Report to the Examiners on Consolidated Edison's East River Article X Project, Case No. 99-F-1314. Background on the Regulatory and Legal Framework of the Federal $PM_{2.5}$ Ambient Air Quality Standards and Associated Data Collection Efforts by DEC*. Exhibit B.

Oberdörster, G. (1996). Significance of particle parameters in the evaluation of exposure–dose–response relationships of inhaled particles. *Inhal. Toxicol.* **8** (Suppl.), 73–89.

Oberdörster, G. (2001). Pulmonary effects of inhaled ultrafine particles. *Int. Arch. Occup. Environ. Health* **74,** 1–8.

Oberdörster, G., Gelein, R. M., Ferin, J., and Weiss, B. (1995). Association of particulate air pollution and acute mortality: involvement of ultrafine particles? *Inhal. Toxicol.* **7,** 111–124.

Pepine, C. J. (1991). Circadian variations in myocardial ischemia: Implications for management. *JAMA* **265,** 386–390.

Peters, A., Dockery, D. W., Muller, J. E., and Mittleman, M. A. (2001). Increased particulate air pollution and the triggering of myocardial infarction. *Circulation* **103,** 2810–2815.

Phalen, R. F. (1998). Uncertainties relating to the health effects of particulate air pollution: The US EPA's particle standard. *Toxicol. Lett.* **96/97,** 263–267.

Phalen, R. F., and Bates, D. V. (1995). Proceedings of the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity. *Inhal. Toxicol.* **7**(1); Proceedings of the Colloquium on Particulate Air Pollution and Human Mortality and Morbidity, Part II. *Inhal. Toxicol.* **7**(5).

Phalen, R. F., and McClellan, R. O. (1995). PM-10 research needs. *Inhal. Toxicol.* **7,** 773–779.

Pitz, M., Kreyling, W., Holshcer, B., Cyrys, J., Wichmann, H. E., and Heinrich, J. (2001). Change of the ambient particle size distribution in East Germany between 1993 and 1999. *Atmos. Environ.* **35,** 4356–4366.

Pope, C. A., III (1989). Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am. J. Pub. Health* **79,** 623–628.

Pope, C. A., III (1996). Particulate pollution and health: A review of the Utah Valley experience. *J. Expo. Anal. Environ. Epidemiol.* **6,** 23–34.

Pope, C. A., III (2000). Epidemiology of fine particulate air pollution and human health: Biologic mechanisms and who's at risk? *Environ. Health Perspect.* **108,** 713–723.

Pope, C. A., Thun, M. J., Namboodiri, M. M., Dockery, D. W., Evans, J. S., Speizer, F. E., and Health, C. W. (1995). Particulate air pollution as a predictor of mortality in a prospective study of U.S. Adults. *Am. J. Respir. Crit. Care Med.* **151,** 669–674.

Razdan, U., and Sidhu, T. S. (2000). Need for research on health hazards due to noise pollution in metropolitan India. *J. Indian Med. Assoc.* **98,** 453–456, 460.

Robins, J. M. (2001). Data, design, and background knowledge in etiologic inference. *Epidemiology* **12,** 313–320.

Ross, N. A., Wolfson, M. C., Dunn, J. R., Berthelot, J., Kaplan, G. A., and Lynch, J. W. (2000). Relation between income inequality and mortality in Canada and in the United States: Cross sectional assessment using census data and vital statistics. *Br. Med. J.* **320,** 898–902.

Samet, J. M., Dominici, F., Curriero, F. C., Coursac, I., and Zeger. S. L. (2000). Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N. Engl. J. Med.* **343,** 1742–1749.

Schwartz, J. (1991). Particulate air pollution and daily mortality in Detroit. *Environ. Res.* **56,** 204–213.

Stocks, P. (1959). Cancer and bronchitis mortality in relation to atmospheric deposit and smoke. *Br. Med. J.* **1,** 74–84.

Stöber, W., Miller, F. J., and McClellan, R. O. (1998). Requirements for a credible extrapolation model derived from health effects in rats exposed to particulate air pollution: A way to minimize the risks of human risk assessment? *Appl. Occup. Environ. Hyg.* **13,** 421–431.

U.S. Environmental Protection Agency (U.S. EPA) (1996). *Air Quality Criteria for Particulate Matter*, Vols. I, II, and III. EPA/600/P-95/001af. Office of Research and Development, Washington, DC; http://www.epa.gov/ncea/archive/pdfs/partmatt/voll/0671v1fm.pdf.

U.S. Environmental Protection Agency (U.S. EPA). (1997). National ambient air quality standards for particulate matter, Final Rule. *Fed. Regist.* **62,** 38676.

U.S. Environmental Protection Agency (U.S. EPA). (2001). *Air Quality Criteria for Particulate Matter. Second External Review Draft*, EPA 600/P-99/002aB Office of Research and Development, Washington, DC.

Utell, M. J. (1995). Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. *Environ. Res.* **69,** 1–14.

Utell, M. J., Morrow, P. E., Speers, D. M., Darling, J., and Hyde, R. W. (1983). Airway responses to sulfate and sulfuric acid aerosols in asthmatics. An exposure–response relationship. *Am. Rev. Respir. Dis.* **128,** 444–450.

Utell, M. J., Frampton, M. W., Morrow, P. E., Cox, C., Levy, P. C., Speers, D. M., and Gibb, F. R. (1994). Oxidant and acid aerosol exposure in healthy subjects and subjects with asthma. Part II: Effects of sequential sulfuric acid and ozone exposures on the pulmonary function of healthy subjects and subjects with asthma. *Res. Rep. Health Eff. Inst.* **70,** 37–93.

Valberg, P.A., and Watson, A. Y. (1998). Alternative hypotheses for PM associations with daily mortality and morbidity. *Inhal. Toxicol.* **10,** 641–662.

Van Loy, M., Bahadori, T., Wyzga, R., Hartsell, B., and Edgerton, E. (2000). The Aerosol Research and Inhalation Epidemiology Study (ARIES): $PM_{2.5}$ mass and aerosol component concentrations and sampler intercomparisons. *J. Air Waste Manage. Assoc.* **50,** 1446–1458.

Wagstaff, A., and van Doorslaer, E. (2000). Income inequality and health: What does the literature tell us? *Annu. Rev. Pub. Health* **21,** 543–567.

Ware, J. H. (2000). Particulate air pollution and mortality: Clearing the air. *N. Engl. J. Med.* **343,** 1798–1799.

Willich, S. N., Lewis, M., Lowel, H., *et al.* (1993). Physical exertion as a trigger of acute myocardial infarction: Triggers and mechanisms of myocardial infarction study group. *N. Engl. J Med.* **329,** 1684–1690.

Wilson, R., Colome, S. D., Spengler, J. D., and Wilson, D. G. (1980). *Health Effects of Fossil Fuel Burning*. Ballinger, Cambridge, MA. See particularly Chapter 6, pp. 191–221.

Wright, S. A., and Bieluch, V. M. (1993). Selected nosocomial viral infections. *Heart Lung* **22,** 183–187.

Yen, I. H., and Kaplan, G. A. (2000). Neighborhood social environment and risk of death: Multilevel evidence from the Alameda County Study. *Am. J. Epidemiol.* **149,** 898–907.

Young, F. W. (2001). An explanation of the persistent doctor–mortality association. *J. Epidemiol. Community Health* **55,** 80–84.

Young, F. W., and Lyson, T. A. (2001) Structural pluralism and all-cause mortality. *Am. J. Pub. Health* **91,** 136–138.