Journal of the Air & Waste Management Association

ISSN: 1096-2247 (Print) 2162-2906 (Online) Journal homepage: http://www.tandfonline.com/loi/uawm20

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To cite this article: Sverre Vedal (1997) Ambient Particles and Health: Lines that Divide, Journal of the Air & Waste Management Association, 47:5, 551-581, DOI: 10.1080/10473289.1997.10463922

To link to this article: https://doi.org/10.1080/10473289.1997.10463922

CRITICAL REVIEW

ISSN 1047-3289 *J. Air & Waste Manage. Assoc.* **47**: 551-581

Ambient Particles and Health: Lines that Divide

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INTRODUCTION

Increases in ambient particle concentrations are associated with an array of adverse health outcomes. These outcomes range from the least adverse, such as increases in symptoms of respiratory irritation and small decreases in level of lung function, to the most adverse, mortality. Because the vast majority of the data supporting the association is generated by observational studies, there has been legitimate concern that the association may not reflect a causal association. Arguments against the association being causal have been based on some of the following: use of inappropriate statistical methodology, inability to account for other factors (e.g., meteorology, co-pollutants, or other time-varying factors) that may result in the observation of spurious associations, and lack of biological plausibility. Arguably the most significant criticism, lack of biological plausibility, was shored up by observations that the associations between particle concentration and ill health were present at concentrations measurable in almost any urban area, and that there was little evidence that a lower threshold concentration existed below which no association was observable.

Attempts have been made to attribute the observed associations to specific features of the ambient particles. Arguments have supported the role of such features as particle size, particle acidity, and particle emission source. Since much of the observational data supporting the role of these particle features have come from studies performed in the eastern United States, the potential lack of generalizability of these observations to other settings is also a reasonable concern.

This Critical Review will begin with a discussion of the relevant epidemiologic study designs and how the data generated from the observational studies are used to argue for a causal relationship between an exposure and a health effect. This will be followed by a brief review of the relevant health studies. The focus of this Critical Review will be on the "lines" of division that characterize much of the discussion on particle health effects. Specifically, the review will address divisions due to significant differences of opinion as to the interpretation of the health studies and the methods that should be used in analyzing them (Line One). Then, the review will address attempts to divide particles into those with lesser or greater pathogenicity based either on particle size or composition (Line Two). This segment will include discussion of differences associated with geography, dividing East from West in North America and dividing North America from Europe. These differences include sources of particle emissions, differences in particle characteristics, and some differences in the results of the health studies. Finally, the review will address attempts to agree upon a "line" defined by particle concentration that, for the purpose of setting an air quality standard or objective, in effect divides concentrations into those thought to cause adverse effects from those that do not (Line Three). It is hoped that this review of "lines that divide" will provide insight into the role of epidemiology, the elusive concept of causation, professional and geographic perspective, and, finally, alternative approaches to expressing air quality standards or objectives.

HOW WE KNOW WHAT WE KNOW

Epidemiology and Causation

The notion of causation is a thorny one. Even though one might accept the philosophical argument of David Hume that a strict cause and effect relationship can never be proven using inductive reasoning (that is, using empirical data), we still act as if it is meaningful to speak of causal relationships, and find such a concept useful. Some have therefore felt it necessary to propose definitions of what a cause is. An example of a recent attempt to provide a general definition posits that "a factor is a cause of an event if its operation increases the frequency of the event."[1] In the biomedical arena, one recent attempt defines "a cause of a disease as an event, condition, or characteristic that plays an essential role in producing an occurrence of the disease."[2] Such definitions appear to be general enough to allow different concepts of causation to be credible. A deterministic approach to causation holds that any outcome can theoretically be predicted given enough information about the starting conditions and the application of scientific laws. A more stochastic approach allows a role for chance, which will not permit

even theoretical strict predictability.[2] However, if concepts of complexity theory are credible, as they seem to be, then many events in nature are neither random nor predictable.[3]

In population research, associations between an "event, condition, or characteristic" and a health outcome are observed. In order to argue that these associations reflect causal relationships, it must first be argued that the purported causes play an "essential" role in producing disease. That is, information must be provided that would argue against the observed associations being merely spurious associations. Criteria have been proposed to allow judgments as to the causal nature of observed associations, the most well known being the Bradford Hill criteria.[4] These required that the association: (1) be strong, (2) exhibit consistency across study, (3) be specific for a few diseases or illnesses, (4) exhibit the appropriate temporal relationship, (5) exhibit an exposure-response relationship, (6) be biologically plausible, and (7) be coherent with other observations. Other ways of enhancing the case for causality, it was suggested, was to appeal to relevant experimental data, or "natural" experiments, and to argue by analogy. The unifying feature of these criteria was the application of "common sense" to any argument for causality. Attempts have been made to apply the Bradford Hill criteria to the case for the causal association between particle pollution and adverse health effects (see What the Health Studies Tell Us [Longitudinal Time Series Data] section).[5]

The motivation for proposing criteria such as that of Bradford Hill is that often action to protect the public health is deemed necessary in the absence of certainty as to the causal nature of an association. In fact, rarely do we have such certainty. The philosophy behind the entire enterprise of risk assessment is to accept uncertainty as a given and to make use of relevant scientific data to calculate estimates of risk for the purpose of guiding public health policy.[6] Epidemiological data often plays a central role in guiding health policy. This has required the use of *judgment* and generation of *consensus* in interpreting the epidemiological data. Some (taking the determinist's perspective) have bemoaned the relative lack of rigor used in arguing for causation when epidemiology serves the interests of public health policy.[7,8] Further, this lack of rigor has, it is argued, critically weakened the more fitting role of epidemiology in contributing to our knowledge of disease. When serving policy interests, the validity of each individual study does not become critical in making a case for causation. Instead, arguments are advanced that involve judgment, and apply some of the Bradford Hill criteria such as consistency, coherence, and plausibility to the entire body of research in an area. Reference to the sheer bulk of studies in support of such criteria therefore has value in this setting. Well-performed studies in which no associations are observed, if they happen to be relatively uncommon, can no longer successfully refute arguments of causality. The different modes of causal reasoning have been contrasted by describing the more traditional mode as attempting to build a *chain* of well-validated causes as opposed to the more modern mode of building a *mosaic* of evidence, no single element of which need be indisputable.[7]

An attempt has been made recently to categorize (caricature) some epidemiologists crudely into two extreme groups: "pragmatists" and "biostatisticians."[9] The pragmatist is described as using epidemiology primarily as a tool for influencing public health policy. The biostatistician, alternatively, engages data largely from a biostatistical perspective, with biostatistical criteria used to assess the validity of observed associations. A preferred alternative, it is suggested, is to view epidemiologists as clinical scientists whose primary interest is understanding disease. This role requires an appreciation of the complexity of biological processes, at both the individual and population level, as well as an understanding that the most significant challenges to the validity of observed associations are biases (or spurious associations) that reflect this complexity. As will be seen, the study of the health effects of ambient particles is plagued by a weak biological foundation. This makes it tempting to base what understanding we have on the results of statistical modeling, but which should, in addition, heighten our healthy suspicion that biases are at work. In addition, the epidemiology of particle pollution health effects has, out of necessity, been subject to the demands of policymakers, demands that bring with them the temptation to use the observational findings to address questions for which the available data are not adequate. Our "pragmatist" and "biostatistician" sides, then, find ready application in the study of particle health effects.

Another dimension to the debate concerning the roles of epidemiology that is relevant to the discussion of particle health effects is that of so-called "black box" epidemiology.[10] It is argued that epidemiology can make meaningful contributions, and is in fact best suited to make such contributions, in settings where there is ignorance or inadequate understanding of biological mechanisms (the mechanisms in a "black box"). Epidemiology has contributed significantly to understanding in such situations; the work on cigarette smoking and lung cancer comes to mind most readily. According to the determinist's perspective, the work of epidemiology without a biological foundation tends to deteriorate into the trivial task of identifying "risk factors" that, although sometimes useful from a public health perspective, contribute little to our understanding of disease (that is, to "dismantling the

'black box'").[11] It is apparent that the epidemiological work on particle health effects is attempting to make contributions to both health policy and understanding disease in the absence of an adequate biological foundation. Cognizance of the issues and perspectives introduced above may help to provide some perspective in assessing the data on particle-associated health effects.

Observational and Experimental Studies

An observational study is one in which the investigator does not control assignment of the exposure (or treatment) in the study subjects. In an experimental study, in contrast, the investigator is free to determine how exposure is distributed among the study subjects. Random assignment of the exposure (randomization) is a common way of distributing exposure in an experimental study since, if successful, it counters potential biases resulting from subjects with varying exposures harboring important differences in characteristics other than the differences in exposure.

For example, respiratory mortality can be compared in relatively polluted and non-polluted cities. If residents of the more polluted cities are more likely to smoke cigarettes than residents of non-polluted cities, the apparent increased respiratory mortality observed in the polluted cities might be due solely to the higher prevalence of smoking. This is an example of a type of bias known as confounding, with the confounder (in this case, cigarette smoking) being associated with both the health outcome (respiratory mortality) and the exposure (air pollution) thereby resulting in a spurious association between pollution and mortality. Random assignment of the air pollution exposure to study subjects would prevent this confounding by distributing the prevalence of cigarette smoking equally among those exposed to high levels of pollution and those exposed to lower levels.

The strength of randomizing exposure, however, is not merely in preventing bias caused by factors the investigator is aware of and can measure (such as cigarette smoking), but in preventing bias caused by factors the investigator is either unaware of or cannot measure. These "hidden" confounders cannot be accounted for in an observational study, whereas analytic techniques are available for countering the effects introduced by the known and measured confounders in observational studies. When successful, randomization equalizes the distribution of *all* confounding factors across exposure levels, whether these are known or "hidden."

In the example above, suppose that the prevalence of exogenous estrogen use was higher in the more polluted cities, resulting in a higher rate of death from pulmonary embolic disease, which results in higher respiratory mortality. If this is neither known nor considered by the investigator, even though the higher prevalence of cigarette smoking is accounted for in the analysis of the data, nothing can be done to account for the effect of exogenous estrogen use. A spurious association between higher air pollution exposure and increased respiratory mortality will be observed. Randomization, if it had been possible, would have removed the association between pollution exposure and exogenous estrogen use whether or not the investigator was aware of the potential bias.

It can be argued that an observational study would be as valid as an experimental study if all confounding factors in an observational study could be accounted for. This is rarely, if ever, possible. The inability to account for all potential confounders causes uncertainty as to the causal nature of any observed association between a health outcome and an exposure in an observational study. How this uncertainty is perceived is the source of basic disagreement between the epidemiologist and the experimentalist. The use of "observational" is preferred to "epidemiological" in this setting because some would consider a clinical trial a type of epidemiological study in which the exposure (the treatment in this case) is randomly assigned.[12] This randomization would make a clinical trial a type of experimental study, as well as, arguably, an epidemiological study.

Epidemiological Study Designs in Air Pollution Research

Most of the study designs available to epidemiologists have been applied in observational studies of the health effects of particle air pollution, although as will become obvious, the majority of recent studies have been of one particular design. Designs used in the past have included both longitudinal designs where study subjects are followed over time, and cross-sectional designs where the association between particle exposure and a health outcome is assessed at one point in time. The longitudinal study designs have largely been of two types: time series studies and cohort studies. In a *time series* study, a time series of particle concentrations is obtained from measurements made frequently on a regular schedule, typically daily. In the type of time series study design utilized in air pollution health research, this pollution time series is compared to another time series that consists of frequent and regular measurements of an adverse health outcome. This type of time series design has become the most commonly used design for the observational study of particle effects. A typical example consists of one series of daily, 24-hour particle concentration measurements and another series of daily counts of deaths. The goal of the analysis of such a time series study is to evaluate the association between

the particle series and the mortality series while attempting to control for effects of other time-varying factors that might result in a spurious association between the two time series. Methodologic considerations in the analysis of these time series designs have been reviewed recently[64,125] and are discussed later (see Line One section).

In a *cohort* study a sample population is identified, exposure is measured and estimated for the members of the sample, which is then observed over a period of time for the occurrence of an adverse health outcome in the individual sample subjects. For example, a sample population from geographic regions experiencing different particle concentrations is followed for a period of time to identify the individuals who die during the follow-up as well as the point in time that deaths occur. The mortality rate observed during the follow-up period is then compared across the different regions characterized by different air pollution concentrations. Less commonly, members of the cohort undergo repeated ascertainment for the occurrence of an outcome or repeated measurement of an outcome. In this variation of the more traditional cohort design, cohort members are surveyed once or several times regarding, for example, respiratory symptoms or illnesses, or undergo measurement of lung function on one or more occasions during the follow-up period. In more traditional cohort studies it is possible to estimate exposure of each subject in the study. This is not typically possible for studies of ambient air pollution effects.

Other longitudinal study designs that would not typically be considered either time series or cohort studies have also been used. These include studies in which a change in particle concentrations occurs in a community and persists for a longer period of time (for example, one year or possibly for the duration of follow-up) than the time scale considered for exposure concentration changes in time series studies. For example, a community might experience a marked drop in particle concentrations due to a significant change in emissions. An outcome, such as hospitalization rate, for example, is then compared for the time periods having different concentrations. Other longitudinal studies include those in which an attempt is made to correlate changes in particle concentrations over other time spans, such as seasons of a year, with seasonal outcome measures such as symptom prevalence and level of lung function. A final variant is the longitudinal study in which an air pollution "episode" is experienced in a community, with the health outcomes of interest measured before, during, and after the episode. These health outcomes can then be compared across these periods of time, and if possible, contrasted with outcomes in a comparison community that had experienced no such episode.

A *cross-sectional* study involves assessing the sample population at one point in time when, for example, data on past or current symptoms or illnesses could be obtained, or level of lung function measured. Exposure could be estimated from concurrent measurements of pollutant concentrations or a history of exposure could be estimated from previous concentration measurements, depending on the hypothesis of interest.

Finally, the concept of an *ecologic* study is also relevant in the context of air pollution health studies. Any of the study designs mentioned above can also be ecologic study designs, either in total or in part. An observational study is also an ecologic study if data on the exposure, the covariates, or the health outcomes is available only at the level of the population.[13] That is, in an ecologic study, no data from individuals in the study are available for all or part of the data used in the analysis. A time series study as presented above is ecologic when particle concentration data (the exposure data) are not available for individuals, but only at an aggregate (or population) level. In this sense, a time series study is ecologic when the entire population is assigned an aggregate particle concentration value for each single day in the study. Not only does this result in measurement error of each individual's exposure, but time-varying covariates that cannot be measured at the population level can confound the association of interest. For example, if study subjects closed their windows on days with higher levels of pollution, exposure to indoor pollutants might increase and actually be responsible for the increase in adverse health outcomes, and therefore confound the particle and health effect association. Such an ecologic study will not allow control for these sources of potential confounding. A cohort study is ecologic in part when exposure is aggregated over the population. For example, in the mortality cohort studies to be described, even though data are available at the individual level on some of the covariates such as cigarette smoking, the particle concentration data are assigned to all individuals residing in a city in aggregate. A potential risk factor for mortality, such as some lifestyle factor, could easily vary across city in concert with the pollution concentrations. When these are not measured at the individual level, there are no good methods for controlling for their effects, with resultant confounding of the particle and mortality association. Therefore, when exposure is assigned in aggregate, not only is there a problem of measurement error with misclassification of exposure, but uncontrolled confounding is also a serious concern.

WHAT THE HEALTH STUDIES TELL US

Observational Data

1. Introduction

It is accepted with little argument that increases in ambi-

ent air pollution concentrations can result in death in susceptible individuals, as well as cause lesser adverse health outcomes, as is dramatically demonstrated by a few historical air pollution "episodes" characterized by very high pollutant concentrations.[14] Whether much lesser pollution concentration increases also can cause the same severity and spectrum of outcomes, albeit affecting fewer individuals, remains to be settled.

In the brief review of the health studies that follows, study findings will be classified by study design, and within each design, by health outcome. An attempt will also be made to group North American studies together when appropriate. Tables 1 to 6 list most of the relevant epidemiological studies performed since 1980. Only studies that allowed an estimate of effect to be calculated for a 10 μg/m^3 increase PM_{10} were included. Since many relevant studies did not include direct measurements of PM_{10} concentrations, crude conversion factors between other particle concentration measures and PM_{10} were used. For the sake of consistency, the conversion factors chosen were similar to those used in a previous review of particle health effects:[15]

$PM_{10} = PM_{13}$
$PM_{10} = BS$ (British Smoke)
$PM_{10} = TSP * 0.55$
$PM_{10} = CoH$ (coefficient of haze)/ 0.55
$PM_{10} = PM_{2.5} / 0.60$
$PM_{10} = SO_4 * 4$

It is realized that these conversion factors are inexact, and undoubtedly vary considerably across the settings (and over time within a given setting) where the studies were performed, especially for BS, CoH, and SO_4. Even for these conversions, however, most effect estimates calculated in this way should be within a factor of 2 or 3 of the effect estimate calculated using the "correct" conversion factor. For studies in which the logarithmic transformation of the particle concentration was used in the regression models, an effect estimate for a 10 μg/m^3 PM_{10} increase above the mean particle concentration was calculated, as was also done in the previous review.[15] Often, several effect estimates from one study will be reported, including estimates from different regression models that include different covariates (different combinations of co-pollutants, for example) or models for different strata defined by time (often season of the year) or population subgroup. When possible, the overall effect estimates from such studies were chosen; when these were not available, the estimate chosen is identified in the table. When inclusion of co-pollutant covariates resulted in changes in the particle effect estimate from those estimated from the model containing only the particle concentration variable, estimates based on the model containing the pollutant covariates only are presented.

2. Longitudinal Time Series Data

Because of the recent spate of particle pollution studies that used the time series design, the large majority of observational studies on particle pollution health effects are time series studies. Tables 1-5 provide a listing of these time series studies from the modern era (since 1980), listing separately the studies on mortality, hospitalizations, emergency room visits, respiratory symptoms, and level of lung function. It is obvious that most have been studies of mortality, which is likely because of the ready availability of mortality data, although almost all of the relevant health outcomes have been studied using this design. Other features of the studies listed in these tables are that: (1) most often particle pollution is but one of several components of air pollution present in any area, with most studies also making use of serial measurements of these other pollution components, (2) the duration of the time series in the different studies ranges from less than one year to over one decade, and (3) a variety of ways of measuring particle concentrations have been used.

Mortality. The mortality time series studies are listed in Table 1.[16-42] Most but not all of the U.S. studies have reported an association between short-term increases in ambient particle concentrations and daily mortality; most were statistically significant associations with the respective 95% confidence intervals not including an effect estimate of no effect. Several reviews of this group of studies have been published.[5,15,43-49]

The U.S. studies as a group have been used to make some compelling arguments in support of a causal link between short-term increases in particle pollution and increases in daily mortality.[5,15,43,46,47] Because this series of studies has covered a wide spectrum of settings characterized by substantial variability in the types and concentrations of co-pollutants and by variability in meteorology, it has been argued that the one common factor that is associated with mortality in this series of studies, as measured by concentrations of particles, is in fact the particle concentration itself.[46]

For example, studies from the eastern United States and Canada have necessarily had to contend with a mix of summer pollutants that includes, in addition to particle pollution, SO_2 and O_3, as well as acid aerosol. Concentrations of these pollutants are correlated to a greater or lesser extent depending on the setting. Attempts to attribute effects to only one component of this mix have prompted expressions of doubt that doing so is possible.[26] The term "acid summer haze" was coined to refer to this specific mix of pollutants, reflecting the difficulty in separating the effects of the individual components.[50,55] However, the series of U.S. studies includes those performed

Table 1. Longitudinal time series studies: mortality.

Location and time	Particle measure	PM_{10} mean (range)	Co-pollutants also analyzed††	% change in mortality for each 10 μg/m^3 increase in PM_{10} (95%CI)	Reference
Santa Clara, CA (1980-82, 84-86)	CoH	35 (N/A)	none	0.8% (0.2, 1. 5) total 3.5% (1.5, 5.6) respiratory 0.8% (0.1, 1.6) cardiac	Fairley, 1990[16]
Los Angeles, CA	KM	N/A	$S0_2$, $N0_2$, C0, 0_x	particles pollution associated with total mortality but not cardiac or respiratory mortality	Kinney, 1991[17]
Detroit, MI (1973-82)	TSP	48 (32-73)**	$S0_2$	1.0% (0.5, 1.6)	Schwartz, 1991[18]
St. Louis, MO (1985-86)	PM_{10}	28 (1-97)	$S0_2$, $N0_2$, 0_3	1.5% (0.1, 2.9)	Dockery, 1992[19]
Kingston, TN (1985-86)	PM_{10}	30 (4-67)	$S0_2$, $N0_2$, 0_3	1.6% (-1.3, 4.6)	Dockery, 1992[19]
Utah Valley, UT (1985-89)	PM_{10}	47 (1-365)	none	1.5% (0.9, 2.1) total 3.7% (0.7, 6.7) respiratory 1.8% (0.4, 3.3) cardiac	Pope, 1992[20]
Philadelphia, PA (1973-80)	TSP	42(20-73)**	$S0_2$	1.2% (0.7, 1.7) total 3.3% (0.1, 6.6) respiratory 1.7% (1.0, 2.4) cardiac	Schwartz, 1992[21]
Steubenville, OH (1978-84)	TSP	61 (22-125)***	$S0_2$	0.7% (0.4, 1.0)	Schwartz, 1992[22]
Birmingham, AL (1985-88)	PM_{10}	48 (21-80)**	none	1.0% (0.2, 1.9) total 1.5% (-5.8, 9.4) respiratory 1.6% (-0.5, 3.7) cardiac 0.6% (0.3,1.0)	Schwartz, 1993[23]
Cincinnati, OH	TSP				Schwartz, 1994[24]
Steubenville, OH (1974-84)	TSP	62 (21-117)**	$S0_2$	0.3% (-0.1, 0.8)	Moolgavkar, 1995[25]
Philadelphia, PA (1973-88)	TSP	37 (8-186)	$S0_2$, 0_3	0.3% (-0.1, 0.7)	Moolgavkar, 1995[26]
Cook County, IL (1985-92)	PM_{10}	37* (4-365)	none	0.5% (0.1, 0.9)	Styer, 1995[27]
Salt Lake City, UT (1985-90)	PM_{10}	48* (9-194)	none	-0.2% (-1.1, 0.7)	Styer, 1995[27]
Erfurt, East Germany (1988-89)	TSP	58* (6-358)	$S0_2$	0.7% (N/A; p = 0.04)	Spix, 1993[28]
Athens, Greece (1984-88)	BS	83 (N/A)	C0, $S0_2$	0.4% (0.1, 0.8)	Touloumi, 1994[29]
Beijing, China (1989)	TSP	206 (85-552)**	$S0_2$	0.9% (0.0, 1.8) only in summer	Xu, 1994[30]
Sao Paulo, Brazil (1990-91)	PM_{10}	82	$S0_2$, 0_3, C0, $N0_2$	1.2% (0.6, 1.7) (age 65+)	Saldiva, 1995[31]
Bratislava, Slovak Republic (1987-91)	TSP	49 (0-396)	$S0_2$	0.0% (-0.7, 0.7)	Bacharova, 1996[32]
Paris, France (1987-92)	PM_{13}	51 (19-137)*	$S0_2$, $N0_2$, 0_3	1.5% (0.4, 2.7) respiratory	Dab, 1996[33]
Mexico City, Mexico	TSP	112* (36-251)	0_3, $S0_2$	0.3% (0.2, 0.4)	Borja-Aburto, 1996[34] (1990-92)

Continued on next page.

Table 1. Longitudinal time series studies: mortality. (Continued from page 556)

Location and time	Particle measure	PM_{10} mean (range)	Co-pollutants also analyzed††	% change in mortality for each 10 μg/m³ increase in PM_{10} (95%CI)	Reference
Santiago, Chile (1989-91)	PM_{10}	115 (32-367)	NO_2, O_3, SO_2	0.7% (0.5, 1.0) total 1.2% (0.7, 1.8) respiratory 0.8% (0.3, 1.1) cardiac	Ostro, 1996[35]
Köln, Germany (1975-85)	TSP	37* (N/A-167)	SO_2, NO_2	0.3% (-0.2, 0.7)	Spix, 1996[36]
Barcelona, Spain (1985-91)	BS	N/A (11-126)	O_3, NO_2, SO_2	0.7% (0.3, 1.1) total 0.9% (-0.1, 2.0) respiratory 0.9% (0.4, 1.4) cardiac	Sunyer, 1996[37]
Athens, Greece (1987-89)	BS	84 (9-333)	CO, SO_2	0.5% (0.3, 0.7)	Touloumi, 1996[38]
Amsterdam, Netherlands (1986-92)	PM_{10} BS	38 (N/A-163)	O_3, SO_2, CO	0.6% (-0.1, 1.4)	Verhoef, 1996[39]
Milan, Italy (1980-89)	TSP	76 (2-291)	SO_2	0.7% (0.1, 1.6)	Vigotti, 1996[40]
Wraclaw, Poland (1979-89)	BS	54* (26-141)***	SO_2	0.1% (-0.2, 0.3)	Wojtyniak, 1996[41]
Poznan, Poland (1983-90)	BS	34* (9-92)***	SO_2	0.1% (-0.1, 0.3)	Wojtyniak, 1996[41]
Cracow, Poland (1977-89)	BS	73* (26-247)***	SO_2	0.2% (0.0, 0.5)	Wojtyniak, 1996[41]
Lodz, Poland (1977-90)	BS	57* (20-151)***	SO_2	0.2% (0.1, 0.4)	Wojtyniak, 1996[41]
Lyon, France (1985-90)	PM_{13}	38 (3-180)	SO_2, NO_2, O_3	0.2% (-0.6, 1.0) total 0.8% (0.0, 1.7) respiratory 0.8% (-0.2, 1.9) cardiac	Zmirou, 1996[42]

* median ** (5th to the 95th percentile) ***(10th to the 90th percentile) †(5th to the 99th percentile) ††(underlined pollutant(s) showed statistically significant effect) N/A = not available

in settings where there is only minimal concern about the effects of these co-pollutants. The Utah Valley, for example, experiences only very low concentrations of SO_2, and because the increases in particle concentrations occur mainly in the winter, as opposed to the East where the high particle concentrations are largely a summertime phenomenon, also very low O_3 concentrations.[51] Very low concentrations of acid aerosol in the Utah Valley have also been documented. The effects on mortality and other outcomes associated with particle concentration increases in Utah Valley have been similar to those reported in the eastern U.S. studies, a finding that has led to the reasonable argument that the effects associated with increases in particle concentrations are in fact due to the particles themselves, rather than reflecting the effects of another component of the pollution mix or being dependent on the presence of another pollutant acting in concert with particles. Because the effects are related to increases in particle concentrations that occur largely in the wintertime, rather than during the summertime as in the East, it has also been reasonably argued that it is unlikely some effect of meteorology not adequately accounted for in the analyses is responsible for what appear to be effects of particles. Given these observations, it has been argued that confounding of the association by either a co-pollutant or by meteorology is unlikely.[15,43,46]

Another approach to supporting the argument for causality is to determine whether the association between particle pollution and mortality can satisfy the Bradford Hill criteria. *First*, is the association strong? There is general agreement that the associations are weak, with estimates of effect being very small. Table 1 presents estimated effects for an arbitrarily chosen 10 μg/m³ increase in PM_{10}, for which the estimated effects are very small. However, the effect estimates are small even for relatively large short-term increases in PM_{10}, such as for a 50 μg/m³ increase. Although a small effect may nevertheless be a real effect, the importance of observing only small effects is that a small estimate of effect is more likely to be due to confounding by factors not controlled by the investigators. In order for large effects to be due to confounding, the effect of the confounder must also be large. Such strong confounders are generally easier to detect and control. *Second*, is the association consistent? Certainly for the U.S. studies, it appears that there is substantial consistency

across study. Inspection of the estimates for percentage change in mortality for a change in particle concentration as presented in Table 1 gives an impression of consistency, a point that has been forcefully argued by others.[15,43,46] *Third*, is the association specific? Table 1 also presents effect estimates for respiratory mortality and for cardiac mortality for those studies where the association with specific causes of death could be investigated. In addition to the associations with total mortality, associations are also present for respiratory and cardiac causes of death. Typically, no associations are present with non-respiratory and non-cardiac causes of death in these studies. The association with respiratory deaths supports the argument for specificity, as does the lack of association with non-respiratory, non-cardiac deaths. Generally, because of the large number of cardiac deaths, when an association with total mortality is observed, one also expects to observe an association with cardiac mortality. It is not so clear why particle pollution would be associated with cardiac deaths, although hypotheses have been proposed.[52,53] Although these hypotheses have merit, it is not known whether they provide some basis for the association. If they do, then the association with cardiac deaths might support the argument for specificity. For now, the association remains somewhat puzzling. There is also some specificity with respect to the age group of the population that is most affected. Studies with the ability to address the association with age have found that the effects are largely limited to the elderly.[25] *Fourth*, does the association exhibit the appropriate temporal relationship? Typically, associations between particle pollution and mortality are reported for increases in both pollution and mortality that occur together on the same day and for increases in mortality that lag behind the particle concentration increases by a day or two. Few study reports explicitly address whether paradoxical associations between particle pollution and mortality are present when mortality precedes the increases in particle concentrations. No paradoxical associations have been observed in those studies where this has been specifically addressed.[54] *Fifth*, does the association exhibit an exposure-response relationship? An exposure-response relationship has been found in most studies where the question has been addressed. In fact, there has been little evidence to support the existence of a threshold concentration below which no association (or exposure-response relationship) is observable (see Line Three in the upcoming section). This observation is unsettling because, if true, it implies that increases in particle concentrations at even the lowest concentrations cause deaths. The observation is also unsettling in that it is not very plausible. This leads to the next criterion. *Sixth*, is the association biologically plausible? Weak biological plausibility has been the single largest stumbling block to accepting the association as causal. There is no known mechanism whereby exposure to very low concentrations of inhaled particles would produce such severe outcomes as death, even from respiratory disease, and certainly not from cardiovascular disease. As noted above, hypotheses have been proposed to explain how the association with cardiovascular deaths might occur,[52,53] but in the absence of data supporting their credibility, these should still very much be viewed as hypotheses. *Seventh*, does the association exhibit coherence? Much has justifiably been made of the array of adverse respiratory health outcomes exhibiting associations with increases in particle concentrations.[52] As further reviewed below, these outcomes range from the least adverse, such as small decrements in lung function, to the most adverse, death. Without such a supporting array of associations, the associations with mortality would be viewed as even more implausible. Even though associations with each of the outcomes in this array could conceivably result from the operation of the same confounding factor, this degree of coherence makes the task of proposing plausible confounders more daunting (seen Line One section [Plausibility]).

According to Bradford Hill, an association need not meet all of the above criteria in order to be causal, or to be considered causal.[4] For example, the criterion of biological plausibility, taken at face value, assumes that our current paradigm will not change as new information becomes available. What is implausible today may be quite plausible tomorrow. Many examples are available of unquestionably causal associations that have not met the criterion for biological plausibility, or other criteria. The association between particle pollution and mortality seems to satisfy many, although not all, of the Bradford Hill criteria.[5] However, agreement is not consistent on this issue.[44] Criticisms of these arguments for causality will be reviewed in the Line One section.

The recently reported series of European mortality studies does not present a consistent picture that particles are having an effect on mortality or that particles are the critical component of the pollution mix responsible for the adverse health effects (Table 1).[32,33,36-38,40-42,55] This contrast with the U.S. studies may have important implications either with respect to population susceptibility, pollutant mix, or study methodology (see Line Two [Geography] section).

Hospitalizations. The recent time series studies of hospitalizations are summarized in Table 2.[33,40,50,56-67] Many of the observations and arguments made above regarding the mortality time series studies can also be made for the

hospitalization time series studies. The U.S. and Canadian studies are reasonably consistent in showing statistically significant associations between short-term increases in particle concentrations and increases in daily hospitalizations for respiratory illnesses. Recent reviews of these hospitalization studies are available.[15,43,49] As for the mortality studies, associations are seen in a variety of settings that differed with respect to the pollutant mix and the season of the year when particle concentrations are highest. Some coherence to the association between particle pollution and deaths from cardiac disease is provided by finding associations in a few studies between particle pollution and hospitalizations for cardiac disease,[59] as would be expected if the association with cardiac deaths is causal. When exposure-response relationships have been evaluated, as for mortality, there is little evidence to support the presence of a threshold concentration below which no adverse effects are detectable.

The recent European studies assessing the association between short-term increases in particle concentrations and increases in respiratory hospitalizations have also not shown effects as consistently, nor been able to attribute the effects specifically to the particle component of the pollution mix, as those from the United States and Canada (Table 2).[33,65-67] As for mortality, the reasons for these differences are not known.

Emergency room visits. The few time series studies performed in which emergency room visits were used as the health outcome are summarized in Table 3.[54,68-72] As for the hospitalization data, effects are observed for respiratory emergency visits. Exposure-response relationships, when examined, have not detected a lower concentration threshold. Results of the European study performed in Barcelona are consistent with the results of the U.S. studies.

Respiratory symptoms/lung function. Most U.S. and European studies have been interpreted as showing particle-associated effects on both increases in respiratory symptoms and decreases in level of lung function, although there are exceptions (Tables 4 and 5).[73-85] The data also indicate that those with pre-existing respiratory illness, particularly asthma, are more susceptible to having respiratory symptoms and reductions in level of lung function following increases in particle concentrations.[77,82]

3. Longitudinal Cohort Data

Mortality. Results from the few cohort studies on particle-associated health effects have been interpreted as showing adverse particle effects for the outcomes studied (Table 6). The two cohort studies of mortality, in which mortality rates across cities were compared, represent a significant advance over earlier cross-sectional studies in which mortality rates across communities were also compared.[91,92] In earlier cross-sectional studies, lack of data from individual study subjects on potential risk factors for mortality, such as cigarette smoking, on individuals in the studies made it impossible to account for a host of potential confounding factors that differed across cities and that could have caused the observation of spurious associations. The cohort studies made use of valuable data from individuals on several potentially important risk factors for mortality, namely, cigarette smoking, occupational exposures, and socio-economic status. These data allowed the investigators to control for the effects of these risk factors in assessing the association between particle concentrations and mortality. Clearly the success of the attempt to control for the effects of other risk factors depends on being able to both identify and measure the important factors. In order for the reported cohort study findings to be convincing, a good case needed to be made that no important unmeasured risk factors were present that could have accounted for the differences in mortality across city. Because it is easier to postulate that such confounders were in fact present for these cohort studies than for the time series studies,[44] the cohort studies do not present as compelling a case for causality.

Apart from the ability to control for factors that could not be controlled in earlier studies, two additional aspects of these cohort studies of mortality have contributed to their influence. First, the results support an argument that the effects of particles on mortality are not simply the result of "harvesting," where the effect of exposure to increases in particle concentrations would be to merely advance the date of death by a few days of those whose deaths are imminent. Any exposure that results in death must necessarily result in advancing the date of death from the time individuals would have died in the absence of the exposure; in this sense, then, "harvesting" must always occur. The time frame over which this "harvesting" occurs determines how seriously we view the impact of the exposure. Exposures that advance the date of death by merely a few days would be viewed as having a less significant impact than exposures that advance the date of death by a few years. If death is advanced by only a few days, a comparison of mortality rates across cities that experience different particle concentrations would detect no differences in mortality associated with differences in particle concentration. However, for sample populations followed for years, if the exposure advances the date of death by a few years, there is a possibility that the cohort study would detect this advance in death date as a difference in mortality rates across the cities. The fact that differences in mortality related to particle concentrations

Table 2. Longitudinal time series studies: hospitalizations.

Location and time	Particle measure	PM_{10} mean (range)*	Co-pollutants also analyzed	% change in hospitalizations for each 10 μg/m^3 increase in PM_{10} (95%CI)	Reference
New York City, NY (1988-89)	SO_4	N/A	O_3	1.9% (0.4, 3.4) asthma 1.0% (0.2, 1.8) respiratory	Thurston, 1992[57]
Buffalo, NY (1988-89)	SO_4	36 (N/A-136)	O_3	2.1% (-0.6, 5.0) asthma 2.2% (0.6, 3.8) respiratory	Thurston, 1992[57]
southern Ontario (1983-88)	SO_4	21 (N/A-50)**	O_3	1.1% (0.8, 1.5) respiratory 0.9% (0.6, 1.2) cardiac	Burnett, 1994[58]
Minneapolis, MN (1986-89)	PM_{10}	36 (18-58)**	O_3	4.5% (1.8, 7.5) COPD (age 65+) 1.6% (0.2, 2.9) pneumonia (age 65+)	Schwartz, 1994[60]
Birmingham, AL (1986-89)	PM_{10}	45 (19-77)**	O_3	2.4% (0.8, 4.1) COPD (age 65+) 1.8% (0.7, 2.8) pneumonia (age 65+)	Schwartz, 1994[61]
Toronto, Canada (1986-88)	PM_{10} SO_4	33 (N/A-96)	O_3, SO_2	2.1% (-0.8, 5.1) asthma 3.4% (0.4, 6.4) respiratory	Thurston, 1994[56]
Tacoma, WA (1988-90)	PM_{10}	37 (14-67)**	O_3, SO_2	1.9% (0.6, 3.2)	Schwartz, 1995[62]
New Haven, CT (1988-90)	PM_{10}	41 (19-67)**	O_3, SO_2	1.2% (0.0, 2.5)	Schwartz, 1995[62]
Spokane, WA (1988-90)	PM_{10}	46 (16-83)**	O_3	1.6% (0.7, 2.5) respiratory (age 65+) 1.0% (-0.3, 2.4) pneumonia 5.0% (-1.1, 11.5) COPD	Schwartz, 1996[63]
Cleveland, OH (1988-90)	PM_{10}	43 (19-72)**	O_3, SO_2	1.1% (0.1, 2.2)	Schwartz, 1996[64]
Paris, France (1987-92)	PM_{13} BS	51 (19-137)***	O_3, SO_2, NO_2	0.4% (0.0, 0.8) respiratory -0.5% (-1.3, 0.4) COPD -0.3% (-1.0, 0.5) asthma	Dab, 1996[33]
London, England (1987-88, 91-92)	BS	15 (6-27)*	O_3, SO_2, NO_2	1.0% (-0.5, 2.5) respiratory (age 65+)	Ponce de Leon, 1996[65]
Helsinki, Finland (1987-89)	TSP	42 (N/A)	O_3, SO_2, NO_2	no association for asthma	Pönkä, 1996[66]
Amsterdam, Netherlands (1977-89)	BS	11 (1-37)*	O_3, SO_2, NO_2	1.2% (-3.7, 6.4) respiratory (age 65+) 3.9% (-2.1, 10.2) COPD -4.4% (-11.6, 3.4) asthma	Schouten, 1996[67]
Rotterdam, Netherlands (1977-89)	BS	26 (6-61)*	O_3, SO_2, NO_2	0.9% (-1.8, 3.6) respiratory (age 65+) 2.2% (-1.3, 5.8) COPD	Schouten, 1996[67]
Milan, Italy (1980-89)	TSP	76 (2-291)	SO_2	0.4% (-0.1, 0.7) respiratory (age 65+)	Vigotti, 1996[40]

*(5th to the 95th percentile) **(10th to the 90th percentile) ***(5th to the 99th percentile) N/A = not available

exposure in these studies. This in no way argues for the observed effects being due to an exposure occurring over an extended period of time rather than to the effects of short-term concentration increases on acute risk of death and, in turn, on the observed mortality rates. Either long-term exposure or acute exposure could result in the same observed effects on mortality in these studies. Such an interpretation has implications as to whether it is reasonable to propose a long-term average standard, such as an annual average standard, in addition to a 24-hour standard (see Line Four section). Similarly, while the studies show increases in mortality rates associated with particle concentrations, they provide no evidence that particle exposure resulted in a chronic condition that caused the differences in total, respiratory, and cardiovascular mortality observed. In both studies an association was observed between living in a city with higher particle concentrations and increased risk of dying from lung cancer. If this association was not due to residual confounding from cigarette smoking or another factor, since the timing of death from lung cancer would not necessarily be expected to be significantly advanced by particle exposure, it can be inferred that the difference was due to the different lung cancer rates in the communities. These data on lung cancer support the argument for an association between particle exposure and development

were observed in both of the cohort mortality studies supports the notion that particle exposure does not merely result in advancing the date of death by only a few days.

Second, the results of these cohort mortality studies have been used to support arguments for effects of *chronic exposure* and for the occurrence of *chronic effects*. Neither of these arguments are well supported by these studies. The annual average concentration of fine particles ($PM_{2.5}$) and other particle measures were used to reflect particle

Table 3. Longitudinal time series studies: emergency visits.

Location and time	Particle measure	PM_{10} mean (range)*	Co-pollutants also analyzed	% change in emergency visits for each 10 μg/m^3 increase in PM_{10} (95%CI)	Reference
Steubenville, OH (1974-77)	TSP	86 (8-383)	SO_2, NO_2, CO, O_3	0.5% (0.0, 1.0) respiratory	Samet, 1981[70]
Vancouver, BC Canada	SO_4 CoH	13 (N/A-58)	SO_2, O_3, NO_2	associated with total respiratory and asthma visits	Bates, 1990[71]
Seattle, WA (1989-90)	PM_{10}	30 (6-103)	SO_2, O_3	3.4% (0.9, 6.0) asthma	Schwartz, 1993[72]
Barcelona, Spain (1985-89)	BS	54 (44-84*)	SO_2	2.3% (1.4, 3.2) COPD	Sunyer, 1993[74]
southern WA (1991)	PM_{10}	40 (3-1,689)	none	0.4% (0.3, 0.4) bronchitis	Hefflin, 1994[73]
Montreal, Canada (1993)	PM_{10}, $PM_{2.5}$, SO_4	22 (N/A-51)	O_3, acid aerosol	7.3% (2.0, 12.6) respiratory (age 65+)	Delfino, 1997[72a]

* 25-75th percentiles in winter

of a chronic condition. Because cigarette smoking is such a strong predictor of death from lung cancer, this finding needs to be replicated with very good control for cigarette smoke exposure.

Respiratory symptoms and illnesses. The incidence of respiratory illnesses and symptoms has also been studied using a cohort design (Table 6). A series of reports on a cohort study of Seventh Day Adventists in California have described an association between exposures to higher concentrations of ambient particles and ozone with new reports of chronic respiratory symptoms.[93-95] The value of this cohort is enhanced by the rarity of cigarette smoking in this population, as well as perhaps by relatively little variability in other potential confounding factors.

4. Other Longitudinal Data

A few studies have used longitudinal designs that differed from both the time series designs and the cohort designs (Table 6). These other longitudinal studies have been used for studying associations with hospitalizations,[96,97] functional limitations (limitation of activity[98] or absenteeism[99]) and with level of lung function[84,100] (Table 6), and for mortality associated with air pollution "episodes."[101]

A potentially extremely valuable type of longitudinal study is one in which a significant change in particle concentrations occurs through extraordinary means. These types of studies can be viewed as "natural experiments." For example, a major source of particle emissions in the Utah Valley is a steel mill.[96,97] The mill closed for one year because of a labor strike. Ambient particle concentrations fell for reasons unrelated to the normal mechanisms that influenced concentration changes. Potential confounding by these mechanisms could therefore largely be ignored, especially if these were similar during periods with the steel mill operating and closed. It was observed that hospital admissions for respiratory conditions (pneumonia, bronchitis, and asthma) were increased in years when the mill was in operation relative to the period when it was closed, especially for children age 5 and younger. Of importance, this pattern was not consistently present for neighboring counties in Utah.[97] Two potential confounding factors have been suggested to explain these observations.[51] The first, that economic hardship accompanying the steel mill closure resulted in reduced access to medical care, has been successfully refuted. The second, that the years preceding and following the mill closure coincided with years of increased viral respiratory infections that typically occur on a cyclical basis (often biannually), was a serious possibility. The strongest argument against that possibility was the absence of a parallel pattern of respiratory hospitalizations in the neighboring counties which would also have been expected to experience a similar biannual pattern of hospitalizations if the viral epidemic hypothesis was credible.

5. Cross-sectional Data

Cross-sectional studies are not now commonly used in the study of particle effects because of at least two limitations. First, as briefly discussed earlier when discussing the mortality cohort studies, in a cross-sectional study there is only a limited ability to control for confounding factors if the study is performed using data from databases generated for other purposes. For example, vital statistics data are often used to compare mortality rates across communities, with the investigators having no access to individual data on cigarette smoking. Second, it is costly to improve upon such a study by collecting data from individuals on potential confounding factors that should be controlled. Cross-sectional studies have been used primarily for studying effects on the prevalence of respiratory symptoms[102,103] and on level of lung function,[104]

Table 4. Longitudinal time series studies: respiratory symptoms.

Location and time	Particle measure	PM_{10} mean (range)	Co-pollutants also analyzed	Population group	Symptom*	% change in symptom for each 10 μg/m^3 increase in PM_{10} (95%CI)	Reference
Chestnut Ridge, PA (1980-81)	CoH	21 (6-72)	SO_2, NO_2, O_3	children	LRI URI	10.0% (-2.6, 24.3) -3.8% (-9.5, 2.5)	Vedal, 1987[74]
Denver, CO	$PM_{2.5}$	37 (1-122)	acid aerosol	asthmatics	asthma cough dyspnea	1.4% (0.0, 2.9) 3.4% (-10.3, 17.0) 7.0% (-10.9, 24.8)	Ostro, 1991[75]
Utah Valley, UT (1989-90)	PM_{10}	46 (11-195)	none	children asthmatics	LRI URI LRI URI	5.1% (1.1, 9.3) 3.7% (0.7, 6.8) 0.2% (-4.2, 4.8) -0.2% (-4.2, 4.0)	Pope, 1991[76]
Utah Valley, UT (1990-91)	PM_{10}	76 (7-251)	none	symptomatic children asymptomatic children	LRI URI cough LRI URI cough	4.8% (1.5, 8.3) 3.7% (0.6, 6.9) 2.4% (-1.8, 6.8) 5.2% (2.3, 8.2) -0.2% (-4.9, 4.7) 3.4% (-0.1, 7.0)	Pope, 1992[77]
Southern CA (1978-79)	CoH, SO_4	34 (8-147)	O_3	adults	LRI URI	5.9% (-1.9, 14.3) 2.7% (-2.5, 8.2)	Ostro, 1993[78]
Six U.S. Cities (1984-88)	PM_{10}	30** (113***-117)	SO_2, NO_2, O_3 acid aerosol	children	LRI URI cough	15.2% (6.3, 24.9) 6.9% (-0.7, 15.0) 8.6% (2.2, 15.4)	Schwartz, 1994[79]
Uniontown, PA (1990)	$PM_{2.5}$ PM_{10} SO_4	36 (N/A-83)	O_3, SO_2 acid aerosol	children	cough	9.3% (1.6, 17.6)	Neas, 1995[80]
State College, PA (1991)	$PM_{2.1}$ PM_{10} SO_4	32 (N/A- 83) `	O_3, SO_2 acid aerosol	children	cough	9.9% (3.7, 16.4)	Neas, 1996[81]
Port Alberni, BC Canada (1990-92)	PM_{10}	27 (1-158)	none	non-asthmatic children asthmatic children	LRI URI cough LRI URI cough	2.4% (-12.0, 19.1) 1.7% (-8.6, 13.0) 4.4% (-7.3, 17.6) -1.3% (-11.7, 8.7) -0.8% (-8.0, 7.1) 8.3% (1.9, 19.7)	Vedal, 1997[82]
Wageningen, Netherlands (1990-91)	PM_{10}	N/A (0-175)	SO_2, NO_2	symptomatic children	cough wheeze	0.7% (-0.2, 1.6)	Roemer, 1993[83]
Four Cities, Netherlands (1987-90)	PM_{10} SO_4	45 (14-126)	SO_2, NO_2	children	LRI URI cough	-1.4% (-9.5, 7.5) 0.6% (-3.6, 5.0) 1.0% (-4.2, 6.5)	Hoek, 1994[84]
Deurne, Netherlands (1989)	PM_{10} SO_4	48 (13-124)	NO_3, O_3	children	LRI URI cough	-0.3% (-3.4, 2.9) -0.2% (-1.6, 1.2) -0.2% (-1.9, 1.6)	Hoek, 1995[85]
Basel and Zurich, Switzerland (1985-86)	TSP	N/A	NO_2, O_3, SO_2	children	URI	2.5% (0.4, 4.9)	Braun-Fahrländer,1992[82a]

* URI = upper respiratory illness
LRI = lower respiratory illness

*(median)
***(10th percentile)

Table 5. Longitudinal time series studies: lung function.

Location and time	Particle measure	PM_{10} mean (range)	Co-pollutants also analyzed	Lung Function measure	Population group	% change in lung function for each 10 μg/m^3 increase in PM_{10} (95%CI)	Reference
Utah Valley, UT (1989-90)	PM_{10}	46 (11-195)	none	PEF	children asthmatics	-0.25% (-.39, -.10) -0.05% (-.22, .13)	Pope, 1991[76]
Utah Valley, UT (1990-91)	PM_{10}	76 (7-251)	none	PEF	asymptomatic symptomatic	-0.04% (-.09, -.02) -0.06% (-.12, -.00)	Pope, 1992[77]
Uniontown, PA (1990)	$PM_{2.5}$ PM_{10} SO_4	36 (N/A-83)	O_3, SO_2 acid aerosol	PEF	children	-0.10% (-.20, -.00)	Neas, 1995[80]
State College, PA (1991)	$PM_{2.1}$ PM_{10} SO_4	32 (N/A-83)	O_3, SO_2 acid aerosol	PEF	children	-0.04% (-.12, -.03)	Neas, 1996[81]
Port Alberni, Canada (1990-92)	PM_{10}	27 (1-158)	none	PEF	non-asthmatic children asthmatic children	0.01% (-.29, .31) -0.18% (-.35, -.01)	Vedal, 1997[82]
Wageningen, Netherlands (1990-91)	BS PM_{10}	N/A (0-175)	NO_2, O_3, SO_2	PEF	symptomatic children	-0.09% (-0.20, 0.01)	Roemer, 1993[83]
Austria (1991)	SO_4 PM_{10}	9 (N/A)	acid aerosol O_3	FEV_1	FEV_1	-0.62% (-1.34, .00)	Studnicka, 1995[88]

*FEV_1 = forced expiratory volume in 1 second
PEF = peak expiratory flow

although the rare mortality study has also made use of this design (see Table 6).[105]

Experimental Data

Data generated from the toxicological studies and the experimental human studies will not be reviewed in detail here. Several reviews of these data have been published recently[106,107] in addition to the review presented in the U.S. Environmental Protection Agency (EPA) criteria document.[108]

Human experimental studies. Studies to be briefly reviewed in this section include controlled studies performed with human subjects in a laboratory setting. Such studies have almost exclusively been limited to those assessing the effects of acid aerosol on level of lung function. Further, because subjects with more severe respiratory or cardiac impairment cannot reasonably be expected to participate in such studies, study findings can only be generalized to a relatively healthy subset of the population.

Most studies have investigated the effects of acid aerosol in mild asthmatics, and results have been variable. The most substantial effects at a relevant concentration were seen in a relatively early study in which mild reductions in airflow in adolescent mild asthmatics with exercise were produced following chamber exposure to a concentration of 100 μg/m^3 of sulfuric acid aerosol.[109] In an even earlier study, no reductions in airflow in a similar sample of asthmatics could be produced by sulfuric acid aerosol in concentrations 10 times higher than those used in the above study.[110] Others have produced small reductions in measures of airflow in asthmatics following exposure to sulfuric acid aerosol, but only in relatively high concentrations.[111,112] However, even these findings have not been consistent.[113] More recent studies by some of the same investigators have failed to show adverse effects on level of lung function in exercising asthmatics,[114,115] although it was suggested that acid aerosol exposure could potentate the response of asthmatics to ozone exposure.[115] Studies using other acid species, or acid species with lower hydrogen ion concentrations for a given mass, have not added significantly to the information obtainable from the studies above. Studies of acid aerosol challenge in normal subjects have generally been negative.

Experimental non-acidic particle exposure studies are essentially lacking. Ferric sulfate challenges have been

Table 6. Other study designs and outcomes: selected studies.

Location and time	Outcome	Design	Particle measures	Reference	Increased particles concentrations associated with:
Steubenville, OH (1978-79)	lung function	longitudinal	TSP	Dockery, 1982[86]	reduced FVC* in children
U.S.A. (1980)	mortality	cross-sectional	$PM_{2.5}$, SO_4 TSP, PM10	Ozkaynak, 1987[105]	increased mortality
Six U.S. Cities (1980-81)	lung function and respiratory symptoms	cross-sectional	$PM_{2.5}$, SO_4 TSP, PM_{15}	Dockery, 1989[102]	increased bronchitis symptoms in children but not lung function
California (1976-81)	activity restriction	longitudinal	$PM_{2.5}$	Ostro, 1989[98]	restriction of activity
Utah Valley, UT (1985-88)	hospital admissions	longitudinal	PM_{10}	Pope, 1989[96] & 1991[97]	increased respiratory hospitalizations
Utah Valley, UT (1985-90)	school absenteeism	longitudinal	PM_{10}	Ransom, 1992[99]	increased school absenteeism in children
Six U.S. Cities (1974-91)	mortality	longitudinal cohort	$PM_{2.5}$, SO_4	Dockery, 1993[91]	increased mortality from lung cancer or cardiopulmonary disease
Seattle, WA (1988-90)	lung function	longitudinal cohort	nephelometry	Koenig, 1993[100]	reduced FVC* in children with asthma only
Salt Lake City, UT (1987-89)	lung function	longitudinal	PM_{10}	Pope, 1993 [87]	reduced FVC* in subjects with COPD*
California (1977-87)	respiratory symptoms	longitudinal cohort	TSP, visibility	Abbey, 1995[93,94,95]	development of respiratory symptoms
U.S.A. (1982-89)	mortality	longitudinal cohort	$PM_{2.5}$	Pope, 1995[92]	increased mortality from lung cancer and cardiopulmonary disease
24 U.S. and Canadian Cities (1988-91)	respiratory symptoms	cross-sectional	$PM_{2.1}$, SO_4, acid aerosol	Dockery, 1996[103]	recent bronchitis in children
24 U.S. and Canadian Cities (1988-91)	lung function	cross-sectional	$PM_{2.1}$, SO_4, acid aerosol	Raizenne, 1996[104]	reduced FVC* in children
Four Cities, Netherlands (1987-90)	lung function	longitudinal	PM_{10}	Hoek, 1994[84]	decreased PEF* in children
London, England (1991)	mortality, hospitalization	episode (longitudinal)	BS	Anderson, 1995[101]	increased mortality and respiratory hospitalization - but not different from control areas

*FVC = forced vital capacity PEF = peak expiratory flow COPD = chronic obstructive pulmonary disease

carried out in normal and asthmatic subjects, with no significant effects on level of lung function being produced in either group.[116] The human experimental data have not provided convincing evidence for adverse effects of particle exposures under realistic exposure conditions.[106] The relevance of the human experimental data will be greatly enhanced as techniques for generating the complex mix of particles present in ambient air are applied in these experimental settings.

Toxicological animal studies. Preliminary reports of recent experimental animal studies have provided some support for the plausibility of the epidemiological observations. Preliminary findings of a study of the relative lung toxicity of ambient particles of varying sizes in rats have recently been reported.[117] Ambient particles in Washington, D.C., were collected and fractionated into particles of the following diameter size ranges: <1.7, 1.7-3.7, and 3.7-20 µm. Broncho-alveolar lavage following tracheal instillation of the particles showed evidence of greatest injury in the animals receiving particles in the smallest size fraction. These smallest particles also contained the highest sulfate, transition metal, and acid content. Interestingly, washing of these smaller particles with water attenuated the injury, suggesting that chemical composition of the particle surface was important.

Preliminary data have also supported the epidemiological findings that subjects with pre-existing respiratory disease are particularly susceptible to the effects of particles. Animal models of pulmonary hypertension[118,119] and of chronic bronchitis[120] have been used to show that lung injury following particle exposure is especially pro-

nounced in the subsets of diseased rats. The observed lags in the epidemiological studies between the increases in particle exposure and health outcomes might support the notion that particles incite an inflammatory reaction that appears to occur during the deposition and initial processing of inhaled particles, rather than later as the particles are further processed.[121] Inflammation may be related to the ability of particles to induce formation of free oxygen radicals, which in turn may depend on the particle concentration of surface-complexed iron (Fe^{3+}).[122-124] The toxicological studies are making a start at identifying specific particle components or features and elucidating mechanisms that may be responsible for the health effects attributed to particle exposure in the observational studies.

LINES THAT DIVIDE

Introduction

In this section, three timely issues relating to the health effects of ambient particle pollution will be discussed, each represented by a dividing line. The *first line* represents the division between health researchers who believe that the health studies provide strong evidence in favor of a causal relationship between ambient particle concentration increases and adverse health effects and those who do not. The *second line* represents the division of particles into more and less pathogenic particles based on differences in particle size or chemical composition, differences that also produce divisions based on geographical lines. The *third line* represents the particle concentration cut-point defined by an ambient air quality standard.

Line One: The Health Studies

1. Criticisms

Many criticisms of the methods used in the studies reviewed have been put forward by air pollution health researchers. These criticisms can be grouped into the following categories: (1) inadequate analytic methods, (2) misclassification of the exposure, and (3) inadequate control for confounding factors.

The most analytically challenging of the study designs used in studying the effects of ambient particles is undoubtedly the longitudinal or time series study of the relationship between short-term increases in particle concentrations and the acute health outcomes. Although confounding by subject characteristics that do not vary over the period of such a study, such as cigarette smoking status, for example, should not bias the effect estimates, potential confounding by factors that do vary over time is equally troublesome. Confounding possibly can lead to attributing the effects of another pollutant to particles, or to obtaining an invalid effect estimate for particles. Factors that vary over substantially different time spans than the particle concentrations can also introduce bias in the time series studies.[64,125] Therefore, long-term trends or cycles in the particle concentrations or health outcomes need to be controlled in any analysis.

The two main approaches that have been used in dealing with confounding by time-varying covariates is either to attempt to remove effects of these factors from the health outcome and the pollution time series before analyzing the exposure-outcome association, or to attempt to control for their effects by incorporating the time-varying covariates into the same models in which the association is analyzed. The choice of approach taken seems to be determined more by the investigator's familiarity with the respective analytical techniques than by the relative merits of the techniques. One point in favor of incorporating the covariates into the same models is to allow estimation of the covariate effects, which for some covariates such as those defining meteorology, may also be of interest.

Another potential complication in analyzing these longitudinal studies of acute effects is that the outcome data may be serially correlated; that is, correlated over time. For example, the mortality rate on any given day may be more similar for two days if one day immediately succeeds the other than if the days are more separated in time. Such data are therefore not independent. Since independence of observations is an assumption that underlies statistical inference, lack of independence can significantly affect the interpretation of analytic results largely by affecting the estimated standard errors and thereby the level of statistical significance.

An additional potential analytic problem is poor model specification, with the models selected failing to reflect important features of the data. One way in which a model could be poorly specified is if it did not reflect the presence of interaction, also known as effect modification, in the data. One common issue in air pollution epidemiology is whether the effects of an air pollutant vary across season. Models that do not allow for such variability, either by incorporating interaction terms in the models that allow the estimated effect of particle pollution to vary by season, or by estimating separate models for each season, may misrepresent the effect of air pollution.

Misclassification of exposure would seem to be an obvious major problem in studies in which attempts are made to define exposure of a population over a large urban area from only a few monitoring sites, and sometimes from only one monitoring site. Not only do particle concentrations vary spatially over an urban area, with use of only a few sites not adequately reflecting that variability, but more seriously, concentrations measured at fixed, cen-

tral monitoring sites do not adequately represent exposures of a population that spends the large majority of time indoors. While it has been argued that the correlation between ambient and personal particle concentrations is higher over time within an individual compared to average ambient and personal concentrations over time averaged across individuals, and that it is the former correlation that is relevant to time series studies,[126] significant misclassification must still be present. The often used argument that non-differential exposure misclassification can only result in biasing an effect estimate toward the null value of no effect is not relevant. First, this notion leads to the absurd conclusion that in any study in which measurement error in the exposure measure is present, which must be commonplace, the effect of the exposure is *always* underestimated. It has been clarified that the effect of biasing an effect measure to the null value refers to the true measure of an effect, not to the estimate of an effect that is derived from our statistical analyses.[127,128] Finally, it is now understood that measurement error in the exposure in settings where several covariates are considered (which is nearly universal), with each covariate also being measured with some error, can result in biasing the estimates of effect in *any* direction.[129-132] Therefore, measurement error in the exposure therefore cannot be relied upon to result in conservative effect estimates; sometimes the true effect will be overestimated and sometimes underestimated in an unpredictable fashion.

The longitudinal investigation into the effects of particle pollution on mortality has prompted criticism of the methods used, which are based on the entire array of potential criticisms outlined earlier in this review. Sometimes this has taken the form of reanalyzing a similar data set that formed the basis of a previously reported study in order to attempt to point out methodologic deficiencies in the earlier study. The mortality data from Steubenville, OH, have been reanalyzed,[25] as have the data from Philadelphia, PA[26,132] and Utah Valley.[134] Findings of these repeat analyses have been interpreted as showing that the results of the initial analyses were neither as consistent as initially reported nor as convincing in demonstrating that the observed effects were attributable to the particle component of the pollution mix.

Reports of the several analyses of the Philadelphia mortality data, and the accompanying editorials and letters, exemplify well the controversy.[21,26,135-138] Results of the initial analysis of the Philadelphia data were reported as showing a statistically significant association between short-term increases in ambient particle concentrations (as measured by TSP) and daily mortality.[21] Time-varying factors such as temperature, the co-pollutants (in this case SO_2), and long-term trends in the data were controlled in the analyses. It was concluded that the estimate of effect for TSP was largely unaffected by control for SO_2 while the effect of SO_2 was greatly diminished following control for TSP. This implied that the effects of TSP were independent of those due to other pollutants; that is, that the effect of TSP was not confounded by a co-pollutant. The associations were strongest for respiratory and cardiac causes of death and for those 65 years of age and older. No association was observed for control causes of death. Results of two subsequent analyses were reported and were interpreted as being at variance with the findings of the original report. One reported that the findings were sensitive to the choice of model used to analyze the data; importantly, it was not clear which models were superior.[133] The second reported that the associations observed were dependent on the season of the year, and that this aspect of the data should be reflected in the models chosen to analyze the data.[26] Further, when two prominent co-pollutants, SO_2 and O_3, were included in the analysis, no statistically significant effects were observed for TSP in any season, but that statistically significant effects were seen for O_3 in the summer and for SO_2 in every season except summer.

These reports were followed by a series of editorials and letters. The initial editorial that accompanied the second reanalysis of the Philadelphia data was supportive of the argument that the modification of the particle effect by season on the year should be reflected in the modeling strategy.[135] Further, singling out particle pollution as the primary cause of the observed mortality effects based on a model that included both TSP and SO_2 was asking too much of a statistical model. That is, the original investigators were criticized for taking a "biostatistical" approach to interpreting the data. In a commentary paper responding to the reanalyses of the Philadelphia data the original investigators criticized the reanalyses as examples of data "overmodeling" (that is, including several highly correlated factors [in this case the air pollutants] in the same model, and stratifying the analyses by season).[136] Also, by not placing the findings of the Philadelphia analyses in the context of the extensive epidemiologic work on air pollution, specifically on particles, these researchers were "not seeing the forest for the trees." In a letter response to this commentary it was argued that even in the "forest" of studies, in no single study was it possible to single out particle pollution as the prime culprit.[137] The authors responded by reasonably arguing that it is possible to exclude a confounding effect of a co-pollutant by performing studies in settings where co-pollutants are not present.[138] For example, the studies from Los Angeles[12] and Utah,[20] where SO_2 concentrations are very low and ozone concentrations are low in the winter, particle-associated effects were still observed. The suggestion that carbon

monoxide may be acting as the confounding co-pollutant in these settings does not seem plausible.

Some points can be distilled from this debate. First, the modifying effect of season probably should be accounted for in the observational studies, either through stratification by season or by attempting to incorporate the particle-season interaction into a unified model. Second, the absence of an adequate biological context has placed great emphasis on statistical models in attempting to attribute the effects of air pollution to particles specifically, models which may not be up to the task. Third, it is unlikely that a co-pollutant is confounding the effects of particle pollution in every single setting where an observational study has been performed.

The array of methodologic criticisms prompted the Health Effects Institute (HEI) to fund a series of analyses of the same data sets used for some of the major American longitudinal epidemiological studies of particle effects on mortality. Some of these analyses have now been completed for Philadelphia.[139] The investigators found that the originally reported findings seemed to be valid and were not very sensitive to the choice of modeling approaches to the analysis. However, the conclusion that these data could not distinguish the effects of particles from those of other pollutants, namely SO_2, was supported by the results of these additional reanalyses. Concerns about misspecification of the form of the meteorological covariates were allayed by analyses incorporating alternative specifications in the models.[140] These alternative specifications did not improve upon the ability of the models to detect the air pollution effects (see section on Plausibility).

Although the following distinction is overly simplistic, and does the respective investigators some injustice, the debate has features that are reminiscent of the "pragmatic" and "biostatistical" approaches to interpreting study results.[9] Rather than identifying investigators as belonging to one camp or the other, it seems more useful to apply this distinction to specific instances where a "pragmatic" or "biostatistical" stance is taken. A single investigator or group of investigators may exhibit both characteristics, sometimes at different times, or sometimes even in the same report. It should be noted that this distinction is not intended to impugn biostatisticians, because, in the sense intended, biostatisticians can take a "pragmatic" approach and non-biostatisticians can take a "biostatistical" approach. The findings of observational studies have played a central role in the deliberations of policymakers attempting to determine whether, and at what concentrations, specific components of air pollution have contributed to ill health. With policy focused on the individual components of a pollutant mix, researchers, including epidemiologists, have also attempted to focus on the effects of individual pollutants.[135] It is unusual for a scientific report on an epidemiological study of air pollution health effects not to include mention of current ambient air quality standards and the role that the study findings play in either supporting the current standards, or most commonly, in arguing for more restrictive standards. While there is nothing inherently wrong with making such policy recommendations, one runs the risk of letting the demands of policy not only determine the focus of scientific inquiry but also mold the form that interpretations of studies take. Studies then have a tendency to become pieces in the "mosaic" being built to make a specific case for a policy change and the epidemiologists become "pragmatists," rather than contributing to our understanding of disease. As noted earlier, the tendency to take the other approach, the "biostatistical" approach, is prompted by the lack of an adequate biological context in which to frame the study conclusions.

A more basic issue than those raised by the methodological criticisms discussed above concerns that of biological plausibility and the nature of the association between the pollution concentration and health outcomes increases. If one accepts for the moment that the observational studies present a consistent and coherent picture of particle-induced health effects, there is little argument that the observational findings would not allow a stronger case for causality if they were complemented by relevant experimental animal and human data and by some understanding of the mechanisms by which particles exert their effects.[106,107,141]

2. Attempting an Alternative Hypothesis

It has been argued, given the consistency and coherence of the series of observational studies, that the burden of proof has been shifted to those who maintain that the observational findings do not reflect a causal association.[47,142] One could ask, then, whether it is possible to make a good case that the findings do not reflect a cause and effect association that is equally, or even more, plausible than the case for causality. Besides the relative lack of relevant, supporting experimental data to enhance plausibility, a case against causality can be based on the following observations: (1) similar associations between increases in particle concentrations and the adverse health effects are found at *any* range of particle concentrations studied, (2) similar associations are observed across settings where the source and chemical composition of the particles differ, (3) the health outcomes associated with particle concentration increases are not very specific, given the associations observed for cardiovascular and other outcomes, and (4) there must be significant misclassification of exposure that results from using central

monitors of ambient particle concentrations for populations that spend the vast majority of time indoors.

Mortality effects are observed across settings where particle concentrations differ by an order of magnitude. In many studies, when the analyses are stratified by season, the strongest associations are observed during seasons with the lowest particle concentrations. In studies in Port Alberni, British Columbia, estimates of effect on level of lung function and on respiratory symptoms were similar during the winter when particle concentrations were relatively high and during the spring when they were very low.[82] Short-term variations in ambient particle concentrations, at both relatively high and low concentrations, are therefore often observed to have similar effects. While it is conceivable that variation in particle concentrations at low levels results in similar adverse effects as variation at high levels, it seems equally plausible, if not more plausible, that the phenomenon of short-term variability in particle concentrations is reflecting temporal variability in another factor or process.

Observing similar associations in settings with different sources of particle emissions has been used to argue that the effects are related to particles generated by combustion processes, regardless of the specific composition differences of these particles. Particle mixes may be composed predominantly of particles from automobile combustion, industrial emissions, wood burning, or coal burning, as well as transported particles. It is surprising that the effects of such heterogeneous particles are similar. It seems equally plausible that whatever contributes to the day-to-day variability in particle concentrations in these different settings, if it also affects health it is confounding the particle-health effects association in every setting.

Exposure to toxic agents need not necessarily result in one specific health effect (again, the effects of cigarette smoke come readily to mind). However, when unexpected associations are observed, in addition to attempting to conjure up plausible explanations as to why an agent may be toxic to another organ system, the possibility of uncontrolled confounding needs to be seriously revisited. Alternative mechanistic hypotheses,[52,53] as well as the notion that those who are dying cardiovascular deaths in fact have respiratory problems,[141] have been proposed to explain the unexpected associations with cardiovascular outcomes. Recently, short-term increases in particle concentrations, as well as concentrations of other air pollutants, were observed to be associated with increased risk of pre-term deliveries.[143] Again, mechanistic explanations for the association were proposed. Seasonal variation in early pregnancy loss has been documented.[144] Similarly, an association with death from cerebrovascular accidents (strokes) has been reported.[142] Although these associations may in fact be due to particle exposure, when yet another unexpected association is observed, more serious consideration of the likelihood of confounding is indicated.

A case has been made that what appears to be significant exposure misclassification in the particle epidemiology studies is really not as significant as it appears.[145] For the time series studies the important measure is the short-term concentration *change*, not the absolute concentration on any given day. The correlation between individual exposure and ambient concentration over time is interpreted to be reasonable.[126] Also, if exposure to submicronic particles is the most critical exposure because they gain ready access to the indoor environment, misclassification of them may not be serious. Although indoor submicronic particle count concentrations may correlate with ambient concentrations, they are much lower.[146] Exposure misclassification remains a serious concern. It is possible that ambient particle concentrations are a better measure of a factor for which exposure is not as badly misclassified as the particle exposure measure itself.

Short-term variability in particle concentrations is caused by short-term changes in meteorological factors and changes in local particle emission rates, and, in some settings, variability due to changes in long-range particle transport. In an urban setting where there is little short-term variability in emission rates, the primary determinant of concentration variability is presumably variability in meteorological factors and particle transport. Meteorology clearly influences the health outcomes of interest.[142-151] Both high and low extremes of temperature are strongly associated with mortality, including respiratory and cardiovascular mortality. Variable lags between the changes in temperature and mortality are present. Associations are also present in cities such as Seattle, WA, where the climate is moderate in all seasons.[151] Temperature effects on blood pressure might be one mechanism whereby effects on cardiovascular outcomes might be mediated,[152] but others are also plausible. Two cities may experience very different absolute particle concentrations as a result of very different particle emission rates and, possibly, topography. Short-term variability in the particle concentrations in both cities is determined by short-term changes in meteorology, which also affect the health outcomes. An observed association between short-term changes in particle concentrations and adverse health effects in each of these cities could therefore be a spurious association, with some feature of meteorology serving as the unifying confounding variable. Such a factor could also explain the apparent unimportance of the chemical composition of the com-

bustion particle, explain the somewhat surprising associations with cardiovascular and pregnancy outcomes, and explain why such apparent misclassification of exposure results in relatively consistent associations.

For this hypothesis to be plausible, attempts to control for the effects of the relevant changes in meteorology in the observational studies must have been inadequate. Because of the very reasonable concern that meteorologic factors could confound the association between particles and ill health, investigators have attempted to be rigorous in controlling for the potential effects of meteorology. Typically, this takes the form of adding variables for temperature, often humidity, and sometimes other meteorological factors to the regression models.[64] It is possible that such approaches still allow confounding of the association by these or other features of meteorology. Another approach to controlling the effects of meteorology has been the use of empiric "nonparametric" functions (generalized additive models or LOESS smooths) that require few distibutional assumptions and are flexible in reflecting nonlinearities in the exposure-response relationships. Again, unless the appropriate meteorological factors are included in the models and are adequately specified, residual confounding is still possible. Given the small sizes of the estimates of effect for particle pollution, even a small degree of confounding may be critical.

As part of the ongoing series of studies supported by the Health Effects Institute (HEI) aimed at improving understanding of the association between particle pollution and mortality, the investigators evaluated alternatives to controlling for the effects of meteorology.[140] Synoptic weather categories have been proposed as an improvement in previous relatively crude approaches to capturing those meteorological features that are important in influencing health outcomes.[153] Incorporating synoptic weather categories into the regression models used in analyzing the Philadelphia mortality data to control for the potential confounding effects of meteorologic factors did not result either in improvement in the models predicting mortality or in affecting the estimates of effect of the particle concentrations on mortality. It is perhaps not surprising that the synoptic weather variables did not perform better, since they are constructed as composite variables made up of a host of individual meteorologic features, some of which (such as wind speed and direction, for example) might not be expected to influence the health outcomes. Therefore, although the synoptic weather variables may generally improve upon cruder approaches to summarizing the features of meteorology, they may not provide any improvement in better specifying those meteorological features that are relevant for influencing health, or those features that determine changes in particle concentrations. That is, the aspect of meteorology that might be acting as the confounding factor may not yet be well specified in these analyses. Results of the planned future HEI analyses of the data from other U.S. sites will provide an opportunity to further assess alternatives for specifying the effects of meteorology.

It is often argued, as noted earlier, that observing consistent associations between particle pollution and adverse health effects in settings where the highest particle concentrations occur in different seasons with very different meteorological features is a strong argument against the potential for confounding caused by some feature of meteorology.[46] However, since meteorology affects health in settings with very different meteorology, as long as short-term variability in particle concentrations is partly determined by changes in meteorology, even if these features are not the same for all settings, uncontrolled meteorologic factors could still act as confounders. This is particularly relevant when the estimates of effect are as small as those estimated in the observational studies. It seems then, given all of the above arguments, that a case can still be made that some meteorologic factor or factors can be acting as a confounding factor and provide a plausible explanation for the apparent particle-related health effects. The challenge now for those who see any merit in this hypothesis is to propose some meteorological factors that have either not been considered, or are more likely poorly specified, as in the observational studies.

Line Two: The Particles

1. Particle Size

The recent EPA proposal to include standards for fine inhalable particles ($PM_{2.5}$) was based on an extensive review in which a strong case was made for considering the fine particle fraction to be more pathogenic than the coarse fraction of the inhalable particle fraction.[154] Although associations of $PM_{2.5}$ concentration with several health outcomes have been evaluated in many observational studies, most have not been able to evaluate in parallel the association with the coarse inhalable particle fraction (CP). These studies are therefore unable to directly assess the relative impacts of the fine and coarse fractions. Fortunately, in a few studies the investigators had access to measurements of both inhalable and coarse fraction concentrations, and were able to evaluate their relative impacts. Although the findings of these are not entirely consistent, a good case can be made that the fine fraction is more pathogenic than the coarse fraction. The strongest evidence is based on findings reported recently on six U.S. cities.[145] Daily mortality in these cities was strongly associated with short-term increases in $PM_{2.5}$ concentrations and only weakly associated with increases in CP.

Further, even the apparent weak association with CP seemed to be influenced by one of the cities in which concentrations of $PM_{2.5}$ and CP were highly correlated, implying that the apparent association with CP in that city was in fact reflecting the impact of $PM_{2.5}$, and that the weak overall association of mortality with CP was in fact attributable to $PM_{2.5}$.

In an earlier study of only two of these six cities with a shorter period of follow-up, effects of both $PM_{2.5}$ and CP were observed.[19] However, a preliminary report on a recent analysis of Philadelphia mortality data[155] and a report on respiratory hospitalizations in Toronto[56] both described effects that were restricted to the $PM_{2.5}$ concentrations, with no effects associated with concentrations of CP. A much earlier study of asthmatics in Denver observed no associations between increases in either $PM_{2.5}$ or CP and exacerbation of asthma.[73]

A recent report of a "western" study from Anchorage, AK, may be the only study that casts doubt on the notion that the health effects attributed to PM_{10} are largely attributable to the $PM_{2.5}$ fraction of combustion-derived particles (see Geography section).[156] It was argued that since there are no major industrial sources of particle emissions in Anchorage and no significant residential wood burning, the major source of particles is resuspended dust from road sanding and from volcanic dust. Reportedly, 80% of the PM_{10} is in the CP fraction, with most of that being silica. The median $PM_{2.5}$ to PM_{15} ratio was 0.26. All of this suggests that most of the PM_{10} measured in Anchorage is composed of relatively large, crustal particles. The health study investigated the association between short-term increases in PM_{10} and daily office visits to a health maintenance organization. Associations were observed for visits for upper respiratory illness and for asthma. At face value this observation suggests that crustal particles in the CP size range can cause adverse health effects, although it is conceivable that the fine particle fraction was still the most pathogenic fraction. Doctor visits is an outcome not often used for the purpose of investigating the effects of air pollution. One difficulty is that it is not always possible to distinguish scheduled from unscheduled visits using retrospectively collected data. Since only unscheduled visits are relevant for assessing the effect of short-term concentration increases, only a fraction of the doctor visits provide useful data. It was not clear from this report whether scheduled visits could be distinguished from unscheduled visits. Further work in settings such as Anchorage is needed in order to confirm these findings. A weak but statistically significant association between dust storms and increased emergency room visits for respiratory illness was observed in an earlier study performed in southern Washington State (see Table 3), another western location, which also suggests that crustal (non-combustion) particles in the CP fraction can result in some adverse effects.[71]

A case has been made that the *ultrafine* particle fraction (particles smaller than 0.1 μm) within the fine particle fraction is the most pathogenic and is largely responsible for the particle-associated findings reported in the observational studies.[157] This case is based on both theoretical arguments and animal experimental data. The theoretical argument is based on the mathematical relationship that combined particle surface area for a given mass concentration increases exponentially as the diameter of the particles decreases. If particle surface area is the primary determinant of particle pathogenicity, then the smaller the particles for a given mass concentration the greater the pathogenic effect. It is not clear that combined surface area is a critical determinant of pathogenicity. Further, the fact that surface area increases given the above assumptions may not be relevant if significant exposure to ultrafine particles does not occur. It is observed that the mass concentration of ambient ultrafine particles is much lower than the mass concentration of larger particles.[158] Therefore, the combined ultrafine particle surface area is much smaller than would be predicted for equivalent mass concentrations. Even the count concentration of the ultrafine fraction tends to decrease as particle size decreases below 0.1 μm.[159] Given the propensity of particles within the ultrafine fraction to rapidly agglomerate into larger particles, significant numbers of ultrafine particles may not reach the portions of the lung that are susceptible to ultrafine particle effects. Recent work on human autopsy lungs has shown that only low concentrations of ultrafine particles are resident in human lungs,[160] implying either that ultrafine particles do not reach those portions of the lung, or if they do, they disappear either because they are soluble or are transported.

Toxicological studies in animal models using high concentrations of aggregates of ultrafine particles have demonstrated that ultrafine particles can cause lung injury as reflected by increases in alveolar and interstitial inflammation[161] and increased lung fibrosis;[162] but in these models the exposure to ultrafine particles did not cause death. Using an ingenious method of generating ultrafine particles that allowed more realistic concentrations of *unaggregated* ultrafine particles to be used, exposed rats developed lung inflammation as measured by increased white blood cells in a lung wash (bronchoalveolar lavage), and the rats died as a result of bloody fluid exuding into the lung (hemorrhagic pulmonary edema).[157] It was argued that the ultrafine particle count concentrations that were generated was only one order of magnitude higher than concentrations that can be observed in urban air.

There are very few epidemiological data that bear on the issue of the role of ultrafine particles. Data presented in preliminary form have been contradictory. A report from Erfurt, Germany, documented associations between ultrafine particle counts and reductions in level of peak expiratory flow (PEF) in adults with asthma that were interpreted as being stronger than those associated with PM_{10}.[90] No significant association was found between increases in ultrafine counts and level of PEF in asthmatic children in Finland, although increases in PM_{10} were associated with PEF.[89]

In order for ultrafine particles to "explain" the health effects attributed to larger particles in the observational studies, concentrations of ultrafine particles must be strongly correlated with concentrations of the larger particles. If the same combustion source that produces larger particles in the PM_{10} fraction in a setting is also the source of the ultrafine particles, one might expect the PM_{10} and ultrafine concentrations to be highly correlated. This is the likely explanation for the strong correlations between ultrafine particle counts and PM_{10} concentration measured in Erfurt, Germany, as reported in abstract form.[90] In the study from Finland, also reported in abstract form, ultrafine counts were only weakly correlated with PM_{10} concentrations.[89] Toxicological research using relevant concentrations of ultrafine particles and data on actual human exposures to ultrafines, in addition to further epidemiological study, will be necessary before ultrafine particles can be implicated in contributing to particle-associated health effects.

2. Particle Composition

The evidence favoring a role for particle composition in determining the health effects of ambient particles is not as convincing as the evidence for a role for particle size. Although particles emitted from combustion processes seem to be more consistently pathogenic than crustal particles,[71] it is not clear that this difference is not merely due to the fact that combustion particles are predominantly in the fine inhalable fraction, whereas crustal particles predominate in the coarse fraction; that is, the difference in the observed effects of combustion and crustal particles may relate to differences in particle size rather than particle composition. Nevertheless, it seems reasonable to suspect that chemical composition is one feature of particles that determines pathogenicity. The role of *particle acidity* has been investigated most extensively. Neither the experimental studies nor the epidemiological studies have been convincing in demonstrating a critical role for particle acidity. Initial human chamber exposure studies showed that exposure to acid aerosol caused a small reduction in level of lung function in adolescent asthmatics.[108,163] However, more recent work has failed to reproduce this finding even in adolescent asthmatics.[114,115] Subjects without asthma do not appear to experience adverse effects on level of lung function from acid aerosol exposure.

The epidemiological data on acid aerosol effects are conflicting. Arguments have been made that support a critical role for acid aerosol in causing the dramatic increase in mortality associated with the London fog of 1952.[164] Airborne acidity was associated with more measures of adverse effects than were concentrations of $PM_{2.5}$ or SO_4 in a panel study of asthmatics in Denver, Colorado.[75] In a time series study of respiratory hospitalizations in Toronto, levels of statistical significance were highest for associations of hydrogen ion concentration with total respiratory and asthma hospitalizations than for other measures of particle concentration.[56] More recent results reported in preliminary form were interpreted as showing a similar picture for mortality.[164] However, no associations between increased concentrations of acid aerosol and either respiratory symptom reporting in children[79] or mortality[144,154] have been reported by others. In a large cross-sectional study of children in 24 U.S. and Canadian cities, increases in symptom prevalence[103] and reduced level of lung function[104] were associated with increased concentrations of acid aerosol. Similar associations were also observed for concentrations of SO_4 and $PM_{2.5}$, which were highly correlated with the acid aerosol concentrations. Therefore, the effects could not be specifically attributed to the acid aerosol component of the particles. Given that the estimated effects associated with particles are similar irrespective of the presence of acid aerosol, and the conflicting findings of the epidemiological studies in settings with acid aerosol, arguments for an important role of acid aerosol in producing the effects of particles are not convincing.

3. Geography

North America: East vs. West. Most of the areas in the United States that have been designated "nonattainment" areas with respect to the EPA PM_{10} standards promulgated in 1987 are in the western states. Of the 70 areas designated in 1990 as nonattainment areas, at least 50 (71%) were in western states.[166] In 1993, five areas were classified as "serious nonattainment" areas; all were in western states. Based on monitoring data from 1993 to 1995, of the 41 regions not meeting the current EPA standards, 31 (76%) were regions in the western states, and another five were in mid-western states.[167] Only five (12%) were in the eastern United States. Of the 167 sites estimated to not meet the proposed EPA $PM_{2.5}$ standard, only 44 (26%) are in western states.[168] This reversal is clearly welcomed by west-

ern states as obviously are results from the lesser contribution of $PM_{2.5}$ to PM_{10} in western states. Emission sources for airborne particles are typically quite different in non-western and western states, with fugitive dust (which consists of a relatively large proportion of particle mass in the CP fraction) being a significant source of PM_{10} in western states. If particles in the CP range are less pathogenic than smaller particles (see below), then the newly proposed standards appropriately lessen the burden of the western states whose largest contibutor to PM_{10} is fugitive dust.

The particle characteristics that distinguish non-western and western states in the United States also distinguish the non-western and western provinces in Canada. A recent report described a study in Canada in which 19 sites across Canada underwent serial particle concentration measurements with simultaneous measurement of TSP, PM_{10}, $PM_{2.5}$, CP, and sulfate concentrations.[169] Prairie sites in Calgary, Edmonton (comparable to typical western states), and Winnipeg (north of the mid-western states) had the lowest $PM_{2.5}$ contribution to PM_{10} and had, apart from one site in Montreal sited in a heavy traffic area, the highest CP concentrations. The crustal source of these particles was reflected in the relatively high silica content of the particles. Interestingly, the sites on the west coast of Canada (Vancouver and Victoria in British Columbia) had relatively high $PM_{2.5}$ concentrations, and therefore large ratios of $PM_{2.5}$ to PM_{10}. Sulfate concentrations were markedly lower in the prairie provinces and the west coast, reflecting the relative absence of SO_2 emissions in those regions.

Interest in attempting to attribute the effects of particles to the *acid aerosol* component reflects to some extent the weight of observational studies performed in settings where acid aerosol concentrations are relatively high, such as the eastern parts of the United States and Canada. Since observations of particle-associated health effects from settings that experience only low concentrations of acid aerosol, such as in the western United States, are seemingly as valid as those performed in settings with high acid aerosol concentrations, it has been reasonably argued that the acid aerosol component is not critical for particle effects to occur. Nevertheless, the vast majority of animal and human experimental particle studies have been studies of acid aerosol effects. It seems that a more concerted effort to study the effects of more relevant types of particles, given the almost total reliance of the argument for causality on the observational data, would have better addressed the uncertainties left by the observational studies. Recent and ongoing experimental work is now attempting to make up for lost time.

North America vs. Europe. As noted earlier, the findings of the recent observational studies on particle pollution health effects performed in Europe (most notably, the APHEA series of studies) did not consistently show associations between increases in particle concentrations and relevant health outcomes (Table 1). Effect estimates were also generally smaller than those estimated in the U.S. studies. In addition, these findings did not strongly implicate the particle component of the pollutant mix as being specifically responsible for the health effects. Possible explanations for these differences include different susceptibility of the populations to pollution effects, differences in pollutant mix or particle composition, or differences in study methodology.

It is not obvious that any methodological differences in either the pollution exposure or mortality measures, or differences in statistical methodology, account for the divergent findings between these European and U.S. studies.[55] Another possible explanation is that the resident population in these European cities is somehow less susceptible to the health impacts of exposure to particles, with the "surviving" populations being relatively hardy. There is no evidence to support that conjecture, and if that were the case, it is unclear why similar dynamics would not prevail in many of the American cities that have been studied as well. If the pollution mix is critical for observing an effect of particles at comparable particle concentrations, then the argument that the particle exposure itself is the critical exposure in the American studies is weakened.

Recent European studies reported before the APHEA series of studies had observed associations between particle concentration increases and mortality (Table 1). In Erfurt, East Germany, a city with high emissions from coal burning, an association between increases in TSP and mortality was observed for the one-year period (1988-1989) when TSP measurements were available, a year when no significant association between SO_2 and mortality was observed.[28] Subsequent ambient air monitoring in Erfurt documented high concentrations of PM_{10}, but relative to North American levels, low concentrations of acid aerosol.[170] It was argued that the acid aerosol component was not important in determining particle toxicity. It is possible, and even likely given the monitoring data from Erfurt and elsewhere, that the particle mix in Europe is very different from that in the eastern parts of North America. It may be that some of the inconsistent findings of particle-associated health effects in the APHEA studies are due to differences in the particles. Only further study will determine whether this is the case.

Line Three: The Standards

1. The EPA Proposals

At this point, the discussion regarding whether the observed associations between increases in particle air pollution concentrations and adverse health outcomes reflect causal relationships will, for the purpose of setting policy, be assumed to be settled in favor of causality. The issue now is how the health data can best be used to set ambient air quality standards that will protect the public health.

The EPA has recently proposed changes to the U.S. National Ambient Air Quality Standards (NAAQS) for both particulate matter and ozone.[170] For particulate matter, these proposed standards include the addition of standards for fine particles ($PM_{2.5}$): an annual average concentration of 15 $\mu g/m^3$ and a 24-hour average concentration of 50 $\mu g/m^3$. The proposed changes to the NAAQS carry on two traditions in setting particle pollution standards: definition of a concentration cut-point and definition of both an annual and a 24-hour standard.

Cut-point. A concentration cut-point implies that the chosen concentration has some meaning, either in terms of the significance of the health effects that occur above that concentration, or in terms of the certainty with which particle pollution effects have been demonstrated above it. The first implies the existence of a threshold concentration below which no, or less significant, health effects are caused by particle exposure. However, the large majority of relevant observational health studies provides no evidence that such a threshold can be identified. Many exposure-response plots for several of the health outcomes have been presented in the literature, sometimes plotting effects by quantile of particle concentration as estimated using regression indicator variables for the quantiles (Figure 1(a)), or using smoothed nonparametric estimates (Figures 1(b) and (c)). Most of these plots indicate a relatively linear relationship with no obvious threshold particle concentration below which no relationship is apparent. The recent reanalysis of the Philadelphia mortality data for the Health Effects Institute indicated that some nonlinearity in the exposure-response relationship was present, although for deaths for those 65 years of age or older, the subset for which most of the particle effect was present, any alinearity occurred at only the very low and very high TSP concentrations for which much fewer data were available (Figure 1(d)). The epidemiological data therefore provide little evidence to support the presence of a lower particle concentration threshold.

Estimates of exposure-response relationships from epidemiological data, however, should be interpreted cautiously. More specifically, identification of thresholds from epidemiological data, even when present, is difficult. First, a linear exposure-response relationship does not imply that *individuals* do not respond at a certain threshold concentration. In a population study composed of individuals with definite but different concentration "thresholds," the population estimate of response, which is a composite of these individual responses, would show a threshold only at concentrations below which no significant individual responses occurred. If some very sensitive individuals provide data, then effects may be observable at very low concentrations, even though the large majority would experience no effects until much higher concentrations are reached. Second, misclassification of the exposure tends to produce a smooth exposure-response relationship even when a threshold type relationship is present.[172] With non-differential misclassification, where true exposure is as likely to be underestimated as overestimated, one could imagine that even if a true population threshold were present at some concentration, the threshold would be blurred by observing effects below the threshold in individuals whose *measured* exposure is below the threshold, but whose true exposure is above it. Third, confounding effects of other factors that may not be adequately controlled can also distort an exposure-response relationship. The interpretation of the exposure-response relationships presented for particle-associated health effects should be cautious, given the measurement error in the particle exposure and the likelihood of some residual confounding. Obviously such concerns complicate attempts to define a particle concentration cut-point for setting standards.

Averaging period. The motivation for proposing both an annual and a 24-hour standard bears examination. The most convincing observational data supporting particle-associated adverse health effects, and the most voluminous, are those generated by the time series studies in which short-term increases in particle concentrations are associated with increases in adverse health outcomes. Proposing a standard for a short-term particle concentration averaging time would seem to naturally follow from such data. As reviewed earlier, there are no data available to support a contention that long-term, low-level exposure, apart from repeated short-term concentration increases, results in adverse effects. Also, the evidence supporting the occurrence of chronic effects, even from such repeated short-term exposures, is relatively weak. The recent EPA proposals not only include both the annual and 24-hour standards, but view the annual standard as the primary standard and the 24-hour standard as supplementary.[171] This seems peculiar. Arguments put forward in support of an annual average standard being the primary standard include: (1) there is no evidence that the health effects associated with long-term exposures are driven by short-term concentration in-

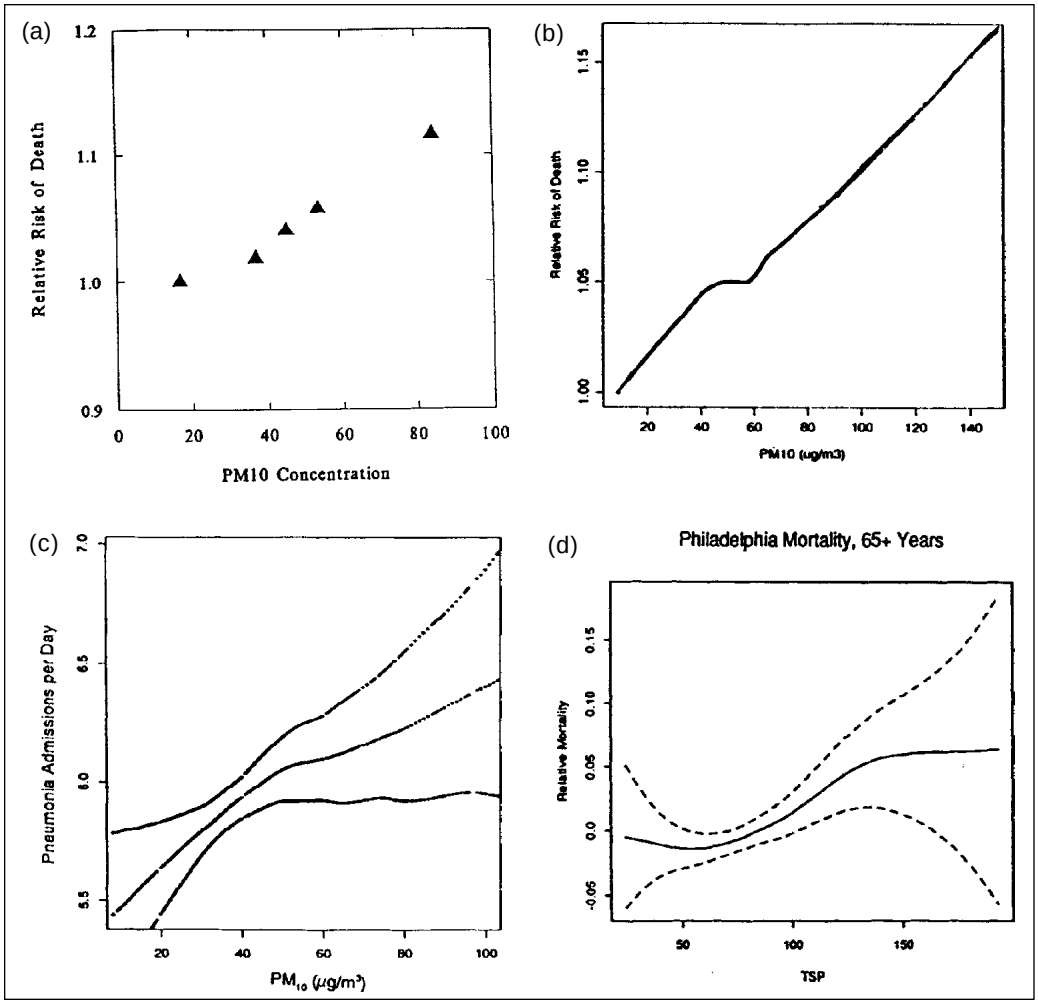

Figure 1. The exposure-response relationships between short-term increases in particle concentrations and daily health outcomes appears reasonably linear with no apparent threshold concentrations. The plots show the estimated relationship between short-term increases in PM_{10} (TSP) concentrations and the health outcomes. (a) risk of death in Utah Valley:[20] using indicator variables for quintiles of PM_{10} concentration; (b) risk of death in Birmingham, AL:[23] nonparametric smoothed plot; (c) pneumonia hospital admissions in Birmingham, AL:[61] nonparametric smoothed plot with associated 95% confidence interval. Note widening of the confidence interval at both extremes of PM_{10} concentration reflecting the relative sparseness of data at the extremes; (d) risk of death in the elderly in Philadelphia, PA:[138] nonparametric smoothed plot with associated 95% confidence interval. Note apparent threshold at a TSP concentration of approximately 70 μg/m^3 and a plateau at approximately 140 μg/m^3.

creases, (2) the consistent picture of associations of particles with acute effects is based on time series studies that typically span time periods greater than one year, (3) annual average concentrations are more stable than 24-hour concentrations and will therefore result in risk reduction strategies for any given region that are more consistent, and (4) an annual standard will also provide protection from effects due to short-term concentration increases. None of these arguments is very compelling. While it is true that there is no evidence that chronic health effects are due to short-term concentration increases, as noted, the evidence for the existence of these effects is relatively weak. An argument that there is no evidence that effects exist apart from those caused by repeated exposures to short-term concentration increases is equally compelling, especially when it is considered that the evidence for acute effects due to short-term concentration increases is relatively strong. The fact that time-series studies last longer than one year does not seem to be relevant. While it is true that an annual average is more stable than a 24-hour average, the choice of a standard should be based on considerations of health protection. The strongest evidence relates to acute effects from short-term increases, regardless of how unstable these concentration increases are. It is true that an annual standard will impact short-term concentrations. However, it seems that direct control of short-term concentrations is preferable to attempting to control them indirectly, while still allowing potentially harmful short-term concentration increases to occur that might not significantly influence an annual average. The supplementary role of the 24-hour standard is intended to prevent this latter scenario. Nevertheless, the emphasis on the annual average in the EPA proposals remains puzzling.

2. Alternative Approaches to Standards

A number of alternatives to the form of air pollution standard exemplified by the EPA proposal could be considered. Other regulatory or government agencies involved in setting air pollution standards, either in the United States or internationally, typically use a similar form of standard, although some exhibit minor differences. Some shortcomings of a particle standard that focuses on a single cut-point are: (1) there is no straightforward way in which the amount or degree of exceedance above that cut-point

can be incorporated, (2) the frequency with which such exceedances of varying degree occur is not easily incorporated, and (3) there is an inordinate emphasis on the specific cut-point chosen, which is difficult to justify given the findings of the relevant health studies. For example, in terms of the adverse health impact, if a 24-hour cut-point of 50 $\mu g/m^3$ is chosen, an exceedance when a concentration of 51 $\mu g/m^3$ is reached is not as significant as one in which a concentration of 151 $\mu g/m^3$ is reached. Reaching concentrations of 51 $\mu g/m^3$ on only five occasions during the year is not as significant as reaching that concentration on 50 occasions during the year. The health study data suggest that some members of a population will experience adverse health effects at very low particle concentrations. A concentration cut-point is selected to allow a "margin of safety" between that concentration and the point where adverse effects will be experienced. However, it seems difficult to justify the selection of any cut-point, unless it were very low indeed, that would provide such a margin of safety for every member of the population.

One of many possible alternative methods of defining standards that may have merit is described below. This method was selected to overcome the shortcomings of a cut-point type of standard noted above. In addition, it may be desirable to have the form of a standard mirror the form of the exposure-response relationships assumed by the statistical models used in analyzing the health data. This allows direct estimation of the health impacts due to exceedances of the standard, as well as the impacts not prevented by a chosen standard. A final feature of the alternative form of standard is to exhibit transparency of the assumptions used in determining the standard. This allows those assumptions to be readily debated, and focuses the needs for future research that would be required to support changes in, or confirm the selection of, the assumptions.

This alternative to the cut-point type of standard incorporates a mechanism for incrementally accumulating the number and extent of exceedances above a selected particle concentration. The assumptions required for such an approach are: (1) a short-term particle concentration can be identified above which health effects occur, (2) the size of short-term concentration *increase* that causes an acute increase in adverse health effect can be identified, and (3) the exposure-response relationship is linear, at least above a concentration where effects can be identified to occur. The first assumption is required in order to know where the counting of exceedances is to begin. The second assumption is required in order to know what to count as an exceedance. The third assumption is not absolute, and is only required for the specific approach described below. The health study regression models do not provide guidance in determining the lowest effect level, since the estimated regression coefficients estimate effects down to baseline particle concentrations, although it is risky to apply model estimates to concentrations outside the range of concentrations present in the data used to estimate the coefficients. Similarly, the models provide no guidance in determining how large a concentration increase is required in order for an effect to occur, estimating instead an effect for any concentration increase that is stipulated. For example, although an effect can be estimated for a 1 $\mu g/m^3$ increase in PM_{10}, there is no evidence, and it is indeed unlikely, that more adverse effects would occur following such a small concentration increase.

First, a PM_{10} concentration will be proposed above which adverse health effects are observed to occur. Since no such concentration can be confidently identified, some guesswork is needed. Although the health studies provide little evidence to support the existence of a threshold concentration below which no effects of ambient particles occur, inspection of a host of dose-response relationships for several of the health outcomes, generated in a number of ways, would suggest that there is only meager evidence to support occurrence of effects below a PM_{10} concentration of 20 $\mu g/m^3$. Because of the limited data available from studies at this low concentration, one can have little confidence that effects are observed below that concentration, even though some dose-response plots suggest that the linear relationship extends below it. It will therefore be proposed that only increases in PM_{10} concentrations that occur somewhere above a concentration of 20 $\mu g/m^3$ are capable of causing adverse health impacts.

Second, a minimal PM_{10} concentration *change* that is required to produce a change in health effects will be proposed. This change should be greater than the variability in the measurement of daily PM_{10} concentrations. Acceptable measurements of 24-hour PM_{10} concentrations should be reproducible within 5 $\mu g/m^3$.[173] The concentration increase chosen should therefore be at least as large as 5 $\mu g/m^3$. Unfortunately there are no data that specifically address how large a concentration increase is necessary to produce a measurable adverse health impact. The regression models estimate effects for *any* concentration increase, and are therefore of little use for this purpose. One approach might be to divide the range of PM_{10} concentrations in a particular study, in which a relatively linear exposure-response relationship was observed, into a number of quantiles (say, quintiles). The quantile for which the estimated effects were observed to be greater than, for example, the lowest

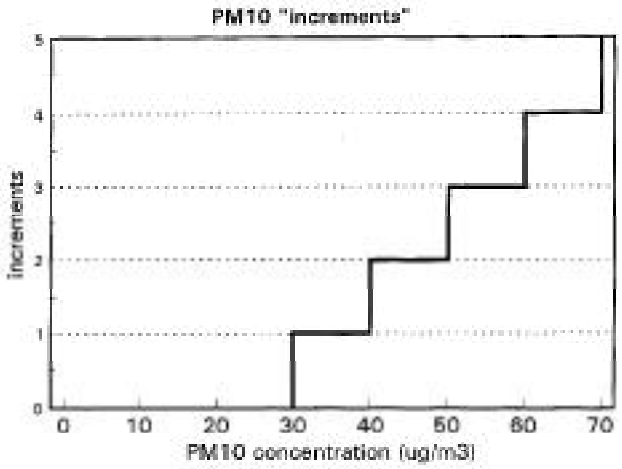

Figure 2. Method used for counting PM_{10} "increments." Counting begins at a PM_{10} concentration of 30 µg/m³ and increases incrementally for each additional 10 µg/m³ increase (see text).

quantile, could then be identified. The difference in mean concentration within each of the two quantiles might be taken to be the smallest concentration difference for which a difference in effects is detectable. Unfortunately, for studies in which such results are presented, there is generally never a statistically significant difference between any but the lowest and highest quantiles, either because study power (that is, sample size) is inadequate to allow a real smaller difference to be detected, or the differences in health effects are in fact too small.

Another approach might be to restrict the analysis of data to days with particle concentrations only within the range of interest. This approach is often taken to argue that effects are still observed for PM_{10} concentrations below the current EPA standards(). However, it is likely that in order for this approach to address the small concentration increases of interest, the amount of data that would be excluded would severely compromise the ability to perform an adequate analysis, particularly when lags between the concentration increases and the health effects are evaluated.

A final approach would be to perform studies in settings where only limited particle concentration increases occur. Limited increases in PM_{10} concentrations were observed during the spring season in a recently completed panel study of children's respiratory symptoms and level of lung function in Port Alberni, British Columbia.[82] Estimated effects on reported cough and level of peak expiratory flow (PEF) in children with asthma were similar to those estimated during the winter when particle concentrations, and particle concentration changes, were greater. When the few days in the spring when PM_{10} concentrations exceeded 40 µg/m³ were excluded from the analyses, no noticeable impact on the effect estimates was seen. Taken at face value, this finding argues for an effect of particles occurring below a PM_{10} concentration of 40 µg/m³, with relevant concentration increases being less than 40 µg/m³. If one can maintain that effects are not observed below a PM_{10} concentration of 20 µg/m³, and that the observations on symptoms and level of lung function are valid for other health outcomes as well, then effects seem to be observable between concentrations of 20 and 40 µg/m³, implying that a PM_{10} concentration change of 20 µg/m³ or less can result in detectable impacts. This line of argument, admittedly weak in this case, could be followed using data from studies in which similar, or even smaller, PM_{10} increases are observed to argue for a particle concentration change that is required for an impact to be detected.

Using this last approach, and accepting the arguments presented above, a short-term change in PM_{10} concentration of 5, 10, 15, or 20 µg/m³ would be required to effect a change in health outcome. There are no data available that are helpful in selecting which of these is more likely to be correct. For the purpose of this example, a 10 µg/m³ will be selected. A PM_{10} "increment" will be counted for each 10 µg/m³ daily increase above 20 µg/m³. Therefore, for a day with a PM_{10} concentration of 30-39 µg/m³, one PM_{10} will be counted; for 40-49 µg/m³, two increments; for 50-59 µg/m³, three increments; and so forth (Figure 2). A day with a PM_{10} concentration of less than 30 µg/m³ is not counted. As argued above, even though effects may be occurring above a concentration of 20 µg/m³, an increment of 10 µg/m³ is required before an effect is detectable. For example, if one year of monitoring data in a region yielded PM_{10} concentrations of less than 30 µg/m³ for 200 days, from 30 to 39 µg/m³ for 100 days, from 40 to 49 µg/m³ for 50 days, and from 50 to 59 µg/m³ for 15 days, the number of PM_{10} increments would total 245 (that is, [100 x 1] + [50 x 2] + [15 x 3]). Health impacts can then be estimated for a region with daily PM_{10} measurements for those impacts for which exposure-response estimates are available. Calculations using this approach for estimating extra deaths due to short-term increases in PM_{10} for the greater Vancouver region are presented in Table 7, assuming the hypothetical PM_{10} concentrations above. Similar estimates can be calculated for the other less adverse health effects for which exposure-response relationships are available.

The advantages of an approach that is based on the *degree and frequency* of increases in PM_{10} concentrations are that it: (1) is a direct application of the form in which exposure-response relationships are expressed in the relevant epidemiological study reports, (2) allows flexibility in setting standards and objectives based on estimated health impacts, and (3) readily allows modifications in

defining the particle concentration "increments" based on new evidence, both with respect to the concentration where counting begins and the size of concentration increase that defines the increase in count.

The health impacts estimated using the increments approach are sensitive to the assumptions that are made. For example, if PM_{10} concentrations in a region rarely exceed 30 μg/m^3, but are often above 20 μg/m^3, starting the increment count at 20 μg/m^3 will result in estimating some deaths resulting from increases in particle pollution, whereas if, as above, the increment count only starts at a concentration of 30 μg/m^3, essentially no deaths attributed to particle pollution increases will be estimated. The magnitude of an increment chosen will also affect the impacts estimated, especially for regions where particle concentrations do not vary greatly over the short term. A strictly linear exposure-response relationship is not absolutely required, since conceivably the relationship assigned for an increment could vary as a function of its position on the PM_{10} concentration scale.

As an alternative to explicitly defining an increment, one could estimate impacts as a *continuous* linear function of PM_{10} concentration, as implied by the regression models. It should be clear, however, that this approach implicitly assumes an increment for the unit of precision in which the PM_{10} concentrations are reported. If reported to the nearest μg/m^3, then the assumed increment is 1 μg/m^3. If reported to the nearest 0.1 μg/m^3, then an increment of 0.1 μg/m^3 is assumed. These assumed increments would need to be justified by presenting arguments that a concentration change of that degree would be expected to have an impact on health.

Setting air quality standards or objectives using this approach requires choosing an increment number above which estimated health impacts are deemed to be unacceptable. This determination might be based on ethical and economic arguments, given that almost any standard chosen will not prevent all health impacts, and might be influenced by the degree of certainty in the impact estimates. For the example provided, it may be decided that the estimated effects on mortality, as well as estimated effects on the other health outcomes, are tolerable and that 245 PM_{10} increments in one year is a reasonable "standard." Alternatively, this level of impact may be deemed intolerable, and a lower level of PM_{10} increments chosen to be more acceptable. The important point is that these policy deliberations, as well as the assumptions, are transparent.

Table 7. Estimated acute impact of short-term PM_{10} concentration increases on mortality in metropolitan Vancouver, British Columbia, using hypothetical PM_{10} data.

Assumptions	Calculations and Impact
• for each 10 μg/m^3 increase in daily PM_{10} (based on reference 19):	• *each* PM_{10} increment is associated with:
- total mortality increases 1.0%	- (31.8 deaths/day) x .010 = 0.32 extra total deaths
- respiratory mortality increases 3.4%	- (2.8 deaths/day) x .034 = 0.10 extra respiratory deaths
- cardiac mortality increases 1.4%	- (7.7 deaths/day) x .014 = 0.11 extra cardiac deaths
• baseline deaths per year (per day):	• *extra* deaths due to increases in PM_{10} *each year*:
- total: 11,625 (31.8)	- 0.32 deaths/increment x 245 increments = 78 extra total deaths
- respiratory: 1,013 (2.8)	- 0.10 deaths/increment x 245 increments = 25 extra respiratory deaths
- cardiac: 2,800 (7.7)	- 0.11 deaths/increment x 245 increments = 27 extra cardiac deaths
• hypothesized number of daily 10 μg/m^3 PM_{10} increments beginning at 30 μg/m^3):	
- 245 per year (see text)	

CONCLUSIONS

1. There continues to be basic disagreement on the interpretation of the epidemiological data on health effects associated with increases in particle air pollution. Although a strong case has been presented that this association reflects a causal relationship, plausible alternative explanations for the association can be suggested. The most appealing, because it potentially "explains" the associations between particles and several health outcomes in many settings and at vastly different particle concentrations, as well as the reasons why an apparently poorly measured exposure appears to work so well, is some uncontrolled feature, or features, of meteorology. Concerns about confounding by such a factor are aggravated by the small size of the estimated particle effects.
2. The observed particle health effects have persisted despite the use of many approaches to control for the effects of meteorology. It is not obvious how these approaches can be significantly improve upon. Nevertheless, given the potential importance of me teorology, future observational studies should explore novel approaches to controlling for all potentially confounding meteorological factors. Further, future studies performed in settings with very low ambient particle concentrations would be valuable in determining whether the exposure-

response relationships extend to low particle concentrations.

3. Measurement error in the particle exposure of individuals results in misclassification of exposure, which can in turn bias the effects estimated from the epidemiological studies in unpredictable ways. It is not certain whether the impact of this misclassification on the particle-associated health findings has been great or small.
4. Issues of confounding and misclassification of exposure compound already serious concerns about the biological plausibility of the observed associations between particle pollution and adverse health effects. Although sometimes it is justifiable to maintain that an association is causal in the absence of supporting experimental data or data on the biological mechanisms involved, in the case of particle-associated health effects such data will be critical in supporting the case for causality.
5. Findings from recent European epidemiological studies do not show associations between increases in particle concentrations and increased mortality or increased hospitalizations as consistently as the American studies. The reasons for these less consistent findingsare not known, although differences in particle composition is one possibility.
6. The recent EPA review motivating the proposed changes in the NAAQS for particles has made a strong case for focusing regulatory efforts on the fine inhalable particle fraction ($PM_{2.5}$). Given the different emission and particle size profiles of "eastern" and "western" ambient particles, the impact of the proposed standards, if implemented, will significantly alter the regional distribution of nonattainment areas in the United States.
7. The evidence that the acid aerosol component of the inhalable particles is important in determining particle pathogenicity is not consistent. The pathogenicity of ambient particles in western regions of the United States and Canada, given the very low ambient acid concentrations measured in those regions, is clearly not related to the acid aerosol component.
8. Although particles in the ultrafine particle fraction are pathogenic, as demonstrated in experimental studies, it is not clear that the concentrations of ultrafine particles in ambient air contribute significantly to the adverse effects associated with the increases in inhalable particle concentration demonstrated by the epidemiological data.
9. Expressing ambient particle standards in terms of concentration cut-points, a tradition carried on in the proposed EPA particle standards, seems out of step with the findings of the relevant epidemiological studies in which relatively linear increases in health risks are observed in association with increases in particle concentrations. One alternative is to express standards in terms of incremental increases in particle concentration.
10. The proposed EPA standards also carry on the tradition of maintaining both a long-term (annual) standard and a short-term (24-hour) standard. There is no evidence that long-term, low-level exposure to particles, apart from repeated, short-term increases in particle concentrations, is associated with adverse health effects. Even the evidence supporting development of chronic illness following long-term particle exposure, either from repeated exposures to short-term particle concentration increases or from chronic exposures to relatively low concentrations, is weak. There seems, therefore, to be little justification for proposing a long-term ambient particle standard in addition to a short-term standard.

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