

Health Effects of Fine Particulate Air Pollution: Lines that Connect

Judith C. Chow and John G. Watson

Desert Research Institute, Reno, NV

Joe L. Mauderly

Lovelace Respiratory Research Institute, Albuquerque, NM

Daniel L. Costa

U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC

Ronald E. Wyzga

Electric Power Research Institute, Palo Alto, CA

Sverre Vedal

University of Washington, Seattle, WA

George M. Hidy

Envair/Aerochem, Placitas, NM

Sam L. Altshuler

Consultant, San Francisco, CA

David Marrack

Fort Bend Medical Clinic, Houston, TX

Jon M. Heuss

Air Improvement Resource, Inc., Novi, MI

George T. Wolff

General Motors Public Policy Center, Detroit, MI

C. Arden Pope III

Brigham Young University, Provo, UT

Douglas W. Dockery

Harvard School of Public Health, Boston, MA

INTRODUCTION

Herein is the discussion of the 2006 A&WMA Critical Review^{1,2} on "Health Effects of Fine Particulate Air Pollution: Lines that Connect." In the review, Drs. C. Arden Pope III and Douglas Dockery addressed the epidemiological evidence for the effects of particulate matter (PM) on human health indicators. The review documents substantial progress since the 1997 Critical Review³ in the areas of: (1) short-term exposure and mortality; (2) long-term exposure and mortality; (3) time scales of exposure; (4) the shape of the concentration-response function; (5) cardiovascular disease; and (6) biological plausibility.

Invited and contributing discussants agree and disagree with points made in the review. Each discussion is self-contained and adds information relevant to the topic. Joint authorship of this article does not imply that a discussant subscribes to the opinions expressed by others. Commentaries are the opinions of the author only and do not necessarily reflect the positions of their respective organizations. In particular, Dr. Costa's comments have not been reviewed by U.S. Environmental Protection Agency (EPA) and do not reflect official positions or policies of the agency.

This discussion was compiled from written submissions and presentation transcripts, which were revised for conciseness and to minimize redundancy. Substantial deviations from the intent of a discussant are unintentional and can be addressed in a follow-up letter to the *Journal*. The invited discussants are as follows:

- Dr. Joe L. Mauderly is vice president and senior scientist at the Lovelace Respiratory Research Institute. He specializes in research on comparative respiratory physiology, comparative pulmonary responses to inhaled toxicants, and health hazards from pollutants in workplace and ambient air. During the past decade, Dr. Mauderly's research has focused on understanding how complex mixtures of air contaminants, especially those from combustion sources, cause adverse effects.
- Dr. Daniel L. Costa is national program director for air research in the Office of Research and Development of EPA. He is responsible for the overall direction and management of the air-quality research program across EPA laboratories and centers, including Science to Achieve Results (STAR) grants. Dr. Costa's research includes the health effects of PM and copollutants, as well as pollutant alteration of cardiopulmonary function through neurophysiologic pathways in various susceptible animal models.
- Dr. Ronald E. Wyzga is technical executive and program manager for the air quality health effects program area at the Electric Power Research Institute. His research activities focus on understanding the relationship between health effects and air pollution. Dr. Wyzga specializes in the design, conduct, and interpretation of epidemiological health studies and development of health risk assessment methods.
- Dr. Sverre Vedal is a professor in the Department of Environmental and Occupational Health Sciences at the University of Washington School of Public Health and Community Medicine. He is board certified in pulmonary medicine. Dr. Vedal's research interests include the epidemiological study of air pollution health effects and of occupational lung disease.

The contributing discussants are as follows:

- Dr. George M. Hidy is primary of Envair/Aerochem. He has served as an advisor to the electric utility industry and government on air quality issues and has authored reviews on airborne particles and atmospheric chemistry. Dr. Hidy's research interests include atmospheric aerosols and their environmental consequences, including health effects.
- Sam L. Altshuler has recently retired as senior program manager of the Clean Air Transportation Group after 37 yr with Pacific Gas and Electric and is now serving as a consultant. His research interests include vehicle emissions, air quality,

global climate change, and life cycle analyses of various vehicle fuels.

- Dr. David Marrack is a practicing physician with Fort Bend Medical Clinic. His research interests include municipal waste treatment and disposal, public health, and public health policies.
- Jon M. Heuss is a principal scientist for Air Improvement Resource, Inc. He specializes in air quality issues.
- Dr. George T. Wolff is the principal scientist for environment and energy in General Motors' Public Policy Center. His research interests include atmospheric aerosols and their fate in the environment. He is a past chair of the EPA Clean Air Scientific Advisory Committee (CASAC).

INVITED COMMENTS FROM DR. JOE L. MAUDERLY

This commentary pertains to the adequacy and accuracy with which the review "connected the lines" regarding the contribution of toxicology to our understanding of linkages between ambient fine PM and health. For this purpose, "toxicology" is defined as studies of nonhuman biological systems (animals and cells). The toxicology chapter of the recent EPA PM criteria document⁴ contains ~490 references, and the review faced the challenging task of sorting through those and more recent studies to summarize the most helpful evidence. The role of toxicology in the evaluation of National Ambient Air Quality Standards (NAAQS) is not readily characterized. To date, toxicology has not provided a quantitative basis for setting NAAQS; epidemiology has served that purpose. Toxicological information is used in a supportive role to provide information that helps to place epidemiological findings into a clearer regulatory perspective. Determining which among the many toxicological studies serve best in this role is not straightforward.

Overall, the authors did a good job of pointing toward examples of the toxicological evidence most helpful in understanding the links between PM and human health. Toxicological evidence is cited for such mechanisms as oxidative stress, inflammation (respiratory and vascular), platelet activation and other hematological prothrombotic effects, peripheral thrombosis, exacerbation of myocardial ischemia, stimulation of bone marrow, perturbation of heart rate and cardiac electrophysiology, vasoconstriction, impaired defenses against infection, and translocation of PM from the respiratory tract to other tissues.

The review avoided the temptation to catalog a broader range of findings that would not necessarily have helped to make the points any better. However, the review could have: (1) mentioned a few more findings that support mechanisms and outcomes of current interest, three examples of which are offered below; (2) provided a more accurate context for toxicology by being more cautious about the "dose plausibility" issue; and (3) not implied that effects of complex source emissions are effects of PM.

There is growing toxicological evidence supporting the hypothesis that inhaled PM intensifies respiratory allergic responses in animals. If also true in humans, as

some evidence suggests, this could be an important factor in associations between PM and respiratory morbidity. This evidence, and potential pathogenetic pathways, should have been cited. As one example, Kleinman et al.⁵ exposed BALB/c mice by inhalation 4 hr/day for 10 days to fine PM (PM_{2.5}) concentrated ambient particles (CAPs) 50 m downwind from a Los Angeles, CA, freeway at a mean concentration of 361 µg/m³. The mice were sensitized to antigen (ovalbumin) during their exposure. After CAPs exposure, allergic antibodies, inflammatory cells, and proinflammatory cytokines were measured. Neutrophils, eosinophils, interleukin (IL)-5, and antigen-specific immunoglobulin (Ig)G and IgE antibodies were two to four times higher than values from similarly sensitized but unexposed mice.

The review mentioned toxicological evidence for the translocation of ultrafine PM (most commonly defined as particles with aerodynamic diameters <100 nm)⁶ to non-respiratory tissues, including the brain. Considering the attention that this phenomenon has drawn, a more complete story would have included evidence that PM has also been shown to exert biological effects in the brain. For example, Campbell et al.⁷ exposed BALB/c mice for 2 weeks to small (<0.18 µm) CAPs in Los Angeles at 283 µg/m³ and measured markers of inflammation in brain tissue. They observed increases in the nuclear transcription factor nuclear factor κβ and the cytoplasmic inflammatory cytokine IL-1α. This and other evidence provide support for the hypothesis that translocated PM causes biological responses, and specifically in the brain.

The review mentions toxicological evidence for effects of ultrafine PM, but it might have further portrayed the potential biological importance of ultrafines with a recent study using cultured cells. Although dosing cultured cells with PM provides only a fuzzy link to PM effects in humans, Li et al.⁸ suggest that the intracellular pathogenetic pathways may differ between PM_{2.5} mass and ultrafine PM number concentrations. Cultured cells from a rat macrophage cell line were exposed to PM with aerodynamic diameters <0.15 µm, PM_{2.5}, and PM with aerodynamic diameters between 2.5 and 10 µm (PM_{10-2.5}) collected from Los Angeles air, then indicators of oxidative stress and the internalization of particles were examined. Increases in hemeoxygenase, an indicator of oxidative stress, were progressively greater with decreasing particle size. The smallest particles were taken up into microsomes, paralleling evidence of microsomal damage. PM_{2.5} was also taken up by cells, but into cytoplasmic vacuoles rather than into microsomes, and with little evidence of cellular damage.

The review should have offered more explicit cautions related to dose. Dose (or exposure concentration as the most frequent surrogate) must be considered when extrapolating from toxicological studies to the plausibility of PM health effects, as well as to the mechanisms of response. At least in some cases, biological mechanisms and outcomes resulting from extreme exposures do not accurately reflect mechanisms and risks at lower exposures. This is not only a matter of threshold or of the statistical significance of small effects; it can also be a matter of inducing types of effects that do not result from

lesser, more environmentally relevant exposures. The majority of toxicological data have resulted from exposures or doses much higher than those experienced by populations in the United States. The scarcity of dose-response studies exploring effects down to realistic exposures is a major weakness of PM toxicology. High and sometimes extreme doses are often rationalized on the bases that: (1) studies are being done in normal (or young) animals, whereas human effects likely occur in abnormally susceptible (or old) people; (2) for short-term studies, high doses are necessary to simulate cumulative doses received by humans over longer periods; and (3) because animal studies involve small group sizes, higher doses are necessary to see effects that might be detected in studies of thousands of humans. All three of the arguments are fallacious. Unless demonstrated otherwise, dose is not a logical substitute for susceptibility, exposure time, or population size. The uncertain applicability of high-dose studies does not discredit the review's use of toxicology to support plausibility; however, consideration of "dose plausibility" is a precaution that should have been stated more explicitly.

The review erred by implying that effects of complex combustion mixtures are attributable to PM without qualifying that presumption with a strong reminder that exposures also include non-PM materials. From toxicology, we have the greatest (and growing) body of evidence that non-PM components of combustion emissions can be important drivers of at least some effects that can also be caused by PM. This point is central to the "copollutant" dilemma, that is, the difficulty of parsing the effects of air pollution among PM and non-PM components, many of which are seldom measured. The review mentions the effects of diesel emissions, "traffic" emissions, environmental tobacco smoke (ETS), and forest fire smoke as support for PM health relationships. PM is nearly always an important component of these exposures, and some effects of these exposures might have been driven largely or entirely by PM. Without confirmation, however, it is illogical to assume a priori that the effects of combustion emissions are the effects solely of the PM component.

Some of the same effects of traffic cited as evidence for PM causality have also been cited as evidence for the importance of other components (e.g., nitrogen oxides [NO_x]) and even noise! Exposure to diesel engine exhaust is an example of a mixture for which the effects are frequently and glibly ascribed to PM. The speciation by McDonald et al.⁹ of emissions from a contemporary (2000), common on-road diesel engine operated on a simulated duty cycle and burning national-average (certification) fuel provides insight. When concentrations of gases (typically reported as parts per million, which yields small numerical values) were reported as mass concentrations (micrograms per cubic meter), the PM component constituted <1% of the total emitted mass, even disregarding carbon dioxide and water vapor. The mass of the vapor-phase semivolatile organic fraction alone exceeded PM mass (as did sulfur dioxide [SO₂] and, to greater extents, carbon monoxide [CO] and NO_x). Although it is true that some of the non-PM mass will, with time and distance, migrate into PM (e.g., the condensation of semivolatile compounds), the composition of fresh emissions is very relevant to on-road and near-road exposures.

As the literature from both animal¹⁰ and human¹¹ studies of the relative effects of PM and non-PM components of combustion emissions grows, it increasingly reveals evidence for the causality of the non-PM fraction. Parsing the effects of components of complex mixtures is all the more, difficult because multiple components can have similar effects. For example, both the PM and semi-volatile organic fractions of pollution collected in a traffic tunnel were found to exert inflammatory effects in the lung,¹² and the non-PM fraction was more potent per unit of mass and caused the majority of the response. Although CAPs have enhanced atherosclerotic changes in vessels of genetically susceptible mice,¹³ recent research has shown that the non-PM components of gasoline engine emissions can have similar vascular effects in the same animal model.¹⁴ The review should have better qualified the association between effects of combustion emissions and our present understanding of the potential role of PM in those effects.

The manner in which the review dealt with combustion emissions is symptomatic of a broader issue that is not adequately portrayed in the review: the relative importance of PM and copollutants, regardless of source. The authors mention that there is uncertainty about the relative roles of PM and copollutants in causing the effects associated statistically with PM. They do not ignore the issue altogether; however, this discussant judges the degree of uncertainty and its impact on our understanding of PM risks to be greater than the review makes evident. Because we do not have the data and have not conducted the research necessary to resolve this issue with anything approaching satisfaction, there is room for a spectrum of views about the role of PM. Data on exposure contrasts (i.e., accurate personal exposures having sufficient contrast in PM and copollutant composition) currently available to epidemiologists are not adequate to allow them to parse the effects among PM and copollutants with confidence. Most copollutants are not measured routinely, and many are seldom measured. This state of the science does not negate the authors' fundamental conclusions, but the situation should have been described more explicitly.

There are a few other frayed strands among the lines that the review attempts to connect but none that impact greatly on its bottom lines. It is stated that "fine particles are derived primarily from combustion processes." This may be true for particle numbers, but it is seldom true for PM_{2.5} mass, which is predominated by secondary aerosol components (e.g., sulfates, nitrates, and organics), except in some microenvironments. They repeat the unfortunately common belief that "fine particles can be breathed more deeply into the lungs" when contrasting PM_{2.5} with PM₁₀ or PM_{10-2.5}. The broader point to which the statement alludes is valid, but the statement is not true. First, because PM₁₀ contains all of the smaller particles, the distinction is fuzzy. Second, a 10- μ m particle can be inhaled to the "deepest" recesses of the respiratory tract (alveoli) but with lower probability than smaller particles.⁵ Third, "deep" is not really a useful working concept anyway; because of variation in the length of the respiratory tract path, some alveoli are quite "shallow" in the system.

INVITED COMMENTS FROM DR. DANIEL L. COSTA

The review provides a convincing argument that there now exist many "lines that connect" in our understanding of the health implications associated with PM. As two of the premier air-pollution epidemiologists, the authors structure their arguments around six basic criteria to which considerable new data have been added since the 1997 Critical Review.³ As with most scientific inquiry, as we gain in our knowledge, new questions arise, sometimes creating new uncertainties. Yet, the essence of the PM story has been remarkable in that what some researchers portrayed as a statistical anomaly a decade ago is now widely accepted, if not wholly, at least in its existence. Ironically, in the late 1970s and early 1980s, EPA considered the PM problem as largely resolved; sulfate (SO₄⁼) was a focus for its environmental impacts, losing priority (relative to ozone [O₃]), because PM levels were falling to a point where health impacts were difficult to discern. This perception that PM is less of a concern was challenged a decade and half ago, and the journey to where we are today is the product of considerable and reasoned arguments about science, public health, and policy.

The review builds mainly from the epidemiology literature, but it also judiciously ventures into the clinical and toxicological literature, for it is in that arena that the evasive kingpin, biological plausibility, has been pursued. Although the review is somewhat selective in its accounting of this literature, it communicates well that there is now biologic plausibility "aplenty." This literature expounds several credible hypotheses, but it is complex with many variables and seeming limitations linked to exposure/dose and species extrapolation issues. The review argues that the interdisciplinary findings are largely coherent in their message, although with obvious caveats. Others have argued that this interdisciplinary coherence is less substantial.¹⁵

A few issues merit special attention. First, the database that is reviewed is "mass-centric." It brings to mind the oft-used analogy of "under the lamp post" in that PM effects are somehow determined by the mass-dose of PM. There is some discussion of size-based determinants of health effects, but the critical question of how PM mass drives toxicity needs to be given due scrutiny. The identification of hazardous PM components has been a research priority, despite the wide acceptance that there is no "magic bullet." Several component-based theories are supported by experimental evidence. These theories are rooted in the context of unitary- or simple-mixture exposures.

The review notes that different PM components and sizes are potentially interactive. As explained above, PM components also interact with coexistent gases. The significance of this interaction merits additional critical and creative thought if the science is to move ahead. If there is to be investment in "more appropriate" metrics of PM, bold advances are needed. Both epidemiological and toxicological studies need to reconsider the value of monotonic assessments that rank the importance of PM components when, in fact, the myriad of potential interactions may argue that "mass" best "represents" the mixture.

One approach identified in the review is to focus on identifying the more toxic "sources" as the real culprits. If sources can be linked to health outcomes through various source-apportionment approaches,^{16,17} then control measures that reduce adverse health outcomes may result. This concept may be true, but it is more intricate than one may perceive from the review, which underestimates the complexity of atmospheric chemistry. More interdisciplinary interaction among PM researchers, much of it among epidemiologists and toxicologists, with growing interest in atmospheric sciences, is tied to source identification and attribution.

Among the components of PM, $\text{SO}_4^{=}$ has perhaps been associated most persistently with health, however weak and variable that thread may be. Yet, in the course of the PM story, there has been a sense among some investigators that "sulfate is dead" because of the apparent inconsistency of the findings and the need for high doses to yield empirical results. The mixture issue once again raises its head begging for attention. One creative study has shown that weak sulfuric acid can solubilize metals from insoluble oxide compounds, but only when exposed to light.¹⁸ The liberated metals may, thus, have increased potential for cardiopulmonary effects. Such photochemistry is not news to atmospheric scientists, who long have known that complex chemical interactions occur between PM components and sunlight.^{18,19} Sulfates also have catalytic properties with volatile organics that generate secondary organic aerosol.¹⁹ As with metals, it has been postulated that organics contribute hazardous component(s) of PM. In light of these interactions, $\text{SO}_4^{=}$ re-emerges as an issue, but one needing a better partnership between health and atmospheric scientists. This research may open epidemiological assessments to new multifactorial approaches to data analyses.

Lastly, the epidemiology contends that there is no evidence of a threshold with regard to PM. However, thresholds have come to represent a cornerstone of toxicology, where demonstrating a no-adverse-effect-level is fundamental to estimating risk. Likewise, homeostasis is an intrinsic biological principle that applies to all living things. Is the lack of threshold a resultant phenomenon of the statistics, or does it reflect a range of susceptible individuals? If the latter is the case, then defining common attributes of susceptibility in hosts could identify effects seen at the lowest PM levels. Understanding the basis of the susceptibility (e.g., differences in dose, defenses, and functional reserve) will allow a more appropriate estimate of risk and would inform the medical community about who is at risk.

INVITED COMMENTS FROM DR. RONALD E. WYZGA

One's opinions of any review article are clearly influenced by personal perceptions and interpretations of the extant science. For that reason, it is important to state my present understanding. It is clear, especially from the epidemiological literature, that there are effects of air pollution on health at levels currently found in North America. When we consider the body of literature, PM, in some

measure, is the pollutant most commonly and consistently associated with health responses. My principal reservations about the overall conclusions of the review concern the role of PM vis-à-vis other pollutants. PM cannot be a generic category; PM composition, as well as particle size, matter.

We have learned a lot during the 9 yr since Vedal's Critical Review³ on this topic. Considerably more evidence associates PM with health responses. Plausible mechanisms for health responses to PM have been identified, and scrutiny of the statistical analysis methods has shown their limitations and allowed them to be addressed. My biggest issue with this review is that it ignores some of the contrary results, which tell us something and suggest greater uncertainty about the PM-health association. Part of the problem is beyond the authors' best efforts. They were asked to summarize and make inferences from a huge reservoir of scientific results. There is no way that this objective could be satisfied in the limited number of pages available to them. They had to be selective in the material they presented. The authors also limited themselves to reviewing and analyzing results from published papers; very often these papers present the results of a highly limited number of analyses.

More attention should have been paid to studies that are more comprehensive than others: studies that consider a range of pollutants in addition to PM in their analyses and studies that examine alternative ways of analyzing the data. For example, Metzger et al.²⁰ (not cited in the review) examined the association between several components of air pollution and cardiovascular disease emergency department visits. They reported statistically significant associations between health end points and several air pollution components in single-pollutant models: nitrogen dioxide (NO_2), CO, $\text{PM}_{2.5}$, organic carbon (OC), elemental carbon (EC), and oxygenated hydrocarbons. Several other pollutants were considered, but they were not found to be statistically significant. In multipollutant models only NO_2 , CO, OC, and EC were statistically significant. Moreover, Metzger et al.²⁰ demonstrated robustness of results by considering a range of models to adjust for seasonality and by presenting results for specific lags to indicate whether the patterns are reasonable. Other factors, such as underlying variability and measurement error, influence the presence or lack of statistical significance. Although care must be taken in the inferences made from such a study, it provides more information than one that presents limited results.

In addition to a more systematic treatment of the major pollutants and PM components, studies should also examine several alternative methods and indicate how robust a result is. For example, Klemm and Mason²¹ examined the relationship between $\text{PM}_{2.5}$ and mortality for six different cities using several alternative adjustments for temporality. The results differ considerably among cities and adjustment methods, even between significance and nonsignificance when the analyses are pooled across all six of the cities. It is unclear which analytical result is "correct"; in this absence, some recognition should be given to the variability of results. The review presents results for only one model in this analysis and

does not mention the variability of results for different models.

Air pollution is a complex mixture. It changes over time in the atmosphere, as well as in the airways. Interactions with other pollutants and with physiological systems are numerous and complex. The air pollution-health relationship is not a simple one that relates a specific regulated pollutant or a regulated collection of pollutants (in the case of PM) to a given health effect.

At least three major steps must be taken to resolve this issue. Air quality needs to be characterized in much greater detail, not only at monitoring sites, but also at portals of personal exposure and in the respiratory system. There needs to be better coordination among major scientific disciplines in approaching this problem: health scientists with atmospheric scientists and toxicologists with epidemiologists. Within epidemiological studies it is necessary to consider a comprehensive set of pollution components and alternative methods in a consistent manner. In toxicological studies, several realistic exposure atmospheres should be considered and characterized in ways that provide insight into those characteristics that may influence response. These studies should also examine a broad set of end points, many of which are consistent with those examined in other studies.

INVITED COMMENTS FROM DR. SVERRE VEDAL

As the author of the 1997 Critical Review,³ I was pleased to be asked to contribute my thoughts on the 2006 review. Several points that I made in my 1997 review³ are no longer true. I maintained that "... weak biological plausibility has been the single largest stumbling block to accepting the association as causal." Because of the large amount of toxicological data accumulated since 1997 and the associated large number of mechanistic hypotheses proposed, this is no longer the case. I also maintained that "... evidence supporting development of chronic illness from long-term particle exposure ... is weak." My point was that the way we measure exposure, using short-term measures in mortality time series studies or longer-term measures in cohort studies, does not necessarily indicate that the observed effects are because of exposures at these different time scales. The findings of the two available mortality cohort studies could have been because of the integrated effect on mortality of short-term exposure effects, although measures averaged over several years were used as the exposure concentration measure. It has since been demonstrated that such integration of short-term effects does not produce the size of effects seen in the cohort studies.²² Subsequent toxicological work has also shown that long-term PM exposure can produce cardiovascular disease.¹³

In the 1997 review,³ I attempted to present an evenhanded picture of the evidence on PM health effects and to identify shortcomings in the evidence that needed to be addressed. Two papers have since been published that reference the title of my 1997 review³ in arguing for a story; and both have contrasted my "lines that divide" with their "lines that connect".^{1,23} We might ask some reasonable questions of a story¹ that attempts to "connect the dots" of biomedical findings on PM health effects: (1)

is it a good story? (2) is it the only story? (3) is it the best story? and (4) is it the whole story? First, yes, it is a good story, a very good story. And, parenthetically, this field has no shortage of talented storytellers. Second, although it is not the only story that might be told, it is becoming increasingly difficult to conjure up a realistic, alternate scenario that integrates the findings. Third, I believe it is the best story that can currently be told; it is for this reason that most of us feel it appropriate to use it as a basis for public health policy. Fourth, however, it is not the whole story, and this will comprise the remainder of my comments. This does not mean that the review is incomplete in a trivial sense. The authors have done a remarkable job in reviewing an almost impossibly large literature. Rather, it is not complete because it does not consider findings that do not accord well with the story they present. A number of instances could be cited in which the review did not present the scientific findings in an entirely evenhanded manner; however, I will touch on just four. These relate to coarse PM (or PM_{10-2.5}) effects, the concentration-response relationship, long-term exposure effects, and very short-term exposure effects.

Regarding PM_{10-2.5}, the review (as is clear from its title) focuses almost entirely on PM_{2.5}, a focus that is in line with the authors' views on the relative importance of fine PM effects. However, the epidemiological evidence for short-term exposure effects to PM_{10-2.5} is nearly as strong as for PM_{2.5}, although there are many fewer published PM_{10-2.5} epidemiological studies than PM_{2.5} studies. The proliferation of time series studies on PM_{2.5} is partly because of the relative ease with which the data for these studies could be obtained. It has been more difficult to obtain PM_{10-2.5} data that can be used for time series studies. However, findings from those studies^{4,24,25} are not substantially different from the findings for PM_{2.5}, even in the face of presumably greater exposure measurement error for PM_{10-2.5} than for PM_{2.5}. In addition, toxicological findings are as supportive of PM_{10-2.5} effects as of PM_{2.5} effects.²⁶⁻²⁸ In contrast to short-term exposure, most evidence indicates little or no effect of long-term exposure to PM_{10-2.5}. Although the conclusion of the review that the role of PM_{10-2.5} is "... yet to be fully resolved" is technically correct, it does not do justice to the state of the evidence on PM_{10-2.5} effects.

Characterizing the concentration-response relationship as "reasonably modeled as linear" is an inadequate description because it suggests that effects persist even at the lowest concentrations that can be measured, when in fact they may not. For example, the concentration-response plot of findings from the California Children's Health Study on attained level of lung function²⁹ displayed in Figure 2 of the review shows no evidence of linearity below an annual PM_{2.5} concentration of 15 µg/m³. The line superimposed on the figure is, therefore, misleading, as is characterizing the relationship as linear. The relationship could be reasonably modeled in any number of ways in addition to linear. Because information on effects at low concentrations is of considerable scientific interest and is of critical importance for policy makers, these effects should not be estimated by assuming linearity of the concentration-response relationship.

The issue of long-term PM exposure effects received appropriate emphasis in the review; however, an important finding in the American Cancer Society (ACS) cohort study³⁰ that does not accord well with the story was not included. Although the effects of PM on total and cardiovascular mortality and the effects of current and previous cigarette smoking on chronic obstructive pulmonary disease (COPD) mortality were easily identified in the ACS study, Pope et al.³⁰ found no effect of long-term PM concentrations on COPD mortality. Although this finding could be interpreted in many ways, the prominent reporting of pulmonary effects in the review without considering this finding indicates a lack of evenhandedness.

Finally, there has been interest in the possibility of very short-term (over a few hours) PM exposure effects, prompted initially by findings of a pilot study on acute myocardial infarction.³¹ A larger and more rigorous study by the same investigators found no evidence to support the findings of the pilot study,³² although findings on effects of short-term presence in traffic were reported.³³ Only the findings of the pilot study and the findings relating to being in traffic, a nonspecific measure of several potentially very different exposures, were included in the review. This example not only reflects the unavoidably selective nature of the review, but in this instance, a biased selection of the evidence.

Research on the health effects of air pollution, as the authors note, is “. . . not always conducive to deliberate, objective scientific inquiry.” They claim, however, that “. . . in this review, the progress of science has been of more interest than debates over legally mandated standards.” Although this may be the case, if summarizing the progress of science is the primary goal, then I would suggest embracing skepticism, rather than discouraging “sources of division.” Skepticism is, after all, the life blood of science. I would also like to see less promotion of the consistency, coherence, and robustness of the findings and a greater effort to tell the whole story, not just the best one. But, alas, it would be naïve to think that only science is at issue here.

CONTRIBUTED COMMENTS BY DR. GEORGE M. HIDY

The review presents a comprehensive case for the view that today's accumulated evidence supports the relationship between outdoor PM_{2.5} concentrations and elevated human health risk. This case is supported by a large number of studies, including >500 literature citations. The review represents most “mainstream thinking” in interpretation of the results from recent epidemiological studies and, to a lesser extent, toxicological rationalization for biological plausibility of PM_{2.5} effects. However, one or two qualifications should be emphasized, and at least two air quality management policy implications should be noted.

Although the review comments on the skeptics who question the inferences in the literature, only three short paragraphs out of 33 pages refer to these “detractors.” Little or none of the substantial controversy still surrounding linkages between PM_{2.5} concentrations and health risk is addressed, and little perspective on the issues and arguments for or against the views of the skeptics

is provided. The skeptics have raised questions about the applicability of statistical models commonly adopted for epidemiological analyses. These include a fundamental, but glossed over, issue about the ability of current models to differentiate “very small” health risks that emerge from the analyses. This question is so fundamental to inferences from recent studies that it needs to be addressed in some detail, well beyond the treatment in the review.

One of the cited studies, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS),³⁴ found that approximately one third of the included cities showed negative risk or no risk associated with PM₁₀ exposure. This ambiguity is dismissed in terms of comments about regional heterogeneity in PM composition or exposure, but it remains to be addressed more carefully. There is often a denial of the ambiguities in historic exposure as measured by a single centrally located air monitor, the indoor-outdoor exposure differences, measurement uncertainties, or mortality/morbidity data. Although these are issues in the epidemiological world, they provide grist for the skeptics to question the veracity of the results as presented in the mainstream literature.

The most recent assessment for PM NAAQS is complete, and EPA is expected to promulgate new standards in fall of 2006. As noted by Chow,³⁵ the proposed NAAQS³⁶ retain the annual limit for PM_{2.5} at 15 µg/m³ while lowering the 24-hr average limit to 35 µg/m³. In addition, a 24-hr coarse particle standard (PM_{10-2.5}) of 70 µg/m³ is under consideration to apply only in urban areas. Alternatives for the annual average PM_{2.5} standard have been proposed in the range of 12–15 µg/m³. This proposal is made because epidemiological results to date do not support a threshold of PM_{2.5} concentration and response where there is no excess risk. The further the standard is decreased, the closer it comes to some baseline or background level that is “unmanageable.”³⁷ One recent analysis³⁷ suggests that the U.S. baseline annual average PM_{2.5} concentrations are in the range of 3–10 µg/m³ in the Eastern United States and 2–4 µg/m³ in the West. Baseline concentrations vary with time and space and with latitude and longitude across the mid-continent. The baseline concentrations in the West appear to be well below NAAQS limits, but the high levels experienced in the East are a concern. From the general industrialization of the Northern Hemisphere, it is unclear whether the baseline PM_{2.5} concentrations will tend to increase with time, but this is possible, although U.S. contributions continue to decline. From a practical point of view, achieving continued reductions in PM_{2.5} concentrations across the United States will be increasingly difficult as levels approach the apparent baseline.

Finally, the review is relatively unconcerned with equating epidemiological results for PM_{2.5} and PM₁₀, particularly in relation to the results of the NMMAP and ACS studies. In making this interconnection, it is important to recognize that PM_{2.5} and PM_{10-2.5} have different chemical compositions. This difference presumably must be a factor in the apparent toxicity of the particle collections. The differences in composition by particle size derive from the primary sources of the PM_{2.5} and PM_{10-2.5} fractions, as well as from the enrichment of secondary components in PM_{2.5}. Many epidemiological studies have

been based on PM₁₀ mass concentrations, which contain about half PM_{2.5}. However, the PM₁₀ inferences are definitely distinctive from PM_{2.5} inferences, taking the composition of particle mixtures into account.

Some future health-related studies will follow one current pathway emphasizing chemical composition.³⁸ At present, the epidemiological and toxicological studies of chemical components and health risks are limited, even for the common denominator of SO₄²⁻.¹⁵ Given the accumulation of at least a rudimentary, basic chemical characterization of PM_{2.5} on a national scale, future epidemiological studies will be forthcoming that will give more insight about the major chemical components and health risk. This direction, combined with recognition that additional intracity studies are needed, supports spatially distributed air monitoring that will eventually provide an improved basis for moving from a chemically unspecified standard to one focused on the more toxic PM components.

CONTRIBUTED COMMENTS BY MR. SAM L. ALSHULTER

These comments relate to potential effects of ammonium nitrate (NH₄NO₃), emissions from motor lube oil, and particle number versus mass as a health indicator. Several of the expert panelists in a companion session on "Air Pollution and Cardiopulmonary Health" at the 2006 Annual Meeting observed no connection between PM nitrate (NO₃⁻) and adverse cardiopulmonary health effects and had no reason to believe that exposure to NH₄NO₃, and perhaps even ammonium sulfate, would impact human health. During subsequent presentations and discussions, other experts also echoed the same sentiments. In the absence of evidence linking NO₃⁻ exposure to adverse health impacts, shouldn't we be excluding NO₃⁻ from the epidemiological analyses and the resulting NAAQS? If we do not, air quality agencies may target the NO₃⁻ fraction of PM for control while neglecting more deleterious components. This is already happening in Central and Southern California where NO₃⁻ is a large fraction of PM_{2.5}.^{39,40} It would be interesting to reanalyze data from epidemiological studies while excluding the PM_{2.5} mass attributable to NO₃⁻. Perhaps a stronger, though different, statistical relationship between PM_{2.5} and mortality/morbidity would emerge.

PM_{2.5} transition metals, such as zinc, iron, and copper, are being linked to PM health effects.⁴¹ Zinc dialkyl dithio phosphate compounds are added to oil to improve its antiwear properties, and zinc and other trace metals are detected in vehicle exhaust.⁴² Some of the lube oil evaporates during combustion and then recondenses as ultrafine PM upon cooling in the atmosphere.⁴³ Any piston engine using lube oil, whether it is fueled with diesel, gasoline, natural gas, or hydrogen, has the potential to emit ultrafine PM as a result of lube oil getting into the combustion chamber. Often the lube oil vapor passes through exhaust filters and catalysts with little retention or reduction. More research on the role of lube oil is being undertaken and needs to be monitored and connected to the PM health studies. Reformulation of oil additives and the value of synthetic motor oil need to be evaluated. Synthetic motor oils, with their higher temperature flash

points and better lubricating characteristics, could reduce PM health effects from engine exhaust. Health-based studies of taxi drivers, toll takers, or bus drivers could provide additional data to support many of the epidemiological studies that have linked PM_{2.5} exposure to mortality and morbidity. Particle number may be a better metric than mass for ultrafine PM.⁶ PM mass may still be useful if the measurements can be expressed for specific chemicals or metals and exclude species, such as PM NO₃⁻, that may not be relevant to public health.

CONTRIBUTED COMMENTS BY DR. DAVID MARRACK

Either you believe that inhaling fine particles is harmless, or at least no more injurious than M&Ms, or you act on the evidence that PM in some way provokes cardiovascular and/or lung injuries. PM size may not be the most appropriate metric for health studies. Ultrafine PM has a much larger surface area onto which toxic chemicals can be adsorbed than the particles that dominate PM_{2.5} mass.

There is sufficient evidence connecting the biologic effects identified clinically as heart and lung injuries with PM exposure gradients from cigarette smoking, ETS, combustion sources (e.g., vehicle exhaust and boilers), and in ambient air. The adverse effects of cigarette smoke were attributed by Drs. Boren, Graham, and Selikoff in the 1940s and 1950s to PM and chemicals it adsorbed, thereby creating "garbage bags of pollution." Although epidemiological studies of PM exposure are of interest, they offer little enlightenment about the underlying cellular biochemistry that is disturbed by PM inhalation. By analogy, it is like seeking the origin of a typhoid epidemic by counting the garbage bags along the street. If you want to seek the source of the causal agents, you open the bags, test the contents for them, and trace them to their sources. I am disappointed that so much intellectual effort, resources, and funding is devoted to pollution's "garbage bags," and so little to what is inside them.

More effort needs to be given to understanding the life cycle of PM from combustion sources—from their birth as 1-nm amorphous carbon units, through their aggregation/assembly to larger sizes, their transport to sensitive parts of the human body, their entry into lung macrophages, and the release of the chemicals they carry. Their intracellular presence triggers release into the circulation of a cascade of cytokines (hormone-like chemicals) with subsequent biological impacts on many tissues, including the cardiovascular system.

Optimistically, the components of the PM complex that are the major villains causing the injuries can be determined and specifically reduced below the "no-effect" level with technically efficient low-cost modifications. Reducing all PM to a no-effect level could be economically unacceptable. Health benefits will only accrue if we redirect research efforts to this goal and determine what is in PM that injures us.

CONTRIBUTED COMMENTS BY MR. JON M. HEUSS AND DR. GEORGE T. WOLFF

Even given the limited scope of the review, there are important points that need to be presented and discussed.

We agree that the unresolved issues provide the opportunity for increased cooperation and collaboration in carrying out research to test various hypotheses. We support the expanded PM research under way for nearly a decade by the Health Effects Institute (HEI), EPA, and many others.

In 1996, EPA⁴⁴ acknowledged that there were large uncertainties associated with establishing standards for PM compared with individual gaseous pollutants. In 2005, EPA⁴⁵ reiterated that fact. For example, PM air pollution is a mixture of many different kinds of particles that vary by 3 orders of magnitude in toxicity per unit mass.⁴⁶ The practice of regulating all PM_{2.5} as if it were equally toxic is a simplification that leads to substantial uncertainty. With regard to acute mortality, the review focuses on meta-analyses and multicity studies, noting that fairly consistent adverse associations continue to be observed. However, a number of findings from the studies in Table 1 of the review need to be considered.

First, there is a biologically implausible wide range in the PM/mortality associations in the individual cities included in the multicity studies. Dominici et al.⁴⁷ indicate that the city-specific maximum likelihood estimates from the 88 largest U.S. cities range from -8% to +8% (with a combined estimate of 0.4%) for a 20- $\mu\text{g}/\text{m}^3$ PM₁₀ increment. In Katsouyanni et al.,⁴⁸ the range was also wide, from -1.6% to +2.7% per 20 $\mu\text{g}/\text{m}^3$ of PM₁₀. The pros and cons of combining such disparate results need to be considered.

Second, the pattern of associations for all of the major pollutants in single pollutant models is similar. In NMMAPS,³⁴ a wide range in individual city mortality associations from negative to positive was observed for each pollutant and lag evaluated.⁴⁹ Ito's⁵⁰ reanalysis of the mortality and morbidity associations in Lippmann et al.⁵¹ showed that there was a wide range of negative and positive risks in Detroit when all of the pollutants, lags, and end points were considered. Stieb et al.^{52,53} show that the pattern of results for each pollutant is remarkably similar.

Third, publication bias is a major concern inflating the size of any true effect. Goodman⁵⁴ cautions that "depending on published single-estimate, single-site analyses is an invitation to bias." Anderson et al.⁵⁵ still report a positive association after correcting for publication bias but note that the regression estimates from the multicity studies (not prone to publication bias) and the corrected single-city studies are about half of the mortality estimates of the mid-1990s, that the correction for publication bias may not be complete, and that differential selection of positive lags may also inflate estimates.

Fourth, model selection is a more important factor than thought in the late 1990s. The HEI Special Panel⁵⁶ concludes that issues such as specification of weather and degree of control for time "introduce an element of uncertainty that has not been widely appreciated previously." The panel also concludes that there is no objective statistical test to show when these factors have been adequately controlled. Koop and Tole⁵⁷ conclude that "point estimates of the effect of numerous air pollutants all tend to be positive, albeit small. However, when model uncertainty is accounted for in the analysis, measures of

uncertainty associated with these point estimates became very large."

Fifth, selective presentation of results is an issue. For the multicity PM_{2.5} studies, the review cites Klemm and Mason,²¹ who showed that alternative modeling of temporal trends can reduce the combined association by a factor of three. Burnett and Goldberg⁵⁸ did not test the main conclusion of Burnett et al.,⁵⁹ that gases played the major role in the health effects in these cities, and the complete results of Ostro et al.⁶⁰ suggest that the combined fine PM association is smaller and less robust than reported in the abstract and conclusions.

Sixth, new studies raise additional concerns. Dominici et al.⁶¹ found little or no coherence between the PM₁₀ mortality and morbidity associations in 14 cities and found little or no correlation between the time series of health events (mortality and hospital admissions) in the various cities. A seasonal NMMAPS analysis is available⁶² with updated mortality data from 1987 to 2000 in 100 cities. Summer was the only season for which the combined effect was statistically significant. An analysis by geographic region showed a strong seasonal pattern in the Northeast with a peak in the summer and little seasonal variation in the southern regions of the country. The authors note several possible explanations. One hypothesis is that the most toxic particles have a spring/summer maximum and are more prevalent in the Northeast.

With regard to long-term exposure and mortality, the review acknowledges the presence of both positive and negative studies. In 1997, EPA relied heavily on two cohort studies, the six-city study⁶³ and the ACS study.⁶⁴ The reanalysis by Krewski et al.⁶⁵ replicated the results, but also showed that: (1) the increased risk was cardiovascular not respiratory; (2) SO₂ had a strong association with mortality; (3) when SO₂ was included in the model, the PM all-cause mortality association was materially reduced and became nonsignificant; and (4) the increased mortality was experienced in the portion of the cohort that had a high school education or less. There was a significant spatial heterogeneity in the association, with no SO₄⁻ effect seen in western U.S. cities. The lack of a PM_{2.5} association with mortality in western cities in the ACS cohort was noted by EPA⁶⁶ in a presentation to CASAC. EPA⁶⁷ indicated an excess risk from 10 $\mu\text{g}/\text{m}^3$ of PM_{2.5} of +29% in the industrial Midwest, +25% in the Southeast, +14% in the Northeast, and -9% in the West (West is a combination of cities in the Northwest, Southwest, Upper Midwest, and Southern California NMMAPS geographic regions). All of these additional findings raise questions concerning the interpretation of the PM_{2.5} associations as a universally applicable chronic PM health effect.

As the review indicates, there are other cohort studies of interest. A Veteran's Administration cohort of 70,000 has been followed for 26 yr with mixed results; in the latest report,⁶⁸ it is shown that previously unconsidered spatial covariates, such as traffic or population density, are strong predictors of mortality. In California, a cohort of 6338 nonsmoking Seventh Day Adventists has been followed for 22 yr. As noted in Table 2 of the review, with 15 yr of follow-up, the excess cardiopulmonary risk for 20 $\mu\text{g}/\text{m}^3$ of PM₁₀ was 0.6% with 95th percentile confidence limits of -8% and 10%. Although Chen et al.⁶⁹ report a

positive association with a subset of cardiovascular mortality in women but not men, they include a comment implying that their update (data not shown) found no overall cardiopulmonary effect; this study does not support the six-city and ACS findings. The Enstrom⁷⁰ study of 11 California counties is also negative, as noted in the review.

In contrast to the chronic mortality studies, there is little evidence of a chronic morbidity signal in the literature. Where effects were reported, it was not possible to attribute the effects to single pollutants or even a specific mix of pollutants. The lack of a strong or consistent chronic morbidity signal is not coherent with the assumption of a strong chronic mortality signal. In addition, the appropriate exposure metric for chronic studies is total personal exposure over time, not the level of ambient PM at a central monitor. Because the nonambient component of personal exposure can be several times the ambient component, there is reason to expect exposure misclassification to be an issue.

The review considers intervention and statistical studies regarding time scales of exposure. Intervention studies are important, because they offer an opportunity to evaluate real-world changes because of the imposition of controls or other reasons. The Utah Valley studies are important but, as the review notes, they implicate metals from a closed steel mill, not generic PM. Other studies implicate SO₂, as well as PM. The statistical studies are difficult to interpret. To identify a PM or air pollution signal in correlated data requires properly controlling for other variables like weather. Unfortunately, we do not know all the day-to-day or seasonal factors that affect health.

The review concludes that the concentration-response function can be modeled as linear. For acute studies, the review notes the regional differences in the response function in NMMAPS. The HEI Review Committee⁷¹ observed that measurement error could obscure any threshold, that city-specific concentration-response curves exhibited a variety of shapes, and that the use of the Akaike Information Criterion may not be an appropriate criterion for choosing between models. The HEI panel cautioned that lack of evidence against a linear model should not be confused with evidence in favor of it.

The PM criteria document⁴ concludes, "In summary, the available evidence does not either support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies" (pp 9–44). For the risk assessment, CASAC⁷² favored the primary use of an assumed threshold of 10 µg/m³ along with sensitivity analyses using other threshold assumptions.

The review notes the interest in PM as a risk factor for cardiovascular disease. As explained above, the health effects signal in the long-term cohort studies is cardiovascular in the central and eastern portion of the United States. The data in Table 5 of the review regarding cardiovascular admissions are subject to all of the uncertainties discussed above for PM and mortality. For example, the 14 individual city NMMAPS estimates⁷³ range from –2% to +4.6% per 20-µg/m³ increase in PM₁₀, which is a biologically implausible range.

The Dominici et al.⁷⁴ study of PM_{2.5} hospital admissions associations for 204 U.S. urban counties gives results for a two-stage Bayesian analysis for various types of admissions and by region. Combined associations of the order of a 1% increase in cardiovascular or respiratory outcomes per 10-µg/m³ increase in PM_{2.5} are reported. There are several issues that render the interpretation of these associations as effects of fine PM questionable. First, there is a clear difference in the combined associations among the regions and particularly between the eastern and western region. The combined association is positive for cardiovascular outcomes in the East but negative in the West, except for heart failure, which is positive in both regions. This is not consistent with an effect of PM_{2.5} on cardiovascular hospital admissions. Dominici et al.⁷⁴ point out the need to shift the focus of research to identifying those characteristics of particles that determine their toxicity. They also note that their combined result is several-fold lower than other associations that they cite from the literature, suggesting publication bias. Dominici et al.⁷⁴ do not show the results of the first-stage analysis, which likely had a range of positive and negative associations in each region. They only considered one other pollutant, O₃, as an effect modifier. However, there is an ample literature of small positive associations of hospital admissions in single pollutant models with a range of air pollutants, particularly for heart failure, for which they report the most consistent association. For physiologic markers of cardiac risk, the review acknowledges that the results are mixed and not easy to interpret. EPA⁴ also urges caution in interpreting this data.

Regarding biological plausibility, there has been great progress in postulating various mechanisms by which PM might cause the effects implied by the epidemiological associations. However, as the review admits, demonstrating that the associations are "real" or "causal" has been difficult and elusive. The bottom line from toxicology in EPA⁴ was the highly qualified statement that "to date, experimental toxicology studies have provided some intriguing, but limited, evidence for ambient PM mixes or specific PM components potentially being responsible for reported health effects of ambient PM" (pp 7–215). In addition, CASAC⁷² commented that, "The chapter must make it clear that there is a large database that indicates that PM is markedly variable in its toxic potency." The assumption that all PM is equally toxic is not supported.

Biologic plausibility involves considerations of the effects an agent causes as well as the doses at which those effects occur. The recent toxicologic studies establish the plausibility of the effects reported in the observational studies but, as Drs. Mauderly and Vedal explain, dose plausibility is another issue.

The review admits the need for continued healthy skepticism. Unfortunately, it does not address many of the arguments raised in the cited literature. To the extent that the single-pollutant associations the review summarizes and that EPA relies on in its PM NAAQS proposal³⁶ are not caused by generic anthropogenic PM, the anticipated benefits will not occur.

Peng et al.⁶² provide evidence that the PM₁₀ mortality signal is seasonal and regional, which is not consistent with the assumption that generic PM (either PM_{2.5} or

PM_{10-2.5}) is causing mortality. Dominici et al.⁷⁴ indicate that there is geographic variability in PM_{2.5} morbidity, particularly in the cardiovascular signal. The various re-analyses and updates of the ACS study indicate that the chronic mortality signal in this database is cardiovascular in nature and stronger in the Eastern United States. As research goes forward, explanations for these patterns need to be evaluated.

If generic particles are causing the serious health effects implied by the statistical associations, then particles should be causing similar effects in other exposure situations. We raise three examples where the health signal does not appear coherent with a strong ambient PM health signal. As noted by EPA,⁴ the exposure to nonambient PM is as high or higher than the exposure to ambient PM. Thus, there should be a health signal for PM mass in the indoor pollution literature. Although there are well-established indoor health risks from ETS and biological particles, no substantial or consistent health signal from PM is apparent.⁷⁵ Gamble and Nicolich⁷⁶ conclude that the risks from the cohort studies were not coherent with the risks derived from smoking or occupational studies. The review does not address this question. The massive indoor exposures from use of biomass fuels in developing nations (milligram per cubic meter PM exposures) have important effects on acute and chronic respiratory disease in many countries and effects on lung cancer from coal use in China, but there is little evidence to date of a strong cardiovascular signal.⁷⁷

Although the first state implementation plans for PM_{2.5} are not due until 2007, the control of ambient PM (including fine PM) has been a major effort in the United States for many decades with dramatic results. Lipfert,⁷⁸ Darlington et al.,⁷⁹ and EPA⁸⁰ have all shown significant reductions in PM over various time periods going back, in some cases, to the 1940s. Thus, air pollution control is occurring in parallel with research on PM health effects. Hopefully, over time, based on sound science, the regulatory focus will shift from the mass of particles to the particles of greatest toxicity.

RESPONSE FROM DR. C. ARDEN POPE III AND DR. DOUGLAS W. DOCKERY, CRITICAL REVIEW AUTHORS

As noted in the review, the amount of published literature regarding the health effects of air pollution has increased tremendously since 1997. The 2006 Critical Review¹ focused on six primary lines of research pursued since 1997 that have substantially helped elucidate our understanding about the human health effects of fine particulate air pollution. There have been many thoughtful and useful comments about the review. Most of the substantive comments or concerns pertain to literature or issues that the commentators would have liked to have seen added to or expanded upon in the review.

For example, Drs. Mauderly and Costa comment on the treatment of toxicological and clinical literature in the review. Although the review relied primarily on epidemiologic and human studies, we fully agree that toxicological studies play an extremely important role in exploring issues related to biological plausibility and mechanisms. Although we are not toxicologists, we agree that there is

much excellent and relevant toxicological evidence that was not included in the review, and we welcome their additional insight and comments stated above. We advocate companion reviews by the discussants on toxicology on which we would be pleased to offer our comments and critiques.

A general issue is the review's focus on fine particles and the limited discussion of the role of specific characteristics, constituents, or sources of PM or the role of various copollutants as part of complex air pollution mixtures. We are in general agreement with most, if not all of these comments. In the review we indicate that ". . . one of the biggest gaps in our knowledge relates to what specific air pollutants, combinations of pollutants, sources of pollutants, and characteristics of pollutants are most responsible for the observed health effects." Nevertheless, as outlined in the review, exposure to fine particulate air pollution plays a substantial and measurable role in adversely affecting human health.

A final general issue addressed in several of the comments pertains to whether or not the review is adequately objective and evenhanded or appropriately skeptical. Of course, objectiveness is in the eye of the beholder. We understand that writing a review of such a large and complex literature, which has implications for controversial public health and environmental policy, that could be considered "entirely evenhanded" by all interested parties, is a daunting task. Nevertheless, we tried to present a succinct critical review of the science related to the health effects of fine PM in a well-defined, focused, thoughtful, balanced, and readable manner. We did this with full knowledge that our review would be complemented by contributions and critiques from capable discussants. We invite all to read the critical review and this discussion and to judge for themselves.

REFERENCES

1. Pope, C.A., III; Dockery, D.W. Health Effects of Fine Particulate Air Pollution: Lines that Connect—2006 Critical Review; *J. Air & Waste Manage. Assoc.* **2006**, *6*, 709-742.
2. Pope, A.C., III; Dockery, D.W. Summary of 2006 Critical Review: Health Effects of Fine Particulate Air Pollution: Lines that Connect; *EM* **2006**, *June*, 30-35.
3. Vedal, S. Critical Review—Ambient Particles and Health: Lines that Divide; *J. Air & Waste Manage. Assoc.* **1997**, *5*, 551-581.
4. *Air Quality Criteria for Particulate Matter*; EPA/600/P-99/002aF; U.S. Environmental Protection Agency: Washington, DC, 2004.
5. Kleinman, M.T.; Hamade, A.; Meacher, D.; Oldham, M.; Sioutas, C.; Chakrabarti, B.; Stram, D.; Froines, J.R.; Cho, A.K. Inhalation of Concentrated Ambient Particulate Matter near a Heavily Trafficked Road Stimulates Antigen-Induced Airway Responses in Mice; *J. Air & Waste Manage. Assoc.* **2005**, *9*, 1277-1288.
6. Biswas, P.; Wu, C.Y. 2005 Critical Review: Nanoparticles and the Environment; *J. Air & Waste Manage. Assoc.* **2005**, *6*, 708-746.
7. Campbell, A.; Becaria, A.; Bondy, S.C.; Meacher, D.; Oldham, M.; Sioutas, C.; Misra, C.; Kleinman, M. Exposure to Particulate Matter in Air Pollution Increases Inflammatory Parameters in Mouse Brain; *Neuro. Toxicol.* **2005**, *1*, 133-140.
8. Li, N.; Sioutas, C.; Cho, A.; Schmitz, D.; Misra, C.; Sempf, J.; Wang, M.Y.; Oberley, T.; Froines, J.; Nel, A. Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage; *Environ. Health Perspect.* **2003**, *4*, 455-460.
9. McDonald, J.D.; Barr, E.B.; White, R.K.; Chow, J.C.; Schauer, J.J.; Zielinska, B.; Grosjean, E. Generation and Characterization of Four Dilutions of Diesel Engine Exhaust for a Subchronic Inhalation Study; *Environ. Sci. Technol.* **2004**, *9*, 2513-2522.
10. Campen, M.J.; Babu, S.; Helms, G.A.; Pett, S.; Wernly, J.; Mehran, R.; McDonald, J.D. Nonparticulate Components of Diesel Exhaust Promote Constriction in Coronary Arteries from ApoE^{-/-} Mice; *Toxicol. Sci.* **2005**, *88*, 95-102.

11. Rudell, B.; Blomberg, A.; Helleday, R.; Ledin, M.C.; Lundback, B.; Stjernberg, N.; Horstedt, P.; Sandstrom, T. Bronchoalveolar Inflammation after Exposure to Diesel Exhaust: Comparison between Unfiltered and Particle Trap Filtered Exhaust; *Occup. Environ. Med.* **1999**, *8*, 527-534.
12. Seagrave, J.C.; Berger, J.; Zielinska, B.; Sagebiel, J.; Rogers, C.F.; McDonald, J.D.; Mauderly, J.L. Comparative Acute Toxicities of Particulate Matter (PM) and Semi-Volatile Organic Compound Fractions of Traffic Tunnel Air; *Toxicologist* **2001**, *60*, 192.
13. Sun, Q.; Wang, A.; Jin, X.; Natanzon, A.; Duquaine, D.; Brook, R.D.; Aguinaldo, J.G.S.; Fayad, Z.A.; Fuster, V.; Lippmann, M.; Chen, L.C.; Rajagopalan, S. Long-Term Air Pollution Exposure and Acceleration of Atherosclerosis and Vascular Inflammation in an Animal Model; *JAMA* **2005**, *23*, 3003-3010.
14. Campen, M.J. Lovelace Respiratory Research Institute, Albuquerque, NM. Personal communication, 2006.
15. Schlesinger, R.B.; Kunzli, N.; Hidy, G.M.; Gotschi, T.; Jerrett, M. The Health Relevance of Ambient Particulate Matter Characteristics: Coherence of Toxicological and Epidemiological Inferences; *Inhal. Toxicol.* **2006**, *2*, 95-125.
16. Watson, J.G.; Zhu, T.; Chow, J.C.; Engelbrecht, J.P.; Fujita, E.M.; Wilson, W.E. Receptor Modeling Application Framework for Particle Source Apportionment; *Chemosphere* **2002**, *9*, 1093-1136.
17. Watson, J.G.; Chow, J.C. Receptor Models for Air Quality Management; *EM* **2004**, Oct., 27-36.
18. Ghio, A.J.; Stonehuerner, J.; McGee, J.K.; Kinsey, J.S. Sulfate Content Correlates with Iron Concentrations in Ambient Air Pollution Particles; *Inhal. Toxicol.* **1999**, *4*, 293-307.
19. Song, H.S.; Bang, W.G.; Chung, N.; Cho, Y.S.; Kim, Y.S.; Cho, M.H. Effect of Chelators and Reductants on the Mobilization of Metals from Ambient Particulate Matter; *Environ. Sci. Technol.* **2003**, *37*, 3531-3536.
20. Metzger, K.B.; Tolbert, P.E.; Klein, M.; Peel, J.L.; Flanders, W.D.; Todd, K.; Mulholland, J.A.; Ryan, P.B.; Frumkin, H. Ambient Air Pollution and Cardiovascular Emergency Department Visits; *Epidemiol.* **2004**, *1*, 46-56.
21. Klemm, R.J.; Mason, R.M., Jr. Replication of Reanalysis of Harvard Six-City Mortality Study. In *Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 165-172.
22. Kunzli, N.; Medina, S.; Kaiser, R.; Quenel, P.; Horak, F.; Studnicka, M. Assessment of Deaths Attributable to Air Pollution: Should We Use Risk Estimates Based on Time Series or on Cohort Studies?; *Am. J. Epidemiol.* **2001**, *153*, 1050-1055.
23. Bates, D.V. Lines that Connect: Assessing the Causality Inference in the Case of Particulate Pollution; *Environ. Health Perspect.* **2000**, *108*, 91-92.
24. Burnett, R.T.; Cakmak, S.; Brook, J.R.; Krewski, D. The Role of Particulate Size and Chemistry in the Association between Summertime Ambient Air Pollution and Hospitalization for Cardiorespiratory Diseases; *Environ. Health Perspect.* **1997**, *6*, 614-620.
25. Ito, K. Associations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit, Michigan. Special Report. In *Revised Analyses of Time-Series Studies of Air Pollution and Health*, Health Effects Institute: Boston, MA, 2003; pp 143-156.
26. Becker, S.; Soukup, J.M.; Sioutas, C.; Cassee, F.R. Response of Human Alveolar Macrophages to Ultrafine, Fine, and Coarse Urban Air Pollution Particles; *Exper. Lung Res.* **2003**, *1*, 29-44.
27. Schins, R.P.F.; Lightbody, J.H.; Borm, P.J.A.; Shi, T.M.; Donaldson, K.; Stone, V. Inflammatory Effects of Coarse and Fine Particulate Matter in Relation to Chemical and Biological Constituents; *Toxicol. Appl. Pharmacol.* **2004**, *1*, 1-11.
28. Hetland, R.B.; Cassee, F.R.; Lag, M.; Refsnes, M.; Dybing, E.; Schwarze, P.E. Cytokine Release from Alveolar Macrophages Exposed to Ambient Particulate Matter: Heterogeneity in Relation to Size, City and Season; *Particle Fibre Toxicol.* 2005. Available at <http://www.particleandfibretoxicology.com/content/2/1/4> (accessed August 21, 2006).
29. Gauderman, W.J.; Avol, E.; Gilliland, F.; Vora, H.; Thomas, D.; Berhane, K.; McConnell, F.; Kuenzli, N.; Lurmann, F.; Rappaport, E.; Margolis, H.; Bates, D.; Peters, J. The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age; *N. Engl. J. Med.* **2004**, *11*, 1057-1067.
30. Pope, C.A., III; Burnett, R.T.; Thurston, G.D.; Thun, M.J.; Calle, E.E.; Krewski, D.; Godleski, J.J. Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution: Epidemiological Evidence of General Pathophysiological Pathways of Disease; *Circulation* **2004**, *1*, 71-77.
31. Peters, A.; Dockery, D.W.; Muller, J.E.; Mittleman, M.A. Increased Particulate Air Pollution and the Triggering of Myocardial Infarction; *Circulation* **2001**, *103*, 2810-2815.
32. Peters, A.; von Klot, S.; Heier, M.; Trentinaglia, I.; Cyrys, J.; Hormann, A.; Hauptmann, H.; Wichmann, H.E.; Lowel, H. *Particulate Air Pollution and Nonfatal Cardiac Events Part I: Air Pollution, Personal Activities, and Onset of Myocardial Infarction in a Case-Crossover Study*; 2005, Research Report 124; Health Effects Institute: Boston, MA. Available at www.healtheffects.org/Pubs/Report124.pdf (accessed August 21, 2006).
33. Peters, A.; von Klot, S.; Heier, M.; Trentinaglia, I.; Hormann, A.; Wichmann, H.E.; Lowel, H. Exposure to Traffic and the Onset of Myocardial Infarction; *N. Engl. J. Med.* **2004**, *17*, 1721-1730.
34. Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S.L.; Samet, J. Shape of the Exposure-Response Relation and Mortality Displacement in the NMMAPS Database. In *Revised Analyses of Time-Series of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 91-96.
35. Chow, J.C. Introduction to the A&WMA 2006 Critical Review—Health Effects of Fine Particulate Air Pollution: Lines that Connect; *J. Air & Waste Manage. Assoc.* **2006**, *6*, 707-708.
36. U.S. Environmental Protection Agency. National Ambient Air Quality Standards for Particulate Matter: Proposed Rule; *Fed. Regist.* **2006**, *10*, 2620-2708.
37. Hidy, G.M.; Blanchard, C.L. The Mid-Latitude North American Background Aerosol and Global Aerosol Variation; *J. Air & Waste Manage. Assoc.* **2005**, *11*, 1585-1599.
38. Seagrave, J.C.; McDonald, J.; Bedrick, E.; Edgerton, E.; Gigliotti, A.; Jansen, J.; Ke, L.; Naeher, L.; Seilkop, S.; Zheng, M.; Mauderly, J. Lung Toxicity of Ambient Particulate Matter from Southeastern U.S. Sites with Different Contributing Sources: Relationships between Composition and Effects; *Environ. Health Perspect.* **2006**, *114*, 1387-1393.
39. Chow, J.C.; Watson, J.G.; Lowenthal, D.H.; Solomon, P.A.; Magliano, K.L.; Ziman, S.D.; Richards, L.W. PM₁₀ Source Apportionment in California's San Joaquin Valley; *Atmos. Environ.* **1992**, *26A*, 3335-3354.
40. Watson, J.G.; Chow, J.C.; Lu, Z.; Fujita, E.M.; Lowenthal, D.H.; Lawson, D.R. Chemical Mass Balance Source Apportionment of PM₁₀ during the Southern California Air Quality Study; *Aerosol Sci. Technol.* **1994**, *21*, 1-36.
41. Ghio, A.J.; Huang, Y.C.T. Exposure to Concentrated Ambient Particles (CAPs): a Review; *Inhal. Toxicol.* **2004**, *16*, 53-59.
42. Zielinska, B.; Sagebiel, J.; Whitney, K.; Lawson, D.R. Emission Rates and Comparative Chemical Composition from Selected In-Use Diesel and Gasoline-Fueled Vehicles; *J. Air & Waste Manage. Assoc.* **2004**, *9*, 1138-1150.
43. Kelly, K.E.; Wagner, D.A.; Lighty, J.S.; Sarofim, A.F.; Rogers, C.F.; Sagebiel, J.; Zielinska, B.; Arnott, W.P.; Palmer, G. Characterization of Exhaust Particles from Military Vehicles Fueled with Diesel, Gasoline, and JP-8; *J. Air & Waste Manage. Assoc.* **2003**, *3*, 273-282.
44. *Review of the National Ambient Air Quality Standards (NAAQS) for Particulate Matter: Policy Assessment of Scientific and Technical Information—OAQPS Staff Paper*; EPA-452/R-96-013; U.S. Environmental Protection Agency: Washington, DC, 1996.
45. *Review of the NAAQS for Particulate Matter: Policy Assessment of Scientific and Technical Information*; OAQPS Staff Paper; EPA-452/R-05-005; U.S. Environmental Protection Agency: Washington, DC, 2005.
46. *ACGIH Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs)*; American Conference of Industrial Hygienists (ACGIH): Cincinnati, OH; 2006.
47. Dominici, F.; McDermott, A.; Zeger, S.L.; Samet, J.M. National Maps of the Effects of Particulate Matter on Mortality: Exploring Geographical Variation; *Environ. Health Perspect.* **2003**, *1*, 39-44.
48. Katsouyanni, K.; Touloumi, G.; Samolu, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H.R.; Wojtyniak, B.; Paldy, A.; Braustein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. Sensitivity Analysis of Various Models of Short-Term Effects of Ambient Particles on Total Mortality in 29 Cities in APHEA2; In *Revised Analyses of Time-Series Studies of Air Pollution and Health*; Health Effects Institute: Boston, MA, 2003; pp 157-164.
49. Heuss, J.M. *General Motors' Comments on the 4th External Review of the Draft Air Quality Criteria Document for Particulate Matter*; submitted to EPA Clean Air Scientific Advisory Committee (CASAC) and U.S. Environmental Protection Agency; Air Improvement Resources, Novi, MI, August 2003.
50. Ito, K. Associations of Particulate Matter Components with Daily Mortality and Morbidity in Detroit, Michigan; In *Revised Analyses of Time-Series Studies of Air Pollution and Health*; Health Effects Institute: Boston, MA, 2003; pp 143-156.
51. Lippmann, M.; Ito, K.; Nadas, A.; Burnett, R.T. *Association of Particulate Matter Components with Daily Mortality and Morbidity in Urban Populations*; Health Effects Institute: Boston, MA; 2000. Available at <http://www.healtheffects.org/Pubs/Lippmann.pdf> (accessed August 21, 2006).
52. Stieb, D.M.; Judek, S.; Burnett, R.T. Meta-Analysis of Time-Series Studies of Air Pollution and Mortality: Effects of Gases and Particles and the Influence of Cause of Death, Age, and Season; *J. Air & Waste Manage. Assoc.* **2002**, *4*, 470-484.
53. Stieb, D.M.; Judek, S.; Burnett, R.T. Meta-Analysis of Time-Series Studies of Air Pollution and Mortality: Update in Relation to the Use of Generalized Additive Models; *J. Air & Waste Manage. Assoc.* **2003**, *3*, 258-261.
54. Goodman, S.N. The Methodologic Ozone Effect; *Epidemiol.* **2005**, *16*, 430-435.

55. Anderson, H.R.; Atkinson, R.W.; Peacock, J.L.; Sweeting, M.J.; Marston, L. Ambient Particulate Matter and Health Effects—Publication Bias in Studies of Short-Term Associations; *Epidemiol.* **2005**, *2*, 155-163.
56. *HEI Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA; 2003. Available at <http://www.healtheffects.org/Pubs/st-timeseries.htm> (accessed August 21, 2006).
57. Koop, G.; Tole, L. Measuring the Health Effects of Air Pollution: To What Extent Can We Really Say that People Are Dying from Bad Air?; *J. Environ. Econ. Manage.* **2004**, *47*, 30-54.
58. Burnett, R.T.; Goldberg, M.S. Size-Fractionated Particulate Mass and Mortality in Eight Canadian Cities; In *Revised Analysis of Air Pollution and Health. Special Report*; Health Effects Institute: Boston, MA, 2003; pp 85-90.
59. Burnett, R.T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M.S.; Krewski, D. Association between Particulate- and Gas-Phase Components of Urban Air Pollution and Daily Mortality in Eight Canadian Cities; *Inhal. Toxicol.* **2000**, *12*, 15-39.
60. Ostro, B.; Broadwin, R.; Green, S.; Feng, W.-Y.; Lipsett, M. Fine Particulate Air Pollution and Mortality in Nine California Counties: Results from CALFINE; *Environ. Health Perspect.* **2006**, *114*, 29-33.
61. Dominici, F.; Zanobetti, A.; Zeger, S.L.; Schwartz, J.; Samet, J. *The National Morbidity, Mortality and Air Pollution Study Part IV: Hierarchical Bivariate Time-Series Models—a Combined Analysis of PM10 Effects on Hospitalizations and Mortality*; HEI Research Report 94, Part IV; Health Effects Institute: Boston, MA; 2005. Available at <http://www.healtheffects.org/Pubs/st94-I.htm> (accessed August 21, 2006).
62. Peng, R.D.; Dominici, F.; Pastor-Barriuso, R.; Zeger, S.L.; Samet, J.M. Seasonal Analyses of Air Pollution and Mortality in 100 U.S. Cities; *Am. J. Epidemiol.* **2005**, *161*, 585-594.
63. Dockery, D.W.; Pope, C.A., III; Xu, X.; Spengler, J.D.; Ware, J.H.; Fay, M.E.; Ferris, B.G.; Speizer, F.E. An Association between Air Pollution and Mortality in Six U.S. Cities; *N. Engl. J. Med.* **1993**, *24*, 1753-1759.
64. Pope, C.A.; Thun, M.J.; Namboodiri, M.M.; Dockery, D.W.; Evans, J.S.; Speizer, F.E.; Heath, C.W. Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults; *Am. J. Respir. Crit. Care Med.* **1995**, *3*, 1, 669-674.
65. Krewski, D.; Burnett, R.T.; Goldberg, M.S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. Special Report*; Health Effects Institute: Boston, MA, 2001. Available at <http://www.healtheffects.org/Pubs/st94-I.htm> (accessed August 21, 2006).
66. Grant, L. *Key Revisions and Scientific Issues for Second External Review Draft of Air Quality Criteria for Particulate Matter*; Slide 46—U.S. Environmental Protection Agency Staff Presentation to EPA Clean Air Scientific Advisory Committee (CASAC): Research Triangle Park, NC, July 23, 2001.
67. U.S. Environmental Protection Agency. 40 CFR, Part 81—Air Quality Designations and Classifications for Fine Particles (PM_{2.5}) NAAQS; Final Rule; *Fed. Regist.* **2005**, *3*, 944-1019.
68. Lipfert, F.W.; Wyzga, R.E.; Baty, J.D.; Miller, J.P. Traffic Density as a Surrogate Measure of Environmental Exposures in Studies of Air Pollution Health Effects: Long-Term Mortality in a Cohort of US Veterans; *Atmos. Environ.* **2006**, *1*, 154-169.
69. Chen, L.H.; Knutsen, S.F.; Shavlik, D.; Beeson, W.L.; Petersen, F.; Ghamsary, M.; Abbey, D. The Association between Fatal Coronary Heart Disease and Ambient Particulate Air Pollution: Are Females at Greater Risk?; *Environ. Health Perspect.* **2005**, *113*, 1723-1729.
70. Enstrom, J.E. Fine Particulate Air Pollution and Total Mortality among Elderly Californians, 1973–2002; *Inhal. Toxicol.* **2005**, *14*, 803-816.
71. *HEI Commentary on the National Morbidity, Mortality and Air Pollution Study Part III: PM10 Concentration-Response Curves and Thresholds for the 20 Largest U.S. Cities*; HEI Research Report No. 94, Part III; Health Effects Institute: Boston, MA, 2004. Available at <http://www.healtheffects.org/Pubs/st94-I.htm> (accessed August 21, 2006).
72. Hopke, P. *Clean Air Scientific Advisory Committee (CASAC) Particulate Matter (PM) Review Panel's Ongoing Peer Review of the Agency's Fourth External Review Draft of Air Quality Criteria for Particulate Matter*, EPA-SAB-CASAC-04-005; U.S. Environmental Protection Agency: Washington, DC, 2004.
73. Schwartz, J.; Zanobetti, A.; Bateson, T. Morbidity and Mortality among Elderly Residents of Cities with Daily PM Measurements; In *Revised Analyses of Time-Series Studies of Air Pollution and Health*; Health Effects Institute: Boston, MA, 2003; pp 25-53.
74. Dominici, F.; Peng, R.; Bell, M.; Pham, L.; McDermott, A.; Zeger, S.; Samet, J. Particles, Air Pollution and Hospital Admissions for Cardiovascular and Respiratory Diseases; *JAMA* **2006**, *295*, 1127-1134.
75. Schneider, T.; Sundell, J.; Bischof, W.; Bohgard, M.; Cherrie, J.W.; Clausen, P.A.; Dreborg, S.; Kildeso, J.; Kjaergaard, S.K.; Lovik, M.; Pasanen, P.; Skyberg, K. EUROPART. Airborne Particles in the Indoor Environment. A European Interdisciplinary Review of Scientific Evidence on Associations between Exposure to Particles in Buildings and Health Effects; *Indoor Air* **2003**, *13*, 38-48.
76. Gamble, J.F.; Nicolich, M.J. Comparison of Ambient PM Risk with Risks Estimated from PM Components of Smoking and Occupational Exposures; *J. Air & Waste Manage. Assoc.* **2000**, *8*, 1514-1531.
77. Bruce, N.; Perez-Padilla, R.; Albalak, R. *The Health Effects of Indoor Air Pollution Exposure in Developing Countries*; WHO/SDE/OEH/02.05; World Health Organization: Geneva, Switzerland, 2002.
78. Lipfert, F. Trends in Airborne Particulate Matter in the United States; *Appl. Occup. Environ. Hyg.* **1998**, *13*, 370-384.
79. Darlington, T.L.; Kahlbaum, D.F.; Heuss, J.M.; Wolff, G.T. Analysis of PM₁₀ Trends in the United States from 1988 through 1995; *J. Air & Waste Manage. Assoc.* **1997**, *10*, 1070-1078.
80. *The Particle Pollution Report: Current Understanding of Air Quality and Emissions through 2003*; EPA 454-R-04-002; U.S. Environmental Protection Agency: Washington, DC, 2004.

About the Authors

Judith C. Chow and John G. Watson are research professors with the Division of Atmospheric Sciences at the Desert Research Institute. Joe L. Mauderly is vice president and senior scientist with the Lovelace Respiratory Research Institute. Daniel L. Costa is national program director for air research with U.S. Environmental Protection Agency, Office of Research and Development. Ronald E. Wyzga is technical executive and program manager for the air quality health effects program area with the Electric Power Research Institute. Sverre Vedal is a professor in the Department of Environmental and Occupational Health Sciences with the University of Washington. George M. Hidy is primary of Envair/Aerochem. Sam L. Altshuler is a consultant and has recently retired as senior program manager of the Clean Air Transportation Group at Pacific Gas and Electric. David Marrack is a practicing physician with the Fort Bend Medical Clinic. Jon M. Heuss is a principal scientist with Air Improvement Resource, Inc. George T. Wolff is the principal scientist for environment and energy in General Motors' Public Policy Center. C. Arden Pope, III, is a Mary Lou Fulton Professor at Brigham Young University. Douglas W. Dockery is a professor of environmental epidemiology at the Department of Environmental Health, Harvard School of Public Health. Address correspondence to: Judith C. Chow, Division of Atmospheric Sciences, Desert Research Institute, 2215 Raggio Parkway, Reno, NV 89512; phone: +1-775-674-7050; fax: +1-775-674-7009; e-mail: judy.chow@dri.edu.