Invited Commentary

Providing Context for Ambient Particulate Matter and Estimates of Attributable Mortality

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Four papers on fine particulate matter ($PM_{2.5}$) by Anenberg *et al.*, Fann *et al.*, Shin *et al.*, and Smith contribute to a growing body of literature on estimated epidemiological associations between ambient $PM_{2.5}$ concentrations and increases in health responses relative to baseline notes. This article provides context for the four articles, including a historical review of provisions of the U.S. Clean Air Act as amended in 1970, requiring the setting of National Ambient Air Quality Standards (NAAQS) for criteria pollutants such as particulate matter (PM). The substantial improvements in both air quality for PM and population health as measured by decreased mortality rates are illustrated. The most recent revision of the NAAQS for $PM_{2.5}$ in 2013 by the Environmental Protection Agency distinguished between (1) uncertainties in characterizing $PM_{2.5}$ as having a causal association with various health endpoints, and as all-cause mortality, and (2) uncertainties in concentration—excess health response relationships at low ambient $PM_{2.5}$ concentrations below the majority of annual concentrations studied in the United States in the past. In future reviews, and potential revisions, of the NAAQS for $PM_{2.5}$, it will be even more important to distinguish between uncertainties in (1) characterizing the causal associations between ambient $PM_{2.5}$ concentrations and specific health outcomes, such as all-source mortality, irrespective of the concentrations, (2) characterizing the potency of major constituents of $PM_{2.5}$, and (3) uncertainties in the association between ambient $PM_{2.5}$ concentrations and specific health outcomes at various ambient $PM_{2.5}$ concentrations. The latter uncertainties are of special concern as ambient $PM_{2.5}$ concentrations and health morbidity and mortality rates approach background or baseline rates.

KEY WORDS: Clean Air Act; criteria pollutants; National Ambient Air Quality Standards; particulate matter; $PM_{2.5}$

The purpose of this commentary is to provide context and perspective for considering the contents and conclusions of four articles in this issue of *Risk Analysis* concerned with ambient fine particulate matter, 2.5 micron ($PM_{2.5}$) and estimates of $PM_{2.5}$ attributable mortality.

1. KEY ELEMENTS OF FOUR ARTICLES

Before offering my comments, I will briefly summarize what I view as key aspects of the four articles.

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Anenberg *et al.*[1] provide a useful review of 12 air pollution health impact assessment tools that have been extensively used internationally. The tools use common data sources for the key inputs: (1) ambient $PM_{2.5}$ concentration–response association functions, (2) measured or estimated ambient concentrations of $PM_{2.5}$, (3) populations evaluated, and (4) baseline mortality rates. The models are all grounded in linear concentration–response functions.

Fann *et al.*[2] focus on the strengths and weaknesses of four research synthesis approaches to characterizing the long-term ambient $PM_{2.5}$ concentration–response functions. They note "whether

implicitly or explicitly, all require considerable judgment by scientists," an admonishment that should be heeded by both scientists and policy-makers. Their focus is on linear models of ambient $PM_{2.5}$ concentration–response relationships. They provide some useful examples of estimated $PM_{2.5}$ attributable premature deaths based on different ambient concentration–response functions, estimates for which I will provide context.

Shin et al.[3] review meta-analysis methods for estimating the shape and uncertainty in the association between long-term exposure to ambient particulate matter (PM) and all-cause mortality. Their article considers both linear concentration–response models and alternative models extending to higher concentrations as required for some global applications. This is an especially important consideration when addressing the global range of $PM_{2.5}$ concentrations from current low ambient concentrations observed in countries such as the United States and Canada that have aggressively regulated air pollutants for half a century to countries like China and India with recent rapid industrialization, more limited regulations, and very high ambient concentrations of $PM_{2.5}$ and other air pollutants. Equally as important and not addressed by Shin et al. are the remarkable differences in various characteristics among the countries and within countries, including population characteristics such as baseline mortality rates, which are key inputs to the models.

The fourth article by Smith[4] illustrates the use of alternative approaches to calculating expected benefits of reducing the U.S. annual National Ambient Air Quality Standard for $PM_{2.5}$ from 15 to 12 μg/m^3. This article contains useful examples of the marked differences in estimates of avoided premature deaths dependent on the assumptions used in the calculations, including whether deaths are projected to occur below the current U.S. annual standard of 12 μg/m^3. I will provide context to those calculated estimates of avoided premature deaths.

2. THE CLEAN AIR ACT AS CONTEXT

The subject matter of the articles is grounded in the Clean Air Act (CAA) originally passed in 1963,[5] extensively amended in 1970[6] and again in 1990.[7] The CAA is the primary legislative basis for addressing air quality in the United States. Key sections of the CAA that require the U.S. Environmental Protection Agency (EPA) to set National Ambient Air Quality Standards (NAAQS)

for certain air pollutants found across the United States and attributable to multiple sources, based on scientific criteria; hence, in common usage they are called criteria pollutants. The CAA identifies two types of NAAQS. Primary standards are intended to protect public health, including protection of "sensitive" populations such as asthmatics, children, and the elderly. The primary standards are the focus of this commentary. The CAA also calls for secondary standards to protect public welfare, which includes visibility and damage to animals, crops, vegetation, and buildings. Bachman[8] reviewed the long history of the NAAQS, a paper that should be read by all who are interested in this topic.

It is useful to recall that passage of the CAA was motivated by widespread recognition in the 1950s and 1960s that the United States had serious air quality problems arising from a marked increase in industrial activity during and after World War II. In addition, it was recognized that air quality was being increasingly impacted by expanded use of motor vehicles. It was generally accepted that poor air quality was impacting the health of the populace. Initial attempts to control air pollution were grounded in local and state legislation. It soon became apparent that these actions were inadequate; hence, the CAA, as passed in 1963, was national in scope. Indeed, it specified the creation of a National Air Pollution Control Agency. This agency would ultimately become the "air office" component of the U.S. EPA when it was created on December 2, 1970.

The CAA amendments of 1970 substantially elevated the federal role in improving air quality, including the setting of NAAQS. The amended CAA (1970) delegates to the EPA Administrator responsibility for policy decisions on setting the four elements of each NAAQS (the indicator such as $PM_{2.5}$, the averaging time such as annual or 24 hour, the concentration, and the statistical form used to determine when the standard is attained). It is important to recognize that the CAA gives the EPA Administrator broad policy-making discretion for setting each NAAQS. The primary or health-based NAAQS are standards set so as to provide requisite protection, neither more nor less stringent than is necessary to protect public health, with an adequate margin of safety. The CAA does not specify a quantitative goal for setting each NAAQS based on some specific level of health protection, i.e., an acceptable level of risk. Thus, the level of risk protection embedded in each NAAQS is a policy judgment delegated to the EPA Administrator. Further, the U.S. Supreme Court in

Whitman vs. American Trucking Association[9] ruled that in setting the NAAQS, the Administrator cannot consider the costs of achieving the standards.

The six original criteria pollutants were PM, photochemical oxidants, carbon monoxide, sulfur dioxides, nitrogen oxides, and hydrocarbons. It was later determined that the hydrocarbons were more appropriately addressed as individual pollutants under the hazardous air pollutants section of the CAA. Legal action in the 1970s initiated by the National Resources Defense Council forced EPA to list lead as a criteria air pollutant. NAAQS have been set for each of the criteria pollutants and the science undergirding each NAAQS periodically reviewed. Most reviews have concluded with revision of the NAAQS. In addition, a national network of monitors has been established, primarily for regulatory compliance purposes. These monitors also provide the data that have been key to the conduct of most long-term epidemiological studies.

PM is a generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a range of sizes in the ambient air. It is important to recall that the original NAAQS for PM set in 1971 used "total suspended particles" (TSP) as an indicator. TSP samples are collected with a high volume sampler and include particles up to 25–45 microns in size. Standards were set for both 24-hour and annual averaging time. The latter was set at 75 μg/m^3, annual geometric mean form. In the discussion that follows, the focus will be on the annual standard. After an extensive review process initiated in the late 1970s, the PM NAAQS was revised in 1987 with the TSP indicator replaced with a particulate matter, 10 microns (PM_{10}) indicator. It is important to recognize that the PM_{10} fraction is included within the size range of TSP samples. The new annual PM_{10} NAAQS was set at 50 μg/m^3 and the form changed to an annual arithmetic mean, averaged over three years.

A contentious review concluded in 1997 resulted in a revision of the PM NAAQS with the addition of a $PM_{2.5}$ indicator despite there being very limited $PM_{2.5}$ ambient concentration–response data available for setting the NAAQS with 2.5 micron $PM_{2.5}$ indicators. Keep in mind that the $PM_{2.5}$ fraction is included within the size range of the PM_{10} fraction. The $PM_{2.5}$ annual NAAQS was set at 15 μg/m^3, annual arithmetic mean, averaged over three years. To give impetus to the adoption of a $PM_{2.5}$ indicator, one EPA official commented: "If you want

monitoring data on $PM_{2.5}$ for epidemiological studies, you need to support setting a NAAQS for $PM_{2.5}$, we only monitor what is regulated." In 2006, after another contentious review, the PM NAAQS was revised with a reduction in the 24-hour standard from 65 to 35 μg/m^3 and no change in the annual standard. In 2012, after another review, the PM standard was again revised with a reduction in the primary annual NAAQS to 12 μg/m^3, annual arithmetic mean averaged over three years. The next cycle of review of the PM NAAQS is already underway. If the agency were to conform with a five-year review cycle, the next review should be concluded by 2018. The agency has already acknowledged that it will not meet that schedule and instead has announced a schedule for release of the final PM rate in 2021.

In my opinion, the changes in the annual PM NAAQS over the decades have been driven largely by (1) improved scientific knowledge on the role of particle size governing the deposition and retention of airborne particles, hence the serial shift from a TSP to PM_{10} to $PM_{2.5}$ indicator, and (2) improved knowledge from epidemiological studies of human populations such as those under discussion in the four articles. The policy decision of the EPA Administrator on the level and form of the NAAQS for PM has largely been informed by the information from epidemiological studies.

All of the PM NAAQS set to date are based on mass concentration and the assumption that all of the PMs in each size fraction are of equal toxicity on a mass basis. This assumption needs careful review in the current PM review cycle.

3. HISTORIC CHANGES IN $PM_{2.5}$ AND MORTALITY

To provide context for considering the contents of the four articles, it is useful to consider the substantial historic changes in ambient $PM_{2.5}$ and mortality rate in the United States. One of the major long-term studies of the association between ambient PM and mortality is the Harvard Six Cities Study, a study conceived by Professor Benjamin Ferris in the 1970s when revision of the NAAQS set in 1971 was under review. Updated findings from this study have been periodically published. The recent paper by Lepeule *et al.*[10] provides a useful summary of the changes in ambient $PM_{2.5}$ concentrations in the six cities from the mid 1970s through 2009. The range of ambient concentrations shown (Fig. 1) is a reasonable representation of the downward trend in
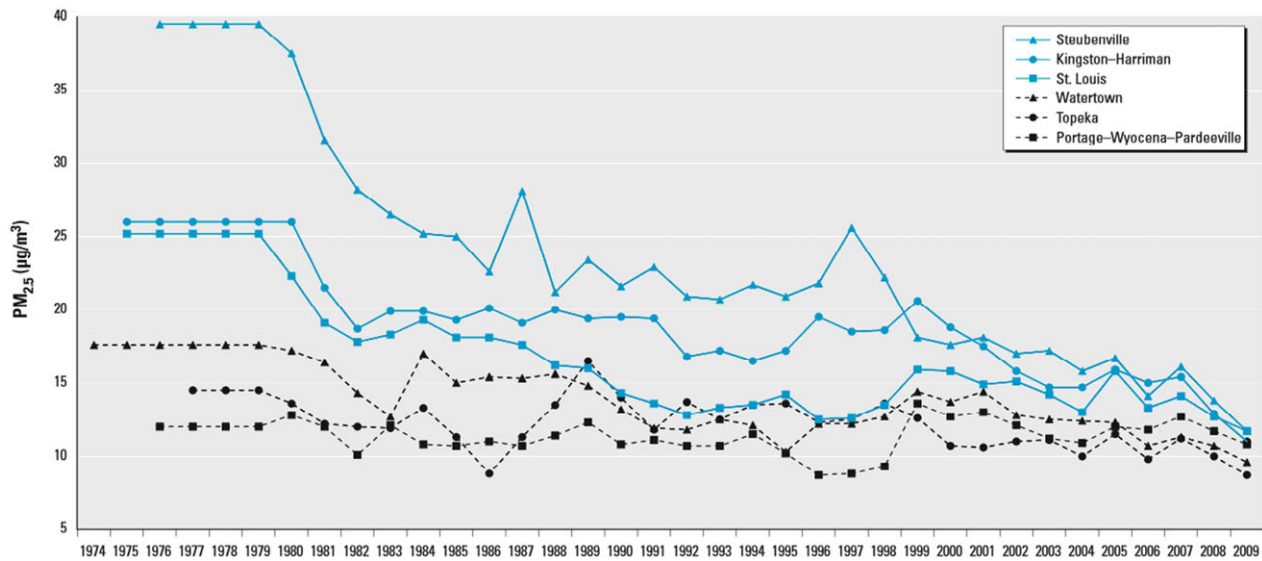
Fig. 1. Annual mean PM$_{2.5}$ levels during 1974–2009 in the Harvard Six Cities Study. (Adapted from Lepeule *et al.*[10] The data points pre-1997 for PM$_{2.5}$ have been extrapolated from TSP and PM$_{10}$ measurements.)

urban areas seen across the United States over this time period. In reviewing the figure, keep in mind that the PM indicator from 1971 to 1978 was TSP and from 1978 to 1997 was PM$_{10}$ with the PM$_{2.5}$ indicator added in 1997. The PM$_{2.5}$ concentrations shown in the figure for the earliest years are extrapolations from other indicators. The reductions in ambient PM$_{2.5}$ are impressive, especially for the three cities that originally had concentrations of 25 μg/m^3 and higher. It is reasonable to assume that these cities experienced even higher concentrations of PM$_{2.5}$ and coarse particles (PM$_{10}$ minus PM$_{2.5}$) at earlier times.

During the last three-quarters of a century, there have also been impressive improvements in mortality rates across the United States, with continuous reductions in crude death rates and even more impressive reductions in age-adjusted death rates.[11] Data for the period 1960–2010 are shown in Fig. 2.[12] It is important to note that these are national statistics with important substantial differences in both crude and age-adjusted death rates (deaths per 100,000 population) among different states and racial groups. For example, the age-adjusted death rate (all causes) in 2010 ranged from 590 in Hawaii to 962 in Mississippi.

Further context is provided by the data in Table I as to cause of death for mortality in the United States in 2010.[12] Consideration of these multiple causes of death provides insight into potential opportunities
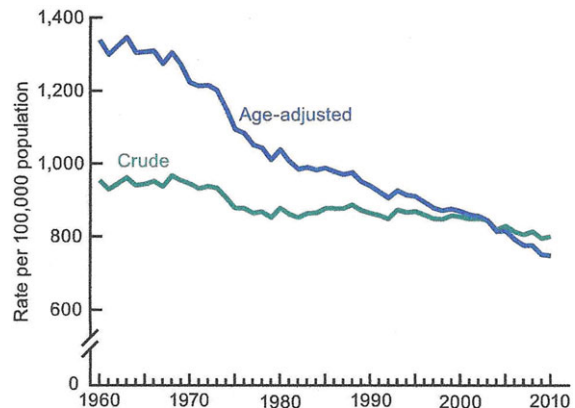
NOTES: Crude death rates are on an annual basis per 100,000 population; age-adjusted rates are per 100,000 U.S. standard population; see Technical Notes. Rates for 2001–2009 are revised using updated intercensal population estimates and may differ from rates previously published; see Technical Notes.
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Fig. 2. Crude and age-adjusted death rates: United States, 1960–2010. (Adapted from Murphy *et al.*[12])

for improving the health of the U.S. population, our ultimate goal.

4. COMMENTER'S BACKGROUND FOR CONTEXT

It is important to recognize that provision of any context, to a large extent, is dependent on the commenters' backgrounds and how they view the

Table I. Causes of Death for the United States for 2010 by Major Causes[12]

Rank	Cause of Death (Based on ICD-10, 2004)	Number
…	All causes	2,468,435
1	Diseases of heart	597,689
2	Malignant neoplasms	574,743
3	Chronic lower respiratory diseases	138,080
4	Cerebrovascular diseases	129,476
5	Accidents (unintentional injuries)	120,859
6	Alzheimer's disease	83,494
7	Diabetes mellitus	69,071
8	Nephritis, nephrotic syndrome, and nephrosis	50,476
9	Influenza and pneumonia	50,097
10	Intentional self-harm (suicide)	38,364
11	Septicemia	34,812
12	Chronic liver disease and cirrhosis	31,903
13	Essential hypertension and hypertensive renal disease	26,634
14	Parkinson's disease	22,032
15	Pneumonitis due to solids and liquids	17,011
…	All other causes	483,694

application of the work being reviewed. The context and perspective I offer is grounded in my experience as a scientist, research manager, and advisor on the use of science to inform public policy decisions. I have been studying the health effects of airborne materials for over half a century, initially focusing on radioactive materials, as might be released in a nuclear reactor accident, and later on airborne emissions from various energy technologies, especially diesel compression ignition engines. Soon after passage of the CAA, I began advising both public agencies and private organizations on air quality issues at the interface between science and public policy. Much of that activity has involved the setting of NAAQS for criteria air pollutants, including PM and implementation of strategies to attain the NAAQS. This service included chairing the EPA's review committee for the first criteria document on airborne lead and later the EPA Clean Air Scientific Advisory Committee (CASAC) and service on the CASAC Panels that reviewed the science undergirding the 1987, 1997, and 2006 revisions of the PM NAAQS. I offered independent comments on the 2013 revision.

Based on my personal experience in the NAAQS setting process, I am firmly convinced that science should inform the policy decisions that are required in the setting of the NAAQS.[13] However, a corollary is that both scientists and policymakers should recognize that the science alone is not sufficient for making policy decisions. This is particularly the case in the absence of a quantitative goal or target for acceptable risk. The alternative approach embedded in the CAA is a policy judgment by the EPA Administrator as to how low is low enough. Tensions develop when scientists want to enter the policy arena and specify numerical standards that implicitly involve policy judgments. Tensions also arise when policymakers cast their policy judgments as being dictated by the science and abdicate their policy judgment role. I addressed those issues in the paper "Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough?"[13]

The passage of the CAA had substantial impact on the research enterprise in the United States, with substantial federal funding provided for investigation of pollutants from their movement from their sources at smoke stacks and tail pipes through the atmosphere to people and the development of an improved understanding of the health effects of airborne pollutants. A national network of monitors has been deployed, primarily for regulatory compliance purposes and secondarily for research purposes. Substantial investments of public and private funds have been made to develop and improve a wide range of technologies to reduce emissions of both regulated and nonregulated air pollutants from various sources. It is widely acknowledged today by multiple parties, the public, government agencies, industry, and politicians that the regulatory programs grounded in the CAA have had widespread positive impact. Air quality in the United States today is markedly improved from that observed in the 1970s and earlier. This leads to a critical question today as to what extent current air quality has any adverse impact on human health and, if so, are even more stringent NAAQS required? The first three articles under consideration address the science that informs policy decisions on the question posed. The fourth article by Smith[4] is at the interface of the science and policy. Some readers may be alarmed by my raising the issue of whether current air quality in the United States has adverse health impacts and requires more stringent standards. In my opinion, addressing that complex issue is at the interface of science and policy and is one reason why the four articles and related commentaries should be of interest to a wide audience of scientists, policymakers, and the public.

5. EVALUATING CAUSALITY

A critical issue related to assembling, integrating, synthesizing, and communicating the science on the health effects of $PM_{2.5}$ revolves around whether there is a "causal" link between exposure to ambient $PM_{2.5}$ and a range of health endpoints including all-cause mortality and specific causes of death such as ischemic heart disease, stroke, chronic obstructive pulmonary disease, and lung cancer. To aid in addressing this issue in an organized way, the EPA has developed a five-level hierarchy that classifies the overall weight of evidence drawn from integration of evidence across epidemiological, controlled human exposure studies, and toxicological studies and the related uncertainties that ultimately influence our understanding of the evidence. The five categories are: (1) causal relationship, (2) likely to be causal relationship, (3) suggestive of a causal relationship, (4) inadequate to infer a causal relationship, and (5) not likely to be causal relationship.[14] This approach is analogous to the hazard identification methodology widely used for decades in addressing cancer hazards of various agents. The *Federal Register* announcement of the National Ambient Air Quality Standards for Particulate Matter: Final Rule[15] has extensive discussion of the use of this qualitative categorical hazard hierarchy in informing the policy judgments supporting the decision (1) to lower the annual NAAQS for $PM_{2.5}$ from 15 to $12\,\mu g/m^3$ and (2) to retain the 24-hour averaging time NAAQS set at $35\,\mu g/m^3$ with a 98th percentile statistical form for attainment purposes.

It is noteworthy that this "causal" categorization process, by its very nature, emphasizes positive findings, which, in turn, emphasize the findings from studies at the highest ambient $PM_{2.5}$ concentrations. It is important to recognize that the categorization process does not rigorously address the equally important question of whether $PM_{2.5}$ at levels currently found in the United States have increased associated morbidity and mortality rates for specific health outcomes over and above baseline rates. That is a critical issue in the review of the science for a policy decision on any potential revision of the NAAQS for $PM_{2.5}$.

The issue of what ambient concentrations of $PM_{2.5}$ have a causal attributable effect on health outcomes such as an increase in all-cause mortality over and above background or baseline rates is not addressed by the five-level causal hazard hierarchy. This is a separate and extremely important issue. It is my opinion that many scientists, perhaps including some of the authors of the four articles, are confused and view the causal hazard hierarchy as extending to ambient $PM_{2.5}$ concentration–response functions.

Shin *et al.*[3] touch on this issue when they note the lowest concentration studied in the American Cancer Society (ACS) cohort was $5.8\,\mu g/m^3$, the 5th percentile was $8.8\,\mu g/m^3$, and the 95th percentile is below $20\,\mu g/m^3$. They note "reliable estimates of risk from the available studies can only be made using the data in the 5th to 95th percentile of exposure, i.e., estimates of the shape in the lower 5th and upper 95th percentile are both imprecise and likely to be inaccurate." I question the implication that the statistical association between ambient concentrations of $PM_{2.5}$ and excess risk is equally reliable over the full range from the 5th to the 95th percentile of $PM_{2.5}$ concentrations. It was disappointing that Shin *et al.*[3] did not more rigorously address the basis for their focus on the 5th percentile in view of EPA's approach to the last NAAQS revision.[15]

Specifically, it would have been of interest to readers if Shin *et al.*[3] had offered a rigorous critique of the related methodology used by the EPA Administrator to make the policy decision lowering the annual $PM_{2.5}$ NAAQS from 15 to $12\,\mu g/m^3$ effective from March 18, 2013.[15] In reaching that policy decision, the final rule stated: "In considering the evidence, the Policy Assessment recognized that NAAQS are standards set so as to provide requisite protection, neither more nor less stringent than necessary to protect public health, with an adequate margin of safety. This judgment ultimately made by the Administrator involves weighing the strength of the evidence and the inherent uncertainties and limitations of that evidence." As summarized in the Final Rule for the $PM_{2.5}$ NAAQS,[15] the Administrator gave special attention to four multicity studies for which distributional statistics of $PM_{2.5}$ ambient concentrations were available. This did not include the Harvard Six Cities Study, for which the Lepeule *et al.*[10] paper is the last update apparently, because the investigators would not release their data on ambient $PM_{2.5}$ concentrations for the populations studied in six cities. The Rule noted: "By considering this approach one could focus on the range of $PM_{2.5}$ concentrations below the long-term mean ambient concentrations over which we continue to have confidence in the associations observed in epidemiological studies (e.g., above the 25th percentile) where commensurate public health protection could be obtained for $PM_{2.5}$-related effects and, conversely, identify the range in the distribution below which our

confidence in the associations is appreciably less, to identify alternative annual standard levels." It is clear that this approach accepts the categorization of some long-term exposure studies as evidence of a causal or likely causal relationship for all-cause mortality; however, only above the 25 percentile of ambient $PM_{2.5}$ concentrations in the four studies. Most importantly, the EPA Administrator viewed the evidence below the 25th percentile as uncertain and not supportive of a causal or likely causal relationship. This contrasts with the conclusions of Shin et al.[3] It is very likely that this issue will be raised again in the next review of the $PM_{2.5}$ NAAQS. This is a critical issue at the interface between scientific information and policy choices. It is important to recognize that each review does not have to necessarily conclude with a revision of the NAAQS.

6. ASSOCIATIONS VERSUS CAUSALITY AT LOW $PM_{2.5}$ CONCENTRATIONS

All four of the articles most often referred to the "association" between ambient $PM_{2.5}$ and health responses. Unfortunately, the tone of three of the articles was that this association represented a causal relationship. As revealed in the earlier discussion of the EPA approach to setting the $PM_{2.5}$ (annual) NAAQS at 12 μg/m^3, it is important to not assume that causality extends to the lowest ambient $PM_{2.5}$ concentrations studied based on a linear model and the lowest ambient $PM_{2.5}$ concentrations studied. At a minimum, this issue deserves rigorous discussion and debate.

Unfortunately, none of the articles contain a robust discussion of the many biomedical uncertainties inherent in ambient $PM_{2.5}$ concentration–response associations over a range of ambient $PM_{2.5}$ concentrations. These uncertainties are multifold, including the official assumption in the last EPA review that all $PM_{2.5}$ is of equal toxicity on a mass basis. The assumption of equal toxicity is especially uncertain when one recognizes that PM reduction strategies have been highly effective in the United States over the past half-century in reducing mass emissions and reduced ambient concentrations of PM_{10} and $PM_{2.5}$. These reductions have resulted in a shift from PM resulting from direct emissions to PM formed from secondary reactions and associated changes in the chemical and size composition of PM. It is important to recognize that these changes are embedded in the ambient PM concentration data used in the major long-term epidemiological studies with the ambi-

ent PM for the earliest time periods in the studies being different from the ambient PM for the most recent updates of the studies. Unfortunately, speciated $PM_{2.5}$ data have rarely been obtained over long periods of time at multiple monitoring sites. Data on speciated $PM_{2.5}$ are necessary to test hypotheses on whether different $PM_{2.5}$ components have different potencies for causing an increase in different health effects. A closely related issue is whether ambient $PM_{2.5}$ concentration–response functions derived from the study of populations in one part of the United States are applicable to populations in other parts of the United States. The importance of this issue was underscored by the results reported by Zeger et al.[16] They found an association between increases in $PM_{2.5}$ and increases in mortality in the eastern and central regions of the United States and no evidence of an association in the western United States for the period 2000–2005. It is also important to recognize that the U.S. populations studied in recent decades were not likely exposed to PM of the composition and high concentrations encountered today in some countries such as China and India.

The Shin et al.[3] article has the most extensive discussion of the issue of causality. However, in my opinion, much of this discussion is quite simplistic and, indeed, naïve with regard to the actual complexity of disease processes. This is illustrated with the statement: "There is now experimental and clinical evidence that exposure to fine particulate matter causes biological responses such as oxidative stress leading to chronic inflammation, which in turn, can lead to increased mortality from chronic cardiovascular and respiratory disease and lung cancer, thereby shortening the lifespan." In my opinion, this is an excessively broad conclusion. I would agree that oxidative stress is one of the current fads in the biomedical sciences; however, such fads come and go. Unfortunately, disease processes are much more complex than this statement indicates, and a single step in complex multistep disease processes has rarely proved to be overwhelmingly dominant across a population afflicted with a particular disease. Shin et al.[3] use the term "causal models" at several places in their article, including reference to the paper of Pope et al.[17] These modeling exercises are useful; however, the models fall short of describing the myriad of complex steps by which responses over many decades to a single risk factor, such as $PM_{2.5}$, undefined as to chemical composition, cause a very small increase in the relative risk of death from a particular disease in a large population.

The Shin et al.[3] article contains what I view as an unjustified statement that: "There is no biological reason to believe that there exists a range in exposure for which no mortality risks exists (i.e., threshold)." It is noteworthy that the authors provided several figures in which data were plotted as hazard ratios or relative risk. The above quote apparently fails to recognize that the hazard ratio or relative risk of 1.0 is not an absence of mortality, it is the baseline mortality rate against which an increase in mortality attributable to the putative risk factor being examined is evaluated, in this case—$PM_{2.5}$—after attempting to control for all other risk factors potentially associated with the disease endpoint of concern. The diseases that are of concern for chronic exposure to $PM_{2.5}$ are very common causes of death (recall Table I) and arise from multiple risk factors. For deaths occurring late in life, many of these risk factors have interacted with normal biological processes, including damage, repair, and homeostatic processes, for decades throughout the individual's life. At the risk of sounding trite, life from conception to death is full of competing risks. The challenge for biomedical scientists, including statisticians, is to determine under what $PM_{2.5}$ exposure conditions over a lifetime of exposures there is a significant role for $PM_{2.5}$ in altering those complex processes and impacting morbidity and mortality rates. The challenge is even more difficult because many of the risk factors identified to date for the diseases of concern do have impact over the individual's total lifetime. As noted earlier (Fig. 1), there has been continuous improvement in mortality rates in the United States over the past half-century. Attempting to tease out the relative importance of a multitude of risk factors for this improvement in health is complex and beyond the scope of this commentary.

In this commentary, I have not discussed a growing body of evidence of a lack of influence of ambient $PM_{2.5}$ concentrations on mortality. An example is the paper by Greven et al.[18] that uses ambient $PM_{2.5}$ monitoring data for 2000–2006 and data on time of death and age for 18.2 million individuals in a Medicare cohort. They developed both national and local coefficients to examine trends. Based on the local coefficient alone, they were not able to demonstrate any change in life expectancy for a reduction in ambient $PM_{2.5}$. These results suggest the need for caution in using national values for estimating $PM_{2.5}$ attributable effects in specific regions of the United States, including California. In this regard, a number of studies have been developed on California populations, some of which suggest an absence of excess risk for recent ambient $PM_{2.5}$ concentration.[16,19]

It is well recognized by scientists and clinicians knowledgeable of the biology and pathobiology of the health endpoints of concern that none of the individual cases carry "markers" or any characteristics that allow $PM_{2.5}$ attributable cases to be distinguished from cases that are attributable to a myriad of other causes. The attribution of deaths associated with $PM_{2.5}$ exposure is done on a statistical and population basis. The statistical models used typically are proportional hazard models that estimate for the population a given portion of the cases over and above the baseline mortality rates attributed to other causes. To provide a context for considering the estimated $PM_{2.5}$ attributable deaths, it is always helpful to present the baseline mortality rate, which, as discussed earlier, varies with time, place, and population as influenced by multiple factors. I will return to that point later. In addition to showing the excess risk attributed to $PM_{2.5}$, it would be informative if the analysts also showed the excess risks estimated for other well-recognized risk factors, such as smoking and socioeconomic status, that must be controlled for in the analyses to develop reliable estimates of excess $PM_{2.5}$ attributable risks. This information would be valuable to the analysts and to other parties to help understand if the calculated results for $PM_{2.5}$ make sense. An array of attributable risk results for different risk factors also provides valuable context for policymakers and the public concerned with how best to positively impact human health. In my opinion, it is important to periodically recall the goal to improve public health; the regulation and control of specific risk factors such as $PM_{2.5}$ is just one means to that end.

7. EXPANDED PRESENTATION OF RESULTS TO PROVIDE CONTEXT

In this section, I will illustrate how an expanded presentation of results can provide useful context and perspective. Fann et al.[2] use their Fig. 3 to graphically illustrate the estimated "premature deaths avoided" based on different ambient $PM_{2.5}$ concentration–response functions. The focus is on comparison of the results using functions from the Harvard Six Cities Study[10] and the ACS study.[20] The graph also showed estimates developed from

Table II. Comparison of 2014 Estimated Premature Deaths Avoided Using Alternative Ambient PM$_{2.5}$ Concentration–Response Functions (Adapted from Fann et al.[2] and Fann [personal communication])

Source of Function	Baseline Mortality (Deaths)	Estimated Premature Deaths Avoided (Deaths 95% Confidence Interval)
Harvard Six Cities Lepeule et al.[10]	2,565,169[a]	10,373 (6,010, 14,698)
ACS Krewski et al. (2009)	2,565,169[a]	4,582 (3,334, 5,821)
Pooled experts	2,565,169[a]	8,327 (1,492, 18,289)
Meta-analysis (beyond 2006)	2,565,169[a]	5,852 (2,527, 9,150)
Meta-analysis (through 2006)	2,565,169[a]	5,530 (3,287, 7,756)
Integrated exposure response	364,408[a]	3,931 (1,935, 4,241)

[a] All cause.
[b] Ischemic heart disease.

functions elicited from 12 experts, a meta-analyses of literature through 2006 and beyond 2006, and a pooling of the 12 experts based on all-cause mortality. Also shown is an estimate from an integrated exposure–response analysis for ischemic heart disease. In Table II, the original estimates of Fann et al.[2] are shown complemented by baseline mortality data added to provide context. In my opinion, showing the baseline mortality values helps the reader to understand this mathematical exercise. The table would be even more informative if it included the total population for 2014.

Smith[4] provides an excellent example of how the assumptions used in estimating benefits can have major impact on the results. In her paper, Table I showed the total risk reduction estimate (avoided premature deaths in 2020) for two approaches. One approach was the traditional approach used by EPA in developing regulatory impact analyses (RIAs). That approach assumes deaths are avoided irrespective of the ambient concentrations of PM$_{2.5}$. Table III yields 456 avoided deaths with the national concentration–response function that was developed by Krewski et al.[20] using the ACS cohort and 1,034 avoided deaths using the concentration–response function that was developed by Lepeule et al.[10] from the Six Cities Study. Smith[4] also gave lower estimates based on the approach that EPA used in the latest revision of the NAAQS for PM$_{2.5}$ described earlier in this commentary. As shown in Table III, the number of residual avoidable deaths is reduced to 21–47, dependent on the concentration–response function used and involves an impacted population of less than 1 million. Alleged benefits in the RIA, of 456–1,034 (or 460–1,000 using the RIA's rounding convention) avoidable deaths, disappear if one uses the qualitative policy judgment used by the EPA Administrator in revising the NAAQS for PM$_{2.5}$. Indeed, a strong argument can be made that there are no avoided PM$_{2.5}$ attributable deaths in California based on the report of Zeger et al.[16] Recall that they reported no finding of evidence of an association between ambient PM$_{2.5}$ and mortality in the western United States. They noted "this lack of association is largely because the Los Angeles Basin counties (California) have higher PM levels than other West Coast urban centers but not higher adjusted mortality rates." As an aside, California was the only state for which benefits of

Table III. Estimates of Avoided Premature Deaths in California in 2020 Estimated for PM$_{2.5}$ NAAQS with a Reduction in the Annual Standard from 15 to 12 μg/m^3 Projected Using BenMAP[21] and Smith (personal communication)

	Population		Baseline Mortality (#)		Avoided Deaths (#)	
	Krewski[a]	Lepeule[b]	Krewski	Lepeule	Krewski	Lepeule
	(30–99)	(25–99)	(30–99)	(25–99)	(30–99)	(25–99)
Not attaining/above margin (>13 μg/m^3)	763,104	875,086	7,574	7,681	21	47
Not attaining/in margin (>12–13 μg/m^3)	3,841,464	4,419,703	41,853	42,342	117	266
Already attaining (≤12 μg/m^3)	7,560,163	8,537,984	86,913	87,735	318	721
Total	12,164,732	13,832,773	136,340	137,758	456	1,034

[a] Krewski et al.[20] evaluate the population from age 30 to 99 years.
[b] Lepeule et al.[10] evaluate the population from age 25 to 99 years.

avoided mortality were projected to occur with a lowering of the PM$_{2.5}$ NAAQS. Other areas had already attained the PM$_{2.5}$ NAAQS. Again, the inclusion of the baseline population and mortality data helps provide context and perspective to the calculated benefits. Note that the population and baseline mortality values are based on actual data rather than hypothesized relationships and, thus, are much more certain than the calculated benefits. This broader array of data not only gives perspective to the calculated benefits, i.e., avoidable deaths, for a PM$_{2.5}$ standard, but invites questions as to where society at large can gain the greatest benefits in improved health.

To give a broader perspective to the estimated avoidable deaths, it is useful to recall Table I, which provides detailed mortality data by causes for 2010. As discussed earlier, consideration of calculated estimates of PM$_{2.5}$ attributable deaths along with an array of mortality data by multiple causes opens the door to a broader discussion of options for improving the health and quality of life for society at large moving beyond a singular focus on PM$_{2.5}$.

The above discussion has focused on providing information on three key inputs: (1) the population under consideration, (2) baseline mortality rate, and (3) the ambient PM$_{2.5}$ concentration–response functions (and the associated uncertainties at various PM$_{2.5}$ levels). It is also useful to have a more complete exposition of the ambient PM$_{2.5}$ data being used as input as illustrated by Smith.[4]

The above discussion also carries with it important implications for setting priorities for research that will help improve human health. Let me first address the adequacy of current models of ambient PM$_{2.5}$ concentration–response functions. In my view, the models currently available provide reasonable upper-bound estimates of PM$_{2.5}$ attributable mortality, i.e., more likely to overestimate than underestimate the true PM$_{2.5}$ attributable mortality. The estimated ambient PM$_{2.5}$ concentration–response functions and PM$_{2.5}$ attributable mortality calculated for those studies are likely related to the exposure of the populations over a lifetime beginning early in life, i.e., in the 1970s and earlier for the vast majority of the deaths. Ambient concentrations of PM$_{2.5}$ have steadily declined across the United States from that time to the present; recall Fig. 1. In addition, the U.S. age-adjusted death rate has steadily decreased, as shown in Fig. 2, related to many factors.

Let me quickly note that some individuals may suggest that improved air quality had a role in the observed reduced death rates. That may be true;

Table IV. The Impact of Socioeconomic Status on Mortality Rate Ratio (Adapted from Steenland *et al.*[22])

Mortality	Men	Women
All causes	2.02 (1.95–209)[a]	1.29 (1.25–1.32)
Heart disease	1.88 (1.83–193)	1.84 (1.76–1.93)
Stroke	2.25 (2.14–2.37)	1.53 (1.44–162)
Diabetes	2.19 (2.07–2.32)	1.85 (1.72–2.00)
COPD	3.59 (3.35–3.83)	2.09 (1.91–230)
Lung cancer	2.15 (2.07–2.23)	1.31 (1.25–1.39)
Breast cancer	–	0.76 (0.73–0.79)
Colorectal cancer	1.21 (1.16–1.27)	0.91 (0.86–0.96)
External causes	2.67 (2.58–2.78)	1.41 (1.35–1.48)

Note: Mortality rate ratio = mortality for lowest quartile of socioeconomic status. Mortality for highest quartile of socioeconomic status.
[a]95% Confidence interval.

however, I suggest the impact of PM$_{2.5}$ reductions is likely very small and difficult to tease out from the myriad of other factors that were likely involved in reducing mortality rates. To provide further perspective, it is useful to note the substantial impact of socioeconomic status on mortality[22] (Table IV). The mortality rate ratio for the lowest quartile over the highest quartile of socioeconomic status is high compared to small changes attributed to PM$_{2.5}$. It is obvious that many individual risk factors are included within socioeconomic states. All of these factors create "noise" that makes it challenging to identify any small signal attributed to PM$_{2.5}$. This speaks for caution in interpreting and using the small signals attributed to PM$_{2.5}$ in these statistical exercises.

The overall point I wish to make is that disease processes are very complex and are influenced by multiple risk factors. For any attempt to tease out the effects of a single risk factor, like PM$_{2.5}$, to be successful it needs to take account of the other risk factors. I urge the investigators who have focused their energy on PM$_{2.5}$ issues to broaden the scope of their research to give greater attention to identifying and characterizing multiple risk factors. In my opinion, this broader perspective offers the best opportunity for having a positive impact on the health of populations.

8. CONCLUSIONS

The information presented in the four articles and discussed here also has important implications for setting future PM NAAQS and for research to better understand mechanisms of disease causation, approaches to mitigation of disease, and treatment of

disease. A review of the data presented here, with a focus on the United States, indicates that any health effects attributable to $PM_{2.5}$ are quite small when considered in the context of the total disease burden. A corollary is the need for caution in advocating for more $PM_{2.5}$ focused research. In my opinion, a better return on societal investment is likely to come from a broader consideration of the complex pathways of disease causation common to multiple risk factors and, perhaps, amplified by certain risk factors.

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