Comments to CASAC on the *Policy Assessment for the Review of the National Ambient Air Quality Standards for Particulate Matter, External Review Draft*

Anne E. Smith, Ph.D.
Managing Director, NERA Economic Consulting
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On September 5, 2019, the U.S. Environmental Protection Agency (EPA, or "the Agency") released its *Policy Assessment for the Review of the National Ambient Air Quality Standards for Particulate Matter, External Review Draft* (hereafter referred to as the "draft PA").[1] On October 24-25, the Clean Air Scientific Advisory Committee (CASAC) will be convening to develop its comments to EPA on the draft PA. The following document is intended to provide additional information from my own research that is of relevance and potential interest to the CASAC, as well as to the Agency. I have prepared these comments with financial support from a coalition of industry associations.

My comments are focused specifically on the question of *whether the section of the draft PA that discusses risk-based considerations provides information that is useful and reliable as guidance to decision makers when considering the merits of the current and alternative potential National Ambient Air Quality Standards (NAAQS).*[2]

This is a research topic on which I have been actively engaged for the past thirty-five years, starting with a study funded by EPA in the early 1980s to explore methods for incorporating uncertainties into NAAQS-focused health risk analyses. (I conducted that study while working in the Decision Analysis Group at SRI International.) I have continued to be actively engaged in developing and demonstrating methods for air pollutant health risk analysis, including preparing technical comments on the risk analyses for many prior NAAQS reviews of $PM_{2.5}$, ozone, SO_2, and NO_2.

Of most relevance to the present deliberations is a set of seven articles that I have written (and have had published in the period 2015-2019) on criteria pollutant heath risk analysis methods. These papers have addressed both the Health Risk and Exposure Assessment (HREA) documents that have been prepared to support in the Administrators' decisions on NAAQS revisions and the risk and benefits estimates that appear in the Regulatory Impact Analyses (RIAs) that must accompany each new major proposed and final rulemaking, such as most NAAQS revisions. This $PM_{2.5}$ review cycle has not produced a separate HREA document, but Section 3.3 of the draft PA contains the same kind of information that is usually first presented in an HREA. For that reason, any reference to methods appropriate for HREAs in my comments below should be viewed as a relevant comment for the contents of Section 3.3 of the draft PA.

My objective in this document is to provide a brief synthesis of the content and conclusions of my articles in the specific context of the current review of the $PM_{2.5}$ primary NAAQS. I provide full references to the

[1] EPA, *Policy Assessment for the Review of the National Ambient Air Quality Standards for Particulate Matter, External Review Draft*, EPA-452/P-19-001, Office of Air Quality Planning and Standards, Research Triangle Park, NC, September 2019.

[2] This discussion is based primarily on Sections 3.3 and Appendix C of the draft PA. It does, of course, also tie into some of the broader questions regarding the causal interpretation of the concentration-response (C-R) functions that EPA has inferred from $PM_{2.5}$ epidemiological studies. Although my focus herein is on the risk analysis in this draft PA, I have previously (in 2009) commented on the Agency's causality framework. Because I consider those comments to be of continued relevance, I am attaching a copy of them in an appendix to this document.

articles in the bullet list below.[3] I list the papers in the order in which I discuss them (rather than by publication date), along with a short name that I will use in the rest of this document to refer to each. Those short names are shown in bold font:

- "Setting Air Quality Standards for $PM_{2.5}$: A Role for Subjective Uncertainty in NAAQS Quantitative Risk Assessments?" *Risk Analysis*, Vol. 38(11), November 2018, pp. 2318-2339. **("HREA History")**

- "Author Synthesis and Response" to Special Issue on Air Pollution Health Risks, *Risk Analysis* Vol. 36(9), September 2016, pp. 1780-1782. **("Special Issue Synthesis")**

- "Enhancing the Characterization of Epistemic Uncertainties in $PM_{2.5}$ Risk Analyses" (with W. Gans), *Risk Analysis*, Vol. 35(3), March 2015, pp. 361-378. **("BenMAP Review")**

- "Response to Commentary by Fann *et al.* on "Enhancing the Characterization of Epistemic Uncertainties in $PM_{2.5}$ Risk Analyses," *Risk Analysis*, Vol. 35(3), March 2015, pp. 381-384. **("Response to EPA")**

- "Integrated Uncertainty Analysis for Ambient Pollutant Health Risk Assessment: A Case Study of Ozone Mortality Risk" (with Garrett Glasgow), *Risk Analysis*, Vol. 38(1), January 2018, pp. 63-176. **("Ozone IUA")**

- "Inconsistencies in Risk Analyses for Ambient Air Pollutant Regulations," *Risk Analysis*, Vol. 36(9), September 2016, pp. 1737-1744. **("Inconsistencies")**

- "Using Uncertainty Analysis to Improve Consistency in Regulatory Assessments Of Criteria Pollutant Standards" (accepted by *Risk Analysis* in September 2019, in press). **("Improving Consistency")**

1. Summary of Key Points

The articles listed above cover several different aspects of issues with and methods for health risk analysis for criteria pollutants. However, each of the articles, and all of them as a group, support my conclusion here that *the risk analysis presented in the draft PA provides insufficient and even misleading guidance for the upcoming $PM_{2.5}$ NAAQS decision*.

The central flaw of this draft PA's risk analysis is its lack of any attempt to quantify or integrate the most important sources of uncertainty inherent in the risk calculations—uncertainties that are variously referred to as "model," "epistemic," or "scientific" uncertainty. Instead, the range around each of the draft PA's reported risk estimates reflects only the statistical error of the respective single concentration-response (C-R) function slope coefficient assumed for that particular risk calculation. That statistical error reflects only the noise in the data of that one epidemiological study; it bears no relationship to additional potential errors in the C-R slope estimate that may be due to misspecification of the C-R shape to be estimated, the manner in which covariates are assumed to influence the PM-risk relationship, potential exposure measurement errors,[4] or potentially different levels of exposure errors for co-pollutants. These latter

[3] Under my copyright agreements, I can send copies of these papers to individuals who request them of me. Such requests can be emailed to me at Anne.Smith@NERA.com.

[4] Exposure mismeasurement is often discussed in terms of whether the estimated ambient concentration of total $PM_{2.5}$ mass that is attributed to the individuals in a study is a correct estimate of their actual ambient total mass exposure. However, there are other important (perhaps more important) errors that fall in the category that are often ignored. One is whether the correct period for exposure is being used, including whether lagged, time-varying and/or cumulative exposures are more appropriate. Another form of mismeasurement error is whether total $PM_{2.5}$ mass is the correct exposure, or some specific $PM_{2.5}$ constituent

forms of potential biases and error have repeatedly been recognized as far larger than the statistical errors. In my own research analyzing these non-statistical uncertainties, I have routinely found that they do not simply widen the range about the risk estimate, but asymmetrically add more probability on the lower rather than higher side of the risk estimate.

Layered on top of the aforementioned host of unquantified model uncertainties is a concern with prediction error.[5] An epidemiological estimate of the relative risk based on a given set of observations—even if highly accurate as an estimate of the average responses of the individuals within that data set that are causally attributable to $PM_{2.5}$—does not necessarily accurately predict what the average population response will be in a future year, at a different future level of exposure to $PM_{2.5}$, or in different locations. However, such extrapolation is the essence of risk analyses based on epidemiological associations: the epidemiological estimation attempts to infer statistically what *did* happen under one set of circumstances, and the risk analysis then attempts to predict what *would* happen under different circumstances. The prediction error of the estimated C-R relationship can be large for individual observations within the original set of observations. However, it is vastly exacerbated when using an estimated C-R relationship for "out of sample" extrapolations to other conditions, which is the essence of the type of health risk analysis reported in Section 3.3 of the draft PA.

By using statistical error as the only measure of uncertainty in its risk estimates, Section 3.3 provides a highly misleading summary of risk-based considerations for decision makers. As written, it could sway decision makers and other readers into a mistaken belief that the ranges around its risk estimates represent a quantitative synopsis of the many uncertainties that the section discusses only qualitatively. The risk analysis in the draft PA is at odds with and completely ignores the available literature on the need for quantitative integrated assessment of the uncertainties that arise when using from epidemiologically-based relative-risk coefficients to predict absolute levels of risk under different circumstances. Lacking any attempt at providing an integrated uncertainty analysis (IUA), the draft PA does not provide the type of decision-relevant information that is core objective of good quantitative risk analysis.

2. The Progressively Declining Usefulness of Risk Analysis in PM NAAQS Decision-making

My November 2018 paper labelled **"HREA History"** tracks the use of and reliance on results from quantitative health risk analysis in the Agency's NAAQS decisions dating back to the 1970s. It first documents how the Agency realized over 40 years ago that integrated assessment of the epistemic uncertainties associated with available scientific evidence was critical to making a well-informed decision on what level of criteria pollutant exposures could be judged to be protective of the public health with an adequate margin of safety. This included recognition by the Agency that such uncertainties could only be fully characterized through the subjective judgments of experts who are able to assess the merits of existing scientific studies.

The **"HREA History"** paper then reviews the HREAs specifically associated with the $PM_{2.5}$ NAAQS, including those for the 1997, 2006, and 2013 $PM_{2.5}$ NAAQS decisions. It tracks how epistemic uncertainty was characterized in the past three $PM_{2.5}$ NAAQS HREAs, and it analyzes how informative each successive HREA was to the respective Administrators' final judgments on the appropriate NAAQS

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that is a subset of the total mass. Serious errors in the C-R slope estimate that is then applied in a risk calculation can be created by either of these latter forms of measurement error, even if the researchers have very accurate information on what the concentration of total $PM_{2.5}$ mass was at a given individual's residence and point in time.

[5] Prediction error of an estimated relationship is not the same thing as statistical error of the slope estimate, which is the only form of statistical uncertainty that EPA uses in its risk analyses in the draft PA. The prediction error of a line fit through a set of observations is larger than the statistical error on the estimated slope of that line, and increasingly so for observations farther from the mean observation.

to establish. Consistent with the structure of the current draft PA, the three prior $PM_{2.5}$ NAAQS decisions considered an "evidence-based" approach and a "risk-based" approach.[6]

The paper describes a progressive elimination of quantitative characterizations of epistemic uncertainty in the $PM_{2.5}$ HREAs, and a concomitant elimination of relevance to the decision makers of the information provided by the HREAs. The research shows that these parallel trends are not a coincidence but are clearly causally related. That is, in each successive NAAQS review decision, it is shown that deterministic assumptions that eliminated consideration of critical epistemic uncertainties in the HREAs' risk estimates undercut the decision makers' ability to rely on those respective HREAs. As a result, in both the 2006 and 2013 rulemakings, the justification for the selected NAAQS level was founded entirely on the evidence-based approach, while the "risk-based considerations" reported in the HREA were ignored.

My article recounts how the first $PM_{2.5}$ HREA, finalized in 1997, contained a set of three alternative potential subjective probability distributions over the key scientific uncertainties in the risk calculations – the most important of which was the level below which the C-R functions might not continue.[7] Given the quantification of epistemic uncertainties in that HREA, it was possible to present a consistent discussion of evidence-based and risk-based considerations. The Administrator at the time was able to select NAAQS levels that were coherently related to the information provided in the HREA.

The second $PM_{2.5}$ HREA (for the rule finalized in 2006) did not include a probability distribution over the epistemic uncertainty on a potential end of the C-R relationship. Instead, following a recommendation by CASAC, that HREA assumed (deterministically) a threshold for long-term mortality risk specifically at 10 $\mu g/m^3$. This deterministic treatment of the most critical, decision-relevant uncertainty associated with the risk calculations had the effect of making 10 $\mu g/m^3$ the only reasonable level at which to set the long-term standard if one were to rely on that HREA's risk estimates. Observing this, the Administrator essentially dismissed that HREA as uninformative to the science-policy judgment that he faced.

In the third $PM_{2.5}$ HREA (for the current standard, promulgated in 2013), the HREA backed-off entirely from any quantitative treatment of scientific uncertainties in the risk calculations. It assumed the C-R functions, including that for long-term mortality, were of unchanging slope or uncertainty down to the the lowest measured level in each epidemiological dataset from which a C-R slope coefficient was obtained. (This was similar to assuming a deterministic threshold at 5.8 $\mu g/m^3$.) Anticipating the impending implications of that HREA's assumptions, CASAC advised the Agency to seek alternative rationales for characterizing the uncertainty in continued health risks at ever lower potential NAAQS levels. The final rule's preamble reflected that warning and used an extended discussion of evidence-based considerations as its sole justification for the final NAAQS decision. The HREA was rendered irrelevant to the decision.

Section 3.3 of the draft PA contains a risk analysis that is much the same as the last in the sequence of past $PM_{2.5}$ HREAs. It lacks any quantification of the still-important epistemic uncertainties associated with estimating health risks and health risk changes associated with alternative NAAQS. In fact, it now calculates risks at $PM_{2.5}$ levels down to zero exposure. The logical consequence of this should be obvious but is also clearly presaged by the history of $PM_{2.5}$ NAAQS decisions: the risk-based considerations presented in Section 3.3 of the draft PA are not informative to a decision maker faced with making a

[6] Section 3.2 of the draft PA contains information in the format associated with the "evidence-based" approach while Section 3.3, upon which I am specifically commenting, contains information in the format associated with the "risk-based" approach.

[7] These three alternative distributions were represented as hypothetical and not attributed to any specific person or group of people.

science-based judgment on a NAAQS level that is protective of the public health with an adequate margin of safety.

3. Themes in Special Issue of *Risk Analysis*

The reason the risk estimates in the past two prior $PM_{2.5}$ HREAs as well as those in the current draft PA are not informative for decision makers is *not* that they are poorly communicated or summarized. It is because they ignore virtually all forms of scientific uncertainty that are critical to the NAAQS policy judgment of what is requisite to protect the public health when zero-risk is not the required goal. When ignoring the impact of the most important factor in the relevant decision process (i.e., scientific uncertainty), a risk analysis renders itself irrelevant *by design*. Ignoring those scientific uncertainties also means that the draft PA's risk estimates are not reliable from any potential decision-making perspective.

The risk analysis profession has developed, over many decades, a structure or paradigm to guide the conduct of risk analyses in the direction of providing reliable decision-guidance. The risk analysis profession describes the process of risk analysis as having four components: (1) hazard identification, (2) exposure assessment, (3) dose-response assessment and (4) risk characterization. The first step, hazard identification, is to determine, through observational, clinical and laboratory investigation whether a health risk exists. If one is determined to exist, then estimates of exposures are combined with estimates of a dose-response relationship (i.e., the outputs of elements 2 and 3) to characterize the risk associated with the identified hazard. There are basic principles developed for each of the four steps.

Within this structure, an HREA reflects the second, third and fourth elements. They provide a synopsis of how the Agency has conducted its exposure assessments and what it assumes for its dose-response relationships, with the goal of reporting results of risk calculations that are based on the exposure and dose-response relationship inputs. However, these HREAs (including Section 3.3 of the draft PA) all start from a *presumption* of the existence of a hazard: that is, they *presume* a causal relationship between $PM_{2.5}$ and the health risk endpoints for which they make quantitative public health risk estimates.

Within this paradigm, epidemiological studies are, first and foremost, of relevance to the question of whether a hazard exists from exposure to ambient $PM_{2.5}$.[8] Unfortunately, the Agency conflates those studies of association with the different (and challenging) risk analysis element of dose-response assessment. That is, the Agency's analysts select a few specific epidemiological studies' coefficients from estimates of a health effects association and use those coefficients *at face value* as a rigid and deterministic prediction of how changes in concentration translate causally into changes in risk of the studied health endpoint. This egregiously short-changes the demands of a thorough dose-response assessment and represents the most fundamental flaw in the Agency's implementation of the risk analysis paradigm in its $PM_{2.5}$ HREAs and Section 3.3 of the draft PA.

In September 2016, the journal *Risk Analysis* presented a Special Issue on Air Pollution Health Risks that contained invited commentaries by six different professionals active in addressing risks associated with criteria pollutants such as $PM_{2.5}$. I was invited to read and respond to this set of commentaries, which resulted in publication in the same special issue of the article I have called **"Special Issue Synthesis"** in my list of papers above. That article points out that a consistent theme across those six sets of commentaries was that the primary challenges ahead for $PM_{2.5}$ risk assessment was associated with shifting from use of the epidemiological studies for the purpose to hazard identification into use of those studies for the dose-response element of the risk analysis paradigm. I do not see any evidence that

[8] Many concerns have been raised about the appropriateness of the Agency's causality framework. While I will not attempt to engage in that current line of discussion here, I did discuss my own concerns in technical comments that I wrote (and which were submitted into the docket) for the $PM_{2.5}$ NAAQS review that culminated in the 2013 rule. As I consider the issues that I raised at that time to remain relevant today, I provide a copy of those comments in an appendix to this document.

Agency staff have taken notice of the need to grapple better with the dose-response assessment challenges that was discussed by multiple different risk analysis professionals in that September 2016 Special Issue of *Risk Analysis*. The draft PA's discussion of risk-based considerations is thus out of touch with and unresponsive to concerns about how to more effectively address the dose-response element of the risk analysis paradigm – concerns that continued to be actively discussed among risk analysis professionals at the outset of the current $PM_{2.5}$ NAAQS review.

4. BenMAP's Capabilities and Limitations

The risk analysis calculations in the draft PA have been conducted using EPA's BenMAP model. BenMAP is a computational tool that calculates health risks when provided with a specific projection of ambient concentrations (i.e., the exposure input) and a specific assumed C-R function (i.e., the dose-response input). In my March 2015 paper that I have called the **"BenMAP Review"** in the list above, I provide a review of BenMAP's capabilities estimating the sensitivity of its risk estimates to uncertainties in the C-R relationships that users choose as inputs.

The actual formula for the risk calculation that BenMAP runs is simple and can be done on a hand-calculator. The reason the Agency has built this tool is so that it can make the application of the formula as disaggregated as one might desire. For example, exposure assumptions are often provided at the level of a 12 km by 12 km gridded surface of the U.S.[9] As there are nearly 50,000 such grid cells covering the 48 conterminous U.S. states, this means the simple risk formula needs to be applied about 50,000 times over. Furthermore, it requires 50,000 separate estimates of the cells' respective population and baseline incidence rates for each health effect. BenMAP's contribution is to estimate these highly disaggregated demographic data for whatever geographic scale is used for the ambient concentration input. However, BenMAP applies the same risk formula to the demographic and exposure estimates for every grid cell. My paper concludes that the main problem with BenMAP is that it suggests a great deal of sophistication in the risk analysis that is simply not there. It converts risk-relevant insights that can be obtained by a few back-of-the-envelope calculations into a vast and inscrutable array of model-generated numbers—a fact that is probably apparent to any reader of Section 3.3 of the draft PA.

BenMAP's design encourages its users to conduct risk calculations at a level of disaggregation that is far out of line with the degree of detail in risk relationships that the epidemiological studies provide. The **"BenMAP Review"** paper also concludes that its potential for computational complexity distracts users from assessing the sensitivity of its risk estimates to some of the most fundamental uncertainties associated with the C-R input assumptions. While a good risk analysis tool should encourage and enable users to conduct both sensitivity and uncertainty analysis, BenMAP cannot be used for integrated uncertainty analysis (IUA) and it discourages even sensitivity analysis.

My article goes on to illustrate three types of sensitivity analysis that would be helpful to add to BenMAP: (1) consideration of ranges of C-R slope estimates consistent with the full literature (rather than providing a "library" limited to the select studies that the Agency prefers to use); (2) a continuum of alternative assumptions about the $PM_{2.5}$ level where the assumed C-R relationship may cease to exist; and (3) alternative assumptions about the relative toxicity of $PM_{2.5}$ constituents.

In the third example (differential toxicity uncertainty), the article shows that the estimate of risk reduction due to a reduction in ambient $PM_{2.5}$ mass depends not just on what constituents are considered toxic, but also on what type of $PM_{2.5}$ reduction strategies would be taken. While the right assumptions are unknown, this sensitivity analysis shows that the risk estimate that the Agency produces under its

[9] This is the grid scale used in the draft PA's risk calculations for 47 urban study areas of the U.S.

standard assumption that all constituents are equally toxic is at the high end of the range of risk estimates that account for uncertainty in the relative toxicity of different $PM_{2.5}$ constituents.

In summary, the **"BenMAP Review"** paper focuses on the appropriateness of BenMAP's design for encouraging risk analyses that can provide useful and reliable guidance to decision makers. It finds that even sensitivity analyses to epistemic uncertainties are difficult to conduct given this tool's emphasis on enabling risk calculations to be conducted as a level of geographical detail that is far out of line with the current state of scientific knowledge about the underlying risk relationships.

In an invited comment on the **"BenMAP Review"** paper that appeared in the same journal issue, Agency staff cited an NAS report to dismiss the potential that there might be any discontinuation in the C-R relationship. In my **"Response to EPA"** (also in that issue), I pointed out that EPA was incorrectly characterizing the conclusions of that NAS report. I further noted that arguing against the existence of any particular scientific uncertainty was just another way of distracting rather than informing decision makers about the role of unresolved uncertainties in risk-based considerations. The commenters also expressed satisfaction that we were able to use BenMAP for our sensitivity analysis, but I noted that we had had to conduct our paper's sensitivity analyses in a spreadsheet outside of BenMAP because the spreadsheet was easier to work with than BenMAP itself, once BenMAP's estimates of the cell-by-cell demographic data had been extracted from it.

In brief, my advice to CASAC members regarding BenMAP is to have less concern about its ability to produce correct risk estimates for a given set of input assumptions and more concern about how its use is preventing the draft PA from exploring a reasonable range of variations in those input assumptions.[10]

5. Integrated Uncertainty Analysis

The discussion thus far has made the case that the risk analysis methods that EPA has historically used (and which are again used in the draft PA) fail to appropriately quantify the scientific uncertainties that are central to the $PM_{2.5}$ NAAQS decision. An important question is whether there are better methods to conduct such a quantification. It is exceedingly late in the current review process to revise the risk analysis, but with sufficient planning and a willingness to embrace the reality that these uncertainties are inherently subjective, there are alternative methodologies that could be taken. Often these approaches are called "integrated uncertainty analysis" (IUA) because they require that the effects of multiple different sources of uncertainty be accounted for in a single probabilistic analysis.

Among my own writings, I discuss several different ways that epistemic uncertainties can be incorporated into a NAAQS-related health risk analysis. I will summarize where these discussions can be found within the papers I have had published since the prior $PM_{2.5}$ NAAQS review:

- Section 2 of my **"HREA History"** paper ("Origins of Quantitative Risk Assessment for Criteria Pollutants") describes how IUA was incorporated into the 1997 HREA for $PM_{2.5}$. It was done by positing three alternative probability distributions (illustrative and implicitly subjective) over key input assumptions. The most important probabilistic input regarded how low the C-R function was believed to continue to exist. The HREA thus presented three alternative probability distributions over the resulting health risk estimates. No single distribution was endorsed, but it

[10] I do not, however, warrant that the particular estimates provided in the draft PA are correct. I have made no attempt to replicate them and am not aware of such effort by any other party. During the prior ozone NAAQS review, NERA identified significant errors in the BenMAP computations of risks for specific urban areas in that ozone HREA, and the Agency had to revise a large fraction of the HREA's risk tables. The errors were due to faulty mappings in BenMAP to access demographic data at different levels of geographic disaggregation—a BenMAP function that is especially "black box" in nature and thus difficult to check.

provided HREA readers and the Administrator with information about the net effect of the scientific uncertainties on the reliability of the risk estimates.

- Section 5 of my **"HREA History"** paper ("Rebuilding Relevance for the NAAQS Risk Assessment") makes a detailed recommendation for how future NAAQS reviews could alter the process by which HREAs could be conducted that would enable multiple alternative probability distributions over the continued existence of a causal C-R relationship to be identified and incorporated into the HREA. These alternative probability distributions would be proposed (and justified) by commenters rather than by EPA staff. Each proposed probability distribution would be run as a separate set of risk calculations, with resulting probabilistic risk estimates presented in collated fashion as the main output of the HREA. This would leave the Administrator free to examine the justifications associated with each submission, and ultimately give weight to the probabilistic risk estimates from the submission(s) that best fit the Administrator's own evaluation of the strengths and /or limitations of the scientific evidence.

- My January 2018 **"Ozone IUA"** paper provides a discussion of how epidemiological evidence of a potential threshold in the long-term ozone respiratory mortality could be incorporated into a probability distribution over that risk endpoint. The approach was to combine an initial (subjective) probability distribution on the potential level of such a threshold[11] with a statistically-based set of likelihoods on where such a threshold may lie. The latter set of likelihoods is based on the relative goodness-of-fit of the many alternative threshold model runs that were reported in the epidemiological paper that was being used as the source for a C-R function on this mortality risk. The result of this operation is a probability distribution over the potential threshold location that accounts for both subjective views and epidemiological evidence.[12] With such an approach, one can avoid having to choose between two deterministic assumptions: that there is no threshold (despite evidence that there may be one) or that there is a threshold at the level that produces the best-fitting model (despite that model having only marginal statistical significance over the no-threshold model). Using this combined distribution as the basis for an IUA-based risk analysis, this paper shows how even highly uncertain indications of a potential threshold, if incorporated probabilistically into the risk analysis, can result in a substantially different indication of the merits of alternative NAAQS levels compared to assuming (as the Agency did) that a linear-to-zero C-R function remained the best single deterministic assumption.

I recognize that the third of these examples was made possible by the availability of a set of epidemiological estimates for a wide range of alternative model specifications. However, the methodological benefits of having such alternative model estimates are apparent. They enabled a direct and quantitative characterization of the model uncertainty in the risk estimates without forcing any definitive (deterministic) judgment on the level of the true threshold. Even the possibility of no threshold continued to be included in the IUA. If it were to become a standard among air pollution epidemiologists to provide the statistical fits of alternative model specifications applied to their dataset, such hybrid statistical-and-subjective judgments could be used more often. This could provide a middle ground between the purely deterministic approach of the current draft PA and the purely subjective approach suggested in the **"HREA Review"** paper.

6. Inconsistencies Between NAAQS and RIA Risk Analysis

All of the above discussion concerns incorporation of epistemic uncertainty into the risk analyses that are used to inform a decision on whether to revise or keep a NAAQS standard, i.e., in the HREAs. Those risk

[11] In technical terms, this initial probability distribution is called a "prior" distribution.

[12] In technical terms, this is called a "posterior" distribution.

analyses are the relevant ones for CASAC to evaluate. However, many of the same issues about epistemic uncertainty pertain to the risk and benefit calculations of the RIAs that accompany a NAAQS rulemaking. The risk calculations in RIAs for criteria pollutants may seem to mirror the risk calculations in the HREAs that occur before a NAAQS decision is made. However, in my recent research I have noticed a significant inconsistency between the rationales that are used to justify a final NAAQS decision and the risk input assumptions that are then used in the RIA for that same NAAQS. This inconsistency is documented in my September 2016 **"Inconsistencies"** paper.

Briefly, the rationale for setting the annual $PM_{2.5}$ NAAQS at 12 $\mu g/m^3$ was largely an evidence-based judgment by the Administrator that the available epidemiological evidence was too limited to give her confidence that the key C-R relationships continued to exist below about 12 to 13 $\mu g/m^3$. Thus, while health risks could not be said to be zero below 12 $\mu g/m^3$, protection against exposure to lower levels of $PM_{2.5}$ was considered not to be requisite. Nevertheless, the accompanying RIA assigned as much confidence to the risks it estimated for $PM_{2.5}$ exposures well below the standard (including those near zero) as it did to those estimated for exposures above or near the standard. My paper demonstrated that 70% to 96% of the benefits attributed to that rulemaking were due to this inconsistent assumption in the RIA.

In my most recently accepted paper, which I have labelled **"Improving Consistency,"** I revisit this inconsistency issue. I make a recommendation for how an Administrator's expressions of uncertainty about the C-R relationship might be incorporated into NAAQS-related RIAs' risk calculations to generate consistency between the reasoning behind a NAAQS decision and its associated RIA. The concept is that the Administrator's subjective probability distribution on the continued existence of the mortality C-R relationship could be formally elicited and directly reported as part of the formal rationale for a NAAQS decision. This elicited distribution would be presented as a quantitative supplement to the usual evidence-based reasoning already found in NAAQS rationales. (It could be provided without any risk-based calculations, or it could also be incorporated into HREA estimates to be summarized in the preamble.) Importantly, however, it would become a direct input to a probabilistic (confidence-weighted) estimate of the rule's benefits that would be presented in the accompanying RIA. In my **"Improving Consistency"** paper, I provide illustrative examples of what the resulting probabilistic risk estimates might be and contrast them to the inconsistent risk estimates that result from the deterministic (no threshold) C-R assumptions presently used in RIAs. (The illustrative example is based on the RIA for the $PM_{2.5}$ NAAQS promulgated in 2013.)

Instituting such a process for preparing RIAs that are logically-consistent with the basis for the NAAQS decision would have no effect on the NAAQS decision itself, as the RIA is not an input to that decision. It would, however, create greater acceptance of the RIA results. Also, the impact on RIA estimates would carry over into RIAs for rules that do not target $PM_{2.5}$, but which treat coincidental reductions in $PM_{2.5}$ as *co-benefits*. Adoption of this confidence-weighted risk calculation for all RIAs could significantly reduce the current controversies over the appropriateness of basing non-NAAQS rulemakings on co-benefits.

APPENDIX.
COPY OF 2009 COMMENTS OF DR. SMITH ON EPA's CAUSALITY FRAMEWORK

Comments on the External Review Draft of EPA's "Risk Assessment to Support the Review of the PM Primary National Ambient Air Quality Standards"

Anne E. Smith, Ph. D.
Charles River Associates
1201 F Street NW, Suite 700
Washington, DC 20004

Prepared at the request of the Utility Air Regulatory Group, American Petroleum Institute and American Chemistry Council

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In September 2009, the U.S. Environmental Protection Agency (EPA) released its external review draft of a document titled "Risk Assessment to Support the Review of the PM Primary National Ambient Air Quality Standards" (hereafter, the "Draft PMRA"). Following are my comments on issues in conducting a quantitative risk assessment for $PM_{2.5}$.

I. Introduction and Summary of Main Points

EPA's Draft PMRA is intended to provide quantitative estimates of the levels of risk from $PM_{2.5}$ actually being experienced by the U.S. population today, and how those risks will change if current ambient $PM_{2.5}$ is reduced by the application of more stringent National Ambient Air Quality Standards (NAAQS). The Draft PMRA only quantifies those risks that have been determined to be "causal" or "likely causal" in the second draft of the Integrated Science Assessment (hereafter, the "Draft ISA"). Once such a determination is made in the ISA, however, the Draft PMRA not only presumes that statistical estimates of $PM_{2.5}$'s relative risks are causal, but also that they can be interpreted quite literally as the quantitative concentration-response functions that determine actual risks. Whatever merit the observed epidemiological associations may have as indicators of a causal relationship, <u>the unquestioning numerical credence that EPA assigns to the epidemiological estimates undermines the credibility and reliability of the Draft PMRA results</u>. A common adage is "association does not imply causation;" to this can be added that even if a statistical association *does* reflect causation, it does not define the actual quantitative response function.

There are several layers of problems with the quantitative risk calculations in the Draft PMRA:

- At the most fundamental level, the Draft PMRA *presumes* that there is a causal association in the epidemiological evidence. That presumption is less than settled, as my comments will explain, because all of the studies may be wrong for the same systematic reason.

- At the next level, the estimates of relative risk from the epidemiological studies are almost certainly highly biased and, as my comments will explain, the bias is likely in the upward direction. Because the Draft PMRA uses those estimates directly for its quantifications of risk, the Draft PMRA's estimates of current premature mortality from $PM_{2.5}$ exposures are probably overstated.
- Topping it off, the epidemiological studies are incapable of defining how the relative risk would tend to vary at increasingly lower levels of $PM_{2.5}$. This creates an increasingly large error as risk reductions are estimated for tighter and tighter alternative ambient $PM_{2.5}$ standards.

All of the above problems in using the epidemiological relative risk estimates for quantitative purposes stem from fundamental data limitations that face every single one of the epidemiological research teams. This situation does not imply any fault on the part of the research teams or that the quality of their work is not of high quality. Unfortunately, however, EPA understates the remaining uncertainties that result from these studies' inherent data limitations when it engages in the quantitative risk assessment in its Draft PMRA.

Given that it does not address this array of problems in using epidemiological studies to attempt to quantify risk, the quantitative risk assessment in the Draft PMRA is highly misleading as an input to policy decisions. EPA could mitigate this situation by finding ways to quantitatively incorporate corrections for the systematic biases. This would produce a larger range of uncertainty in its estimates of risk, but one that reflects the true current state of knowledge. If this is not done, however, then the Draft PMRA should not be used in the consideration of alternative $PM_{2.5}$ NAAQS.

The rest of my comments are organized in the following way:

- Section II explains the problem in making a presumption of causality in the Draft PMRA, even though this is the determination in the Draft ISA.
- Section III discusses how the data limitations of the available $PM_{2.5}$ epidemiology literature make it inappropriate to use the estimated relative risks from those studies directly in a quantitative risk assessment as the Draft PMRA does.
- Section IV points out that even the epidemiological studies indicate a non-negligible chance that $PM_{2.5}$ imposes no long-term risk to all-cause mortality at all, once they are reviewed in a less selective manner than in the Draft PMRA.
- Section V summarizes and concludes that until these uncertainties are addressed quantitatively in the PMRA, it will be unreliable, and should not be used in the consideration of alternative $PM_{2.5}$ NAAQS.

II. EPA's Causality Criteria Are Inappropriate and Promote False Confidence in Quantified Risk Estimates in the Draft PMRA.

The Draft ISA provides a review of the weight of evidence in favor of alternative degrees of causal inference for various effects, such as between long-term exposures to $PM_{2.5}$ and cardiovascular mortality. The Draft ISA's determinations of causality for long-term $PM_{2.5}$ associations with CVD mortality and likely-causal for all-cause mortality associations are heavily driven by evidence of statistical associations in observational epidemiology studies. As explained below, this degree of reliance on the epidemiological evidence is excessive, highlighting a weakness in the criteria for causality that EPA establishes in that document. Given that uncertainties in the causality determination are never questioned again in the Draft PMRA, they are important to discuss in these comments on the Draft PMRA.

(II.A.) EPA's criteria allow excessive reliance on epidemiological findings in making a determination whether pollutants are causally associated with health effects.

The Draft ISA provides a set of criteria that must be met to determine that a particular health effect is causally related to $PM_{2.5}$ exposure. I quote the criteria below, which I have broken into two parts for purposes of the discussion that follows:[1]

Part 1: "The pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (*e.g.*, animal studies or mode of action information)."

Part 2: "Evidence includes replicated and consistent high-quality studies by multiple investigators."

On its own, Part 1 provides what would seem to be a perfectly appropriate set of criteria for making a causal determination. However, the addendum of Part 2 greatly weakens the requirements, because as a logical "or" statement, it provides a way for EPA to conclude in favor of causality even if controlled human exposures studies do *not* demonstrate consistent effects, *and* observational studies *can* be explained by plausible alternatives *and* are not supported by animal studies or mechanistic actions; Part 2 allows EPA to conclude in favor of causality even in the face of all of the foregoing findings as long as multiple authors have published quality epidemiological studies that replicate each other. Thus, the single sentence of Part 2, treated as a logical "or" rather than as a logical "and" to the requirements of Part 1, serves to absolve EPA from having to demonstrate that the associations in chronic studies "cannot be explained by plausible alternatives" before it can make its causal determination.

[1] Draft ISA, Table 1-3, p. 1-29.

Unfortunately, EPA relies almost entirely on the type of evidence allowed by Part 2 to make its causal determination regarding long-term mortality risks of $PM_{2.5}$. Take the case of long-term cardiovascular (CVD) mortality risk, for example. The Draft ISA relies almost entirely on the existence of a multiplicity of separate chronic studies that all find a $PM_{2.5}$-mortality association. It begins and ends that causality discussion with the following respective quotes:

> "A number of large, multicity U.S. studies (the ACS, Six Cities Study, WHI, and AHSMOG) provide consistent evidence of an effect between long-term exposure to $PM_{2.5}$ and cardiovascular mortality."[2]

and:

> "In summary, a number of large U.S. cohort studies report associations of long-term $PM_{2.5}$ concentration with cardiovascular mortality. These studies provide the strongest evidence for an effect of long-term $PM_{2.5}$ exposure on CVD effects."[3]

EPA determines that this evidence from multiple chronic studies suffices to identify a causal relationship, even though the remainder of the supporting evidence that the Draft ISA musters in support of a long-term CVD mortality risk are some inconsistent morbidity studies, inconsistent clinical studies, and a few toxicological studies that are suggestive of some possible relevant responses. The Draft ISA does not offer any reasons to believe that any of the many observational studies have met EPA's conditions for making a causal determination under Part 1. Nowhere does EPA make a case that the associations in the chronic mortality studies "cannot be explained by plausible alternatives." In fact, it could not possibly make such a claim given that epidemiologists continue actively to try to rule out various plausible alternatives. The plausible alternatives that researchers have not yet been able to rule out include confounding (residual or otherwise) by co-pollutants, noise, stress, and socioeconomic factors.[4] For example, the most recent ACS cohort analysis (Krewski *et al.*, 2009) focused vigorously on more effectively controlling for socioeconomic factors than in past studies, but it made no attempt to rule out possible confounding by co-pollutants.

Thus, the available evidence for long-term mortality risk does not meet the causality criteria contained within Part 1, and EPA is relying very heavily on Part 2 to defend its "causal" determination. <u>Part 2, however, is not a valid basis for a causal determination if observational studies are not also supported by consistent effects in controlled studies</u>. It would be a reasonable addendum if it were required *in addition* to Part 1 conditions, but not when used *instead of* meeting Part 1 conditions. The reason it is insufficient for

[2] Draft ISA, p. 7-25.
[3] Draft ISA, p. 7-26.
[4] The effect modification by educational status in the chronic studies remains as an indication of some residual confounding by socioeconomic factors. Although this pattern was reduced in the Krewski *et al* (2009) study, it was not eliminated.

identifying whether a statistical association is causal is because it fails to address the possibility of *systematic biases*, which cannot be ruled out except with evidence from controlled studies.

Systematic biases will occur if the studies in question have relied on similar methodologies and similar data sources. In this case, if a bias (*e.g.* due to residual confounding) exists in one study, then it is likely to exist in all the studies. All of the epidemiological results can be wrong for the same reason. A multiplicity of studies finding a statistical association do not provide independent confirmation supporting a causal inference unless one can demonstrate that there is no potential for such systematic bias among those multiple studies. Thus, Part 2 of EPA's causality criteria enables causality to be declared even if there remains a very large likelihood of no causality.

There is substantial potential for systematic bias in the case of chronic $PM_{2.5}$-mortality epidemiology.[5] Table 7-8 of the Draft ISA lists 14 recent U.S. cohort studies that find an association between $PM_{2.5}$ and mortality.[6] All of these studies draw from the same fundamental data set, however, because they all sample individuals across the U.S. and assess the correlation between their local monitors' $PM_{2.5}$ levels and their mortality risks after attempting to control as best possible for the very broad swath of much stronger determinants of risk (*e.g.*, age, sex, diet, smoking habits, and socioeconomic factors). Controlling effectively for these other factors is the key to getting a sound answer, y*et al*l of the studies are reduced to using approximately the same approximate data, all of them facing enormous amounts of error in how those variables are assigned to individual cohort members. In any single study, there is a good chance that the controls for the primary determinants of mortality risk are incomplete, and some confounding remains to bias the association estimated for $PM_{2.5}$. Unfortunately, all of these studies face the same problem, in a systematic way, because they all rely on the same types of data, and face the same fundamental data limitations.[7]

The fact that these studies rely on several different cohorts does not make them independent of each other with respect to confounding and effect modification. If ambient $PM_{2.5}$ is correlated with the missing or poorly measured non-PM explanatory variables across the U.S., then almost any reasonably diverse subset of the U.S population are likely to embody that same underlying correlation. For example, a sample of mostly white volunteers for a cancer study and a sample of veterans may have quite different socioeconomic profiles, but both will reflect the general correlations that exist across the U.S. between $PM_{2.5}$ measured at central monitors and key socioeconomic or other non-$PM_{2.5}$ causal factors. The same biases can apply to every single cohort of people drawn from the U.S. population. This is a particular systematic concern for

[5] Goodman (2009), pp. 8-9, makes a similar point.
[6] Draft ISA, pp. 7-119 to 120.
[7] There is also uniformity in the methodologies being used, in that almost all of the researchers use the same statistical model, the Cox proportional-hazards (PH) model, and thus systematically share any biases that may derive from the limitations of this statistical model. For example, the Cox PH model assumes the effects of pollution levels and of potential confounders on the logarithm of hazard are all linear. The assumption of proportional hazards has received limited testing, but that which has been done raises serious questions about this key assumption (see, for example, Abrahamowicz *et al.*, 2003).

variables that must be controlled at the ecological level. Thus, the biases from confounding and effect modification that are most difficult to control are also likely to be systematic across multiple U.S. cohorts.

This is not a criticism of the quality of the research teams' efforts; it is just an unfortunate reality of the limitations of the available data and tools to study such a subtle possible risk without the ability to perform controlled experiments. Nevertheless, the potential for systematic bias should not be ignored.

(II.B.) Differential measurement error can systematically create bias from confounding, even if confounders are included in the epidemiological study.

The potential for systematic confounding and effect modification cannot be eliminated simply by including the relevant explanatory variable in the data analysis if there is measurement error. A confounder is a variable that has a direct effect of its own on risk, *and* which is correlated with the pollutant being studied. When this is the case, if the confounder is left out of the analysis, the pollutant will be attributed some of the explanatory power that is actually due to the missing confounder, and thus the relative risk estimate will be biased. If personal exposures to all the confounders and effect modifiers can be measured accurately, the bias in the $PM_{2.5}$ exposure-risk association can be eliminated by identifying and including the confounder in the data analysis. However, if the confounder cannot be measured with accuracy, even if it is included in the data analysis, *residual* confounding will remain in the estimated association between the exposure variable and risk.

The situation is complex, but simulation studies can help understand the potential for biased effects estimates in situations that have confounders with differential measurement error. One such study (Fewell *et al.*, 2007) demonstrates that typical amounts of confounding, combined with typical amounts of measurement error, can cause quite large relative risks to be assigned to an exposure variable that has no effect at all, even when measures of the confounder are included among the controlling covariates in the analysis. The size of the potential erroneous relative risk reported by Fewell *et al.* exceeds the magnitude of the $PM_{2.5}$ relative risk in the $PM_{2.5}$ epidemiological literature. The implication is that the estimated chronic $PM_{2.5}$ relative risks – given their fairly small magnitude – could be the result of residual and unmeasured confounding by either socioeconomic factors or other environmental factors. Because these potential confounding relationships are likely to exist for every cohort if they exist for one, all of the multiple, independent long-term $PM_{2.5}$-risk associations could be reflecting the same systematic biases (Boffeta *et al.*, 2008).

Cohort studies in other countries might not face all of the same systematic errors that would apply to cohort studies all from the U.S. However, if the source of the confounder is physically related to PM sources, then one would see the same systematic bias even for cohort studies outside of the U.S. Thus, positive findings from cohort studies in other countries might reduce some of the concern with a socioeconomic-pollutant correlation, but cannot eliminate concerns that PM is a proxy for another co-emitted pollutant, some

non-chemical effect coinciding with chemical emissions (*e.g.*, noise), or for a single constituent of PM. Table 7-8 of the Draft ISA identifies one $PM_{2.5}$-mortality cohort study from the Netherlands (Brunekreef *et al.*, 2009). The abstract for this study states that it "differs from cohort studies based on city-level differences in exposure" because it considered exposures to pollution sources that exist mainly *within* cities. The U.S. cohort studies, which are based on city-level differences in pollution, are reporting an association between health and the total, undifferentiated mass of *all* forms of $PM_{2.5}$. It is those total mass associations that are then being used for risk calculations in the Draft PMRA. Thus, this non-U.S. study does not provide corroborating evidence of the same kinds of relationships being estimated by the U.S. cohort studies, and so it does not help eliminate concerns that potential systematic biases may pervade the latter.

(II.C.) Other pollutants are a likely source of residual and unmeasured confounding bias in the long-term associations.

The potential for the long-term $PM_{2.5}$ estimates to all share bias due to confounding from other pollutants is clear, regardless of what one might think about residual socioeconomic variable confounding in this body of literature. Rarely are other pollutants or pollutant-sources included in $PM_{2.5}$ epidemiological regressions; however, when they are included, there is often a marked reduction in the size and statistical significance of the $PM_{2.5}$ effect. Such a sensitivity upon the inclusion of SO_2 was a major finding of the reanalysis of the ACS data by Krewski *et al.* (2000); yet, the subsequent papers of Pope *et al.* (2002) and Krewski *et al.* (2009) that extended the ACS cohort analysis did not report any $PM_{2.5}$ relative risks that had also been controlled for SO_2. This omission in recent ACS-based studies leaves an important question regarding the quantitative validity of the $PM_{2.5}$ associations taken from Krewski *et al.* (2009) that the Draft PMRA uses.

The other study that EPA places high reliance on is the update of the Harvard Six Cities study by Laden *et al.* (2006). EPA cites this study as providing confirmatory evidence that long-term reductions in $PM_{2.5}$ produce a corresponding reduction in mortality. However, this study does not consider any pollutants other than $PM_{2.5}$, even though the levels of various gaseous pollutants have fallen concomitantly with $PM_{2.5}$ in the six cities. Rather, Laden *et al.* attribute the entire change in health risk associated with air pollution reduction to $PM_{2.5}$ without any apparent attempt to test whether any other pollutant might have equivalent explanatory value.[8] The paucity of data points available with this cohort make it impossible for statisticians to even attempt to control for more than one pollutant at a time. That is, with the Harvard Six Cities cohort, the estimate of the effect of pollution on inter-city mortality risk differences must be based on only 6 cities/data points. In contrast, as many as 150 cities/data points are available for inferring relative risk estimates with the ACS data set. Nevertheless, the researchers still could have used a series of one-pollutant models to explore whether pollutants other than $PM_{2.5}$ might also be associated with the observed changes in inter-city mortality risks.

[8] Furthermore, in the critical second period of this study, the results were not based on actual fine PM measurements. Rather, they are rather based on measurement of another NAAQS pollutant (PM_{10}) and extinction coefficients.

Even if other pollutants were to be included in these long-term risk studies, it is quite likely that they would fail to control for confounding because of differential measurement error. $PM_{2.5}$ is generally believed to have a much more uniform distribution in space than other pollutants with which it is correlated, including NO_2, CO, coarse PM, and even ozone. Thus, the standard practice of using data from a central monitor to estimate individuals' exposures probably results in greater exposure misclassification for these other pollutants than for $PM_{2.5}$. The result could be that $PM_{2.5}$ will persistently appear to carry the best explanatory power, yet just be serving as a proxy for the health effects of the other, more erroneously measured pollutant exposures. This possibility was demonstrated in a simulation study that contained considered two hypothetical correlated pollutants, one a "True Culprit" measured with relatively large error, and the other an "Innocent", but measured with relatively small error. The simulation results showed that:

> "in circumstances like this, *which* pollutant would appear to have the most significant and consistent relationship with health may be determined more by its relative observation error than by its actual contribution to the health effects in question. The greatest problem with this spurious association of Innocent with health is that it remains stable whether or not True Culprit is added into the regression. Further, if only True Culprit is included in the regression, the R^2 falls to zero. True Culprit is the pollutant that seems to have a highly unstable association and very little explanatory power on its own. Thus, unlike in the simple confounding case, the usual methods for checking for confounding no longer function well when there are observation errors as well as strong correlation among pollutants."[9]

(II.D.) Evidence of proxy effect exists in changes in estimated $PM_{2.5}$ relative risk coefficients over time.

One signal that a non-causal proxy effect might account for the $PM_{2.5}$-mortality associations would occur if the estimated relative risk for $PM_{2.5}$ mass were to increase over time as $PM_{2.5}$ levels decline. That is, if there is a given amount of risk associated with a certain non-$PM_{2.5}$ causal factor that is correlated with $PM_{2.5}$ mass, if the unidentified causal factor was not reduced while $PM_{2.5}$ was reduced, then the remaining lower levels of $PM_{2.5}$ would account for the same total level of risk from the unidentified factor. The result would be a greater relative risk associated with a given amount of PM difference.[10]

[9] Smith and Chan (1997), p. 21. (The observed correlation between the two pollutants in this analysis was 0.56, which is in the range often observed in the US.)

[10] This signal will not necessarily occur even if $PM_{2.5}$ is serving solely as a proxy for some unnamed causal factor, if the causal factor were to be reduced in roughly the same degree as $PM_{2.5}$ over that same period of time. That could be the case if $PM_{2.5}$ is serving as proxy for a gaseous pollutant, since most of the pollutants have been declining simultaneously due to parallel environmental regulations.

We do observe this pattern in the extended analyses of the ACS cohort. For example, in Pope *et al.* (2002), the estimated relative risk per 10 µg/m^3 of $PM_{2.5}$ for all-cause mortality rose from 1.04 when using 1979-1983 $PM_{2.5}$ data (which averaged 21.2 µg/m^3) to 1.06 when using 1999-2000 data (which averaged 14.0 µg/m^3). The estimated relative risk for cardiopulmonary risks rose from 1.06 to 1.08.[11] Similarly, in Krewski *et al.* (2009), the all-cause relative risk rises from 1.043 to 1.056 and the cardiopulmonary relative risk rises from 1.089 to 1.129 when estimated with the earlier or later $PM_{2.5}$ data.[12] (Laden *et al.* (2006) report a decline in the relative risks from an earlier period to a later period of exposure, but this is not the same comparison. In the ACS examples, the risk over the same follow up period is estimated using $PM_{2.5}$ from two different parts of the time period. Laden *et al.* do not report estimates or relative risk for the entire time period using first the earlier, then the later $PM_{2.5}$ measures. Since they do not report a comparable set of relative risks, their finding cannot be said to conflict with the ACS finding just described.)

The increase in the estimated relative risk that occurs in the ACS data set when more recent $PM_{2.5}$ data are used might also occur if there is a real effect from $PM_{2.5}$ mass that is truly long-term in nature. In that case, on-going mortality outcomes might be a function of earlier exposures to $PM_{2.5}$, when it was at higher levels, while more recent $PM_{2.5}$ measures might be serving as a proxy for the historically higher $PM_{2.5}$ exposures. Even if this does explain the upward trend in estimates of $PM_{2.5}$ relative risks, it implies that any quantitative estimate of benefits from reducing current $PM_{2.5}$ based on the numerical results of recent epidemiological associations will be biased upwards. That is, adoption of a relative risk estimated using the more recent $PM_{2.5}$ "at face value" as the quantitative $PM_{2.5}$ concentration-response function would be erroneously assuming that the entire increase in risk due to higher historical $PM_{2.5}$ exposure is caused by a much smaller amount of $PM_{2.5}$ exposure. This concentration-response function would overstate the risk from as-is $PM_{2.5}$, and it would overstate reductions in risk that could be expected by reducing today's lower $PM_{2.5}$ to yet lower levels.

In summary, proxy effects can be at play in chronic studies, even if there is a causal relationship for $PM_{2.5}$ mass generally, and this proxy effect would create erroneous (overstated) risk and risk-reduction estimates in the PMRA. The bias would then be exacerbated even further when considering the benefits of further reductions in $PM_{2.5}$ due to rollbacks to alternative, more stringent $PM_{2.5}$ standards. The latter possibility is discussed further in Section III.B.

(II.E.) Epidemiological findings on short-term mortality are far more heterogeneous, and do not provide strong back-up to long-term studies.

Some people prefer to rely on short-term, time-series studies for evidence of an effect from $PM_{2.5}$ because effects observed within each city provide more inherent control for

[11] Pope *et al.* (2002), Table 2, p. 1136.
[12] Krewski *et al.* (2009), Table 6, p. 23. Values reported are for regressions with MSA & DIFF ecological controls, but the pattern also appears in other regression in the table.

socioeconomic factors that are otherwise difficult to measure accurately. While this may be true to some extent for the socioeconomic factors, short-term studies are still subject to potentially uncontrollable confounding from other pollutants. Nevertheless, existing short-term risk studies offer very little support for a causal interpretation of the observed long-term $PM_{2.5}$ associations. In particular, the quantitative level of the risk in the long-term studies is roughly an order of magnitude higher than associations found in short-term studies. The difference could be entirely due to confounding bias, or – as EPA prefers to explain it – the difference could be that cumulative, long-term effects are much larger than acute effects. Neither explanation can be held up as more correct, but even EPA's preferred explanation implies that the short-term studies cannot be viewed as corroborating the long-term study findings, because it implies that the long-term associations would have to be for an effect that acute studies cannot even detect.

Short-term studies also produce results that vary enormously from city to city and regionally, often finding no effect at all, even in cities and regions with relatively high $PM_{2.5}$ levels. This heterogeneity may indicate that the smaller, short-term $PM_{2.5}$ associations are not necessarily causal either.

III. Even If the $PM_{2.5}$ Association Is Causal, Statistical Estimates of $PM_{2.5}$ Relative Risk Remain Subject to Biases that Make Them Unreliable for Quantifying Risks.

(III.A.) Biases in estimates of the average magnitude of the $PM_{2.5}$ association are likely due to four types of data problems.

As explained in Section II, the Draft ISA's conclusion that $PM_{2.5}$ is causally related to cardiovascular mortality risks (and likely causally related to mortality risks in general) remains open to reasoned debate. However, a variety of uncertainties also exist that directly undermine the *quantitative* interpretation of the epidemiological findings for determining what numbers of deaths are premature at present, and especially for predicting how mortality risks would change if $PM_{2.5}$ mass were reduced. There are at least four ways in which quantitative biases can be present in the epidemiologically-estimated associations that would undercut their reliability for quantification of risks, as discussed below.

<u>(1) Differences in potency of various $PM_{2.5}$ constituents.</u> There are uncertainties about the relative potency of different constituents within the $PM_{2.5}$ mass.[13] Thus, even if a relative risk estimate is quantitatively valid as an *average* effect of the current mix of $PM_{2.5}$, if some constituents would not be reduced as much as others when an alternative $PM_{2.5}$ standard is imposed, then the reduction in risk from that standard would not be what one would predict using the *average* relative risk. In fact, if some small subset of the mass is highly potent and accounts for most or all of the observed association, it is

[13] The Draft ISA states (at p. 7-129) that "only a very limited number of the chronic exposure cohort studies have included direct measurements of chemical-specific PM constituents other than sulfates, or assessments of source-oriented effects, [in] their analyses." Also (at p. 2-25): "It remains a challenge to determine relationships between specific constituents, combination of constituents, or sources of $PM_{2.5}$ and the various health effects observed."

quite likely that this culprit would escape implementation plans, which will naturally be focused on reducing the constituents that account for the largest portions of the mass. The result could be no risk reduction at all, despite reductions in $PM_{2.5}$ mass; yet the Draft PMRA's methodology would predict substantial benefits from the tighter standard.

(2) Missing or inaccurate socio-economic variables correlated with regional $PM_{2.5}$ levels. All of the epidemiological studies have taken steps to provide controls for socioeconomic variables that affect mortality risks, but information is insufficient to ensure that these have been fully specified; also, many of the potential socioeconomic confounders and effect modifiers can only be measured with substantial amounts of error. Sometimes these errors can be found and eliminated through careful data quality work.[14] However, the errors of concern here are for socioeconomic data that are simply not possible to obtain. For example, although various updates of the key ACS study have been published up through 2009, they rely on the same individual and socioeconomic data collected in 1982, almost 30 years ago. Thus, it is not possible to assess changes in key confounding factors such as smoking cessation rates that are well known to fall along socioeconomic lines.[15] Other socioeconomic variables, such as data on the degree of stress in family life, are simply not possible to obtain and will never be possible to control for in the chronic risk studies.

Thus, despite extensive socioeconomic controls in all of the chronic risk studies, there remains the possibility that $PM_{2.5}$ mass is at least partially serving as a proxy for unidentified, or poorly measured, socioeconomic variables. If so, the $PM_{2.5}$ risk coefficient is biased. In this case, while it is not certain what the direction of bias would be, it is likely to be in the upward direction because lower socioeconomic status tends to be positively correlated with mortality risk and also with living in areas with higher pollution.[16] Regardless of direction of bias, quantified risk estimates that use the estimated $PM_{2.5}$ relative risk "at face value" will be incorrect.

(3) Other pollutants, even if included in the analysis. Much has been said about the possibility that $PM_{2.5}$ is serving as a proxy for another pollutant that has the true causal role. Studies have, at times, considered the role of other pollutants but this practice has been inconsistent.[17] When multi-pollutant results are not reported, one never knows if

[14] For example, the reanalysis by Krewski *et al.* (2000) of the Harvard Six Cities Study found that the coding protocol allowed cigar and pipe smokers to be classified as "non smokers;" the calculation of pack-years of smoking cigarettes was inconsistent, resulting in an underestimate of smoking pack-years of about 3% in some cities; and the error rate for the education variable on the earliest form used was 18%; etc. These kinds of errors can be avoided through careful review, and fixed, if detected.

[15] Some hypothesize that the errors in data on smoking cessation might explain the education gradient in $PM_{2.5}$ mortality observed in this study as well as the Harvard Six Cities Study; if so, the $PM_{2.5}$ relative risk estimate is probably a biased estimate.

[16] In the one known example where those with higher socioeconomic status happen to live in an area where the $PM_{2.5}$ is higher (*i.e.*, New York City), the lack of any increased mortality risk attributed to exposure to $PM_{2.5}$ in this group, versus those with lower socioeconomic status and lower $PM_{2.5}$ exposure, may illustrate the importance of socioeconomic confounding in air pollution epidemiology studies (Krewski *et al.* 2009).

[17] The Draft ISA states (at p. 7-82): "Given similar sources for multiple pollutants (e.g., traffic), disentangling the health responses of co-pollutants is a challenge in the study of ambient air pollution."

they may have been performed and found to have had the effect of attenuating the reported association for $PM_{2.5}$. Even if those studies simply did not perform any multi-pollutant regressions, one must wonder, why not? For example, the most recent papers based on the ACS cohort (Pope *et al.*, 2002; Krewski *et al.*, 2009) did not attempt to explore whether SO_2 had greater explanatory power than $PM_{2.5}$ mass, even though this was a widely discussed source of sensitivity reported in the preceding ACS paper (Krewski *et al.*, 2000).[18] Thus, the most recent epidemiological studies are not necessarily the most thorough in their efforts to explore confounding by other co-pollutants; as a result, their quantitative estimates cannot be viewed as more reliable for use in a quantitative assessment of $PM_{2.5}$-related risks. Relative risk estimates from the earlier studies that *did* account for co-pollutants could be less biased than the more recent relative risk estimates, even though the earlier ones have less statistical power due to their reliance on shorter cohort follow-up periods.

(4) Other environmental factors. Gaseous pollutants are not necessarily the only other non-$PM_{2.5}$ environmental factor for which $PM_{2.5}$ might be serving as a proxy. Measures such as proximity to traffic and intensity of local traffic have been the subject of much recent exploration of the basis for the $PM_{2.5}$ associations (*e.g.*, Lipfert, Wyzga *et al.*, 2006; Lipfert, Baty, *et al.*, 2006; Jerrett *et al.*, 2005; Beelen *et al.*, 2008a). In most cases where they have been accounted for in the data analysis, traffic-related variables appear to have the stronger associations. This could point to certain $PM_{2.5}$ constituents, or to some gaseous pollutants, and it could point to other factors such as noise or stress (Lipfert, Baty *et al.*, 2006; Beelen *et al.* 2008b).[19] Rolling back $PM_{2.5}$ mass would not have any effect on these other possible causal factors; again, the quantitative interpretation of a $PM_{2.5}$ relative risk would produce completely erroneous estimates of risk reductions from alternative $PM_{2.5}$ standards.

The point is obvious: even if the associations with $PM_{2.5}$ have a causal element, the many limitations of the epidemiological data mean that the relative risks estimated by epidemiological studies do not offer a direct quantitative relationship for how $PM_{2.5}$ mass alone affects either current health risks, or changes in risks if $PM_{2.5}$ mass is reduced. In all of the situations described above, the observed association could be "statistically significant," yet the health benefits from rolling back $PM_{2.5}$ could be as low as zero, because statistical significance calculations cannot detect the presence of bias; in fact, they presume it does not exist. Also, if differential measurement errors are at work, then

[18] HEI's commenters on the 2009 Krewski *et al.* study lament the lack of further study of confounding by copollutants, but offer their own excuse for this omission: "Given that the Reanalysis (Krewski *et al.*, 2000) had extensively tested the potential for the gaseous pollutants to confound the relationship between exposure to $PM_{2.5}$ and mortality and had not found any significant confounding (other than by SO_2), it is understandable that the current investigators chose to focus their limited resources on the extensive exploration of spatial autocorrelation in a series of one-pollutant models." (Krewski *et al.*, 2009, p. 130, emphasis added). This is a rather weak reason if their goal is to explore the strength of the $PM_{2.5}$ mass association in greater detail, given that their previous paper's findings on that association were the most sensitive to the inclusion of SO_2 as a co-pollutant.

[19] Bukowski (2008) has suggested that noise and stress could be an uncontrolled factor also affecting short-term $PM_{2.5}$-exposure risk studies.

one cannot have confidence that the bias would be eliminated, or even mitigated, by having included these other factors in the epidemiological regressions.

(III.B.) The magnitude of the $PM_{2.5}$ association at varying $PM_{2.5}$ exposure levels (i.e., the "shape" of the relationship) is estimated with error.

Brauer *et al.* (2002), among others, have demonstrated that measurement error for personal exposures when using central monitor data can hide a threshold from the statistical methods, even when one exists in reality.[20] Thus EPA's assumption of a linear relationship is not valid for quantitative risk analysis, even if the estimated constant relative risk were quantitatively valid as an average over the range of observed exposure levels.

EPA does not consider concerns with measurement error at all when it concludes that a linear relationship "most adequately" represents the association for purposes of statistical fit. When the Draft ISA states that "the C-R curve was found to be indistinguishable from linear,"[21] it is only making a statement about statistical goodness of fit to the available data. These statistical tests offer no information about whether the shape of the underlying true relationship has been obscured by measurement error, yet this is the critical question when trying to develop a quantitative estimate of risk from statistical associations using messy data.[22] The risk quantification step of the PMRA requires a functional relationship that properly reflects the true shape of the underlying relationship in order to reliably predict the changes in risk that would result from changes in $PM_{2.5}$. If a risk relationship has a non-linear shape (as one would logically expect for a true concentration-response situation, given a normally distributed degree of sensitivity across a population), then it is not appropriate to simply use a linear relationship just because the available epidemiological data do not offer the sensitivity necessary to detect that shape.

Errors due to an incorrect shape of the concentration-response function will become more and more pronounced with rollbacks to increasingly lower levels of $PM_{2.5}$ because the amount of change in risk associated with increasingly lower $PM_{2.5}$ exposures may

[20] Smith and Chan (1997) also demonstrated the impossibility of statistically detecting a real threshold in the presence of exposure measurement error. For simulated data with a pronounced ("hockey-stick") threshold at 20, the best fit for alternative thresholds was no threshold at all. They also fit a nonparametrically smoothed curve to the simulated data, with the resulting estimated relationship appearing to have the opposite of a threshold, that is, that the estimated concentration-response curve became *steeper* at concentrations closer to zero (and well below the point of the actual threshold). See Figure 9 and associated discussion in Smith and Chan (1997), p. 14, for the nonparametrically smoothed estimate of the concentration-response curve.

[21] Draft ISA, p. 2-37.

[22] Even the conclusion that linearity is the best *statistical fit* remains a debatable conclusion: see, for example, Abrahamowicz *et al.* (2003), and Goodman (2009), pp. 21-22. Without even considering debates about statistical tests of nonlinearity, potential evidence of nonlinearity can be found in the extended cohort analyses. For example, the finding reported by Laden *et al.* (2006) that estimated relative risks were lowered as $PM_{2.5}$ levels fell over time implies a non-linear relationship, while Gamble and Nicolich (2006) argue that a non-linear relationship may be observable even in the relative risks for a single time period. Also, the ACS evidence discussed in II.D that recent $PM_{2.5}$ levels used to estimate long-term associations could be serving as a proxy for earlier, higher $PM_{2.5}$ exposures also implies a non-linear actual relationship.

become vanishingly small, while the presumed linear statistical association assumes equally large amounts of risk reduction for a unit of improvement in $PM_{2.5}$, whether that change occurs from high levels of as-is exposure, or from near-background levels. The practice in the Draft PMRA of not counting risks below the lowest measured level (LML) of $PM_{2.5}$ does not eliminate this quantitative error. In fact, this practice exacerbates the misleading nature of the PMRA because it produces the bizarre effect of suggesting that there is no threshold, y*et al*so that 100% of the currently existing risk attributed to $PM_{2.5}$ would be eliminated if $PM_{2.5}$ is rolled-back only as far as the LML.

(Setting aside the logical inconsistency, if one truly believes that a linear relationship can be assumed, then the Draft PMRA is misleading when it reports that nearly 100% the long-term $PM_{2.5}$ risk can be eliminated by tightening the standard for $PM_{2.5}$ to 12 $\mu g/m^3$ annual average. All EPA can really say is that the latter standard would reduce $PM_{2.5}$ to the lowest levels that were observed in the most recent years among the cities included in the ACS cohort studies.)

IV. The Epidemiological Evidence Itself Indicates a Meaningful Chance that Long-Term $PM_{2.5}$ Exposures Do Not Elevate Public Health Risk.

Sections II and III have provided multiple reasons why quantitative estimates of risk in the Draft PMRA are unreliable. The Draft PMRA uses estimates of relative risks from the epidemiological studies at "face value" for its quantitative concentration-response functions, ignoring the many likely sources of bias those estimates. At a minimum, this results in large errors in its estimates of risk and risk reductions from reducing ambient $PM_{2.5}$ exposures that are not captured in statistical confidence intervals. However, EPA also commits an error of omission in its Draft PMRA by relying selectively on a few relative risk estimates from a few studies. This hides the degree of uncertainty that is detectable in the full body of epidemiological evidence, even if taken "at face value."

Even if one accepts the existing body of long-term epidemiological relative risk estimates at face value, one can observe a substantial chance that no effect exists at all if the full set of available relative risk estimates is given fair consideration. Figure 7-6 of the Draft ISA (p. 7-123) shows a very selective set of results. However, the entire body of evidence includes past as well as current studies. Even earlier estimates from the ACS studies remain relevant to the extent that certain regressions in them have not been reproduced in more recent ACS analyses. (The results that include SO_2 as well as $PM_{2.5}$ in the regressions from Krewski *et al.*, 2000, are a case in point.) Other studies also not shown in Figure 7-6 have produced non-positive and/or no statistically significant association between $PM_{2.5}$ and chronic mortality.[23] Nothing in the more recent literature

[23] Lipfert *et al.* (2000) is an example that found a negative association. More recent papers for the Veterans cohort (*e.g.*, Lipfert, Wyzga, *et al.*, 2006) have reported positive $PM_{2.5}$-risk associations (although significant only in 1-P formulations) but these newer findings do not make the earlier findings irrelevant. The earlier findings used a different subset of the Veteran's Cohort than the later findings, where the subset was driven by the locations of the available pollution data being used. The earlier studies also considered mortality risk in a different (earlier) time period. Thus, one can find both negative and positive associations within this single cohort, depending solely on the time period and air pollution data used.

necessarily supersedes those other studies. When the entire set of regressions are considered, giving equal weights to single and multipollutant models, and giving equal weights to the various cohorts that have been studied, one finds that this literature *as a whole* suggests that there is about a 15-20% chance that there is zero risk from $PM_{2.5}$.[24] This reflects the fact that the literature does contain quite a few findings of insignificance, which imply, based on statistical error alone, that the effect is zero. (In fact, it implies a possibility of a negative effect, but for this discussion, those are considered zero, not beneficial, effects.)

V. Conclusion

EPA's criteria for determining whether a causal relationship exists between exposures to $PM_{2.5}$ and health endpoints are fundamentally flawed because they allow an incorrect determination of causality to be made in circumstances that are marked by systematic biases. The epidemiological literature for long-term $PM_{2.5}$ exposure risks is clearly open to the possibility, and even likelihood, of systematic bias. Therefore, EPA's "causal" determination for long-term cardiovascular mortality risk and its "likely-causal" determination for long-term all-cause mortality risk in the Draft ISA are subject to a much greater chance of being wrong than the words themselves suggest. This fact alone places significant limitations on the usefulness and reliability of EPA's quantitative estimates of long-term mortality risks in its Draft PMRA, because the entire risk assessment is predicated on an unquestioned *presumption* of causality.

The quantitative estimates of mortality risk in the Draft PMRA remain unreliable, however, even if it is correct that there is some causal relationship between $PM_{2.5}$ and risk of dying. This is because the Draft PMRA also presumes that the statistical associations in the epidemiological literature can be interpreted *literally* as the actual concentration-response relationships for quantifying current levels of risk, and changes in risks for altered ambient $PM_{2.5}$ conditions.

The translation from an epidemiologically-derived association to a real "concentration-response function" that quantifies how much risk would change if PM mass were changed is highly problematic, regardless of the quality of the epidemiological studies that are being relied on. Even if one has great confidence that an association between $PM_{2.5}$ and health risk detected in an epidemiological study is reflecting a true causal relationship, the statistical model and its parameter estimates (*e.g.*, the "relative risk") cannot be assumed to be a precise numerical estimate of the true causal relationship, given the many limitations of the available data. As explained above, there remain good reasons to suspect that some or all of the estimated association bears no causal implication for $PM_{2.5}$ mass itself, or even of one of its constituents. If there are any missing explanatory variables – which is almost certainly true – then the statistical estimate of relative risk is not quantitatively reliable to assess either "as-is" risks, or

[24] This includes consideration of relative risks in Eftim *et al.* (2008), Enstrom (2005), Jerrett *et al.* (2005), Krewski *et al.* (2000, 2009), Laden *et al.* (2006) Lipfert *et al.* (2002), Lipfert, Baty *et al.* (2006), Lipfert, Wyzga *et al.* (2006), McDonnell *et al.* (2000), Pope *et al.* (2002), and Villeneuve *et al.* (2002).

changes in risk as $PM_{2.5}$ is reduced. The kinds of measurement errors and confounding that are present in the $PM_{2.5}$ epidemiological data also mean that the shape of the true relationship cannot be identified. The inability to define the shape of the true relationship means that one can have no confidence in statements of how risk will change as $PM_{2.5}$ is reduced.

The statistical confidence intervals that the Draft PMRA offers up as "uncertainty" do not measure biases due to missing variables or measurement error, and thus do not offer a way of characterizing the numerical uncertainty in actual risk levels at current or rolled-back $PM_{2.5}$ levels. The Draft PMRA's sensitivity analyses, which simply substitute one statistical estimate of relative risk for another, also cannot begin to characterize the quantitative uncertainty, given that all the available epidemiological estimates suffer from the same limitations in data and methods, and are thus subject to a systematic bias. As a result, the numerical estimates provided in the Draft PMRA have no reliable relationship to reality, even if one accepts the presumption that the epidemiological studies are detecting a causal relationship between one or more constituents of $PM_{2.5}$ and health risk. With all of these unstated and unanalyzed presumptions, one can have no confidence in the estimates of how much health risk is being created by current $PM_{2.5}$ exposures, nor whether any of that estimated risk would be reduced by reducing an undifferentiated measure of total $PM_{2.5}$ mass. The Draft PMRA's quantitative estimates of risk from as-is $PM_{2.5}$, and quantitative estimates of reductions in due to lowered $PM_{2.5}$, are unreliable.

Until it contains a more explicit analysis of the quantitative implications of these inherent challenges for estimating risks under current and alternative ambient $PM_{2.5}$ standards, the quantitative risk assessment of the Draft PMRA is, at best, not useful; at worst, its results are highly misleading as an input to policy decisions for setting a NAAQS. The only way to obtain reliable estimates would be to find ways to quantitatively incorporate corrections for systematic biases due to differential measurement errors, and potentially unmeasured causal confounders of a non-pollutant nature. This would produce a larger range of uncertainty, but one that reflects the true current state of knowledge. If this is not done, however, then the Draft PMRA should not be used in the consideration of alternative $PM_{2.5}$ NAAQS.

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