Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the "Integrated Science Assessment for Particulate Matter"

By
Jon M. Heuss
George T. Wolff
Air Improvement Resource, Inc.

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The Engine Manufacturers Association

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Based on a review of the draft EPA Integrated Science Assessment for Particulate Matter, a number of changes need to be made to assure that the document accurately reflects the latest scientific knowledge concerning the health effects of particulate matter. In our general and specific comments, we identify a number of key findings in the literature that are especially relevant to the integrative synthesis. The most important of these are as follows:

Summary of New Scientific Information

Based on large U. S. multi-city studies:

- The magnitude of the associations of $PM_{2.5}$ with cardiovascular and respiratory hospital admissions and mortality are smaller than thought during the previous review.[1] (pages 34-43)

- There is a spatial and temporal pattern in the associations with little or no association in significant portions of the country and during a significant portion of the year. (pages 11-13, 26, 34-37, 39-41)

- A similar spatial pattern is found in acute morbidity and mortality as well as in chronic mortality studies. (pages 34-37, 39-43, 46-49)

The pattern in multi-city studies:

[1] See discussion in main text at pages denoted.

- Is not consistent with an effect of generic $PM_{2.5}$ mass. (pages 40-41, 43, 45-49)

- Provides strong evidence that single-city studies substantially bias the apparent associations upward due to publication bias. (pages 10-11)

- Provides strong evidence that stochastic variability is greater than heretofore thought. (pages 13-16, 26, 35)

In systematic studies of acute effects:

- Similar patterns are found for each criteria pollutant in single-pollutant models, making it difficult to attribute observed effects to individual pollutants. (pages 16-17)

Toxicology and human clinical studies:

- Report many biological responses but the findings are often mixed and inconsistent and of uncertain clinical relevance. (pages 22-23, 35)

- Provide limited support for many potential biological mechanisms but have not yet demonstrated how generic particles (or accompanying gases) can cause the purported effects at relevant ambient doses. (pages 26, 33-34, 44-45)

- Demonstrate the toxicity of PM components varies widely. (pages 19-21)

Based on these findings, all the determinations of causality in the ISA must be qualified as they were in the 2004 Criteria Document to refer to "PM (or one or more PM component) acting alone and/or in combination with gaseous pollutants" rather than to PM mass alone.

The discussion in the draft ISA does not provide an adequate integrative synthesis. Rather it focuses on single-pollutant model results and downplays or ignores important issues that were acknowledged in the prior review. When the full weight of evidence is considered, the case for causality is weaker than expressed in the document.

While there has been progress in postulating various mechanisms by which PM might cause the health effects implied by the epidemiological associations, demonstrating that the associations are "real" or "causal" has been difficult and somewhat elusive. Biologic plausibility involves considerations of the kinds of effects an agent causes as well as the doses at which those effects occur. For ambient $PM_{2.5}$ or its constituents, the recent toxicologic studies establish the plausibility of the kinds of effects reported in the observational studies, but dose

plausibility has not been demonstrated. Since there is a similar pattern of acute epidemiological associations for each of the criteria pollutants, the extent to which gaseous air pollutants can cause the biological responses attributed to PM in the ISA should be rigorously evaluated as part of the integrated synthesis.

Introduction

The U. S Environmental Protection Agency (EPA) initiated the next review of the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) with the issuance of the first external review draft of the Integrated Science Assessment for Particulate Matter[2] (ISA) in December 2008. PM air pollution is a complex mixture of solid and liquid particles that vary in number, size, shape, surface area, chemical composition, solubility, and origin. Historically, ambient PM air pollution has been regulated in the U.S. by setting national air quality standards for the total mass of particles (irrespective of their chemical composition). Over the years, the focus has changed from consideration of all particles that are suspended in the ambient air to particles within specific size ranges. The draft discusses three size ranges of particles: "coarse" particles that have aerodynamic diameters between 10 and 2.5 micrometers (denoted $PM_{10\text{-}2.5}$); "fine" particles that have aerodynamic diameters below 2.5 micrometers (denoted $PM_{2.5}$); and "ultrafine" particles that have aerodynamic diameters between 0.01 and 0.1 micrometers.

The previous review of PM air quality standards was completed in September 2006 when EPA announced final decisions[3] to revise the primary and secondary NAAQS for PM to provide increased protection of public health and welfare. At that time, EPA revised the level of the 24-h $PM_{2.5}$ standard to 35 $\mu g/m^3$, retained the level of the annual $PM_{2.5}$ annual standard at 15 $\mu g/m^3$, and revised the form of the annual $PM_{2.5}$ standard by narrowing the constraints on the optional use of spatial averaging. EPA also retained the 24-h PM_{10} standard of 150 $\mu g/m^3$ and revoked the PM_{10} annual standard because the available evidence did not show a link between long-term exposure to current ambient levels of coarse particles and health effects.

Under the Clean Air Act, EPA is charged with identifying air pollutants that may reasonably be anticipated to endanger public health and welfare and to issue air quality criteria for those pollutants that accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of the pollutant in ambient air. For many years these criteria were called "Criteria Documents." To date, except for PM, which is a mixture of many different chemical species, the air pollutants that EPA has regulated as "criteria pollutants" have been either specific gaseous compounds or an element of concern, such as lead.

In recent years, the Agency has revised the process for review of NAAQS. The criteria called for in the Act is now designated as an Integrated Science Assessment (ISA). The ISA should be a concise review, synthesis, and evaluation of the most policy-relevant science that communicates critical science judgments relevant to the NAAQS review. Thus, the ISA provides the scientific foundation for the review of the

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[2] U. S. Environmental Protection Agency, First external review draft of the Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139, December 2008.
[3] 71 Federal Register 61144, September 21, 2006.

primary (health-based) and secondary (welfare-based) NAAQS for the air pollutant of concern.

AIR, Inc. reviewed the draft ISA with this objective in mind. In the following comments, we identify areas where the draft is incomplete, misleading, or otherwise deficient. We restricted our review to the science that relates to and should inform the primary (health-based) standard. Both general comments and specific comments on the chapters of the draft ISA are provided in the following sections.

General Comments

In several important ways, the draft ISA glosses over the state of PM science from the prior review particularly with regard to the PM components that may be causing health effects and the dose-response relation.

Since the PM ISA is designed to build upon the science that was summarized in the previous review, the 2004 PM Criteria Document (CD)[4], it is particularly important that the ISA properly characterize the state of science in that review and then explicitly discuss the new information that would lead to a change in the conclusions from the prior review. Two examples are discussed in these general comments; others are noted in the specific comments.

The first example comes from the conclusions regarding $PM_{2.5}$ and causality. The 2004 PM CD described a growing body of evidence from both epidemiological and toxicological studies supporting the general conclusion that

> "$PM_{2.5}$ (or one or more $PM_{2.5}$ components), acting alone and/or in combination with gaseous co-pollutants, are likely causally related to observed ambient fine particle-associated health effects."[5]

The important qualifications "or one or more components " and "acting alone and/or in combination with co-pollutants" are left off the conclusions regarding causality in the draft ISA. The evidence for including or removing those important qualifications needs to be explicitly discussed in the ISA. This is a major issue because, as noted below, the pattern of epidemiological associations, as well as the findings from extensive toxicological studies, is not consistent with the assumption that all $PM_{2.5}$ can be considered equally toxic.

The second example comes from the discussion regarding concentration-response relationships. In Chapter 6, the draft ISA notes that "the results from large multi-city studies reviewed in the 2004 PM AQCD suggested that strong evidence did not exist for a clear threshold for PM mortality effects."[6] The text goes on to properly raise several qualifications and limitations to the assumption that the concentration-response function can reasonably be modeled as linear. However, when this issue is discussed in Chapter 8 only some of the limitations are noted and the summary notes "these studies have used various statistical methods, but overall have consistently found that a no-threshold log-linear model adequately portrays the PM-mortality C-R relationship in multi-city analyses."[7] Furthermore, when discussed in

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[4] U. S. Environmental Protection Agency, Air Quality Criteria for Particulate Matter, Volume I, EPA/600/P-99/002aF, October 2004; Volume II, EPA/600/P-99/002bF, October 2004, "PM CD."
[5] PM CD at pages 8-338 and 9-79.
[6] PM ISA at page 6-237.
[7] PM ISA at page 8-3.

Chapter 2, the support for use of a no-threshold log-linear model is expressed as a consensus.[8]

The question of the shape of the concentration-response function was a major consideration during the prior PM review. It is important because it impacts the risk assessment which is used to estimate health effects and, in turn, to inform the level that is chosen for the standard. Although early drafts of the 2004 CD indicated that the PM studies generally show linear concentration-response associations, responding to a request in CASAC's October 4, 2004 letter, the final CD specifically concluded that "in summary, the available evidence does not either support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies."[9] The final CD also noted that "the available information does not allow for a clear choice of 'threshold' or 'no threshold' over the other."[10] This view is consistent with points made by the Special Panel of the Health Effects Institute (HEI) Review Committee that raised several cautions in interpreting the NMMAPS concentration-response results. They pointed out[11] that measurement error could obscure any threshold that might exist, that city-specific concentration-response curves exhibited a variety of shapes, and that the use of Akaike Information Criterion may not be an appropriate criterion for choosing between models. The HEI Panel cautioned that lack of evidence against a linear model should not be confused with evidence in favor of it.

CASAC re-iterated its concern in its June 6, 2005 letter noting "the available epidemiological database on daily mortality and morbidity does not establish either the presence or absence of threshold concentrations for adverse health effects." For the risk assessment, CASAC's letter indicates "the Panel favored the primary use of an assumed threshold of 10 $\mu g/m^3$" along with sensitivity analyses using other threshold assumptions.

The draft ISA does not include any discussion or analysis that would change this interpretation. In fact, the body of the ISA raises the concern that, given the pattern of seasonal and regional differences in PM risk estimates in recent multicity studies, the very concept of the concentration-response relationships estimated across cities and for all-year data may not be informative.[12]

While the draft ISA refers to the opinions concerning dose-response from the participants in an expert solicitation sponsored by the Agency, questions have been raised over the selection of participants (including authors and co-authors of the studies being evaluated while excluding more independent scientists). In addition,

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[8] PM ISA at page 2-23.
[9] PM CD at page 9-44.
[10] PM CD at page 8-320.
[11] See Commentary in HEI Research Report Number 94, Part III, May 2004.
[12] PM ISA at page 6-39.

the participants were not asked for their views on the assumption of equal toxicity for all $PM_{2.5}$ components.

The draft mischaracterizes the consistency and coherence of both acute and chronic health effects from epidemiology.

- There is a wide range of associations reported for both chronic and acute mortality and morbidity with ambient $PM_{2.5}$. However, publication bias, model selection uncertainty, and potential confounding cloud the interpretation of the data.

In interpreting the epidemiological evidence, the draft downplays major new findings concerning uncertainty due to model selection issues. Model selection uncertainty relates to confounding of air pollutant associations by temporal trends, weather and co-pollutants. During the last ozone review, EPA acknowledged that the uncertainties in the estimates of pollutant effects are understated by consideration of the statistical uncertainty of the fitted model alone. Much more uncertainty arises from the lack of information regarding the choice of appropriate models for adjusting confounding by other covariates, and the choice of appropriate lag structures. As Lumley and Sheppard (2003) point out:

> Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results.[13]

Others have also pointed out the critical importance of model choice, particularly when effect estimates are small. For example, Smith et al. caution:

> From a statistical point of view, the common epidemiological practice of choosing variables (including lagged variables, co-pollutants, etc.) that maximize the resulting effect estimates is a dangerous approach to model selection, particularly when the effect estimates are close to 0 (i.e., RR close to 1).[14]

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[13] T. Lumley and L. Sheppard, "Time series analyses of air pollution and health: straining at gnats and swallowing camels?" Epidemiology, 14, 13-14, 2003.

[14] R. Smith , P. Guttorp, L. Sheppard, T. Lumley, and N. Ishikawa, "Comments on the Criteria Document for Particulate Matter Air Pollution," Northwest Research Center for Statistics and the Environment Technical Report Series No. 66, July 2001.

Smith et al. note that Lumley and Sheppard (2000)[15] showed that the effect of choosing lags in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated. Morris has also shown a similar result. [16] He showed using the theory of extreme value distributions that evaluating multiple lags and reporting the maximum effect, even when there is no underlying effect, can yield estimates of effect size with a magnitude similar to those routinely reported for particles.

The revised analyses necessitated by the problems with the commonly used software for time-series analyses clearly show that methods used for controlling temporal trends and weather can profoundly affect the results. To make matters worse, there appears to be no objective statistical test to determine whether these factors have been adequately controlled. The HEI Expert Panel[17] for the re-analysis states, "Ritov and Bickel (1990)[18] have shown, however, that for any continuous variable, no strictly data-based (i.e., statistical) method can exist by which to choose a sufficient number of degrees of freedom to insure that the amount of residual confounding due to that variable is small. This means that no matter what statistical method one uses to select the degrees of freedom, it is always logically possible that even if the true effect of pollution is null, the estimated effect is far from null due to confounding bias." The HEI Expert Panel concluded further, "Neither the appropriate degree of control for time, nor the appropriate specification of the effects of weather, has been determined for time-series analyses". In other words, it is impossible to adjust temporal trends without accurate information from external sources regarding the appropriate degrees of freedom to use. Such information, however, simply does not exist.

With regard to uncertainty due to model selection, the Koop and Tole 2004[19] Bayesian model averaging study, which thoroughly evaluated model selection in one city for many air pollution and meteorological variables, concludes:

> Point estimates of the effect of numerous air pollutants all tend to be positive, albeit small. However, when model uncertainty is accounted for in

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[15] T. Lumley and L. Sheppard, "Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses," Environmetrics, 11, 705-717 (2000).

[16] R. Moris, "Airborne Particulates and Hospital Admissions for Cardiovascular Disease: A Quantitative Review of the Evidence," Environ. Health Perspect.., **109**, Supplement 4, 495-500 (2001).

[17] Health Effects Institute, Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, Health Effects Institute, Cambridge, Massachusetts, at 267, 269 (2003).

[18] Y. Ritov and P. Bickel, "Achieving information bounds in non- and semi-parametric models," Ann. Stat., 18, 925-938 (1990).

[19] G. Koop and L. Tole, Measuring the Health Effects of Air Pollution: to What Extent Can We Really Say that People are Dying from Bad Air, J. of Environmental Economics and Management, 47, 30-54. (2004).

> the analysis, measures of uncertainty associated with these point estimates became very large. Indeed they became so large that the hypothesis that air pollution has no effect on mortality is not implausible. On the basis of these results, we recommend against the use of point estimates from time-series data to set regulatory standards for air pollution exposure.

Koop and Tole showed that a single model based on a sequence of hypothesis tests will overestimate the certainty of the results. This is not a new finding in the statistical literature. The 2004 CD notes that "testing many models to identify the model with the best fit can lead to an underestimation of uncertainty" and "if the observed confidence intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider."[20]

Despite the issues concerning uncertainty due to model selection in the 2004 PM CD, in the HEI Special Panel report, and in the publications referenced above, the draft ISA is essentially silent on this issue (and any changes in the relevant science) except to acknowledge[21] in the introductory section on methodology in Chapter 6 that to date, a clear consensus as to the extent of modeling required to accurately control for weather or confounding by other pollutants or to measure PM-mortality/morbidity effects has not been reached. The final ISA must acknowledge and address the uncertainty due to model selection as it affects the interpretation of epidemiological results.

Publication bias is another major issue in interpreting the epidemiology. The commentary by Goodman concerning meta-analyses is particularly insightful.[22] He noted a factor of at least three difference between the results of ozone meta-analyses and the NMMAPS data which are not affected by publication bias. Goodman concludes that the implications of an EPA-sponsored exercise of funding three separate meta-analyses "go far beyond the question of the ozone mortality effect." He cautions that "depending on published single-estimate, single-site analyses are an invitation to bias." He notes that "the most plausible explanation is the one suggested by the authors, that investigators tend to report, if not believe, the analysis that produces the strongest signal; and in each single-site analysis, there are innumerable model choices that affect the estimated strength of that signal." A separate review by a panel of ten knowledgeable scientists[23] concluded that "taken together, the meta-analyses provide evidence of a disturbingly large publication bias and model selection bias."

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[20] PM CD at page 8-226.
[21] PM ISA at pages 6-2 and 6-3.
[22] S. Goodman, "The Methodologic Ozone Effect," Epidemiology, 16, 430-435 (2005).
[23] Report of a Working Conference, Critical Considerations in Evaluating Scientific Evidence of Health Effects of Ambient Ozone, held in Rochester, New York, June 2007.

Similarly, Anderson et al. 2005[24] concluded that publication bias is present in single-city time series studies of ambient particles. After correcting for publication bias, they still report a positive association. However, they also note that the regression estimates from the multi-city studies (which are not prone to publication bias) and the corrected single-city studies are approximately half of the mortality estimates of the mid-1990's, that the correction for publication bias may not be complete, and that differential selection of positive lags may also inflate estimates.

Thus, publication bias is a major concern inflating the size of any potential effect. As EPA has reviewed other criteria pollutants, the Agency has acknowledged[25] that the summary of health effects evidence is vulnerable to the errors of publication bias and multiple testing. The only reference in the draft ISA to publication bias is found on page 6-11 in a discussion of the heart rate variability findings. Since there is now substantial evidence that publication bias inflates the apparent magnitude and consistency of air pollution health effects in single-city studies, the final PM ISA must address and discuss the important impact of publication bias in the integrative sections.

- New large multi-city studies show that the PM health signal varies spatially and temporally with little or no effect in major sections of the country and at many times of the year. This finding indicates a need to switch from considering all PM as equally toxic and focus efforts at identifying the specific components/mixtures that cause the pattern of associations.

The ISA correctly notes new multi-city studies that report major differences in PM associations as a function of geography and season. For example, the section on geographic location, Section 8.2.5, notes that all of the studies identified in the current PM ISA that have examined the PM-mortality relationship, in regards to geographic location within the U.S., have concluded that the effects are greater in the East compared to the West.

The NMMAPS analysis by season and region by Peng et al.[26], which used updated mortality data from 1987-2000 in 100 cities, reported that summer was the only season for which the combined effect was statistically significant. An analysis by geographical regions showed a strong seasonal pattern in the Northeast with a peak in the summer and little seasonal variation in the southern regions of the country.

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[24] H. Anderson, R. Atkinson, J. Peacock, M. Sweeting, and L. Marston, "Ambient Particulate Matter and Health Effects: Publication Bias in Studies of Short-Term Associations," Epidemiology, **16**, 155-163 (2005).

[25] U. S. EPA, Second External Review Draft of Integrated Science Assessment for Oxides of Nitrogen-Health Criteria, EPA 600/R-07/093aB, March 2008 at page 3-2; U. S. EPA, Integrated Science Assessment for Oxides of Sulfur-Health Criteria, EPA/600/R-07/047F, September 2008 at pages 3-1 and 3-48.

[26] Peng, R. D.; Dominici, F.; Pastor-Barriuso, R.; Zeger, S. L.; Samet, J. M.; Seasonal analyses of air pollution and mortality in 100 U. S. Cities, *Am. J. Epidemiol.*, **2005**, 161, 585-594.

The authors acknowledge that there are several possible explanations for their results. One obvious hypothesis is that the most toxic particles have a spring/summer maximum and are more prevalent in the Northeast. Another hypothesis mentioned by the authors is that there could be a seasonally varying bias from an, as yet, unidentified source.

The largest hospital admissions study also clearly shows differences in cardiovascular hospital admissions between East and West. The Dominici et al. 2006[27] study evaluated fine PM hospital admissions associations for 204 U. S. urban counties with a population greater than 200,000 using 1999-2002 Medicare hospital admission data. The results are presented for a two-stage Bayesian analysis for various types of admissions and by region. Combined associations on the order of a 1 % increase in various cardiovascular or respiratory outcomes per 10μg/m^3 increase in $PM_{2.5}$ are reported. However, there are issues that call into question the interpretation of this as an effect from generic fine PM.

The authors present results from seven separate regions as well as a comparison of the three western regions with the four eastern regions. There is a clear difference in the combined associations among the regions and particularly between the eastern and western region. The combined association is positive for cardiovascular outcomes in the east, but negative in the west except for heart failure that is positive in both areas. This is not consistent with an effect of generic $PM_{2.5}$ on cardiovascular hospital admissions and, indeed, the authors point out the need to shift the focus of research to identifying those characteristics of particles that determine their toxicity.

A similar spatial pattern exists in the chronic studies. The HEI-sponsored re-analysis of the Six-City and ACS studies showed that: 1) the increased risk was cardiovascular not respiratory, and 2) there was a significant spatial heterogeneity in the association, with no effect seen in western U. S. cities. In particular, during the review of the federal PM standards in 2001, EPA staff pointed out the significant spatial variation in the data with actually a negative estimate of excess $PM_{2.5}$ mortality risk in the West.[28] The HEI re-analysis also identified other patterns in the data, including the facts that: 1) one gaseous pollutant, SO_2, had a strong association with mortality; 2) when SO_2 was included in the model the PM all-cause mortality association was materially reduced and became non-significant; and 3) the

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[27] Dominici F.; Peng, D; Bell,; M.; Pham.; McDermott, A.; Zeger, S. L.; Samet, J. M.; Particles, Air Pollution and Hospital Admissions for Cardiovascular and Respiratory Diseases, *J. American Medical Association*, **2006**, ***295***, 1127-1134.

[25] Grant, L.; EPA Staff Presentation to CASAC, July 23, 2001; Key Revisions and Scientific Issues for Second External Review Draft of Air Quality Criteria for Particulate Matter; Slide 46 indicates an excess risk from 10 μg/m^3 $PM_{2.5}$ in the ACS cohort of +29 % in the Industrial Midwest, +25 % in the Southeast, +14 % in the Northeast, and –9 % in the West (West is a combination of cities in the Northwest, Southwest, Upper Midwest, and Southern California. NMMAPS geographic regions).

increased mortality was experienced in the portion of the cohort that had a high school education or less.

A recent analysis by Zeger et al.[29] confirms the large spatial difference in chronic mortality association in a cohort of 13 million Medicare enrollees. Zeger et al. reported statistically significant results for the eastern and central United States that are in general agreement with previous publications, but Zeger et al. found no significant effect of $PM_{2.5}$ on mortality in the western United States. A caution in interpreting the Zeger study is that effect estimates for the Medicare cohort may be biased upward due to lack of adjustment for individual level risk factors.

In summary, the spatial and temporal pattern in both the acute and chronic studies is not consistent with treating all fine PM as equally toxic. The ISA tries to minimize this concern by concluding that "overall, the epidemiologic literature suggests that individuals residing in the Eastern U.S. are more vulnerable to PM-related health effects."[30] This interpretation, however, is not scientifically justified and should be removed.

- Although multi-city studies avoid publication bias, they also report a biologically impossible wide range of associations from positive to negative. The pattern indicates substantial stochastic variation with many false positive and false negative associations.

In contrast to the pattern of associations in publications reporting single-city time-series results, there is a biologically implausible, very wide range in the PM/mortality associations in the individual cities included in multi-city studies, including a substantial portion of negative associations between air pollutants and heath endpoints. For example, Dominici et al.[31] acknowledge that the city-specific maximum likelihood estimates from their study of the 88 largest U. S. cities range from - 4 % to + 4 % per 10 $\mu g/m^3$ increase in PM_{10}. This wide range can be compared to the more limited range included in Figures 6-19 and 6-20 of the ISA.

In the Katsouyanni 2003 29-city European multi-city study, the range in total mortality associations was also very wide, from – 1 % to + 2% per 10 $\mu g/m^3$ increase in PM_{10}. In the Analitis, et al. 2006 report on respiratory and cardiovascular associations from the same cities, the range is also large for each category of death, with negative associations in some cities, but positive associations in the bulk of the cities. However, for six of the twenty-one cities in

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[29] Zeger, S.L.; Dominici, F.; McDermott, A.; Samet, J.M. Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005). Environ. Health Perspect. (2008), online August.

[30] PM ISA at page 8-19.

[31] F. Dominici et al. National Maps of the Effects of Particulate Matter on Mortality: Exploring Geographic Variation, Environmental Health Perspectives, **111**, pages 39-43 (2003).

which there was a negative association for either respiratory or cardiovascular death, the association for the other cause of death was strongly positive, which is biologically implausible. For example, in Stockholm, the associations were + 8 % for cardiovascular death and – 1 % for respiratory death per 10 $\mu g/m^3$ increase in PM_{10}.

The Franklin et al. 2007 study of acute mortality in 27 U. S. cities reported individual city associations ranging from – 5 % to + 10 % per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Franklin et al. discuss the cities with strong positive associations, but never acknowledge the strong and statistically significant negative associations in cities like Houston and Dallas. They do note that there is stochastic variability in their results.

The Medina-Ramon, et al. 2006[32] study of respiratory hospital admissions in 36 U. S. cities shows that a 10 $\mu g/m^3$ increase in PM10 is associated with anywhere from a 10 % increase to a 10 % decrease in COPD admissions in individual cities in a single-pollutant model. For pneumonia admissions, the ranges were almost as wide. In addition, a 0.010 ppm increase in ozone is associated with anywhere from a 10 % increase to a 10 % decrease in COPD admissions in individual cities.

Although a wide range of associations (both positive and negative) is clearly evident in systematic studies, the authors of the studies either do not mention the range or mention it only in regard to there being heterogeneity in the results. However, the presence of a substantial portion of actually negative associations in individual cities in the multi-city studies is evidence for a larger degree of stochastic variation than heretofore acknowledged. The pros and cons of combining such disparate results needs to be carefully considered and discussed by EPA, CASAC, and the scientific community, including in the ISA.

Additional evidence for substantial stochastic variation comes from an important new HEI study[33] that evaluated coherence between the time-series associations of mortality and hospital admissions in 14 cities. That study found little or no coherence between the PM_{10} mortality and morbidity associations and, importantly,

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[32] M. Medina-Ramon, A. Zanobetti, and J. Schwartz, "The effect of ozone and PM-10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: A national multi-city study," Am. J. Epidemiol., 163, 579-588 (2006).
[33] F. Dominici, et al. HEI Research Report 94, Part IV, 2005.

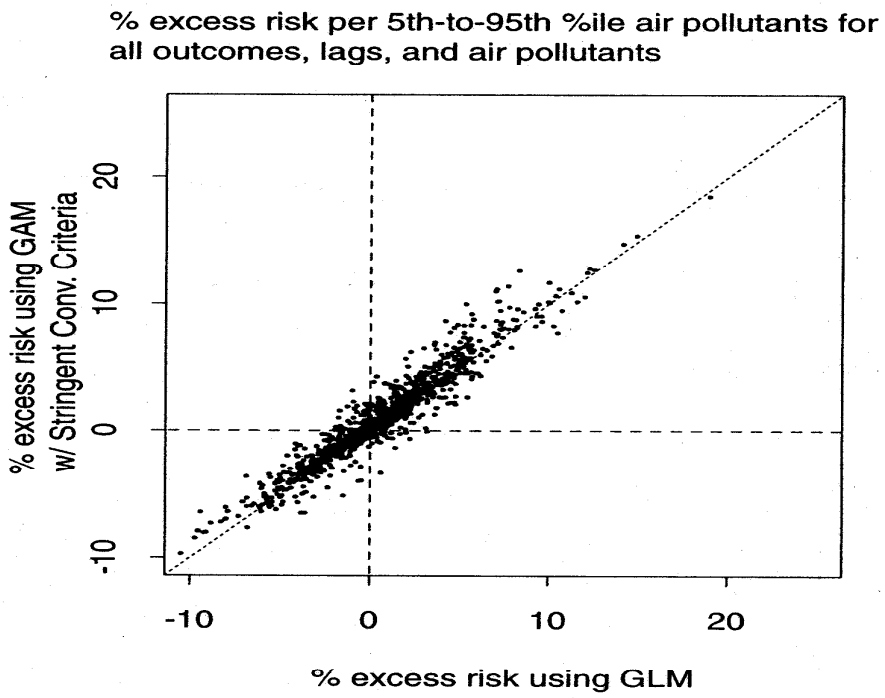

Figure 2 from Ito 2003

found little or no correlation between the time series of health event counts (mortality and hospital admissions) in the various cities. As in other multi-city studies, the individual associations for mortality and morbidity covered a wide range from positive to negative. Given the substantial stochastic variation, the EPA needs to acknowledge and consider the wide range of associations with regard to both biological plausibility and the limitations on the use of time series and other epidemiological studies to set ambient standards.

Another example of the wide-range of associations in systematic analyses comes from Ito 2003. When the statistical software issue noted in the ISA was raised and many time series studies were re-analyzed, Ito 2003 carried out a systematic re-analysis of the air pollution associations within a given city. Ito[34] re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. 2000 HEI study of Detroit. As shown in the figure above, there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito showed in separate figures that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann et al. study, as it is in almost all the published literature, was on

[34] K. Ito, pages 143-156 in HEI Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health, May 5, 2003.

the positive associations, Ito's plot shows that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much noise or variability in the data, that identifying which positive associations may be real health effects and which are not appears beyond the capability of current methods. Moreover, in the Ito re-analysis, the overall pattern for each pollutant is similar so that one pollutant or one PM indicator is not implicated over any of the others.

- The pattern of acute associations is remarkably similar for all the criteria pollutants, raising the issue of double or triple counting of health effects.

A similar pattern of associations was observed for all the major pollutants in single pollutant models in NMMAPS. For each pollutant, at each of the three lags evaluated, an implausibly wide range in individual-city associations from negative to positive was observed.[35]

Steib et al.[36] evaluated 109 acute mortality studies and reported that there are positive associations with mortality for all the major pollutants in single pollutant models, and that for each, when other pollutants are included, the association with the first pollutant, on average, is decreased. In addition, the Steib et al. analysis shows that the distribution of results published for each pollutant is remarkably similar, ranging from a few negative associations, to many small positive but non-significant associations, to some larger and significant associations. Thus, based on a comprehensive survey of the acute mortality epidemiology, no one pollutant is implicated over the others in single pollutant models. Although effect sizes were generally reduced in multi-pollutant models, the effects for PM_{10} and SO_2 remained statistically different from zero. The results for multi-pollutant models cannot be considered definitive because the underlying data base differs for each pollutant, there being wide differences from study to study for how many and which pollutants were included.

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[35] While the full range of individual city results is presented in some multi-city studies, there has been a tendency to omit the individual city results in some recent publications. However, when the HEI sponsors requested that the individual city results from the re-analysis of NMMAPS be made available, the individual city results for PM_{10} and the various gases were posted on the Johns Hopkins website. The data show a remarkable similarity in that there was a biologically impossible wide range of associations from positive to negative for each pollutant on each lag that was evaluated. This data was also provided to EPA and CASAC during the PM review process; J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.

[36] D. Steib, S. Judek, and R. Burnett, "Meta-analysis of time series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season," *J. Air & Waste Manage. Assoc.*, **52**, 470-484 (2002) and Stieb et al., *J. Air & Waste Management Association*, **53**, 258-261, 2003.

As EPA has considered each criteria pollutant in turn, single-pollutant model results have been used to estimate the strength and consistency of association. Single-pollutant PM associations were used in the recent PM review as evidence of a causal relation between PM and respiratory endpoints.[37] In addition, single-pollutant ozone associations were used in the recent ozone review as evidence of a causal relation between ozone and the same respiratory endpoints.[38] The recently completed NOx and SOx ISAs[39] have also used selected single-pollutant model results as evidence of respiratory health effects from these pollutants.

In each case, the Agency has plotted selected individual city associations from the literature in the same manner and used the resulting figures to make the argument for respiratory health effects caused by the pollutant under consideration. Visual inspection of the figures referenced above reveals a remarkably similar pattern. This raises three issues. First, as the air quality standard for each pollutant is reviewed in turn, the current practice of selecting specific studies and selecting specific single-pollutant associations for that pollutant results in a false appearance of consistency. If the various ISA documents for different pollutants are to be a scientifically sound basis for policy, more thorough analyses considering the full suite of pollutants is mandatory. Second, claiming health effects for each pollutant based on single-pollutant models raises the issue of double-, triple-, or even quadruple-counting of health effects.

Third, the remarkably similar pattern for each pollutant, together with the evidence of stochastic variability, model selection uncertainty, and publication bias, raise the concern that it is beyond the capability of current methods to identify which positive associations may be real health effects and which are not. Time-series epidemiology of air pollution associations is only capable of very blunt analysis. CASAC raised this issue in a June 2006 letter to the Administrator, noting that "because results of time-series studies implicate all of the criteria pollutants, findings of mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants."[40] Further, due mainly to exposure misclassification concerns, CASAC also questioned the utility of the time-series mortality estimates. The ISA needs to acknowledge the stochastic variability in time series associations (both positive and negative) and consider the implications of that variability in both the interpretation of the epidemiology and its integration with results from controlled studies.

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[37] Figure 1 in proposed PM rule, 71 Federal Register 2620, January 17, 2006.
[38] Figure 1 in proposed ozone rule, 72 Federal Register 37818, July 11, 2007.
[39] July 2008 NOx ISA, EPA/600/R-08/071, at page 5-9, Figure 5.3-1; September 2008 SOx ISA, Figures 5-1 and 5-2 at pages 5-6 and 5-7.
[40] R. Henderson, CASAC letter, EPA-CASAC-06-07, June 5, 2006 at page 3.

Important information on health risks that should be considered by the Agency is omitted.

There are several bodies of scientific information concerning health risk that are relevant to the ISA's judgments regarding the risk from ambient PM that are not included in the draft ISA. These include the observed risks from PM exposures due to PM other than ambient particles, the risks and effects identified in toxicological studies of PM components, the risks and effects from exposure to other components of the ambient air pollution mix, and the risks associated with changes in weather and weather variables. The rationale for why each of these categories of information is relevant to the ISA is provided below.

- If low doses of generic ambient particles were causing the serious health effects implied by the acute and chronic PM associations relied on by the Agency, then low doses of particles should be causing similar effects in other exposure situations, which is not the case.

As noted in the 2004 CD and in the draft ISA, the exposure to nonambient particles is as high or higher than the exposure to ambient particles. Therefore, there should be a health signal for generic particles as measured by mass in the indoor pollution literature. Although there are well-established indoor health risks from environmental tobacco smoke and from particles of biological origin such as house dust-mite, cockroach, and animal allergens, no substantial or consistent health signal from generic PM has been documented. A recent review of the scientific literature focusing on non-industrial indoor environments looked for evidence of particle health effects.[41] An interdisciplinary group of European researchers surveyed over 10,000 articles by title, chose 1725 abstracts to screen, and chose 70 articles for full review. They concluded that "there is inadequate scientific evidence that airborne, indoor particulate mass or number concentrations can be used as generally applicable risk indicators of health effects in non-industrial buildings." The lack of a health signal from generic indoor PM is not coherent with the assumed presence of a strong outdoor generic ambient PM health signal.

Gamble and Nicolich[42] compared the risks from smoking and occupational exposures with the risks implied by several of the cohort studies and concluded that the toxicity per unit mass of ambient PM would have to be 2 to 4 orders of magnitude higher than that from smoking to explain the reported ambient risks.

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[41] Schneider, T.; Sundell, J.; Bischof, W.; Bohgard, M.; Cherrie, J. W.; Clausen, P. A.; Dreborg, S.; Kildeso, J.; Kjaergaard, S. K.; Lovik, M.; Pasanen, P.; Skyberg, K.; EUROPART. Airborne Particles in the Indoor Environment. A European Interdisciplinary Review of Scientific Evidence on Associations between Exposure to Particles in Buildings and Health Effects, *Indoor Air*, **2003**, *13,* 38-48.

[42] Gamble J. F.; Nicolich, M. J.; Comparison of Ambient PM Risk with Risks Estimated from PM Components of Smoking and Occupational Exposures, *J. Air & Waste Manage. Assoc.*, **2000**, *50*, 1514-1531.

That finding led them to conclude that the risks from the cohort studies were not coherent with the risks derived from smoking or occupational studies.

The findings from massive indoor pollutant exposures in developing nations are also relevant. Approximately half the world's population relies on unprocessed biomass fuels (wood, coal, crop residues, or animal dung) for cooking and space heating. Those fuels are typically burned indoors in simple unvented cookstoves. The exposures to both gases and particles are many times higher than the indoor exposures in developed countries. For example, a detailed exposure study[43] of 55 households in rural Kenya reports that PM10 exposures of adult women (who normally cook and tend the fire) were on the order of 5 mg/m^3 while adult male exposures were on the order of 1 mg/m^3. These levels are 40 to 200 times higher than the current average U. S. outdoor PM_{10} levels of 25 $\mu g/m^3$. A 2002 World Health Organization report[44] of the health effects of indoor pollution exposures in developing countries reviews the evidence for health effects from these exposures. While there is strong evidence of important effects on acute and chronic respiratory disease in many countries and effects on lung cancer from coal use in China, there is little evidence to date of a strong cardiovascular signal from these massive exposures. This also does not appear to be coherent with the assumption of a strong cardiovascular signal from low doses of generic ambient PM.

As part of the integrative discussion of coherence in the ISA, the risks (or lack thereof) in these other exposure situations should be evaluated and compared to the reported risks from ambient observational studies.

- The ISA should evaluate the coherence between the toxicological data on PM components and the assumption in the draft ISA that all $PM_{2.5}$ can be treated as equally toxic.

PM air pollution is a complex mixture of solid and liquid particles that vary in number, size, shape, surface area, chemical composition, solubility, and origin. Treating all $PM_{2.5}$ as if it were equally toxic is a gross simplification that is not consistent with the large body of toxicological data on either individual $PM_{2.5}$ components or ambient $PM_{2.5}$ mixtures. The 2004 CD indicates that different PM materials also vary extensively in toxicity, based on over 30 years of toxicological study.[45] This substantial body of information is routinely used to establish chemical-specific standards that are used in occupational and other settings, and demonstrates that the relative toxicity of different PM species per unit mass varies

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[43]. Ezzati, M.; Saleh, H.; Kammen, D. M.; The Contributions of Emissions and Spatial Microenvironments to Exposure to Indoor Air Pollution from Biomass Combustion in Kenya, *Environmental Health Perspectives*, **2000**, ***108***, 833-839.

[44] N. Bruce, R. Perez-Padilla, and R. Albalak, The health effects of indoor air pollution exposure in developing countries, World Health Organization Report WHO/SDE/OEH/02.05, 2002.

[45] PM CD at page 7-85.

by over three orders of magnitude.[46]

We now have considerable information on the composition of ambient PM and human exposures to PM of ambient origin. This information should be used together with the body of toxicological data on individual components to evaluate the kinds of effects and levels that may cause those effects expected from exposures to the components of ambient PM. Valberg[47] has addressed this issue and reported a major disconnect between the application of chemical-specific health effects data using standard EPA health risk assessment procedures and the application of epidemiological associations in the PM review. The findings from this analysis should be integrated into the current discussion of toxicology of PM mixtures in the ISA.

The ISAs and CDs for other criteria pollutants include extensive discussion of toxicological and human clinical studies of the respective compounds under review -- ozone, NO_2, SO_2 etc. Therefore, the PM ISA should also include a discussion of the effects reported in controlled studies of the PM components not just of PM mixtures.

A recent evaluation of the coherence between PM toxicology and epidemiology provides an example of the way the ISA should approach the task of evaluating coherence in the integrative synthesis. Schlesinger et al.[48] integrate the results from toxicology and epidemiology using data up through mid-2005. Schlesinger et al. point out that "the search for PM-specific effects has been difficult in the context of a complex mix of particulate and gaseous air pollutants, particularly since the latter may have biologically plausible associations that are also potentially related to PM." In discussing whether particle size is a modulator of PM toxicity, they conclude that current evidence provides only an equivocal answer to the question of a nonspecific role for PM in modulating toxicity. In contrast, in discussing whether chemical composition is a modulator of PM toxicity, they conclude that there is ample evidence suggesting that specific chemical properties of PM link with biological response. They indicate that toxicology indicates that it is not solely PM mass that relates to the biological effects but rather that specific chemistry is clearly a factor. They also caution that biological responses to PM in any of the size modes may not always be linked with major constituents but rather with toxicologically important minor components.

With regard to carbon-based material, which is a major component of ambient PM, the authors note that it is a complex mixture of literally hundreds of separate high

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[46] Threshold Limit Values for Chemical Substances in the Work Environment, published Annually by the American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio.
[47] P. Valberg, Inhalation Toxicology, **16**, Issue 11, Supplement 1, pages 19-29 (2004).
[48] R. Schlesinger, N. Kunzli, G. Hidy, T. Gotshi, and M. Jerrett, "The Health Relevance of Ambient Particulate Matter Characteristics: Coherence of Toxicological and Epidemiological Inferences," Inhalation Toxicology, **18**, pages 95-125 (2006).

molecular weight organic compounds along with elemental carbon particles as well as a wide range of biological components, including pollens, molds, spores, and biological toxins, such as bacteria, viruses, and bacterial fragments. Schlesinger et al. note that some biologic materials are known toxins and that other biological debris may initiate allergic reactions.

- The extent to which gaseous air pollutants can cause the biological responses attributed to PM in the ISA should be rigorously evaluated

Since the pattern of epidemiological associations is very similar for each of the various criteria pollutants, the extent to which the various gases cause similar biological responses in controlled studies to those evaluated for PM in the draft ISA should be rigorously evaluated. This effort should include an evaluation of both the kinds of responses and the doses that can cause those responses.

- The extent to which weather systems, weather variables, and/or changes in weather can cause the health effects or biological changes similar to those attributed to PM should be fully evaluated.

In reviewing the outcome of the 2004 CD, the draft ISA notes that epidemiologic studies have used a variety of approaches to control for weather effects to try to disentangle the true effect due to PM.[49] The text refers to studies "that appear to demonstrate increased PM-related mortality/morbidity risks beyond those attributed to weather influences alone." However, the text also acknowledges that a clear consensus was not reached as to what constitutes an appropriate or adequate model to control for possible weather contributions to the mortality/morbidity effects attributed to PM exposure. Thus, the extent to which inadequate control for weather may be biasing or confounding the PM and other air pollution health associations is not known. There is an extensive body of bio-meteorological information which should be evaluated to determine (1) how the nature and magnitude of weather effects compares to the nature and magnitude of air pollution effects, (2) whether current approaches to control for weather are consistent with the current understanding in biometeorology regarding the variables and timeframes involved, and (3) whether the understanding of the mechanisms of weather effects can inform the PM/health effects issue.

Both models and observations need to be considered in estimating Policy Relevant Background.

In the draft ISA, EPA has made a determination that all measurements are contaminated and that Policy Relevant Background (PRB) can only be determined by modeling. Given the present state-of-the-art of the $PM_{2.5}$ models, which show poor temporal and spatial correlation to observed $PM_{2.5}$, this would lead to

[49] PM ISA at pages 6-2 and 6-3.

inaccurate values. Additionally, the PRB would be underestimated because all U.S, and bordering Canadian and Mexican, anthropogenic sources would be excluded and assumed to be zero. The draft ISA should revert to the previous 2004 CD's combination of using both measurements and modeling to estimate PRB.

There is much greater uncertainty than the draft acknowledges.

- In previous reviews, EPA acknowledged that setting air quality standards for a complex mixture such as PM involves unusually large uncertainties. The extent of progress or not in reducing those uncertainties should be explicitly discussed.

When the first $PM_{2.5}$ standards were set in 1996/7, the EPA acknowledged that there were unusually large uncertainties associated with establishing standards for PM compared to individual gaseous pollutants. The Agency went on to list nine major areas of uncertainty.[50] The 2005 PM Staff Paper reiterated the fact that setting air quality standards for particulate matter involves unusually large uncertainties relative to setting standards for other single component pollutants.[51] The acknowledged uncertainties led the EPA and the scientific community to ask for and receive greatly expanded federal funding for PM air pollution research. Since 1997, there has been greatly expanded research on PM health effects guided by input from a blue-ribbon National Research Council Panel. Although that research has resulted in a large number of new studies over what is now more than a decade, there is still a great deal of uncertainty as to how to interpret all of the various results. For example, Samet,[52] in a 2005 paper summarizing his perspective on the activities of the National Research Committee on Research Priorities for Airborne Particulate Matter, notes that using large databases, relatively weak signals of the health effects of air pollution have been detected. He goes on to indicate that although these small increases in relative risk signal an adverse health effect, there is uncertainty as to the long-term implications of the findings and the overall health impact. He particularly notes the slow progress in identifying the hazardous components of particulate matter. He also notes that with increasingly sophisticated and sensitive indicators of biological response, including various biomarkers, effects of air pollution exposure on biological systems that are of

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[50] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information-OAQPS Staff Paper, EPA-452\R-96-013, July 1996 at pages VII-41 to VII-44.
[51] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information-OAQPS Staff Paper, EPA-452\R-05-005, June 2005 at page 5-71.
[52] J. Samet, "The Perspective of the National Research Council's Committee on Research Priorities for Airborne Particulate Matter," J. of Toxicology and Environmental Health, Part A, **68**, 1063-1067 (2005).

uncertain health relevance can be detected.

The draft ISA begins by noting that the focus of the assessment is on the science that is relevant to answering several questions. Among those questions are the following:

- To what extent have important uncertainties identified in the last review been reduced?

- Have new uncertainties emerged?

However, the draft ISA does not explicitly or adequately address those critically important questions. The final ISA must. For example, there has been little progress in reducing the uncertainty due to:

- Potential influence of measurement error and exposure error
- Potential confounding by co-pollutants
- The shape of concentration-response relationships
- Methodological uncertainties in epidemiologic analyses
- Identifying the most relevant exposure periods for causing PM effects
- Understanding the effects of coarse fraction particles

There has been some progress in:

- Identifying specific components linked with health effects
- Identifying potential mechanisms whereby PM or PM components may cause health effects

New uncertainties that have emerged include:

- A lack of explanation for the regional and seasonal patterns in PM association
- A lack of understanding why similar associations occur for each pollutant
- A lack of understanding of the role of stochastic variation versus heterogeneity of response in multi-city studies
- A lack of recognition of the importance of publication bias

What's new and relevant to understanding PM health effects is not carefully delineated.

In the specific comments, we identify a number of key findings in the literature that are especially relevant to the integrative synthesis. The most important of these are as follows:

Based on large U. S. multi-city studies:

- The magnitude of the associations of $PM_{2.5}$ with cardiovascular and respiratory hospital admissions and mortality are smaller than thought during the previous review.

- There is a spatial and temporal pattern in the associations with little or no association in significant portions of the country and during a significant portion of the year.

- A similar spatial pattern is found in acute morbidity and mortality as well as in chronic mortality studies.

The pattern in multi-city studies:

- Is not consistent with an effect of generic $PM_{2.5}$ mass.

- Provides strong evidence that single-city studies substantially bias the apparent associations upward due to publication bias.

- Provides strong evidence that stochastic variability is greater than heretofore thought.

In systematic studies of acute effects:

- Similar patterns are found for each criteria pollutant in single-pollutant models, making it difficult to attribute observed effects to individual pollutants.

Toxicology and human clinical studies:

- Report many biological responses but the findings are often mixed and inconsistent and of uncertain clinical relevance.

- Provide limited support for many potential biological mechanisms but have not yet demonstrated how generic particles (or accompanying gases) can cause the purported effects at relevant ambient doses.

- Demonstrate that the toxicity of PM components varies widely.

Specific Comments

Chapter 1 – Literature selection and Framework for causality

Literature. The process for literature selection is described on page 1-9. It includes on-going literature searches and other means. In addition, the text indicates that all relevant studies were considered. It does not appear that this process is rigorous or transparent. Relevant studies by Valberg 2004, Koop and Tole 2004, Anderson et al. 2005, and Schlesinger et al. 2006 which are provided in footnotes to these comments, are not included. The Pope and Dockery 2006 Air and Waste Management Association Critical Review is included, but discussions by Mauderly, Vedal, Hidy, Heuss, Wolff and others[53] that raise important issues relevant to the ISA are not. EPA should provide CASAC and the public a list of all the search terms that were used as well as a list of all articles that were identified but not included because of EPA's judgments that they were not relevant.

Framework. The introduction of a framework for assessing causality is an improvement over the approach in the 2004 CD. However, the framework contains two very similar categories – likely causal and suggestive of causality. The difference between these categories appears to involve making subtle distinctions between cases "in which chance and bias can be ruled out with reasonable confidence but potential issues remain" and cases in which "chance, bias and confounding cannot be ruled out". Given the many uncertainties in evaluating this body of evidence, choosing one category over the other becomes a very (if not entirely) subjective decision and competent evaluators may have widely varying opinions. Therefore, the two categories should be collapsed into one. This would be consistent with the CDC and IOM frameworks as noted in Footnote 1 on page 1-21. EPA notes that the 5-category approach is followed in EPA's carcinogen guidelines and allows a more nuanced approach. However, the carcinogen guidelines are set up to evaluate specific chemicals not widely varying mixtures of particles embedded in a variable mix of gases.

In addition, since PM or any particular size cut of PM is a diverse mixture of substances, restricting the causality determination to the mass of PM in a given size range is not appropriate. In the previous review, allowance was made for the well-established variability in toxicity of specific particles by using the term "PM (or one or more PM component)." This precedent should be followed in the ISA.

Finally, the application of the framework must be clearly explained in the ISA so the reader understands why a given category was chosen. Since the previous review did not use the new framework, the ISA should also refer back to the conclusions of

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[53] J. Chow, J. Watson, J. Mauderly, D. Costa, R. Wyzga, S. Vedal, G. Hidy, S. Altshuler, D. Marrack, J. Heuss, G. Wolff, C. Pope, and D. Dockery, "Critical Review Discussion: Health Effects of Fine Particulate Air Pollution: Lines that Connect," J. Air & Waste Manage. Assoc., **56**, 1368-1380 (2006).

the previous CD and explain the reasons for any substantive changes to the understanding of the science.

Chapter 2 - Overview

Based on the general and specific comments in this review, considerable changes are needed to the overview and summary chapter. While the ISA claims that there is consistent epidemiological evidence for cardiovascular and respiratory hospital admissions and emergency department (ED) visits as well as for acute mortality, in reality there is an implausibly wide range of associations in the individual cities included in multi-city studies. By only including the combined results from multi-city studies, the ISA masks the real stochastic variability in the data. In addition, the presence of publication bias inflates the perceived magnitude of PM health effects. Finally, the uncertainty due to model selection is ignored.

There is a pattern in the combined results from multi-city studies that indicates an acute PM_{10} and $PM_{2.5}$ health signal that is much weaker than thought in 2004 and limited to certain seasons and regions. A similar pattern is present in the chronic studies indicating a cardiovascular mortality association in the Eastern U. S. but no association in the Western U. S. Because of these patterns, the assumption of equal toxicity for PM components cannot be supported. Therefore, all the determinations of causality must be qualified as they were in the 2004 CD to refer to "PM (or one or more PM component) acting alone and/or in combination with gaseous pollutants" rather than to PM mass alone.

The discussion in the draft ISA does not provide an adequate integrative synthesis. Rather it focuses on single-pollutant model results and downplays or ignores issues and studies that do not fit with the 'PM causes health effects' paradigm. When the full weight of evidence (regarding model selection uncertainty, limitations of single-pollutant models, stochastic variation, multiple testing, publication bias, and the regional pattern of associations) is considered, the case for causality is weaker than expressed in the document.

While there has been progress in postulating various mechanisms by which PM might cause the health effects implied by the epidemiological associations, demonstrating that the associations are "real" or "causal" has been difficult and somewhat elusive. Biologic plausibility involves considerations of the kinds of effects an agent causes as well as the doses at which those effects occur. For ambient $PM_{2.5}$ or its constituents, the recent toxicologic studies establish the plausibility of the kinds of effects reported in the observational studies, but dose plausibility has not been demonstrated. Since there is a similar pattern of epidemiological associations for each of the criteria pollutants, the extent to which gaseous air pollutants can cause the biological responses attributed to PM in the ISA should be rigorously evaluated and discussed as part of the integrated synthesis.

Chapter 3 – Source to human exposure

There are a number of relevant findings in the material covered in this chapter that need to be highlighted because they will inform the integrative discussion in later chapters. First, the composition of the major size PM fractions needs to be documented better in the ISA. There are U. S maps with color-coded ranges of concentrations of major components in the body of Chapter 3 and similar maps of metal concentrations in Annex A. However, there is little analysis to develop information on the regional and seasonal variation in components which can be compared to the regional and seasonal variation in acute PM associations documented in Chapter 6.

In addition, important information on the composition of the carbon fraction is missing. Carbonaceous material is a major component of both fine and coarse PM. A substantial portion of that material is not fossil carbon. There are both natural and anthropogenic sources of modern carbon, including woodburning, meat cooking, primary biological material, and secondary carbon formation from biogenic emissions. The Schichtel et al. 2008 paper discussed in Chapter 9 and references therein document a large contribution of contemporary (or modern) carbon to urban, suburban, and rural total fine particulate carbon concentrations based on radiocarbon measurements. Half the fine particulate carbon in urban areas and a substantially larger portion in rural areas comes from non-fossil sources. A recent paper by Edgerton et al. 2009[54] also reported that biological material (fungal spores, pollen, and vegetative detritus) accounted for 60-70 % of the carbonaceous mass in coarse PM samples at two urban and two rural sites in the Southeastern U. S. Total carbon represented 30 % of the coarse mass at these sites. Thus, primary biological particles and other sources of modern carbon need to be considered along with fossil fuel emissions and crustal materials as potential causal factors in PM health effects.

Second, the section on source contributions draws a misleading conclusion. The ISA states that a small number of broadly-defined source categories are need to explain the majority of the observed mass. In the example given in Figure 3-57, a broad category of mobile sources is used with a very wide range of resulting fractional contributions. Based on inventories, however, there are many different sources of carbon from fossil fuel use, with varying contributions coming from on-road vehicles, off-road vehicles, the use of gasoline, diesel, and natural gas in stationary engines and small area sources, as well as planes, trains, and ships. Lumping the contributions from all these various sources together and calling it a mobile source contribution is misleading. Studies with specific organic marker species confirm that a much more complex mix of sources contribute to fossil carbon.

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[54] E. Edgerton, G. Casuccio, R. Saylor, T. Lersch, B. Hartsell, J. Jansen, and D. Hansen, "Measurements of OC and EC in Coarse Particulate in the Southeastern United States," J. Air & Waste Manage. Assoc., **59**, 78-90 (2009).

Third, since the vast bulk of exposure occurs indoors as shown in Figure 3-70, changes in composition and exposure indoors for the various PM components needs to be fully considered in the integrative chapters. A major new finding documented in the ISA is that nitrate volatilizes as it penetrates indoors with the nitric acid being lost at surfaces. Therefore, even in situations with substantial nitrate concentrations in the ambient air, the average human exposure to nitrate will be reduced substantially. Differential penetration of nitrate and other PM species should be considered as a possible explanation for regional and seasonal differences in PM toxicity.

Fourth, the discussion of measurement error should be broadened to discuss possible reasons for the extremely wide stochastic variation observed in acute epidemiological associations. The idea expressed in many papers that measurement error will bias towards the null is not congruent with the extremely wide stochastic variation observed in systematic studies. This paradox should be noted and discussed.

Fifth, the measurement error associated with the use of ambient concentrations at central monitors as a surrogate for total personal exposures in the chronic studies needs to be discussed in greater detail. A limitation in interpreting the cohort studies is that, as both the PM CD and draft ISA acknowledge,[55] the appropriate exposure metric for chronic studies is total personal exposure over time, not the level of ambient PM at a central monitor. The major chronic PM studies use long-term average ambient PM concentrations as the exposure metric and do not consider the nonambient component of personal exposure. However, nonambient exposures contribute significantly to the cohort's total exposure and there is substantial evidence that exposure to nonambient PM is often considerably higher than the exposure to PM from ambient sources. For example, in five studies of personal exposure analyzed by Dominici et al. (2000), the average nonambient contribution to exposure ranged from 29.9 to 85.1 $\mu g/m^3$ for PM10, while the average ambient contribution to personal exposure ranged from 7.7 to 50.7 $\mu g/m^3$. For the five studies, the ratio of nonambient to ambient PM10 contributions ranged from 1.16 to 4.63. Since the participants in those studies primarily were non-smokers, the non-ambient PM exposure is an underestimate of that for the population that includes both smokers and non-smokers.

In an extensive study of exposures of inner-city children with asthma in seven communities in the U. S., Wallace et al.[56] report that ambient $PM_{2.5}$ is responsible for only about 25 % of the mean indoor exposures. In addition to indoor sources of PM, the 2004 CD documents the presence of a "personal cloud" of PM that adds to personal exposure. The personal cloud consists primarily of biological particles and

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[55] PM CD at page 5-119 and draft PM ISA at page 3-138.

[56] L. Wallace, et al., "Particle concentrations in inner-city homes of children with asthma: the effect of smoking, cooking, and outdoor pollution," Environmental Health Perspectives, **111**, 1265-1272, 2003.

soil dust and arises from personal movement and activities as we go about our daily lives. Measurements of the personal cloud report exposures between 6 and 27 $\mu g/m^3$ of $PM_{2.5}$ and even higher exposures of PM_{10}.

As documented in the PM CD[57], the exposure to PM of non-ambient origin (i.e., indoor sources) in the U. S. can be substantially higher than that from ambient sources. As noted in the section on air exchange rates, indoor PM sources predominate when air exchange rates are 1.0 or less. As documented in Figure 5-6, measured air exchange rates from a survey of U. S. homes average below 1.0 in 14 of the 16 combinations of region and season. The average air exchange rate was about 0.5, meaning that indoor sources predominate in most locations and seasons. Thus, if ambient PM is causing a significant mortality and morbidity risk, then the PM from indoor sources would be expected to be causing a substantially larger mortality and morbidity risk.

The CD also indicated that it is not easy to differentiate the role of historic exposure from that of recent exposure in the chronic studies and that the inability to account for exposures prior to enrollment of the cohort hampers interpretation of these studies.[58] Thus, the use of central monitor data from a particular time interval (and ignoring the nonambient exposures) leaves significant potential for exposure misclassification in the chronic studies. This should be discussed in both Chapter 3 and Chapter 7 of the ISA. Currently, the draft ISA acknowledges[59] that if exposure errors are different in the different communities, the differences in long-term ambient concentrations among communities may not represent the differences in long-term average exposures and that this could add error and bias the slope up or down.

Sixth, the Agency's new assessment of background using models rather than a combination of observations and models underestimates the policy background due to uncontrollable sources. Because "Policy Relevant Background" (PRB) will be used in the Risk and Exposure Assessment (REA) document to evaluate the benefits of alternative levels of NAAQS, it is important that its value is determined as accurately as possible. However, as now defined by EPA, it handicaps state and local air pollution agencies that border a country with significant PM sources. EPA assumes international agreements with Canada and Mexico can eliminate the transport of anthropogenic $PM_{2.5}$ emissions in those countries from crossing the U.S. boarder. International agreements can certainly be used to reduce the transport, but only virtual elimination of all sources near the borders would insure zero transport. Consequently as defined, PRB will result in an overestimation of the benefits of any given NAAQS.

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[57] J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.
[58] PM CD at page 5-118.
[59] PM ISA at page 3-138.

In the previous PM Criteria Documents, the annual mean natural background $PM_{2.5}$ concentrations was estimated to be 1 – 4 μg/m^3 in the Western U.S. and 2 – 5 μg/m^3 in the Eastern U.S. For $PM_{10-2.5}$ it was estimated to be 1 – 7 μg/m^3 in the West and 1 – 9 μg/m^3 in the East. These estimates were based on analyses performed on data sets from remotely-located sites. In the present ISA, EPA has concluded that all measurements are contaminated and that PRB can only be determined by modeling. Theoretically, models have the potential to provide a more precise estimate, but given the present state-of-the-art of the $PM_{2.5}$ models, that is not yet the case.

In the current ISA, EPA concludes that the universal U.S. PRB level for $PM_{2.5}$ is less than 1 μg/m^3. This is based on the application of a Chemical Transport Model (CTM) which couples the global-scale circulation model, GEOS-Chem, with a regional-scale air quality model, CMAQ, to simulate one year of air quality data over the U.S. Two runs were performed. In the first, all anthropogenic and biogenic sources of $PM_{2.5}$ and $PM_{2.5}$ precursors were included, while in the second, all U.S., Canadian, and Mexican anthropogenic sources were set to zero. $PM_{2.5}$ concentrations modeled in this second run were used to define the PRB. The ISA contains no discussions or estimates of the PRBs for PM_{10} and $PM_{10-2.5}$. This is a major shortcoming of the ISA.

The model performance data given by EPA in the draft ISA does not demonstrate good model performance either temporally or spatially. Figure 3-64 (A&B) demonstrates poor temporal correlations for predicted and observed $PM_{2.5}$ mass at two eastern US sites, while Figures 3-65 and 3-66 show even poorer correlations for all the western US sites. Unfortunately, the r^2 are not given.

Another measure for performance is demonstrated in Figures 3-67 and 3-68 where frequency distributions of predicted and observed concentrations are plotted. For the eastern sites, the predicted and observed curves track fairly well, but because of the poor temporal correlation observed in Figure 3-64 (A&B), this is misleading. On the other hand, at the western sites shown in Figure 3-6 the modeled concentrations have a significant negative bias. This likely means the PRB levels would also be biased low.

Such poor performance suggests that model performance for individual $PM_{2.5}$ species is also poor. Previous CMAQ performance evaluations (Appel et al., 2008, Eder and Yu, 2006, Tesche et al., 2006, Mebust et al., 2003) indicate that this is indeed the case. With the exception of sulfates, performance is poor. Appel et al., 2008 and Mebust et al., 2003 point out that particulate organic carbon (OC) is systematically underpredicted, especially in the spring and summer, while Eder and Yu, 2006, give an r^2 of 0.12 between daily predictions and IMPROVE measurements. Since OC is a significant component of the natural aerosol, its contribution to the PRB is likely to be underestimated as well.

For nitrate, Eder and Yu show it is underpredicted at the rural IMPROVE sites (r^2=0.27), but over predicted at the urban STN sites (r^2=0.14). Other r^2 given by Eder and Yu for the rural IMPROVE sites are elemental carbon (EC), 0.22, sulfate,

0.72, and $PM_{2.5}$, 0.49. Since Schichtel et al. 2008 and references therein show that the vast bulk of total carbon in remote areas (82 to 100 %) is modern carbon and the model's performance for carbon and other species is so poor, EPA should not rely solely on modeling to estimate PRB.

In the 2004 CD a combination of both measurements and modeling was used to estimate PRB. Both should also be considered in the ISA. The influence of long range transport of Asian and African dust, wildfires in the U. S and elsewhere, sea spray, crustal weathering, local dust storms, biogenic emissions of VOC and NOx, and release and re-suspension of primary biological materials all contribute to PRB and should be evaluated for different size fractions, time frames, and regions as was done in the 2004 CD.

The definition of PRB is problematic both because it assumes zero anthropogenic influence from bordering countries but also because zero anthropogenic influence in the U. S. is not realistic. There are sources of anthropogenic emissions in the U. S. from other than fossil fuel use. Even if all the energy used in the U. S. were from non-polluting sources, there would still be emissions related to agriculture, cooking, goods movement, and other human activities. Therefore, PRB should be re-defined to recognize that there are anthropogenic emissions from sources and activities for which there are no known or anticipated controls possible within the timeframe of the State Implementation Plans that would be required under a revised standard.

Chapter 4 – Dosimetry

Dosimetry is important because it is the dose deposited in the body that is the proximal cause of any PM health effects, not the exposure as measured at a central monitor or any other location. This is why the ISA indicates that "knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition therein is necessary for understanding and interpreting the health effects associated with exposure to particles. " The draft chapter summarizes a substantial body of relevant information noting that the basic understanding of the mechanisms of deposition and clearance has not changed. However, the chapter is missing a very important piece – the actual doses to target tissues in biologically relevant metrics such as mass per unit surface area.

The 2004 CD included such information at the request of CASAC. The ISA also should include information on deposited doses of PM and PM components in biologically relevant metrics. In addition, the information from dosimetry should be used to address the question of the fate of the various components after being deposited in the body. Currently, little of the information from dosimetry is used in the integrative sections of the document. There is now substantial information on the composition of ambient PM components that can be used, together with information on deposition, retention, clearance and translocation to address questions such as: Is there reason to continue the focus on fine particles? Are there differences between the fate of different kinds of particles in the body that are

relevant to understanding the mechanism(s) of possible action causing health effects? For the various components, is there sufficient material deposited during inhalation to cause the purported effects?

Relative to the first question, Snipes et al.[60] showed that particle deposition per unit surface area decreases by orders of magnitude from the extrathoracic to the tracheobronchial and to the alveolar regions. In addition, coarse and fine particles are deposited in both the tracheobronchial and alveolar regions. Thus, Snipes et al. concluded that based on dosimetry, the focus should be on PM_{10} not just $PM_{2.5}$.

Relative to the other questions as regards fine particles, Vostal,[61] based on the Snipes et al. study, calculated the mass of fine particles deposited in the alveolar region for both total fine PM and for individual PM components. Vostal showed that actual doses of particles per square centimeter of surface area or per gram of lung tissue were extremely small, the order of fractions of a nanogram of particles (10^{-9} gram) per square centimeter, or tens of nanograms per gram of tissue per day for an average ambient concentration of 17.55 $\mu g/m^3$. For PM components, the amounts deposited were correspondingly smaller. These calculations assumed uniform deposition, and it is known that there is heterogeneity in the deposition pattern. In addition, there are differences in deposition between healthy people and those with chronic respiratory disease. However, such differences would increase local tissue levels of fine particles by modest multiplicative factors, not orders of magnitude.

The challenge of PM research is to show how such extremely small deposits could cause the acute morbidity and mortality implied by the statistical associations. Integrating the dosimetry information with composition information and toxicological information may reveal candidate components and hypotheses.

The dosimetry chapter does not explicitly identify any important new information. One question that was unclear in the 2004 CD was whether ultrafine particles could be rapidly cleared from the lungs into the systemic circulation where they could be transported to extrapulmonary regions. The reasoning was that such transport could provide a mechanism whereby particles could affect cardiovascular function as reported in the epidemiologic studies. As documented in the ISA, it is now well-established, however, that transport of ultrafine carbon particles is much slower than that of soluble particles.

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[60] M. Snipes, A. James, and A. Jarabek, "The 1994 ICRP66 Human Respiratory Tract Dosimetry Model as a Tool for Predicting Lung Burdens From Exposures to Environmental Aerosols," *Appl. Occup. Environ. Hyg.,* **12**, 547-554 (1997)

[61] J. Vostal, "Statistical Associations between Ambient Particulate Matter and Daily Morbidity and Mortality: Can we Identify Mechanisms Responsible for these Health Effects?", in Proceedings of the Air & Waste Management Association's 93rd Annual Conference & Exhibition, Salt Lake City, Utah, June 18-22, 2000, Publ. VIP 97, Air & Waste Management Association, Pittsburgh, PA, 2000

Chapter 5 – Possible modes of action

Since $PM_{2.5}$ standards were established in 1997, there has been a massive effort to establish how low exposures to PM could cause the effects implied by epidemiological associations. In the 2004 CD, a separate toxicology chapter summarized the state of scientific understanding at that time. That information was also considered in the integrative synthesis. The draft ISA does not contain separate chapters on epidemiology, toxicology, and synthesis. Rather it combines the findings from toxicology and epidemiology in chapters that attempt to summarize and then synthesize the information from the various disciplines that contribute to the overall conclusions. While either organizational approach can be effective, there are weaknesses in the draft ISA that need to be addressed before it can fulfill the requirements of the Clean Air Act.

The 2004 CD indicated that two of the main questions addressed by toxicological research were 1) what types of pathophysiological effects are exerted by ambient PM or constituent substances and what are the potential mechanisms underlying them, and 2) what PM characteristics in terms of size and chemical composition cause or contribute to health effects.[62] The extensive toxicological literature since 2004 continues to emphasize those questions.

However, in the draft ISA, especially Chapter 5, the emphasis on PM components in toxicology is essentially ignored. Many potential mechanisms are discussed in terms of generic PM in Chapter 5. In fact, the ISA specifically notes that "the characterization of evidence here is for PM in general, since most of the potential pathways or modes of action described below do not appear to be specific to a particular size class of PM."[63] That assertion is not sufficient. The role of chemical composition should not be ignored or downplayed in Chapter 5 or in the succeeding discussion in the integrative chapters.

Another issue well-known in toxicology that is not sufficiently addressed in Chapter 5 or elsewhere in the draft ISA is that the responses found in high concentration experiments may not occur at lower ambient particle exposures. The 2004 CD specifically cautioned that much care should be taken when attempting to interpret and extrapolate effects seen in studies conducted at relatively high concentration to provide insight into the biological plausibility and mechanisms of action underlying effects seen in humans under "real world" exposure conditions.[64] This caution should be considered fully in both Chapter 5 and the integrative chapters. Currently the discussion of pathways is decoupled from information on the doses involved.

The Chapter discusses potential pathways in a general sense and refers to Figures 5-1 to 5-5 which provide schematic summaries of potential mechanistic pathways.

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[62] PM CD at page 7-1.
[63] Ibid.
[64] PM CD at page 7-3.

Each of these figures contains many postulated processes and links. The chapter should be revised to provide a clear delineation between the processes and links that are established (as well as the doses used) and those that are speculative. In addition, the possible modes of action should be discussed in relation to the major and minor components of PM. There is some acknowledgement of the differential toxicity of PM components in the chapter, but a systematic evaluation is needed. In addition, the extent to which various gases or weather variables have been found to cause similar biological changes should be discussed.

The chapter concludes with a list of effects reported in new inhalation studies. However, the list gives a misleading view of the degree to which these findings are consistent, or to which they implicated generic PM or specific PM components, or to which they confirm the proposed mechanisms, or to which they are relevant to ambient exposures. If there is a desire to include the list in this Chapter, it should be transformed into a matrix which rates each finding with regard to the factors noted above along with a reference to the pages in the following chapters that provide the additional detail.

Chapter 6 – Acute effects

The draft ISA organizes the discussion of acute effects into sections on acute cardiovascular morbidity and acute respiratory morbidity with separate subsections in each major section for different health-related endpoints. There is also a separate major section discussing acute mortality. Within each major section and health endpoint-subsection, the draft ISA summarizes the data from epidemiology, toxicology, and human clinical studies. For the most part, these individual subsections contain a narrative summarizing relevant studies with varying degrees of overall summarization. There are also separate sections providing the ISA's conclusions regarding causality for each of the three major categories (cardiovascular morbidity, respiratory morbidity, and mortality) with separate determinations for the three PM size ranges evaluated in the ISA. In the following we provide comments on these three major sections.

Cardiovascular and systemic effects

While there is now a very large data base of studies for almost all of the cardiovascular and systemic health endpoints compared to the situation in 2004, there are many inconsistencies in the data which render its use in drawing positive conclusions regarding causality problematic. In addition, the way the draft ISA presents and discusses the results of many studies can be misleading. Due to publication bias, almost all studies report some positive finding. However, the ability to measure many possible biomarkers or other endpoints in a given study means that there can be many positive outcomes in the literature when the overall impact is that of no effect. Moreover, the ISA reports findings from studies with up to three orders of magnitude higher PM concentrations than ambient. There is little

or no discussion of the relevance of high dose findings. Also, the ISA focuses on PM associations in epidemiological studies where other possible confounding pollutants and weather effects also are present. Finally, there are many cases where studies have evaluated the contributions of PM components and reported effects of or associations with specific components, not PM mass. As a result of these shortcomings, the draft ISA does not provide an integrative synthesis that allows one to properly weigh the strength of evidence.

For many endpoints, the draft ISA notes mixed and inconsistent results. These include HR and HRV, arrhythmias, markers of systemic inflammation, BP, cardiac contractility, and markers of blood coagulation. Where the ISA claims consistency of results -- in vasculature effects, systemic oxidative stress, and hospital admissions and ED visits – the data is not as consistent as claimed in the ISA. The most important example is for hospital admissions and ED visits. The ISA claims that recent large studies conducted in the U.S. and elsewhere have observed consistent associations between $PM_{2.5}$ and cardiovascular hospitalizations but that findings from single city studies have demonstrated regional heterogeneity in effect estimates. The ISA also notes that the observed increases in cardiovascular hospitalizations are largely due to admissions for ischemic heart disease and congestive heart failure.

Figures 6-1, 6-2, and 6-3 are used to demonstrate the claimed consistency. However, as noted in our general comments, the range in individual-city results in multi-city time series studies of hospital admissions and mortality is extremely wide, with individual-city associations ranging from strongly negative to strongly positive. This wide range is obscured by the practice of plotting only selected combined results from the multi-city studies along with selected results from individual-city publications in these figures. If the full range of individual-city results were shown in Figures 6-1 to 6-3 it would be apparent that the draft ISA could appropriately not claim consistency in these data. What is described as heterogeneity is a mix of heterogeneity and a significant amount of stochastic variation. Even though some multi-city studies do not report the first-stage individual-city results, EPA can obtain the results from the authors for inclusion in the next draft ISA. This was done with NMMAPS data for the ozone CD and should be done for the PM ISA.

In addition to showing the full range of individual-city results, the draft ISA should show the complete combined results from multi-city studies. By showing only selected results from the multi-city studies, the ISA portrays a false sense of the consistency and magnitude of the associations. For example, the Bell et al. 2008 study reported a matrix of 25 combined cardiovascular risk estimates at lag 0, including a breakdown by region and season. Figure 6-1, however, includes only four, the strongest associations. If all 25 were shown, five of which are actually negative, the reader's judgment concerning both the consistency and magnitude of the association would change markedly. Furthermore, Bell et al. also report combined national results for lag 1 and lag 2. These should also be plotted on Figure

6-1 since associations at a variety of lags are plotted for other studies. If the complete results from Bell et al. were displayed on Figure 6-1, the regional and seasonal nature of the positive associations in this statistically powerful multi-city analysis would become apparent. In addition, since the multi-city combined association is only a fraction of the associations in the bulk of the single city studies, the strong impact of publication bias would also be apparent.

Similarly, when the complete results of the Dominici et al. 2006 study of 204 counties are considered in Figures 6-2 and 6-3, the lack of any cardiovascular signal in the West except for congestive heart failure stands out as a very important finding. Dominici et al. 2006[65] evaluated fine PM hospital admissions associations for 204 U. S. urban counties with a population greater than 200,000 using 1999-2002 Medicare hospital admission data. The results are presented for a two-stage Bayesian analysis for various types of admissions and by region. Combined associations of the order of a 1 % increase in various cardiovascular or respiratory outcomes per 10μg/m^3 increase in $PM_{2.5}$ are reported. While this is a comprehensive and important analysis, there are several issues that render its interpretation as an effect of generic fine PM questionable.

First, there is a clear difference in the combined associations among the 7 regions and particularly between the East and West. The combined association is positive for cardiovascular outcomes in the East, but negative in the West except for heart failure that is positive in both areas. This is not consistent with an effect of generic $PM_{2.5}$ on cardiovascular hospital admissions and, indeed, the authors point out the need to shift the focus of research to identifying those characteristics of particles that determine their toxicity.

Second, the authors present the results for a range of lags and then focus on the lag that provides the strongest combined association for each endpoint. This may bias the results. Until we have more data on the actual mechanisms of PM toxicity, we will not know if their choice of lags is consistent with the toxic action of PM or its components. Third, the authors acknowledge that the complex statistical models used may not eliminate all bias.

Although this is an important study, it is deficient in two major ways. First, the authors do not show any of the results of the first stage analysis. Based on other multi-city analyses by the same authors or other multi-city studies where the first stage results are presented, one would expect large variations in individual county associations in each region. Thus, even though there may be an overall combined positive association in a given region with a given category of hospital admissions, there are undoubtedly counties with both strong positive and strong negative associations in that region. This is an important finding that the authors do not disclose. By showing all their first stage results and comparing the range of results

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[65] Dominici et al. Fine Particulate Pollution and Hospital Admissions for Cardiovascular and Respiratory Disease, J. American Medical Association, **295**, pages 1127-1134, 2006.

with that in the general literature, the extent of publication bias for hospital admissions could be estimated. The authors do note that their combined result is several-fold lower than other associations they cite from the literature.

The second major deficiency has to do with consideration of other air pollutants. The authors only considered one other pollutant, ozone, and considered it only as a potential effect modifier. However, there is an ample literature of small positive associations of hospital admissions in single pollutant models with a range of air pollutants, particularly for heart failure, the admission for which they report the most consistent association.

Even though the most consistent combined cardiovascular $PM_{2.5}$ association is with congestive heart failure in single-pollutant models, it is not clear that this is a causal relation. There are a large number of studies reporting positive associations of congestive heart failure admissions with other pollutants. One of the weaknesses of the draft ISA is the reliance on single-pollutant models and the limited discussion of the extent of evidence for similar findings with other pollutants and/or weather parameters.

For example, Ebi et al. 2004[66] evaluated associations between weather parameters and cardiovascular hospital admissions in three California regions. They document a strong seasonality in heart failure admissions and report that temperature changes increased hospitalizations by 6%–11% for acute myocardial infarction and congestive heart failure. In discussing the pathophysiological changes underlying such associations they note that seasonal and temperature variations have been described for blood pressure, blood viscosity, vasoconstriction, serum lipids, fibrinogen levels, and other blood components. Since changes in some of these biomarkers and physiological parameters are associated with morbidity and mortality from cardiovascular disease, the ISA should evaluate the bio-meteorology literature to determine the magnitude of physiological changes associated with weather and weather changes to compare with those associated with PM and other pollutants. A thorough search of the biometeorology literature may reveal alternative weather variables and factors to implement in air pollution regression models. For example, Kolb et al. 2007[67] report that a number of changes in weather are associated with changes in daily mortality in an elderly population diagnosed with congestive heart failure in Montreal.

Summary of cardiovascular effects. In summary, despite the many new studies of cardiovascular endpoints, the estimate of the magnitude of acute cardiovascular

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[66] K. Ebi, K. Exuzides, E. Lau, M. Kelsh, and A. Barnston, "Weather changes associated with hospitalizations for cardiovascular diseases and stroke in California, 1983–1998," Int. J. Biometeor., **49**, 48-58 (2004).

[67] S. Kolb, K. Radon, M-F Valois, L. Hugey, and M. Goldberg, "The short-term influence of weather on daily mortality in congestive heart failure," Arch. Environ. Occup. Health, **62**, 169-176 (2007).

effects, such as hospital admissions and ED visits, associated with $PM_{2.5}$ is smaller than thought in 2004-2006. There is also less consistency than thought in 2004, and based on large multi-city studies, there are spatial and temporal patterns in combined analyses that implicate PM components rather than generic PM mass.

Respiratory effects

As is the case with regard to cardiovascular effects, the draft ISA overstates the consistency and magnitude of respiratory effects. The ISA acknowledges that there is no evidence of respiratory symptoms associated with PM in healthy individuals, but claims consistent positive effects in asthmatic children and adults. However, the pattern in Figures 6-5 and 6-7 does not support such a conclusion. Given the existence of publication bias, the pattern in Figure 6-5 represents a mix of some positive results from single-city studies of asthmatic children together with no effect in the multi-city study by Schildcrout et al. 2006. Even with the presence of publication bias, there is little evidence of consistent associations in Figure 6-7 for asthmatic adults. At best, the data can be described as mixed and inconsistent for respiratory symptoms and medication use in asthmatics.

With regard to respiratory ED visits and hospital admissions, the ISA says "an association between PM and respiratory hospitalizations and emergency department visits was consistently positive across studies" and that "(R)ecent studies have provided further support to this relationship, with larger effect estimates observed among children and older adults." For the newer studies, EPA relies heavily on the multi-city studies because they, in general, have more statistical power and on single city studies conducted in the U.S. or Canada. For PM_{10} the results of these studies are shown in Figure 6-9 of the ISA.

EPA is correct in saying the associations that are plotted are consistently positive. Of the 30 results presented in Figure 6-9, 25 are positive and only 5 are negative. However, what EPA fails to -say is that only 6 of 30 results presented are statistically significant and positive. That means in 24 of the 30 cases presented, the conclusion of "no effect" cannot be dismissed.

Furthermore, the inclusion of only 30 results in Figure 6-9 is misleading, because the largest multi-city study, Barnett et al., 2005 (seven cities in Australia and New Zealand), reported many more non-statistically significant or negative results that were left out of Figure 6-9. For example, the first data point (2.4 % increase with a CI of 0 to 3.8 %) listed for this study in Figure 6-9 is for children 1-year of age or less from 4 of the 7 cities studied. Inclusion of any or all of the remaining 3 cities or any combination of these 3 cities with any of the 4 included, produce non-statistically significant results. Consequently, there are more combinations of cities that produce non-significant results than the one 4-city combination that does. This statement also holds true for the other results from Barnett et al. that are displayed in Figure 6-9. Furthermore, Barnett et al. also contains results for $PM_{2.5}$, light-scattering, SO_2, and NO_2. For each one of those variables, Barnett et al. find some

combination of at least 3 cities that produce a statistically significant model result. In summary, Barnett et al. examined hundreds of possible models and found a few that have a positive and statistically significant relationship between each pollutant measure and admissions. One cannot conclude from such a matrix of results that any causal relationship with PM alone has been established.

The ED and hospitalization results for $PM_{2.5}$ are presented in Figure 6-10. Of the 20 results presented for $PM_{2.5}$, only 5 are statistically significant and positive, while 2 are negative. The results from the Barnett et al. for $PM_{2.5}$ are also featured beginning on the second line. Everything stated above about the results of this paper apply here. In addition, other mistakes have been made. The value for the first point appears to be about 6.0 % with a CI of about 2 to 10. This is by far the largest effect shown in this figure. Unfortunately there is no $PM_{2.5}$ association that is anywhere near this magnitude in Barnett et al. However, there is one model for 24-hour NO_2 that has a coefficient of 5.8 and a CI of 1.7 to 10.1. The other 2 data points in Figure 6-10 attributed to Barnett et al. also appear to be incorrect.

Another multi-city study displayed in Figure 6-10 is that of Bell et al. (2008) which examined $PM_{2.5}$ and emergency admissions in 202 U.S. counties. The first three data points attributed to Bell et al. appear to match three points in Table 1 of their paper. The last two data points attributed to Bell et al., which are two of the statistically significant points, seem to match the increase in hospital admission rates shown in Table 2 of their paper for winter admissions in all of the U.S. (4th point) and in the Northeastern U.S. (5th point). In Table 2, Bell et al. give a matrix of results for respiratory admissions by season for four geographic sectors plus the U.S. as a whole. It contains a 5 x 5 matrix of results. EPA identified the only two statistically significant positive results in this matrix and added them to Figure 6-10. Of the other 23 results in Table 2, only 8 are positive and 15 are negative. If the full results from Bell et al. were included in Figure 6-10, then there would be 5 significant positive associations, 26 non-significant positive associations, and 17 negative associations for $PM_{2.5}$.

Even though the text acknowledges that the MCAPS investigators (Bell et al.) observed largely null findings for $PM_{2.5}$ and respiratory hospitalizations (COPD, lower and upper respiratory infections) for the U.S. as a whole, the EPA staff chose to display only selected results from the study. Thus, the way EPA staff selects studies and associations to include in the figures presenting epidemiological results creates a false appearance of consistency. If all the individual-city results in the multi-city studies and the full complement of combined results from multi-city studies were included, the conclusions regarding consistency would change dramatically.

Another example of largely null findings is contained in Figure 6-10 which illustrates the ED and hospitalization results for $PM_{10-2.5}$. Of the 15 results presented only 5 are positive and significant while 2 are negative. The largest study

here is Peng et al. (2008) which examined the relationship in 108 counties. None of their results for three lags (0, 1 & 2) were significant after adjusting for $PM_{2.5}$.

The results for asthma ED and hospitalizations are presented in Figure 6-11 for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$. Overall there are 55 results, 7 of which are positive and significant, 15 are negative, while the remainder, 48, were not statistically significant. For PM_{10}, 21 out of 22 results were not statistically significant. For $PM_{2.5}$, 18 out of 21 results were not statistically significant while for $PM_{10-2.5}$, 9 out of 12 were not significant. Thus, the weight of evidence does not support PM as a cause of asthma ED visits or hospitalizations.

Results for COPD ED visits and hospitalizations are presented in Figure 6-12 for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$. Of the 34 results presented in the Figure, 10 out of 34 find a statistically significant positive relationship, which is a much greater percentage than previous figures. Most notably, the largest multi-city study (Dominici et al, 2006) which examined 204 counties in the U.S. shows a very small but significant and positive relationship for both lag 0 and 1. Although they do not present individual city results, they do break down the results by 7 geographical regions. Importantly, only one of the geographical regions (the southeast) displayed a statistically significant result, while 2 showed a negative result. These results, therefore, in conjunction with the fact that no co-pollutants were considered, are insufficient evidence to conclude that any fraction of the PM is causing COPD admissions. Two other multi-city studies (Zanobetti and Schwartz 2003, 14 cities; Medina-Ramon et al. 2006, 36 cities) report the individual city estimates. These should be included in Figure 6-12.

Figure 6-13 presents results for pneumonia and respiratory infections. The Medina-Ramon individual-city results should also be added to this figure. In addition, the range of individual-city results from Dominici et al. 2006 should be obtained from the investigators and added to the figure.

Summary regarding respiratory effects. The draft ISA stresses the multi-city studies because of their greater statistical power and the fact they avoid publication bias. The ISA acknowledges that the pattern of results in multi-city studies is of many null findings with positive results that vary by region and season. Figures 6-9 to 6-12 include the range of risk estimates from the 2004 PM CD. The risks reported in the multi-city studies are consistently at the low end of the range from the 2004 CD. Therefore, despite the many new studies of respiratory endpoints, the estimate of the magnitude of acute respiratory effects associated with $PM_{2.5}$, such as symptoms and medication use by asthmatics and respiratory hospital admissions and ED visits, is substantially smaller than thought in 2004. There is also less consistency than thought in 2004, and based on large multi-city studies, there are spatial and temporal patterns in the combined analyses that implicate PM components rather than generic PM mass.

Short-Term Mortality

Since the 2004 Criteria Document was completed, there have been a number of additional single-city and multi-city studies published for both PM_{10} and $PM_{2.5}$ that show similar associations between PM and mortality to those cited in the 2004 CD. However, there is now strong evidence of regional and seasonal patterns in the data. The draft ISA focuses primarily on the multi-city studies and concludes that the evidence for the effect of short-term exposure to both PM_{10} and $PM_{2.5}$ on mortality is sufficient to conclude that a causal relationship is likely to exist at ambient concentrations. This is a stronger statement than in the 2004 CD and is not supported by the findings reported in the ISA. The conclusion in the 2004 CD that "coarse (PM10) and fine (PM2.5), or one or more PM2.5 components, acting alone and/or in combination with gaseous copollutants, are associated with total (non-accidental) mortality and various cause-specific mortality outcomes" is and remains as strong a statement as can be justified by the data.

The regional and seasonal patterns in PM_{10} mortality associations from the Peng et al. 2005 study [68] are clearly demonstrated in Figure 6-14. This PM signal includes both fine and coarse PM effects. Peng et al. used updated mortality data from 1987-2000 in 100 cities with analyses by season that showed the combined association at lag 1 was greatest during the summer. Summer was the only season for which the combined effect was statistically significant. An analysis by geographical regions showed a strong seasonal pattern in the Northeast with a peak in the summer and little seasonal variation in the southern regions of the country. The authors acknowledge that there are several possible explanations for their results. One obvious hypothesis is that the most toxic particles have a spring/summer maximum and are more prevalent in the Northeast. Another mentioned by the authors is that there is a seasonally varying bias from an, as yet, unidentified source.

In further analyses of this data, shown in Table 6-14, Dominici et al. 2007b reported a major regional difference with a small positive (but statistically significant) combined association in the 62 eastern cities and a smaller (and non-significant) combined mortality association in the 38 western cities. The lack of a statistically significant association in the West held for both all-cause mortality and the two sub-categories, cardiorespiratory and other. The lack of a significant acute mortality signal in the west in this large multi-city database is similar to the lack of acute cardiovascular morbidity signal in the west reported in the Dominici et al. 2006 multi-city study.

The draft ISA also reports on several multi-city studies using $PM_{2.5}$ data. The Franklin et al. 2007 and Ostro et al. 2006 studies are highlighted. Although the ISA does not show the individual-city results in the various multi-city studies, there is ample evidence of an implausibly wide range in individual city associations in

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[44] Peng, R. D.; Dominici, F.; Pastor-Barriuso, R.; Zeger, S. L.; Samet, J. M.; Seasonal analyses of air pollution and mortality in 100 U. S. Cities, *Am. J. Epidemiol.*, **2005**, 161, 585-594.

numerous multi-city studies. For example, the Franklin et al. 2007 study of acute mortality in 27 U. S. cities reports individual city associations ranging from – 5 % to + 10 % per 10 μg/m^3 increase in $PM_{2.5}$. Franklin et al. discuss the cities with strong positive associations, but never acknowledge the strong and statistically significant negative associations in cities like Houston and Dallas. They do note that there is stochastic variability in their results. Of the 27 communities, 9 had negative risks while 18 were positive. Of the positive, 9 were statistically significant while 2 of the negatives were. The fact that the pooled result is positive and significant and that there are more positive effects than negative effects observed is not surprising because as Lumley and Sheppard (2003) and Smith et al point out, the model was selected to maximize the effect estimate. The fundamental question is whether the combined effect estimate is meaningful when the individual city results vary in a biologically implausible way, and that question has not been addressed.

Franklin et al. further stratify their results by lag, mortality cause, age, gender, geographic region, attainment/nonattainment status, and air conditioning prevalence and present several tables of results of which only about one-third are statistically significant. One notable finding is that they report a significant positive association in the East but no association in the West as shown in Figure 6-21 of the draft ISA.

A multi-city study was conducted in nine heavily populated California counties by Ostro et al. 2006[69] The combined association highlighted in the study, 0.6 % per 10 μg/m^3, is less than half the combined association reported in the original Schwartz et al. six-city study that EPA relied upon when setting the first $PM_{2.5}$ NAAQS in the 1996/97 review. However, the complete results Ostro et al. report suggest that the combined fine PM association is smaller and less robust than reported in their conclusions. Ostro et al. report analyses using natural splines as well as penalized splines to smooth for temporal trends, each with varying degrees of freedom (4, 8 and 12) to smooth for time. Only the model with 4 dfs produced a statistically significant positive result. No justification as to why this result should be more appropriate than the other two is offered by the authors. As the degrees of freedom increased, the association became smaller and less significant. None of the all-cause mortality associations were statistically significant using natural splines. The authors also report that most of the fine PM mortality associations were attenuated in multi-pollutant models with CO or NO_2, but no results are shown. Thus, in total, the combined fine PM association is weaker, less significant, and less robust than the authors infer when all the analyses that were carried out are considered. The draft ISA specifically acknowledges that it is unclear whether gaseous pollutants confound the $PM_{2.5}$ mortality associations. [70]

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[45] Ostro, B.; Broadwin, R.; Green, S.; Feng, W.-Y.; Lipsett, M.; Fine Particulate Air Pollution and Mortality in Nine California Counties: Results from CALFINE; *Environ. Health Perspect.* **2006**, *114,* 29-33.

[70] PM ISA at page 6-222.

The Ostro study is particularly important because the average $PM_{2.5}$ levels in the California counties they studied are among the highest in the U. S. ranging from 14 to 29 μg/m^3. There appears to be little relation between the nine individual effect estimates and the fine PM levels. The strongest and weakest associations occur in counties with nearly identical fine PM concentrations and the county with the highest concentrations, Riverside, has no evidence of a significant association. Interestingly, Los Angeles and Riverside had slightly negative $PM_{2.5}$ associations in the Franklin et al. 2007 study while Sacramento and San Diego had positive associations. In summary, the overall pattern of results in acute studies in California is not consistent.

The draft ISA states that all-cause and cardiovascular effects are similar and consistently positive. The cardiovascular results are summarized in Figure 6-23 for $PM_{2.5}$, which shows 11 new results published since the 2004 CD. Although 10 of 11 of the results are positive, only 1 is statistically significant. Such weak evidence does not support causality.

The draft ISA also states that for $PM_{2.5}$ the respiratory-related mortality were consistently larger than all-cause or cardiovascular based primarily on Franklin et al. 2007 and Ostro et al. 2006. These results are also displayed in Figure 6-23. Our concerns with Franklin et al. are described above. Ostro et al. showed the highest percent increase (2.2%, CI 0.6 to 3.9%) in respiratory mortality for his pooled results. However, he also presented the individual city results for the 9 cities for lag 2 and lag 1+2, and of those 18 results, only 5 were positive and statistically significant and 4 were negative. In addition, as noted above, only the model with 4 dfs produced a statistically significant positive result. Because of the issues with model selection in Ostro et al. noted above, the claim to a stronger respiratory signal cannot be supported.

Summary for acute mortality

Despite many new studies, the evidence for acute mortality associated with PM_{10} or $PM_{2.5}$ is not any stronger than it was in 2004. The combined associations in new multi-city analyses document strong seasonal and regional differences that indicate little or no association in the West and even in some seasons in the East. This pattern is not consistent with making a causal determination for PM in general. In addition, the effects are so small that they may be dominated by residual bias, and confounding by gases cannot be ruled out. Finally, as noted in our general comments, similar associations are reported for all the major pollutants raising the question as to the overall utility of these time series studies.

Chapter 7 – Chronic effects

Chapter 7 is organized in a similar fashion to Chapter 6, evaluating causality with respect to long-term PM exposures for various generalized endpoint categories. We

provide comments on those effects for which the draft concludes the evidence is strongest.

Cardiovascular and systemic morbidity

The draft ISA draws conclusions that the evidence for PM_{10} is suggestive but the evidence for $PM_{2.5}$ is likely causal. The rationale for the choice of the suggestive category for PM_{10} is that studies of pre-clinical markers of cardiovascular disease report largely null findings and there are inconsistencies in the results of epidemiological studies evaluating other endpoints. But for $PM_{2.5}$ the same can be said as well. Therefore, a conclusion to assign the suggestive category for $PM_{2.5}$ is also warranted. In the case of $PM_{2.5}$ the studies of pre-clinical markers contain many null findings. The epidemiological results evaluating other endpoints are also mixed and subject to the criticism that model selection and publication bias overstate the true association.

The strongest evidence noted in the draft ISA for a chronic effect of $PM_{2.5}$ on cardiovascular health is from the Sun et al. 2005 toxicological study using CAPS (concentrated air particles) that suggests a mechanism by which PM could contribute to cardiovascular disease. However, the acceleration of atherosclerosis in this highly susceptible mouse model is not specific to PM and is not consistent at sites across the country. There are now similar studies of the susceptible mouse model at various sites across the country as well as to engine exhaust samples. The pattern of results in these studies indicates that both high concentrations of gases and particles can cause the accelerated atherosclerosis response and that the mass of ambient $PM_{2.5}$ is not the causal agent.

The draft ISA acknowledges that, in the gasoline and diesel exhaust experiments, the response is still seen when the particles are removed. This is shown in Lund et al. 2007 and Campen et al. 2005, 2006 and acknowledged in the ISA.

The draft ISA refers to the Araujo et al. 2008 study as implicating ultrafine particles in the acceleration of atherosclerosis in a study of concentrated particles near a freeway in Los Angeles. However, the ISA notes that for the fine particles (at 440 $\mu g/m^3$) the response did not differ from the controls. In addition, the initial results of the HEI's NPACT study, as reported by Lippmann at the recent HEI annual conference,[71] showed dramatically different responses from CAPS exposures in Tuxedo, NY (where the Sun et al. 2005 work was conducted) and CAPS exposures in Manhattan. Lippmann reported that there were significant changes in atherosclerosis after 3 months in Tuxedo but not in Manhattan. These discrepant findings in different locations indicate that the cause of the adverse response is not the mass of $PM_{2.5}$. While the susceptible mouse model provides evidence that air pollution at high concentrations can affect cardiovascular health, it is still not clear

[71] Lippmann, M et al. "Characteristics of PM associated with health effects," poster at the Health Effects Institute Annual Conference, April 27-29, 2008, Philadelphia, PA.

which components of the gases and/or particles are causing these effects and at what doses.

For other possible markers of cardiovascular risk, such as systemic inflammation or coagulation responses, the draft ISA acknowledges that there were not robust findings in rats following 6-month exposures to diesel exhaust, hardwood smoke, or gasoline exhaust. The draft ISA indicates that the limited effects that were observed could possibly be due to the varying gas concentrations in the exposure mixtures.

In summary, given the many null findings in the pre-clinical markers of cardiovascular disease and the inability to implicate generic $PM_{2.5}$ as the cause of the response in the toxicological studies, the conclusion regarding $PM_{2.5}$ being likely causal cannot be supported.

Respiratory morbidity

Although the draft ISA concludes that there is a likely causal relation between PM_{10} and $PM_{2.5}$ exposure and respiratory morbidity, the evidence comes primarily from epidemiology and high dose toxicology. Decrements in lung function growth have been reported in a number of studies, but the ISA cautions that strong correlation between PM and other pollutants complicates the identification of PM as an independent causal factor. This caution is also expressed for many of the positive respiratory findings for other endpoints. As EPA reviews each pollutant in turn, the focus has been on identifying all the positive associations and outcomes with that pollutant. This can lead to double- or triple-counting of health effects. In our general comments, we noted that this approach resulted in similar claims for acute respiratory morbidity in four criteria pollutants that have been evaluated recently.

In the case of lung function growth, the NOx ISA uses the associations in the Southern California Children's Health Study as support for an NO_2 effect. In the PM ISA, the associations with PM metrics in the same cohort are stressed to lend support to the likely casual determination for PM. To avoid such double- or triple-counting of health effects, EPA needs to evaluate the likelihood of PM or PM components being the likely causal agent in the chronic respiratory outcomes evaluated in the ISA. A true integrative synthesis is needed looking across air pollutants and at PM effects in other exposure situations to determine whether the chronic respiratory effects claimed at ambient concentrations in the draft ISA can be supported.

Chronic mortality

The draft ISA indicates that there were both positive and negative cohort studies of chronic mortality risk at the time of the 2004 PM CD but that the greatest weight was placed on the two positive studies, the American Cancer Society (ACS) and Six-City studies. The ISA goes on to indicate that 1) new epidemiologic evidence reports a consistent association between long-term exposure to $PM_{2.5}$ and increased risk of

mortality, and 2) there is little evidence for the long-term effects of PM_{10} and $PM_{10-2.5}$ on mortality. However, a thorough review of the available studies indicates that there are major spatial differences across the country that argue against assuming that $PM_{2.5}$ mass (rather than one or more PM components) is consistently associated with chronic mortality.

The HEI-sponsored re-analysis of the Six-City and ACS studies showed that 1) the increased risk was cardiovascular not respiratory, 2) one gaseous pollutant, SO_2, had a strong association with mortality, 3) when SO_2 was included in the model, the PM all-cause mortality association was materially reduced and became non-significant, 4) the increased mortality was experienced in the portion of the cohort that had a high school education or less, and 5) there was a significant spatial heterogeneity in the association, with no effect seen in western U. S. cities. In particular, during the review of the federal PM standards in 2001, EPA staff pointed out the significant spatial variation in the data with actually a negative estimate of excess $PM_{2.5}$ mortality risk in the West.[72]

A recent analysis by Zeger et al.[73] confirms the large spatial difference in effect in a cohort of 13 million Medicare enrollees. Although Zeger et al. reported statistically significant results for the eastern and central United States that are in general agreement with previous publications, Zeger et al. found no significant effect of $PM_{2.5}$ on mortality in the western United States. One caution in interpreting this study is that effect estimates for the Medicare cohort may be biased upward due to lack of adjustment for individual level risk factors. This suggests that effects reported in the eastern and central U S. may be biased upward.

The ACS study was updated by Pope et al. 2002[74] following the cohort for a total of 16 years. The PM and SO_2 associations persisted as did the education effect, but the authors did not evaluate the east/west difference or the impact of including both PM and SO_2 in the model. This is a serious omission. The Laden et al. (2006)[75] study extended the follow-up in the Six Cities cohort by eight years to 1998. In the

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[47] Grant, L.; EPA Staff Presentation to CASAC, July 23, 2001; Key Revisions and Scientific Issues for Second External Review Draft of Air Quality Criteria for Particulate Matter; Slide 46 indicates an excess risk from 10 $\mu g/m^3$ $PM_{2.5}$ in the ACS cohort of +29 % in the Industrial Midwest, +25 % in the Southeast, +14 % in the Northeast, and –9 % in the West (West is a combination of cities in the Northwest, Southwest, Upper Midwest, and Southern California. NMMAPS geographic regions).

[73] Zeger, S.L.; Dominici, F.; McDermott, A.; Samet, J.M. Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005). Environ. Health Perspect. (2008), online August.

[49] Pope, C. A.; Burnett, R.; Thun, M.; Calle, E.; Krewski, D.; Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution," *J. American Medical Assoc.*, **2002**, *287*, 1132-1141.

[50] Laden, F.; Schwartz, J.; Speizer, F.; Dockery, D.; Reduction in Fine Particulate Air Pollution and Mortality: Extended Follow-Up of the Harvard Six-Cities Study; *Am. J. Respir. Crit. Care Med.,* **2006**, *173,*667-672.

original Six City Study the mortality rates were plotted against various pollution measures, and $PM_{2.5}$ gave the best fit. However, in the update, only $PM_{2.5}$ was evaluated and the fit in the second period is very poor. The poor fit in the second period is masked in their Figure 2b by plotting the results for both time periods in the same figure. Because of the poor fit with $PM_{2.5}$ in the update, other pollutants should be evaluated in this data set.

In both of these updates, the authors neglected to carry out the same analyses that had been conducted in the original study. This is a serious oversight and is an example of the subtle way that confirmation bias creeps into the literature.

There are two California-specific cohort studies that found little or no PM mortality signal, in agreement with the overall finding of no chronic mortality signal in the West. The first is the Enstom (2005)[76] study of a cohort of 36,000 individuals in 11 California counties. The second is the AHSMOG cohort of 6,338 non-smoking Seventh Day Adventists.[77] No significant positive associations of PM with mortality were found in AHSMOG with 15 years of follow-up (the excess cardiopulmonary risk for 20 $\mu g/m^3$ PM_{10} was 0.6 % with 95th percentile confidence limits of -8%, 10%). Although the Chen et al. (2005)[78] update reports a positive association with a subset of cardiovascular deaths in females but not males with 22 years of follow-up, they include a comment that in extended follow-up of cardiopulmonary mortality in the total AHSMOG cohort through 1998 using the same models as previously, "we continue to find slightly stronger association in males than in females (unpublished data)." The fact that Chen et al. do not report these results suggests that their update found no overall cardiopulmonary effect, so this study does not support the ACS and Six City findings. The omission of results calculated in a way that can be directly compared with the earlier study and with other studies in the literature is a serious oversight. EPA should contact the authors and request that the data be provided in a manner that can be compared to the other studies in the literature.

Another California cohort, reported in Jerrett et al. 2005, is discussed in the draft ISA. Jerrett et al. extracted data on almost 23,000 subjects in the Los Angeles area from the ACS cohort for the period 1982–2000, with more than 5,000 deaths. Pollution exposures were interpolated from 23 fine PM and 42 ozone fixed-site monitors. After controlling for 44 individual covariates, they reported a significantly increased risk of mortality associated with fine PM for all-cause, ischemic heart disease, and lung cancer mortality. The only joint pollutant analyses

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[51] Enstrom, J.E.; Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973-2002; *Inhal. Toxicol.,* **2005**, *17,* 803-816.
[52] Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knusten, S.F.; Beeson, W. L.; Yang, J. S,; Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Non-Smokers, *Am. J. Resp. Crit. Care Med.*, **1999**, *59*, 373-382.
[53] Chen, L.H.; Knutsen, S.F.; Shavlik, D.; Beeson, W.L.; Petersen, F,; Ghamsary, M.; Abbey, D.; The Association between Fatal Coronary Heart Disease and Ambient Particulate Air pollution: Are Females at Greater Risk?; *Environ. Health Perspect.,* **2005**, *113,* 1723-1729.

were with ozone, and the authors conclude that the PM results were robust to adjustments for ozone and expressway exposure. The authors also state that the magnitude of fine PM effects are about three times as large as those found in earlier studies, the clear implication being that the better exposure estimates obtained by interpolation of the pollution data "suggest the chronic health effects associated with within-city gradients in exposure to $PM_{2.5}$ may be even larger than previously reported across metropolitan areas."

Based on two studies discussed below, we now know that this is not necessarily the case. In addition, when contextual covariates related to socioeconomic status were included in the analyses, the associations of fine PM with total, ischemic heart disease, and lung cancer mortality were substantially attenuated and became either statistically insignificant or only borderline significant. For example, the all-cause mortality association was reduced from 1.17 (1.05-1.30) to 1.11 (0.99-1.25) per 10 $\mu g/m^3$ increase in $PM_{2.5}$. Moreover, the major cause of death that dominated the excess risk and that was the only major cause statistically significantly elevated in the analyses with fine PM and individual covariates was ischemic heart disease. Thus, the mortality signal in Jerrett et al. is with a subset of cardiovascular diseases and that signal is only borderline significant in the more complete analyses.

Jerrett et al. suggest that they found higher effects because of the refined exposure estimates based on sophisticated modeling. However, there are two other examples of refined spatial analyses that do not support this conclusion. An extended follow-up and spatial analysis of the ACS cohort being carried out for the Health Effects Institute in New York found that, unlike the Los Angeles results, "mortality for all-cause, cardiopulmonary, and lung cancer deaths was not elevated in the New York spatial analysis."[79] The new HEI study reports, in agreement with earlier analyses, that the $PM_{2.5}$ signal in the ACS cohort is an association with cardiovascular and not respiratory deaths; in fact, elevated $PM_{2.5}$ appeared to be somewhat protective against respiratory deaths.

The other refined spatial analysis comes from the Netherlands. Hoek et al. 2002 reported positive associations in a pilot study of 5,000 subjects from a larger cohort of 120,000. However, Beelen et al. 2008 assessed air pollution on an even finer spatial scale for the entire cohort than Jerrett et al. had, and they report lower relative risks than the pilot study reported and, if anything, a respiratory signal as compared to the cardiovascular signal in the ACS cohort. In fact, none of the $PM_{2.5}$ associations in the full cohort were statistically significant although the strongest association was with respiratory mortality.

There is another study that evaluated within-city risk. The Women's Health Initiative Study reported higher cardiovascular risk estimates than other studies.

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[79] D. Krewski,et al., Health Effects Institute Annual Conference 2008, Program and Abstracts, abstract at page 33.

However, scientists from Exponent, Inc.[80] have pointed out that the within-city risk (the risk associated with differences in fine PM levels within cities) for a 10 μg/m^3 increase in $PM_{2.5}$ is greater than the risk associated with smoking 40 cigarettes a day, findings that defy plausibility, casting doubt on the results of the study.

In summary, there are clearly major spatial differences in the full body of cohort studies of chronic mortality. The high probability that the association of risk of cardiovascular death in the central and eastern U. S. with $PM_{2.5}$ is unique must be considered in the ISA. Additional issues concerning the interpretation of chronic exposure studies were noted in our general comments.

The overall pattern in acute observational studies with a major difference between associations in the East and West is similar to the pattern identified in these comments for the chronic mortality studies lending addition credence to the conclusion that, to the extent there are positive $PM_{2.5}$ associations, they are caused by components of PM not PM mass.

Chapter 8 – Public health impacts

As discussed in our general comments, even though the draft ISA acknowledges that "all of the studies identified in the current PM ISA that have examined the PM-mortality relationship, in regards to geographic location within the U.S., have concluded that the effects are greater in the East compared to the West", the explanation offered to explain this pattern is that "individuals residing in the Eastern U.S. are more vulnerable to PM-related health effects."[81] This interpretation is not scientifically justified and should be removed. The more rationale explanation, and the one offered in the studies themselves, is that there is a spatial and temporal pattern in the toxic components of ambient PM.

In addition, in the high dose toxicological and human clinical studies reviewed in the 2004 PM CD and in the draft ISA there are many examples that show that biological response varies dramatically depending on the chemical composition of the PM used. The 2004 CD summarized this material noting "overall, the new studies suggest that some particles are more toxic than others." The CASAC specifically commented on this issue indicating "the chapter must make it clear that there is a large data base that indicates that PM is markedly variable in its toxic potency." [82] With the inclusion of the studies reviewed in the ISA, the data base is even larger. Thus, the assumption that all PM is equally toxic cannot be supported based on either the epidemiologic or toxicologic findings. This needs to be explained in the ISA.

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[80] J. Turim, S. Moogavkar, and E. Anderson, Comments on EPA's Integrated Science Assessment for Sulfur Oxides-Health Criteria, Exponent, Inc. Report, November 30, 2007.
[81] PM ISA at page 8-19.
[82] CASAC March 1, 2004 letter to Administrator Leavitt.

Chapter 8 also is misleading in the discussion of concentration-response relationships. As noted in our general comments, Chapter 8 downplays the concerns and limitations noted in the previous review regarding concentration-response relationships when it indicates "these studies have used various statistical methods, but overall have consistently found that a no-threshold log-linear model adequately portrays the PM-mortality C-R relationship in multi-city analyses."

In contrast, the 2004 CD, in response to a request in CASAC's October 4, 2004 letter, concluded "in summary, the available evidence does not either support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies."[83] In discussing the risk assessment, CASAC reiterated its concern in its June 6, 2005 letter noting "the available epidemiological database on daily mortality and morbidity does not establish either the presence or absence of threshold concentrations for adverse health effects." For the risk assessment, CASAC indicated "the Panel favored the primary use of an assumed threshold of 10 $\mu g/m^3$" along with sensitivity analyses using other threshold assumptions. The draft ISA does not include any discussion or analysis that would change this conclusion. Accordingly, the same conclusion should be included in the ISA.

[83] PM CD at page 9-44.