

9-30-09 Preliminary Draft Comments on the PM Health Risk Assessment from Clean Air Scientific Advisory Committee (CASAC) Particulate Matter Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Compendium of Preliminary Pre-Meeting Comments
CASAC Particulate Matter Review Panel on
Risk Assessment to Support the Review of the
PM Primary National Ambient Air Quality Standards (September 2009)

<i>Avol Comments (Mr. Ed Avol)</i>	2
<i>Brain Comments (Dr. Joe Brain)</i>	3
<i>Lead Discussant Response to Charge Question 3</i>	3
<i>Cascio Comments (Dr. Wayne Cascio)</i>	5
<i>Frey Comments (Dr. Chris Frey)</i>	6
<i>Lead Discussant Response to Charge Question 8</i>	6
<i>Henderson Comments (Dr. Rogene Henderson)</i>	15
<i>Lead Discussant Response to Charge Question 9</i>	15
<i>Hopke Comments (Dr. Phil Hopke)</i>	20
<i>Lippmann Comments (Dr. Mort Lippmann)</i>	21
<i>Phalen Comments (Dr. Robert Phalen)</i>	23
<i>Lead Discussant Response to Charge Question 2</i>	23
<i>Poirot Comments (Mr. Rich Poirot)</i>	25
<i>Russell Comments (Dr. Ted Russell)</i>	27
<i>Speizer Comments (Dr. Frank Speizer)</i>	30
<i>Lead Discussant Response to Charge Question 6</i>	31
<i>Suh Comments (Dr. Helen Suh)</i>	32
<i>Vedal Comments (Dr. Sverre Vedal)</i>	36
<i>Lead Discussant Response to Charge Question 7</i>	37

9-30-09 Preliminary Draft Comments on the PM Health Risk Assessment from Clean Air Scientific Advisory Committee (CASAC) Particulate Matter Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Avol Comments (Mr. Ed Avol)

I found the Risk Assessment document to be thoughtfully done, in great detail, and with many useful linkages to the previous review, CASAC comments, and agency decisions such that a demonstrably logical evolution to the current document was clear to the reader.

My specific charge was to consider the rationale and presentation for selection of the 15 urban study areas for subsequent risk assessment use. Here too, I thought the presentation was well-crafted, well-supported, and carefully linked to available data and design concerns.

The document understandably focuses on risk in the urban study areas (where major population concentrations are), but I was left wondering about rural regional PM effects. Do the considerations presented in the document and prioritized in the approaches utilized provide any substantive insights for rural population, rural exposures, and rural health effects? If any comments about these issues were presented in the main body of the document, I apologize for missing them, but they were not readily apparent. I raise this issue because recent studies have repeatedly emphasized the importance of near-road and proximity exposures, but there are reports of both local and regional effects on respiratory health (and possibly other health outcomes with which I am less familiar). In thinking about protecting the health of the public, shouldn't some comment regarding this segment of the public be included, or at least acknowledged?

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Brain Comments (Dr. Joe Brain)

REA: (6) Selection of Urban Study Areas

Table 3-4 and the accompanying map, Figure 3-4, shows a reasonable distribution of the 15 urban study areas selected. They span the country, and they encompass varying mixes of pollutant sources and different meteorological conditions. In part, the rationale for the selection of these urban study areas reflects practical considerations, such as the availability of data and the relationship between these locations and the availability of appropriate epidemiologic studies. I also like the criterion of selecting locations that provide heterogeneity in regard to risk factor and demographics (for example, SES status, use of air conditioners, ethnicity, and PM sources).

Some concerns persist, such as the location of monitoring stations and their relationship to the most common human exposures. For example, this section and the current strategy does not deal adequately with the issues of heterogeneity of exposure. How do we include proximity to roadways or special sources like cement plants. *In toto*, however, section 3.3.2 seems well written and reasonable.

Lead Discussant Response to Charge Question 3

Based on consideration of evidence presented in the second draft ISA, we have identified four combinations of 24-hour and annual alternative standard levels for analysis in the risk assessment. Please comment on the extent to which the rationale provided in section 2.5 appropriately supports these combinations of alternative standard levels for this assessment.

At the center of a discussion of relevant combinations of alternative standard levels is the range of ambient concentrations of PM_{2.5} associated with adverse health outcomes in multiple large multi-city epidemiological studies. The advantages of utilizing such studies are clearly conveyed, and their use appears to be justified.

There is an assumption early in section 2.5 that bears additional thought. The risk assessment focuses exclusively on fine particles, and thus is based entirely on PM_{2.5}. Perhaps this makes sense, since the most extensive epidemiologic data is health outcome in relation to PM_{2.5}. Do we have any reservations regarding ignoring coarse or ultrafine particles? A standard based on these other size fractions may be impractical, but can we indicate more clearly their presence and potential contribution.

Staff does a reasonable job of developing the rationale for the long term standard: 13 $\mu\text{g}/\text{m}^3$ vs. 12 $\mu\text{g}/\text{m}^3$. But they seem so close to each other. Do they represent significant alternatives? Can

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our relatively crude sampling strategies effectively distinguish 13 vs. 12? Either one is below the current annual standard. We are not sure there is any practical difference between the two. A more interesting alternative would be 11 $\mu\text{g}/\text{m}^3$. Then we would have the current standard of 15 $\mu\text{g}/\text{m}^3$, which could be compared to 13 $\mu\text{g}/\text{m}^3$ and 11 $\mu\text{g}/\text{m}^3$. The 24-hour standard exhibits a greater range: 35 vs. 30 vs. 25 $\mu\text{g}/\text{m}^3$.

Given the current alternatives, why not eliminate the third bullet from the bottom, "Alternative $\text{PM}_{2.5}$ standards: annual 12 $\mu\text{g}/\text{m}^3$; 24-hours 35 $\mu\text{g}/\text{m}^3$. Then we would be left with three alternative $\text{PM}_{2.5}$ standards, which would progressively be more conservative: 13 and 35, 13 and 30, 12 and 25 $\mu\text{g}/\text{m}^3$. Currently, alternative 1 vs. alternative 2 offers too little choice, and the rationale for choosing between them seems unclear.

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Cascio Comments (Dr. Wayne Cascio)

REA-1
WE Cascio
24 September 2009

Charge Question 1 (Lead discussant: Crapo)

Is the Panel generally supportive of a quantitative risk assessment with both short- and long-term exposure to PM_{2.5} only.

Abundant epidemiological, clinical, and animal toxicology studies implicate a causal relationship between exposure to PM_{2.5} and adverse cardiovascular and respiratory outcomes, and mortality. Yet at the present time, and as summarized in the ISA there is inconclusive evidence of causal relationships between PM_{10-2.5}, ultrafine, or PM components and short-term and long-term cardiovascular and respiratory health endpoints. As such it is appropriate to focus the quantitative risk assessment solely on PM_{2.5} where there is convincing evidence of causality with cardiovascular effects and likely causal relationship with respiratory effects and mortality. Likewise the long-term impact of PM_{2.5} exposure is well supported by the data and appears to be causal for cardiovascular effects, and likely causal for respiratory effects and mortality.

Charge Question 2 (Lead discussant: Phalen)

Comment on the approach taken and on the clarity of the rationale for selecting health effect categories for inclusion in the quantitative risk assessment.

For the purpose of the risk assessment an important issue is one of the certainty of the effect. Uncertainty in the level of association will be compounded by any risk assessment model and will yield predictions that will lack confidence. The present approach minimizes the uncertainty of the risk assessment by limiting the model development to only outcomes that are judged to highly and consistently associated to PM_{2.5} exposure, thereby judged causal or likely causal.

Charge Question 3 (Lead discussant: Brain)

Comment on the extent to which the rationale provided in section 2.5 appropriately supports the four combinations of 24-hour and annual alternative standard levels for analysis in the risk assessment.

At the center of the determination of relevant combinations of alternative standard levels is the range of ambient concentrations of PM_{2.5} associated with adverse health outcomes and several large multi-city epidemiological studies. The advantages of utilizing such studies are clearly conveyed, and their use appears to be justified.

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Frey Comments (Dr. Chris Frey)

Lead Discussant Response to Charge Question 8

I was asked to prepare a summary of responses to Charge Question 8(a) through 8(d). In addition to preparing my own individual pre-meeting comments, I have received input from the following CASAC PM Review Panel members: Hopke, Lippmann, and Suh. This document is a synthesis of the comments from the four of us.

There are two overall comments. First, the decision to forego a risk assessment for PM_{10-2.5} should be discussed further, as a limited risk assessment for PM_{10-2.5} would provide information helpful to the standard setting process in a manner consistent with the document's stated goals. Second, the decision to forego a population exposure assessment is inadequately supported and should be revisited.

Charge Question 8(a): *Addressing uncertainty and variability --*

The treatment of uncertainty and variability in the analysis is based on the multi-tiered approach presented in a recent WHO document (WHO, 2008). Specifically, as outlined in section 3.5, we have included qualitative analysis of both variability and uncertainty (WHO Tier 1), as well as single-factor and multi-factor sensitivity analyses aimed at identifying which potential sources of uncertainty have the greatest impact on the core risk estimates (WHO Tier 2). In addition, the sensitivity analyses have been designed to provide a reasonable set of alternate risk estimates to supplement the core risk estimates and inform consideration of uncertainty associated with the core analysis. To what extent does the Panel support the overall approach for addressing uncertainty and variability? To what extent does the Panel agree that the overall approach is appropriate and consistent with the goals of the risk assessment as outlined in chapter 1? Does the Panel have any recommendations for improving the characterization of variability and/or uncertainty?

Response:

The overall approach is reasonable, appropriate, consistent with assessment goals, and supported by the Panel.

As pointed out in Table 3-13, perhaps the largest source of uncertainty in the assessment is exposure misclassification, which leads to bias and imprecision in risk estimates and is associated with a high degree of knowledge-based uncertainty. An analysis of inter-individual variability in exposure for sample cases will illustrate the exposure misclassification problem that is inherent in epidemiological studies, and further bolster the point that epidemiological studies inherently underestimate the relationship between exposure and effect. Hence, exposure modeling should be included in the REA. A probabilistic Tier 3 approach should be used for the exposure assessment.

Charge Question 8(b): *The qualitative discussion of key sources of variability, and the degree to which the analysis design captures those sources of variability, are presented in section 3.5.2.*

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Please provide comments on the approach used. Specifically, do the analyses sufficiently address the issue of variability? Are there key sources of variability that have not been addressed within the qualitative analysis but which could have an important impact on modeling population-level risk associated with PM_{2.5} exposure?

Response:

Section 3.5.2 is generally very good. However, the use of the term “Key” in this section raises the question as to how the various potential sources of variability were compared and prioritized, and implies that there may be other sources of variability that are not “key.” This should be clarified and explained.

Six key sources of variability were identified and addressed qualitatively. These should either be modified or augmented to include differences in PM co-pollutant concentrations in the context of source variability, and to include land use, source locations, housing stock, and socio-economic factors in the context of demographics.

EPA should take credit for the sources of variability that are quantified in the assessment, such as spatial and temporal variability in ambient PM_{2.5} concentration. Thus, a list should be given of sources of variability that are quantified.

Although some of the factors discussed here are not quantified in terms of attempting to apportion exposure or risk by composition, demographics, activity patterns, and so on, EPA should provide insight into the variability of these factors and their implications for variability in the risk estimates. This examination could be analogous to the analyses done to examine the generalizability of the 15 cities to the rest of the US.

Charge Question 8(c): *Table 3-13 provides a qualitative characterization of uncertainties including the potential direction, magnitude, and degree of confidence associated with our understanding of the sources of uncertainty. To what extent does the Panel support the characterizations of the key sources of uncertainties identified and the relative rankings of the importance of those sources of uncertainty? Are there additional uncertainties that should be considered?*

Response: Table 3-13 is excellent. The panel supports the material contained in this table.

A source of uncertainty that was not included was the C-R function itself, which was developed from single studies. Source J should also take into account differences in C-R functional form associated with studies that addressed long-term or short-term effects for single or multi-city studies even if they were not the basis for the final set of C-R functions used in the REA. Definitions, even if only vague, should be given for the categories “low”, “medium”, and “high,” as a footnote in to the table with some discussion in the text.

EPA should comment on the extent to which there are dependencies among pairwise combinations of sources of uncertainty, and whether these dependencies would tend to offset or

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to increase the overall range and direction of uncertainty in the assessment results. For example, the statistical fit of the C-R functions, and the shape of the functions, are inter-related.

There should be a summary that describes implications of these uncertainties, including their relative importance, for interpreting results of the REA.

In the Results Section (Section 5.3), the results should be interpreted with respect to key sources of uncertainty – i.e. how robust are the results, and what are the likely biases. In particular, given exposure misclassification, it is likely that the estimates of Table 5-1 are biased low. This is an important point to convey consistently.

Charge Question 8(d): *The results of the sensitivity analyses have been used to gain insights into which sources of uncertainty significantly impact the core risk estimates and to provide a reasonable set of alternate risk estimates to supplement the core analysis. We are mindful that these estimates do not represent a true uncertainty distribution. With regard to the single- and multi-factor sensitivity analyses, to what extent is the Panel supportive of the approach used to conduct and characterize the results of the sensitivity analyses? Please provide comments on the extent to which the presentation of the results of the sensitivity analyses are clearly and reasonably described? Does the Panel have any recommendations for how the results of the sensitivity analyses could be used more effectively or appropriately in characterizing uncertainty associated with the core risk estimates?.*

Response:

The evaluation of alternative model structure is critically important, because model structure can potentially be a larger source of uncertainty than the range of values for an input to a given model. The range of uncertainty associated with confidence intervals for a given C-R function should be compared to the range of estimates obtained by comparing alternative functional forms. This would provide insight as to whether model structure, or random error for a given model, is a more important source of uncertainty.

EPA should indicate the direction of the percent changes in risk. In addition to the percent difference, the actual difference in risk should be reported to provide further context. This section should conclude with a brief but explicit summary of the decision to use the sensitivity results only from the long-term exposure mortality analysis, which is touched upon in Section 4.5.2.

A key question for the sensitivity analysis is whether it is a useful range estimate – i.e. do the lower and upper bounds from the results (as shown later in Figure 4-22) represent plausible lower and upper bounds on the true but unknown answer? For some readers and decision makers, a key question is whether the lower bound of the sensitivity analysis results (of 1.3% of total incidence of all cause mortality attributable to PM_{2.5}) is significantly greater than zero.

The results of the sensitivity analysis should be compared with the results from the qualitative assessment of uncertainty to offer judgments such as: (a) how would the qualitatively

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characterized sources of uncertainty affect the quantitative answers (e.g., because of bias from exposure misclassification, the actual percent total incidence is expected to be higher than the numbers shown here); (b) what is the relative importance between the factors in the sensitivity analysis and the qualitatively assessed uncertainties; and (c) what is the bottom line in terms of a judgment regarding the robustness of the effects estimates?

Charge Question 8(a): *Addressing uncertainty and variability --*

The treatment of uncertainty and variability in the analysis is based on the multi-tiered approach presented in a recent WHO document (WHO, 2008). Specifically, as outlined in section 3.5, we have included qualitative analysis of both variability and uncertainty (WHO Tier 1), as well as single-factor and multi-factor sensitivity analyses aimed at identifying which potential sources of uncertainty have the greatest impact on the core risk estimates (WHO Tier 2). In addition, the sensitivity analyses have been designed to provide a reasonable set of alternate risk estimates to supplement the core risk estimates and inform consideration of uncertainty associated with the core analysis. To what extent does the Panel support the overall approach for addressing uncertainty and variability? To what extent does the Panel agree that the overall approach is appropriate and consistent with the goals of the risk assessment as outlined in chapter 1? Does the Panel have any recommendations for improving the characterization of variability and/or uncertainty?

Response: The overall approach for addressing variability and uncertainty is reasonable, appropriate, and consistent with the assessment goals outlined in Chapter 1. The document appropriately undertakes Tier 1 and Tier 2 assessments, which are qualitative assessment and sensitivity analysis, respectively. The document should add that confidence intervals in effects are quantified based on the statistical properties of the concentration-response functions, which is consistent with partial application of a Tier 3 approach.

The single-factor and multi-factor sensitivity analyses are well-motivated and well-summarized in Table 3-8. The REA needs some tightening of terminology. In some places, the document refers to “elements” and in other it refers to “factors.” The term “elements” is sufficiently vage as to be the least preferred term. Much of the sensitivity analysis appears to be based on comparison of alternative model structures (e.g., different functional forms of the Concentration-Response function, or use of alternative roll-back methods). The REA should more clearly explain that the sensitivity analysis addresses structural uncertainties moreso than simply range estimates for inputs to a particular model.

It is reasonable and appropriate that the sensitivity analysis is based on plausible alternatives that have scientific support.

However, the document as a whole does not adequately articulate or justify why the microenvironmental-based population exposure estimation proposed in the Scope and Methods Plan has been dropped from the REA. As pointed out in Table 3-13, perhaps the largest source of uncertainty in the assessment is exposure misclassification, which leads to bias and imprecision in risk estimates and is associated with a high degree of knowledge-based

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uncertainty. At this time, the REA fails to provide any quantitative insight regarding inter-individual variability in exposure and its comparison to area-wide concentration data used in epidemiology studies. Although there may be limitations to exposure estimates, these are not necessarily any worse than the limitations inherent in other parts of the assessment. Furthermore, it is unclear as to why a purpose cannot be articulated for doing exposure assessment. At a minimum, an analysis of inter-individual variability in exposure for sample cases can illustrate the exposure misclassification problem that is inherent in epidemiological studies, and further bolster the point that epidemiological studies inherently underestimate the relationship between exposure and effect. As an example, Ozkaynak *et al.* (2008) quantified the variability in the ratio of exposure to ambient concentration based on a case study for the state of North Carolina. At a minimum, this paper and others should be summarized in a literature review and their implications for bias related to exposure misclassification should be discussed. The rationale for which exposure assessment has been dropped from the REA is entirely unclear to this reader.

To the extent that exposure modeling would (and should) be included in the REA, then a probabilistic Tier 3 approach should be used for the exposure assessment. There is precedent for this type of assessment (e.g., Burke et al., 2001; Ozkaynak et al., 2008&2009; Cullen and Frey, 1999).

References Cited

Burke, J.M., F. Zufall, H. Özkaynak. A Population Exposure Model for Particulate Matter: Case Study Results for PM_{2.5} in Philadelphia, PA. *Journal of Exposure Analysis and Environmental Epidemiology*, 11(6):470-489 (2001).

Cullen, A.C., and H.C. Frey. *The Use of Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs*. Plenum: New York, 1999. 335 pages.

Ozkaynak, H., H.C. Frey, J. Burke, and R.W. Pinder, "Analysis of coupled model uncertainties in source to dose modeling of human exposures to ambient air pollution: a PM_{2.5} case-study," *Atmospheric Environment*, 43(9): 1641-1649 (March 2009).

Özkaynak, H., H.C. Frey, and B. Hubbell, "Characterizing Variability and Uncertainty in Exposure Assessment Improves Links to Environmental Decision-Making," *EM Magazine* (Air & Waste Management Association), July 2008, pp. 18-22

Charge Question 8(b): *The qualitative discussion of key sources of variability, and the degree to which the analysis design captures those sources of variability, are presented in section 3.5.2. Please provide comments on the approach used. Specifically, do the analyses sufficiently address the issue of variability? Are there key sources of variability that have not been addressed within the qualitative analysis but which could have an important impact on modeling population-level risk associated with PM_{2.5} exposure?*

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Response: Section 3.5.2 is generally very good. The list of sources of potential variability is appropriate, and includes PM_{2.5} composition, intra-urban variability in ambient PM_{2.5} levels, demographics, “behavior affecting exposure to PM_{2.5},” baseline incidence, and longer-term temporal variability. However, the use of the term “Key” in this section raises the question as to whether EPA identified other potential sources of variability that were deemed not to be “key,” and how the various potential sources of variability were prioritized. Usually, the use of the word “key” implies that there is some kind of ranking of importance. However, it does not appear to be the case that there is any attempt at comparing the importance of these various sources of variability. Therefore, it is not clear how a conclusion is reached that they are “key.” “Key” to what, or with respect to what, and in what way?

Also, this section does not cover all sources of variability. It seems to cover the sources of variability that were not quantified in the assessment. However, there should be two lists given: one of sources of variability that are quantified, and then this list of ones that are implicit in the data used but not separately quantified in terms of their contribution to overall variability in concentration, response, or risk characterization. For example, spatial and temporal variability in ambient concentration of PM_{2.5} is quantified. However, spatial and temporal variability in the composition of PM_{2.5} is not separately taken into account in the quantitative assessment. This relates back to the use of the term “key.” Spatial and temporal variability in PM_{2.5} mass concentration is most likely a key source of variability, but is not listed in this section. Another way of saying this is that EPA should take credit for the sources of variability that are quantified in the assessment.

Although some of the factors discussed here are not quantified in terms of attempting to apportion exposure or risk by composition, demographics, activity patterns, and so on, EPA can at least provide insight into the variability of these factors to support the discussion of whether and why these factors may lead to variations in response and risk characterization. As an example, the four lines of text regarding demographics on p. 76 (lines 37-40) could be accompanied by a table that indicates the percentage of the population by gender and age (and perhaps racial/ethnic and/or socio-economic) categories for each of the 15 urban areas that are used in the assessment. This would provide much more clarity on whether and to what extent there are variations in these demographics, and would further support the claim that the 15 urban areas include “differences in demographics in different regions of the country.”

The potential source of variability mentioned at the bottom of page 76 (lines 41-45) and top of page 77 (lines 1-4) is critically important to one of the largest sources of uncertainty mentioned in the next section. Therefore, this needs more than just a brief qualitative discussion. At a minimum, there should be an example case study that illustrates (quantitatively) the distribution of exposures among microenvironments (outdoor, residential, office, school, in-vehicle, restaurant, bar, etc.), that these distributions tend to differ by demographic groups (e.g., children, working adults, elderly, commuters, etc.), that the distribution of demographic groups differs (see above), that the types of housing stock and ventilation practices differ; and that infrastructure and landuse differ. The latter leads to differences in transportation mode choice (e.g., private vehicle, bus, subway) that affects in-vehicle exposures. While it is not possible to

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separate the contribution of these factors on epidemiological concentration-response functions, it is possible to estimate the contribution of these factors to inter-individual variability in exposure.

Charge Question 8(c): *Table 3-13 provides a qualitative characterization of uncertainties including the potential direction, magnitude, and degree of confidence associated with our understanding of the sources of uncertainty. To what extent does the Panel support the characterizations of the key sources of uncertainties identified and the relative rankings of the importance of those sources of uncertainty? Are there additional uncertainties that should be considered?*

Response: Table 3-13 is excellent.

The text of Section 3.5.3 could more fully interpret the information contained in Table 3-13. For example, there could be a summary that describes the relative importance of the various sources of uncertainty, and the implications of these uncertainties for interpreting results of the REA.

Likewise, in the Results Section (Section 5.3), the results should be interpreted with respect to key sources of uncertainty – i.e. how robust are the results, and what are the likely biases. In particular, given exposure misclassification, it is likely that the estimates of Table 5-1 are biased low. This is an important point to convey consistently.

Another addition to the discussion of Table 3-13 is to comment on the extent to which there are dependencies among pairwise combinations of sources of uncertainty, and whether these dependencies would tend to offset or to increase the overall range and direction of uncertainty in the assessment results. For example, the statistical fit of the C-R functions, and the shape of the functions, are inter-related.

A specific comment regarding Table 3-13 is to either further justify or possibly reconsider the statement regarding the “medium” magnitude of Source I: lag effects. The key question is how much do answers change if different lag effects are considered, for which there is some treatment in the literature. Perhaps the comments portion needs to say a bit more – e.g., that although some studies have compared alternative lag structures, they have been limited in the values chosen for the lag, k , and may overlook lags beyond a day or so.

Charge Question 8(d): *The results of the sensitivity analyses have been used to gain insights into which sources of uncertainty significantly impact the core risk estimates and to provide a reasonable set of alternate risk estimates to supplement the core analysis. We are mindful that these estimates do not represent a true uncertainty distribution. With regard to the single- and multi-factor sensitivity analyses, to what extent is the Panel supportive of the approach used to conduct and characterize the results of the sensitivity analyses? Please provide comments on the extent to which the presentation of the results of the sensitivity analyses are clearly and reasonably described? Does the Panel have any recommendations for how the results of the sensitivity analyses could be used more effectively or appropriately in characterizing uncertainty associated with the core risk estimates?.*

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Response: As noted in some comments above, the sensitivity analysis focuses more on model structure than it does on parameter values, which is a good thing. The evaluation of alternative model structure is critically important, because model structure can potentially be a larger source of uncertainty than the range of values for an input to a given model. Page 85, line 3, it would help to emphasize that the sensitivity analysis focuses on alternative forms of the C-R functions and comparison of modeling approaches for evaluating rollback. The results represent plausible intervals, even if the likelihood of values within the interval is unknown.

In the air quality field, this type of analysis is analogous to evaluating ensembles of multiple meteorological episodes. One could describe this kind of sensitivity analysis as aimed at alternative parameterizations of the C-R function and rollback method.

Additionally, one could conduct sensitivity analysis on uncertain parameters or inputs for any given functional form of the C-R function. This appears to have been addressed by using statistical confidence intervals based on the fitted C-R equations. This should be introduced. The range of uncertainty associated with confidence intervals for a given C-R function should be compared to the range of estimates obtained by comparing alternative functional forms, to illustrate whether there is a wider range of values based on comparison of plausible alternative model forms than there is based on statistical inference for any individual model form. This would provide insight as to whether model structure, or random error for a given model, is a more important source of uncertainty.

Although the sensitivity analysis is not a probability sample, which is a point that is appropriately and well-made, one could envision that with enough plausible alternatives, one might cover the “sample space” of alternative model forms in some reasonable way. This notion has been applied to the use of ensembles in air quality modeling. Ensemble are not a probability sample, but as the number of members of an ensemble becomes large, and to the extent that they each represent different conditions, they could be argued to cover the sample space and to provide insight into variability or uncertainty. The key question for the sensitivity analysis is whether it is a useful range estimate – i.e. do the lower and upper bounds from the results (as shown later in Figure 4-22) represent plausible lower and upper bounds on the true but unknown answer? Or are there plausible alternatives that would further widen the range of estimates? For some readers and decision makers, a key question is whether the lower bound of the sensitivity analysis results (of 1.3% of total incidence of all cause mortality attributable to PM_{2.5}) is significantly greater than zero.

For Figure 4-22, I would experiment with presenting the results slightly differently. I would graph the Percent of total incidence of all cause mortality attributable to PM_{2.5} on the y-axis, and on the x-axis I would show the following categories: “Core risk estimates” (as a range from 1.7 to 2.2 percent; “Random Effects Log-Linear C-R Model” (with its range), and so on. In this way, it would be easier for the reader to see and compare individual sensitivity cases, rather than look at a series of dots that are difficult to associated with any particular case.

The results of the sensitivity analysis should be compared with the results from the qualitative assessment of uncertainty to offer judgments such as: (a) how would the qualitatively

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characterized sources of uncertainty affect the quantitative answers (e.g., because of bias from exposure misclassification, the actual percent total incidence is expected to be higher than the numbers shown here); (b) what is the relative importance between the factors in the sensitivity analysis and the qualitatively assessed uncertainties; and (c) what is the bottom line in terms of a judgment regarding the robustness of the health effects estimates?

Minor comment, pertaining to Table 4-5: please add a row showing the base case results.

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Henderson Comments (Dr. Rogene Henderson)

Charge question 1:

I am disappointed that the Agency still does not have enough information to evaluate the risk associated with exposure to coarse and ultrafine particles, but from a practical viewpoint, I think that is probably all you can do. The need to consider the composition of PM in relation to toxicity is major and should be addressed with some urgency. The NRC and BOSC have both urged the Agency to study this problem. The research required to address this issue is separate from what is normally done to set regulations. It is true that we do not now have the information to set a regulation based on PM composition, but I hope this will change in the future. Also, I think we should point out that, in order to move in the direction of looking at PM composition, as the Agency has been urged to do, they are going to have to conduct more comprehensive monitoring and not just measure mass and size.

Charge question 2:

I very much agree to limiting the scope of the risk assessment to those health effects that fit in the causal or likely causal categories. The rationale for doing this was clearly presented. There is no indication that "suggestive" endpoints are more sensitive to PM exposure than the causal endpoints, so even if the "suggestive" endpoints are later found to be causal, the public should be protected by the standards set to protect against the causal endpoints.

Charge question 3:

I thought the rationale for the choice of possible short (25 or 30 ug/m³) and long term (12 or 13 ug/m³) PM standards to be considered was quite clear. The combinations shown were not as clear. For example, the short-term standards chosen were 25 or 30 ug/m³, but two of the combinations included 35 ug/m³. So I think the combinations chosen need a little more explanation

Lead Discussant Response to Charge Question 9

Charge Question 9:

A number of risk metrics as well as different approaches for presenting these metrics are included in tabular and graphical format for both the core analysis and sensitivity analyses.

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Generally, the approaches and metrics for assessing various health risks are logically conceived, and the results of the “core” risk estimates, and sensitivity analyses are clearly presented in Chapter 4. The number of figures could be greatly reduced, since some appear almost identical and might better be moved to an appendix. While the PM Panel agrees that the risk assessment results based on a PM_{2.5} mass indicator are clearly presented here, we remain disappointed that no attempts were made to evaluate risks associated with the different PM components that are mixed in different proportions in the different urban areas.”

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Helble Comments (Dr. Joe Helble)

J. Helble September 25, 2009

Comments on Risk Assessment document – “Health REA-1”

Chapter 4 Results, Charge Question 9: “Please comment on the extent to which the risk estimates are clearly and appropriately characterized and presented.”

The risk estimates described in Chapter 4 of this document are presented at an appropriate level of detail. The initial sections of the chapter (4.1 and 4.2) are a bit tedious to read, but all of the necessary information is present. Later sections, particularly the sensitivity analysis, are well-written and clearly presented.

The tabular presentation of data in the Chapter and in the relevant appendices is generally clear. Tables are very detailed, and this is helpful when comparing risk assessment for different locations and different PM standards.

Table 4-1 is particularly clear despite the large amount of detail, and the individual references to specific tables in Appendix F are very helpful.

While the idea of including figures is sound, as they make it easy to compare the risk assessment resulting from the different NAAQS standards for a given location, overlapping city data make it difficult to follow trends. Many of the figures are nearly identical, and the data plotted are available in the accompanying tables. Given this, it might be better if only a representative year (2007) were shown. In addition, there is overlap between figures in the text and figures in Appendix E; it is not clear why both are needed. For example, Figure 4-1 is identical to Figure E-3, although the figure title is worded slightly differently. If this and similar figures are to be included in the text, they should either be removed from Appendix E, or labeled identically in Appendix E with the name of the corresponding figure from the text indicated in a footnote.

Regarding Figure E-1 and related figures – since the independent variable here is in fact the current standard, recent [PM], or an alternate standard, it is misleading to label the axis “alternate standard.” “Current or Alternate Standard” or other terminology would be a more accurate descriptor of what is represented in the figures.

Additional editorial comments follow.

1. Page 92, line 19: define concentration-response here, rather than later (in line 23)
2. Page 92, line 22 – define PRB here (rather than later in line 25)
3. Page 93, line 8, 2nd word should be “effect,” not “affect”

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4. Page 93 line 10, “are” should be changed to “is”
5. The entries in the tables (e.g, Table E-2) are the point estimate (absolute number) followed by the 95th percentile confidence intervals, as discussed on page 93, lines 16-20. This should also be noted in a footnote on the table.
6. A footnote regarding the significance of a negative value in the percent reduction tables (example, Table E-7) using language similar to that in the narrative (line 1, page 96) should be added to the relevant tables.
7. Page 99 line 2 – “Generally, results for the same are fairly similar... “ is followed by a discussion of one with 30% variability. It would be clearer if the text were more specific, e.g “...of the 15 cities considered, X were generally invariant (i.e. < y % year to year variation). Z of the cities showed greater variation, from *** up to 30%...”
8. p 100 line 30, “head” should be ‘had’
9. p. 101 line 15 – estimates, or estimate?
10. Discussion on p. 108 re number of monitors (line 4), would be helpful to reference Table 3-1 that lists the number of monitors at each study location
11. line 13, p. 123 – delete the right parenthesis)
12. p. 132 line 17, p. 134 line 34, p. 136 line 20 - shouldn't this read Table 4-1?
13. p. 137 line 15, “compare” should read “comparison of”
14. p. 149 line 3 “shows” should be “show”
15. p. 149 line 19, “8oth” ‘should read “80th ”
16. explanatory notes written on Figure 4-14, 4-16 4-19 through 4-21 are helpful
17. p. 165 line 22, “see” should be “seen”

Chapter 3 – Scope , Charge Question 5 Air Quality Inputs: “Please provide comments on the alternative approach as presented in section 3.2.3 and Appendix B.”

The alternative, hybrid method used for simulating PM_{2.5} concentrations appears to be a reasonable approach to simulating the effects of local controls applied to point sources in

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combination with regional controls expected to achieve a proportional reduction in PM concentrations.

The explanation in Appendix B is clearer than the explanation in Section 3.2.3. Given that it is a relatively short amount of text, it may be worth folding this appendix into the body of the report.

Minor typographical errors in Section 3.2.3:

1. page 36 line 31, the \ should be deleted
2. page 37, line 20, missing left parenthesis in the denominator
3. page 38, line 6, missing left parenthesis in the denominator

Chapter 5 – National Scale Assessment, Charge Question 11, Approach

The approach is reasonable based on the analysis presented in section 4. It is reasonably clearly presented.

p. 24 lines 24-25 indicate that the use of 2006-2008 baseline data have little effect on the results presented in section 5 due to a sensitivity analysis. Is this sensitivity analysis described elsewhere in the report (incl. Appendix G)?

Chapter 5 – National Scale Assessment , Charge Question 12, specific analysis

The results in Section 5 are fairly clearly presented. Providing Figure 5-4 as an analysis of where the 31 counties included in the urban case study counties lie on the overall national risk distribution is helpful for putting the results in context. Instead of simply mentioning 2 representative counties in the lower end of the distribution and 2 in the upper end, a more complete description of all 31 should either be included, or referenced here if it is located elsewhere in the document.

Minor comments on this section

Page G-1, “Supplement” is spelled incorrectly in title

p. 172, line 3, pm2.5 should read PM2.5

p. 172, footnote 48, last line, “is” should be “are”

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Hopke Comments (Dr. Phil Hopke)

Comments by P.K. Hopke on Health Risk Assessment

It is hard to provide any substantive comments on this document since they have followed the methodology that was laid out in the plan that had been previously reviewed by the Panel.

Air Quality Inputs

The air quality inputs are reasonable. Given what they want to explore, the rollback methodology that was used also seems reasonable.

Sources of Variability and Uncertainty

Again the approach is reasonable. Given the nature of the broader uncertainties in the whole RA process, I do not think there is much more that would be sensible to do.

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Lippmann Comments (Dr. Mort Lippmann)

PM RA 1st Draft

M. Lippmann Review Comments

General Comments:

I commend OAQPS Staff for creating a straightforward text that clearly describes the objectives and methods used to develop risk assessments (RAs) for the PM_{2.5}-associated health effects judged in the PM ISA 2nd draft to be either causally or likely to be causally related to the exposures. As a long-term observer of the development of RAs for NAAQS, I am impressed with the progress that has been made in the development and applications of the methodology. I believe that the choices that were made in terms of monitoring data and concentration-response functions for this latest PM RA were reasonable and appropriate, and I therefore find the estimations of the health effects to be expected in meeting the current 15/35 $\mu\text{g}/\text{m}^3$ NAAQS, and of meeting the alternate NAAQS under consideration, provide a reasonable basis for the selection of the next suite of PM NAAQS.

I did find a few nits to pick, and these are described below under Specific Comments.

Specific Comments:

Page(s)	Line(s)	Comment
18	1-4	Population exposure assessment is hardly a new issue in setting PM NAAQS. There is little justification for putting it off until “the next PM NAAQS review.”
33	Table 3-1	There is only one New York City (NYC) risk assessment location. The Ito et al. (2007) was <u>not</u> restricted in New York County (Manhattan) but rather covered all five counties within NYC.
34	1 + 2	Delete
48	29	Delete “Manhattan”.
57	-	For the “Risk Assessment Location” entry for NYC, change the entry for “New York City (Manhattan)” to “New York City”, and indicate that the same five counties apply to the Ito et al (2007) paper.
66	Table 3-10	Correct the county listings for New York, NY as above.
72	11	Insert “be expected to” before “respond”.
75	5	Insert a comma after “variability”.
99	Footnote 38	This footnote states: “Specifically, the baseline incidence rates for IHD mortality for New York City are 380 per 100,000 while national is 242 per 100,000 (See section 3.5, Table 3-9). This translates into New York City having approximately 1.5 times the rate of IHD deaths relative to the national average. All cause mortality baseline incidence also differs, although to a lesser extent, with New York City having 1,077 per 100,000 and the national average being 1,327 per 100,000. This

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		<p>translates into New York City having a baseline incidence rate for all-cause mortality that is 23% lower than the national average.”</p> <p>This cited quote is important information, which should be discussed in the final draft of PM ISA.</p>
109-116	Figures 4-1 through 4-8	<p>These figures indicate rather dramatic benefits from more stringent PM NAAQS in terms of reduced incidence of mortality (All cause, cardiopulmonary, and lung cancer), as well as substantial mortality benefits of achieving the pre-existing NAAQS for cities now in noncompliance. For 13 of the 15 cities, the 12/25 option would reduce PM_{2.5} –related mortality by 30-60% as compared to just meeting to current 15/35 NAAQS. It is important to note that the estimated benefits were based on neutral rather than conservative models of airborne PM_{2.5} concentrations and concentration-response relationships. While the estimations are subject to consideration of uncertainties in the data and models, it would be very hard to ascribe them to bias, and they do not rely on “margin of safety” considerations, which should, if anything, lead to even more stringent NAAQS.</p>
120-121	Figures 4-9 to 4-10	<p>Recognizing that the short-term mortality impacts of peak concentrations are considerably lower than those due to cumulative exposures, the similarities in the patterns lend credence to the validity of the benefits to be gained from more stringent PM NAAQS.</p>
125-126	Figures 4-12 to 4-13	<p>The cardiovascular hospital admissions estimates are also supportive, especially in terms of new “coherence” with the mortality estimates.</p>
130	Table 4-1	<p>I suspect that the % differences have the wrong sign, since the alternate long-term exposure mortality study to the ACS cohort is the 6-cities cohort. The coefficient for 6-cities cohort is considerably greater than that for to ACS cohort.</p>
133	24-40	<p>I suspect that the % differences have the wrong sign, since the alternate long-term exposure mortality study to the ACS cohort is the 6-cities cohort. The coefficient for 6-cities cohort is considerably greater than that for the ACS cohort.</p>

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Phalen Comments (Dr. Robert Phalen)

Lead Discussant Response to Charge Question 2

The material is well written and the logic is clear with respect to the selection of health endpoint categories to include in the risk assessment.

However, causality is a serious claim when it is applied to public health.

Causality implies that the true culprit that is producing adverse health effects is known with sufficient certainty to both commit resources for control, and to disrupt people's lives (and productivity) in the process.

Although the associations linking several health outcomes to PM_{2.5} exposures pass the criteria that EPA used to conclude causality, I don't believe that PM_{2.5} mass per se is responsible. Studies by Bell et al. (2008, 2009) convincingly indicate that of 20 components of PM_{2.5} only Vanadium, Nickel, and elemental carbon were statistically-significant with respect to cardiovascular respiratory hospital admissions in 65-plus year olds. The study included 106 continental U.S. counties with populations of 200,000 or more. The study represents a major advance in the process of uncovering valid specific causal factors.

Having seen some unwelcome tradeoffs associated with mass-based PM NAAQS, I am concerned about accepting PM_{2.5} mass as a causal factor for adverse health outcomes. A formal risk assessment carries the assumption that the cause is clearly identified. As a result, I would drop the category "likely to be a causal relationship" from the health risk assessment. Also, the category "causal relationship" is questionable, and if it is included in the risk assessment, a discussion of the uncertainties related to a mass-based indicator should be added.

As an aside, now is not the right time to assume that the causal factors are known. True causal factors including specific components, component combinations, and exposure conditions must be identified in order to target efficient appropriate control actions. Inefficient control actions can do more harm to public health than good.

References cited.

Bell, M.L.; Ebisu, K.; Peng, R.D.; Walker, J.; Samet, J.M.; Zeger, S.L.; Dominici, F. (2008). Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999-2005, *Am. J. Epidemiol.* 168(11):1301-1310

Bell, M.L.; Ebisu, K.; Peng, R.D.; Samet, J.M.; Dominici, F. (2009).

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Hospital admissions and chemical composition of fine particle air pollution. *Am. J. Respir. Crit. Care Med.* 179(12):1115-20.

Section 3.3.2 reads well and I have no concerns regarding the rationale and study locations selected. Some minor suggestions are:

In Table 3-4: 1. Spell out “Los Angeles”; and 2. define “design value” in a table footnote, or in the main text.

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Poirot Comments (Mr. Rich Poirot)

September 2009 PM Health Risk Assessment, Charge Question 9:

A number of risk metrics as well as different approaches for presenting these metrics are included in tabular and graphical format for both the core analysis and sensitivity analyses. Please comment on the extent to which the risk estimates are clearly and appropriately characterized and presented.

Generally, the approaches and metrics for assessing various health risks are logically conceived, and the results of the “core” risk estimates, sensitivity analyses and national representativeness are all clearly presented in Chapter 4. The section 4.5 “summary and key observations” is especially well-written, and in some cases easier to understand than the more detailed presentation of the same information earlier in the chapter. It might be helpful to move this summary to the beginning of the chapter, or at least adopt some of its clear wording in earlier sections. The section 4.4 evaluation of the “representativeness” of the 15 urban study areas in the larger national context is also clearly written, and the presentation of results in both tabular and graphical form is excellent! I also thought the sensitivity analyses in section 4.3 was well conceived and clearly presented, with an informative and concise summary in Table 4-1.

Section 4.1, which basically describes the contents of the tables in Appendix E, is tedious to read and/or requires frequent referrals to the appendices to see the results (or to maintain interest). It might be more effective to just include some of the referenced tables in the chapter rather than only as appendices.

The section 4.2 assessment of risks associated with just meeting current and alternative standards is clearly written. However, I’m not sure the graphical presentation of results in Figures 4-1 through 4-13 is all that effective. For one thing, I note that (except for the different legends which convey details that could be presented as well or better in tabular form), Figures 4-1 through 4-8 appear to me to be exactly (or very, very nearly) the same figure. In a similar way, I can’t see any differences in Figures 4-9 through 4-11, and 4-12 and 4-13 look the same to me (and are darned similar to 4-9 through 4-11). I wonder if there’s possibly a mistake here, and if there isn’t, what point is being illustrated by so many figures that can’t be discerned from each other? I don’t suppose it’s possible that the Y axes are actually showing the % reductions in concentrations (rather than in the indicated effects) as this might account for why all the figures look the same. Possibly some of these apparently redundant figures could be moved to an appendix, or possibly similar graphs which show differences (assuming there are some) among the different effects endpoints for each individual city might convey more useful or interesting information.

Specific Comments on Chapter 4

p. 92, line 26: It seems counterintuitive that the lowest measured levels were lower than the policy-relevant background across all studies. Could a brief explanation for this be provided here?

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pp. 98, lines 10 & 12: Change “Seep” to “See” and add “ly” to “significant”.

p. 100, line 19 (& elsewhere): Is “reflecting use of” the right phrase here? I would think the negative lower bound estimates of incidence are the indicators of insignificant effects estimates rather than reflections of the use of insignificant effects estimates.

p. 100, line 30: Change “head” to “had”.

p. 107, line 13: The word “conditions” seems out of place and could be deleted.

p. 118, line 32: “long-term morality” is indeed a noble aspiration, and a quick word search shows similar references to “exposure morality” (p. 135, line 40), “non-accidental morality” (p 134, line 12) and (my favorite) “premature morality” (p. 45, line 22).

p. 140 or elsewhere in this section: A majority of the sensitivity analysis results summarized in Table 4-1 (or Table 4-5 and Figure 4-22) seem to show a positive bias (i.e. a larger degree of risk than indicated by the core analyses. Is there any implication to this apparent “directionality”? If so (or if not), should it be discussed here?

p. 148, line 18: Change “hear” to “heart”.

pp. 151-158, Figures 4-14 through 4-21: I really like these figures. Might it be possible to use different colored vertical lines and a legend to indicate which of the study cities is which?

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Russell Comments (Dr. Ted Russell)

Review of EPA PM Risk Assessment-
Health Risk and Exposure Assessment
Armistead (Ted) Russell

The first draft of the Risk Assessment to Support the Review of the PM Primary NAAQS (hereafter, RA) represents a significant amount of work, and provides a good deal of information to inform the Administrator, as well as other stakeholders, as to issues relevant to the review of the Primary PM NAAQS. It largely executes the path laid out by the Scope and Methods document and provides quantitative information as to the various health risks related to PM exposure and how those risks may respond to revised PM NAAQS (primarily only PM_{2.5} with some discussion relating to PM_{10-2.5}). The Sensitivity Analysis section was probably the best I have seen in any of the REAs and was informative. I believe that Chapter 4 is well set up to provide the location specific analyses of the range of health endpoints of interest and how the chosen locations are representative of the broader national conditions.

While the RA has largely followed the SM, and accounted for CASAC comments, there is significant room for improvement.

First, I note that it would be very desirable to have an upfront (Chapter 2?) summary as to the approach and results. This should build upon the policy-relevant questions identified in the PM ISA, and provide answers as appropriate (or identify why such answers are not provided).

Second, while the RA does represent a tremendous amount of work, it is not as effectively presented as it could be. First, it is rather repetitive in places, particularly the transition from Chapter 3 to Chapter 4. It seems as though Chapter 3 tells us what is going to be done in Chapter 4, and then Chapter 4 goes back over the same. Given the detail in Chapter 3, it is possible to just jump in to results in Chapter 4. Next, Chapter 4 is a bit laborious to get through, and after reading the material, it is a struggle to keep it all sorted out in one's mind. The various paragraphs in Sections 4.1 and 4.2 providing numerical results of the various risk assessments for different endpoints (there are 27 such paragraphs) lose punch as one goes through them. It is recognized that the results are somewhat condensed from what is more thoroughly presented in over 100 tables in the appendices, but a few summary tables or graphs would go a long way here. Choose the most influential endpoint(s), and summarize across cases and alternatives. Further, the figures in this chapter are not overly effectively presented as Figs. 4-1 through 4-8 and Figs. 4-9 through 4-11 are rather indistinguishable and the text does not identify what is really different and important between them.

I was hoping to see more from Chapter 5 as I was looking for a national scale assessment of a broader set of endpoints. While I recognize the detail and care that went in to matching of studies in Chapter 4, something should be done to take the city-specific results from Chapter 4 to provide the national scale assessment of more health end-points than just long-term mortality. Further, Chapter 5 did not assess the change in risk at different alternative standards.

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Given that the SM planned to do the national scale assessment only on long-term mortality, what really may be missing is a synthesis as part of Chapter 4 or 5, or a new Chapter 6 that really synthesizes the results from both Chapters 4 and 5. Looking back at the chapter, this synthesis is started by the section discussing how the chosen areas are representative of the nation, but more is needed to interpret how those results reflect likely risks to the population, and this is the point where absolute numbers of individuals likely to be impacted (and which endpoints) would be valuable. As part of a new Chapter, or somewhere else, how the risks associated with the alternative PM standards compare to the other NAAQS. I why one might stop with just investigating down to $12 \mu\text{g m}^{-3}$ (annual)/ $25 \mu\text{g m}^{-3}$ (24-hour) when it appears substantial risks are still found at the levels currently in the RA, and the choice of alternatives might consider how those alternatives compare to the NAAQS (proposed or effective) for other pollutants.

Response to Charge Questions:

5. The inclusion of a hybrid approach is appropriate and a nice extension to the analysis. While the approach is rather ad hoc, any method would be at this point, and a simplified approach allows assessing the sensitivity to a recognized concern that in some locations, there will be a blend of local and regional controls to reach attainment. The approach currently likely overestimates this effect in some locations (e.g., those areas mainly affected by mobile source and secondary PM) and underestimates in others (where specific industries and activities have a major local influence). The approach developed is reasonable and of appropriate complexity given the vast unknowns as to how specific areas would choose to control emissions.
10. I was generally pleased with the approaches used to demonstrate how (or how not) the chosen urban areas represent the nation as a whole. The discussion of how one should interpret the cases where specific risk attributes in the chosen areas are/are not similar to the nation as a whole, and the use of CDFs, was informative and at a good level.
11. As noted above, I was disappointed with the national scale assessment as it is limited to one endpoint and did not include an assessment associated with alternative standards or a synthesis of the results of the city-specific analyses. Consider a final chapter synthesizing the results from Chapters 4 and 5, identifying the key considerations that might drive the revision of the NAAQS, and how the alternatives compare with other NAAQS.
12. Showing that the chosen areas fall near the top of the CDF is a good start, and does provide information as to how one might interpret the information provided by the detailed assessments presented in Chapter 4. Again, what is missing is going the other direction, that being taking the information in Chapter 4 and developing a national assessment for endpoints other than long-term mortality.

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An overall concern for both the Primary NAAQS and Urban Visibility Reviews: The way the current RA and Visibility documents are currently formulated, the potential importance of controlling sources of elemental and primary organic carbon are understated versus other components. Health studies are suggesting that EC/OC are more associated with cardiovascular disease issues than many other components (e.g., ionic inorganic species making up much of the mass of PM_{2.5} in much of the US), and EC absorbs sunlight and can exacerbate climate warming. On the other hand, inorganic ionic species likely lead to a net cooling. While a visibility assessment can be more confidently done (or the results would be subject to less uncertainty), climate impacts are a much greater concern (at least to me and I think a great fraction of others). Information that is transmitted to decision makers should more fully express the importance of controlling sources of EC and primary OC.

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Speizer Comments (Dr. Frank Speizer)

Pre-meeting Comments on REA Draft dated Sept2009—answer to (paraphrased) charge questions

Submitted by: Frank E. Speizer, MD

September 24, 2009

Scope of the Assessment and Methods used for the urban case studies

1) Choice of assessing PM_{2.5} only

Page 15, section 2.4.1, first and third bullet:

At this point I would argue that insufficient detail is provided to justify dropping doing a quantitative risk assessment for PM_{10-2.5}. Unless more detail is provided Staff is making the same decision make in previous PM assessment. Since in Chapter 6 (and chapter 7) of the ISA conclusions that PM₁₀ are likely causal, we asked for more modeling of how PM₁₀ along with PM_{2.5} data might be used to improve understanding of the coarse fraction component. In the ISA effort in this direction is taken, and seemingly some quantification is reported. Why, having gone to the trouble there not use it here? Reference is made to section 3.3.1. The relevant section is at the end of the section, just before the start of 3.3.2. I do not believe the argument is sufficient to drop the coarse fraction and this will need to be debated at the CASAC meeting.

2) Selection of causal or likely causal associations with PM_{2.5} only.

Again, this will need to be discussed. It is not clear that there was or is a consensus as claimed that CASAC was not interested in looking at the suggestive category. In fact, there might be a consensus that for different disease outcomes different levels of certainty of causality, with appropriate considerations of the size of the margin of safety might be considered. (For example, a risk affecting 1% of newborns with a lower level of certainty might have a substantially greater impact than a risk affecting 5% of emergency room admissions of elderly patients with respiratory disease with a greater degree of certainty. Simply stating that the degree of certainty would make quantitative estimates less useful without providing some calculations seems inappropriate.

3) Rational provided in section 2.5 for alternative standard levels for assessment.

Logically and well described in section.

4. General approach

The considerations discussed in the remainder of Chapter 3 are logical and clear. However, I cannot accept that they would only apply to PM_{2.5}. If the same arguments were made for the other components of PM one would expect that the analysis itself would be able to show where the uncertainty becomes so great as to make the calculations useless and were some additional information was obtained that would help the us and the Administrator make informed judgments about the risks. By simply dismissing doing such calculations we simply don't have the data with which to make a decision.

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The choice of LML to assess long-term PM exposures, but not extrapolating to PRB (if I understand what was done seems appropriate. Similarly, for short-term PM exposures going to PRB rather than LML, assuming continuous exposure-response function is reasonable. Thus, I would be generally supported of these approaches.

The results are rather dramatic and consistent. For the long term effects it appears that for substantial reduction of risk to be made that the alternative levels of PM 2.5 must be 12/25. In contrast for short term effects it looks as though anything below 13/35 is relatively flat. How this will be used in reporting will need to be discussed.

7. Selection of epi studies and C-R functions within these studies.

For what was done, the descriptions are fine and the choices made seem justified in the text. My argument remains that the same criteria could have been applied to other PM components, or at least modeled with PM10 and PM2.5 to get estimates of PM10-2.5 and similarly put to the test as to whether the data were adequate. Staff may have done this, but the data are either buried in an appendix and not referenced to or wasn't done, thus making the decision not to do it less defensible. Similarly with regard to end point decisions, by simply choosing not to explore in more detail the suggestive categories, whole disease categories are being left out. (eg reproductive outcomes and lung cancer). This latter omission is particularly troublesome since the exposure characteristics from the ACS studies are being used for the long term exposure mortality and it would have been a simple matter to do the same analysis with lung cancer. We would then be able to see how the uncertainty would play out at least for one disease category.

Lead Discussant Response to Charge Question 6

The document understandably focuses on risk in the urban study areas (where major population concentrations are), and appear to be an appropriate selection of cities, using defined criteria. However, little information is provided on rural regional PM effects. We are aware of regional data estimates that could have been used to justify inclusion (or exclusion) of these regions in carrying out the risk assessment. Some discussion of major traffic corridors in rural areas would seem warranted, even if only to exclude these data. Considerations should have been presented in the document and prioritized in the approaches to provide substantive insights for rural population, rural exposures, and rural health effects. If these are included in the appendices they should at least be referenced.

The importance of these considerations is made even larger if the resultant document maintains that it will carry out risk assessment only for PM 2.5. The regional differences in the proportion of total PM that is in the PM2.5 range may vary widely and thus results related to the other components of PM may be selectively excluded by focusing on urban areas.

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Suh Comments (Dr. Helen Suh)

The REA set forth a clear and thoughtful approach to assess particle-mediated health risks. The goals of the REA are well-defined and for the most part the REA does an admirable job of achieving these goals. As an overall comment, the decision to forego a risk assessment for $PM_{10-2.5}$ should be discussed further, as a limited risk assessment for $PM_{10-2.5}$ would provide information helpful to the standard setting process in a manner consistent with the document's stated goals. This limited risk assessment could be based on the same multi-city studies as used in the risk assessment for $PM_{2.5}$ (Zanobetti and Schwartz, 2009 and Peng et al., 2008). Correspondingly, the decision to forego a population exposure assessment should also be revisited. Although the previously proposed approach requires further development before its application to the REA, a simpler, more targeted exposure assessment approach could be used to help identify factors that contribute to observed variability in the C-R functions or to city-specific differences in risks.

The Summary and Key Observations section at the end of the document provided a very nice summary of the key findings. Coming at the end of the document, this section was buried and it would be helpful if it was moved forward, perhaps before or after Chapter 2. [If before, a small paragraph on the scope should probably be added.]

Charge Question 7: Selection of epidemiological studies and C-R functions within those studies:

In estimating risks associated with $PM_{2.5}$ exposures, we focused on selecting C-R functions from large multi-city studies based on staff's conclusion that these studies provided more defensible effect estimates (see section 3.3.1). Concentration-response functions from several single-city studies evaluating short-term $PM_{2.5}$ exposures were also included to provide coverage for additional health effect endpoints (e.g., emergency department visits). To what extent is the Panel supportive of this approach for selecting C-R functions for modeling risk related to short-term and long-term $PM_{2.5}$ exposures?

a) Specifically with regard to short-term exposure-related mortality, focusing on a study of 112 US cities by Zanobetti and Schwartz (2009), we obtained Empirical Bayes "shrunk" city-specific estimates from the study authors that provided a distinct C-R function for each urban study area location. For short-term exposure-related morbidity, focusing on a study of 202 U.S. counties by Bell et al. (2008), we used regionally-differentiated effect estimates provided by the study authors. Please comment on the selection of C-R functions for evaluating short-term morbidity and mortality effects. To what extent do the Panel members consider the rationales supporting the selection of C-R functions to be clearly and appropriately presented?

The methods used to select the C-R functions were clearly presented. The rationale for the focus on multi-city studies is clearly presented and is appropriate, as is the reason for the inclusion of select single city studies to assess $PM_{2.5}$ -mediated ED risks. While the Zanobetti and Schwartz (2009) and the Bell et al. (2008) studies are excellent studies to select, it is not clear why the analysis is limited to just these studies. The specific reasons for their selection and for the omission of other multi-city studies should be provided for clarity. Currently, other multi-city studies meet the three criteria set forth in the document, namely that they be:

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- published, peer-reviewed study that was evaluated in the PM ISA and judged to be adequate by EPA staff
- direct measurements of PM_{2.5} had to be used on reasonable proportion of the days
- could not rely on GAMs using S-Plus software

In this effort, the definitions of “adequate” and “more defensible estimates”, which were used to describe the selection process, would be important.

The use of “shrunk” estimates to obtain the C-R function for mortality is reasonable, especially for the small cities. It may also make sense to use regional specific C-R functions as well, perhaps as a sensitivity analysis, since these regional specific estimates would correspond to and help interpret the appropriateness of using regional C-R functions to assess risks for hospital admissions.

b) Specifically with regard to long-term exposure-related mortality, we identified a number of effect estimates using the extended follow-up of the American Cancer Society (ACS) study to use in the core analysis (Krewski et al., 2009). These effect estimates include standard Cox proportional hazards models, with 44 individual and 7 ecologic covariates, derived using two separate PM_{2.5} monitoring data sets (i.e., 1979-1983 and 1999-2000) (see section 3.3.3 of the RA). To what extent is the rationale for these choices clear and sufficiently justified as the basis for the core analysis involving long-term PM_{2.5}-related mortality?

The rationale for choosing effect estimates from the extended follow-up of the ACS cohort was clearly and logically presented. Given the size of the ACS cohort, it makes sense to select effect estimates from this study for the core analysis. However, given that there are only a relatively few number of chronic cohort studies have been conducted to date, it would be interesting and useful to see how the selected C-R functions compare to those from other studies. This could be done as part of a sensitivity analysis.

Charge Question 8: Addressing uncertainty and variability

- a) *The treatment of uncertainty and variability in the analysis is based on the multi-tiered approach presented in a recent WHO document (WHO, 2008). Specifically, as outlined in section 3.5, we have included qualitative analysis of both variability and uncertainty (WHO Tier 1), as well as single-factor and multi-factor sensitivity analyses aimed at identifying which potential sources of uncertainty have the greatest impact on the core risk estimates (WHO Tier 2). In addition, the sensitivity analyses have been designed to provide a reasonable set of alternate risk estimates to supplement the core risk estimates and inform consideration of uncertainty associated with the core analysis. To what extent does the Panel support the overall approach for addressing uncertainty and variability? To what extent does the Panel agree that the overall approach is appropriate and consistent with the goals of the risk assessment as outlined in chapter 1? Does the Panel have any recommendations for improving the characterization of variability and/or uncertainty?*

The approach used to examine variability and uncertainty in the risk estimates is generally well described and consistent with the stated goals of the risk assessment. The WHO framework is an appropriate and well established approach to assess uncertainty in risk estimates. The decision to forego a probabilistic (or WHO Tier 3) analysis to examine uncertainty and variability in risk estimates seems appropriate given the resource- and time-constraints. The two additional analyses intended to place the risk results for the 15 study areas in a broader national context is an important addition to the document.

- b) *The qualitative discussion of key sources of variability, and the degree to which the analysis design captures those sources of variability, are presented in section 3.5.2. Please provide comments on the approach used. Specifically, do the analyses sufficiently address the issue of variability? Are there key sources of variability that have not been addressed within the qualitative analysis but which could have an important impact on modeling population-level risk associated with PM_{2.5} exposure?*

For the assessment of variability, six key sources of variability were identified. The identified six sources are appropriate; however, their definitions should be broadened or additional categories should be included. For example, differences in PM co-pollutant concentrations (e.g., overall pollutant mixture) should be included as a source of potential variability in PM-associated risks. This factor could be included by broadening the PM_{2.5} composition category to include all pollutants. [While co-pollutants are a source of uncertainty, they may also be a source of variability if there are synergistic or multiple pollutant effects.] Correspondingly, demographics could be broadened to also include land use, source locations, housing stock, and SES.

Beyond source identification, additional work should be performed to assess the potential impact of the variability sources on the risk estimates. While it is true that it is not possible to separate their contribution to risk estimates completely, single- or multiple-factor, WHO Tier 2 analyses could be conducted, with results used to examine the impacts of these variability sources on the C-R function or risk estimates. This examination could correspond to the analyses done to examine the generalizability of the 15 cities to the rest of the US, possibly through a simple weighted-regression of the city-specific risk estimates on the variability source.

9-30-09 Preliminary Draft Comments on the PM Health Risk Assessment from Clean Air Scientific Advisory Committee (CASAC) Particulate Matter Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

- c) *Table 3-13 provides a qualitative characterization of uncertainties including the potential direction, magnitude, and degree of confidence associated with our understanding of the sources of uncertainty. To what extent does the Panel support the characterizations of the key sources of uncertainties identified and the relative rankings of the importance of those sources of uncertainty? Are there additional uncertainties that should be considered?*

Table 3-13 is relatively complete and provides a good overview of the sources of uncertainty and their potential impacts. A source of uncertainty that was not included was the C-R function itself, which was developed from single studies. In this regard, it would be helpful to broaden or alter Source J. (Transferability of C-R functions from study locations to urban study area locations) to include examination of long-term risks using C-R functions from different long-term mortality studies (WHI, NHS, ASHMOG, etc.) or of short-term risks using C-R functions from other cities included in the Zanobetti and Schwartz or Bell et al. studies or from other multi-city studies that include at least one of the target cities. If possible, it would also be helpful to define, perhaps as a Table footnote and even if only vaguely, what is meant by the categories “low”, “medium”, and “high”.

- d) *The results of the sensitivity analyses have been used to gain insights into which sources of uncertainty significantly impact the core risk estimates and to provide a reasonable set of alternate risk estimates to supplement the core analysis. We are mindful that these estimates do not represent a true uncertainty distribution. With regard to the single- and multi-factor sensitivity analyses, to what extent is the Panel supportive of the approach used to conduct and characterize the results of the sensitivity analyses? Please provide comments on the extent to which the presentation of the results of the sensitivity analyses are clearly and reasonably described? Does the Panel have any recommendations for how the results of the sensitivity analyses could be used more effectively or appropriately in characterizing uncertainty associated with the core risk estimates?*

The approach to the sensitivity analysis is reasonable. It would be worthwhile in the text to indicate the direction of the percent changes in risk. Further, the large and variable percent changes by city for some analyses (such as that for seasons-specific C-R) raises concerns over the use of the percent difference to characterize the findings. These findings suggest that in addition to the percent difference, the actual difference in risk should be reported to provide further context. This section should conclude with a brief but explicit summary of the decision to use the sensitivity results only from the long-term exposure mortality analysis, as I think that it now only appears in the summary of results (Section 4.5.2).

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Vedal Comments (Dr. Sverre Vedal)

PM REA 1st draft September 23, 2009

Question 3. Standard levels for risk assessment. Brain lead discussant.

The difficulty here is that epidemiological studies do not provide much help in deciding on the level of the standards. They certainly do not provide much information on levels below which no effects are seen. So, attempting to use them, as is valiantly done here, to identify standards of interest, is not easily justifiable.

Long-term concentration levels. Based on the observations made about mean study concentrations and confidence in effect estimates, it is difficult to understand how the judgments as to the concentrations to be used for this purpose were actually made. The focus on means seems reasonable in light of the form of the annual standard. Using long-term mean concentrations from short-term studies (line 12, p. 19), however, seems a strange approach, and harkens back to the time when the long-term standard was used to attempt to reduce short-term exposure effects.

Instead of using a number of unconvincing approaches to justifying selection of alternatives, why not just take the simple approach of going below the current standard in increments of $1 \mu\text{g}/\text{m}^3$, say 14, 13 and $12 \mu\text{g}/\text{m}^3$? That should pretty much cover it for our purposes. I would not want to exclude $14 \mu\text{g}/\text{m}^3$ because that was clearly a level of interest at the last round and remains of interest.

Short-term concentration levels.

I would make the same point here about the exercise of wrestling with the short-term study concentrations to try to arrive at some justifiable levels being ultimately unsatisfactory. Here the simple approach of going down below the current standard in increments of $5 \mu\text{g}/\text{m}^3$ to, say 25, would have been an equally defensible one, and, interestingly, would have resulted in the same concentrations to use that were in fact selected.

In short, then, I would suggest a 3x2 matrix of standards for use in making risk estimates: three long-term levels of 12, 13 and $14 \mu\text{g}/\text{m}^3$ and two short-term levels of 25 and $30 \mu\text{g}/\text{m}^3$.

Question 4. Suh lead discussant

4.a. Core CRFs: selection approach and description.

A core set of CRFs with identified lag periods were selected. Sensitivity analyses assess the importance of these selections in affecting/influencing risk estimates.

Based on the arguments provided on selection of endpoints for which CRFs will be chosen and risk estimates made, which I agree with, the choice of lung cancer mortality as an endpoint (line 21, p. 40) is inconsistent.

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The rationale for choosing to emphasize multi-city study estimates for short-term and long-term CRFs is sound. However, the approach to selecting which multi-city studies on which to focus is not particularly clear. Although I could probably supply some arguments, the casual reader of the REA might wonder why the original NMMAPS study was not being used for short-term mortality CRFs, for example. That is, there is no presentation of the rationale for deciding among several large multi-city time series studies. The same applies to the choice of long-term exposure studies, given the several there are to choose from currently.

I agree with the choice and rationale for not proceeding with estimating risks of coarse PM exposures. First, no causal assessment for any effect of coarse PM rises above the grade of “suggestive,” and second, selection of adequate CRFs for coarse PM would be problematic at this time.

4.b. Short-term and long-term lowest modeled levels.

I agree with the basic argument that we should only be concerned with estimating risk above the so-called policy relevant background (PRB) as in previous risk assessments, in spite of there being controversy as to how PRB is calculated. I do not see the point of estimating risks associated with PM that cannot be influenced by human activities and estimating risks down to a zero concentration.

In the absence of equally compelling alternatives, I agree with the choice to only estimate risk down to the lowest measured level (LML) in the core study used for long-term CRFs. However, it would be valuable to see the impact even here of estimating risks down to PRB, even though extrapolation is needed. For short-term risk estimates, the choice is easy because the LMLs (which are daily) are below the PRB.

Question 7. Vedal lead discussant

7.a. Short-term exposure mortality and morbidity CRF selections and rationale.

Vedal only placeholder. I agree with the choice to emphasize multi-city studies and the reasons cited to support that choice (p. 46). I also agree with the specific choices of studies from which short-term CRFs were derived and with the use of “shrunk” estimates for these CRFs. While it is OK to use the single-pollutant PM_{2.5} model estimate, since coarse PM (here, the co-pollutant) is only weakly correlated with PM_{2.5}, it hardly makes a difference. I am less convinced that choice of the 2-day lag effect from the Bell study is the best choice for the respiratory hospitalizations CRF – this is likely biased high. Sensitivity analysis results with different lag estimates from the Bell study would be reassuring to see. Hopefully the effect of lag choice will not be restricted to an evaluation of the Moolgavkar (2003) studies.

7.b. Long-term exposure mortality and morbidity CRF selections and rationale.

Vedal only placeholder. I agree with the specific choices of study from which long-term CRFs were derived.

Lead Discussant Response to Charge Question 7

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7.a. Short-term exposure mortality and morbidity CRF selections and rationale.

The decision to emphasize multi-city studies and the reasons cited to support that choice are both sound (p. 46). The specific choices of studies from which short-term CRFs were derived were good choices. It is justified to use “shrunk” estimates for these CRFs. Because there is another large multi-city mortality studies that utilizes PM_{2.5} as the exposure metric (Dominici 2007), it is not absolutely clear why the Zanobetti study was selected, although as noted above, it is a good choice. That study also satisfies the selection criteria used (p. 46).

The selected single-city studies used in the ED risk assessments were also good choices. Because the effect estimates from the single-city studies do not carry the same weight as those from the multi-city studies, addition care will needed in interpreting the ED risk estimates. Also, these ED risk assessments are necessarily limited by being only applicable to the cities from which they were generated.

Staff should consider, as a sensitivity analysis, applying the large region-specific CRFs from the Zanobetti multi-city study (p. 47), instead of just the city-specific shrunk estimates, in order to allow the mortality risk estimates to more closely parallel the morbidity (hospitalization) risk estimates which could only be based on region-specific (albeit different regions) effect estimates available from the Bell study.

While it is reasonable to use the single-pollutant PM_{2.5} model estimate, because coarse PM (here, the co-pollutant) is only weakly correlated with PM_{2.5}, it should make little difference.

The choice to use the 2-day lag effect from the Bell study for the respiratory hospitalizations CRF, largely because the effect estimate was the largest, is less defensible – this is likely biased high. Support in the REA for this choice is also based on a conclusion from the ISA (section 2.4.2.2) claiming that respiratory health effects are strongest at a lag of 2 days. This conclusion is not supported by a review of the relevant tables in the ISA (Tables 6-10 – 6-14). Sensitivity analysis results with different lag estimates from the Bell study (only lag 0 and lag 2 effects were published) would be reassuring to see. The effect of lag choice should not be restricted to an evaluation of the Moolgavkar (2003) studies.

7.b. Long-term exposure mortality and morbidity CRF selections and rationale.

The choice of the specific study (the extended follow-up of the ACS cohort – Krewski 2009) from which long-term CRFs were derived is justified. However, there are now several large cohort studies that could potentially be used for this purpose. The specific justification for selecting the Krewski study over these other cohort studies is not presented. A sense of the range of mortality effect estimates from the several cohort studies, and where that of the Krewski study lies, can be obtained by examining Figure 7-7 (p.7-124) of the ISA. The range of effect estimates is large and indicates that the effect estimate chosen for use in the risk assessment would have a large impact on risk estimates. To avoid the need for an extensive sensitivity analysis that employs effect estimates from other cohort studies, a better justification for using the Krewski study effect estimates is needed.

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Because of the myriad model estimates presented in the published findings, selection of “core” effect estimates was required for the risk assessment. The decision to select estimates from analyses that used the standard Cox proportional hazards model (i.e., the fixed effects model), that used a large set of individual-level covariates and a set of ecologic covariates, and that were based on two separate PM_{2.5} monitoring periods was probably reasonable. Justification of some of the features of the specific “core” model selected is relegated to a footnote (fixed effects vs. random effects, p.49). With regard to some model specifications, however, it is not immediately obvious which were used for the “core” risk estimates and which were relegated to a sensitivity analysis. Without reviewing the original Krewski report (only the log-linear specification was used for the fixed effects analysis), it only becomes entirely clear that the log-linear specification of the model is being used for the core risk analysis by examining Table 3-8 (p. 61) in which it is noted that the other model specifications are examined in a sensitivity analysis. It is recommended that these model choices be made more obvious