

**03-25-19 Preliminary Draft Comments from Dr. Mark Frampton on the 03-07-19 Draft CASAC PM ISA Report.**

These preliminary pre-meeting comments are from individual members of the CASAC to assist in meeting deliberations and do not represent CASAC consensus comments nor EPA policy.

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DATE

EPA-CASAC-19-XXX

The Honorable Andrew R. Wheeler  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Integrated Science Assessment for Particulate Matter*  
(*External Review Draft – October 2018*)

Dear Administrator Wheeler:

The Chartered Clean Air Scientific Advisory Committee (CASAC) met on December 12-13, 2018, to peer review the EPA's *Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)*, hereafter referred to as the Draft ISA. The CASAC's consensus responses to the agency's charge questions and individual review comments from members of the CASAC are enclosed. Major comments and recommendations are highlighted below and detailed in the consensus responses to charge questions.

Overall, the CASAC finds that the Draft ISA does not provide a sufficiently comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to fine particulate matter, ~~nor does it follow widely accepted scientific methods for deriving sound, independently verifiable, scientific conclusions from available data.~~ The CASAC recommends that the following fundamental limitations be remedied in a second draft of the ISA for CASAC review. In addition, the CASAC requests additional expertise in reviewing the second draft of the ISA.

- Lack of comprehensive, systematic review. Much* Some of the relevant and important scientific literature ~~is~~ are not reviewed, and study quality is not systematically considered.
- Inadequate evidence for altered causal determinations* The CASAC finds that the Draft ISA does not present adequate evidence to conclude that there is likely to be a causal relationship between long-term PM<sub>2.5</sub> exposure and nervous system effects; between long-term ultrafine

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particulate (UFP) exposure and nervous system effects; or between long-term PM<sub>2.5</sub> exposure and cancer.

- ~~Lack of scientific method and of verifiable derivations of conclusions. The Draft ISA and its key references do not follow standard scientific method by formulating, testing, modifying, and applying predictive hypotheses based on data. The Draft ISA does not provide clear operational definitions or systematically apply explicitly stated principles for drawing conclusions from data and studies.~~
- ~~Use of unverifiable opinions to draw major policy-relevant conclusions. The Draft ISA's major conclusions rest on subjective judgments expressed in vague and undefined terms. They are not transparently verifiable (or falsifiable) scientific statements that can be determined to be true or false by other independent scientists.~~
- ~~Lack of scientific support for policy deliberations and decision-making. The Draft ISA provides no empirically validated predictions or implications for how or whether possible future changes in particulate matter (PM) exposures would change public health risks.~~

The CASAC strongly recommends that all key conclusions in the final ISA should be supported by independently reproducible and verifiable derivations from stated data and hypotheses. All derivations of conclusions should be explained in enough detail, using standard terms with clear operational definitions, to allow the validity of the reasoning and conclusions to be independently verified.

The need for substantial revisions to the Draft ISA to provide adequate definitions, scientific method, and technical details in order to enable meaningful independent scientific review leads to the following two process recommendations:

1. The CASAC recommends development of a Second Draft ISA for CASAC review.
2. The CASAC recommends that it be provided with ~~access to~~ additional ~~technical-scientific~~ expertise, ~~as needed~~, to thoroughly review the Second Draft ISA.

Turning to the parts of the Draft ISA, the CASAC finds that the Executive Summary provides a concise and accessible summary of many of the key findings and conclusions of the Draft ISA for a broad range of audiences, but that its key findings and conclusions do not distinguish between true and estimated PM exposure values; between effects of PM and effects of confounders such as poverty and temperature; between individual and population risks; between observed changes and model-predicted changes in public health risks following changes in exposures; between assumptions and data; between results from the total body of scientific evidence and results from selected subsets of evidence; and between association and causation. This lack of clarity leads to mistaken and misleading statements. The CASAC recommends that the Executive Summary be revised to clarify these distinctions and to explicitly discuss, for each health effect, whether ambient concentrations of PM can or cannot independently cause it; discuss inconsistencies in epidemiological evidence across geographic locations (e.g., absence of PM<sub>2.5</sub>-mortality associations in some studies); evaluate the extent to which concentration-response (C-R) associations are caused by confounders such as lagged weather variables; determine the coherence or lack of it across studies when conflicting evidence is fully taken into account; and assess the influence of

**Commented [FM2]:** This is a key CASAC finding, and should be included with the overall summary in the second paragraph of the letter.

**Commented [FM3]:** Suggest removing this paragraph. Parts of it are redundant, and other phrases are unclear in meaning. The ISA is a review of the evidence. The individual studies that comprise that evidence apply "scientific methods", which are often discipline specific, with varying degrees of success. Part of the purpose of the ISA is to assess the quality of those studies, and this needs to be improved, as indicated in the preceding edited paragraph and elsewhere in this letter.

**Commented [FM4]:** Suggest removing this paragraph. The major conclusions drawn in the ISA do involve judgements based on the available scientific evidence. This is the way science works, whether we are talking about health effects of air pollution, approving a new drug for treating cancer, or the cause of global warming. Policy-relevant conclusions depend on the weight of the scientific evidence, a process which involves judgement. This differs from "unverifiable opinions". We indicate elsewhere in the letter the areas where CASAC disagrees with the EPA's conclusions regarding causality. For those conclusions, in the judgement of CASAC, the available scientific data are insufficient to support the proposed changes.

**Commented [FM5]:** Suggest removing this paragraph. The ISA does consider the available accountability studies in the context of providing support for causality determinations. However, purpose of the ISA is not to provide predictions about the consequences of future changes in PM exposures.

**Commented [FM6]:** The term "independently reproducible and verifiable derivations" is unclear here. The key conclusions should be supported by the totality of the scientific evidence. Since the key conclusions in the ISA with which CASAC disagrees are stated elsewhere, suggest removing this paragraph.

**Commented [FM7]:** This paragraph appears directed to the ISA as a whole, rather than the Executive Summary. In general, they are not reflective of the CASAC consensus on the relevant chapters.

**Commented [FM8]:** Not clear what is meant by "true" exposure values. All exposures are estimates. This statement is not reflective of the summary comments that follow for chapter 3.

**Commented [FM9]:** This statement is not reflective of the summary comments for chapters 4-11.

**Commented [FM10]:** Again these statements are not reflective of the comments and discussions for the relevant health effects chapters.

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1 error and uncertainty on the relationship between estimated PM exposure and health using appropriate  
2 technical (e.g., errors-in-variables) methods.  
3

4 The CASAC finds that Chapter 1, similar to the Executive Summary, provides an effective summary of  
5 material from subsequent chapters, ~~but that this material does not clearly characterize conditions under  
6 which reducing PM<sub>2.5</sub> exposures alone (without changing other variables that are correlated with PM<sub>2.5</sub>  
7 exposures, such as poverty or lagged values of weather variables) reduces human health risks. [The  
8 CASAC recommends that Chapter 1 should explicitly list and apply systematic review criteria used to  
9 decide which articles to include in the ISA's review of scientific evidence and to evaluate, summarize,  
10 reconcile, synthesize, and summarize their results.~~

11  
12 The CASAC finds that Chapter 2 adequately characterizes the sources, chemistry, measurements and  
13 modeling of PM<sub>2.5</sub>, PM<sub>10</sub>, and PM<sub>10-2.5</sub> (coarse fraction) and usefully describes the extent of available  
14 information on the spatial and temporal trends of ambient PM concentrations at various scales. Chapter  
15 3 clearly and accurately describes methods for exposure measurement and modeling. Errors in exposure  
16 estimates arising from different methods, and their effects on risk estimates and on estimates of  
17 concentration-response functions, should be characterized and discussed more fully. Recommendations  
18 for several additions and clarifications for both chapters are detailed in the consensus responses to  
19 charge questions.  
20

21 ~~The CASAC finds that, in the absence of clear, operational definitions for key terms and concepts,  
22 including the causal determination categories, Chapters 4-12 can lead to varying opinions about the  
23 extent to which key conclusions have been established as valid. The Draft ISA should give unambiguous  
24 operational definitions of its key terms, including its causal determination categories, to allow such  
25 conflicting interpretations to be resolved.~~ Chapter 4 provides a useful, thorough review of the  
26 deposition, clearance, retention, and translocation of inhaled PM, but the CASAC recommends  
27 additional discussion of dosimetry exposure concentrations and of how dosimetry study results can be  
28 translated to humans exposed to ambient PM concentrations.  
29

30 The CASAC finds that Chapters 5-13 do not provide ~~adequate discussions of biological plausibility, a  
31 clearly designed and executed systematic review and summary of the relevant scientific literature. They  
32 omit many several relevant and high quality studies, and mis-characterize others.~~ The CASAC  
33 recommends that study inclusion and exclusion criteria for literature referenced in Chapters 5-13 should  
34 be more explicitly stated and systematically applied. Chance, bias, and confounding should be more  
35 explicitly and completely addressed in presenting and evaluating study results. The CASAC  
36 recommends several refinements, improvements, and extensions in the presentation of biological  
37 information in Chapters 5-12, as discussed in the consensus responses to charge questions and the  
38 individual comments on Chapters 5-12. The CASAC finds that the Draft ISA does not present adequate  
39 evidence to conclude that there is likely to be a causal ~~association-relationship~~ between long-term PM<sub>2.5</sub>  
40 exposure and nervous system effects; between long-term ultrafine particulate (UFP) exposure and  
41 nervous system effects; or between long-term PM<sub>2.5</sub> exposure and cancer.  
42

**Commented [FM11]:** This statement appears to refer to accountability data. The ISA does provide a reasonable review of the available accountability studies. The problem here is not the ISA, but the limited data.

**Commented [FM12]:** These criteria are provided in the Preface, section P.3, and in the Preamble. This should be removed.

**Commented [FM13]:** At least some CASAC members were of the opinion that the causal determination categories and their descriptions were clear and adequate.

**Commented [FM14]:** This is a key CASAC finding, and should be included with the overall summary in the second paragraph of the letter.

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Clean Air Scientific Advisory Committee**

**CHAIR**

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1                                   **Consensus Responses to Charge Questions on the EPA’s**  
2                                   ***Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)***  
3

4  
5 **Overall Comments and Recommendations on the Integrated Science Assessment (ISA)**  
6

7 *Background*  
8

9 Over the past two decades, an ISA review process has evolved that puts heavy weight on judgments in  
10 deciding which health effects should be classified as having a “causal” relationship to exposure and  
11 considered further in the context of revising National Ambient Air Quality Standards (NAAQS). This  
12 process has not emphasized clear operational definitions of all key terms, or deriving and validating  
13 empirically testable and independently verifiable statements and predictions about changes in health  
14 effects caused by changing criteria pollutant exposures. It has not insisted on, or produced, thorough  
15 systematic reviews of relevant high-quality scientific literature using clearly stated, objective,  
16 independently reproducible criteria. Evaluations of evidence and conclusions presented in the course of  
17 ISA reviews since at least 2009 have also routinely conflated each of the following pairs of importantly  
18 distinct quantities:

- 19 • True vs. estimated exposure concentrations;
- 20 • Effects of criteria pollutants vs. effects of factors associated with or modifying effects of criteria
- 21 pollutants;
- 22 • Shapes of individual-level vs. population average concentration-response (C-R) functions;
- 23 • Observed changes in health effects vs. model-predicted changes in health effects;
- 24 • Assumptions vs. observations about the shapes of C-R functions;
- 25 • Association vs. causation in interpreting C-R observations.

26  
27  
28 Modern techniques for evaluating and improving the validity of expert opinions and judgments under  
29 uncertainty have not been systematically applied.  
30

31 As a result of these practices, the conclusions presented in recent ISAs and in the EPA’s  
32 *Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)*, hereafter  
33 referred to as the Draft ISA, have uncertain scientific validity as well as unclear meanings. They do not  
34 provide clear trustworthy, comprehensive, objective summaries of the scientific evidence and remaining  
35 uncertainties about changes in human health and welfare caused by changing exposures that are most  
36 essential for informing policy deliberations and decisions. The unknown scientific validity and unclear  
37 meanings of its conclusions, its reliance on subjective opinions that cannot necessarily be independently  
38 verified, and its failure to objectively and comprehensively address relevant high-quality evidence  
39 (especially from studies that conflict with the consensus opinions reached) all show that substantial  
40 improvements are needed in both the scientific content and the communication of that content to better  
41 inform users of the Draft ISA about human health and welfare effects caused by reducing particulate  
42 matter (PM) exposures.  
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**Commented [FM15]:** These views do not represent a consensus of CASAC members.

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*Major Limitations of the Draft ISA that Should be Addressed in a Revision*

Overall, the CASAC finds that the Draft ISA does not provide a comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to fine particulate matter, nor does it follow widely accepted scientific methods for deriving sound, independently verifiable, scientific conclusions from available data. The CASAC recommends that the following fundamental limitations be remedied in a second draft of the ISA for CASAC review.

**Commented [FM16]:** See earlier comments

- *Lack of comprehensive, systematic review.* Much of the relevant and important scientific literature is not reviewed. For example, in response to follow-up questions from Dr. Tony Cox from the December 12-13 public meeting, the Health Effects Institute (HEI) provided an overview of accountability studies funded by HEI, noting that “we do view accountability research as a valuable opportunity to test causality in real world settings” (Greenbaum, 2019). Table 1 of their overview (entitled “Overview of accountability studies funded by HEI”) lists 15 studies. The Draft ISA omits 14 of them. Similarly, the Draft ISA mentions none of the more than a dozen peer-reviewed scientific studies published since 2015 on the roles of inflammasomes in mediating PM<sub>2.5</sub>-induced health effects, including airway hyperresponsiveness, cardiac injury, lung and airway inflammation, atherosclerosis, neurodegenerative diseases, and reproductive toxicity. More generally, the Draft ISA does not provide a comprehensive, systematic assessment of relevant available scientific literature on PM<sub>2.5</sub> health effects.
- *Lack of scientific method and of verifiable derivations of conclusions.* The standard (hypothetico-deductive) scientific method requires specifying empirically testable generalizations, called *hypotheses*, from observations; using them to predict outcomes for new situations, typically via hypothetical calculations; comparing these predictions to observations when new situations are encountered in reality (e.g., in designed experiments, controlled trials, or natural experiments); and using discrepancies to modify and improve the initial hypotheses if needed. The scientific method is thus “A method of procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses.” ([https://en.oxforddictionaries.com/definition/scientific\\_method](https://en.oxforddictionaries.com/definition/scientific_method)). This scientific method is missing from the Draft ISA and its key references. The Draft ISA formulates no testable scientific hypotheses. It presents no validation results comparing hypothetical predictions or calculations for new situations to observations. No hypothetical analyses are performed or validated in developing the Draft ISA’s causality determinations (Vandenberg, 2019). The ISA does not provide clear operational definitions and principles explaining how evidence *should* be used to draw conclusions; illustrate them with hypothetical examples and calculations to demonstrate their soundness and utility; and then apply them to the particular evidence considered for PM to draw conclusions that can be independently verified by applying the same principles to the same evidence. Thus, the CASAC could not verify and agree on the soundness of the scientific derivations leading to the Draft ISA’s major policy-relevant conclusions because no such scientific derivations are presented. They should be included in the ISA.

**Commented [FM17]:** Agree with SL edits/comments on this statement.

**Commented [FM18]:** This very specific biological mechanism is part of cellular mechanisms of inflammation in general. Inflammation is extensively reviewed and commented upon in the ISA. This sentence should be removed.

**Commented [FM19]:** This paragraph does not represent a CASAC consensus. The purpose of the ISA is to review and summarize the relevant literature regarding PM, not to formulate or test hypotheses.

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- *Use of unverifiable opinions to draw major policy-relevant conclusions.* Instead of applying the scientific method as just described, the Draft ISA relies on judgements about which of five different labels (“causal determination” category names) will be applied to each of a number of associations between PM exposures and adverse health responses. These policy-relevant causal determination labels have no clear operational definitions or empirically testable, potentially falsifiable, implications. For example, the Draft ISA’s determination that an exposure-response association is to be labeled “causal” is not defined as implying any particular testable or falsifiable real-world consequences, such as that reducing exposure (but not correlates of exposure such as poverty or extreme temperatures) necessarily reduces risks of adverse health effects in some or all members of the exposed population. No rules or procedures for assigning a unique causal determination label to available evidence are stated; indeed, the causal determination categories are *not* mutually exclusive and collectively exhaustive (Vandenberg, 2019). This makes it logically impossible to independently reproduce or verify assignments of unique causal determination categories to data that fit more than one category (or none). In the absence of clear operational definitions in the Draft ISA, the CASAC could not reach consensus on whether some of the causal determinations in the Draft ISA were implied by or consistent with current scientific knowledge. In this sense, the Draft ISA’s major conclusions are not transparently verifiable (or falsifiable) scientific statements that can be determined to be true or false by other independent scientists. Rather, they express the subjective judgments of the authors using ambiguous terms with important policy-relevant consequences but no clearly defined operational meanings.
  - *Lack of scientific support for policy deliberations and decision-making.* Sound science can support improved policy and decision-making insofar as it provides trustworthy methods for calculating answers to decision-relevant hypothetical questions (e.g., “If reactants are mixed under stated conditions, what products would result?” or “If we were to reduce exposure concentrations by a stated amount, how would disease risks change?”) Sound scientific causal determination and risk assessment calculate and compare risks under alternative hypothetical (“counterfactual”) conditions, e.g., with exposures set to different levels; and use data to reject, if possible, “null hypotheses” such as that changes in exposure do not predict changes in health effects. Rational risk management decision-making in the public interest requires comparing the human health and welfare consequences of hypothetical alternative policy decisions and identifying those that achieve desired ends, such as protecting human health and welfare with an adequate margin of safety. Thus, hypothetical calculations are crucial to the application of science to inform rational policy and decision-making to protect human health. However, the Draft ISA omits hypothetical analyses in developing its major conclusions (e.g., causality determinations) (Vandenberg, 2019). It provides no empirically-validated predictions or implications for how or whether possible future changes in PM exposures would change public health risks. It does not discuss whether or to what extent policy makers can be confident that reducing PM<sub>2.5</sub> alone, without reducing its correlates (such as poverty, co-morbidities, co-exposures, and weather conditions correlated with high PM<sub>2.5</sub> levels) would reduce adverse health effects. This missing what-if information is crucial for the ISA to fulfill its intended role in supporting policy. Without it, the ISA provides no empirically-validated or independently-

**Commented [FM20]:** See earlier comments. This paragraph does not represent a CASAC consensus.

**Commented [FM21]:** See earlier comments. While many of the statements in this paragraph about sound scientific method are true, they are of questionable relevance here. The purpose of the ISA is to review the existing scientific evidence, not to make and validate predictions. Risk assessment and policy determinations will be made at later stages in the standard setting process.

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1           verifiable scientific basis for identifying what changes in exposures, if any, would be effective or  
2           necessary to protect human health with an adequate margin of safety.

3  
4       These limitations are unnecessary. Results of both toxicological and accountability studies are available  
5       in the peer-reviewed scientific literature that formulate testable predictive hypotheses about health  
6       effects of changes in PM<sub>2.5</sub> exposures, test them with data from natural experiments and other sources,  
7       and draw useful, empirically-grounded conclusions about whether and how much changes in PM  
8       exposure affect human health risks (Greenbaum, 2019). Much of this evidence is omitted in the Draft  
9       ISA. The ISA should include these and other high-quality scientific studies that emphasize empirical  
10      data and test predictions about effects on human health risks of changing PM exposure levels.

11  
12      *Overall Recommendations*

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14      The CASAC strongly recommends that, throughout the ISA, all key conclusions be supported by  
15      independently reproducible and verifiable derivations from stated data and hypotheses. All derivations  
16      of conclusions should be explained in enough detail, using standard terms with clear operational  
17      definitions, to allow the validity of the reasoning and conclusions to be independently verified. High-  
18      level explanations of how key conclusions are reached that lack the operational detail needed for  
19      independent verification, such as “All causality determinations... are based on the approach of  
20      considering the collective body of evidence” (Vandenberg, 2019), are not sufficient to enable the  
21      CASAC (or others) to trace and check the steps and logic that lead from stated data and hypotheses to  
22      stated conclusions. The ISA should provide this additional detailed information. The ISA should explain  
23      exactly how its conclusions are derived from evidence (using independently verifiable operational  
24      procedures); and what evidence is included and excluded and why (using explicit, independently  
25      verifiable criteria for systematic review). All assumptions or hypotheses used in deriving conclusions  
26      should be explicitly stated. Results of empirical tests of these assumptions or hypotheses should be  
27      provided wherever possible; otherwise, sensitivity and uncertainty analyses should be used to inform  
28      readers about the sensitivity of conclusions to untested hypotheses. These best practices for identifying  
29      and communicating hazard information are necessary to enable the CASAC to properly fulfill its duty to  
30      provide independent advice to the EPA Administrator on the technical bases for EPA’s NAAQS.

31  
32      The need for substantial revisions to the Draft ISA to provide adequate definitions, scientific method,  
33      and technical details in order to enable meaningful independent scientific review and to better represent  
34      what science currently knows about human health effects of PM leads to the following two process  
35      recommendations:

- 36  
37      • Create additional opportunities for review by the CASAC and the public following revision of  
38      the Draft ISA. The revised version should address all of the issues summarized herein. At a  
39      minimum, the CASAC recommends another round of review of the Draft ISA after it has been  
40      revised, with the participation of additional experts (see below). A revised version providing  
41      clear operational definitions of key terms and details of derivations of conclusions is needed to  
42      enable independent scientific review of the ISA’s scientific reasoning and conclusions. The  
43      CASAC stands ready to provide this review.

**Commented [FM22]:** See prior comments. The framework used by the EPA for determining causality was extensively discussed in the comments of individual CASAC members, and in the public meeting of 12/12-13/2018. This paragraph does not accurately reflect the results of that discussion or represent a consensus among CASAC members.

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- The CASAC recommends that it be provided with ~~access to~~ additional ~~technical-scientific~~ expertise ~~as needed to thoroughly~~ in the review ~~of~~ a revised version of the Draft ISA.

Over the past 30 years, CASAC advice to the EPA on NAAQS reviews has been assisted by expert review panels that supplement and expand the scientific expertise brought to bear. Such a review panel was appointed by the EPA for the current PM review. However, the panel was disbanded by the EPA prior to the release of the current Draft ISA.

The breadth and diversity of evidence to be considered exceeds the expertise of the statutory CASAC members, or indeed of any seven individuals. For example, the chartered CASAC has found it difficult to achieve consensus in some areas (summarized below), and to do so likely requires further scientific expertise from, and discussion with, . Some of the proposed changes in causality determinations in the Draft ISA, for example changing the causality designation of long-term exposure to UFP on nervous system outcomes from “inadequate” to “likely”, are driven primarily by animal toxicology studies. Therefore, depending in part on how the Draft ISA is revised, additional expertise is needed in the following areas:

- a. Epidemiology;
- b. Human clinical studies;
- c. Comparative toxicology, dosimetry, and extrapolation of findings in animals to humans;

~~• Depending on how the Draft ISA is revised to clarify the detailed derivations of its key conclusions, different sets of detailed expertise may add value in verifying those derivations and in commenting on the plausibility of any remaining untested assumptions and on the sensitivity of conclusions to plausible variations in those assumptions. Likely areas where access to additional expertise may prove useful include the following:~~

- ~~a-d.~~ Characterization of sampling errors and biases from continuous ambient PM measurements and satellite remote sensing aerosol optical depth (AOD) analysis;
- ~~b-c.~~ Errors and biases in dispersion modeling and photochemical grid modeling;
- ~~e-f.~~ Errors-in-variables methods and effects of exposure (and covariate) estimation errors on epidemiologic study results;
- ~~d-g.~~ Epidemiology of low-dose causal concentration-response functions;
- ~~e.~~ Comparative toxicology, dosimetry, and extrapolation of findings in animals to humans;
- ~~f-h.~~ Effects of PM on visibility impairment, climate, and materials.

The CASAC recommends that experts with relevant background, experience, and publications in these areas be identified to assist in this PM review, prior to the release of a revised ISA. Experts should be asked to review sections of the revised ISA with relevance to their expertise, provide written comments in advance of CASAC meetings, and participate in those meetings in person.

In addition, the EPA might greatly benefit by seeking and following advice from external experts (e.g., from the Good Judgement Project or related efforts in management science, decision science, and risk

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**Commented [FM23]:** This section has been combined with the text that was originally under “general comments” in the consensus responses on chapters 4-12.

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1 analysis) on how to revise the ISA review process to make better use of scientific judgment and diverse  
2 sources of scientific evidence and how best to avoid or overcome common pitfalls of consensus  
3 judgment processes (e.g., Dhami et al., 2015; Tetlock et al., 2017). Such meta-expertise could help to  
4 maximize the value from EPA's investment in expertise and literature reviews of health effects that  
5 could be prevented by reducing PM exposures.

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7  
8 **Executive Summary**

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10 *The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of*  
11 *the PM ISA for a broad range of audiences. Please comment on the **clarity** with which the Executive*  
12 *Summary communicates the key information from the PM ISA. Please provide **recommendations on***  
13 ***information that should be added** or information that should be left for discussion in the subsequent*  
14 *chapters of the PM ISA. (Emphases added.)*

15  
16 The CASAC finds that the Executive Summary provides a concise and accessible summary of many of  
17 the key findings and conclusions of the Draft ISA for a broad range of audiences, but that it does not  
18 accurately represent other key findings or the totality of available high-quality scientific evidence. The  
19 material summarized is unclear in the following respects. Statements of key findings and conclusions do  
20 not distinguish between true and estimated PM exposure values; between effects of PM and effects of  
21 correlates of PM (such as poverty, lagged daily temperature extreme, or humidity); between individual  
22 health risks and population averages of individual health risks; between observed changes and model-  
23 predicted changes in public health risks following changes in exposures; between assumptions and data  
24 on shapes of C-R functions; between results from the total body of scientific evidence and results from  
25 selected subsets of evidence; and between association and causation. For example, the Executive  
26 Summary refers repeatedly to the shape of the C-R relationship in contexts where it appears that what is  
27 meant is actually the shape of the *historical population average* of individual effect indicators plotted  
28 against *estimated* concentrations in *selected* populations, averaged over unspecified values of other  
29 variables that greatly affect the shape of the C-R association, such as weather, demographic, and  
30 socioeconomic variables. The shape of the C-R relationship defined this way has no necessary  
31 implications or relevance for the shape of the C-R function describing how future changes in PM would  
32 change individual or population health risks. (For example, their slopes can have opposite signs, as in  
33 Simpson's paradox).

34  
35 As a consequence of these blurred distinctions, the Draft ISA does not clearly communicate what  
36 science has revealed about the real-world effects of changing PM exposures on human health and  
37 welfare – and hence about whether or under what conditions changes in PM are needed to protect human  
38 health. Substantial discordant and conflicting evidence remains ignored or unresolved, leading to  
39 repeated assertions that the literature shows consistent and coherent positive associations when in fact it  
40 shows a mixture of positive and negative results. How information was selected for inclusion or  
41 exclusion in the Draft ISA is not always clear. How, if at all, its major conclusions would change if other  
42 valid selections of information were made and if discrepancies among study results were more  
43 adequately resolved has not been described. In addition:

**Commented [FM24]:** Many of the comments in this section are directed at the ISA as a whole, and especially at the framework for determining causality. These should be separated from comments on the Executive Summary, which should be limited to the degree to which the ES accurately reflects and expresses the key findings and conclusions of the ISA as a whole.

**Commented [FM25]:** These statements do not reflect CASAC consensus.

**Commented [FM26]:** These comments about the ISA discussion of C-R relationships do not reflect CASAC consensus.

**Commented [FM27]:** This is not an accurate assessment of most of the draft ISA, and such sweeping statements are inappropriate. There are specific areas of weakness in the ISA that are detailed elsewhere in this report. In general, these statements do not reflect CASAC consensus. The ISA is not the appropriate document in which to address "...whether or under what conditions changes in PM are needed to protect human health."

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- Key terms used to communicate findings are highly ambiguous and are not clearly defined, especially those related to exposure, cause and effect.
- The Draft ISA leaves unclear whether or to what extent the human health risks attributed to PM are in fact jointly caused by weather, demographic, socioeconomic, and health variables such as temperature extremes, sex and age, income, and obesity; and whether or to what extent reducing PM exposures alone could reduce risk to human health and welfare.
- The Draft ISA's causal determination conclusions make no clear, testable, potentially falsifiable, empirically validated predictions about the existence or direction of effects on human health risks of changing PM exposures.
- Evidence cited to support causal determination judgments relies on untested modeling assumptions of unknown validity. A prevalent untested assumption is that observed PM concentration-response associations are not fully explained by well-known but omitted confounders, such as lagged daily minimum and maximum temperatures and humidity. Thus, the final causal determination judgments represent an unclear mix of factual evidence and interpretive assumptions.

This lack of clarity in the Executive Summary leads to several mistaken and misleading statements, including the following:

- The Executive Summary says that "The causality determinations for PM<sub>2.5</sub> reflect the total body of scientific evidence" but in fact these determinations ignore large bodies of relevant scientific evidence, including 14 of the 15 references tabulated by HEI for accountability studies in Table 1 of Greenbaum (2019).
- The Executive Summary states that a causality determination of "causal" or "likely to be causal" reflects "the highest degree to which the evidence reduces chance, confounding, and other biases in the exposure-health effect relationship." In reality, however, these determinations reflect many studies that do not control at all – let alone "to the highest degree" – for important confounders such as poverty and temperature. Examples are given in the individual comments.
- The Executive Summary does not accurately reflect the extent of inconsistent, inconclusive, and ambiguous evidence on PM exposure-response associations in the literature. The Executive Summary provides a narrative of consistent, positive associations. It refers to: *consistent, positive associations observed for asthma and chronic obstructive pulmonary disease (COPD) emergency department visits and hospital admissions; consistent, positive associations between PM<sub>2.5</sub> and respiratory mortality; consistent, positive associations between short-term PM<sub>2.5</sub> exposure and cardiovascular-related emergency department visits and hospital admissions; consistent, positive associations between long-term PM<sub>2.5</sub> exposure and cardiovascular mortality; primarily consistent, positive associations between long-term PM<sub>2.5</sub> exposure and lung cancer incidence and mortality; and consistent, positive associations between short-term PM<sub>2.5</sub> exposure and total mortality.* The CASAC finds that this account does not fully represent the mix of evidence in the underlying scientific literature, which includes many individual studies and

**Commented [FM28]:** Specifics are needed here.

**Commented [FM29]:** These statements do not reflect CASAC consensus.

**Commented [FM30]:** These statements do not reflect CASAC consensus.

**Commented [FM31]:** See comments by SL; several of those studies did not measure PM concentrations, and therefore did not meet that inclusion criterion

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1 meta-analyses that do not report consistent, positive associations. Examples are given in the  
2 individual comments.

- 3 • The Executive Summary states that “In summary, exposure error tends to produce  
4 underestimation of health effects in epidemiologic studies of PM exposure, although bias in  
5 either direction can occur.” The CASAC finds no justification for this generalization and notes  
6 that the underlying scientific literature (not cited in the Draft ISA) discusses the fact that  
7 exposure estimation error in many cases tends to produce substantial over-estimates of health  
8 effects at low exposure concentrations. References are given in the individual comments.
- 9 • The Executive Summary states that “Evidence from U.S. studies examining short-term PM<sub>2.5</sub>  
10 exposure and mortality indicate a linear relationship at concentrations as low as 5 µg/m<sup>3</sup> with  
11 cut-point analyses providing no evidence of a threshold. ... Epidemiologic studies of long-term  
12 PM<sub>2.5</sub> exposure and mortality used a variety of statistical approaches and cut-point analyses,  
13 which support a linear, no-threshold relationship for total (nonaccidental) mortality, especially at  
14 lower ambient PM<sub>2.5</sub> concentrations, with confidence in some studies in the range of 5–8 µg/m<sup>3</sup>.  
15 Additionally, there is initial evidence indicating that the slope of the C-R curve may be steeper  
16 (supralinear) at lower concentrations for cardiovascular mortality.” The CASAC finds that these  
17 statements do not distinguish between true and estimated concentrations. In this regard, they are  
18 not correct as stated. Some of the relevant scientific literature not cited in the Draft ISA shows  
19 that exposure estimation errors can conceal exposure-response thresholds if they exist; it is  
20 therefore not appropriate to interpret lack of a threshold in estimated exposure-response data as  
21 evidence for a lack of threshold in the true exposure-response relationship or as supporting a  
22 linear no-threshold relationship.

23  
24 The CASAC agrees with the statement in the Executive Summary that “Important considerations  
25 include: (1) determining whether laboratory studies of humans and animals, in combination with  
26 epidemiologic studies, inform the biological mechanisms by which PM can impart health effects and  
27 provide evidence demonstrating that PM exposure can independently cause a health effect; (2)  
28 determining whether there is consistency in epidemiologic evidence across various geographic locations,  
29 populations, and methods used to estimate PM exposure; (3) evaluating epidemiologic studies that  
30 examine potential influence of factors (i.e., confounders) that could bias associations observed with PM  
31 exposure; (4) determining the coherence of findings integrated across controlled human exposure,  
32 epidemiologic, and toxicological studies; and (5) making judgments regarding the influence of error and  
33 uncertainty on the relationship between PM exposure and health effects in the collective body of  
34 available studies.” The CASAC recommends that the ISA address these considerations explicitly in the  
35 Executive Summary. For example, a revised version of Table ES-1 could note, for each health effect,  
36 whether relevant toxicology and inflammation biology demonstrate that ambient concentrations of PM  
37 can or cannot independently cause it; discuss inconsistencies in epidemiological evidence across  
38 geographic locations (e.g., absence of PM<sub>2.5</sub>-mortality associations in some studies); evaluate the extent  
39 to which C-R associations are caused by confounders such as lagged weather variables; determine the  
40 coherence or lack of it across studies when conflicting evidence is fully taken into account; and assess  
41 the influence of error and uncertainty on the relationship between estimated PM exposure and health  
42 using appropriate technical (e.g., errors-in-variables) methods.

Commented [FM32]:

Commented [FM33]: All concentration and exposure data in epidemiological air pollution studies represent estimates. The “true” exposure of a given person to a given pollutant at a given point in time is unknowable.

Commented [FM34]: These kinds of detailed evaluations are more appropriate for presentation in the relevant chapters than in the Executive Summary. The areas in which additional information is needed are commented upon elsewhere. This recommendation does not represent CASAC consensus.

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1 The CASAC recommends the following steps for improving the clarity and value of the Executive  
2 Summary:

- 3
- 4 1. *Define key terms clearly and operationally.* Add a glossary with definitions of all key terms used  
5 to communicate about exposure, cause, and effect. Use standard terms, concepts, and methods  
6 from mainstream epidemiology as appropriate in place of current ambiguous and undefined  
7 terms such as “effect,” “independent effect,” and “causal.” For example, use “controlled direct  
8 effect” or “total effect” to disambiguate importantly different meanings of the ambiguous term  
9 “effect.” Provide operational definitions for key terms.
- 10 2. *Revise the definitions of causal determination categories for clarity, correctness, and*  
11 *consistency.* For example, if the categories are intended to be mutually exclusive, then the words  
12 used to define them should not allow more than one category to match the same description of  
13 evidence. The definitions should be clear enough so that different people can apply them  
14 independently to the same simple test cases and get the same answers. Operational definitions  
15 and empirically testable (and potentially falsifiable) implications or predictions for each category  
16 should be clearly stated. How to classify uncertain evidence that appears to be consistent with  
17 more than one category should be clarified. We strongly recommend that the ISA define and use  
18 a concept of causation in which exposure is considered to be a cause of an effect if and only if  
19 reducing exposure without changing other variables (e.g., income, temperature, or co-pollutants)  
20 would reduce the effect. (This is sometimes referred to as “manipulative causation.”)
- 21 3. *Distinguish between true and estimated exposures.* Do not ignore exposure estimation errors. Do  
22 not accept at face value the results of studies that ignore them.
- 23 4. *State and apply explicit inclusion and exclusion criteria for selecting evidence to evaluate.*  
24 Provide independently reproducible methods or rules for applying the criteria to individual  
25 studies and results. Document the results of applying them. For example, if the EPA decides to  
26 exclude studies that report PM C-R associations without controlling for well-known potential  
27 confounders such as temperature or income, then the results of applying this exclusion criterion  
28 to each study should be documented.
- 29 5. *Provide explicit, objective, independently verifiable criteria for how individual studies and*  
30 *evidence are to be evaluated and their results synthesized, reconciled, and summarized.* Specify  
31 criteria and methods for how results are to be combined or synthesized, resolved when they  
32 conflict, and summarized.
- 33 6. *Document the results* of applying these criteria and methods systematically to reach the ISA’s  
34 conclusions. Derive all conclusions about C-R functions and causal determinations via explicit,  
35 independently verifiable derivations using stated criteria and methods from explicitly stated  
36 premises (facts, data, and assumptions) derived from the previously included and evaluated  
37 studies.
- 38 7. *Present explicit derivations for all key conclusions,* clarifying the exact sequence of steps used to  
39 derive them, in enough detail so that they can be independently checked and verified.
- 40 8. *Discuss sensitivity and validation of conclusions.* State the testable predictions implied by the  
41 conclusions and by any untested assumptions on which they depend (e.g., that reported  
42 associations are not fully explained by omitted confounders). Discuss the extent to which these  
43 testable implications have been tested and verified and the extent to which alternative

**Commented [FM35]:** This does not reflect CASAC consensus. The causal determination categories as used in this as well as previous ISAs, provide clear and workable descriptions of the level of certainty for potentially causal relationships. The concept of causation “strongly recommended” here (“...exposure is considered to be a cause of an effect if and only if reducing exposure without changing other variables...would reduce the effect”) would essentially eliminate determination that a PM effect is causal because such a requirement is unachievable in accountability studies. That is one of the major challenges in accountability studies: other variables are always changing.

**Commented [FM36]:** See previous comments.

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1 explanations and interpretations of the same facts and data are supported or refuted by available  
2 data, or remain untested. Discuss the extent to which conclusions depend on unverified  
3 assumptions and to modeling uncertainties.

4  
5 Adding these components to the Draft ISA and its Executive Summary will promote more objective,  
6 sound, and reproducible science in the ISA process and help to better meet the EPA's objectives for  
7 thorough and transparent assessment.

8  
9 Following steps 6 and 7 of these additions, the summaries and conclusions in the Draft ISA and its  
10 Executive Summary should be revisited in light of the results and revised as necessary for accuracy. For  
11 example, the Executive Summary currently refers multiple times to "consistent positive associations"  
12 that support its C-R findings and causal determinations. However, many other reviews of the literature  
13 have discussed important inconsistencies or negative findings that are ignored or left unresolved in the  
14 Draft ISA and that are not represented in its summary statements. Following a systematic, explicit  
15 process for selecting evidence to consider and for evaluating and summarizing that evidence may require  
16 revising conclusions and summary statements in the Draft ISA to better recognize and account for  
17 discordant evidence and inconsistencies from high-quality studies.

18  
19 The Draft ISA and Executive Summary repeatedly suggest that C-R functions are approximately linear,  
20 with no evidence of thresholds, even at PM<sub>2.5</sub> exposure concentrations below current NAAQS levels.  
21 For example, p. ES-21 states that "Evidence continues to support a linear, no-threshold concentration-  
22 response relationship." However, the evidence referred to comes mainly from studies that do not  
23 distinguish between true exposure levels and estimated exposure levels. Such studies typically cannot  
24 detect exposure thresholds even if they exist, due to ignored measurement errors in exposure estimates;  
25 these flatten out threshold C-R functions and make them appear to be linear (e.g., Cox, 2018). This  
26 appearance is therefore not valid evidence for a true linear no-threshold C-R function. The Draft ISA  
27 and its Executive Summary discuss measurement error (e.g., Sections 3.4.2 and 3.4.5), but mistakenly  
28 conclude that "In summary, exposure error tends to produce underestimation of health effects in  
29 epidemiologic studies of PM exposure, although bias in either direction can occur." This conclusion is  
30 based on analyses and simulation studies such as that of Cefalu and Dominici (2014), which states that  
31 "We assumed simple linear relationships between the outcome, the exposure, and the confounders." It  
32 does not hold more generally, e.g., if exposure thresholds are important. The ISA should revisit, and if  
33 necessary correct, conclusions on effects of measurement errors and on what is known about the shapes  
34 of C-R functions.

35  
36 The ISA should also carefully reconsider the use and interpretation of conclusions from studies with  
37 important uncontrolled confounders (temperature is a prevalent example), untested and unverified  
38 modeling assumptions that drive conclusions (such as that unmeasured lagged temperatures are not  
39 important confounders), ignored errors and uncertainties in exposure estimates, and data from  
40 experiments with species, systems or exposure conditions having no clear relevance to real-world human  
41 health effects. The ISA should clarify the extent to which its causal determination and C-R conclusions  
42 change if evidence is restricted to studies that properly control for major confounders (e.g., temperature  
43 and income), exposure estimation error, and model uncertainties and assumptions. Conclusions on

Commented [FM37]: See previous comment.

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1 shapes of C-R functions and causal determinations for mortality, lung cancer, cardiovascular, and  
2 neurological effects should be carefully reconsidered in light of these potential threats to valid  
3 conclusions. If associations have several possible causal interpretations that are equally consistent with  
4 the data (e.g., that (a) elevated levels of PM<sub>2.5</sub> cause increased same-day elderly mortality rates; or (b)  
5 daily temperature extremes over the past two weeks cause both and fully explain their observed  
6 association), then the ambiguity of the data should be acknowledged. The EPA and CASAC members  
7 should not seek to reach consensus agreements on the causal interpretation of ambiguous data when  
8 there is no factual basis for doing so, nor should the ISA assign causal determination categories when  
9 doing so requires using personal opinions that go beyond what can be objectively determined from  
10 available data. Extensive research in management science, decision science, and risk analysis has  
11 established that scientific judgment is prone to many errors and biases and is not usually a reliable guide  
12 to the truth, although initiatives in the intelligence community and decision science, such as the Good  
13 Judgment Project, have developed effective techniques to improve individual and group judgments  
14 through extensive practice and feedback using testable, quantitative predictions (e.g., Dhimi et al., 2015;  
15 Tetlock et al., 2017). Therefore, the ISA should add uncertainty and sensitivity analyses indicating the  
16 extent to which causal determinations for C-R relationships are underdetermined by available data and  
17 how sensitive conclusions are to uncertainties about modeling assumptions, exposures, unmeasured  
18 variables, and residual confounding.

19  
20  
21 **Integrated Synthesis (Chapter 1)**

22  
23 *Chapter 1 presents an integrated summary and the overall conclusions from the subsequent detailed*  
24 *chapters of the PM ISA and characterizes available scientific information on policy-relevant issues.*  
25 *Please comment on the **usefulness and effectiveness of the summary** presentation. Please provide*  
26 ***recommendations on approaches that may improve the communication** of key findings to varied*  
27 *audiences **and the synthesis** of available information across subject areas. **What information should be***  
28 ***added** or is more appropriate to leave for discussion in the subsequent detailed chapters? (Emphases*  
29 *added.)*

30  
31 The CASAC finds that Chapter 1, similar to the Executive Summary, provides an effective summary of  
32 material from subsequent chapters, but that this material does not clearly characterize conditions under  
33 which reducing PM<sub>2.5</sub> exposures alone (without changing other variables that are correlated with PM<sub>2.5</sub>  
34 exposures, such as poverty or lagged values of weather variables) reduces human health risks; nor does  
35 it characterize whether or to what extent reducing PM<sub>2.5</sub> concentration levels further would materially  
36 affect human health. The uncertainty and sensitivity of conclusions to further information is not clearly  
37 described.

38  
39 Also similar to the Executive Summary, Chapter 1 repeatedly describes findings as consistent and  
40 coherent. This narrative is misleading, insofar as it disregards and leaves unresolved substantial  
41 conflicting evidence and findings from high-quality individual studies that present evidence to the  
42 contrary. For example, Section 1.4.1.5 states that “Consistent with the conclusions of the 2009 PM ISA,  
43 more recently published scientific evidence reaffirms and further strengthens that there is a ‘causal

**Commented [FM38]:** See previous comments. This is not a CASAC consensus statement.

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1 *relationship*’ between both short- and long-term PM<sub>2.5</sub> exposure and total mortality. These causality  
2 determinations are based on the consistency of findings across a large body of epidemiologic studies and  
3 coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies,  
4 as well as biological plausibility for respiratory and cardiovascular morbidity effects by which short- and  
5 long-term PM<sub>2.5</sub> exposure could result in mortality.” This statement ignores findings from studies in  
6 which neither short-term nor long-term PM<sub>2.5</sub> exposures are found to be associated with total mortality,  
7 and in which changes in PM<sub>2.5</sub> are not found to affect changes in total (or cardiovascular) mortality rates.  
8 A few examples of such discordant evidence include the following (further examples and discussion are  
9 provided in Dr. Cox’s individual comments):

- 10 • Enstrom (2015) states that “These epidemiologic results do not support a current relationship  
11 between fine particulate pollution and total mortality in elderly Californians.”
- 12 • Greven et al. (2011) concludes that “Based on the local coefficient alone, we are not able to  
13 demonstrate any change in life expectancy for a reduction in PM<sub>2.5</sub>.”
- 14 • You et al. (2018) reports that “There is no statistically significant association between either  
15 ozone or PM<sub>2.5</sub> and acute human mortality” in a large dataset for eight air basins in California for  
16 the years 2004-2007, after statistical adjustment for seasonal and weather effects. (The Draft  
17 ISA, p. 11-9, discusses other negative studies by Young et al., 2017, and Lanzinger et al., 2016.)
- 18 • Zhou et al. (2015) found that “After controlling for temperature, humidity, dew point and wind,  
19 the statistical significance [of the association between PM<sub>2.5</sub> levels and mortality] disappears in  
20 all urban districts.”

21  
22  
23 The usefulness and effectiveness of the summary presentation in Chapter 1 are undermined by its  
24 omission of results from relevant high-quality studies that conflict with the narrative of consistency and  
25 coherence. Readers who wish to consider the totality of scientific evidence must look elsewhere for  
26 thorough discussions of such conflicting evidence and to understand important factors such as the roles  
27 of recent temperature and humidity in causing adverse health effects attributed to PM<sub>2.5</sub> exposures. A  
28 thorough scientific understanding of C-R functions for PM and mortality and morbidity that would  
29 explain puzzling observations, such as why large reductions in particulate air pollution in Ireland had no  
30 detectable effects on total mortality rates or cardiovascular rates, requires considering the total evidence  
31 from all relevant high-quality studies. The Draft ISA does not provide such a comprehensive review and  
32 summary of results from relevant scientific literature.

33  
34 To improve the synthesis of available information across subject areas and the communication of key  
35 findings to varied audiences, the CASAC recommends that the Chapter 1 of the ISA should add the  
36 following components:

- 37 • *Explicitly list systematic review criteria* used to decide which articles to include in the ISA’s  
38 review of scientific evidence and how to evaluate, summarize, reconcile, and synthesize them.  
39 Study selection criteria should be clearly stated. Criteria for excluding studies and conclusions  
40 (e.g., failure to control for known confounders such as temperature extremes in recent weeks, or  
41 conflating estimated exposures with true exposures), as well as criteria for including them,  
42 should be articulated and systematically applied to the literature. Criteria for evaluating  
43

**Commented [FM39]:** This does not represent CASAC consensus. Overall the ISA presents a reasonably balanced view of the convincing evidence linking long-term PM<sub>2.5</sub> exposure and mortality.

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1 It would be helpful for the CASAC to have ready access to an expert in errors-in-variables methods and  
2 effects of exposure (and covariate) estimation errors in epidemiology to allow for a better understanding  
3 of the impact of exposure errors on epidemiologic study results.  
4  
5

6 **Comments on Chapters 4 -12**

7  
8 General Comments

9  
10 ~~Additional expertise is needed for the CASAC to provide a thorough review of the PM NAAQS~~  
11 ~~documents. The breadth and diversity of evidence to be considered exceeds the expertise of the~~  
12 ~~statutory CASAC members, or indeed of any seven individuals. For example, the chartered CASAC has~~  
13 ~~found it difficult to achieve consensus in some areas (summarized below), and to do so likely requires~~  
14 ~~further scientific expertise from, and discussion with, epidemiologists and additional experts in human~~  
15 ~~clinical studies and toxicology. Some of the proposed changes in causality determinations in the Draft~~  
16 ~~ISA, for example changing the causality designation of long term exposure to UFP on nervous system~~  
17 ~~outcomes from “inadequate” to “likely”, are driven primarily by animal toxicology studies. Therefore,~~  
18 ~~additional expertise is needed in comparative toxicology, dosimetry, and extrapolation of findings in~~  
19 ~~animals to humans.~~

20  
21 ~~Over the past 30 years, CASAC advice to the EPA on NAAQS reviews has been assisted by expert~~  
22 ~~review panels that supplement and expand the scientific expertise brought to bear. Such a review panel~~  
23 ~~was appointed by the EPA for the current PM review. However, the panel was disbanded by the EPA~~  
24 ~~prior to the release of the current ISA.~~

25  
26 ~~The CASAC now requests that experts with relevant background, experience, and publications be~~  
27 ~~identified to assist in this PM review, prior to the release of a revised ISA. Experts should be asked to~~  
28 ~~review sections of the revised ISA with relevance to their expertise, provide written comments in~~  
29 ~~advance of CASAC meetings, and participate in those meetings in person.~~

30  
31 Causality Determination of Mortality from PM<sub>2.5</sub> Exposure

32  
33 The CASAC is unable to reach consensus on the causality determination of mortality from PM<sub>2.5</sub>  
34 exposure.  
35

36 **Some members of the CASAC** think that the EPA must better justify their determination that short-  
37 term or long-term exposure to PM<sub>2.5</sub> causes mortality. The EPA should address the following  
38 considerations:  
39

- 40 • Biological action of PM. How do low concentrations of PM<sub>2.5</sub> cause mortality? The EPA should  
41 discuss not just general, possible mechanisms, but specifically how ambient concentrations of  
42 PM<sub>2.5</sub> can move into and through the biological systems in the body to activate a cascade of  
43 effects that ultimately lead to a person’s death.