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 comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to ~~fine~~ particulate matter (PM), 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.

- *Lack of comprehensive, systematic review.* ~~Much~~Some of the relevant and important scientific literature is not reviewed and study quality is not systematically considered.
- *Lack of scientific method and of verifiable derivations of conclusions.* The Draft ISA and its key references do not follow the 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.

Commented [SL1]: I think that this point is already made above, and so I recommend that this paragraph be removed.

The need for substantial revisions to the Draft ISA to provide adequate definitions, scientific method, and technical details and methods 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 expertise, as needed, to thoroughly review the Second Draft ISA.

Commented [SL2]: I suggest that this be moved to the end of the letter.

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. However, the Executive Summary's~~, but that its~~ key findings and conclusions (as well as those in much of the rest of the document) 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 $PM_{2.5}$-mortality associations in some study cities~~ies~~); evaluate the extent to which concentration-response (C-R) associations are caused by confounders such as lagged weather variables; determine the coherence (or lack thereof) ~~of it~~ across studies when conflicting evidence is fully taken into account; and assess the influence of error and uncertainty on the relationship between estimated PM exposure and health using appropriate technical (e.g., errors-in-variables) methods.

The CASAC finds that Chapter 1, similar to the Executive Summary, provides an effective summary of material from subsequent chapters, but that this material does not clearly characterize conditions under which reducing $PM_{2.5}$ exposures alone (without changing other variables that are correlated with $PM_{2.5}$ exposures, such as poverty or lagged values of weather variables) reduces human health risks. The

03-20-19 Preliminary Draft Comments from Dr. Sabine Lange 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.
-Do Not Cite or Quote-

CASAC recommends that Chapter 1 should explicitly list and apply systematic review criteria for inclusion of relevant studies, ~~used to decide which articles to include in the ISA's review of scientific evidence~~ and to evaluate~~, summarize~~, reconcile, synthesize, and summarize their results.

The CASAC finds that Chapter 2 adequately characterizes the sources, chemistry, measurements, and modeling of $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ (coarse fraction) and usefully describes the extent of available information on the spatial and temporal trends of ambient PM concentrations at various scales. However, clarification is required on some of the PM monitoring and modeling information. Chapter 3 for the most part clearly and accurately describes methods for exposure measurement and modeling, although corrections are needed for some of the modeling information. Errors in exposure estimates arising from different methods, and their effects on risk estimates and on estimates of ~~concentration-response~~C-R functions, should be characterized and discussed more fully. Recommendations for several additions and clarifications for both chapters are detailed in the consensus responses to charge questions.

Commented [SL3]: And UFP?

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

Commented [SL4]: I don't think that operational definitions will allow us to resolve our varying opinions on whether PM causes mortality at ambient concentrations. I suggest deleting, and I have added suggested text to the Chapters 5-12 paragraph to address the difference in opinion amongst CASAC members.

The CASAC finds that Chapters 5-13 do not provide a clearly designed and executed systematic review and summary of the relevant scientific literature. They omit ~~many~~some relevant and high-quality studies. The CASAC recommends that study inclusion and exclusion~~,~~ and study quality criteria for literature referenced in Chapters 5-13 ~~should~~ be explicitly stated and systematically applied. Chance, bias, and confounding should be more explicitly and completely addressed in presenting and evaluating study results. The CASAC recommends several refinements, improvements, and extensions in the presentation of biological information in Chapters 5-12.~~,~~ Our recommendations include improving the organization and presentation of the document; revising the biological plausibility sections to clarify and correct several pathways; including concentration information when discussing study results; identifying no- and low-adverse effect levels from the human controlled exposure studies; addressing discrepant results between studies; and further integrating study results in Chapter 12. The CASAC did not reach consensus on whether the EPA had adequately considered and caveated the presented C-R functions. Details about the CASAC's recommendations for Chapters 5-12 are~~as discussed~~ in the consensus responses to charge questions and the individual comments~~ on Chapters 5-12~~.

For the causality determinations described in Chapters 5-11, ~~T~~the CASAC finds that the Draft ISA does not present adequate evidence to conclude that there is likely to be a causal association between long-term $PM_{2.5}$ exposure and nervous system effects; between long-term ultrafine particulate (UFP) exposure and nervous system effects; or between long-term $PM_{2.5}$ exposure and cancer. The CASAC

members had varying opinions on whether there are robust and convincing evidence to support the EPA's conclusion that there is a causal relationship between $PM_{2.5}$ exposure and mortality.

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The CASAC finds that Chapter 13 provides evidence supporting a causal relationship between PM and visibility impairment, climate effects, and effects on materials, but recommends that the Draft ISA include more analyses for different size fractions and add discussion of the direct effects of PM or other pollutants (e.g., photochemical oxidants) on visual acuity.

The CASAC appreciates the opportunity to provide advice to the EPA on the Draft PM ISA and looks forward to the agency's response.

Sincerely,

Dr. Louis Anthony Cox, Jr., Chair
Clean Air Scientific Advisory Committee

Enclosures

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee

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

Overall Comments and Recommendations on the Integrated Science Assessment (ISA)

NAAQS Causality Determination Process~~Background~~

Over the past two decades, an ISA review process has evolved that puts heavy weight on judgment calls~~s~~ in deciding which health effects should be classified as having a "causal" relationship with~~to~~ exposure~~ and considered further in the context of revising National Ambient Air Quality Standards (NAAQS)~~. This process has not emphasized clear operational definitions of all key terms. An operational definition is one that defines the effect in terms of how it is measured in order to provide precision and the ability to compare across studies, for example, defining an adverse effect on lung function as a decrease in forced expiratory volume of more than 10%. The causal determination process has also not adequately~~, or~~ derived~~ing~~ and validated~~ing~~ empirically testable and independently verifiable statements and predictions about changes in health effects caused by changing criteria pollutant exposures. In addition, in the NAAQS review the EPA ~~It~~ has not~~ insisted on, or~~ produced ~~,~~ thorough systematic reviews of relevant~~ high-quality~~ scientific literature using clearly stated, objective, independently reproducible criteria with transparent study quality evaluations. Evaluations of evidence and conclusions presented in the course of ISA reviews since at least 2009 have also routinely conflated each of the following pairs of importantly distinct quantities:

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

Modern techniques for evaluating and improving the validity of expert opinions and judgments under uncertainty have also not been systematically applied.

As a result of these practices, the conclusions presented in recent ISAs and in the EPA's *Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)*, hereafter referred to as the Draft ISA, have uncertain scientific validity as well as unclear meanings. The conclusions ~~y~~ do not provide clear trustworthy, comprehensive, objective summaries of the scientific evidence and remaining uncertainties about a crucial policy-relevant question: will changing exposures to particulate matter (PM) cause changes in human health and welfare~~ caused by changing exposures that are most essential for informing policy deliberations and decisions~~. The unknown scientific validity and unclear meanings of the Draft ISA's ~~its~~ conclusions, its reliance on subjective opinions that cannot necessarily be independently verified, and its failure to objectively and comprehensively address

Commented [SL5]: These two first sections are presented as overall comments and recommendations, but they address causality almost exclusively without really summarizing the other findings. I think that these should be in a separate section labeled "Process for Causal Determination" that is after the overall recommendations, but before the chapter-specific comments.

Commented [SL6]: This isn't really background, it is about the historical NAAQS causality process

relevant high-quality evidence (especially from studies that conflict with the consensus opinions reached) all show that the Draft ISA requires substantial improvements ~~are needed~~ in both the scientific content and the communication of that content to better inform ~~users of the Draft ISA about~~ human health and welfare effects caused by reducing ~~particulate matter (~~PM ~~)~~ exposures.

Major Limitations in the Causality Determinations 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~~ PM~~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.

- *Lack of a comprehensive ~~,~~ systematic review.* The Draft ISA does not provide a comprehensive, systematic assessment of relevant available scientific literature on PM health effects, and ~~Much~~some 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. Four of these studies could provide useful information about the relationship between coarse, fine, or ultra fine PM and health effects, but were omitted by the Draft ISA (Peters et al.. 2009, Noonen et al. 2011, Zhang et al. 2013, and Russell et al. 2018). ~~The Draft ISA omits 14 of them.~~ Similarly, the Draft ISA often does not discuss results from some highly relevant controlled human exposures studies, such as the results of Gong et al. 2004 or Urch et al. 2010 on lung function effects in asthmatics, or Langrish et al. 2014's analysis of cardiac arrhythmias. ~~mentions none of the more than a dozen peer-reviewed scientific studies published since 2015 on the roles of inflammasomes in mediating $PM_{2.5}$-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 $PM_{2.5}$ health effects.~~
- *Lack of scientific method and ~~of~~ verifiable derivations of conclusions.* Instead of relying on qualitative summaries and expert judgements to draw conclusions about the health and welfare effects of PM, the ISA should use the scientific method to generate and test hypotheses, and to draw objective reproducible conclusions. The standard (hypothetico-deductive) scientific method requires specifying empirically testable generalizations (hypotheses)~~, 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,~~

Commented [SL7]: This does belong in the general overview, but the accountability studies should be in a later bullet point.

Commented [SL8]: The following of the HEI references wouldn't have met EPA's inclusion criteria (i.e. they don't have info about coarse PM, or fine PM, or UFP): Clancy 2002 & Dockery 2013 (Irish coal ban, no total PM measurement); Kelly 2011a & 2011 b (congestion changes in London; PM10); Morgenstern 2012 (looked at pollutant changes with regulation, not health effects); Freedman 2001 & Peel 2010 (Atlanta Olympics, PM10); Hedley 2002 & Wong 2010 (Hong Kong emissions changes, PM10); Ziegler 2016 (looked at health effects changes with PM10 only). They may still be informative, but don't directly inform the effects of coarse, fine, or UF PM.

Commented [SL9]: I have added these references to the reference list.

Commented [SL10]: I don't think that this is a great example to use in the general summary – many of those studies were conducted in vitro, making it difficult to determine their relevance to ambient PM exposures in humans.

Commented [SL11]: For example?

~~consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses."~~ ~~(https://en.oxforddictionaries.com/definition/scientific_method).~~ This scientific method is missing from the Draft ISA and its key references. While t~~T~~he Draft ISA draws conclusions that could be tested as a scientific hypothesis using available information, it does not present the conclusions as hypotheses, nor does it test them. ~~formulates no testable scientific hypotheses.~~ The Draft ISA ~~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.

- *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~~consistently -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 on the expected outcomes of reducing PM concentrations~~s 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 determinations and risk assessments 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. In contrast, this Draft ISA ~~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. This Draft ISA ~~It~~ does not discuss whether or to what extent policy makers can be confident that reducing $PM_{2.5}$ alone, without reducing its correlates (such as poverty, co-morbidities, co-exposures, and weather conditions correlated with ~~high~~ $PM_{2.5}$ levels) would reduce adverse health effects. This ~~missing~~type of what-if information is crucial for the ISA to fulfill its intended role in supporting policy. Without this information~~it~~, the ISA provides no empirically-validated or independently-verifiable scientific basis for identifying what changes in exposures, if any, would be effective or necessary to protect human health with an adequate margin of safety.

There are data available to remedy these~~ese~~ limitations~~ are unnecessary~~. Results of both ~~toxicological~~ experimental and accountability studies are available in the peer-reviewed scientific literature that formulate testable predictive hypotheses about health effects of changes in $PM_{2.5}$ exposures, test them with data from natural experiments and other sources, and draw useful, empirically-grounded conclusions about whether and how much changes in PM exposure affect human health risks (e.g. Greenbaum, 2019). ~~Much~~Some of this evidence is omitted in the Draft ISA. The ISA should include these and other high-quality scientific studies that emphasize empirical data and test predictions about effects on human health risks of changing PM exposure levels.

Overall Recommendations

The CASAC strongly recommends that, throughout the ISA, all key conclusions 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. High-level explanations of how key conclusions are reached that lack the operational detail needed for independent verification, such as "All causality determinations… are based on the approach of considering the collective body of evidence" (Vandenberg, 2019), are not sufficient to enable the CASAC (or others) to trace and check the steps and logic that lead from stated data and hypotheses to stated conclusions. The ISA should provide this additional detailed information. The ISA should also explain ~~exactly how its conclusions are derived from evidence (using independently verifiable operational procedures); and~~ what evidence is included and excluded and why (using explicit, independently verifiable criteria for systematic review), and should explicitly discuss study quality considerations when reviewing study results. All assumptions or hypotheses used in deriving

conclusions should be explicitly stated. Results of empirical tests of these assumptions or hypotheses should be provided wherever possible; otherwise, sensitivity and uncertainty analyses should be used to inform readers about the sensitivity of conclusions to untested hypotheses. The concentrations of PM that do and do not cause certain health effects should be identified to inform the dose-response assessment. These best practices for identifying and communicating hazard and dose-response information are necessary to enable the CASAC to properly fulfill its duty to provide independent advice to the EPA Administrator on the technical bases for the EPA's NAAQS.

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 and to better represent ~~what~~the current science ~~currently knows~~ about human health effects of PM leads to the following two process recommendations:

- Create additional opportunities for review by the CASAC and the public following revision of the Draft ISA. At a minimum, the CASAC recommends another round of review of the Draft ISA after it has been revised. A revised version providing clear operational definitions of key terms and details of derivations of conclusions is needed to enable independent scientific review of the ISA's scientific reasoning and conclusions. The CASAC stands ready to provide this review.
- The CASAC recommends that it be provided with access to additional technical expertise as needed to thoroughly review a revised version of the Draft ISA. 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. Characterization of sampling errors and biases from continuous ambient PM measurements and satellite remote sensing aerosol optical depth (AOD) analysis;
    b. Errors and biases in dispersion modeling and photochemical grid modeling;
    c. Errors-in-variables methods and effects of exposure (and covariate) estimation errors on epidemiologic study results;
    d. Epidemiology of low-dose causal concentration-response functions;
    e. Comparative toxicology, dosimetry, and extrapolation of findings in animals to humans;
    f. Effects of PM on visibility impairment, climate, and materials.

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

Executive Summary

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

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 it does not accurately represent other key findings or the totality of available high-quality scientific evidence. The material summarized is unclear in the following respects. Statements of key findings and conclusions do not distinguish between true and estimated PM exposure values; between effects of PM and effects of correlates of PM (such as poverty, lagged daily temperature extreme, or humidity); between individual health risks and population averages of individual health risks; between observed changes and model-predicted changes in public health risks following changes in exposures; between assumptions and ~~data~~evidence on shapes of C-R functions; between results from the total body of scientific evidence and results from selected subsets of evidence; and between association and causation. For example, the Executive Summary refers repeatedly to the shape of the C-R relationship in contexts where it appears that what is meant is actually the shape of the *historical population average* of individual effect indicators plotted against *estimated* concentrations in *selected* populations, averaged over unspecified values of other variables that greatly affect the shape of the C-R association, such as weather, demographic, and socioeconomic variables. The shape of the C-R relationship defined this way has no necessary implications or relevance for the shape of the C-R function describing how future changes in PM would change individual or population health risks. (For example, their slopes can have opposite signs, as in Simpson's paradox). Many of these same concerns apply to the individual chapters where results are discussed in more detail.

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

- Key terms used to communicate findings are highly ambiguous and are not clearly defined, especially those related to exposure, cause and effect.

Commented [SL12]: How much of this information belongs here, and how much in the other, more detailed chapters?

Commented [SL13]: Can we add specific page references for this?

Commented [SL14]: My understanding of Simpson's paradox is that it refers to opposites signs of effects of aggregated versus dis-aggregated data. Is what you are suggesting here really a problem of aggregation?

- The Draft ISA leaves unclear whether or to what extent the human health risks attributed to PM are in fact jointly caused by weather, sex, age, obesity, and demographic~~,~~ or socioeconomic factors~~, and health variables such as temperature extremes, sex and age, income, and obesity~~; and what is known about 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~~C-R 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 PM2.5 reflect the total body of scientific evidence" but in fact these determinations ignore large bodies of relevant scientific evidence, including ~~14 of the 15~~4 of the 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 $PM_{2.5}$ and respiratory mortality; consistent, positive associations between short-term $PM_{2.5}$ exposure and cardiovascular-related emergency department visits and hospital admissions; consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality; primarily consistent, positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence and mortality;* and *consistent, positive associations between short-term $PM_{2.5}$ 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 meta-analyses that do not report consistent, positive associations. Examples are given in the individual comments and the chapter-specific comments.

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

The CASAC agrees with the statement in the Executive Summary that "Important considerations [for causality determinations] include: (1) determining whether laboratory studies of humans and animals, in combination with epidemiologic studies, inform the biological mechanisms by which PM can impart health effects and provide evidence demonstrating that PM exposure can independently cause a health effect; (2) determining whether there is consistency in epidemiologic evidence across various geographic locations, populations, and methods used to estimate PM exposure; (3) evaluating epidemiologic studies that examine potential influence of factors (i.e., confounders) that could bias associations observed with PM exposure; (4) determining the coherence of findings integrated across controlled human exposure, epidemiologic, and toxicological studies; and (5) making judgments regarding the influence of error and uncertainty on the relationship between PM exposure and health effects in the collective body of available studies." The CASAC recommends that the ISA address these considerations explicitly in the Executive Summary. For example, a revised version of Table ES-1 could note, for each health effect, whether relevant ~~toxicology and inflammation biology~~experimental evidence from animals and humans demonstrate that ambient concentrations of PM can or cannot independently cause it; discuss inconsistencies in epidemiological evidence across geographic locations (e.g., absence of $PM_{2.5}$-mortality associations in some studies or in subsets of geographic locations within studies); evaluate the extent to which ~~C-R associations are caused by~~ confounders such as lagged weather variables contribute to observed PM C-R associations; determine the coherence or lack of it across studies when conflicting evidence is fully taken into account; and assess the influence of error and uncertainty on the relationship between estimated PM exposure and health using appropriate technical (e.g., errors-in-variables) methods.

The CASAC recommends the following steps for improving the clarity and value of the Executive Summary (some of these would also appropriately be applied to the individual chapters of the ISA):

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

Commented [SL15]: It would be great if we could provide an example of a different way to structure or describe the causal categories here to provide guidance to EPA. Alternatively we could refer to an example in someone's comments, if there is one.

> testable implications have been tested and verified and the extent to which alternative explanations and interpretations of the same facts and data are supported or refuted by available data, or remain untested. Discuss the extent to which conclusions depend on unverified assumptions and to modeling uncertainties.

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

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

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

Commented [SL16]: This paragraph addresses issues that were already covered in the comments, so I suggest removal, with addition of the references to the other sections.

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

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

Integrated Synthesis (Chapter 1)

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

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

Also similar to the Executive Summary, Chapter 1 repeatedly describes findings as consistent and coherent. This narrative is misleading, insofar as it disregards and leaves unresolved substantial conflicting evidence and findings from high-quality individual studies that present evidence to the contrary. For example, Section 1.4.1.5 states that "Consistent with the conclusions of the 2009 PM ISA,

more recently published scientific evidence reaffirms and further strengthens that there is a '*causal relationship*' between both short- and long-term $PM_{2.5}$ exposure and total mortality. These causality determinations are based on the consistency of findings across a large body of epidemiologic studies and coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, as well as biological plausibility for respiratory and cardiovascular morbidity effects by which short- and long-term $PM_{2.5}$ exposure could result in mortality." This statement ignores findings from studies in which neither short-term nor long-term $PM_{2.5}$ exposures are found to be associated with total mortality, and in which changes in $PM_{2.5}$ are not found to affect changes in total (or cardiovascular) mortality rates. A few examples of such discordant evidence include the following (further examples and discussion are provided in Dr. Cox's individual comments):

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

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

Commented [SL17]: Presumably referring to the Dockery 2013 HEI study? While this study's results are suggestive, they did not actually look at PM – they measured black smoke and total gaseous acid activity. I suggest looking at the Russell 2018 study, which is an accountability study that investigates the effects of PM2.5 changes from implementing regulations on ED visits in Atlanta, including for respiratory disease, asthma, cardiovascular disease, and congestive heart failure.

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

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

should be articulated and systematically applied to the literature. Criteria for evaluating individual studies should be stated, including criteria for evaluating the internal and external validity of study results, the soundness of the methods used, and the sensitivity of conclusions to unverified assumptions. Results of applying these criteria should be summarized. Criteria for summarizing, reconciling, and synthesizing diverse results across studies should be stated and used to systematically summarize the available scientific literature. All criteria should be specified with sufficient clarity and objectivity that the results of applying them to individual studies can be independently reproduced.

- *Summarize and tabulate the results* of applying these criteria systematically to the scientific literature.
- *Discuss results of relevant high-quality scientific literature,* including studies with negative results (i.e., lack of C-R associations or lack of effects of changes in PM on health risks). Discuss results from accountability studies, natural experiments, quasi-experiments, and causal mediation studies and analyses of how changes in PM exposures change human health risks. Add to both the ISA and the summary in Chapter 1 a discussion of the role of inflammasomes in mediating effects of $PM_{2.5}$ on respiratory and cardiovascular mortality and morbidity. Discuss the consistency and coherence of available evidence with the existence of exposure thresholds for inducing inflammation-mediated adverse health effects and chronic inflammation in the lung, taking into account that studies that do not find a threshold when exposure estimation error is ignored do not thereby necessarily provide evidence against a threshold.
- *Characterize changes in human health effects caused by real-world changes in PM exposures* in relevant high-quality accountability studies, natural experiments, quasi-experiments, and causal mediation studies.
- *Characterize the consistency and coherence of available evidence with thresholds* for inflammation-mediated adverse health effects.
- *Describe what is known about how socioeconomic, co-morbidity, co-pollutant, and weather variables jointly affect human health and wellbeing*, and how the effect on health risks of a reduction in PM alone may depend ~~s~~ on these other variables. PM exposures are linked to adverse health effects via networks of causes and effects that also include all ~~of~~ these variables. The ISA should discuss empirical evidence on how they jointly affect human health and well-being, and how the effect on health risks of a reduction in PM alone depends on the context of these other variables. For example, does reducing $PM_{2.5}$ mainly reduce mortality and morbidity rates caused by heat waves or cold snaps? Do the health benefits of reduced $PM_{2.5}$ occur mainly or only for people with certain combinations of age, sex, income, and medical histories? How do C-R functions for PM depend on these other factors? How well do these multivariate causal dependencies explain and predict why positive C-R associations are observed in some studies or locations but not others? The ISA should explain both what is now known and what is still uncertain about effects of combinations of causally relevant factors, including PM exposure, on human health risks and welfare.
- ~~*Explain both what is now known and what is still uncertain about effects of combinations of causally relevant factors,* including PM exposure, on human health risks and welfare.~~

Commented [SL18]: This is a pretty specific detail. How strong is the evidence for the role of inflammasomes, to make it specifically relevant to add to Chapter 1? It seems like the studies are mostly in vitro, the results of which are difficult to relate to the effects of ambient concentrations in vivo. I suggest removal.

Commented [SL19]: The points made in both of these bullets are already included in the bullet point before, so I suggest removal.

These additions will strengthen the usefulness and effectiveness of Chapter 1 in characterizing and communicating essential scientific information about policy relevant issues of PM.

Sources, Atmospheric Chemistry, and Ambient Concentrations (Chapter 2)

To what extent is the information presented in Chapter 2 regarding sources, chemistry, and measurement and modeling of ambient concentrations of PM clearly and accurately conveyed and appropriately characterized?

Overall, Chapter 2 does a sufficient job of conveying and characterizing the sources, chemistry, and measurements and modeling of $PM_{2.5}$, PM_{10}, and $PM_{10\text{-}2.5}$ (coarse fraction).

Commented [SL20]: What about UFP?

Section 2.3 discusses primary sources of PM. Figures 2-2, 2-3, and 2-6 show the importance of various types of dust to total $PM_{2.5}$ and PM_{10} primary emissions based on the U.S. EPA 2014 National Emissions Inventory. However, when these emissions are used as inputs to chemical transport models (CTMs), the modeled concentrations are significantly higher than the observed concentrations at the speciation monitors. The reason for the overprediction is that there is no adjustment for near-source removal due to small sub-grid scale turbulence and impaction on building and vegetative surfaces (Pouliot et al., 2012). It is estimated that local source removal typically accounts for 75% of total removal of fine particulate matter nationally (Pace, 2005). This removal factor is defined as a "capture fraction" and varies by location. The amount that is not removed is defined as the "transportable fraction." A discussion of capture fraction and transportable fraction should be included in this chapter to help place the importance of dust emissions into proper perspective.

Although the predominant sources of coarse PM primary emissions are thoroughly explained, there should also be ~~appears to be no~~ discussion on the potential for the formation and/or sources of formation of secondary coarse PM. This chapter does a good job of identifying the sources of ultrafine particles (UFP); however, there ~~is no~~should also be discussion on the transport or the potential for transport of UFP and ~~no discussion~~ on the possible existence (or lack thereof) of biogenic, natural background concentrations of UFP.

With respect to monitoring of $PM_{2.5}$ and PM_{10}, Section 2.4.1 does a sufficient job of discussing the difference between Federal Reference Method (FRM) and Federal Equivalency Method (FEM) monitors and describes the three most widely used FEMs. FRMs typically measure 24-hour integrated samples every third or sixth day. Short time resolution automated FEMs can measure hourly samples every day. In the past, FEMs typically measured higher $PM_{2.5}$ concentrations than FRMs; therefore, some states were reluctant to switch to FEMs. However, the new Teledyne optical spectrometer FEMs are much more reliable and consistent and many states are now converting their FRMs to FEMs. In July 2017, the Georgia Environmental Protection Division (EPD) ran two regulatory FEMs. ~~Currently~~As of March 2019, the Georgia EPD runs nine regulatory FEMs and will be running twelve regulatory FEMs by June 2019. A similar trend is occurring across many parts of the country which will produce significantly more $PM_{2.5}$ data at hourly resolution. In addition, the measurement technology for $PM_{10\text{-}2.5}$ is

considerably improved compared to previous methods (i.e., subtraction methods). As a result of the improved accuracy and reliability in measurements of $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ using FEM monitors, exposure and health effects assessments should consider the availability of these continuous and robust datasets.

With respect to the utilization of satellite remote sensing for obtaining ambient concentrations of PM, caution should be given to any results obtained from such techniques ~~due to~~ because the computational algorithms use~~involving~~ a range of assumptions ~~that must be applied~~ to obtain estimates of $PM_{2.5}$ concentrations. These inferred measurements involve potential errors that are not encountered with the FRM or other ground-based $PM_{2.5}$ measurements. In addition, data cannot be collected when clouds and snow are present or from excessive amounts of smoke being mistaken for clouds. Conclusively, the many factors that impact the relationship between aerosol optical depth (AOD) and $PM_{2.5}$ concentrations sometimes lead to widely varying and relatively low correlations when linear relationships are developed.

~~There does not appear to be any salient d~~Discussions on the limitations and/or uncertainties of utilizing CTM to estimate ambient concentrations of PM should be added to Chapter 2, although Section 2.4.7 does a good job of documenting the relative scientific advances in CTMs.

Please comment on the extent to which available information on the spatial and temporal trends of ambient PM concentrations at various scales has been adequately and accurately described.

Overall, Chapter 2 does a sufficient job of adequately and accurately describing the extent to which information is available on the spatial and temporal trends of ambient PM concentrations at various scales.

There are a few noted discrepancies in the figures. Figure 2-14 shows the 98th percentile 24-hour $PM_{2.5}$ concentrations for 2013-2015. The red monitor (indicating concentrations of 35-40 $\mu g/m^3$) in southern Georgia appears to be Albany (13-095-0007). However, according to certified US EPA Air Quality System (AQS) data, the 24-hour 2013-2015 design value for Albany is 23 $\mu g/m^3$ (should be a blue dot, not a red dot). Figure 2-15 shows the 98th percentile PM_{10} concentrations for 2013-2015. There are no measurements shown in Georgia, although Georgia has three PM_{10} monitors (13-089-0002, 13-121-0039, and 13-245-0091) with certified data in AQS from 2013-2015. The 98th percentile PM_{10} concentrations for all three PM_{10} monitors in Georgia are well below 75 $\mu g/m^3$ (designated by blue dots).

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Regarding spatial trends, there does not appear to be an adequate discussion about the regional (state-to-state) transport of PM. In addition, Figures 2-13 through 2-16 show 2013-2015 PM design values. These figures should be updated with 2015-2017 design values.

The CASAC should be given ready access to one or more experts in ambient PM measurements and satellite remote sensing AOD analysis to assist in review of the next iteration of the ISA. This would allow for a better understanding of sampling errors and biases associated with integrated and continuous

ambient PM measurements and satellite data. This is particularly important since this information will be used to characterize ambient concentrations in the Risk and Exposure Assessment (REA) document.

Exposure to Ambient Particulate Matter (Chapter 3)

Chapter 3 describes scientific information on exposure to ambient PM and implications for epidemiologic studies. To what extent is the discussion on methodological considerations for exposure measurement and modeling clearly and accurately conveyed and appropriately characterized?

Overall, this chapter does a good job describing methods for exposure measurements and modeling. New developments in PM exposure assessment methods have reduced bias and uncertainty in health effect estimates by improving the spatial resolution and accuracy of exposure predictions. High correlations of $PM_{2.5}$ with some gaseous copollutants necessitate evaluating the impacts of confounding on health effect estimates. There is typically more uncertainty for health effect~~s~~ estimates caused by exposure to $PM_{10-2.5}$ and UFP than for health effects associated with $PM_{2.5}$.

Section 3.3.1.2 and Table 3-1 discuss personal monitoring and measurement error characteristics. Additional discussion of the personal-exposure measurement literature is warranted, and the ISA should include information from two key systematic reviews published in 2010 (Avery et al., 2010a, 2010b). These reviews describe the variability in personal-ambient relationships. They state that "The wide range in estimated correlations between personal and ambient $PM_{2.5}$, as well as the associations with participant, study and environment characteristics, suggest that the potential for exposure misclassification can be substantial." This should be further discussed in the ISA and used to better inform interpretations of studies that assume a simple, or even perfect, relationship between ambient and personal $PM_{2.5}$ concentrations. There are a wide variety of personal samplers and some perform better than others. Therefore, a detailed evaluation of the sampler performance compared to FEM monitors or FRM monitors should be performed before using personal sampling data as the definitive estimate of exposure. In some cases, the data may be better suited for examining gradients in $PM_{2.5}$ exposures rather than directly using the measured $PM_{2.5}$ concentrations.

Table 3-2 compares models for estimating "exposure concentrations or exposure." The EPA should clarify the difference between "exposure concentration" and "exposure." If they are used interchangeably, only one term should be used rather than "exposure concentrations or exposure." Under the column for "Dispersion" there is an "X" for Chemistry. However, it is stated on page 3-28 "Dispersion models…typically have limited ability to model chemistry (if any)." A footnote should be added to the table to indicate that many dispersion models do *not* account for chemistry (alternatively, the "X" could be removed from the "Chemistry" row in the "Dispersion" column). Table 3-3 presents statistical measures used for air quality model performance evaluations. While the four performance measures listed are commonly used, the table should also include normalized mean bias and normalized mean error. These are also commonly used and will provide information about percent differences in addition to absolute differences (mean bias and mean estimate).

several groups (Carrothers and Evans, 2000; Fewell et al., 2007; Lipfert and Wyzga, 1996) and makes interpreting copollutant models quite challenging. It requires considerations of joint exposure measurement errors for each component. Studies that have investigated the effects of better exposure estimates on health effect estimates (e.g. Ebelt et al., 2005; Hart et al., 2015; McGuinn et al., 2017; Trenga et al., 2006) have demonstrated that there is no or little difference in health effects estimates or width of confidence intervals with different (presumably better) exposure estimates. This evidence does not support the EPA's general conclusion that increased exposure error biases health effect estimates towards the null.

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

~~**Comments on Chapters 4–12**~~

General Comments

Commented [SL21]: Should this information be incorporated in the overall comments?

Additional expertise is needed for the CASAC to provide a thorough review of the PM NAAQS documents. 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, epidemiologists and additional experts in human clinical studies and toxicology. 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, additional expertise is needed in comparative toxicology, dosimetry, and extrapolation of findings in animals to humans.

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 ISA.

The CASAC now requests that experts with relevant background, experience, and publications 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.

Causality Determination of Mortality from $PM_{2.5}$ Exposure

The CASAC is unable to reach consensus on the causality determination of mortality from $PM_{2.5}$ exposure.

observed heterogeneity in effect sizes across geographical locations, and whether (or to what degree) particle translocation away from the lung mediates health effects. These uncertainties have been for the most part thoroughly discussed in the draft ISA, as well as in previous PM ISAs. The fact that there is uncertainty with regard to specific issues does not negate the overwhelming evidence that $PM_{2.5}$ exposure increases mortality.

Dosimetry of Particulate Matter (Chapter 4)

Commented [SL22]: This section should be moved ahead of the general comments for Chapters 5-11.

Chapter 4 characterizes scientific evidence on the dosimetry of PM. To what extent does the discussion clearly and accurately convey the dosimetry of inhaled PM and the processes of deposition, clearance, retention, and translocation?

Organization

This chapter provides a very important and thorough review of the deposition, clearance, retention, and translocation of inhaled PM. However, the text would benefit from careful copy editing. In addition, the EPA could streamline the chapter by removing some extraneous information, such as discussions of the history of scientific views on post-natal alveolar development, and ventilation distribution in dogs and horses.

Additional Information

Some additional information would improve the translation of these dosimetric study results to human-relevant exposures. The EPA should include the concentrations at which the dosimetry exposures were conducted, along with a discussion of the impact of the concentration on the measured dosimetric observations. Concentration information is particularly important for the translocation studies that tend to use very high exposure concentrations. The CASAC also recommends that the EPA add a discussion about how the dosimetry study results can be translated to humans exposed to ambient PM concentrations. For example, in the section on interspecies clearance and retention, the EPA could add the PM dose or dose-rate at which particle overload occurs in rats to provide a reference dose at which extrapolation to humans would become inaccurate. In the section about translocation of soluble versus insoluble components, the EPA could add information about how big a contribution is made by soluble particles to total particles. This information is important because these particles could have a more direct or obvious linkage to systemic effects than insoluble particle translocation (which occurs at a very low frequency). The EPA should also provide greater consideration of the impact of exercise on dose-rate, and how this may affect study interpretation in subsequent health effect chapters. In addition, particle deposition density per cm^2 of surface area in various anatomical regions is an important factor, particularly in evaluating studies of pulmonary defense mechanisms. A table of particle deposition densities should be added.

Another important addition to this chapter would be a reference to the study by Kendall et al. (2002) in which $PM_{2.5}$ samples were immersed in normal lung lining liquid (surfactant). The small (~35 nm)

Page 10-49, line 27 - This statement is incorrect: "Specifically, an assessment of adenocarcinoma, the only subtype that develops in nonsmokers…" Adenocarcinoma is not the only type of lung cancer that occurs in nonsmokers. "Only" should be changed to "predominant." The same applies to page 10-53, line 11, and page 10-74, line 29.

Application of scientific information to inform causal conclusions:

Nervous System Effects

Chapter 8, Nervous System Effects – $PM_{2.5}$ - The EPA does not provide adequate evidence for the conclusion that there is likely to be a causal association between long-term $PM_{2.5}$ exposure and nervous system effects. In Table 8-20, the EPA identifies the following as providing high quality or consistent evidence of this relationship: toxicology studies on brain inflammation and reduced cognitive function, and epidemiology studies of reductions in brain volume and reduced cognitive function in adults. For a likely causal conclusion, there would have to be evidence of health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the overall evidence. In addition, the determination should be made based on multiple studies by multiple research groups (p. P-12). The toxicology studies have largely been done by a single group. Those animal toxicology studies that were completed by other groups do not provide adequate evidence because the control animals were exposed to gaseous pollutants (Tyler et al., 2016) or were exposed for only two weeks in addition to OVA-sensitization (Campbell et al., 2005). For the brain size epidemiology studies, brain volumes were only measured once in each person and were compared between people. But brain volume can vary up to two-fold between normal people (Reardon et al., 2018), so this seems like an endpoint that could be subject to substantial error. Additionally, the cognitive function epidemiology studies found largely non-statistically significant results (see Figures 8-3, 8-4, and 8-5), including two of the studies that the EPA cited in Table 8-20 (Weuve et al., 2012 and Tonne et al., 2014). Altogether, this ~~evidence~~data does not provide evidence of health effects that are not explained by chance, confounding, or bias, and that have been done by multiple research groups.

Chapter 8, Nervous System Effects - UFP - The ISA does not provide adequate evidence to support the conclusion that there is likely to be a causal association between long-term UFP exposure and nervous system effects. There are no supportive human studies, and the EPA has not considered the appropriate dosimetric adjustments, or rodent-to-human differences in the respiratory tract, that would help extrapolate the animal data to humans. In addition, most of the animal studies that provide coherence were done by a single group in a single location.

Cancer

There is inadequate evidence for the "likely to be causal" conclusion for long-term $PM_{2.5}$ exposure and cancer. This determination relies largely on epidemiology studies that, as noted above, do not provide exposure time frames that are appropriate for cancer causation. There are no animal studies showing direct effects of $PM_{2.5}$ on cancer formation, with the only positive animal results coming from a group that pre-initiated the animals with urethane.

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