DATE

EPA-CASAC-22-XXX

The Honorable Michael S. Regan
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Supplement to the 2019 Integrated Science Assessment for Particulate Matter (External Review Draft – October 2021)*

Dear Administrator Regan:

The 2021 Clean Air Scientific Advisory Committee (CASAC) Particulate Matter (PM) Review Panel, hereafter referred to as the Panel, met on October 14, 2021, November 17-19, 2021, December 1-2, 2021 and <<Insert follow-up meeting dates>> to peer review the EPA's *Supplement to the 2019 Integrated Science Assessment for Particulate Matter (External Review Draft – October 2021)*, hereafter referred to as the Draft ISA Supplement. The Chartered CASAC approved the Panel's report on <<Insert follow-up meeting date>>. The CASAC's consensus responses to the agency's charge questions and the individual review comments from the Panel are enclosed.

The CASAC commends the EPA for returning to its long-standing practice of constituting an ad hoc panel of experts to complement the expertise of the Chartered CASAC. The CASAC recommends that the practice of convening a panel of additional experts continue for all future NAAQS reviews because the give-and-take deliberation and participation of multiple scientific experts, including multiple experts from all key disciplines needed to conduct a high-quality scientific review, is fundamental to the Chartered CASAC's ability to provide the highest quality scientific advice. With a fully constituted ad hoc panel of experts, the CASAC has a broad depth and breadth of perspectives that enables it to fulfill its mandate to provide advice and recommendations to the EPA.

Overall, the CASAC finds the Draft ISA Supplement to be a well-written, comprehensive evaluation of the new scientific information published since the 2019 PM Integrated Science Assessment (ISA). There

are several recommendations for strengthening and improving the document highlighted below and detailed in the consensus responses.

The scope of the Draft ISA Supplement is limited to health effect categories where the 2019 PM ISA concluded a causal relationship (i.e., short- and long-term $PM_{2.5}$ exposure and cardiovascular effects and mortality). Although this limitation is appropriate for the targeted purpose of the Draft ISA Supplement, the CASAC notes that this limitation precludes consideration of any new evidence that might change a causality determination from a likely to be causal relationship to a causal relationship. This limitation should be explicitly acknowledged. It should also be noted in the Draft ISA Supplement that this limiting of scope is only for this document and not setting a precedent for future ISAs. A discussion of the rationale for limiting the scope of the document to U.S. and Canadian studies should also be included. The Draft ISA supplement should also provide additional background and rationale for the reconsideration of the December 2020 decision to retain the PM National Ambient Air Quality Standards (NAAQS). Although continued refinements to the current weight-of-evidence (WOE) causal determination framework are possible, the CASAC unanimously finds the current WOE causal determination framework, as described in the 2015 Preamble to the ISA, to be the best tool available and supports the continued use of the framework in NAAQS reviews.

The CASAC finds the summary of health effects to be well-written and thorough, with appropriate identification, evaluation, and characterization of available scientific evidence, within the stated scope of the Draft ISA Supplement. The text on "causal modeling methods" should be reworded to clarify these methods' role in the WOE causality determinations. While recent emergence of studies employing such methods is important to the Draft ISA Supplement, the CASAC recommends alternative descriptive language to avoid the potential misconception that labeling some studies as "causal" carries an implication that more traditional epidemiologic analysis methods cannot support a causal determination or should receive less weight in any WOE causality determinations. The CASAC notes the importance of these methodologies in the Draft ISA Supplement for their ability to reduce some of the uncertainties raised by the previous CASAC and the previous Administrator in response to the 2019 ISA. It is important to clarify that these methods are not intended to replace the causality determinations of previous ISAs, but rather have been recently adopted in service of strengthening the body of evidence for causality determinations.

Regarding study descriptions and findings, more detail would be useful to give context to the results (e.g., hazard ratios, sample size, methods for exposure assessment). Specifically, conclusions are needed for these studies regarding what was learned, and the ways and degrees in which the studies strengthen or weaken the state of scientific evidence. There should be consistent presentation of statistical significance, descriptions of exposure measurement, and better distinguishing of individual-level and community-level measures of SES data for the studies presented.

The CASAC notes that there is a progression going from the 2009 ISA to the 2019 ISA to this Draft ISA Supplement indicating continued strengthening of the causal health endpoints relationship with $PM_{2.5}$. The literature, as it is expanding, continues to show strong associations with health effects, even though concentrations of $PM_{2.5}$ in the air have been dropping over time.

The CASAC recommends using different language when discussing race/ethnicity in the Draft ISA Supplement. The summaries and conclusions within this document use the terms "White" and "non-White" as the broadest categories. The Draft ISA Supplement should refer to the group "non-White" as "People of Color (POC)" or "Communities of Color (COC)," as appropriate.

The CASAC agrees that recent evidence confirms the causal relationship between PM and visibility impairment. However, a few clarifications are needed. Section 4 acknowledges variations in humanly perceivable acceptance of visibility levels. The use of "apparent contrast" instead of "total light extinction" shows less variability to determine acceptable visual air quality. Values for the cut-off between unacceptable versus acceptable levels for atmospheric extinction coefficients and consistent acceptable contrast levels should be clarified. Science-based visibility standards warrant additional research using objective scenarios to quantify visibility improvement.

With increases in the frequency and intensity of wildfires and reductions in sulfur dioxide (SO_2) and oxides of nitrogen (NOx) emissions, mass scattering coefficients for the major $PM_{2.5}$ components (e.g., organic and elemental carbon, sulfate, and nitrate) need to be further examined with more recent data (e.g., 2015 onward). The "revised" Interagency Monitoring of Protected Visual Environments (IMPROVE) chemical extinction equation should be included, the Lowenthal and Kumar IMPROVE equation should be included, and differences among the various IMPROVE equations that use split component algorithms need to be addressed.

The CASAC is concerned that the compressed timeframe for this and other recent CASAC reviews has made it difficult for the CASAC to provide the highest quality review possible. The compressed timeframe for simultaneously reviewing large documents is not optimal. It is also not optimal that the timeframe does not allow for development of second drafts of documents that incorporate CASAC advice (should the CASAC recommend second drafts). The CASAC recommends that for future reviews, the EPA follow a review plan that allows for adequate time for the CASAC to review the documents and for sufficient time for the EPA to incorporate CASAC advice into second drafts (if requested by the CASAC). The review plan should also allow sufficient time for CASAC advice on earlier documents (e.g., ISA) to also be incorporated into subsequent documents (e.g., REA and PA). Documents that are supposed to be developed sequentially (e.g. the ISA and PA) should not be developed simultaneously and presented to the CASAC for simultaneous review.

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

Sincerely,

Dr. Elizabeth A. (Lianne) Sheppard, Chair
Clean Air Scientific Advisory Committee

Enclosures

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: https://casac.epa.gov.

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

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Particulate Matter Review Panel (2021)

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Consensus Responses to Charge Questions on the EPA's *Supplement to the 2019 Integrated Science Assessment for Particulate Matter (External Review Draft – October 2021)*

Executive Summary

The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the draft PM Supplement for a broad range of audiences.

a. Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.

b. Please provide recommendations on whether additional information should be added to the Executive Summary or information that should be left for discussion in the subsequent sections of the draft PM Supplement.

The Executive Summary is appropriately brief, two pages total. It clearly and concisely explains the purpose and limited scope of the Draft Supplement to the 2021 Integrated Science Assessment (ISA) for Particulate Matter (PM), hereafter referred to the Draft ISA Supplement, and notes inclusion of recent studies on causal modeling methods or accountability analyses, near-ambient experimental studies, disparities in $PM_{2.5}$ exposure or health risk by race or socioeconomic status (SES), and effects of $PM_{2.5}$ exposure on COVID-19 health outcomes. Passing mention is made of visibility topics, which is appropriate, given the scope and focus of Draft ISA Supplement. Importantly, the Executive Summary explicitly states that the Draft ISA Supplement does not include the entire body of literature that supports weight-of-evidence (WOE) conclusions. It notes the focus of the Draft ISA Supplement on recent studies that support and extend the causality determinations that were the subject of extensive discussions during the 2019 PM National Ambient Air Quality Standards (NAAQS) review. The level of detail and information included in the Executive Summary is appropriate for its intended purpose.

The sentence on page ES-1, lines 21-24, is confusing and unclear, given that the Draft ISA Supplement attempts to put recent studies into context, and also to draw new WOE conclusions in light of the added studies. It is not a complete literature review, but is a multidisciplinary evaluation. This sentence could be reworded to be more specific. Additional recommended changes for clarity elsewhere in the document need to be incorporated into the Executive Summary.

Section 1 – Introduction and Scope

Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

Section 1 is a clear and concise summary of the purpose and scope of the Draft ISA Supplement. It explains that the scope is limited to health-effect evidence categories that the 2019 PM ISA concluded had a causal relationship, i.e., cardiovascular effects and mortality associated with short- and long-term $PM_{2.5}$ exposure. Although this limitation is appropriate for the targeted purpose of the Draft ISA Supplement where consideration is focused on recent literature that could support alternative $PM_{2.5}$ annual and/or daily standards, the Clean Air Scientific Advisory Committee (CASAC) notes that this limitation precludes consideration of any new evidence that might change a causality determination from likely to causal (e.g. nervous system effects or respiratory effects). Although this is not likely unless there is substantial new evidence for those effects, this limitation should be explicitly acknowledged in the introduction.

This section should give some additional background, context, and rationale for the reconsideration of the December 2020 decision to retain the National Ambient Air Quality Standards (NAAQS) for PM. The CASAC emphasizes the importance of documenting actions taken by the Environmental Protection Agency (EPA) prior to and during the previous PM NAAQS review, including the CASAC reviews of the 2019 ISA and 2019 PA. It should include a description of the previous CASAC's recommendation that a "more explicit, systematic, and transparent process" be used for determining causal relationships. This recommendation resulted in the National Academies of Sciences, Engineering, and Medicine (NASEM) committee on "Assessing Causality from a Multidisciplinary Evidence Base for National Ambient Air Quality Standards" (https://www.nationalacademies.org/our-work/assessing-causality-from-a-multidisciplinary-evidence-base-for-national-ambient-air-quality-standards). Additional detail on this would inform the reader on the recent developments on this topic since the last review.

The causal determination framework, as documented in the 2015 Preamble to the ISA, is based on weight-of-evidence (WOE) and professional judgement. While continued refinements to this WOE framework are possible and welcomed by the CASAC, the causal determination framework is currently the best available tool and the CASAC unanimously supports continued application of it for NAAQS reviews. The causal framework has been developed over many years and has been reviewed and supported by the CASAC during multiple previous reviews.

The CASAC has concerns that constraining the scope of the Draft ISA Supplement to only including updated studies for the effects that had a determination of a causal relationship could set precedent in future ISAs. The EPA clarified that this would only be the case for this Draft ISA Supplement and that future ISAs would include the full range of causal classifications. This should be noted in the introduction.

The scope of the Draft ISA Supplement is limited to U.S. and Canadian epidemiologic studies, and this needs to be explained in the introduction. Although the EPA provided the rationale for this constraint during the meeting and clarified that it is only for this Draft ISA supplement, the CASAC finds this to be

somewhat weak, given that the U.S. and Canadian health care systems and population characteristics are very different and that the composition of east coast U.S. PM pollution can be very different from west coast pollution. The Liu et al. (2019) study cited in the ISA supplement is an example of $PM_{2.5}$ health effects coherence across the world. There are also new and relevant European study publications on the health-effects of low level $PM_{2.5}$ such as the Health Effects Institute (HEI) ELAPSE project; see HEI's ISA Supplement public comments on the ISA Supplement (https://casac.epa.gov/ords/sab/f?p=105:19:17351896549913:::RP,19:P19_ID:962#materials) and the September 2021 ELAPSE study publication (Strak et al., 2021).

The Draft ISA Supplement notes the inclusion of several "causal modeling" studies that have appeared since the 2019 ISA, without specifying exactly what types of modeling strategies this entails. It seems clear that the EPA is using this term to describe a specific class of established methodologies often called "causal modeling" or "causal inference" methodologies found particularly in the statistics, epidemiology, and social science literature that are relatively novel to the purview of the PM ISA, such as studies that use instrumental variables, difference in differences, propensity scores, and doubly-robust additive modeling strategies. These methods are distinct from and should not be conflated with the WOE framework for causal determinations described in the ISA Preamble. The CASAC recommends some introductory comments clarifying why the "causal" label is used for these studies, even if only for the purpose of contextualizing these studies within the broader epidemiologic literature. The CASAC is particularly concerned that some will interpret the labeling of some studies as "causal" as an implication that other epidemiological studies do not support a causal determination or should receive less weight in any WOE causality determinations. Alternative labeling of these methodologies as "novel causal methodologies," "advanced causal modeling," or "modern (or novel) confounding adjustment methods" would be appropriate. Whatever their label, the CASAC identifies the importance of these methodologies in the Draft ISA Supplement for their ability to reduce some of the uncertainties raised by the previous CASAC and the previous Administrator in response to the 2019 ISA. It is important to clarify that these methods are not intended to replace the causality determinations of previous ISAs, but rather have been recently adopted in service of strengthening the body of evidence for causality determinations.

Regarding the PM causality determinations, the CASAC notes that there is a progression going from the 2009 ISA to the 2019 ISA to this Draft ISA Supplement indicating continued strengthening of the causal health endpoints relationship with $PM_{2.5}$. The literature, as it is expanding, continues to show strong associations with health effects, even though concentrations of $PM_{2.5}$ in the air have been dropping over time.

The material on welfare effects in this section is brief and limited to visibility impairment, but that is appropriate given scope of this Draft ISA Supplement.

CASAC Advice on the Process and Timeline for CASAC Reviews

The CASAC commends the EPA for returning to its long-standing practice of constituting an ad hoc panel of experts to complement the expertise of the Chartered CASAC. The previous CASAC recognized the need for a larger review panel, stating in its letter to the Administrator on April 11, 2019: "Additional expertise is needed for the Clean Air Scientific Advisory Committee (CASAC) to provide a thorough review of the particulate matter (PM) National Ambient Air Quality Standards (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." The CASAC recommends that the practice of convening a panel of additional experts continue for all future NAAQS reviews because the give-and-take deliberation and participation of multiple scientific experts, including multiple experts from all key disciplines needed to conduct a high-quality scientific review, is fundamental to the Chartered CASAC's ability to provide the highest-quality scientific advice. With a fully constituted ad hoc panel of experts, the CASAC has a broad depth and breadth of perspectives that enables it to fulfill its mandate to provide advice and recommendations to the EPA.

The CASAC is concerned that the compressed timeframe for this and other recent CASAC reviews has made it difficult for the CASAC to provide the highest quality review possible. The compressed timeframe for simultaneously reviewing large documents is not optimal. It is also not optimal that the timeframe does not allow for development of second drafts of documents that incorporate CASAC advice (should the CASAC recommend second drafts). The CASAC recommends that for future reviews, the EPA follow a review plan that allows for adequate time for the CASAC to review the documents and sufficient time for the EPA to incorporate CASAC advice into second drafts (if requested by the CASAC). The review plan should also allow sufficient time for CASAC advice on earlier documents (e.g., ISA) to also be incorporated into subsequent documents (e.g., REA and PA). Documents that are supposed to be developed sequentially (e.g., the ISA and PA) should not be developed simultaneously and presented to the CASAC for simultaneous review.

Section 2 – Overview of Main Conclusions of the 2019 Integrated Science Assessment for Particulate Matter

To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

Section 2 provides context for the recent studies in the Draft ISA Supplement from the conclusions of the 2019 PM ISA. Although the repetition of this contextual material may make it more difficult to quickly focus on the summary and integration of new material in the Draft ISA Supplement and its relevance to this reconsideration, Section 2 is still a useful addition.

Chapter 3 summarizes the relevant causal determinations from the 2019 ISA in sections 3.1.1.1, 3.1.2.1, 3.2.1.1, and 3.2.2.1. Each is four to six pages long including tables. Combined, the text and tables provide clear and concise summaries of the information necessary to provide context for the material on new studies that follow. The CASAC finds these background summaries useful and helpful, but notes that the transitions from them to the new study material being presented in each section could be improved to make the overall section more reader-friendly. For a specific example, Section 3.1.1.2 (Recent U.S. and Canadian Epidemiologic Studies), follows a bolded sentence concluding the discussion of the causal determination of the 2019 ISA with an entire paragraph that is about biological mechanism before starting to discuss recent U.S. and Canadian epidemiologic studies in the next paragraph. While the information in the first paragraph of this section is correctly given, the placement of this paragraph is an example of a difficult transition.

Section 3 – Evaluation of Recent Health Effects Evidence

Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

Overall, the CASAC finds the summary of health effects to be well-written and thorough, with appropriate identification, evaluation, and characterization of available scientific evidence, including in the context of the conclusions from the 2019 PM ISA. A few additional studies are identified in Panel members' individual comments. The CASAC recommends the following improvements.

The text on "causal modeling methods" should be reworded to clarify these methods' role in and distinction from the WOE causality determinations outlined in the 2015 Preamble to the ISA. While recent emergence of studies employing such methods is important to the Draft ISA Supplement, the CASAC recommends alternative descriptive language to avoid the potential misconception that labeling some studies as "causal" carries an implication that more traditional epidemiologic analysis methods cannot support a causal determination or should receive less weight in any WOE causality determinations. Both traditional and more novel causal inference analysis methods should be employed in service of strengthening the body of evidence.

Regarding the study descriptions and findings, the evaluation and characterization of some studies could be improved. There are places where more detail would be useful to give context to the results (e.g., hazard ratios, sample size, methods for exposure assessment, whether co-pollutant confounding was assessed by 2-pollutant or multi-pollutant models). Specifically, conclusions are needed for these studies regarding what was learned, and the ways and degrees in which the studies strengthen or weaken the state of scientific evidence. Language on sample size should be rephrased to avoid the misconception that larger studies are always better, and instead focus on the tradeoffs of larger sample size (e.g., statistical power) with smaller studies (e.g., often more detailed individual-level data or exposure assessment). Similarly, wording on multi-city versus single-city studies should acknowledge similar tradeoffs. More information on uncertainty is warranted, such as differences in studies by location, differences in concentration-response functions (in particular, potential differences in the shape of the functions and characterization of uncertainty in the shape reported in different publications), etc. The discussion of heterogeneity of effect estimates largely focuses on variation in particulate matter itself (i.e., components, which may indicate key sources), but more attention should be given towards distinguishing this variation from effect modification by other individual- and contextual-level variables (e.g., race/ethnicity, urbanicity, housing stock, air conditioning prevalence) that influence variation in effect estimates. This is critical for a fuller understanding of observed heterogeneity in risk, especially as it relates to the issue of environmental justice.

Publication bias should be acknowledged in this section, though clearly noting that publication bias cannot explain these overall scientific findings (i.e., concentration-response functions).

There are multiple terms utilized to describe races and ethnicities in the United States, which is reflected by the studies included in the Draft ISA Supplement. Race/ethnicity is a fluid concept that is relevant by time, country, region, population and government. Therefore, the most useful terminology for the purpose of protecting public health has changed over time. The CASAC suggests consideration of different language on susceptibility/vulnerability/sensitivity in the Draft ISA Supplement, if it is appropriate to deviate from terminology that matches the 2019 ISA. The CASAC recommends updated language for discussions of race/ethnicity, such as "People of Color (POC)" or "Communities of Color (COC)" rather than "non-White," and "indicator" rather than "proxy."

Additional specific comments:

- While a footnote on page 3-1 does indicate that "risk estimates from epidemiologic studies examining short-term exposures are for a 10-$\mu g/m^3$ increase in 24-hour avg $PM_{2.5}$ concentrations and long-term exposures are for a 5-$\mu g/m^3$ increase in annual concentrations," this scaling approach is not as clear as it might be throughout the section. These $PM_{2.5}$ scaling factors should be included in each introduction paragraph of each disease specific section.

- Although there is a definition of how the Draft ISA Supplement defines short-term versus long-term exposures in Section 2.1, the difference between what is considered short-term and long-term exposure also needs to be highlighted.

- Section 3.3 should be re-ordered, placing the discussion of at-risk populations first and COVID-19 last. This is recommended to correspond to the more recent nature of the COVID-19 pandemic and considerations for the ISA.

- Additional suggested edits and minor errors requiring correction can be found in the individual comments from Panel members.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary sub-sections appropriately characterize recent evidence in the context of the causal determinations of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

The biological plausibility and mechanistic pathways of the associations between both short-term and long-term exposures to $PM_{2.5}$ and health outcomes could be better highlighted and developed. While there is no need to discuss biological plausibility and mechanisms in great detail, as was done in the 2019 PM ISA, it should be made clear that the evidence in support of these concepts remains strong and these lend confidence to the causal determinations.

The level of SES data is an important component in understanding research questions, modeling and interpretation of results. Section 3.3.3 (Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect) would benefit from the greater discussion related to this. The CASAC suggests that studies that utilize individual-level SES data be distinguished from those that use community-level data, including in summaries of findings. Dividing the discussion into individual- and community-level measures will help the reader digest the data. Individual-level and community-level data differ with regards to their representativeness and accuracy, and the level of resolution utilized in a study could drastically change interpretation of results.

The articles by Yitshak-Shade et al., Son et al. (2020), Crouse et al. (2019), Stieb et al. (2020) include the impact of green space on associations between $PM_{2.5}$ and mortality. However, there is no discussion of green space in the Draft ISA Supplement. The EPA could consider removing these references. If these studies are to be included in the Draft ISA Supplement, then there should be additional assessment of the linkages between green space and $PM_{2.5}$ concentrations; green space and health; and quality of green space by race/ethnicity.

In Section 3.3.3.1., the EPA could consider including interpretation of results from studies that include race within indices of vulnerability. Race is not a necessary component of vulnerability.

In future PM ISAs, the CASAC suggests that the EPA include panel studies that investigate relationships between $PM_{2.5}$ and health markers (e.g. inflammation). The inclusion of these studies will allow for a broader assessment of health morbidity beyond examining mortality alone.

Section 4 – Evaluation of Recent Welfare Effects Evidence

Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.

The CASAC agrees with the assessment in Section 4 that recent evidence confirms the "causal relationship" between PM and visibility impairment. However, a few clarifications are needed. Section 4 acknowledges variations in humanly perceivable acceptance of visibility levels. The use of "apparent contrast" instead of "total light extinction" shows less variability to determine acceptable visual air quality. Values for the cut-off for unacceptable versus acceptable levels for atmospheric extinction coefficients and consistent acceptable contrast levels should be clarified. Science-based visibility standards warrant additional research using objective scenarios to quantify visibility improvement.

With increases in the frequency and intensity of wildfires and reductions in sulfur dioxide (SO_2) and oxides of nitrogen (NOx) emissions, mass scattering coefficients for the major $PM_{2.5}$ components (e.g., organic and elemental carbon, sulfate, and nitrate) need to be further examined with more recent data (e.g., 2015 onward). The "revised" Interagency Monitoring of Protected Visual Environments (IMPROVE) chemical extinction equation (Pitchford et al., 2007) that has been recommended by the EPA and applied to the most recent Regional Haze State Implementation Plans should be included. In addition, the Lowenthal and Kumar (2016) IMPROVE equation should be added to the document along with discussion in detail. Differences among the various IMPROVE equations that use split component algorithms need to be addressed.

Analysis of regional variations between $PM_{2.5}$ composition, light extinction, and views may provide some perspective on causes and variations of organic mass in the intermountain west and southwest, increases in nitrate and ammonium in the central U.S., along with a decline in sulfate/organic ratios and

increasing organosulfate/total sulfate ratios in the southeast (Riva et al., 2019). These changes may alter optical properties that are not accounted for by the IMPROVE chemical extinction equations.

Recent evidence points to effects of microplastics in PM on climate (e.g., Revell et al., 2021), dry and wet deposition (Brahney et al., 2020), and ecosystems (e.g., Halle et al., 2020; Sobhani et al., 2022). These and other emerging PM components require further consideration in future reviews.

Section 5 – Summary and Conclusions

The Summary and Conclusions section (Section 5) provides an overview of the evidence evaluated in the draft PM Supplement.

Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence.

Section 5 is a concise 4-page summary of the Supplement. There is a single paragraph summarizing each of the four major health outcomes for which exposure to $PM_{2.5}$ was determined to have a causal relationship in the 2019 ISA (short- and long-term cardiovascular and mortality effects). The "Additional Considerations" are also summarized. The summary is accurate, with an appropriate level of detail. The CASAC suggests conclusions be added to the summaries focused on COVID-19 (page 5-3), and visibility effects (page 5-4). Additional recommended changes for clarity made elsewhere in the document should be incorporated into this section. Finally, the CASAC recommends that the EPA incorporate into this section some specific proposed edits contained in Panel members' individual comments that will further improve balance and clarity.

References

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Appendix A

Individual Comments by the 2021 CASAC Particulate Matter Review Panel Members on the EPA's *Supplement to the 2019 Integrated Science Assessment for Particulate Matter (External Review Draft – October 2021)*

Mr. George A. Allen

Charge Question 2 - Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

Section 1 is a clear and concise summary of the purpose and scope of the ISA Supplement. This section explains(1.2.1) that the scope of the document is limited to health effect evidence categories that the 2019 PM ISA concluded had a causal relationship, e.g. limited to short- and long-term PM2.5 exposure and cardiovascular effects and mortality. This is appropriate for the targeted purpose of the ISA Supplement, where consideration is focused on recent literature that could support alternative PM2.5 annual and/or daily standards.

The scope of the Supplement is limited to U.S. and Canadian epidemiologic studies. I did not find an explanation for that in this section; there are new and relevant European study publications on health-effects of low level PM2.5 such as the HEI ELAPSE project. See HEI's ISA Supplement comments and the September 2021 ELAPSE study publication (https://www.bmj.com/content/374/bmj.n1904).

The material on welfare effects in this section is brief and limited to visibility impairment, but that is appropriate given scope of this Supplement and its primary focus on the PM2.5 health-based standards.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

While providing context of recent studies to the conclusions of the 2019 PM ISA is necessary, I found the repeated emphasis of the 2019 findings somewhat excessive for an audience who is already familiar

with the previous PM review. The repetition of this contextual material made it more difficult for me to quickly focus on the summary and integration of new material in the Supplement and its relevance to this review. This document is a Supplement and, as is stated in the introduction, is not intended to stand on its own for support of this reconsideration review.

Chapter 3 summarizes the relevant material from the 2019 ISA in sections 3.1.1.1, 3.1.2.1, 3.2.1.1, and 3.2.2.1. Each is four to six pages long including tables. Combined, the text and tables provide a good summary of the information necessary to provide context for the material on new studies that follow. The summaries are clear and concise. Given these summaries, perhaps the 2019 Integrated Synthesis material in Chapter 2 could be incorporated by reference to help focus the document on new studies.

For the summary of PM2.5 short-term cardiovascular effects, the reference to table 3-4 (total mortality) on page 3-3 line 8 should be to table 3-1 directly below it.

Charge Question 1 - The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the draft PM Supplement for a broad range of audiences.

a. Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.

b. Please provide recommendations on whether additional information should be added to the Executive Summary or information that should be left for discussion in the subsequent sections of the draft PM Supplement.

The Executive Summary is brief, two pages total. It clearly and concisely explains the purpose and limited scope of the Supplement, and notes inclusion of recent studies on causal modeling methods or accountability analyses, near-ambient experimental studies, disparities in PM2.5 exposure or health risk by race or SES, and effects of PM2.5 exposure on Covid-19 health outcomes. Passing mention is made of visibility topics, which is ok given the focus of this reconsideration on the primary health standards. Importantly, this Summary explicitly states that the Supplement does not include the entire body of literature that supports WOE conclusions. It notes the focus of the Supplement on recent studies that support and extend the causality determinations that were the subject of extensive discussions during the 2019 PM NAAQS review. The level of detail and information included in the Summary is appropriate for its intended purpose.

Charge Question 6 - The Summary and Conclusions section (Section 5) provides an overview of the evidence evaluated in the draft PM Supplement.

a. Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence.

Section 5 is a concise 4-page summary of the findings from recent studies considered in this Supplement. There is a single paragraph summarizing each of the four major PM2.5 health outcome causal categories (short- and long-term cardiovascular and mortality effects). Detail on each is minimal but sufficient for this overview.

Consider using "causal" relationship for these summaries, because causality is a critical topic of this reconsideration. Example: "… different statistical approaches and cohorts spanning diverse geographic locations and populations provide additional support for the <<*causal*>> PM2.5-mortality relationship."

Two additional short paragraphs cover near-ambient experimental studies and Covid-19, and two additional bullets summarize populations and lifestages risk findings with SES and race. Health risk disparities for Black populations seems to be de-emphasized relative to higher PM2.5 exposures in predominantly Black neighborhoods. I'd consider this backwards (see Di et al. 2017b, (NEJM, figure 2a), and worthy of more attention in general.

Visibility effects are bulleted under the Populations and Lifestages heading and should be separate.

Dr. John R. Balmes

Charge Question 1 - The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the draft PM Supplement for a broad range of audiences.

a. Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.

The Executive Summary clearly and appropriately communicates the information underlying the causal relationship determinations for short-term and long-term exposures to PM2.5 and cardiovascular effects and mortality.

Charge Question 2 - Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

The scope and clarity of Section 1 are appropriate for the introduction to the organization of the Supplement.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

My major comment about the approach to the integration of evidence in both the 2019 PM ISA and the Supplement is the characterization of the relationship of both short-term and long-term exposures to PM2.5 of the respiratory effects as “likely to be causal.” First, my assessment of the epidemiological

evidence is that it supports a causal relationship, even if experimental evidence is weaker than for cardiovascular effects. Second, I find it somewhat logically inconsistent with the likely causal determination for respiratory effects that in Chapter 3 of the Supplement respiratory tract inflammation is used as part of the biological mechanism rationale for cardiovascular effects. I also find this inconsistency with regard to the discussions of respiratory-specific mortality (used to support the mortality causal relationship determination) and growth of lung function in children (used to support the vulnerability of children). In addition, the likely causal relationship determination for lung cancer (and lack of evidence for other cancers) also supports the respiratory toxicity of exposures to PM2.5 exposures.

I also think that the discussion of the experimental evidence regarding the carcinogenicity of PM2.5 "as a whole" is somewhat misleading. While I understand that the NAAQS is based on particle size and that the epidemiological evidence is largely for PM2.5 rather than for its components, chemical composition undoubtedly determines carcinogenicity. Discussing experimental studies of PM2.5 carcinogenicity without comment about the source and characterization of the particulate matter used in the studies gives the impression that exposure to any type of PM2.5 can increase risk of lung cancer, but I doubt that this is likely.

Section 2.2.5 on Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect should list all of the populations determined in the 2019 ISA to be vulnerable so as to avoid confusion.

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

In general, it is my opinion that the characterization and evaluation of the available evidence in Section 3 is appropriate.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

It is my opinion that the summary sub-sections of Section 3 appropriately characterize the recent evidence.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

I would like to see a discussion of Respiratory Effects, especially given new evidence that wildfire-specific PM may be more potent than non-wildfire PM for respiratory outcomes.

Charge Question 5 - Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.

No comments at this time.

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

No comments at this time.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.

No comments at this time.

Charge Question 6 - The Summary and Conclusions section (Section 5) provides an overview of the evidence evaluated in the draft PM Supplement.

a. Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence

I think the level of detail is OK.

Dr. Michelle Bell

Overall, the supplement to the ISA is extremely well-written and thorough. Below are my preliminary comments.

Page ES-2 and ES-3: The statement that "there may be PM2.5 exposure and health risk disparities by socioeconomic status (SES), specifically among people of low SES." seems understated given the current scientific evidence. I appreciate that this bullet point distinguishes between exposure and health risk disparities for both racial/ethnic minorities and SES.

Executive Summary: Growing evidence indicates that PM chemical structure impacts the health impact of PM, although the current scientific literature cannot disentangle the various sources, chemical structures, and components to identify a specific PM characteristic to target, other than by size. This might be worth noting as a bullet point in the Executive Summary. Although it does not change the outcome of the resulting recommendation, the growing science in this area may be worth highlighting.

Page 1-1: The definition of "welfare effects" to exclude ecological effects associated with particulate matter, even if used consistently in this document, differs from how this phrase is commonly applied. This is described as a footnote on page 1-1. To make sure readers are aware of this definition of welfare effects, it may be worth moving this footnote to the main text. If possible, it may be useful to have different wording other than "welfare effects" to note that this is a subset of welfare effects, if appropriate alternative phrasing can be developed.

Page 1-3 and 1-4: The focus on U.S. and Canadian studies is reasonable but could be justified if there is room. A focus is different from excluding other studies. Excluding studies from other locations entirely is questionable is they do provide critical scientific evidence. Similarly, excluding studies without causal methods of accountability analysis is negating decades of critical literature including many more recent and valuable studies that. The evaluation of causality based only on these methods is questionable. Although, it is appreciated that the text notes that other studies exist (end of Section 1.2). This issue arises throughout the supplement.

Page 2-7: Define CAPS at first use. This is important as CAPS is sometimes used in the air pollution context to mean criteria air pollutants.

Page 3-1: The exclusion of studies outside of Canada and the United States needs more justification (see comment above). A focus on these regions could relate to population characteristics and pollution levels as well as composition. However, excluding all other studies would require more justification than is

provided. This issue is further complicated by the inclusion of studies from outside these countries, such as Asian and Australian studies in Section 3.

Page 3-1: The disparities of race/ethnicity and socioeconomic status (SES) are examples of environmental health disparities, not the only ones. This sentence states that they were the only ones considered. Are they meant to be listed as examples?

Tables 3-1: The column heading of PM2.5 Concentrations Associated with Effects is unclear and the footnote is not particularly helpful ("c Describes the PM2.5 concentrations with which the evidence is substantiated.") This could refer to concentrations for which effects were estimated in situations for which no effect was estimated for other concentrations, or to merely the levels of PM2.5 for those study areas and timeframe, meaning the levels for the study, in which case it might mean the average concentration over the study or incorporate the full range. As a minor point, but one that will aid clarity, "effects" could be positive or negative and here this column means harmful effects. It is also unclear why concentrations are missing from some rows where they could be provided.

Page 3-4: As a minor note, the footnote to this table could denote CMAQ as the Community Multiscale Air Quality model, as some readers will not know this is a modeling framework.

Page 3-9: The sentence "As expected, the city specific estimates were relatively uncertain and heterogeneous across cities when there were a small number of daily ED visits." does add much. It may not be needed.

Page 3-10: The description of Figure 3-1 should explain what lag structures were selected as most of these studies included sensitivity analysis with multiple lag structures. This is particularly important as results are generally robust to alternative lags. This could link to Section 3.1.1.2.8.

Page 3-11: Minor note: For Figure 3-1, the notes column seems inconsistent in terms of what information is included as location information is included both there and in the location column.

Page 3-12: When describing a study that was intended to study racial differences, those results could be presented here.

Pages 3-14, 3-16, and 3-18: The comment regarding lag structure for Figure 3-1 also applies to Figure 3-2, Figure 3-3, and 3-4.

Page 3-18: The phrasing that large studies have higher counts "potentially providing statistical power needed to perform stratified analyses." could be better worded. What is meant here is the ability to detect associations. Small datasets can be stratified, although they are less informative. Such analyses in large, or small, datasets may be stratified or may be through other methodologies.

Page 3-20: Throughout this document, it would be helpful to note where new findings are consistent with the earlier literature. Page 3-20 on co-pollutant adjustment is an example, but this is a broader issue. Section 3.1.1.2.7 nicely describes some studies on co-pollutants, but these are not addressing a new issue and a reader might misinterpret this as new evidence rather than building on the existing evidence of co-pollutants as potential confounders for the PM-health associations.

Page 3-20: The joint exposure studies are interesting, but still limited in their ability to disentangle the complex effects of PM with other pollutants, similar to the efforts to disentangle impacts from various PM sources. The text here does not adequately describe this issue. Also, it is in a section titled Potential Copollutant Confounding, although looking at joint effects is not a true confounding study.

Page 3-24: There is no basis for the statement "Uncertainty related to exposure assessment was generally reduced with consideration of studies 6 included in the 2019 PM ISA that applied hybrid exposure assessment techniques that combined land use 7 regression with satellite AOD measurements and PM2.5 concentrations measured at fixed site monitors." In fact, the opposite is likely true. These approaches add uncertainty in exposure assessment and add more study areas, and therefor populations. They do not make exposure estimates more certain better than a monitor measurement.

Page 3-26: Table 3-2: The comment above for Table 3-1 regarding concentration specifications applies here as well.

Page 3-47: Figure 3-12 may not be needed.

Page 3-49: This section is on mortality with subsections on short and long-term exposure, whereas the previous sections are on short or long-term exposure with subsections on types of mortality. The overall structure of this document could be confusing and repetitive.

Page 3-50: The above comment for Table 3-1 regarding concentration specifications applies here as well. This also applies to subsequent tables with similar format.

Page 3-51: Differences in population characteristics also contribute to the different findings of PM and health across regions.

Page 3-51: The phrase "exposure factors" is vague. Perhaps this could be more specific or include some examples to aid readers.

Page 3-52: There are not studies that use "all available PM2.5 data" but studies that use additional sources of PM2.5 data beyond monitors.

Page 3-53: The discussion of factors contributing to regional heterogeneity on PM-health associations is missing text on differences in population characteristics, which has been examined in several studies.

Page 3-56: The comment above regarding lag structure for Figure 3-1 also applies to Figure 3-13. In this case, footnotes for some studies not sensitivity analysis for lag structures, but others do not. An alternative strategy would be to note, in the text describing this figure, that multiple lag structures were examined and findings were generally robust, and to explain why the specific lags were selected for inclusion in the figure.

Page 3-56: The Liu et al. study is best described as "worldwide" as there are some regions that are not well represented (e.g., Africa).

Page 3-56 to 3-57. Liu et al. did not "establish" the MCC network, but this study is part of the MCC projects. The MCC existed well before this paper and was not established by Liu. This text needs to be reworded.

Page 3-59: The comment above for Figure 3-1 regarding lag structure applies here as well.

Page 3-60: The section on effect modification is a bit muddled as it discusses confounding as well. It also focuses on effect modification by specific community-level factors and ignores many others that have been examined, such as community-level demographics beyond those mentioned here. This whole subsection warrants a closer look at its goal, focus, and structure.

Page 3-63: Figure 3-16 is fine, but it provides information on the magnitude of the central estimate without any information on its statistical uncertainty. If a map of different effect estimates across location is used, one that incorporates statistical uncertainty would be more informative.

Page 3-65: See comment above regarding Liu et al., which is not "worldwide". A global multi-city study would be more accurate.

Page 3-81: The text noting HEI is a odd as the funding sources of other studies are not mentioned.

Page 3-93: Figure 3-25 needs a better title that is more descriptive. This is the estimated loss in life expectancy for existing levels of PM2.5 compared to a threshold of 2.8 migrogm/m3, which is the lowest observed level.

Page 3-95: These methods to address confounding have been used in many previous studies, so they might not be best labelled as novel. This information would be better placed in a section on confounders rather than its own section on methods.

Page 3-95: The text on temporal trends needs to be clear that this refers to temporal trends in confounders, not in the association. This applies to text in later pages as well.

Page 3-128: Section 3.3.3.1.1 should note that disparities in exposure are noted by PM2.5 chemical composition, not just total mass of PM2.5

Section 3 charge question: Overall, this section well characterizes the identification, evaluation, and characterization of the available scientific evidence; appropriate characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

Dr. James Boylan

1. The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the draft PM Supplement for a broad range of audiences.

a. Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.

b. Please provide recommendations on whether additional information should be added to the Executive Summary or information that should be left for discussion in the subsequent sections of the draft PM Supplement.

The Executive Summary clearly communicates the key information from the draft PM Supplement. I have no recommendations for information that should be added or deleted from the Executive Summary.

2. Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

In general, the purpose and scope of the draft PM ISA Supplement is clearly presented. It is appropriate for the draft PM ISA Supplement to focuses on the health effects and the welfare effects where the 2019 PM ISA concluded a causal relationship.

One of the important objectives of the ISA is to make causal determinations that are then used in the REA and PA documents. In the previous PM review, CASAC questioned the current causal determination framework which is based on weight-of-evidence and professional judgement leading to results than can't be replicated by others. Instead, the CASAC recommended that a "more explicit, systematic, and transparent process" should be used for determining causal relationships. According to the CASAC letter dated April 11, 2019 to Administrator Wheeler, "…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 $PM_{2.5}$ 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." **This is an example of two <u>different</u> groups looking at the <u>same</u> evidence and coming to <u>different</u> conclusions on the causal relationships.** In the final ISA, EPA agreed that the causal relationship

between long-term ultrafine particulate (UFP) exposure and nervous system effects should be changed from "Likely to be Causal Relationship" to "Suggestive of, but not Sufficient to Infer, a Causal Relationship". **This is an example of the same group looking at the same evidence and coming to a different conclusion.**

The previous CASAC recommendation on the current causal determination framework resulted in the National Academies of Sciences, Engineering, and Medicine (NASEM) committee on "Assessing Causality from a Multidisciplinary Evidence Base for National Ambient Air Quality Standards" (https://www.nationalacademies.org/our-work/assessing-causality-from-a-multidisciplinary-evidence-base-for-national-ambient-air-quality-standards). Additional detail on this would inform the reader on the recent developments on this topic since the last review.

3. To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

Pulling information directly from the 2019 PM ISA is a good approach to lay the foundation for the new information presented in the draft PM ISA Supplement.

5. Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.

The use of contrast rather than total light extinction appears to make the level of acceptable visual air quality across different locations more consistent.

Pages 4-4 and 4-5 discusses "an unacceptable level of visibility impairment". However, the definition of "unacceptable" is not discussed. It appears that if 50% or more of the observers rated the visibility acceptable, then it was classified as "acceptable"; and if less than 50% of the observers rated the visibility acceptable, then it was classified as "unacceptable". If so, the document should clearly state this definition.

Page 4-5 states "When the features approximately reach the visual range, corresponding to a contrast between about **-0.03 to -0.05**, about 50% of observers rated the image as not acceptable." However, Page 4-6 states "…that visibility preference studies suggest that about 50% of individuals would find visibility unacceptable if at any time the more distant landscape features nearly disappear, and that this occurs when these features are near the visual range and have contrast levels of approximately **-0.02 to -0.05**". The text should be updated to be consistent since both sentences are discussing the 50% unacceptable contrast level based on Figure 4-2. To me, it appears that -0.03 is more appropriate than -0.02.

Page 4-6 states "Further, an acceptability level of 90% would require contrast levels to remain above a level of about -0.01." That statement does not seem accurate. To me, it appears that an acceptability level of 90% would require contrast levels to remain below a level of about -0.05 or -0.07.

Page 4-7 mentions the "original" IMPROVE equation, "revised" IMPROVE equation, and the "modified" IMPROVE equation. The differences between the "revised" IMPROVE equation and the "modified" IMPROVE equation should be discussed in more detail. The document states:

> "This algorithm was **modified** with the goal of reducing bias that had been observed in applications of the original IMPROVE equation by splitting major PM components between small and large size modes in recognition that atmospheric PM generally follows a bimodal size distribution (Pitchford et al., 2007). This approach has been referred to as the **revised** IMPROVE equation (U.S. EPA, 2019) or the split component algorithm (Prenni et al., 2019). However, by the time of publication of the 2019 PM ISA, new studies had concluded that the **modified** IMPROVE equation had not been generally successful in decreasing the bias in atmospheric extinction estimates associated with the original equation (U.S. EPA, 2019)."

Based on this statement, the document appears to imply that the "revised" IMPROVE equation is the same as the "modified" IMPROVE equation, which is not correct.

The "original" IMPROVE algorithm (Equation 13-6) and the "modified" original IMPROVE algorithm (Equation 13-7) are presented in the 2019 PM ISA on pages 13-11 and 13-12, respectively. These equations tend to underestimate the highest light scattering values and overestimate the lowest values at IMPROVE monitors throughout the U.S. To resolve these biases, a "revised" IMPROVE equation was

developed (Pitchford et al., 2007) that divides PM components into small and large particle sizes with separate mass scattering efficiencies and hygroscopic growth functions for each size. The "revised" IMPROVE equation both reduced bias at the lowest and highest scattering values and improved the accuracy of the reconstructed b_{ext}. However, the "revised" IMPROVE equation is not presented in the 2019 PM ISA or the draft PM ISA Supplement. Here is the "revised" IMPROVE equation:

b_{ext} = 2.2 x fs(RH) x [Small Sulfate] + 4.8 x fL(RH) x [Large Sulfate]
+ 2.4 x fs(RH) x [Small Nitrate] + 5.1 x fL(RH) x [Large Nitrate]
+ 2.8 x [Small Organic Mass] + 6.1 x [Large Organic Mass]
+ 10 x [Elemental Carbon]
+ 1 x [Fine Soil]
+ 1.7 x fss(RH) x [Sea Salt]
+ 0.6 x [Coarse Mass]
+ Rayleigh Scattering (site specific)
+ 0.33 x [NO2 (ppb)]

This equation should be added to the document and discussed in detail. This equation has been the preferred IMPROVE equation for the past 15 years and is being used by all states in their most recent Regional Haze State Implementation Plans (for the second implementation period). In addition, use of this equation is recommended by EPA in their "Modeling Guidance for Demonstrating Air Quality Goals for Ozone, $PM_{2.5}$, and Regional Haze" (November 29, 2018), pages 146-148.

In addition, the Leventhol and Kumar IMPROVE equation (2016) should be added to the document and discussed in detail. Both the "revised" IMPROVE equation and the Leventhol and Kumar IMPROVE equation are utilized in the draft PM PA document.

Page 4-8 states "The large and rapid change in mass scattering efficiencies during atmospheric aging presents a challenge for accurately estimating atmospheric light extinction based on constant mass scattering coefficients, as in the IMPROVE equation." However, it should be noted that the "revised" IMPROVE equation and the Leventhol and Kumar IMPROVE equation divides sulfate, nitrate, and organic mass PM components into small and large particle sizes with separate mass scattering efficiencies for each size.

Page 4-8 discusses "mass scattering efficiencies for wildland fire smoke" but does not discuss the composition of wildland fire smoke. The document should add a breakdown of typical wildland fire smoke by PM components (e.g., organic carbon, elemental carbon, sulfate, nitrate, etc.).

Dr. Judith C. Chow

Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.

A better integration may be needed to connect Section 2.3 on "Welfare Effects" and Section 4 on "Evaluation of Recent Welfare Effects Evidence". Both sections emphasize visibility impairment, but not climate change, material damage, or ecosystem degradation.

Section 2.3.1 on "Visibility Impairment" acknowledged the changes in $PM_{2.5}$ composition by region and season that have affected the apportionment of light extinction among $PM_{2.5}$ species. It highlights the steep decline in sulfate of ~4.6-6.1% per year in both rural and urban areas from 2002-2012 (U.S.EPA, 2019). However, this record is nearly a decade old, not representative of current status. Section 4.1 on "Summary of Evidence for Visibility Effects from 2019 Integrated Science Assessment for Particulate Matter" further emphasizes the importance of ammonium sulfate in particle light scattering. However, neither Section 2.3.1 nor Section 4 adequately provide overall perspectives on relationships between $PM_{2.5}$ composition and light extinction as well as their seasonal and annual changes over the last decade. It also contains incorrect statements. For example, Section 2.3.1 states that "… although $PM_{2.5}$ sulfate is still responsible for more light extinction than any other single species…" (Lines 21-22, page 2-38) and Section 4.1 emphasizes "… ammonium sulfate has historically accounted for a larger fraction of $PM_{2.5}$ mass than other components…" (Lines 24-25, page 4-1). These statements are not entirely true, they are too generalized as they don't apply to the western U.S. where organic mass accounts for a large fraction of $PM_{2.5}$ mass as illustrated in Figures 13-4 and 13-5 (page 13-25 and 13-26) of the ISA (U.S.EPA, 2019). Overall, more detailed analysis of recent $PM_{2.5}$ speciation data and their association with light extinction are needed.

Section 4.2.1 on "Visibility Preference and Light Extinction" is based on Malm et al. (2019) that summarizes relationships between public acceptability and atmospheric light extinction in four U.S.

(Washington, D.C., Denver, CO, Phoenix, AZ, and Grand Canyon, AZ) and two Canada (Chilliwack, B.C., and Abbotsford, BC) locations. Although the acceptability levels among the studies are more consistent when plotted against apparent contrast of distant features that are most sensitive to haze (e.g., Malm et al., 2019), it appears that public perception of visibility impairment or the importance of scenic views is qualitative and judgmental with large uncertainties (Smith, 2013). A science-based visibility standard warrants additional research using objective scenarios that quantify visibility improvements (e.g., haziness index or deciview) by relating changes in light extinction to human perceived variations or perceptible changes.

With respect to recent advances in visibility monitoring and assessment, Section 4.2.2 on "Visibility Monitoring and Assessment" briefly summarizes average atmospheric extinction reduction in the U.S. of 1.8% per year for the period of 1990-2018 and 2.8% per year for the period of 2002-2018. This is based on reconstruction of total light extinction estimated from IMPROVE network speciated PM concentrations by Hand et al. (2020). Although seasonal and spatial patterns of visibility impairment are documented in the 2019 ISA (Chapter 13.2.4, U.S. EPA 2019), the analysis is based on older (2005-2008 and 2011-2014) data that does not represent new information for the most recent period (e.g., 2015-2018 or 2016-2019). Hand et al. (2019) find increasing organic mass (OM) to organic carbon (OC) ratios across the IMPROVE network after 2011, highest during summer in the east and not necessarily influenced by particle bound water. Information on spatial interpolation of average monthly reconstructed light extinction coefficient (b_{ext}, Mm^{-1}) by major chemical component for each region for the most recent period will provide some perspective on overall changes, especially on increases in OM in the mountain west and southwest and increases in nitrate and ammonium in the central U.S., since the last review (2011-2014).

Section 4 would benefit from additional weight-of-evidence analyses and methods to monitor secondary PM NAAQS indicators of visibility (Pitchford, 2010). Based on linear regression, So et al. (2015) estimated time-resolved hourly total light extinction using continuous hourly $PM_{2.5}$, NO_2, relative humidity, and historical monthly averaged aerosol chemical composition at four monitoring sites in the Lower Frazer Valley of British Columbia, Canada. The Pitchford (2010) approach may warrant a revisit. Case studies can be conducted at selected sites to evaluate if the hybrid modeling approach can provide relatively accurate and time-resolved light extinction estimate in regions with sparse visibility monitoring, thereby extending the spatial coverage of the nationwide visibility monitoring network.

Section 4 calls for evaluation of recent welfare effect evidence, but only addresses the visibility effects without discussing climate, ecosystem, and material effects. Brief statements are made on Section 2.3.2 on "Climate Effects" and Section 2.3.3 on "Materials Effects", but only the 2019 ISA is cited, without providing any new insights. Recent reviews on environmental and health impacts of air pollution (e.g., Manisalidis et al, 2020) and the physical science basis of climate change (IPCC, 2021) provide background on non-visibility effects. Recent evidence points to effects of microplastics in PM on climate (e.g. Revell et al., 2021), dry and wet deposition (Brahney et al., 2020), and ecosystems (e.g.

Halle et al., 2020; Sobhani et al., 2022). These and other emerging PM components require further consideration.

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Dr. Jane Clougherty

Overall, I found the ISA supplement to be an impressive, thorough review of the relevant literature. It is generally well-written, through very repetitive, and the structure (perhaps unavoidable) can be very challenging to follow.

My preliminary comments focus on Section 3. (I have no specific comments on Sections 1 and 2, except that they are very repetitive).

Perhaps also worth noting that publication bias is likely present, though probably unlikely to explain observed concentration-response functions.

The heading for section 3.1.2.4 should refer to cardiovascular effects, not mortality.

Section 3.2: Mortality

3.2.1: Short-Term $PM_{2.5}$ Exposure

I agree with the broad assessment that the bulk of the epidemiologic evidence supports a positive association between $PM_{2.5}$ and mortality (p. 3-56 ISA Table 11-1), though associations vary substantially, as would be expected with between-study variation in methods, spatial differences in PM composition and population susceptibility, etc. (geographic heterogeneity).

I'm a bit hesitant on the issue of co-pollutant adjustment, as many of the recent studies examining this confounding are based in Europe (where local traffic emissions contain more $PM_{2.5}$ due to high diesel prevalence) and Asia (where PM levels are generally much higher). It is noted on p. 3-60 that only one multi-city US study investigated co-pollutant confounding (Lavigne et al, 2018). My concern in that many of the larger US studies have leaned on larger-scale regional models for $PM_{2.5}$ at 1 km2 resolution or larger, which is appropriate to the spatial scale of variation for $PM_{2.5}$, but either not thoroughly adjusted for NO_2 or other local emissions indicators, or not done so at the much finer spatial scales at which local sources vary.

Table 3-4 section on biological plausibility seems to lean on epidemiologic evidence, rather than toxicology or mechanistic studies, to establish biologic plausibility. Likewise, on p. 3-75 (first para) there is reference to epidemiologic studies for cardiovascular and respiratory morbidity lending "biologic plausibility" to epidemiologic evidence for mortality, rather than simply corroboration.

There is an emphasis on multi-city studies, which makes sense from a policy standpoint, and some epidemiologic considerations (larger sample size and generalizability), but raises issues in considering effect modification and co-pollutant confounding, specifically:

(1) It is a slightly awkward definition of effect modification that includes between-city variation, because inter-urban variation may be due to differences in exposures (sources, composition) or characterization thereof (e.g., modeling error), rather than factors that may actually alter exposure-health relationships (e.g., population characteristics).
(2) Multi-city studies can suffer from imperfect capture of exposure variation within each city (if using common model everywhere & not fully accounting for composition/ source differences), or mis-specification of co-pollutant effects (if not captured with fine spatial resolution within each city). Compromises are often made for consistency in exposure modeling across multiple cities, which may lead to within-city mis-characterization of exposures or C-R relationships. This is not to say multi-city studies are not valid, but single-city studies may, in many cases, provide a cleaner base of comparison for effect modification analyses.

3.2.2: Long-Term $PM_{2.5}$ Exposure

In the overall review of updated studies (p. 3-78), as elsewhere, it appears taken for granted that larger sample size (and multi-city study) implies a higher-quality study, though there are often important trade-offs between sample size and accuracy/ resolution in exposure assignment.

3.3.3. Populations and lifestages

p. 3-128: "these additional studies provide further evidence that lower SES communities are exposed to higher concentrations of $PM_{2.5}$ compared to higher SES communities." Please insert "on average," or similar. This statement is certainly true on average, though there important nuances to this relationship (eg, better transportation and therefore higher PM in some higher-SES communities) that lend to non-linearities & settings where exposures are higher in wealthier central parts of some US and European cities.

A good example of the issue raised above re: co-pollutant adjustment is demonstrated on p.3-94: "$PM_{2.5}$ -mortality associations are null in models with ozone (HR = 1.00 [95% CI: 1.00, 1.01]) and oxidants (HR = 1.00 [95% CI: 0.99, 1.01]), and attenuated in a model with NO_2 (HR = 1.01 [95% CI: 1.00, 1.02])." It is challenging to interpret this result in the absence of information on the scales of measurement for each. This is important because most of the other multi-pollutant studies cited report that adjustment does not measurably alter PM-mortality associations. What is different here? Is there perhaps better measurement for NO_2 simply by measuring it at a finer scale? If not, how should we reconcile this result with others?
Excellent that disparities in both exposures and C-R relationships are addressed separately and clearly.

Consider removing Canadian studies from this section – different social & economic context, context of health disparities very different, different patterns of historical discrimination by race and ethnic group, universal access to healthcare and education alter interpretability of SES indicators for US regulatory context.

Example where larger (geographic) studies may be harder to interpret, in that **SES indices** don't transfer well across space/ social settings, or across urban-rural gradients. Different costs of living, material assets (car ownership).

Consider removing references to greenspace, as a determinant of PM and exposures, differential distributions by race and SES (also quality, access) – multiple pathways linking greenspace to health simultaneously. Probably complicates more than adds.

Dr. Deborah Cory-Slechta

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

In my view, the scientific evidence presented in Section 3 is amply identified, evaluated and characterized. It is clearly stated as to the studies included in the Draft Supplement in terms of those most informative with respect to potential revisions to the PM NAAQS and the extent to which these findings compare to the scientific conclusions reached in the 2019 PM ISA. In addition, studies were included that had the potential to mitigate potential confounds and further inform the strength of the relationships/associations. In addition, study weaknesses are noted as are inconsistent results.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The conclusions reached in the draft supplement are appropriately related to the 2019 PM ISA. Specifically, evidence that is consistent with the 2019 PM ISA conclusions is noted, and evidence that is inconsistent or not consistent is also noted. Summaries, particularly the figures that are included, are appropriate as well. For this reviewer, the fact of the overwhelming number of positive associations, whether technically significant or not, in spite of all of the differences between the studies is particularly compelling. Further, differences in strength of the association be expected given that contaminant profiles of the PM2.5 is going to differ by geography, climate, weather, etc.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

The focus on cardiovascular and mortality endpoints is appropriate given the intent of the Supplement to evaluate the data that has been reported since the 2019 ISA as these were both listed as causal, relationships between other endpoints and PM2.5 are not yet as clear nor does new published data since the cutoff for the 2019 ISA contribute sufficiently to change the conclusions with respect to those endpoints. In my understanding, the draft PM supplement includes all of the relevant studies that have been published. It might be useful for various reasons to include a summary table in the supplement specifically detailing the US and Canadian studies being relied on and details of those studies. In

addition, the notes in the figures, e.g., updates of Figures from the 2019 PM ISA might be include sample sizes/age, etc. rather than just the name of the cohort that the study was based on.

One topic that does come to mind, although not necessarily related to the current document or its ultimate purpose and which may be included in the 2019 PM ISA is the fact that exposure to air pollution is lifelong, beginning in utero. Obviously, this cannot be accommodated in terms of data or specific calculations but may be an important reminder with respect to the problem itself, given that right now we're not even focused on lifetime exposures.

Dr. Mark W. Frampton

Charge Question 1 - Executive Summary

a. Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.

In general, the Executive Summary clearly communicates the key findings of the Supplement.

Specific comments:

Page ES-1, line 21. This sentence is somewhat confusing and unclear. "This Supplement to the 2019 PM ISA is not intended to represent the full multidisciplinary evaluation of evidence that results in the formation of weight-of-evidence conclusions, but instead is an assessment that puts the results of recent studies in the context of the scientific conclusions (i.e., causality determinations) presented within the 2019 PM ISA." It seems that both parts of this sentence are true; the Supplement attempts to put recent studies into context, and also to draw new weight of evidence conclusions in light of the added studies. Suggest rewording this sentence.

b. Please provide recommendations on whether additional information should be added to the Executive Summary or information that should be left for discussion in the subsequent sections of the draft PM Supplement.

No suggestions.

Charge Question 2 - Introduction

a. Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

Page 1-3, Health Effects. This section needs rewording. It states that,

"…for these health effect categories the recent studies evaluated are limited to: …Epidemiologic studies that employed causal modeling methods or conducted accountability analyses…". This statement is not true; these types of studies were included in the Supplement, but it was not "limited to…". Perhaps this bullet point should be moved to "Key Scientific Topics".

The Introduction states, "Therefore, within this Supplement the focus is only on the health effects evidence where the 2019 PM ISA concluded a *causal relationship."* This precludes consideration that new evidence might move a determination from likely to causal for another health effect, such as nervous system effects, respiratory effects, or cancer. It also precludes consideration that the causality judgement may change in this review, even if the overall evidence base has not changed substantially. In other words, opinions/judgements of the EPA authors, and of the current CASAC, may differ from those of the previous review, even with a similar evidence base, such that a health effect considered to be "likely" in the previous review would be considered causal in this review. This approach does not allow for that, although admittedly the possibility seems unlikely.

The Introduction should provide additional background on the reasons and rationale for the reconsideration. It should also list the key CASAC findings in its review of the draft ISA, as detailed in the CASAC letter to the Administrator of April 11, 2019, and the EPA responses. Specifically in this regard, the CASAC letter states "…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 PM2.5 exposure and nervous system effects; between long-term UFP exposure and nervous system effects; or between long-term PM2.5 exposure and cancer." In the final ISA, EPA did change UFP and nervous system effects to "suggestive", but did not accept CASAC's recommendations on causality determinations for PM2.5 and nervous system effects and cancer. The justifications for those decisions should be stated.

The justification for limiting studies to those in the US and Canada should be stated in the Supplement. It appears that considered studies were not always limited to US and Canada. See Figure 3-13, for example.

"Cardiometabolic disease" should be defined as it is used in this document.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

The current structure, providing the Integrated Synthesis Chapter from the 2019 ISA, and leading off each effects section with the Summary and Causality Determination from the 2019 ISA, is effective and helps integrate the new findings with those in 2019.

One minor structural change is suggested:

In Section 3.1, Cardiovascular Effects, the sub-sections start with summaries of the key findings in the 2019 ISA, as noted above, and this is helpful. However, Section 3.1.1.2, "Recent U.S. and Canadian Epidemiologic Studies", begins not with new findings as expected, but with descriptions of biologically plausible mechanisms described in the 2019 ISA. Then the next paragraph begins with the new studies. This first paragraph is out of place; it could be eliminated, or worked into the summary of the 2019 ISA. The same is true for sections 3.1.2.2, 3.2.1.2, and 3.2.2.2.

Charge Question 4 - Section 3

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

In general, Section 3 is clearly and concisely presented, and the conclusions are well-supported by the evidence.

Specific comments:

Many of the figures are difficult to read, and need more vertical space. Fig 3-23 in particular does not display well.

Page 3-28: "However, a recent toxicological study adds to similar evidence from the 2009 PM ISA…". The reference should be provided here, and it should be clarified whether this is a new study not covered in the 2019 ISA. If this refers to Lippmann 2013, that study was reviewed in the 2019 ISA, and is not really "recent".

Page 3-31, describing findings from Bai, et al. 2019: "A stronger association was observed in the highest tertile of (>38.97 ppm) Ox concentrations (HR: 1.12 [95% CI: 1.09, 1.15])." Suggest clarifying what association is being referred to here. If this is from Table 5 of the paper, the data are incorrect. The HR for incident AMI and PM2.5, in the highest tertile of Ox, was 1.08 (1.06, 1.10).

Similarly, with regard to Section **3.1.2.2.4**, page 3-37, Bai et al. Table 5 indicates the HR for incident CHF in the highest tertile was 1.08 (1.07, 1.09), rather than the 1.12 given in the text of the Supplement. Page 3-39, 2nd paragraph of Section **3.1.2.2.8**: This paragraph needs revising; it is often unclear what the various HRs refer to.

Page 3-57, subsection "**Other nonaccidental mortality".** This discussion of sudden death and the Rappazzo et al. study is confusing. This section appears to deal specifically with out of hospital cardiac arrest, so the section title should reflect that. Also, the OR CIs in the Rappazzo study include 1.0, so, although the ORs are positive, they are statistically non-significant, and this should be so indicated.

Section 3.3.1, page 3-121. The Hemmingsen et al. human study was reviewed in the 2019 ISA, but only in the context of cancer, with regard to the negative findings on DNA damage and blood mononuclear cell gene expression. The positive findings on vascular and cardiac function, reported in a separate publication, were not reviewed in 2019, even though the publication date was 2015. Perhaps that should be mentioned in the Supplement for clarity.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary sections do appropriately characterize the new evidence, and are very helpful.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

No additional comments.

Charge Question 6 - Summary and Conclusions section (Section 5)

a. Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence.

This section provides a concise and accurate summary of the findings of the Supplement, with an appropriate level of detail.

Specific comments:

Page 5-2, first paragraph under Cardiovascular Effects, Short Term PM2.5 Exposure: "In addition, these studies report evidence that continues to indicate an immediate effect of PM2.5 on cardiovascular-related outcomes primarily within the first few days after exposure…". An "immediate" effect somewhat contradicts the latter part of the sentence, "within the first few days". Immediate suggests minutes or at most hours. Section 2.2.2.2 defines the lags as follows: "…immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days)…". Suggest specifying that the evidence predominantly supports immediate or slightly delayed effects.

Page 5-3, Mortality, Long Term PM2.5 Exposure. The following sentence seems contradictory, and needs further clarification; underlining added. "The assessment of the C-R relationship continues to generally support a linear, no-threshold relationship with certainty down to 4 µg/m3. However, some uncertainties remain about the shape of the C-R curve at relatively low PM2.5 concentrations (<8 µg/m3)…".

Dr. Christina H. Fuller

Comments on Section 3.3 Key Scientific Topics

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

The Key Scientific Topics covered within section 3.3 include the following: (a) recent experimental studies conducted at near-ambient concentrations; (b) effects at the ambient concentrations reported in epidemiologic studies (Section 3.3.1); (c) the role of PM2.5 exposure on COVID-19 infection and death (Section 3.3.2) and (d) an evaluation of studies that examine PM2.5 exposure and health risk disparities among racial and ethnic groups and socioeconomic status (SES) (Section 3.3.3).

Recommendations:

The summaries and conclusions within this document use the term White and non-White as the broadest categories. I suggest the Supplement refer to the group non-White as People of Color (POC) or Communities of Color (COC), as appropriate. There are multiple terms utilized to describe the span of races and ethnicities in the United States, which is reflected by the studies included in this Supplement. Race/ethnicity is a fluid concept that is relevant by time, country, region, population and government. Therefore, the most useful terminology for the purpose of protecting public health has changed over time.

There is a lack of consistency in the manner in which statistical significance is noted in this section. Therefore, I recommend that the same level of detail be provided for each study. Include the statistical significance of the findings for studies included in this section so that readers can best interpret the results and implications on the conclusions presented herein. Statements of statistical significance can utilize, p-values or 95% CI as appropriate.

A key point in critically evaluating each study is knowing the details of exposure measurement. There are differences in confidence and validity based on $PM_{2.5}$ measurement and exposure assessment.

Therefore, I recommend that exposure measurement be described for each study included in the Draft 2019 PM Supplement.

The most robust epidemiologic studies examining both $PM_{2.5}$ and race/ethnicity (or SES) as predictors of health outcomes includes assessment of autocorrelation. In addition to exploring the existence of autocorrelation there should be adjustment via statistical modeling when autocorrelation is significant. Unfortunately, many studies do not employ these measures. I suggest the inclusion of information autocorrelation when each study is first presented in this section.

The level of SES data is an important component in understanding research questions, modeling and interpretation of results. Section 3.3.3 (Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect) would benefit from the greater discussion related to this.

Specific comments regarding recommended changes:

Section 3.3.1 Recent Experimental Studies at Near-Ambient Concentrations:
Page 3-121, Lines 28 - 31: Align the terms "nonfiltered" and "unfiltered" air, by selecting only one term for these sentences.

Page 3-122, Line 22: It would be helpful to state the directions of effect for men and women here, in addition to writing that they are in opposite directions.

Section 3.3.2 PM2.5 Exposure and COVID-19 Infection and Death:

This section could use expansion, especially since COVID-19 and $PM_{2.5}$ disproportionately impact populations of color (POC).

The evidence for the relationship between $PM_{2.5}$ exposure and COVID-19 incidence, severity and mortality is that PM2.5 exposure can increase susceptibility. This is a similar mechanism of all infectious respiratory diseases and is very different from that of CVD. Although mentioned in this section, the language on PM2.5 increasing susceptibility can be stressed further. This also lines up with the disparate exposures of lower-income and people of color communities (covered in 3.3.3.1.2 and 3.3.3.2.1) who have been hit hardest by COVID in terms of cases, severity and mortality in that population.

3.3.1.2 Long-term $PM_{2.5}$ Exposure:

Page 3-124, Line 11: Specify the exact range of the study. From X date to June 18, 2020.

Page 3-124, Line 22 – 24: There is an incongruence between the PM2.5 measurements and outcomes assessment. Include the authors' explanation for the acceptability of these choices.

Page 3-125, Line 2: Include the start date for the study.

3.3.3 Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect

The level of SES data is an important component in understanding research questions, modeling and interpretation of results. Individual-level and community-level data differ with regards to their accuracy and interpretations. Divide the discussion of the included studies further by individual-level and community-level of SES and race/ethnicity. Pay particular attention to discussion of studies being compared that use different scales such as census block-group level, census tract level, zip code and county.

3.3.3.1 Socioeconomic Status

Page 3-127, line 24: Add the term "populations" before "having".

Page 3-127, line 27: It is more accurate to describe educational attainment as an "indicator" or "measure" of SES compared to a "proxy". SES is complicated construct that cannot me estimated by any single item. This is similar to BMI, which is a measure of obesity.

3.3.3.1.1 Exposure Disparity

Page 3-128, lines 8-19: As an example of the added detail on $PM_{2.5}$ exposure assessment, the source of the $PM_{2.5}$ estimation is necessary to evaluate this study by Lee (2019) and compare to that of Rosofsky et al (2018). Although this information is contained in the linked articles a brief mention here would be useful.

Page 3-128, lines 26-27: I assume the groups here are mutually exclusive, however, it is not clear from the description. Please clarify.

Page 3-129, line 8: Similar to the definition/clarification of composite PM provided in Chapter 2, I suggest including a definition of composite here as it pertains to measures of SES.

Page 3-129, line 37: The study by Weaver et al (2019) is in need of a summary sentence to bring together an interpretation of the findings. Although the Clusters are defined it is difficult to identify a pattern (or not) in the findings. Clarify in one or a few sentences.

Figure 3-30: The figure is full of information and overall is a good presentation. However, it could be improved by including horizontal lines separating the measures of SES and increasing the font size. I

would change the heading of the third column to Comparison groups instead of Reference Group and list the referent group first.

3.3.3.1.2 Health Risk Disparity

Here again it is advisable to separate the studies further based on individual or community level indicators of SES.

Long-term $PM_{2.5}$ Exposure

Page 3-131, Line 30: Was income also measured at the zip code level? Clarify this point.

Page 3-132, Lines 1-4: Provide detail on the study type and spatial resolution of data for Zhang et al 2021. Since this is a Canadian study you can describe based on its U.S> equivalent, such as zip code, census block-group, etc.

Page 3-133, Line 3: Add cardio metabolic mortality and cardiovascular mortality here, because those endpoints show a similar differential between low greenspace, low deprivation and low greenspace, high deprivation groups.

Page 3-137: After the final paragraph add a summary sentence or two about the findings from Weaver et al (2019).

3.3.3.2 Race/Ethnicity

Page 3-138, line 4: "The 2009 PM ISA observed little evidence for increased PM2.5-related risk by race and some evidence of increased risk by Hispanic ethnicity." Is it the conclusion of the 2009 PM ISA that this was due to a lack of studies examining these associations or that there was sufficient research to draw this conclusion? Given that there has been exponential growth in studies examining race/ethnicity and air pollution in recent years answering this question has implications for the current review of research.

Long-Term $PM_{2.5}$ Exposure

Page 3-146, line 8: The statement that, "Since moving was essentially random" is not accurate given the research on redlining and segregation. Although these terms were utilized by the study authors, I do not find that they are appropriate here. I suggest replacing the existing sentence with this one: Utilizing data from the subpopulation of Medicare enrollees that moved the authors were able to examine changes in $PM_{2.5}$ exposure.

Suggestions:

Consider removing Canadian studies from this section because their findings may not be generalized to the U.S. Canada differs from the U.S. with regards to its social & economic context; health disparities; historical discrimination by race and ethnic group; and universal access to healthcare and education. These differences alter the interpretability of SES indicators for US regulatory context.

The articles by Yitshak-Shade et al, Son et al (2020), Crouse et al (2019), Stieb et al (2020) all include the impact of green space on associations between $PM_{2.5}$ and mortality. However, there is no discussion of green space in the Supplement. The inclusion of these articles require added information regarding the linkages between green space and $PM_{2.5}$ concentrations; green space and health; and quality of green space by race/ethnicity.

Charge Question 6

Comments on Section 5 (Summary/Conclusions)

Overall this section is well written and provides an accurate and succinct summary of Sections 1-4 of the Draft Supplement to the 2019 PM ISA.

Recommendations:

The summaries and conclusions within this document use the term White and non-White as the broadest categories. I suggest the Supplement refer to the group non-White as People of Color (POC) or Communities of Color (COC), as appropriate. There are multiple terms utilized to describe the span of races and ethnicities in the United States, which is reflected by the studies included in this Supplement. Race/ethnicity is a fluid concept that is relevant by time, country, region, population and government. Therefore, the most useful terminology for the purpose of protecting public health has changed over time.

There are some areas where conclusions need to be added, which I have noted in the specific comments below.

Specific comments regarding recommended changes:

Line 26-27: I recommend altering, “specifically Black individuals, and low SES individuals” to “specifically Black and low-SES populations”. The use of the term populations emphasizes that the identified vulnerabilities are linked to population health and also that the evidence shown refers to population studies.

Cardiovascular Effects → Long-term $PM_{2.5}$ Exposure:

Line 25:"more diverse populations" is a term not specific enough for its use here. In most settings in the United State "diverse populations" implies diversity in race/ethnicity, which is not the intended meaning here. Replace this expression with "general population" or "population without preexisting conditions".

Additional Considerations Regarding the Health Effects of $PM_{2.5}$ → COVID-19 Infection and Death:
Unlike most other summary paragraphs in this section, the subsection focused on COVID-19 does not have a conclusion. Add a statement(s) that draw a conclusion from the data summarized.

Populations and Lifestages at Potentially Increased Risk of a PM-Related Health Effect

Socioeconomic Status:
This summary paragraphs needs to distinguish between individual-level and community-level indicators of SES. (Please see my comments to Section 3 for a more broad discussion.) Present the differences in findings from each of these types of indicators and the implications on their interpretation and comparison.

Visibility Effects:
Similar to the subsection on COVID-19, this paragraph does not have a conclusion. The paragraph discusses methods and methodological improvements utilized in the included studies. State what the compiled evidence reveals to be the effect of $PM_{2.5}$ on contrast and light extinction and the level of confidence of this conclusion.

Dr. Terry Gordon

Charge Question 2 - Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.

The scope of the introduction for the Supplement were very well written and justified the purpose and need for the Supplemental PM ISA. In particular, the focus on the health effects associations that were 'causal' versus 'likely causal' was very appropriate.

Minor Comment: In the Executive Summary, the bulleted list is a bit unclear. The order made this confusing – a bullet on short-term morbidity, then long-term mortality, and then a separate para going back to short-term mortality could be rearranged.

Line 4, page 2-2 – PM^3 must be a typo.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.

I believe the approach to include the Integrated Synthesis Chapter of the 2019 PM ISA was very appropriate for starting off this Supplemental PM ISA. The approach was warranted and the pathway for reviewing the supplement was very clear. Starting with the Summary and Causality Determination from the 2019 PM ISA was warranted in terms of clarity and efficiency.

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

Section 3.1 Cardiovascular Disease

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.1.

The appropriate summaries and tables are presented in an efficient manner. I agree with the evaluation and characterization of the short-term and long-term evidence linking CVD to $PM_{2.5}$ exposures. The Supplemental ISA clearly bolsters the PM ISA evidence that the association of CVD disease (and mortality) is key to the evaluation of the protection of the current PM NAAQS.

b. Please comment on whether the summary sections in Section 3.1 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary section is well written and identifies and summarizes the recent evidence that supplements the conclusions of the 2019 PM ISA. The Relative Risk figures are important summaries of the studies (and the color coding made the inter-ISA Review comparisons much easier/efficient).

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3.1 or any topics for which discussion should be shortened or removed from Section 3.1.

In general, the scope covered by Section 3.1 was very well written. For example, the Summary for the association between short-term $PM_{2.5}$ exposure and cardiovascular effects was concise and on target. As far as potential topics for shortening/removal, the somewhat long description of the weak or 'null' association between short-term $PM_{2.5}$ and stroke was surprising in its detail and could perhaps be shortened. Conversely, the description of recent studies on aggregated cardiovascular endpoints lacks a conclusion and could thus be expanded. Similarly, the section of long-term $PM_{2.5}$ and hypertension describes a moderate amount of evidence for altered blood pressure in post-menopausal women, yet there is no conclusion statement(s) for that section and the potential susceptibility for this sub-population is rarely mentioned elsewhere.

As far as additional topics or studies in regards to the short-term effects of $PM_{2.5}$, the study by LC Chen (Lippmann, 2013 HEI report which was reviewed in the 2019 PM ISA) demonstrated that relatively short-term changes in ambient particle sources (e.g., 72 hours or less) could affect cardiovascular endpoints in mice exposed to concentrated ambient PM.

Section 3.2 Mortality

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.2.

The mortality section was very well written and clearly evaluated the causal evidence for the association between PM exposure and mortality (cardiovascular-related and respiratory-related). In particular, for a non-epidemiologist, the explanation and evaluation of the confounding concerns and uncertainty factors were clearly written. Table 2-2 and 3-1 were particularly useful.

b. Please comment on whether the summary sections in Section 3.2 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary section is well written and identifies and summarizes the recent evidence that supplements the conclusions of the 2019 PM ISA. The one area that could be clarified is the susceptible population discussions – while the increased exposure concentrations vs. inherent susceptibility responses was initially explained, attribution to one or the other reasoning was less clear in some subsections.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3.2 or any topics for which discussion should be shortened or removed from Section 3.2.

No suggestions for additional topics or studies.

Minor comments

Table 3-2 – should the final column on $PM_{2.5}$ concentrations have more data for the different sections?

Line 7, page 3-37 – Is a word missing (increase?).

The title for 3.1.2.4 states ‘mortality’ but should be cardiovascular effects/disease.

Defining descriptors for the C-R curve at low concentrations is needed. Linear is obvious but not so for some of the others.

Section 3.3 Key Scientific Topics

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.3.

As mentioned above, the disparities discussion needs to be tightened in respect to exposure differences or innate susceptibility differences.

The near ambient clinical studies provide strong evidence for short-term effects, but this evidence didn't seem to carry over to the PA.

I would suggest shortening the covid section –it's worth discussing but does the evidence for associations with ambient $PM_{2.5}$ warrant the several pages of discussion?

Minor Comments:

Figure 3-36 is unclear. Perhaps the figure legend can be expanded. Also, its title is confusing: $PM_{2.5}$ cause by?

b. Please comment on whether the summary sections in Section 3.3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary sections are clear and do an excellent job in characterizing the conclusions of the recent evidence.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3.3 or any topics for which discussion should be shortened or removed from Section 3.3.

The covid section is meant to stand on its own but given the immune altering effects of $PM_{2.5}$ exposure, it is puzzling why this supporting immune-$PM_{2.5}$ interactions is not included.

Dr. Michael T. Kleinman

Charge Question 1 - The Executive Summary is intended to provide a concise synopsis of the key findings and conclusions of the draft PM Supplement for a broad range of audiences.

a. *Please comment on the clarity with which the Executive Summary communicates the key information from the draft PM Supplement.*

- Clearly sets up the purpose of the supplemental analyses with respect to the extension of the 2019 document.
- Provides an excellent summary of the 2019 findings and provides a summary of additional supporting information from recent studies to bolster the finding of causal effects of PM2.5 for both cardiovascular effects and mortality.
- Provides a brief summary of the additional support for the finding that there are PM2.5 exposure and health disparities by race, ethnicity and social economic status.

b. *Please provide recommendations on whether additional information should be added to the Executive Summary or information that should be left for discussion in the subsequent sections of the draft PM Supplement.*

- Perhaps add a final statement the analyses and findings from the 32019 ISA were, with few exceptions, strengthened by the addition of the analyses of the recently published studies.
- The Box table on 2-1 (Overall conclusions of the 2019 ISA) could be copied to the end of the Exec Summary with the addition of a column showing the corresponding findings from the recent studies.

Charge Question 2 - Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. *Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.*

- Effectively sets up the rationale, scope and organization of the supplement.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. *Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.*

    - There seems to be a fair amount of redundancy between Sections 2 and 3.
    - Could Section 2 be shortened?

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. *Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.*

    - It would make it easier for readers if there was more parallelism between sections 2 and 3.
    - Putting the findings of section 3 into a table similar to the box on 2-1 would be difficult but could highlight the important findings in this section.

b. *Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.*

    - The review of the recent literature is quite comprehensive and the approach to analyzing and integrating the information is appropriate.

c. *Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.*

    - There could be more emphasis on sex as a biological variable especially with respect to cardiovascular effects of PM.

Charge Question 5 - Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. *Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.*

- Appropriate

b. *Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.*

- Information is suitably presented

c. *Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.*

- Climate effects are important factors in the increased numbers and severity of wild fires and a more thorough discussion could be helpful. Localized drought conditions that, for example, create reduced humidity conditions in some areas and increased humidity conditions in others can imbalance the relationship of PM to visibility.

Charge Question 6 - The Summary and Conclusions section (Section 5) provides an overview of the evidence evaluated in the draft PM Supplement.

a. *Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence.*

- It should be made clear that the focus of this supplement was directed at outcomes that were identified as causally related to PM and that new respiratory and neurotoxicity studies were not included.
- Future analyses should re-examine the causal relationships between PM exposures and respiratory disease, degenerative nervous system effects, birth outcomes and other outcomes.

Dr. Stephanie Lovinsky-Desir

General Comments:

In Section 3.3.3.1 that describes disparities in exposure and risk based on socioeconomic status (SES), there are several studies that were included that used composite indexes to identify the "at risk" populations. However, many of those indexes are not limited to SES factors, and also include race and/or ethnicity in their index (e.g. Canadian Marginal Index and Social Vulnerability Index). It does not seem appropriate to include these studies in the section dedicated to SES since race and ethnicity are not indicators of SES and are more likely functioning as indicators of racial segregation in the context of these indexes. I would suggest removing these studies from this section and including a separate section for studies that evaluate SES, race, and ethnicity together to emphasize the distinction that race, and ethnicity are not proxies for SES, but rather they are highly correlated with SES because of systemic racism. The Jorgenson 2020 study mentioned on page 3-147 would be another study to include is a section dedicated to the combined effects of race and SES.

The supplement may benefit from an update on the literature regarding PM2.5 exposure in children who are a vulnerable population. Examples of studies that may be considered for inclusion in the supplement include the following:

1. Strosnider HM, Chang HH, Darrow LA, Liu Y, Vaidyanathan A, Strickland MJ. Age-specific associations of ozone and fine particulate matter with respiratory emergency department visits in the United States. *Am J Respir Crit Care Med* 2019;199:882–890.
2. Cserbik D, Chen Jiu-Chiuan, McConnell Rob, Berhane K, Sowell ER, Schwartz J, Hackman DA, Kan E, Fan CC, Herting MM. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environment International* 2020; 143: 1059332.
3. Kim KN, Kim S, Lim YH, Song IG, Hong YC. Effects of short-term fine particulate matter exposure on acute respiratory infection in children. *International Journal of Hygiene and Environmental Health* 2020; 229: 113571.
4. Miao Liu, Wenting Guo, Yunyao Cai, Huihua Yang, Wenze Li, Liangle Yang, Xuefeng Lai, Qin Fang, Lin Ma, Rui Zhu, Xiaomin Zhang. Personal exposure to fine particulate matter and renal function in children: A panel study. *Environmental Pollution* 2020; 266(2): 115129.
5. Shan Liu, Qingyu Huang, Yan Wu, Yi Song, Wei Dong, Mengtian Chu, Di Yang, Xi Zhang, Jie Zhang, Chen Chen, Bin Zhao, Heqing Shen, Xinbiao Guo, Furong Deng, Metabolic linkages between indoor negative air ions, particulate matter and

cardiorespiratory function: A randomized, double-blind crossover study among children. *Environment International* 2020; 138: 105663.

Specific Comments:

Page 3-121, lines 27-31: it would be helpful to briefly contextualize why a reduction in heart rate variability is clinically meaningful.

Page 3-127, lines 1-3: There is a reference to the Preamble to the ISA that notes a special emphasis placed on studies that compare responses to a 'reference population'. The term 'reference population' is often applied to a White population and thus using this terminology has the potential to perpetuate bias. For the purposes of this ISA supplement, it may be more appropriate to rephrase this sentence to state "studies that compare between different populations."

Page 3-144, line 18: 'regard less' should be change to regardless.

Page 3-145, line 3: Please clarify that this sentence is referring to IRD groups since there was a difference observed across RRS groups and the figure that is referenced at the end of the sentence includes both IRD and RRS metrics.

Page 3-147, lines 5-11: The brief mention of the Wang 2020 and Son 2020 studies do not include a mention of PM2.5.

Page 3-149, line 8: the Wang 2020 study is mentioned again without being placed in the context of PM2.5 exposure.

Minor Comments:

Overall, I find that the figure titles/legends are not very informative, often making them difficult to interpret. It would be helpful if there were more details included in the form of a figure legend to emphasize the key findings that are being highlighted in the figures.

Dr. Jennifer Peel

General Comments about the draft ISA document:

- The document is a robust evaluation of the literature, with consideration of coherence from several lines of evidence. The document includes a clearly defined scope and is a clear and transparent.
- Consider more explicitly justifying the scope for the supplement.
- Consider clarifying terms and description of populations at risk in the document, particularly when using the term factor. For example, children is not really describing a factor; younger age (and even better, specific age groups) would be clearer, in addition to including the comparison group (younger ages compared to adults, or to older adults?). The same suggestion holds for race as a factor.
- In the Executive Summary section discussing the evidence for long term exposure and mortality, it may be helpful to clearly explain how studies evaluating life expectancy differ from other studies evaluating long term exposure and mortality.
- I suggest reducing the use of abbreviations as much as possible. Common abbreviations such as PM and ED and CVD may be fine, but others may not be necessary nor helpful in such a document.
- The Figures used throughout the document are very helpful for delineating the evidence since the 2019 document and since the 2009 document.
- It would be helpful to repeat frequently that the unit increase for results presented are per 10 ug/m3 unless otherwise stated.
- This suggestion is likely outside of the defined scope and is a recommendation for future ISAs; however, the interaction between extreme heat and PM could be considered in the sections evaluating populations at increased risk (with the exception of the consideration of season) (particularly for short term mortality)

Comments on sections outside of assigned charge questions (draft ISA document):

- Page 3-21: The section describing Zhang et al. 2018 and Wang et al. 2018 could be clarified, including a clear description of what the analysis and results adds to the body of evidence.
- Page 3-23: It may be helpful here to clarify the assumptions of the IPW modeling, including how the assumptions were evaluated and if those assumptions were met.
- The sections referencing mortality within Section 3.1 are appropriately brief and refer to more details in the Section 3.2

- Section 3.1.1.2.6 (short term exposure, CVD mortality): This paragraph lacks references and may be incomplete?
- Section 3.1.2.4 May have an incorrect title? Should be cardiovascular effects (not mortality)?
- Section 3.3.1 and Section 5, Experimental Studies at Near-Ambient PM2.5 Concentrations, (page 5-3); consider including the following publications:
    - Cole-Hunter T, Dhingra R, Fedak KM, Good N, L'Orange CL, Luckasen G, Mehaffy J, Walker E, Wilson A, Balmes J, Brook RD, Clark ML, Devlin RB, Volckens J, Peel JL. Short-term differences in cardiac function following controlled exposure to cookstove air pollution: the subclincal tests on volunteers exposure to smoke (SToVES) study. Env Int. 2021
    - Walker ES, Fedak KM, Good N, Balmes J, Brook RD, Clark ML, Cole-Hunter T, Dinenno F, Devlin R, L'Orange C, Luckasen G, Mehaffy J, Shelton R, Wilson A, Volckens J, Peel JL. Acute Differences in Pulse Wave Velocity, Augmentation Index, and Central Pulse Pressure Following Controlled Exposures to Cookstove Air Pollution in the Subclinical Tests of Volunteers Exposed to Smoke (SToVES) Study. Environmental Research, 2020. https://doi.org/10.1016/j.envres.2019.108831
    - Fedak KM, Good N, Walker ES, Balmes J, Brook RD, Clark ML, Cole-Hunter T, Devlin R, L'Orange C, Luckasen G, Mehaffy J, Shelton R, Wilson A, Volckens J, Peel JL. Acute changes in lung function following controlled exposure to cookstove air pollution in the subclinical tests of volunteers exposed to smoke (STOVES) study. Inhalation Toxicology. 2020.
    - Fedak KM. Good N, Walker ES, Balmes J, Brook RD, Clark ML, Cole-Hunter T, Devlin R, L'Orange C, Luckasen G, Mehaffy J, Shelton R, Wilson A, Volckens J, Peel JL. Acute effects on blood pressure following controlled exposure to cookstove air pollution in the SToVES study. J Am Heart Assoc. 2019. 8:e012246. https://doi.org/10.1161/JAHA.119.012246

Charge Question 4 Section 3.2 Mortality (Draft ISA supplement)

- Section 3.2, including sections on short term and long term exposure to $PM_{2.5}$, are clear in scope and include relevant studies in the identified time frame (January 2018 – March 2021).
- The evidence from the previous 2019 PM ISA is clearly articulated, and the more recent studies are accurately described and added to the context of the evidence that was in the 2019 PM ISA.
- Page 3-57: Line 16 refers to Section 3.1.1.2.4; this seems to not be the correct section; should be Section 3.2.1.2.4 (page 3-61).
- Page 3-61: The description of the Lavigne et al. 2018 study, including an evaluation of effect modification by oxidant gases, could be clarified by adding information about the definition

and assessment of oxidant gases and perhaps some information about how to interpret this evidence in the context of PM and health.

- Page 3-65: Figure 3-17 is a little confusing given that the y-axis is percentage change (from Liu t al. 2019); this figure description could clarify the axis.
- Page 3-66, Figure 3-18: The statement about evidence of effects down to 5 ug/m3 could be clarified by adding justification for this statement. Is this statement based on the lower confidence interval going below 0 around 5ug/m3, or something else? Is this statement true based on Figure 3-17 as well?
- Page 3-66, Figure 3-18: And it may be helpful to explain why the uncertainty goes to 0 at the lowest concentrations?
- Section 3.2.1.3: The description of the Wei et al. 2020 and Wei et al. 2021 studies is almost 2 pages long; this section could be shortened, including the most relevant information.
- The lack of visible confidence intervals for the Di et al. 2017 results in Figure 3-19 is understandable given the very large sample size and resulting lack of sampling variability (with virtually the entire population sampled). Is this the case for other point estimates in this figure with no visible CIs? It maybe be helpful to explain this.
- Page 3-79: in the description of the Lefler et al. 2019 study, it may be helpful to explain briefly the purpose of the spatial decomposition approach, and also clarify what we learn from the result of the regionally sourced PM being closer to the primary exposure.
- Page 3-103, Figure 3-27: It would be helpful to explain the uncertainty bands here, and why they go to 0 at lower concentrations.
- Section 3.2.2.2.7: The recent studies (e.g., Pope et al. 2019 and Pinault et al. 2017) have somewhat contradicting results for the shape of the concentration-response curve at lower concentrations. It may be helpful in this section to provide more details on the evidence from the 2019 document, including the evidence of certainty down to 4ug/3 (and explain how the cut point of 4 was determined).

Dr. Alexandra Ponette-González

Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.

Overall, section 4 is concise and well written. Section 4 clearly describes the most recent evidence regarding the relationship between particulate matter and visibility impairment, the non-ecological welfare effect category considered in the PM ISA supplement.

Section 4.1 provides a clear and succinct summary of the evidence for visibility effects detailed in the 2019 PM ISA.

Section 4.2.1 highlights the lack of visibility preference studies in the US for the period 2009-2019. This section presents findings from one new visibility preference study by Malm et al. (2019), which demonstrates how choice of metric (contrast vs. visual range) influences variation in the level of visibility considered to be acceptable, with contrast resulting in less variation in acceptability levels among participants.

- On page 4-3, there is a brief description of how visibility preference studies are conducted. Respondents are shown a series of photographs with differing visibility conditions and asked to rate the quality of the scene and whether the scene is considered acceptable or unacceptable in terms of visual air quality. A brief description of how the data are analyzed would be useful to aid in the interpretation of the text and figures that follow.

- Specifically, it is unclear what the terms “acceptable” and “unacceptable” mean in the context of visibility preference studies. To better understand Figures 4-1 and 4-2, the split point (e.g., 50%) between “acceptable” and “unacceptable” in terms of visibility should be reported in the text.

- The term contrast is defined on page 4-3 as the “sharpness with which an object can be distinguished from another object or background”. Additional text could be added here to clarify that scenes with no apparent contrast have a value of 0 (as plotted in Figure 4-2), and that as contrast increases values become increasingly negative.

- Page 4-3 states that visibility preference studies use "similar protocols", which is inconsistent with the PA assessment. On pages 5-25 and 5-26, the PA assessment indicates that the few existing visibility studies employ different methods and that those methods have been applied inconsistently. The text in the PM ISA Supplement should therefore be edited for consistency with the draft PA assessment.

- Figure 4-2 does not include the WASH site (it is also not included in Malm et al. 2019) and therefore "WASH" should be omitted from the caption.

- The Figure 4-2 caption states that "an acceptability level of 90% would require contrast levels to remain above a level of about -0.01". Per the figure and the citation, this should state that the contrast would need to remain above -0.1.

Section 4.2.2 on advancements in visibility monitoring and assessment describes how PM composition is changing in the US and how these changes have affected light extinction estimates.

- Given the paucity of new studies since the 2019 PM ISA, a brief description of advances in the use of photographic images for quantifying atmospheric extinction is warranted.

- This section notes that the relative contribution of biomass burning, dust, and international transport to visibility impairment is increasing. Given the importance of changing PM composition, it would be useful to note the growing body of knowledge on airborne microplastics (Brahney et al. 2020, 2021) and the nascent literature on microplastic effects on light scattering and absorption (Revell et al. 2021). For instance, Brahney et al. (2020) found that 2.5 to 5% (on average, 4%) of identifiable dust particles in a subset of atmospheric deposition samples were synthetic polymers. Brahney et al. (2021) and Revell et al. (2021) were published just after the period which was the focus of the review for the supplement.

- Page 4-8, it may be important to mention that decreases in SO_2 and NO_x emissions have coincided with increasing PM emissions from wildland fires *as well as dust* in some US regions, such as the Great Plains (Lambert et al. 2020).

- The correlations mentioned between the results of image processing and measured atmospheric extinction in hazy atmospheres were for which sites in the US? Were these relationships only for the western US?

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

Section 4.3 provides a good overall summary of the recent evidence.

- Accounting for the distance between the observer and landscape feature results in less variability in reported acceptability levels for visibility. It would be good to state the range of distances for the sites in the text.

- A simple table similar to that on page 2-40 could be added to show how conclusions from the 2019 PM ISA (in one column) compare with new information presented in the Supplement.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 4 or any topics for which discussion should be shortened or removed from Section 4.

- As mentioned above, in the context of changing PM composition, additional references are needed on rising dust emissions in some US regions and on airborne microplastics, a component of PM for which we know little regarding visibility impairment.

Minor edits

- Page 4-9, line 5 should read "additionally" and line 8 should read "PM ISA have addressed"

References

Brahney, J., Hallerud, M., Heim, E., Hahnenberger, M., & Sukumaran, S. (2020). Plastic rain in protected areas of the United States. Science, 368(6496), 1257-1260.

Brahney, J., Mahowald, N., Prank, M., Cornwell, G., Klimont, Z., Matsui, H., & Prather, K. A. (2021). Constraining the atmospheric limb of the plastic cycle. Proceedings of the National Academy of Sciences, 118(16).

Lambert, A., Hallar, A. G., Garcia, M., Strong, C., Andrews, E., & Hand, J. L. (2020). Dust impacts of rapid agricultural expansion on the great plains. *Geophysical Research Letters*, *47*(20), e2020GL090347.

Malm, W. C., Schichtel, B., Molenar, J., Prenni, A., & Peters, M. (2019). Which visibility indicators best represent a population's preference for a level of visual air quality?. Journal of the Air & Waste Management Association, 69(2), 145-161.

Revell, L. E., Kuma, P., Le Ru, E. C., Somerville, W. R., & Gaw, S. (2021). Direct radiative effects of airborne microplastics. Nature, 598(7881), 462-467.

Dr. David Rich

Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

Overall, Chapter 3 of the ISA supplement is well written, and includes appropriate studies published since the previous ISA. A few papers that could/should be added are provided below. The document summarizes evidence for each study appropriately, but there are several sections where modification or additional information is requested to provide greater clarity. These are described below as well.

1. Throughout each disease category reviewed in Section 3, the text descriptions of each study's findings do not present the incremental $PM_{2.5}$ concentration to which each effect estimate is scaled. Based on the figures, these appear to all be scaled to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration. However, a statement providing this increment and stating that all study findings provided are scaled to this increment needs to be added to each section. Without such a statement, results cannot be compared across studies.
2. Consistent language could be used for each statement of findings across all sections to improve clarity. In some sections (e.g., Page 3-17, lines 17-19; Page 3-19, line 19-20), an effect estimate is described as a "positive association" or just "association", while in other sections, effect estimates are described as the risk of disease X associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the previous 3 days. To improve clarity, the specific effect measure for the study should be provided, and "positive association" used only when summarizing evidence across studies for a specific disease section.
3. Page 3-9, lines 28-36 – Discussion of Liu et al (2020) and interpretation of the effect estimates should be changed. The main OR presented is 1.03 (95% CI = 0.96, 1.12), which is too imprecise to say that it supports anything but a null association. Further, the text currently states that effects increased within tertiles of 'long-term NO_2

concentrations", but again these effects are imprecise. I suggest that this be rewritten to state that there appeared to be an increased odds of MI hospitalization associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in lag days 0-2, but only among the highest tertile of long-term NO_2 concentration.

4. Page 3-9, line 38 – Another study by our group is also relevant here and should be added. Wang et al (2019) also examined the rate of ST elevation myocardial infarction associated with several PM markers including $PM_{2.5}$ and ultrafine particles, as well as several gaseous pollutants. This study is discussed in the Accountability Studies section, but should be included here as well. Wang et al (2019) examined whether associations between each pollutant and the rate of STEMI changed following a series of air quality policies and an economic recession. However, it provides estimates of the rate of ST elevation myocardial infarction associated with each interquartile range increase in $PM_{2.5}$, ultrafine particle, and other particle measures in the previous few hours and days, and should be included in this section and Figure 3-1 as well.

   Wang M, et al. Triggering of ST-elevation myocardial infarction by particulate air pollution in Monroe County, New York; before, during, and after multiple air quality policies and economic changes. Environmental Health 2019;18(1):82.

5. Page 3-9 and 3-10; Page 3-12 and 3-13; Page 3-13 line 33; Page 3-17 – In each of these locations, a study by our group (Zhang et al, 2018) is missing. It is described on Page 3-21 lines 24-33 as an accountability study. However, Zhang et al (2018) is also relevant to these sections and should be added to each section's text and to each summary figure for each section. The study estimated associations between 1 to 7 day average ambient $PM_{2.5}$ concentrations and the rate of hospitalizations for ischemic heart disease, heart failure, arrhythmia, cerebrovascular disease, and other CVD category hospitalizations among NY adult residents from 2005-2016. Further, it provides such estimates separately for 3 time periods (2005-2007, 2008-2013, 2014-2016) with progressively lower average $PM_{2.5}$ concentrations, and also separately for the 3 upstate NY sites and the 3 New York City sites (also with different average $PM_{2.5}$ concentrations). These findings should be included in the text and summary figures for these sections as well. The corresponding publication describing trends in $PM_{2.5}$ and other pollutants during the study could also be cited (Squizzato et al 2018).

   Zhang W, et al. Triggering of cardiovascular hospital admissions by fine particle concentrations in New York State: before, during, and after implementation of multiple environmental policies and a recession. Environmental Pollution 2018;242(Pt B):1404-1416.

Squizzato S, et al. $PM_{2.5}$ and gaseous pollutants in New York State during 2005-2016: spatial variability, temporal trends, and economic influences. Atmospheric Environment 2018;183:209-224.

6. Page 3-13 lines 16-20 – I suggest you add a conclusion statement as to whether these studies are or are not consistent with the causal conclusion in the 2019 ISA, similar to that on page 3-15 lines 35-37 that states *"Overall, these studies support and extend the limited evidence in the 2019 PM ISA, reporting positive associations between short-term PM2.5 exposure and HF".* For all studies presented in the supplement, this kind of a conclusion statement would provide a clearer interpretation of the recent evidence for that disease group.
7. Page 3-17, line 26-27 – Not all of the 4 studies described support an association between $PM_{2.5}$ and arrhythmia. Only 3 do. What do you mean by the statement that these studies "extend" the findings of the 2019 PM ISA? Please clarify.
8. Page 3-19 – Section 3.1.1.2.6 – Text is lacking detail to support the conclusions made in this section. Please add references and or descriptions of the studies/findings that support all of these conclusions. For example, please provide the references and findings from the studies on which the following conclusions were made, or the locations in the ISA Supplement text where they are discussed in more detail:
    a. Lines 24-25 – "recent studies indicate that associations between short term $PM_{2.5}$ exposure and cardiovascular mortality are relatively unchanged in co-pollutant models".
    b. Line 27 – "factors that have been shown to vary between cities and regions of the US, such as housing characteristics, have been shown to explain some of the city-to-city and regional variability observed in $PM_{2.5}$ mortality associations in multi-city epidemiologic studies".
    c. Line 30-32 – "the concentration response relationship between short-term $PM_{2.5}$ exposure and mortality further supports a linear relationship, with less confidence in the shape at concentrations below 5 $\mu g/m^3$".
9. Page 3-20 line 13-19 – You provide an effect estimate and 95% CI for deSouza et al (2021), but not the other studies that reported null associations. Please add the effect estimates and confidence intervals for these other studies as well, to justify the conclusions you make. These are needed for both studies finding associations and those that do not.
10. Page 3-20 line 11 - You say that these studies "expand upon the overall assessment of potential confounding", but what conclusion do you make outside of just that they expand the assessment? Do they strengthen the association/conclusions made in the 2019 ISA or do they weaken them? Please provide such a conclusion for these studies.

11. Page 3-20 line 21 – What lag periods/days define "immediate", "delayed", and "prolonged"? This is provided elsewhere in the ISA Supplement, but should be added here for clarity.
12. Page 3-22 - line 4-5 – The text describing Zhang et al (2018) findings is provided before the statement: *"Overall, across the endpoints examined, there were notable differences (i.e., reductions in hospital admissions) after policies were implemented compared to before."* This should be removed from the supplement, as this was a descriptive statement only, and not the purpose or a full analysis of the study/paper. In Zhang et al (2018), overall across the endpoints examined, the main conclusion of the study is that the relative rate (rate of CVD and cause specific CVD hospitalizations associated with each specified unit increase in $PM_{2.5}$ concentration in the previous 1 to 7 days) increased after the policies were implemented and the economic recession occurred (which was inconsistent with our a priori hypotheses) suggesting the same dose/concentration of $PM_{2.5}$ was associated with a greater rate of CVD hospitalizations (perhaps increased PM toxicity due to changes in PM composition).

Chapter 3 – Cardiovascular effects – long term $PM_{2.5}$

1. Again, throughout this whole section, the concentration increase to which each effect estimate is scaled needs to be provided to the reader. As provided in the figures, these appear to be scaled to a 5 $\mu g/m^3$ increase. This increment needs to be provided at the beginning of each section, or provided for each study result description.
2. For each study described in this section, say what time frame defined "long term", as that is not consistently provided in each section.
3. Page 3-28 – Throughout this whole section, it would help with clarity if you could provide the main effect estimates and confidence intervals for the studies on which you state there was an association or there were no associations between cardiovascular mortality and $PM_{2.5}$ concentrations. This would allow a comparison of effect size (i.e. what is the rate/risk/odds of mortality associated with each 5 µg/m3 increase in $PM_{2.5}$ concentration in the previous 1 year). Again, please indicate to what increment these effects are scaled, and what time period in each study defines "long term". This is not required, but would help greatly and allow a more quantitative comparison of study findings over time rather than just a comparison of "association" or "no association".
4. Page 3-29, lines 22-31. – Details on several studies on which conclusions are made are not provided and need to be added here. Please provide references for the studies you describe, and the main effect estimates on which the conclusions in the paragraph are made. Alternatively, provide the section(s) in the ISA Supplement where they are provided.
5. Page 3-31 lines 10-11 – Please provide the other tertile effect estimates if you are arguing that the highest tertile effects are "stronger".

6. Page 3-32, line 18 – What is ML? Do you mean MI?
7. Page 3-33, line 4-6 – Please provide the effect estimate and 95% confidence interval for Miller et al, so that it matches the quantitative results presentation of the new studies reviewed below. Thus, the reader can make a quantitative comparison of the size of any effect estimates between new studies and studies presented in previous ISA's, not just a comparison of "no association" or "association".
8. Page 3-36, line 3 – Please provide the effect estimate and 95% confidence interval for the study with the conclusion of "no association with cIMT" to be consistent with the positive association with CAC presented above it.
9. Page 3-37, line 5-6 – "…was observed among MESA participants." Provide the reference for this study
10. Page 3-37, line 15 – Please provide effect estimates for other tertiles, not just the highest. Was the deciding factor determining whether there was a positive association based on the effect estimate or whether the effect was statistically significant? The text needs to provide all the tertile effect estimates to allow the reader to judge that.
11. Page 3-38, line 12 – What effect estimate is this 1.17? Is this a risk ratio? odds ratio?
12. Page 3-39, line 12 – Please provide the effect estimate and 95% confidence interval for the "null association" of Wang et al (2020).
13. Page 3-39, line 25 – Provide the main effect for Shin et al (2019), to allow the reader to compare that to the effects when adjusting for NO_2 and O_3 that are provided

Dr. Jeremy Sarnat

Charge Question 4 – Section 3 (Health Effects)

3.2. Mortality

I want to commend EPA staff for their diligence and careful preparation of the supplement to the PM ISA. The supplemental material serves as a critically useful update to the state-of-the-science regarding PM and health. I am comfortable with most of the interpretations and general conclusions made within this chapter (and within this ISA supplement, in general).

- Broadly, the additional, recent epidemiologic findings related to mortality are exceedingly important. In preparing the 2019 ISA, the relatively few studies on long-term exposure and mortality cast, in particular, provided relatively limited observational evidence of causal associations at levels below the annual PM NAAQS. The current supplement addresses this shortcoming, showing excess mortality at concentrations below, in some locations substantially, the current annual NAAQS levels. There is also notable, added attention in the supplement to issues of confounding, which I'll address in the points below.
- The discussion of specific exposure factors as a source of heterogeneity in observed short- and long-term PM mortality risk is important and probably deserves more attention than given in the supplement. EPA notes that the housing stock and commuting, as well as land use and traffic) may explain some heterogeneity, but that these differences 'cannot be attributed to one factor' (3-53). This seems like an accurate conclusion which should be examined a bit more fully. Clearly, some of the factors mentioned are truly exposure-related (e.g., housing stock and indoor exposure to ambient PM), while others are more closely associated with differential emissions and chemical composition. I'd recommend including some language on why these factors are associated with observed heterogeneity, maybe in the discussion of the very interesting Baxter et al (2019) results (3-63). Maybe reference to Section 3.4 in the 2019 ISA is needed?
- Generally, I found the inclusion of alternative methods for assessing potential confounding to be an improvement over the previous versions of the ISA (Section 3.2.1.2.3), where there was close to sole reliance on the findings from multipollutant modeling. The causal models and results from accountability studies, in particular, provide added confidence that the observational findings related to PM are not unduly confounded by PM co-pollutants.
- While the treatment of confounding in this draft is an improvement over previous discussions in past ISA's, I continue to struggle with the weight multipollutant models are given when ascertaining the presence of confounding, and the relatively simple manner that the results are discussed.

Generally, I feel that the ISA parses extremely small differences in coefficients or confidence intervals around coefficients as meaningful, where I view these differences as likely by-products of residual errors in the exposure assignment approach. This does not imply that the results don't have value, they most certainly do in the context of a wider body of similar findings, but the observed differences from individual studies should be interpreted narrowly.

I would also recommend that language be included in the supplement regarding the utility AND limitations of multipollutant modelling as a means of ascertaining confounding. These limitations necessitated, in part, the development of alternative approaches. As currently written, coefficient stability or consistently is still presented as a 'gold standard' for addressing this issue – which it is not. Similarly, while there is ample discussion of the specific difference among the causal models, there is very little discussion on the limits of the various approaches or the relative benefits of one model over another.

- There is a question of overall ISA scope, for each of the criteria pollutants, which comes up when reviewing the multipollutant models. As with previous ISA's, the supplemental material on PM multipollutant modeling is still solely focused on controlling for confounding (i.e., looking for changes in coefficients while including other pollutants), but not on co-pollutant effects or synergistic effects which might be expressed through observed joint effects or effect modification. I appreciate that the scope of the PM ISA is to determine PM health effects, but the discussion involving the multipollutant modeling findings begs, in my opinion, some mention of mixtures and co-pollutant exposures. A related issue concerns specification of the multipollutant models. A key area of uncertainty is whether epidemiologic models more properly designed to assess the effects of pollutant mixtures, either in a joint effects or effect modification setting, that may include interaction terms among the pollutants, are more efficient and provide better fits to the C-R relationship than models with two, independent pollutant terms. As long as a multipollutant ISA does not currently exist, there should be space to address these issues in the individual pollutant ISA's.
- A related source of uncertainty regarding specification of the co-pollutant models is the potential non-linearity of associations between PM and its co-pollutants. The use of linear expressions, within a co-pollutant setting, to control for confounding of non-linearly correlated co-pollutants could lead to imprecision and/or bias; an appearance of effects associated with PM, where they do not exist.
- There have been several recent epidemiologic studies examining out-of-hospital cardiac arrest and PM, mainly from wildfires (Section 3.2.1.2.1; 3-57). In addition to several recent non-US studies (from Japan, Israel, Europe), a US study that can be cited is:
    - Jones, Caitlin G., et al. "Out-of-Hospital Cardiac Arrests and Wildfire-Related Particulate Matter During 2015–2017 California Wildfires." Journal of the American Heart Association 9.8 (2020): e014125. Authors found OHCA-biomass smoke association, strongest on lag day 2 (OR = 1.70; CI = 1.18–2.13).

- Figure 3-17. Please present both curves on the same scale to aid in interpretability.
- A theoretical question related to the shape of C-R curves (for mainly long-term exposure and mortality is whether we might expect to see differential measurement error at lower observed PM concentrations. For studies based primarily on measured estimates of population exposure I could hypothesize why differential error may exist and lead to differences in the shape of the curve along its full observed range. For studies using modeling or hybrid approaches, I have a harder time thinking of specific sources of error, but imagine that they too may exist. I raise this point only to draw attention to the role of measurement error as a potential driver of the shape of this function and as a note of caution in overinterpretation of observed supralinear or superlinear trends.

3.3. Key Scientific Topics

Section 3.3 represents a very important addition to the 2019 ISA and the EPA deserves tremendous credit for presenting more expansive identification of 'at-risk' to include both traditional definitions involving biological susceptibility, as well as those exposed to elevated PM due to social and economic disparities. In the 2019 ISA, an explicit discussion of environmental justice was largely absent, born disproportionately among Black and Hispanic communities, which is rightly interpreted as a key factor leading to disparities in PM risk within the current supplement.

Dr. Neeta Thakur

Section 3.3 Key Scientific Topics

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

Overall assessment:

I found the document incredible comprehensive yet disorienting. In section 3, there is a lack of consistency on how studies are discussed, specifically describing the study populations included to better contextualize results, for example a study that includes a predominantly higher SES, younger population, results are not comparable to a study in an older, Medicare population. The study population differences are only discussed in detail when the study includes an analysis across populations, such as on page 3-31, ln 30-38 discussing results from Elliot, Hart, and Weaver. This will also be helpful in defining what an "adequate margin of safety is," in that, studies that include or are predominantly in what has been established as "vulnerable groups" that these studies should perhaps be lifted in the review – especially in light of the stated focus on equity and environmental justice.

Section 3.3.1 (studies at near ambient concentrations):

The two exposure studies, increase mechanistic plausibility, particularly for cardiovascular effect. I did have issue with some of the details of how the studies are presented which effect interpretability (both towards the null or towards effect) that I have included in specific comments that follow.

Page 3-121 ln 19-31: For the 2015 Hemmingsen study it would be important to highlight that this was conducted in NON-smokers in addition to obese individuals given the focus on vasomotor function (endothelium mediated & non-mediated) and heart rate variability response to short-term PM2.5 exposure. In addition, the way the results are currently summarized, it is unclear

which arm (exposed to filtered air vs. non-filtered air) had decreased vasomotor function after exposure. It would be important to highlight that this is in the non-filtered air arm as evidence of a potential biologic mechanism.
Page 3-122: Wyatt 2020 exposure study, could likely be summarized more succinctly with attention to significant results. Specific comments regarding the presentation of this study follow.

Page 3-122, ln 9-10: Results for pulmonary function measures need to be clarified. As written, the change in values (e.g. 1.2% decrease in FEV1/FVC) implies that this is a 1.2% decrease from the pre-measurements, while in fact it is 1.2% difference in FEV1/FVC from those in the unexposed group as the authors conducted a mean difference analysis controlling for baseline (pre) measures rather than a repeated measures analysis. For PEF and FEV1 it would be important to make this distinction as well given that these measures are often written as %predicted and the use of %difference without annotation mistakenly inflates the findings.

Page 3-122, ln 12-18: Similar comment to above, need to clarify that these are mean differences between the exposed and unexposed group. The Supplement file includes these raw results were it is more clear that these are mean differences and not percent changes.

Page 3-122, ln 37-39: Could consider adding that the approach to the analysis, mean difference vs. repeated measures analysis, was also a limitation to the study.

<u>Section 3.3.1 (studies of associations between PM2.5 with COVID19):</u>

For this section, I think the ordering of the section should be reconsidered, with the at-risk section proceeding the covid 19 section given that this latter section is brand new. Otherwise, I don't have much to add regarding the assessment of the data for COVID19 and PM2.5 and agree with the conclusion that this area needs further study.

Page 3-126, ln 10: Should "However" be changed to "In addition," as these factors likely co-occur with regions with higher PM2.5 exposure and, thus, confound the findings of the mostly ecological studies presented (which is highlighted in the paragraph below with the inclusion of the critiques by Bourdrel et al. and Villeneuve and Goldberg).

<u>Section 3.3.1 (assessment across at-risk populations):</u>

For this last section, At-risk populations, I struggle with the way the new data re health effects of PM2.5 across SES strata. When consider as single indicators, the results are mixed, but as SES is a complex construct, this approach simplifies SES and may lead to mis-classification and varied results based on what indicator is used. However, pretty consistently, the included studies that use a composite measure of socioeconomic status, rather than a single indicator (such as income)

that there is both disproportionate burden of exposure (Figure 3-30, Tanzer 2019, Lee 2020, Weaver 2019, Han 2020) and health effects, particularly for long-term effects, including disease-related mortality (Zhang 2021, Bevan 2021, Wyatt 2020b [particularly panel D of Fig 3-34]). Defining what composite measure of SES is for the purpose of this ISA supplement would be helpful for comparability. For example, several of the composite measures also include race/ethnicity and other vulnerability factors, such as comorbid conditions. These composite measures that include these other vulnerability factors highlight that the facets of SES are complex and interactive. This may or may not be appropriate depending on the goal of distilling effect – is it looking for single risk factors, versus vulnerability factors that co-occur or are highly correlated with one another. Some discussion of how to consider the results from these studies versus those that look at single indicators should be included.

Re the included studies on race/ethnicity, have concerns about use the term "non-white" populations as opposed to explicitly stating comparator group(s). I also struggle with requiring studies to have to have a comparative population, this excludes a number of studies that may have relevance.

Page 3-144, Short-term exposure studies and mortality general comment: This is more a comment on the limitation of interpretation of the studies. Short-term exposure studies would stand to benefit from considering the annual PM2.5 exposure in their model to better understand whether it is the higher chronic exposure to PM2.5 that increases susceptibility to short-term increases in PM2.5 or the change in exposure itself. Understanding how differing levels of chronic exposure modify response to short-term changes would be useful when defining an "adequate margin of safety". Would consider highlighting this as a potential limitation to interpreting these studies and an area for future research.

<u>Specific Comments:</u>

Page 3-129, ln 24-25: Would help to add how clusters were determined, e.g., "neighborhood clusters, derived by Ward's hierarchical clustering of 11 census-derived socioeconomic variables, located in within three counties…"

<u>3.3.3.2 Race/Ethnicity</u>

Page 3-140, ln 20-39. Appreciate the EPA staff inclusion of studies that demonstrate that the overall decline in PM2.5 exposure is largely driven by decrease exposure in White populations but that there has been an increase in exposure for BIPOC groups and that exposure is inequitable distributed when considering populations generating vs. those exposed.

Dr. Barbara Turpin

Charge Question 2 - Section 1 consists of an introduction detailing why the draft PM Supplement is being developed along with the rationale and scope for the topics and studies considered.

a. *Please comment on the clarity of the section, whether the scope is appropriate for the purpose of the draft PM Supplement, and whether additional information is needed to convey the purpose of the draft PM Supplement and the basis for the targeted evaluation conducted.*

Section 1 was generally clear. However, I strongly suggest that the EPA clarify the rationale for the scope of the ISA Supplement. The ISA Supplement is limited to providing new information concerning effects that were determined to be causal in the original ISA. This means that new data that may change the "causality assessment" for nervous system effects (for example) is not considered.

Charge Question 3 - To ensure that recent studies are put in the context of the conclusions of the 2019 PM ISA the draft PM Supplement pulls in information verbatim from the 2019 PM ISA to orient the audience. Two ways this was done in the draft PM Supplement is through Section 2 which is the Integrated Synthesis Chapter (i.e., Chapter 1) of the 2019 PM ISA and leading off each health and welfare effects discussion in Section 3 and 4 with the Summary and Causality Determination from the 2019 PM ISA.

a. *Please comment on this approach and whether any additional modifications to the structure of the document can be made to better integrate evidence evaluated in the draft PM Supplement with conclusions from the 2019 PM ISA.*

This approach makes sense. It was quite helpful for the ISA Supplement to begin with the rational, followed by the Integrated Synthesis Chapter from the 2019 PM ISA.

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. *Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.*
b. *Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.*

The strengths and limitations of various types of evidence were clearly presented. The tables summarize findings from last review and demonstrate coherence across epidemiologic, animal

toxicology and controlled human exposure studies, supporting a causal relationship with cardiovascular effects. The addition of new studies demonstrate consistent results while applying advanced methods for addressing confounding, strengthening the case for causality.

c. *Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.*

There is considerable evidence calling into question the adequacy of the short term PM2.5 standard. This includes three epidemiologic studies with analyses restricted to 24-hr concentrations below 25 ug/m3 (Table 3-10). But the integrated science assessment, risk assessment and policy assessment do not provide the analyses needed to evaluate alternative levels and forms of the short term standard.

Regarding the section on effects by race and socioeconomic status, it is worth noting that the words "vulnerability," "sensitivity," and "susceptibility" are defined differently across the fields of research covered in the report. Consider using the words "intrinsic factor" and "extrinsic factor" instead.

COVID-19 material would be better placed at the end of the section where it is presented.

People of color or communities of color is a more appropriate descriptor than non-white.

Charge Question 5 - Section 4 characterizes the recent welfare effects evidence that falls within the scope of the draft PM Supplement.

a. *Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 4.*

Identification, evaluation and characterization of available evidence in Section 4 is satisfactory. However, please also consider the following:

Section 4 of the ISA supplement notes that changes in PM2.5 composition are resulting in an increasing "closure" gap between light extinction and light extinction predicted from particle composition. (Revised prediction methods address this.) One convincing reason, which is noted in the ISA Supplement, is the increase in the contribution of wildfire PM2.5. Another possible contributor is worth considering. Riva et al (2019) argues that as the sulfate/organic ratio decreases, the fraction of sulfate present as organosulfate increases. Organosulfate and inorganic sulfate have different optical properties and hygroscopicity which are not accounted for in the

IMPROVE light extinction model. The impact of organosulfates on the closure gap will be most important in the southeast.

Riva, M., Chen, Y., Zhang, Y., Lei, Z., Olson, N. E., Boyer, H. C., ... & Surratt, J. D. (2019). Increasing isoprene epoxydiol-to-inorganic sulfate aerosol ratio results in extensive conversion of inorganic sulfate to organosulfur forms: implications for aerosol physicochemical properties. Environmental science & technology, 53(15), 8682-8694.

b. Please comment on whether the summary section in Section 4 appropriately characterizes recent evidence in the context of the conclusions of the 2019 PM ISA.

I agree with the assessment in Section 4 of the ISA Supplement that recent evidence confirms the "well-established relationship between PM and visibility" and evidence is sufficient to conclude this relationship is causal.

Charge Question 6 - The Summary and Conclusions section (Section 5) provides an overview of the evidence evaluated in the draft PM Supplement.

a. Please comment on the level of detail provided within this section and whether revisions should be made to further summarize recent evidence.

Level of details seems appropriate.

Please change "non-white" to "people of color."

Dr. Marc Weisskopf

Charge Question 4 - Section 3 characterizes the recent health effects evidence that falls within the scope of the draft PM Supplement.

a. Please comment on the identification, evaluation, and characterization of the available scientific evidence in Section 3.

Overall the draft PM supplement has captured and characterized the new literature well. However, given the importance of studies that focus on lower levels of exposure—in particular levels below current standards—for making decisions on limit setting, it would be helpful to have a section that groups these papers and describes their findings.

See also specific comments below for some minor issues.

b. Please comment on whether the summary sections in Section 3 appropriately characterize recent evidence in the context of the conclusions of the 2019 PM ISA.

The summary in general does a good job of characterizing recent evidence. I have a couple of broad comments, though:

1) Where adjustment for co-pollutants is discussed, though (3-48, ll. 8-10, 26-27) it is not clear whether co-pollutant models are just two pollutant models or multi-pollutant models. I would think multi-pollutant models would be stronger evidence for a specific effect of PM2.5, although the issue that co-adjusting for a pollutant that reflects something in PM2.5 (e.g. NO2 as a marker of traffic pollution that is part of PM2.5) is complicated as it then changes the interpretation of the PM2.5 estimate. Adjustment for co-pollutants that are not reflecting components of PM2.5 (e.g. secondary gases) doesn't have that problem.

2) I am a little uncomfortable with the use of language like "causal modelling methods" to refer to the specific set of studies it is currently referring to. Standard studies (most of the ones referenced in this ISA and past ones) should be considered causal modelling methods, under the assumption that control of biases (e.g. by adjustment for confounders) has been accomplished. The studies that that language now refers to take different approaches to avoid or rule out biases, and for certain types of bias these can be considered advanced or more robust than the other literature. But these perhaps more advanced methods also have their own assumptions and also sometimes have issues they

cannot address. So I would favor replacing "causal modeling methods" to describe this literature with something else—maybe "advanced causal modeling methods", "modern causal modeling methods", or the like? The robustness of findings to the different approaches is perhaps of most relevance here. Focusing on describing the kinds of threats to validity that the newer methods are better at avoiding would be better than just referring them as causal modeling methods.

c. Please comment on whether there are any topics or studies that fall within the scope of the draft PM Supplement that should be added or receive additional discussion in Section 3 or any topics for which discussion should be shortened or removed from Section 3.

Other than perhaps clarifying the two points above, I think what is there is good.

Specific comments:

1) P. 3-3, l.8: Should be Table 3-1 I believe
2) P. 3-6, ll. 30-32: Much of the evidence in the 2019 ISA seems to be from just two-pollutant models. But such results are tougher to work through to inform lack of confounding than if multiple co-pollutants were in the model together (e.g. co-adjusting for O3 could still be confounded by NO2).
    a. Same two pollutant issue in 3.1.1.2.6
    b. 3.1.1.2.7, ll 13-19. This is limited additional evidence against confounding by co-pollutants and still has the issue of only 2-pollutant models.
3) 3.1.1.2.2, l.7-8: personal variables like sex, obesity, smoking cannot really confound a relation with an estimate of ambient PM2.5 (see Weisskopf and Webster, Epidemiology, 2017) as they do not contribute to that exposure metric (perhaps outside of SES factors driving residence location. So only to the extent they vary by location even after whatever SES/residential adjustment has been done). I would not downgrade any study results because of lack of control for such personal factors.
    a. This issue shows up in several other places in the document as well.
4) 3.1.1.2.3 Should there be some mention in summary of newer literature seeming to show more in vulnerable pops? No mention now.
5) 3.1.1.2.5: It's not clear to me what the overall conclusion is from what is presented in this section.
6) 3.1.1.2.6, ll. 31-32: What is the literature being referred to for this statement about linearity in the C-R function?
7) 3.1.1.3, l.14: See overall comment about using the term "causal methods".
8) 3.1.1.3, 3-21, ll.30-33 (related to Zhang et al., 2018): Need to indicate that the results indicated are for the 0-6 day lag average.
    a. I don't think the description of this study captures the results well. What is described seems to focus more on the 0-6 day average, but the results seem a little

different for shorter lags and those seem to be what the authors point to more. The main result seems to be that the per IQR change in outcomes doesn't change much over the different periods, except possibly for IHD and MI for which effect sizes seem to get larger in the later periods (although there is variability by lag period and part of NY). While differing composition of the PM could be behind this, it could also result from a steeper C-R at lower exposure levels (although the authors don't comment on this).

9) 3.1.1.3, 3-22 (related to Wang et al., 2019)
    a. ll.10-12: Should indicate that the authors' hypothesis was based on the thinking that secondary species were more important and these went down more in the after period.
    b. Ll. 22-28: This description of the findings is written as if the results are suggesting some changes. Instead these results all seem rather null and indeed are interpreted that way by the authors. I think that interpretation, rather than associations differ by time periods, needs to come across.
10) 3-22, ll. 33-35 (and top of 3-23): This is not really more causal an approach than typical adjustment, just a slightly different way of controlling for potential confounders (with maybe the exception of positivity as they apparently checked the PS distribution for cases and controls for this).
11) 3-23, l.16 (Qiu et al., 2020): the phrase "with the caveat that the authors had the resources to obtain all the 16 potential unmeasured confounders" is not correct. The authors state that a key assumption is no unmeasured confounding and note that they *don't* have the resources to get all unmeasured confounders. However, they assume one of the most critical is temperature and their findings are robust to different treatments of temperature. Variables that do not vary over time are eliminated as possible confounders by the case-crossover design.
12) 3-34, ll. 16-18: Why is "associations" used here? Is this meant to indicate less certainty about causality?
13) Figure 3-6: Should the results among diabetics be shown separately here for the Hart et al. 2015 paper?
14) 3.1.2.2.6, 3-38, l.12: Where does the 1.17; 95%CI: 1.10-1.22 come from in the paper? I see 1.13 (1.08, 1.17). And need to indicate that it is an HR and what the unit is—for the 1.13 it is an IQR (3.98 μg/m3) higher level.
15) 3-39, ll. 27-28: Not clear which HR refer to which pollutant (same for ll. 30-321).
16) 3-69, ll. 3-4: A more important aspect of the negative control exposure approach is that if no association is seen with the negative control exposure (which the authors report, indicated in ll. 11-12), then that indicates no confounding by any measured or unmeasured variables that affect both the exposure of interest and the negative control exposure. This should be stated as well.

17) 3-69, ll. 8-11: With the IV approach I don't see how the effects can necessarily be attributed to PM2.5—they suggest an effect of the pollution, but can't distinguish which pollutants affected by the IV account for the effect.
18) 3-95, l.27: I believe the suggestion is that the non-null associations are confounded. Also not clear to me that the coefficients are not interpretable if the whole point is that each PM2.5 metric should be giving the effect of PM2.5.
19) 3-99, ll. 7-9: As stated just above, I think this approach is very dependent on the exposure-covariate relations in the two populations. Not clear to me how strong the indirect adjustment results really are.
20) 3-108, table 3-7 Wu et al., 2021 results: HR are for a 10ug/m3 *increase* in PM2.5 (not decrease as stated). (also fix at 3-116, l.1)
21) 3-110, table 3-7 Schwartz et al., 2018b results: need to add "less" to the effect estimate (0.89 less years)
22) Table 3-7: DID studies can be quite powerful. Would be good in future to consider ones that also tried to address co-pollutants that could also be affected by the changes (e.g. policy, plant closure) if that is a possibility.

Dr. Corwin Zigler

The Draft Supplement to the 2019 PM ISA (henceforth, the "Draft Supplement") includes ample discussion of recent studies employing so-called "causal modeling methods" to evaluate the health effects of PM. The emphasis on causal modeling studies that have appeared since the the 2019 PM ISA is important and appropriate, and I commend EPA staff on their navigation of this evolving area. The emergence of these studies as new evidence propelling the reconsideration of the PM standard seems motivated by at least two connected threads; 1) these methodologies, while established across the domains of statistics, epidemiology, medicine, computer science, and the social sciences, represent a set of novel approaches for estimating the health effects of PM exposure with potential to reduce uncertainties in the current body of evidence, and 2) they are particularly well suited to address many of the uncertainties highlighted by members of the previous CASAC and the previous Administrator in the 2020 decision to retain the PM2.5 standards.

I believe that the inclusion of these "causal modeling" studies that have appeared since the 2019 PM ISA support and strengthen the EPA's and the current CASAC's conclusions regarding PM exposure and mortality. It is essential that the ISA process adopt a modern stance on "causal inference" in the context of air pollution epidemiology and keep up with this fast-evolving area. However, no operational definition of "causal modeling methods" is offered in the Draft Supplement, making it difficult to evaluate how exactly the emergence of these methods contributes to the existing body of evidence, particularly for readers without a detailed understanding of the methodological technicalities. I have several comments and concerns related to clarifying the role of these methods in the Draft Supplement.

General Comments

1. The role of "causal modeling methods" in the weight of evidence causality determinations.
    a. While the Draft Supplement does not provide any operational definition of "causal modeling methods," it seems clear that EPA is using this term to describe a specific class of established methodologies found across literature in statistics, epidemiology, computer science, medicine, and the social sciences, but relatively new to the body of evidence on PM health effects. As a means to distinguish a certain class of statistical or epidemiologic analysis approaches, iden- tifying certain methods as "causal inference" (or similar) does serve a purpose, as it connotes the use of some specific concepts and analysis tools such as propensity scores, explicit mod- eling of potential (or counterfactual) outcomes, double

robustness, or the features of quasi- experimental designs. However, when read in the context of the PM ISA, I am very concerned that the outright labeling of some studies as "causal" could confuse the purpose of these studies amid the weight of evidence causality determinations laid out in the 2015 ISA Preamble. For example, readers of the PM ISA less acquainted with these areas of statistical and epidemio- logic methods research might inappropriately surmise that methods that are not described as "causal modeling" should somehow be judged as less relevant for the causality determinations when considering the weight of evidence when, in fact, both "causal modeling" and more tra- ditional epidemiologic methods should be employed in service of establishing the entire body of evidence. In my view, the recent emergence of studies employing these types of method- ologies for PM health effects supports and strengthens the EPA's conclusions through reducing uncertainties around some common threats to validity of observational epidemiology, most notably, concerns around confounding bias. However, the importance of these studies should not be misconstrued as detracting from the importance of high quality but more traditionally- conducted epidemiologic analyses, which should also contribute substantial weight to the body of evidence.

2. Justify the importance of specific "causal modeling approaches" according to the threats or uncertainties they purport to mitigate.
    a. What makes the "causal modeling methods" described in the Draft Supplement important is their specific features for clarifying, mitigating, or even resolving common threats to causal validity in observational epidemiology. In this regard, these methods are no different from a variety of other types of analysis strategies that appear in the body of evidence that do not receive the "causal" label. An illustrative example is the discussion in Section 3.2.2.2.6 of the Draft Supplement on Novel Methods to Address Potential Confounding. This section outlines how a series of papers dating back to at least 2007 attempt to assess whether there is evidence of unmeasured confounding in the relationship between long-term PM exposure and mortality. Why, then, are these methods not described as "causal" for the purposes of interpreting them within the body of evidence? It would seem to me that the distinction here is that these methods outlined in Section 3.2.2.2.6 emerge from a different corner of the statistics and epidemiologic literature, but this strikes me as secondary to the important point that these methodologies are, much like "causal modeling methods," specifically targeted to reduce uncertainty around specific types of confounding. My view is that the novel methodologies that have emerged since the 2019 PM ISA should be discussed in terms of the specific threats to validity they are designed to address and the specific uncertainties they reduce (or not) in the body of evi- dence. The fact that these methodologies have been described as "causal inference" or "causal modeling" in

some corners of the literature is important, but, in my view, secondary to the primary goals of the PM ISA. As written, I believe opportunities remain in the Draft Supplement to more explicitly distinguish the features of causal modeling studies that render them important for clarifying and resolving common threats to validity of epidemiologic studies. In many cases, the potential benefits of the different types of causal methodologies are never made explicit beyond vague appeals to "the counterfactual framework." There is an expository literature on the role of causal inference in air pollution epidemiology consisting of (at least) [Carone et al., 2020, Dominici and Zigler, 2017, Zigler et al., 2018, Zigler and Dominici, 2014] that may be useful in framing the discussion in the Draft Supplement. In short, I do not believe it is nearly as important for EPA to litigate whether any individual study should or should not be called "causal" as it is for EPA to identify the general quality and conduct of a study and the specific threats to validity any novel methodology purports to address.

3. Consider alternative labeling of what are currently described as "causal modeling studies"
    a. The routine use of the word "causal" in the Draft Supplement must accommodate the varied scientific and colloquial uses of the word. My opinion is that the most emphasized and repeated use of the word "causal" in the context of the ISA should be reserved for the causality deter- minations as laid out in the 2015 ISA Preamble. The fact that the word "causal" is also used to classify the methods currently described as "causal modeling" is a reality of the colloquial use of the term and how the statistics and epidemiologic literature has evolved. In highlighting the importance of novel "causal modeling" for its role in the weight of evidence "causality determinations," EPA should consider an alternative labeling of the specific methodologies to avoid confusion. That is, EPA should be careful not to elevate the importance of "causal modeling" at the cost of suggesting that the weight of evidence causality determinations should be abandoned or de-emphasized. Labeling some studies as "causal modeling" as though they existed in an entirely different modeling paradigm may serve to perpetuate a dichotomy that studies are "causal" or otherwise "not causal," which I do not believe is an appropriate organization of the body of evidence (nor do I believe it was EPA intent to imply so). I suggest that the Draft Supplement first establish that the methods currently described as "causal modeling" are grown from a long tradition known in the statistical and epidemiologic literature as "causal inference," but otherwise refer to them as "novel epidemiologic analysis strategies," and ingest them into this and future ISAs according to which threats to validity they are designed to ad- dress (much as the papers described in Section 3.2.2.2.6 are now described). This may help to avoid confusion regarding the role these methods play in the weight of evidence causality determinations.

Specific Comments

Comments on the Executive Summary

1. The executive summary clearly states that the studies forming the basis of the evaluation within the supplement include U.S. and Canadian epidemiologic studies that employed "causal modeling methods or conducted accountability analyses." Absent any further detail on what distinguishes the evidence from these studies relative to epidemiologic studies that do not use "causal modeling methods," the importance of this distinction is unclear in the executive summary. I agree with the apparent assertion that the studies labeled as causal modeling add important evidence to what was available at the time of the 2019 PM ISA, but detect room in the Executive Summary for more specific description of why these studies add important information to the body of evidence. Perhaps it would suffice to state that these studies rely on novel analysis methodologies designed specifically to resolve common threats to validity in observational epidemiology, and defer details to other sections beyond the executive summary. Page ES-2 does specify that these studies "used a variety of statistical methods to control for confounding bias" which I find to be a much more helpful statement alluding to their potential utility over studies available at the time of the 2019 PM ISA.

2. Given the Draft Supplement's role in the reconsideration of the December 2020 decision to retain the PM standard, I found it puzzling that the Draft Supplement did not provide any context as to the stated rationale for the December 2020 decision (as provided, for example, in the 2021 Draft Policy Assessment). I do not have strong opinion as to what material belongs in the ISA vs. the Policy Assessment, but I do believe that some of the science that has emerged since the 2019 ISA can specifically address some of the uncertainties highlighted by the previous Administrator and the previous CASAC, and would have found a discussion of this helpful in contextualizing the Draft Supplement.

Comments on Section 1

1. Section 1.2.2 describes specific criteria for the types of studies considered for evaluation in the Supplement, including "epidemiologic studies that employed causal modeling methods." A more specific description of how studies were judged to meet this criterion would help clarify the role of these studies in the Draft Supplement. To be clear, I have no concerns about which studies are included under this criterion; later sections of the Supplement provide more detail and leave me confident that the EPA has correctly identified the importance of the studies judged to satisfy this criterion. But the criterion as stated is open for interpretation and difficult to define, which may lead to unnecessary confusion. I suggest some indication of why these particular causal analysis studies were

chosen, which I presume entails more than the mere fact that the study authors described their methodologies as "causal."

Comments on Section 3

1. In reference to evidence described in the 2019 PM ISA, page 3-21 states that "However, the body of evidence that supported this causality determination did not include any epidemiologic studies that conducted accountability analyses or employed causal modeling methods" (with a similar statement on page 3-46). Absent definition of "causal modeling methods," it is difficult to tell what exactly is implied by a body of evidence that does not include such studies. Taken at face value, this could call into question the causal determination in the 2019 ISA, which I do not believe it should nor do I believe it is EPA intent to imply so.
2. Page3-23 describes, in relation to the Qiu et al. [2020] study, that "several assumptions used by the authors when applying the IPW methods that are important to recognize." The explicit description of the series of sensitivity analyses to unmeasured confounding is important and worth noting. But the following two assumptions - positivity and consistency - are stated without any comment as to whether they are expected to hold in the Qiu et al. [2020] study or whether the authors provided any assessment of their validity. This is one example of a possible missed opportunity for the Draft Supplement to specify what threats to validity might be clarified (or resolved) with methods such as IPW. Information around the positivity assumption strikes me as particularly relevant, with many causal inference methods offering a framework to assess threats to validity that might manifest as a violation of this assumption in a way that may not be available with more traditional epidemiologic approaches.
3. Line ~9 of page 3-67 attempts to describe what causal modeling methods seek to do. This may be the closest the Draft Supplement comes to a definition of causal modeling. The general point about mimicking a randomized experiment through study design and statistical methods is a good one, but the description of how GPS methods do this is not particularly illuminating, nor am I sure it is correct. In particular, the statement that "the probability of being exposed is the same as the probability of being unexposed and the exposure can be considered as 'random"' is incorrect and/or requires clarification.
4. Section 3.2.1.3 on causal modeling and accountability studies of the PM-mortality relationship is an example of where there is emphasis on many implementation details of causal modeling methods (in this case, Wei et al. [2020] and Wei et al. [2021a]) but comparatively little on what features of these studies contribute to the body of evidence or what threats to validity these methods are meant to resolve. As written, I believe much of the mechanical details of these studies could be omitted. As a point of contrast, I found the description of how the methods in Schwartz et al. [2018] are designed to protect against certain threats to validity much more helpful in this context.

5. Section 3.2.2.2 provides enormous amounts of important information on the surprisingly vast array of recent studies investigating long-term exposures and mortality. The detail on different cohorts, exposure assignments, and investigation at different levels, is well laid out in relation to information available in the 2019 PM ISA.
6. Section 3.2.2.2.6 on Novel Methods to Address Potential Confounding focuses on a methodological area that decomposes the PM-mortality relationship into spatial and temporal component. Many of these studies are included in Section 11.2.2.4 of the 2019 PM ISA (titled Studies with Analyses that Inform Causal Inference), but the language of the Draft Supplement seems to not label them as "causal modeling." I am not convinced this labeling distinction is strictly necessary, but at a minimum it risks introducing confusion as to what the EPA considers a "causal modeling" study. More importantly, this indicates to me that the Draft Supplement (and previous ISAs) may already contain a framework for describing how certain "causal modeling" studies reduce uncertainties in the body of available evidence since, regardless of whether the studies cited in this section are labeled "causal modeling," there is clear description of their particular features for addressing potential confounding.
7. The discussion of the study in Wu et al. [2020], including in the summary information in Table 3-7, includes explicit mention of covariate balance. This is an excellent example of an analysis feature of this type of methodology that is important in order to assess the ability to adjust for confounding, and distinguishes this class of methodology from other more traditional (e.g., regression) modeling strategies. In this sense, it is an opportunity to emphasize the ability of one type of "causal modeling" to protect against the threat of confounding and thus add to the existing body of evidence. I do not believe it was mentioned with respect to any of the other cited "causal modeling" studies that use propensity scores.
8. Page 3-117 makes reference (when discussing Wei et al. [2021b]) to the assumption that "the coun- terfactual framework is valid." Without full context, it is a) not clear what exactly it means for the framework to be valid and b) not clear why this statement wouldn't also apply to all other methods described as "causal modeling." I am not convinced that this assumption needs to be stated at all, but if it is it should be accompanied by the appropriate context to discern what it means.
9. In Section 3.2.2.4, the final paragraph describes the "causal modeling" and accountability studies, noting that they used different statistical approaches in a causal modeling framework, and that they collectively provide additional support for the consistent positive associations. I agree with the statement, but note this as another opportunity where more detail about why these studies provide new or different evidence would help place these studies in proper context.

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