Public Comment on the
CASAC Review of EPA's Integrated Science Assessment for Particulate Matter
(External Review Draft – October 2018)

Deficiencies of Procedure and Expertise Must Be Corrected

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These comments are solely on behalf of Dr. Frey.

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1. Introduction: Overview of Key Comments

This section provides an overview of key points that emerge from observation of CASAC's December 12-13, 2018 public meeting, review of the minutes that meeting, and review of CASAC's draft letter to the Administrator.

1.1. Congress, Not CASAC, Decides on the Policy and Decision Context of the National Ambient Air Quality Standards

CASAC may not redefine the policy and decision context of NAAQS review. This context is set forth by Congress in the Clean Air Act, including but not limited to the following excerpts. From Section 108:

> The NAAQS must address "air pollution which may reasonably be anticipated to endanger public health or welfare"
>
> "Air quality criteria for an air pollutant shall accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities." and "any known or anticipated adverse effects on welfare"

And from Section 109:

> The Administrator "shall complete a thorough review of the criteria" published under Section 108.
>
> "National primary ambient air quality standards, prescribed under subsection (a) shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."

Note that nowhere does the Clean Air Act state that EPA should take a risk-neutral or risk-seeking attitude toward risk, nor that EPA should limit its assessment only to those studies that individually can demonstrate manipulative causality consistent with particular quantitative causal tests and inference methods. The language of the Clean Air Act means that EPA cannot throw out studies according to arbitrary "quality" criteria if that would compromise the ability to conduct a thorough review and account for the full scope of review as mandated in the Act.

1.2. The Ground Rules for the Draft Integrated Science Assessment Were Previously Established

The Draft ISA is a document of over 1,800 pages.[1] The Draft ISA cites approximately 2,800 references, most of them new since the 2009 ISA. The Draft ISA follows the methodology set forth in the Preamble to the ISAs,[2] the 2016 Integrated Review Plan for Particulate Matter,[3] and the preface to the draft ISA.

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[1] U.S. EPA, Integrated Science Assessment for Particulate Matter, U.S. Environmental Protection Agency, Research Triangle Park, NC, EPA/600/R-18/179, 2018. https://yosemite.epa.gov/sab/sabproduct.nsf/0/932D1DF8C2A9043F852581000048170D/$File/PM-1STERD-OCT2018.PDF

[2] U.S. EPA. Preamble to the Integrated Science Assessments (ISA). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-15/067, 2015. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

[3] U.S. EPA, Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter, U.S. Environmental Protection Agency, Washington, DC, EPA/452/R-16/005, 2016. https://www3.epa.gov/ttn/naaqs/standards/pm/data/201612-final-integrated-review-plan.pdf

The Preamble to the ISAs is based on CASAC advice delivered over many review cycles. The 2016 IRP is based on CASAC advice in *this* review cycle.

The CASAC should adhere to the Integrated Review Plan (EPA-452/R-16-005, December 2016) for this review cycle, and to its own advice to EPA on the Integrated Review Plan. The basic ground rules of this review have already been established in 2016 and as a matter of proper and consistent administrative procedure must be followed. CASAC members should read the IRP.

The science review process in prior EPA documents and CASAC reports has demonstrably been based on thorough systematic reviews of relevant scientific literature. Furthermore, such reviews have been proven to be relevant because they have informed policy decisions that have survived judicial review. Criteria (ground rules) for the reviews have been clearly stated taking into account operational practicality and that the ISA deals with a broad range of scientific disciplines and heterogeneity in the characteristics of policy-relevant studies. There is an explicit role for expert judgment in this process.

1.3. Points in CASAC's Letter Must be Based on Public Deliberations

As detailed elsewhere, there are many statements in the letter that cannot be traced to a consensus of the CASAC or to public deliberations. Some of the statements were simply never made during CASAC's meeting on December 12-13, 2018. Other statements might have been made by one person but there was not explicit agreement on such statements from all members of the CASAC. It is not clear that CASAC members had any understanding that if one member made a statement and no one said anything in response, then that statement would be interpreted as unanimous consensus of the entire CASAC. Several CASAC members were largely silent on many issues and may not have understood that they should say something if they disagreed with a statement made by others.

For example, I recall that some members of CASAC expressed support for the current framework for making causal determinations. These views are not represented in the text of CASAC's draft letter. Thus, the draft letter is not an accurate reflection of what was deliberated in public.

1.4. The CASAC Should Familiarize Itself with the Review Process as Set Forth in the Integrated Review Plan

The CASAC appears to fail to understand the role of the ISA in the review process. The ISA is not about making predictions. It is about assessing the current state of the science based on published studies. It is not about conducting new analyses or making predictions. The Risk and Exposure Assessment is the step in the review process in which scientific evidence from the ISA is applied to make estimates of risk at the current standard and risks for alternative scenarios below the current standard.

The Irish coal ban study is not policy-relevant to the Draft PM ISA based on *a priori* criteria established in the Preamble to the ISAs and that further was vetted by CASAC in its review of the PM Integrated Review Plan for this review cycle in 2016.

As a matter of proper administrative procedure, the EPA must follow its own procedures in a consistent matter. The chartered CASAC has previously reviewed and provided advice regarding the methodology for how the Draft ISA should be developed in 2016. Yet, in 2019, the chartered CASAC is now attempting to change the fundamental ground rules in the middle of a review cycle. This is not consistent with any reasonable procedure for how CASAC should conduct its own business. The CASAC fails to reference its own advice regarding the Integrated Review Plan or to explain why CASAC should change its advice regarding the methodology of the PM review midstream in the middle of a review cycle.

1.5. There Cannot Be An Arbitrary Cookie-Cutter Approach to Assessing Epidemiologic Evidence

Because epidemiologic studies of the effect of ambient particulate matter are observational and not controlled studies, every epidemiologic study is different and has different strengths and limitations. A particular epidemiologic study may be strong in addressing a particular confounder that is not as well addressed in other studies, but may itself have other shortcomings. This is why appropriate experts need to be engaged in review of the state of science regarding epidemiology and inferences from epidemiologic studies. This CASAC lacks such expertise. As such, CASAC is not able to provide expert judgment on matters related to epidemiology and its interpretation because CASAC lacks an appropriate group of experts.

1.6. EPA Arbitrarily and Capriciously Disbanded the CASAC PM Review Panel

By charter, the CASAC was and has been the principal advisor to the agency. For four decades, CASAC has been augmented by review panels: details are given in Frey et al. (2018).[4] Thus, a procedure has been well-established for the formation of review panels. The procedural precedent is important in demonstrating that the EPA follows its own procedures consistent with the Administrative Procedures Act.

The unprecedented high rate of turn-over in the last two years means that the current CASAC panel is inexperienced and unfamiliar with well-established procedures. Lack of experience and lack of familiarity leads to an inevitable learning curve that leads to inefficiencies.

Furthermore, with the larger augmented panel the workload for review of a document such as an 1800+ page draft ISA would be distributed over a larger group of experts, which is a more time-efficient manner in which to conduct a review of such a large document. The lack of breadth and depth of expertise of the current chartered CASAC also means that it cannot authoritatively address many of the key scientific issues that are critical to the ISA, which is another form of inefficiency in a scientific review process.

Given the lack of breadth and depth of expertise of the current seven member CASAC, the current review activities of CASAC are not consistent with language in the Clean Air Act regarding the needed scope of review, nor is the current review consistent with four decades of well-established precedent regarding augmenting CASAC. The latter is especially problematic in the likely event that the Agency is challenged with judicial review regarding departures from established operating procedures under the Administrative Procedures Act.

It is puzzling why the chair of CASAC has not simply stated that EPA should reinstate the CASAC PM Review Panel. In contrast, the chair of CASAC expressed interest in ad hoc approaches to engaging experts. The middle of a review cycle is not the time to change established administrative procedures. When an agency fails to observe well-established procedures and engages in ad hoc approaches, it

[4] Frey, H.C., A.V. Diez Roux, J. Balmes, J.C. Chow, D.W. Dockery, J.R. Harkema, J. Kaufman, D.M. Kenski, M. Kleinman, R.L. Poirot, J.A. Sarnat, E.A. Sheppard, B. Turpin, and S. Vedal, "CASAC Review of EPA's Integrated Science Assessment (ISA) for Particulate Matter (External Review Draft – October 2018)," 34 page letter and 100 pages of attachments submitted to Chair, Clean Air Scientific Advisory Committee, U.S. Environmental Protection Agency and to Docket EPA–HQ–ORD–2014-0859, December 10, 2018.
https://yosemite.epa.gov/sab/sabproduct.nsf/086D8B853E0B63AE8525835F004DC679/$File/PMRP+Letter+to+CASAC+181210+Final+181210.pdf

becomes susceptible to judicial review under the Administrative Procedures Act. There is a very simple solution here: reinstate the CASAC PM Review Panel.

In a situation for which CASAC and its review panels comprise the needed breadth and depth of experts, ad hoc departures from past practices would not be needed. Within the rules of FACA, members of CASAC and of augmented CASAC Review Panels can have communications. Among the advantage of having an augmented review panel is that the members of the augmented panel, like the members of the chartered CASAC, are appointed as Special Government Employees and are subject to the same ethics requirements as CASAC members.

Given the important role of expert judgment in CASAC's work, it is essential that CASAC be augmented with additional experts in the multiple scientific disciplines needed for this review. Furthermore, there must be multiple experts in key areas, such as air quality physics and chemistry, exposure assessment, toxicology, controlled human studies, epidemiology, and others, to have a diversity of perspectives to assure that judgment is based on the large body of relevant scientific evidence using accepted inference methods. For four decades, CASAC has been augmented with expert panels as documented by Frey et al. (2018) and others. The rationale given by EPA for disbanding the PM review panel is that by statute the CASAC and not a review panel is the advisory body. This rationale is specious because under its charter with Congress, it is clear that augmented panels report via the CASAC and not directly to EPA; therefore, per its charter, CASAC has been the advisory body. Augmented panels advise the CASAC and supplement it with the expertise it needs. Absent such augmented expertise, the chartered CASAC is scientifically unqualified to conduct a review consistent with language in the Clean Air Act.

To correct the procedural deficiency of arbitrarily and capriciously disbanding the CASAC PM Review Panel, EPA should immediately reinstate the CASAC PM Review Panel. The second draft of the ISA should be reviewed the by chartered CASAC augmented with the reinstated CASAC PM Review Panel.

Furthermore, as a matter of professional credibility, the members of CASAC should more strongly acknowledge the limits of their expertise and that they are not able to offer comments on many aspects of the ISA until such time as the CASAC PM Review Panel is reinstated.

EPA should not cherry-pick experts during the middle of a review process. The proper procedure is to establish the panel BEFORE the start of the review process. That proper procedure was followed and the panel was formed before the draft IRP was provided to CASAC for review. Thus, the disbanded CASAC PM Review Panel, which was appointed prior to the start of the review process, should be reinstated.

1.7. This CASAC is Inexperienced

Current members of CASAC were appointed in 2017 and 2018, representing an extraordinarily high level of member turnover that renders this as the most inexperienced CASAC to review a Draft ISA. Furthermore, given the arbitrary and capricious disbanding of the CASAC PM Review Panel and the lack of adequate breadth and depth of expertise of the current CASAC, this is the most unqualified CASAC to review a Draft ISA. To some extent, the CASAC admits and recognizes its lack of expertise and offers recommendations for "access" to additional experts. However, the CASAC fails to address this deficiency appropriately and adequately.

1.8. Inexperienced CASAC Members May Not Understand the Meaning and Implication of "Consensus"

Individual members of CASAC must understand that if they disagree with a statement made by another member, including the chair, they must speak up. **The Chair and DFO should explain to the CASAC members the ground rules regarding how consensus is inferred**.

CASAC cannot imply as a matter of consensus that all members agree with strident statements in the draft letter such as "lack of scientific method" if individual members have made clear statements to the contrary that are not accurately reflected by such a statement.

Members of CASAC should realize that their names are associated with CASAC's report to EPA, and that unless otherwise stated it is assumed by the reader (i.e. the EPA Administrator) that every statement in the letter and "consensus" attachment is agreed to by all members. If this is not the case, individual members must so indicate and the letter and attachment must so indicate.

1.9. Terminology

If this CASAC wants to engage in development of a detailed glossary, it could spend the remainder of this review cycle and beyond in so doing, leading to delays and paralysis. As a practical matter, it will be more fruitful to recognize that there is a role for judgment in developing and communicating scientific interpretations.

Dr. Cox, the current chair of CASAC, presented his comments on the executive summary and Chapter 1 at the December 2018 meeting, but there is little record of deliberation on these comments. Dr. Frampton, a member of CASAC, stated that he "did not find that the causal definitions introduced by Dr. Cox to be helpful in understanding what is going on and felt they just obfuscate and would lead to confusion if included in the ISA." However, there is no indication of the viewpoint offered by Dr. Frampton in CASAC's draft letter. Thus, CASAC's draft letter is not an accurate depiction of CASAC's deliberation or advice. It does not represent a consensus.

1.10. CASAC is an Advisory, not Decision-Making, Body

Ultimately, CASAC provides advice but it does not dictate what EPA staff must do, particularly if CASAC's advice is poorly grounded or poorly formulated and if CASAC's advice is contradictory to its own prior advice and to existing groundrules of the review cycle.

1.11. A Good Foundation for Expert Judgment Is Missing from CASAC

The draft letter offers some commentary regarding expert judgment. Although that material appears to be untethered to public deliberations of CASAC, that material suggests another way of characterizing deficiencies of CASAC itself. One key principle of formulating expert judgment is that there must be a "conditioning" step based on a thorough review of all relevant scientific information. It is well-known that the conditioning step is enhanced based on knowledge of a large and diverse group of experts, who represent the full range of relevant disciplines and diversity of perspectives within disciplines. The need for conditioning of expert judgment is precisely why it has been a routine and properly established practice for four decades to augment CASAC with review panels that contain experts in disciplines relevant to each assessment, and that contain multiple experts in key disciplines to assure diversity of knowledge and inference methods will be available in deliberations

1.12. CASAC Lacks the Appropriate Breadth, Depth, and Diversity of Expertise to Offer Advice

Given that this CASAC lacks expertise in many key disciplinary areas, especially epidemiology, and that EPA arbitrarily and capriciously disbanded the CASAC PM Review Panel a few days before the Draft ISA was released, thereby depriving CASAC of the needed expertise, this CASAC is not in a credible position to offer judgments regarding causal determinations or many other aspects of the EPA charge questions nor is it credibly positioned to call for major and controversial overhaul of well-established methodology for the NAAQS science review.

Given that this CASAC lacks experts in the appropriate scientific domains, it is unqualified to offer judgments that require expertise from the missing or inadequately represented domains. Secondly, expert judgment should be based on conditioning of available evidence and inference methods. The conditioning step is substantially more credible when it is based on a larger group of experts with breadth and depth of expertise, and diversity of perspectives. EPA had the larger group in the form of the CASAC PM Review Panel and yet arbitrarily and capriciously dismissed that panel without prior notice and without public consultations with CASAC. Third, there are well known biases in expert elicitation, some of which are cognitive and some of which are motivational. An example of a motivational bias is the so-called "expert bias," which is when people who are not the relevant experts pretend that they are to make themselves appear to be important experts. Another well-known motivational bias is when an "expert" wants to influence the outcome of a scientific review process to achieve a particular policy or regulatory outcome. Such biases might be indicated, for example, when members of a scientific review committee earn their living based on funding from regulated industries, and offer opinions that are consistent with policy outcomes of interest to their funders or to positions of such stakeholders. Motivational biases also arise when an expert has taken strongly stated public positions previously, as a result of which it becomes more difficult for that person to change their views.

1.13. What the CASAC Letter SHOULD Say

The CASAC should commend EPA staff for development of an excellent first draft of the ISA that provides comprehensive and systematic assessment of the available science relevant to understanding the health impacts of exposure to particulate matter. The CASAC should recognizes that the 1800+ page Draft ISA cites over 2,800 references, most of them new since the last review cycle. The Draft ISA follows methods previously reviewed by CASAC, including the approach to literature review, the causal determination framework, the framework for assessing at risk populations and lifestages, and assessment of concentration-response functions, consistent with the Preamble to the ISAs and the 2016 Integrated Review Plan for the current review cycle. However, as with any first draft, the CASAC may recommend some revisions. For example, if publicly deliberated and if a consensus of CASAC members, the CASAC may recommend that EPA staff consider a list of accountability studies recently provided by HEI with respect to policy-relevance and, if policy relevant, assess their importance.

CASAC should find that EPA staff have followed the framework for causal determination that has been developed over the last decade. This framework is similar to that from other agencies and has been reviewed by over 60 experts on CASAC and CASAC review panels. This is a well-established, accepted, and appropriate practical approach that is based on integrative consideration of evidence across various disciplines such as toxicology, controlled human studies, and epidemiology. There is explicitly a role for expert judgment in this process. Given the important role of expert judgment, it is also important that the ISA explain as clearly and transparently as possible the basis for judgments regarding causal determination. As an example, more transparency is needed regarding the causal determination for UFPs and central nervous system effects.

The CASAC should acknowledge that the ISA takes into account poverty, temperature, including lags related to temperature, and season, and makes inferences regarding whether ambient PM concentration independently causes adverse effects and whether concentration and response relationships are either confounded or modified by other variables. Some of these inferences could be explained more clearly or in more detail.

At its December 2018 meeting, CASAC received extensive public comments regarding the decision by EPA to disband the CASAC PM Review Panel just days before the Draft ISA was released for review by CASAC. For four decades, and consistent with its Charter, CASAC has been augmented with additional experts in the form of review panels. These panels report through the chartered CASAC. Thus, CASAC is the body, as mandated by statute, that provides advice to EPA, not any of its panels. Nonetheless, the panels are critical to providing CASAC with the breadth and depth of expertise, and diversity of perspectives, required to meet the statutory mandate of the Clean Air Act for a review that "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities" for pollutants that "cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare." Therefore, CASAC should recommend that the CASAC PM Review Panel be re-instated in time for the panel to augment CASAC for the review of the Second External Review Draft of the ISA and subsequent documents in this review cycle.

Consistent with the statutory mandate of the Clean Air Act, the EPA and the CASAC must consider the wide ranging kind and extent of possible health effects that may accrue from exposure to criteria air pollutants. Although a portion of the scientific evidence can be established with a high degree of confidence and certainty, in other cases the CAA asks EPA and CASAC to make judgments for situations in which the science is incomplete. Thus, inevitably, portions of the Draft ISA rest on expert judgments. Such judgments should be explained so that scientific readers can understand the scientific evidence and inferences from which EPA staff reach their conclusions, as clearly and transparently as reasonably possible. CASAC is currently poorly positioned to provide expert judgment because it has been deprived of the CASAC PM Review Panel. A key tenet of development of scientific expert judgment is to share information among a diverse group of experts across disciplines and to have diversity of opinion of multiple experts in key disciplines. Thus, EPA should reinstate the CASAC PM Review Panel.

CASAC should be augmented with additional experts by reinstating the disbanded CASAC PM Review Panel prior to reviewing the Second External Review Draft of the ISA and prior to reviewing any other EPA assessment documents in this review cycle.

2. Comments on the Summary Minutes of the U.S. Environmental Protection Agency (EPA) Chartered Clean Air Scientific Advisory Committee (CASAC) Public Meeting on Particulate Matter, December 12-13, 2018

This section is based on review of the summary minutes of the U.S. Environmental Protection Agency (EPA) Chartered Clean Air Scientific Advisory Committee (CASAC) Public Meeting on Particulate Matter, December 12-13, 2018.[5]

2.1. Wrong Policy Context

Regarding Dr. Cox's instructions to CASAC: *"In thinking about what kinds of advice would be most useful, his own thinking focuses on preventable harm"* – this is not the mandate given to EPA and CASAC by the Clean Air Act. As such, the CASAC Chair, Dr. Cox, is attempting to redefine the policy and decision context of the science review. The policy and decision context of the science review is set forth by Congress in the Clean Air Act, as interpreted by Federal courts, and is not amenable to ad hoc redefinition by CASAC or its chair.

Dr. Cox "*asked members of the CASAC to listen carefully to public comments, and to build on the work they have already done, to address that question of quantitative measures of preventable harm."* Here again, this is not consistent with the statutory mandate from Congress as given in the Clean Air Act regarding how the NAAQS should be set. See the Clean Air Act Sections 108 and 109. In particular, from Section 108:

> "cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare"
>
> "Air quality criteria for an air pollutant shall accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities." and "any known or anticipated adverse effects on welfare"

And from Section 109:

> The Administrator "shall complete a thorough review of the criteria" published under Section 108.
>
> "National primary ambient air quality standards, prescribed under subsection (a) shall be ambient air quality standards the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."
>
> "Any national secondary ambient air quality standard prescribed under subsection (a) shall specify a level of air quality the attainment and maintenance of which in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air."

[5] Summary Minutes of the U.S. Environmental Protection Agency (EPA) Chartered Clean Air Scientific Advisory Committee (CASAC) Public Meeting on Particulate Matter December 12-13, 2018, https://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/33BB9FC41F61A40085258328005B3EF6/$File/CASAC+PM+Dec+12-13+2018+Minutes.pdf

Among the implications of the statute are the following:

- "may reasonably be anticipated" does not require complete scientific certainty and, in fact, obligates both EPA and CASAC to consider effects of pollution even if there is not scientific certainty.
- "all identifiable effects" implies that as wide a range of effects as possible must be considered. Taking into account other language in the Act, it is not required that there be complete scientific certainty for EPA to set a standard.
- "which may be expected" is another indication that scientific certainty is not required. Expectation could arise based on scientific judgment, for example.
- "any known or anticipated adverse effects on welfare": anticipated adverse effects do not have to be known with certainty
- "an adequate margin of safety": margin of safety is widely understood to be a means of taking into account uncertainties in ways that are protective of public health. From a decision making perspective, this is a risk-averse attitude toward risk as expressed by Congress.
- "protect the public health" – the concept of protecting public health is widely understood to be related to that of safety and improving the health of communities and the public. From a decision-making perspective, the decision context of protecting public health is understood to be risk averse. Some would argue that protection of public health is inherently precautionary. Operationally, EPA interprets this language to mean that the NAAQS should protect the general public and at risk populations and lifestages in the population.

Note that nowhere does the Clean Air Act state that EPA should take a risk-neutral or risk-seeking attitude toward risk, nor that EPA should limit its assessment only to those studies that individually can demonstrate manipulative causality consistent with particular quantitative causal tests and inference methods. The language of the Clean Air Act means that EPA may not throw out studies according to arbitrary "quality" criteria if that would compromise the ability to conduct a thorough review and account for the full scope of review as mandated in the Act.

2.2. Misunderstanding of the Causal Determination Framework

Regarding causal determination versus concentration-response functions, there was much discussion by CASAC at its December 12-13, 2018 public meeting that was based on misunderstanding of the causal determination framework. The causal determination framework is based on a weight of evidence approach as described in the Preamble to the ISAs. The determination is based on judgment regarding whether exposure to a given pollutant over a given exposure duration causes a given adverse effect independent of other factors. Separately, evidence regarding concentration-response functions is reviewed to arrive at findings regarding such functions.

2.3. Misunderstanding of the Role of the Integrated Science Assessment

Furthermore, the CASAC appears to fail to understand the role of the ISA in the review process. The ISA is not about making predictions. It is about assessing the current state of the science based on published studies. It is not about conducting new analyses or making predictions. The Risk and Exposure Assessment is the step in the review process in which scientific evidence from the ISA is applied to make estimates of risk at the current standard and risks for alternative scenarios below the current standard.

2.4. Need for Epidemiologic Expertise that is Missing from CASAC

"Dr. Cox stated that when a concentration-response association is seen, very often in reality, that association will be partly due to confounding or modeling choices, maybe partly due to direct effects, and partly due to indirect effects." This is quite possible in some situations. This is precisely why CASAC and EPA take a holistic weight of evidence approach that includes reviewing multiple policy-relevant studies and does not base causality determinations on quantitative causality tests of individual studies. Because epidemiologic studies of the effect of ambient particulate matter are observational and not controlled studies, every epidemiologic study is different and has different strengths and limitations. A particular epidemiologic study may be strong in addressing a particular confounder that is not as well addressed in other studies, but may itself have other shortcomings. This is why appropriate experts need to be engaged in review of the state of science regarding epidemiology and inferences from epidemiologic studies. This CASAC has no such expertise. As such, CASAC is not able to provide expert judgment on matters related to epidemiology and its interpretation because CASAC lacks an appropriate group of experts.

2.5. Lack of Understanding of Policy-Relevant Science

"Dr. Cox asked about the Health Effects Institute (HEI) accountability studies which have shown inconsistent associations for cardiovascular mortality. He asked why the EPA did not discuss studies of the Irish coal burning ban. Mr. Sacks indicated that those studies looked at PM10 and sulfate, which was outside of the scope of the ISA, which focused on coarse and fine particles (per the advice of CASAC on the previous ISA)." The Irish coal ban study was based on different indicators than this NAAQS review and thus is not policy relevant. Moreover, the Irish coal ban study showed a decrease in respiratory mortality. Contrary to implications by some members of CASAC, the Irish coal ban study did not show that the reduction in emissions did not contribute to the decline in adverse, only that it was difficult in that particular study to separate the pollution contribution. Furthermore, this is an illustration of why a goal of the ISA is to identify and assess as many policy-relevant studies as possible.

The draft CASAC letter includes strong statements that the Draft ISA is not comprehensive because it omits HEI studies such as this. However, CASAC did not take into account the reply given here by Mr. Sacks to the effect that the Irish coal ban study is not policy-relevant to the Draft PM ISA based on a priori criteria established in the Preamble to the ISAs and that further was vetted by CASAC in its review of the PM Integrated Review Plan for this review cycle in 2016. The well-established underlying ground rules of the ISA are laid forth in the Preamble to the ISAs, the Integrated Review Plan for particulate matter, and the preface to the Draft ISA.

2.6. Techniques Advocated by the Chair are in their Infancy

Dr. Lianne Sheppard of the University of Washington made the point that "*there is a distinction between causal inference tools in a single study and the weight of evidence causal determinations made by the EPA, and that causal inference methods for application to air pollution are in their infancy and not ready to be required for use in regulatory policy.*" Furthermore, she described that "changes to the CASAC and NAAQS review process were done without consultation with the CASAC and are arbitrary and capricious."

2.7. Potential Lack of Impartiality

Not mentioned in the minutes or in CASAC's draft letter is any disclosure or explanation by CASAC member Dr. Sabine Lange that at the same time she prepared comments on the Draft ISA, her employer

prepared and submitted comments to the ISA Docket (Docket ID No. EPA-HQ-ORD-2014-0859) as an official statement of the Texas Commission on Environmental Quality. The TCEQ comments on the Draft ISA were submitted with a cover letter signed by Toby Baker, Executive Director of TCEQ. The cover letter states that questions concerning the TCEQ's comments may be referred to Ms. Allison Jenkins. Dr. Lange is listed as Section Manager of the Toxicology, Risk Assessment, and Research Division. Ms. Allison Jenkins is an employee in the Division who reports to Dr. Lange, according to the publicly posted information about the Division. Dr. Lange reports to the Division Director who reports to Toby Baker. The TCEQ engaged NERA Economic Consulting Project Team and its lead consultant Anne Smith under TCEQ Work Order 10. Anne Smith submitted public comments to CASAC on behalf of the Utility Air Resources Group. CASAC member Dr. Lange should explain why these circumstances do not indicate lack of impartiality and lack of independence.

2.8. Causality is Based on Weight of Evidence Not Individual Epidemiologic Studies

Dr. Corwin Zigler of the University of Texas at Austin stated that "the current "weight of evidence" determinations of causality in the ISA are useful for judging the causal consequences of an anticipated change in PM concentrations." He further described that "Individual studies contributing to these determinations should be interrogated and weighed according to their design, data structure, statistical analysis, and plausibility of underlying assumptions, not simply based on whether the methods used are nominally described as "causal."" This is an important comment and also is relevant to discussions by this CASAC related to issues of systematic review and evaluation of study relevance. However, CASAC has ignored this important public comment. By ignoring advice from experts in causal inference such as Dr. Zigler, CASAC undermines the credibility of its own advice.

Dr. Jon Samet of the Colorado School of Public Health, and a past-chair of CASAC, stated that "the approach used by the agency in its causal determinations reflects the state of practice used by others, such as the Centers for Disease Control and Prevention, in evaluating the evidence on smoking and health. He stated that the Chartered CASAC does not have all the expertise that is needed for this review."

Dr. Kevin Cromar of New York University stated that the Draft ISA "is a good representation of the scientific evidence concerning health effects of particle pollution and the scientific conclusions and causal determinations are supported by a well-constructed framework." He further stated that there is "a high level of confidence that the causal conclusions reported in the ISA cannot be explained away by unmeasured confounders or other unidentified biases." CASAC has ignored this important public comment.

2.9. Neither EPA Nor CASAC Have Relied on Statistical Association

Dr. Roger McClellan, a former chair of CASAC, stated that the Draft ISA "erroneously assumes that statistical associations are evidence of causality." This is not an accurate statement. Causal determinations are not based on any individual study and take into account evidence from multiple lines of scientific inquiry. While statistical associations may be part of the reviewed scientific information, they are not sufficient individually to support a finding of causality. The causal determination framework is based on the principle that causation requires more than association in any individual study. More information on these points can be gleaned from reading CASAC and final CASAC-reviewed EPA reports in the last decade.

2.10. Disbanding the CASAC PM Review Panel is Arbitrary and Capricious

Regarding the reasons for recent changes to the NAAQS review process by EPA, specifically related to disbanding the CASAC PM Review Panel, "Dr. Sasser stated that there was a desire, in the spirit of making the reviews more efficient, to return to the core statutory obligations of the CASAC and to reaffirm the committee as the principle advisor to the agency on the NAAQS. She noted, however, that this decision was not made at the staff level."

However, as noted elsewhere in these comments, and in the public comments submitted by Frey et al. (2018) to CASAC on December 10, 2018, the core statutory obligation of CASAC is incorporated into CASAC's charter with Congress.[6] Under that charter, CASAC may be augmented with experts but such experts report via the CASAC and not directly to the EPA Administrator. Specifically, the charter states:

> "EPA, or CASAC with the Agency's approval, may form subcommittees or workgroups for any purpose consistent with this charter. Such subcommittees or workgroups may not work independently of the chartered committee and must report their recommendations and advice to the chartered CASAC for full deliberation and discussion. Subcommittees or workgroups have no authority to make decisions on behalf of the chartered committee, nor can they report directly to the EPA."

Thus, by charter, the CASAC was and has been the principal advisor to the agency. For four decades, CASAC has been augmented by review panels: details are given in Frey et al. (2018). Thus, a procedure has been well-established for the formation of review panels. The procedural precedent is important in demonstrating that the EPA follows its own procedures consistent with the Administrative Procedures Act.

CASAC Review Panels report via the CASAC, and the chartered CASAC must review and approve advisory letters from CASAC to the Administrator. Furthermore, as illustrated in the comments below, removing experienced experts from CASAC and its augmented panels does not make reviews "more efficient."

Two of the current seven members of CASAC were appointed in 2017, and five were appointed in 2018. In the past, members typically served two three-year terms and terms overlapped, such that typically one one or two members were replaced each year. The unprecedented high rate of turn-over in the last two years means that the current CASAC panel is inexperienced and unfamiliar with well-established procedures. Lack of experience and lack of familiarity leads to an inevitable learning curve that leads to inefficiencies.

Furthermore, with the larger augmented panel the workload for review of a document such as an 1800+ page draft ISA would be distributed over a larger group of experts, which is a more time-efficient manner in which to conduct a review of such a large document. The lack of breadth and depth of expertise of the current chartered CASAC also means that it cannot authoritatively address many of the key scientific issues that are critical to the ISA, which is another form of inefficiency in a scientific review process.

Given the lack of breadth and depth of expertise of the current seven member CASAC, and the arbitrary and capricious disbanding of the CASAC PM Review Panel, the current review activities of CASAC are not consistent with language in the Clean Air Act regarding the needed scope of review, nor is the current

[6] United States Environmental Protection Agency Charter, Clean Air Scientific Advisory Committee, Filed with Congress June 5, 2017, https://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/2017casaccharter/$File/CASAC%202017%20Renewal%20Charter%20Filed%206-5-17.pdf

review consistent with four decades of well-established precedent regarding augmenting CASAC. The latter is especially problematic in the likely event that the Agency is challenged with judicial review regarding departures from established operating procedures under the Administrative Procedures Act.

2.11. EPA is Doing Systematic Review Appropriate to the Subject Matter

With regard to systematic review, Dr. Vandenberg of EPA described that EPA does "systematic review, but have not used the same terminology about it that has been used in other venues. He stated that they do an evaluation of the science, identify the most policy-relevant studies, review those studies very carefully, and characterize them in the tables in the ISA. They do not do a point-by-point evaluation that sometimes is done in the systematic review of some of the Integrated Risk Information System (IRIS) assessments." Another key point is that there is a difference between systematic review of controlled studies, such as animal bioassays that are often a focus of IRIS assessments, and systematic review of observational studies related to air quality and the general public or at risk populations or lifestages, for which there is inherently much more variability in study design and other factors. While it is desirable to have clear and transparent explanations of causal determinations, it is inappropriate to develop study "quality" criteria that would be used to throw out studies that have useful information despite limitations.

2.12. CASAC is Ignoring Its Own Advice on the Integrated Review Plan

In issuing instructions to CASAC, Dr. Cox stated that "evaluation includes systematic review, evaluation included study quality criteria, and characterization included uncertainty." However, there was no acknowledgment that the ground rules for the current review cycle were reviewed by CASAC in 2016 as part of CASAC's review of EPA's Draft Integrated Review Plan for this review cycle. Procedurally, CASAC failed to acknowledge its own prior advice on the systematic review approach. While *a priori* criteria for study selection may be appropriate in scientific disciplines that are based on controlled studies, they are far more challenging to develop for observational studies that are characteristics of air pollution epidemiology. Every air pollution epidemiologic study has limitations but many also offer strengths and valuable information. To prevent discarding potentially useful information, it is premature to impose restrictive study "quality" criteria. This does not mean that the characteristics of individual studies should not be, or have not been, considered when evaluating their relevance to making inferences regarding causality and regarding concentration-response functions. It is not necessary to the NAAQS review to rate studies in terms of "quality" but rather it is relevant to evaluate them in terms of relevance. It is not uncommon that CASAC comments on a first draft of an ISA will include requests to EPA staff for more clarity and transparency of what factors were considered interpreting studies with regard to causal determination, at risk populations and life stages, and the shape of concentration-response functions.

2.13. CASAC Exists to Advise EPA Not the Chair

"Dr. Cox indicated that a few weeks prior to the meeting, he asked the CASAC to consider additional supplemental questions pertaining to treatment of exposure estimation errors, adequacy of lags and of modeling for lagged effects, control for latent variables, modeling of interactions and dependencies among explanatory variables and between explanatory and risk variables, treatment of manipulative causality, clear definition and quantification of direct, mediated, and total causal effects for causal concentration-response functions, treatment of inter-individual variability and heterogeneity in causal concentration-response functions, and uncertainty characterization."

It is highly unusual and inappropriate for the chair of CASAC to, in effect, create their own set of charge questions, as was the case in the undated "CASAC Chair Memo to Chartered CASAC". Although the memo is undated, the file name includes "10302018" which implies it may have been issued on October

30, 2018. However, it was not publicly disclosed until December 12, 2018 and thus members of the public did not have an opportunity to consider this memorandum in deciding whether to prepare public comments. The content of this memo, and the failure to provide this memo publicly in a timely manner, is inconsistent with proper operating procedures of CASAC.

It is inappropriate for an individual member of the CASAC, including the chair, to issue detailed questions for the other members of CASAC. CASAC does not exist to answer questions posed by the chair. CASAC exists to provide advice to EPA. EPA formulates charge questions and CASAC is expected to address the charge questions. CASAC may offer other advice as it deems appropriate. CASAC members are nominally expert scientists and can judge for themselves regarding what are the key scientific issues to consider in formulating their own comments. Members of CASAC should be informed that they have no obligation whatsoever to answer the ad hoc questions that were posed by the chair.

Furthermore, the instructions given by the chair have the effect of subverting CASAC away from the scope of review implied by Congress in the Clean Air Act.

2.14. There Is No Evidence of a Non-Zero Threshold

"Dr. Jennifer Richmond-Bryant, EPA NCEA, "indicated that a single concentration-response relationship is not useful to suggest causality by itself." "To address Dr. Cox's comment that exposure error causes the response to be underestimated at high concentrations and overestimated at low concentrations, this assumes a non-zero threshold. However, she said that there are no identified studies that demonstrate a non-zero threshold." Although some members of CASAC have questioned this inference, those members of CASAC have not provided any evidence that there is a threshold other than based on opinions that are not supported by scientific evidence.

2.15. CASAC Has Previously Deliberated and Offered Advice Regarding the Role of Statistical Significance in Making Inferences

Dr. Lange stated that the "*There was not much discussion about chance and the document is missing consideration of statistical significance.*" In prior reviews, CASAC has deliberated and offered advice regarding the general issue of statistical significance. Current members of CASAC may find the outcome of those deliberations in previous CASAC reports.

2.16. EPA Should Reinstate the Arbitrarily and Capriciously Disbanded CASAC PM Review Panel

Dr. Cox stated that "CASAC should recommend that it be given access to whatever expertise it needs to provide the best review possible." It is puzzling why the chair of CASAC has not simply stated that EPA should reinstate the CASAC PM Review Panel. In contrast, the chair of CASAC expressed interest in ad hoc approaches to engaging experts. The middle of a review cycle is not the time to change established administrative procedures. When an agency fails to observe well-established procedures and engages in ad hoc approaches, it becomes susceptible to judicial review under the Administrative Procedures Act. There is a very simple solution here: reinstate the CASAC PM Review Panel.

"Dr. Boylan added that not only should there be breadth of expertise added, but also depth of expertise added, for more than one expert per discipline." However, this is not mentioned in the letter.

"Drs. Frampton and Lewis both agreed on the need for additional expertise and suggested reinstating the previous CASAC PM panel." This was not a suggestion. It was a strong recommendation. These recommendations are not adequately reflected in the draft CASAC letter to the Administrator.

2.17. Inexperienced CASAC Members Need to Understand Meaning of "Consensus": Speak Up If You Do Not Agree with the Chair or Other Members

"Mr. Yeow clarified that the CASAC's main job was to develop consensus responses to the charge questions." The term "consensus" is different in the context of CASAC than its general usage. A "consensus" response can and should include representation of disagreements or diverse viewpoints in cases for which the CASAC did not arrive at a unanimous response. Individual members of CASAC must understand that if they disagree with a statement made by another member, including the chair, they must speak up. **The Chair and DFO should explain to the CASAC members the ground rules regarding how consensus is inferred**. If one member makes a statement at a public meeting, and no other member says anything about it, is that considered to be a consensus response?

2.18. Definitions and Practical Reality

In response to a comment by Dr. Packham regarding more clarity in the definition of adverse effect, Dr. Frampton "*indicated that these issues were not resolved and probably never would be resolved and that he did not find a problem with it not being resolved in the Draft ISA. He did not find any problems with the causality framework that the EPA has used in the Draft ISA."*

This perspective of at least one CASAC member regarding lack of problems with the causality framework is NOT accurately reflect in CASAC's draft report. Specifically, **CASAC cannot imply as a matter of consensus that all members agree with strident statements in the draft letter such as "lack of scientific method" if individual members have made clear statements to the contrary that are not accurately reflected by such a statement**.

Secondly, questions of definitions have been grappled with by EPA and CASAC for many years. The question of what is an "effect" versus what is an "adverse effect" is an important one that CASAC has deliberated on numerous times in my experience. As was mentioned in the discussion, the American Thoracic Society offers its recommendation the distinction between these two terms with regard to lung function and typically CASAC has referred to and adopted the same perspective. If this CASAC wants to engage in development of a detailed glossary for this and other terms, it could spend the remainder of this review cycle and beyond in so doing, leading to delays and paralysis. As a practical matter, it will be more fruitful to recognize that there is a role for judgment in developing and communicating scientific interpretations.

2.19. Dr. Cox's Causal Definitions are Not Helpful and They "Obfuscate"

Dr. Cox presented his comments on the executive summary and Chapter 1, but there is little record of deliberation on these comments. Dr. Frampton stated that he "did not find that the causal definitions introduced by Dr. Cox to be helpful in understanding what is going on and felt they just obfuscate and would lead to confusion if included in the ISA." However, there is no indication of the viewpoint offered by Dr. Frampton in CASAC's draft letter. Thus, CASAC's draft letter is not an accurate depiction of CASAC's deliberation or advice.

2.20. Congress Has Decided on the Decision Context of the NAAQS Review

"Dr. Cox stated that decision makers need to know about manipulative causation because they are in charge of manipulation." However, Dr. Cox did not refer to the statutory language of the Clean Air Act that sets forth the decision context of the NAAQS. The decision context of the NAAQS is determined by Congress via the Clean Air Act, not by the chair of CASAC (See Section 2.1 for details).

2.21. CASAC Should Follow Well-Established Procedures, Not Ad Hoc Approaches, to Engaging Experts

"If after deliberation they felt they needed to ask specific scientific questions from outside experts, he asked them to work through him, as the DFO, to ensure that the requirements of FACA are met." It is highly unusual that members of CASAC would be encouraged to get answers to scientific questions from outside experts. In a situation for which CASAC and its review panels comprise the needed breadth and depth of experts, such ad hoc departures from past practices would not be needed. Within the rules of FACA, members of CASAC and of augmented CASAC Review Panels can have communications. Among the advantage of having an augmented review panel is that the members of the augmented panel, like the members of the chartered CASAC, are appointed as Special Government Employees and are subject to the same ethics requirements as CASAC members.

2.22. CASAC Members Should Read Prior CASAC Reports to Avoid Rehashing Well-Resolved Issues

"Dr. Lange indicated that it would be helpful to differentiate susceptibility, vulnerability, intrinsic factors, and extrinsic factors. Are they at risk because of increased exposure or innate vulnerabilities?" These types of issues have been debated numerous times by prior CASAC panels. Current members of CASAC are encouraged to read past CASAC reports which may help avoid inefficient use of CASAC public meeting time on matters that have been thoroughly deliberated in the past.

2.23. CASAC Deliberations Do Not Support Strident Statements in CASAC's Draft Letter

The minutes do not indicate mention of, much less deliberation regarding, very strong statements that have been introduced into the draft letter by CASAC. For example, there was no deliberation that led to agreement on points such as (these examples are from page 1 of the draft letter report):

- Lines 32-34: "the Draft ISA does not provide a comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to fine particulate matter"
- Lines 34-35: The Draft ISA does not "follow widely accepted scientific methods for deriving sound, independently verifiable, scientific conclusions from available data."
- Lines 38-39: "Lack of comprehensive, systematic review. Much of the relevant and important scientific literature is not reviewed."
- Lines 40-42: "Lack of scientific method and of verifiable derivations of conclusions. The Draft ISA and its key references do not follow standard scientific method by formulating, testing, modifying, and applying predictive hypotheses based on data."

These are just examples. As detailed elsewhere, there are many statements in the letter that cannot be traced to a consensus of the CASAC or to public deliberations. Some of the statements were simply never made during CASAC's meeting on December 12-13, 2018. Other statements might have been made by one person but there was not explicit agreement on such statements from all members of the CASAC. It is not clear that CASAC members had any understanding that if one member made a statement and no one said anything in response, then that statement would be interpreted as unanimous consensus of the entire CASAC. Several CASAC members were largely silent on many issues and may not have understood that they should say something if they disagreed with a statement made by others.

3. Key Points from CASAC's March 2019 undated Draft Letter Regarding "CASAC Review of the EPA's Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)"

This section is based on review of CASAC's draft letter to the Administrator, with attached "consensus" responses to charge questions, regarding "CASAC Review of the EPA's Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018)".[7]

3.1. The Draft ISA Provides a Comprehensive and Systematic Assessment

Page 1, Page 1: Lines 32-34: "the Draft ISA does not provide a comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to fine particulate matter"

This statement is unfounded and inaccurate.

The Draft ISA is a document of over 1,800 pages. The Draft ISA cites approximately 2,800 references, most of them new since the 2009 ISA. The Draft ISA follows the methodology set forth in the Preamble to the ISAs, the 2016 Integrated Review Plan for Particulate Matter, and the preface to the draft ISA. CASAC fails to acknowledge these basic points, which undermines the credibility of CASAC's statement. Any reasonable observer readily concludes that the Draft ISA does in fact provide a comprehensive and systematic assessment of broad scope. The Draft ISA is based on a literature review of tremendous scope and comprehensive and systematic assessments that take into account a great many factors. While there may be ways to improve the document, it is unfair to EPA scientific staff to offer such a sweeping and dismissive characterization of their work.

The Draft ISA addresses available science related to health impacts of exposure to particulate matter, including ultrafine particles, fine particles, and coarse particles.

Based on other comments from this current seven member group of CASAC (see below), the argument offered in CASAC's draft letter that the Draft ISA is not "comprehensive" seems to boil down to an assertion that the EPA failed to cite 14 HEI papers or reports plus "over a dozen" other papers related to inflammasomes.

It is possible to communicate a desire for a revision without unduly slamming EPA staff, who have worked hard in good faith and have produced an outstanding first draft ISA. No first draft of an ISA is ever perfect. I've served on ten CASAC review panels and the public record demonstrates that I have had critical things to say about many draft documents. I personally commend the staff for their hard work and the quality of their effort. The staff are used to hearing criticisms and accept well-founded criticism professionally and with appreciation, because they want the final ISA to be the best possible product that they can produce (given resource constraints). CASAC should exercise a higher degree of professionalism in formulating its comments.

This statement should be rewritten as follows:

"The CASAC commends EPA staff for development of an excellent first draft of the ISA that provides comprehensive and systematic assessment of the available science relevant to understanding the health

[7] 03-07-19 Draft CASAC Review of the EPA's Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018), https://yosemite.epa.gov/sab/sabproduct.nsf/ea5d9a9b55cc319285256cbd005a472e/fe50d8fd06ea9b17852583b6006b7499!OpenDocument

impacts of exposure to particulate matter. The CASAC recognizes that the 1800+ page Draft ISA cites over 2,800 references, most of them new since the last review cycle. The Draft ISA follows methods previously reviewed by CASAC, including the approach to literature review, the causal determination framework, the framework for assessing at risk populations and lifestages, and assessment of concentration-response functions, consistent with the Preamble to the ISAs and the 2016 Integrated Review Plan for the current review cycle. However, as with any first draft, the CASAC recommends some revisions. We recommend that EPA staff consider a list of accountability studies recently provided by HEI with respect to policy-relevance and, if policy relevant, assess their importance."

There seems to be some disagreement among CASAC members regarding whether the dozen or so papers regarding inflammasomes cited by Dr. Cox should be mentioned in the letter or charge question responses. If they are mentioned, they could be mentioned in a similar vein.

3.2. The Draft ISA is Based on a Comprehensive, Systematic Review

The CASAC has failed to demonstrate that the Draft ISA is not a comprehensive and systematic assessment. It is clearly the first draft of such an assessment, and it is comprehensive and based on a specified methodological approach. Specifically, the Draft ISA was developed according to principles articulated in the Preamble to the ISA's that have been vetted and reviewed by prior CASACs numerous times over the last decade, including (most recently) by CASAC in 2016 with regard to the Integrated Review Plan for the current review cycle. While this CASAC may have opinions about other ways to develop an Integrated Science Assessment, this does not mean that the review conducted by EPA was not based on previously identified factors and previously developed procedures. Furthermore, as noted in public comments and by EPA staff on December 12, 2018 at CASAC's public meeting, the concepts in the Preamble to the ISAs have been reviewed and vetted by a far larger group of experts, with far more relevant expertise, than this current seven member CASAC.

In their draft letter, the CASAC repeatedly offers advice regarding systematic review. It is not clear that such advice is a unanimous consensus of the CASAC. I do not recall that CASAC reached consensus regarding systematic review at its December 12-13, 2018 meeting. During that meeting, EPA staff indicated that the ISA is based on a form of systematic review, and that over time they intend to modify the review procedure to continually adopt lessons learned from the application of systematic review in other areas.

Systematic review in scientific areas that deal with air pollution epidemiology is far more challenging and less mature than in areas that deal with controlled studies. While it is desirable to ensure consistency and transparency in how reviews of epidemiologic studies are done, systematic reviews of air pollution epidemiology should not be based on prematurely posited and poorly grounded arbitrary rules that have the effect of excluding studies that have informational value in scientific assessment. There is no such thing as a perfect epidemiologic study. This is precisely why the long-established methodology of the ISAs is to review the overall body of evidence based on multiple studies. For example, some studies may address a particular confounder or effect modifier but not another confounder or effect modifier, or may do so in a better manner than other studies. Yet, another study may likewise address some feature that is a shortcoming of the first. Moreover, individual studies might not have enough variability in the ambient levels of co-pollutants to assess an independent effect of PM, but comparisons of many studies with different levels of co-pollutants can lead to a more robust inference. (And so on). Should each and every epidemiologic study be thrown out if it does not individually fully address every possible confounder or effect modifier? Obviously not. Furthermore, the relative contribution of a particular study to the overall

body of knowledge depends on what is known from other studies. Thus, it does not make sense to apply study-by-study scoring as a means to inappropriately throw out individual studies.

CASAC advice regarding systematic review and study "quality" should be revised substantially. Before finalizing advice on the Draft IRP, CASAC should be augmented with the reinstated CASAC PM Review Panel to have the needed breadth and depth of expertise, and diversity of perspectives, needed for deliberations on systematic review methods that are appropriate to the PM ISA. CASAC should also engage in dialogue with EPA staff regarding what can and cannot reasonable done in this review cycle with regard to incremental modifications to procedures for study selection and systematic review, to the extent that any such modifications are warranted. For example, EPA staff may have suggestions for relatively straightforward things that could be done and could discuss trade-offs regarding an IRIS-like systematic review. Such trade-offs might include time and resource implications with respect to the value-added of implementation. Discussions and deliberations on systematic review should take into account that systematic review of air pollution epidemiologic studies is not as amenable to a "cookbook" approach as might be the case for controlled studies. Furthermore, changes to the systematic review process should not be a subterfuge for throwing out relevant studies. Ultimately, CASAC provides advice but it does not dictate precisely what EPA staff must do, particularly if CASAC's advice is poorly grounded or poorly formulated. The current CASAC is not qualified to offer recommendations for broad changes to the study selection and systematic review process given its lack of breadth, depth, and diversity of needed expertise. Thus, such deliberations should be postponed until CASAC is augmented with the reinstated CASAC PM Review Panel.

3.3. EPA Has Created High CASAC Member Turnover While Also Disbanding the CASAC PM Review Panel, Leading to the Predictable Problems of Lack of Member Experience and Lack of Appropriate Breadth and Depth of Expertise

Current members of CASAC were appointed in 2017 and 2018, representing an extraordinarily high level of member turnover that renders this as the most inexperienced CASAC to review a Draft ISA. Furthermore, given the arbitrary and capricious disbanding of the CASAC PM Review Panel and the lack of adequate breadth and depth of expertise of the current CASAC, this is the most unqualified CASAC to review a Draft ISA. To some extent, the CASAC admits and recognizes its lack of expertise and offers recommendations for "access" to additional experts. However, the CASAC fails to address this deficiency appropriately and adequately.

CASAC should include a very clear paragraph in the letter to the Administrator as follows:

"CASAC received extensive public comments regarding the decision by EPA to disband the CASAC PM Review Panel just days before the Draft ISA was released for review by CASAC. For four decades, and consistent with its Charter, CASAC has been augmented with additional experts in the form of review panels. These panels report through the chartered CASAC. Thus, CASAC is the body, as mandated by statute, that provides advice to EPA, not any of its panels. Nonetheless, the panels are critical to providing CASAC with the breadth and depth of expertiseand diversity of perspectives required to meet the statutory mandate of the Clean Air Act for a review that "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities" for pollutants that "cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare." Furthermore, the panels provide diversity of perspectives in key scientific disciplines that are required to ensure that key issues are thoroughly considered to avoid motivational biases. Therefore, we recommend that the CASAC PM Review Panel be re-instated in time for the panel

to augment CASAC for the review of the Second External Review Draft of the ISA and subsequent documents in this review cycle."

3.4. The PM NAAQS Review Cycle Was Already In Progress. CASAC Should Not Ignore Its Own Advice.

The CASAC fails to acknowledge that they are joining a review cycle that was already in progress before any one of the seven existing members were appointed to the CASAC. The PM review began in 2015 with the appointment of CASAC PM Review Panel that reviewed the Integrated Review Plan for Particulate Matter in 2016 (details are given in the letter by Frey et al. (2018) submitted as public comment to CASAC on December 10, 2018 and to the ISA Docket). The results of that review were reported via the chartered CASAC to the EPA Administrator. As a matter of proper administrative procedure, the EPA must follow its own procedures in a consistent matter. The chartered CASAC has previously reviewed and provided advice regarding the methodology for how the Draft ISA should be developed in 2016. Yet, in 2019, the chartered CASAC is now attempting to change the fundamental ground rules in the middle of a review cycle. This is not consistent with any reasonable procedure for how CASAC should conduct its own business. The CASAC fails to reference its own advice regarding the Integrated Review Plan or to explain why CASAC should change its advice regarding the methodology of the PM review midstream in the middle of a review cycle.

Some have argued that because the membership of CASAC is different now than it was in 2016 when CASAC reviewed EPA's Draft Integrated Review Plan for the current review cycle, that it is fair game for CASAC to recommend sweeping changes to the methodology for development of the ISA. This argument is problematic from a procedural perspective. The implication of this argument is that any time current EPA political leadership does not like the advice it has received, it can just replace membership until it gets the answer it wants. Agencies must consistently follow their own procedures. The IRP becomes meaningless as a step in the NAAQS review process if it can be set aside on the whim of changing advice of a reconstituted CASAC. Furthermore, it is arbitrary and capricious to change the ground rules in the middle of the review process for how the ISA should be developed. Finally, despite statements by the current CASAC chair that he wants to help the EPA administrator achieve the goal to complete the review of the PM standard by 2020, advising on major changes in the process by which the ISA should be developed and how information should be interpreted will, if accepted by EPA, lead to delays in the review process. In the meantime, EPA must comply with the Clean Air Act as described in detailed by Frey et al. (2018) and in Section 2.1 of these comments.

CASAC should incorporate into its report information that clearly indicates that CASAC is aware of and understands the IRP for this review cycle. CASAC lacks the needed breadth, depth, and diversity of expertise, and therefore credibility, necessary to consideration of methodological issues with broad multidisciplinary implications such as controversial changes to ground rules for study selection and systematic review. CASAC should not attempt to go beyond its competence. The arbitrarily and capriciously disbanded CASAC PM Review Panel, which has the necessary breadth, depth, and diversity of expertise, should be reinstated to enable CASAC to more credibly address, as appropriate, such issues.

Ultimately, CASAC provides advice but it does not dictate what EPA staff must do, particularly if CASAC's advice is poorly grounded or poorly formulated and if CASAC's advice is contradictory to its own prior advice and to existing groundrules of the review cycle.

3.5. The Draft ISA Follows Widely Accepted Scientific Methods for Inferring Causality and Characterizing the State of Science

Page 1, Lines 34-35: The Draft ISA does not "follow widely accepted scientific methods for deriving sound, independently verifiable, scientific conclusions from available data."

This statement by the current seven member CASAC is unfounded. First of all, it is not at all clear that this is a consensus opinion of all seven members of CASAC. This statement is extremely arrogant, considering that it is directed to an EPA staff comprised of expert scientists, and relates to a causal determination framework that has been vetted by nationally and internationally recognized experts in the multiple disciplines required for a review of this type who have served on CASAC and its review panels over the last dozen years. As noted elsewhere, the causal determination framework is similar to that used by other agencies. **This current seven member CASAC is far less qualified to offer advice regarding scientific methods and the state of science than any prior CASAC or CASAC Review Panel**.

The Draft PM ISA is explicitly concerned with the central hypothesis that pollutant A independently causes adverse effect B for short or long term exposures at levels comparable to or lower than the current applicable National Ambient Air Quality Standards, or current levels of air pollution for not yet regulated pollutants of concern. In recognition of the reality that available scientific information in any individual study is not always definitive, EPA staff follow a previously developed, vetted and systematic causal determination framework for testing this hypothesis based on weight of evidence of the body of information currently available. The causal determinations are assigned to categories depending on the nature and strength of the available evidence. This is a well-established and accepted practical approach that is based on integrative consideration of evidence across various disciplines such as toxicology, controlled human studies, and epidemiology. There is explicitly a role for expert judgment in this process (see later comments for more discussion about "objectivity" versus "judgment" in science). This approach was reviewed and accepted by CASAC in numerous prior reviews, including this review cycle (see CASAC advice on the Integrated Review Plan). Furthermore, **this review approach is consistent with the statutory mandate of the Clean Air Act**.

Given that the current seven member CASAC lacks epidemiologists, is deficient in other ways in terms of lack of adequate breadth and depth of expertise and diversity of perspectives as noted in prior public comments (e.g., see letter by Frey et al., 2018 and other public comments), and therefore does not have the requisite scientific expertise to conduct this review, it is ironic that CASAC is characterizing others as being unscientific. **As a group, this seven member CASAC is not adequately qualified to conduct a review for which epidemiology is a central and key discipline**.

CASAC is ignoring the origins of the current causal determination framework and its widespread use not just in NAAQS reviews over the last decade but similar frameworks by other agencies for other public health assessments. CASAC has been presented with this history by EPA staff and by public commenters at its December 12-13, 2018 meeting, and by EPA staff in the form of the Draft ISA itself, but chooses to ignore it. **CASAC had the opportunity to review and provide advice on the methodology of the ISA in 2016 when CASAC provided advice to the EPA on the Integrated Review Plan**.

CASAC members may avail themselves of the on-line archive of prior CASAC reports to the Administrator to review for themselves the track record of CASAC review and advice of the causal framework and other elements of ISAs. Given that the framework has been extensively developed and used in the context of NAAQS review, and is similar to frameworks in use by other agencies and organizations, in fact the well-vetted causal determination framework as embodied to the Preamble to the

ISAs is a "widely accepted scientific method[s] for deriving sound, independently verifiable, scientific conclusions from available data."

Therefore, the language of CASAC's letter should be changed to the following:

"CASAC finds that EPA staff have followed the framework for causal determination that has been developed over the last decade. This framework is similar to that from other agencies and has been reviewed by over 60 experts on CASAC and CASAC review panels. This is a well-established, accepted, and appropriate practical approach that is based on integrative consideration of evidence across various disciplines such as toxicology, controlled human studies, and epidemiology. There is explicitly a role for expert judgment in this process. However, given the important role of expert judgment, it is also important that the ISA explain as clearly and transparently as possible the basis for judgments regarding causal determination." Some specific examples where more transparency may be needed could be mentioned, such as regarding the causal determination for UFPs and central nervous system effects.

3.6. "Much" of the "Relevant" and "Important" Literature is "Not Reviewed": Much = two dozen references? Out of Over 2,800 references? Policy Relevant? If Relevant, Important?

Page 1, Lines 38-39: "Lack of comprehensive, systematic review. Much of the relevant and important scientific literature is not reviewed."

As noted above and detailed below, this comment by the current seven member CASAC seems to be predicated on the notion that EPA staff did not cite ~26 reports and papers that are mentioned later in CASAC's draft letter. See comments below for more details. **CASAC's characterization that ~26 references compared to over 2,800 already cited constitute "much" of the "relevant" and "important" literature is highly exaggerated and not justified**. While perhaps these references may later be found to be "relevant" and "important," it is premature to make such a claim given that CASAC has not established that these references are policy-relevant or important. As explained in the Preamble to the ISAs, part of the systematic process for conducting the assessment in the ISA is a well vetted procedure for literature review that focuses on the concept of "policy-relevant" science. In its public deliberations, this seven member CASAC had not identified these ~26 papers and reports, much less established that these ~26 papers and reports are policy-relevant . It is further not yet clear if any of these references, even if policy-relevant, are important.

CASAC should change this wording to the following:

"Comprehensive, systematic review: EPA staff have commendably prepared an excellent first draft of the ISA and appropriately applied the methodologies described in the Preamble to the ISAs, the Integrated Review Plan, and the Preface of the ISA regarding literature review, causal determination, evaluation of at risk populations and life stages, and assessment of implications of the existing literature regarding what is known about the shape of concentration-response functions. However, we have specific recommendations for additional studies that EPA should review for their policy-relevance and potential importance." (some detail could follow, if based on public deliberations).

3.7. Everyone Else is Unscientific?

*Page 1, Lines 40-42: "Lack of scientific method and of verifiable derivations of conclusions. The Draft ISA **and its key references** do not follow standard scientific method by formulating, testing, modifying, and applying predictive hypotheses based on data." (emphasis added).*

This is a sweeping generalization that simultaneously impugns EPA staff, all prior CASAC reviews in the last decade, and the large number of researchers whose work is cited in the ISA. However, perhaps more importantly, as a careful observer of the December 12-13, 2018 public meeting of the CASAC, **I cannot recall any public deliberation that would be a basis for this comment**. Thus, **procedurally, this statement is not allowable, because it does not represent a consensus that emerged from interactive public deliberation**. Scientifically, this statement is baffling since the ISA by its very design deals with important policy-relevant science questions.

CASAC members who disagree with these hyperbolic, strident, and unhinged statements should speak up.

In particular:

- The Draft ISA is based on testing hypothesis regarding causality, as noted above.
- The Draft ISA also tests hypotheses regarding concentration-response functions (e.g., linear, no threshold). While there may be various ways to test hypotheses, just because a document does not follow a particular reviewer's preferred approach does not mean it does not give attention to exploring hypotheses.
- The Draft ISA is based on a well-established, well-vetted methodology for causal determination.
- The Draft ISA is based on well-established scientific practice regarding assessment of concentration-response functions.
- "Key" and other references are based on hypothesis testing or data motivated by a hypothesis (e.g., "exposure to pollutant A causes effect B…" and others). If CASAC wants to argue that key references are unscientific, then they should provide a systematic and thorough critique to support this sweeping generalization. Which studies are not scientific, and on what basis?
- As noted above, this statement is not allowable because it has not emerged as a result of deliberation by CASAC in public that lead to a clear finding that this statement is a consensus of all seven members of CASAC.
- The term "standard scientific method" appears to be a loaded term. Scientific work includes a variety of methodologies, such as computational simulation, controlled experiments in a laboratory, and field observations in the real-world. While all of these methods can be described in terms of hypothesis testing, the particular ways in which research is conducted and inferences are made depend on the inquiry. Furthermore, it is not the role of the ISA to engage in making predictions. The ISA is a review of the current state of policy relevant science. Risk and exposure modeling takes place in the Risk and Exposure Assessment, not the ISA.
- CASAC does not have the right mix and depth of expertise, and diversity of perspectives within key disciplines, to make such a statement.

CASAC should simply drop this statement from the letter.

3.8. Terminology and Principles

Page 1, Lines 42-44: The Draft ISA does not provide clear operational definitions or systematically apply explicitly stated principles for drawing conclusions from data and studies."

This statement is mostly if not entirely untrue. EPA employs operational definitions and EPA systematically applies explicitly stated principles for drawing conclusions from data and studies.

While there may be some opportunities to clarify or refine definitions of some terminology, it is simply not the case that the Draft ISA lacks explicitly stated principles for drawing conclusions or lacks

operational definitions. For example, the various considerations in developing causal determinations are explained in the Preamble to the ISAs and have been considered already in CASAC's review of the Draft Integrated Review Plan. The terminology for this framework has existed for many years and has been widely vetted and applied operationally for many years. While there may be opportunities for EPA staff to improve the clarity and transparency of the explanations of the inferences it makes and the conclusions it draws, this is not a fundamental limitation of the underlying framework but rather a matter of routine scientific review and iteration to improve the clarity and transparency of the final document.

As detailed in comments I have provided previously to CASAC, there is a clear written record that CASAC advice regarding draft ISAs has transitioned over the years from improvements to the definitions and framework itself toward advising EPA to apply the framework transparently. CASAC has ignored my prior comment on this very point. This track record demonstrates that the causal determination framework is 'operational' and thus that it is based on operational terminology. If CASAC now wants to offer advice to refine definitions or the framework, it should consider doing so in a practical and incremental manner that does not unduly exclude scientific evidence nor interfere with completion of the ISA with a scope that is consistent with requirements of the Clean Air Act. As noted elsewhere in these comments, this CASAC is poorly qualified to undertake revisions to a framework that is multidisciplinary and that involves key disciplines that are not adequately represented on the current CASAC.

Furthermore, it is not clear that this statement was a consensus of the seven member CASAC. Based on my observations during the December 12-13, 2018 meeting, I do not recall that all seven members of CASAC agreed to this statement. In fact, the contrary. **I recall that some members of CASAC expressed support for the current framework for making causal determinations**. **These views are not represented in the text of CASAC's draft letter**. **Thus, the draft letter is not an accurate reflection of what was deliberated in public**. **Therefore, this statement as written is not allowable**.

The CASAC should withdraw this statement, or should narrow and refine it so that it does not over-generalize, and so that it more accurately and specifically communicates a clear recommendation to EPA staff. CASAC is also encouraged to engage in some dialogue with EPA staff before finalizing the letter to assess the timing and resource implications of this advice if CASAC intends to include some form of this statement in its final letter.

Ultimately, CASAC provides advice but it does not dictate precisely what EPA staff must do, particularly if CASAC's advice is poorly grounded or poorly formulated and if CASAC's advice is contradictory to its own prior advice and to existing groundrules of the review cycle.

3.9. Congress Intended for EPA and CASAC to Use Judgment

Page 2, Lines 1-4: "Use of unverifiable opinions to draw major policy-relevant conclusions. The Draft ISA's major conclusions rest on subjective judgments expressed in vague and undefined terms. They are not transparently verifiable (or falsifiable) scientific statements that can be determined to be true or false by other independent scientists."

This statement as written was not deliberated in public among the members of the chartered CASAC. On the other hand, if CASAC members disagree with this statement, they must say so in public.

Aside from the procedural irregulatory of attempting to introduce into the letter sweeping generalizations that do not represent consensus and that lack support from public deliberation, the statement itself is poorly grounded.

In a public comment that I made on December 12, 2018, I recommended that CASAC ask EPA's Office of General Counsel for advice regarding the meaning of the Clean Air Act pertaining to the statutory mandate for the NAAQS and CASAC. CASAC should avail itself of this resource since it is evident that this seven member CASAC is unaware of the meaning of language in the Clean Air Act and its applicability to how CASAC should conduct its work. In fact, it is the statutory role of CASAC to formulate policy-relevant advice based on its expert judgment. The Federal courts recognize that CASAC may exercise reasonable scientific judgment.

CASAC has on many occasions provided feedback to EPA staff that the reasoning behind key findings, such as causal determinations, need to be more communicated more transparently. Thus, it is not unusual that in a draft ISA, comments may emerge along these lines. However, this does not mean that the final document would not be transparent or that the method for reaching findings is unscientific.

This CASAC appears to be focusing on developing laundry lists of as many deficiencies of as many studies as possible, as a strategy to raise doubt. However, this CASAC has not simultaneously, in an even-handed and unbiased manner, considered the strengths of various studies. In some cases, the limitations and doubts are legitimate, but unless they are accompanied by consideration of the potential strength and value of each study, or the strengths as well as limitations of the overall body of evidence, then what CASAC is veering toward is a denialist rhetorical and semantic charade aimed at unduly undermining an accurate and appropriate interpretation of the overall body of evidence.

A desired outcome of the ISA is that scientific readers can understand the scientific evidence and inferences from which EPA staff reach their conclusions, as clearly and transparently as reasonably possible. Judgment is inevitably involved in study selection, study evaluation, and inferences.

With regard to the general topic of expert judgment, which is additionally touched upon in the draft attached responses to charge questions, it seems that CASAC is not taking into account well established principles of expert elicitation. One key principle is that there must be a "conditioning" step based on a thorough review of all relevant scientific information. It is well-known that the conditioning step is enhanced based on knowledge of a large and diverse group of experts, who represent the full range of relevant disciplines and diversity of perspectives within disciplines. This is precisely why it has been a routine and properly established practice for three decades to augment CASAC with review panels that contain experts in disciplines relevant to each assessment, and that contain multiple experts in key disciplines to assure diversity of knowledge and inference methods will be available in deliberations.

Thus, this statement should be withdrawn and replaced with the following:

"Consistent with the statutory mandate of the Clean Air Act, the EPA and the CASAC must consider the wide range of the kind and extent of possible health effects that may accrue from exposure to criteria air pollutants. Although a portion of the scientific evidence can be established with a high degree of confidence and certainty, in other cases the CAA asks EPA and CASAC to make judgments for situations in which the science is incomplete. Thus, inevitably, portions of the Draft ISA rest on expert judgments. Such judgments should be explained so that scientific readers can understand the scientific evidence and inferences from which EPA staff reach their conclusions, as clearly and transparently as reasonably possible. CASAC is currently poorly positioned to provide expert judgment because it has been deprived the CASAC PM Review Panel. A key tenet of development of scientific expert judgment is to share information among a diverse group of experts across disciplines and to have diversity of opinion of multiple experts in key disciplines. Thus, EPA should reinstate the CASAC PM Review Panel."

CASAC should reserve judgment on many issues for which it lacks adequate competence until it is augmented with the reinstated CASAC PM Review Panel.

3.10. Congress, Not CASAC, Decides on the Decision Context for NAAQS Review.

Page 2, Lines 5-7: "Lack of scientific support for policy deliberations and decision-making. The Draft ISA provides no empirically validated predictions or implications for how or whether possible future changes in particulate matter (PM) exposures would change public health risks."

The CASAC should follow the advice that I provided to avail themselves of the opportunity to obtain advice from the EPA Office of General Counsel regarding the statutory mandate of the Clean Air Act for the NAAQS review and for CASAC. Other legal experts are encouraged to provide public comment to CASAC to help inform this highly inexperienced group regarding the legal and policy context of this review. The decision context of the NAAQS is to "protect public health" with an "adequate margin of safety." The language related to "protect public health" has context that does not require complete scientific certainty. Inferences of adequate margin of safety are inherently based on judgment. See Section 2.1 of these comments for more details.

The CASAC should review and adhere to the Integrated Review Plan (EPA-452/R-16-005, December 2016) for this review cycle, and to its own advice to EPA on the Integrated Review Plan. The basic ground rules of this review were established in 2016 and as a matter of proper and consistent administrative procedure must be followed. CASAC members should read the IRP. As an example, Figure 2-1 in the IRP provides a good summary of the policy context for this review cycle.

CASAC may not redefine the decision and policy context for this review, which is set forth in the Clean Air Act and has been interpreted by EPA based on decades of experience informed by outcomes of various relevant Federal court cases. Furthermore, CASAC has already reviewed the Integrated Review Plan which lays the ground rules and foundation for this review cycle. The decision and policy context is set forth in the IRP.

The scientific review process ultimately, in later stages, will focus on the policy-relevant question regarding whether there are adverse effects under the current standard and, if so, what are alternatives to the current standard and their implications for adverse effects. However, these questions are properly addressed later in the context of the Policy Assessment, which does not occur until later in the review cycle, and should be informed by a prior Risk and Exposure Assessment. To avoid commingling science and policy judgments, the NAAQS review process was designed in 2006 to focus first on the scientific foundation of the review, via the ISA, before getting into the REA and later the PA. Thus, CASAC's statement appears to be one of simple ignorance of how the review process is structured. Read the IRP.

A reading of the IRP will reveal that the REA and PA to follow are based on interpreting policy-relevant empirical evidence and the expert judgment of EPA staff as reviewed based on scientific judgment of CASAC and the public. Examples of the key policy questions, which are to be addressed later in the review cycle, not as part of review of the Draft ISA, include: (1) "Does the currently available scientific evidence and exposure-/risk-based information support or call into question the adequacy of the protection afforded by the current primary and/or secondary PM standards?" and (if not) (2) "What alternative standards are supported by the currently available scientific evidence and exposure-/risk-based information, and are appropriate for consideration?" These questions are answered based on available empirical evidence interpreted based on scientific expert judgment, given that available studies may not directly address all factors pertinent to assessing whether current standards or alternative standards protect public health with an adequate margin of safety.

Thus, this statement reflects a significant misunderstanding by CASAC of the role of the ISA: *"The Draft ISA provides no empirically validated predictions or implications for how or whether possible future changes in particulate matter (PM) exposures would change public health risks."* It is not the purpose of the ISA to make predictions or to assess possible future changes. Members of CASAC should read the Integrated Review Plan (IRP) that was finalized in 2016 after review by CASAC to better understand the key steps in the assessment process, including the ISA, Risk and Exposure Assessment (REA), and Policy Assessment. The REA is the document that would typically include estimates of health and welfare risk related to exposures consistent with the current standard and possible alternative standards. These are not strictly "predictions" in the sense that they are based on recent or current data and employ concentration-response models that are based on empirical observations at policy-relevant exposure levels. That is, they are not intended to predict some distant future but are intended to represent current knowledge of health and welfare effects in the present or very near future under different assumptions regarding the NAAQS.

This statement should be withdrawn or, alternatively, rewritten as follows:

"By its design, the Draft ISA deals with policy-relevant science as set forth in the Preamble to the ISAs, the Integrated Review Plan, and the ISA preface. Although we have some specific suggestions for additional studies that EPA should consider, and regarding interpretations of some of the studies that EPA has considered, we find that EPA has appropriately identified policy-relevant science. This science will form the foundation for later steps of the review process, including the Risk and Exposure Assessment and the Policy Assessment."

Given that the ISA does not deal with predictions, CASAC should drop the advice regarding predictions.

3.11. The ISA is Not a Cookbook

Page 2, Lines 9-10: "The CASAC strongly recommends that all key conclusions in the final ISA should be supported by independently reproducible and verifiable derivations from stated data and hypotheses."

This statement in CASAC's draft letter implies that there is a 'plug-and-chug' cookie-cutter approach to putting data into an algorithm, turning the crank, and spitting out an answer. Given the heterogeneity of scientific disciplines, study populations, study areas, study time frames, ambient conditions, exposure conditions, exposure durations, health effect endpoints, and so on, there is not any existing algorithm that is validated and proven to provide a 'plug-and-chug' solution for making inferences from the existing body of evidence.

This statement appears to ignore the observational nature of epidemiologic studies from which real-world health effects of air pollution for real people are inferred. Such studies are not "reproducible" in a strict since as would be the case for a benchtop laboratory experiment, for example.

Furthermore, this statement by CASAC is attempting to redefine the decision context and the statutory role of CASAC. See Section 2.1 for more details on this point.

What would an ISA look like that strictly met this recommendation? Is CASAC stating that only data analysis of an individual study can be used to infer causality, for example? On Page A-76 of his individual comments, the chair appears to be arguing to throw out as many epidemiologic studies as possible, citing the specific example of Table 11-5 regarding epidemiologic studies related to $PM_{2.5}$ and mortality. Is that the end-game here?

This statement should be deleted. Alternatively, a statement such as this could be made that is consistent with the statutory mandate of the CAA and with the role of the ISA in the NAAQS review process:

"The CASAC strongly recommends that all key conclusions in the final ISA, such as those related to causal determinations, at risk populations and life stages, and concentration-response relationships, should be supported by clear and transparent explanations that derive from available data and inference methods consistent with those given in the Preamble to the ISAs, Integrated Review Plan, and Preface to the ISA, while also addressing judgments regarding potential harms to public health and welfare that are within the scope of the decision context for the NAAQS."

3.12. The ISA Should Demonstrate Transparency of Application of Expert Judgment

Page 2, Lines 10-12: "All derivations of conclusions should be explained in enough detail, using standard terms with clear operational definitions, to allow the validity of the reasoning and conclusions to be independently verified."

Scientific judgment is required under the mandate of the Clean Air Act, as described above. For individual studies, the generally accepted goal in documenting the work is to provide enough information so that an independent investigator could apply the same methods with the same input data and obtain the same output. This is consistent with the notion of 'objectivity' in scientific work: i.e. that different investigators using the same data and methods should be able to arrive at the same answer. For scientific work that can be conducted in a laboratory or "in silico" (computer simulation), a reasonable standard of scientific reporting is to give enough information so that independent investigators can replicate the experiment itself by using the same methods, tools, apparatus, etc. For example, different researchers measuring the speed of light with the same instruments under the same conditions should be able to get the same answer, within experimental error.

However, scientific study of the effect of air pollution on humans can be conducted in the lab to only a limited extent, especially for particulate matter. There is inter-subject variability, and IRB approval of controlled human studies for particulate matter typically address only a narrow range of subjects or pollutant characteristics. Toxicological studies might address a wider range of exposures and particle characteristics but do not provide directly relevant human data. Hence, there is large interest in observational studies of actual human populations and their real-world exposures to particles in the ambient air.

However, given heterogeneities (e.g., study populations, study locations, meteorology, emissions, transport, ambient concentration, exposure, etc), air pollution health research based on epidemiology is best informed by repeated studies as the basis for making inferences. Such studies may have varying study design, populations, and so on. A study weak in one area may be strong in another, and vice versa for other studies. This is why EPA, based on prior advice from CASAC, takes a holistic approach to reviewing a large body of scientific evidence across many scientific disciplines taking into account heterogeneous studies, combined with the application of expert scientific judgment, to arrive at findings regarding causal determinations, concentration-response functions, and other assessment endpoints.

Putatively, the draft CASAC letter implies that all seven members of the current CASAC agree with the statement as made, although I do not recall any deliberation at the December 12-13, 2018 meeting from which a consensus emerged to support this statement.

The language "to allow the validity of the reasoning and conclusions to be independently verified" is problematic. It is unclear what CASAC intends with this statement. It is CASAC's role to provide an independent review of the scientific basis and inferences and offer its advice, based on expert judgment. As is well known, expert judgment depends on factors such as motivating, conditioning, structuring, and inferences, and it is possible that different experts (and different groups of experts) may arrive at different

judgments based on the same evidentiary basis. Clearly, Congress anticipated that this may be the case, and thereby mandated that an independent scientific committee review and provide advice based on its judgment, thereby bringing an additional group of experts into the NAAQS review process beyond that of experts on the EPA staff or that EPA accesses in developing its assessment products. Furthermore, based on four decades of precedent and well-established procedures, it has long been recognized that the seven member CASAC cannot have the breadth, depth, and diversity of expertise since there are many science disciplines pertinent to NAAQS review. Thus, CASAC has, for four decades, been augmented with expert review panels developed prior to the start of a review cycle. This improves the conditioning and structuring aspects of expert-based judgment, and also mitigates against the deliberations being dominated by one or a few individuals with their own agendas.

CASAC should withdraw this unclear statement or replace it with a statement such as: "The ISA should clearly and transparently synthesize available evidence and draw inferences from that evidence regarding causality, at risk populations and life stages, and concentration-response relationships, taking into account both known and anticipated effects at levels comparable to and below the level of the current standard to assure policy-relevance of the scientific findings. The Draft ISA largely does this, but could be improved in specific ways." (give reasonable examples).

3.13. Need for Breadth and Depth of Expertise and Diversity of Perspectives to Support Robust Judgments

In the current review process the Administrator has arbitrarily and capriciously done away with the CASAC PM Review Panel. Details on this point are in Frey et al. (2018). Given the important role of expert judgment in CASAC's work, it is essential that CASAC be augmented with additional experts in the multiple scientific disciplines needed for this review. Furthermore, there must be multiple experts in key areas, such as air quality physics and chemistry, exposure assessment, toxicology, controlled human studies, epidemiology, and others, to have a diversity of perspectives to assure that judgment is based on the large body of relevant scientific evidence using accepted inference methods. For four decades, CASAC has been augmented with expert panels as documented by Frey et al. (2018) and others. The rationale given by EPA for disbanding the PM review panel is that by statute the CASAC and not a review panel is the advisory body. This rationale is specious because under its charter with Congress, it is clear that augmented panels report via the CASAC and not directly to EPA; therefore, per its charter, CASAC has been the advisory body. Augmented panels advise the CASAC and supplement it with the expertise it needs. Absent such augmented expertise, the chartered CASAC is scientifically unqualified to conduct a review consistent with language in the Clean Air Act.

The CASAC should insert the recommended statement given in Section 3.3 to advise EPA to reinstate the disbanded CASAC PM Review Panel.

3.14. A Second Draft of the ISA Should be Reviewed by CASAC Augmented With Reinstatement of the CASAC PM Review Panel

Page 2, Line 18: "The CASAC recommends development of a Second Draft ISA for CASAC review."

Many observers would agree with this statement, but would arrive at this statement for different reasons. As stated by Frey et al. (2018) and others, usually two drafts of the ISA are needed in a NAAQS review cycle. Thus, a second draft of an ISA is a routine part of a typical review cycle. The current seven member CASAC lacks the breadth and depth of expertise, and diversity of perspectives within key disiplines, to conduct review of the ISA as demonstrated by CASAC's own comments. To correct the procedural deficiency of arbitrarily and capriciously disbanding the CASAC PM Review Panel, EPA

should immediately reinstate the CASAC PM Review Panel. The second draft of the ISA should be reviewed by chartered CASAC augmented with the reinstated CASAC PM Review Panel.

CASAC should incorporate the following text into its letter:

"The CASAC recommends development of a Second Draft ISA for CASAC review. CASAC should be augmented with additional experts by reinstating the disbanded CASAC PM Review Panel prior to reviewing the Second External Review Draft of the ISA and prior to reviewing any other EPA assessment documents in this review cycle."

3.15. EPA Should Reinstate the Arbitrarily and Capriciously Disbanded CASAC PM Review Panel

Page 2, Lines 19-20: "The CASAC recommends that it be provided with access to additional technical expertise, as needed, to thoroughly review the Second Draft ISA."

This recommendation is insufficient.

EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. EPA should not engage in an ad hoc and post hoc process of cherry-picking experts. EPA followed well-established procedures in call for nominations for the CASAC PM Review Panel, selecting members, and forming the panel.

See Section 3.14 for recommended replacement language.

3.16. CASAC Comments Are Unclear and Do Not Acknowledge Existing Treatment of Issues in the Draft ISA

Page 2, Lines 24-25: The key findings and conclusions of the Executive Summary "do not distinguish between true and estimated PM exposure values;"

This is a puzzling statement considering, for example, estimated exposure is explicitly mentioned on page ES-6, line 6, and elsewhere in this paragraph. Furthermore, CASAC does not acknowledge that the Draft ISA covers a variety of exposure estimation methods in Chapter 3. Not every detail may rise to the executive summary.

Page 2, Line 26: "…between individual and population risks;"

CASAC could be more clear here regarding the intent of this comment. By and large, the draft ISA is concerned with concentration-response or exposure-response relationships for populations.

3.17. The ISA Deals with the State of the Current Science, Not With Predictions

Page 2, Line 26-27: "…between observed changes and model-predicted changes in public health risks following changes in exposures;"

The ground rules of the ISA are that is based on review of empirical evidence for effects at levels comparable to or below the current air quality standard. The ISA does not develop a model for predicting changes. The separate Risk and Exposure Assessment is the portion of the NAAQS science review that deals with translating scientific evidence reviewed in the ISA into exposure and risk modeling to address policy-relevant science questions as described in the Integrated Review Plan.

3.18. Inferences Regarding Causal Determinations Take Into Account the Total Body of Scientific Evidence

Page 2, Lines 27-28: "…between results from the total body of scientific evidence and results from selected subsets of evidence;"

In reviewing the "total body of scientific evidence" it is possible give more weight to some "subsets" and less weight to others. An inference can be made with awareness of and accounting for discordant evidence. In either case, the inference is made based on review of the overall body of evidence and not just a subset of the evidence.

Page 2, Lines 28-29: "…and between association and causation."

The Draft ISA is largely devoted to making causal determinations based on an integrated review of the policy-relevant body of scientific evidence. The causal determinations are determinations of causality that go beyond association. Table P-2 in the Preface addresses this.

3.19. The Executive Summary Summarizes Findings Regarding Causal Determinations

Page 2, Lines 29-32: "This lack of clarity leads to mistaken and misleading statements. The CASAC recommends that the Executive Summary be revised to clarify these distinctions and to explicitly discuss, for each health effect, whether ambient concentrations of PM can or cannot independently cause it;"

CASAC should be more specific regarding statements that it judges are mistaken or misleading. Also, CASAC's report should be clear as to whether there is consensus of the CASAC on these statements and, if not, should reflect the diversity of opinions of members of CASAC.

The causal determinations are based on an inference regarding whether policy-relevant ambient concentrations of PM independently cause identified health effects. Thus, the Executive Summary already addresses this point.

Page 2, Lines 32-33: "…discuss inconsistencies in epidemiological evidence across geographic locations (e.g., absence of $PM_{2.5}$-mortality associations in some studies);"

Details of such discussions are in the main body of the report. The Executive Summary mentions inconsistencies several times when inconsistencies were a key factor in a causal determination. More detail could be elevated to the ES but this would lengthen the ES. Thus, CASAC might reconsider asking for more and more details in the ES, which defeats the purpose of having an ES.

The text in CASAC's letter implies that the Draft ISA does not discuss inconsistencies among epidemiologic studies, but in fact it does. Inconsistencies among epidemiologic studies are mentioned, for example, on p ES-14, lines 27-30 and p. ES-21, lines 3-8, and throughout the main body of the Draft ISA.

Page 2, Lines 33-34: "…evaluate the extent to which concentration-response (C-R) associations are caused by confounders such as lagged weather variables;"

The Draft ISA includes evaluation of whether temperature (including lags) and season are effect modifiers, particularly in sections 5.1.10.4, 6.1.14.2, 11.1.6.1, 11.1.6.2, and 11.3.5.1. CASAC may want to be more specific as to what additional information should be included in the ES, since the role of the ES is to be an executive summary of the most important points. CASAC should also distinguish between confounding and effect modification.

Page 2, Lines 34-35: "…determine the coherence or lack of it across studies when conflicting evidence is fully taken into account;"

It is not clear what the CASAC means by "when conflicting evidence is fully taken into account." Consistency (or lack thereof) and coherence (or lack thereof) are part of the methodology for causal determination as set forth in the Preamble to the ISAs, the Integrated Review Plan, and the Preface to the draft ISA.

3.20. It Is Not the Role of the ISA to Conduct New Analyses

Page 2, Lines 35-37: "…and assess the influence of error and uncertainty on the relationship between estimated PM exposure and health using appropriate technical (e.g., errors-in-variables) methods."

The role of the ISA is to review existing evidence. If members of CASAC know of particular policy-relevant published peer reviewed studies that have this particular information, they could recommend such studies to the attention of EPA. To the extent that study authors assess the influence of error and uncertainty then of course this can be incorporated into discussion and inference in the ISA. However, it is not the role of the ISA to conduct new analyses. Thus, this comment is misplaced in that it is irrelevant to the ISA. Members of CASAC are encouraged to read the Integrated Review Plan for a better understanding of the purpose and role of the ISA.

Page 2, Lines 39-42: "The CASAC finds that Chapter 1, similar to the Executive Summary, provides an effective summary of material from subsequent chapters, but that this material does not clearly characterize conditions under which reducing $PM_{2.5}$ exposures alone (without changing other variables that are correlated with $PM_{2.5}$ exposures, such as poverty or lagged values of weather variables) reduces human health risks."

The draft ISA addresses several general topics. One general topic is causal determinations. These determinations are not specific to any one study or to any one concentration-response function. Secondly, the ISA reviews evidence regarding concentration-response (or exposure-response) relationships, and offers findings regarding the shape of such functions (e.g., linear? threshold?). Third, the ISA reviews the state of knowledge regarding at risk populations and life stages. Fourth, the ISA provides the scientific foundation for judgments later in the review process regarding pertaining to policy-relevant questions, as set forth in the Integrated Review Plan. The ISA does take into account poverty, temperature, and season, including lags related to temperature, and makes inferences regarding whether ambient PM concentration independently causes adverse effects and whether concentration and response relationships are either confounded or modified by other variables.

3.21. Systematic Review. See Also Sections 2.8, 2.11, 2.12, 3.2, 3.4, 3.6, 3.7, 3.8, 3.11, 3.12, and 3.20 Of These Comments

Page 2, Line 42 to Page 3, line 2: "The CASAC recommends that Chapter 1 should explicitly list and apply systematic review criteria used to decide which articles to include in the ISA's review of scientific evidence and to evaluate, summarize, reconcile, synthesize, and summarize their results."

Page 3, Lines 22-23: "The CASAC finds that Chapters 5-13 do not provide a clearly designed and executed systematic review and summary of the relevant scientific literature."

Page 3, Line 23: "…They omit many relevant and high-quality studies."

Page 3, Line 23-25: "The CASAC recommends that study inclusion and exclusion criteria for literature referenced in Chapters 5-13 should be explicitly stated and systematically applied."

Page 3, Lines 25-26: "Chance, bias, and confounding should be more explicitly and completely addressed in presenting and evaluating study results."

See comments that pertain to systematic review in Sections 2.8, 2.11, 2.12, 3.2, 3.4, and 3.6. To summarize those comments, the ground rules for the Draft ISA were set forth in the Preamble to the ISAs and the 2016 IRP. The process for selection of studies and how they were reviewed is already described in those documents and in the Preface to the Draft ISA.

As noted elsewhere in these comments, CASAC has failed to demonstrate that EPA has omitted "many" "relevant" and "high-quality" studies. CASAC has indicated that EPA may have not cited perhaps two dozen studies (which is hardly "many" compared to the 2,800 studies that are cited). It is not clear that all of the studies mentioned by CASAC are policy-relevant. Whether they are "high-quality" has not been determined either. The appropriate factor in study selection is policy relevance. Thus, the CASAC should tone-down this language.

3.22. Motivational Biases Undermine Credibility of CASAC Advice on Causal Determinations

Page 3, Lines 29-32: "The CASAC finds that the Draft ISA does not present adequate evidence to conclude that there is likely to be a causal association between long-term $PM_{2.5}$ exposure and nervous system effects; between long-term ultrafine particulate (UFP) exposure and nervous system effects; or between long-term $PM_{2.5}$ exposure and cancer."

Given that this CASAC lacks expertise in many key disciplinary areas, especially epidemiology, and that EPA arbitrarily and capriciously disbanded the CASAC PM Review Panel a few days before the Draft ISA was released, thereby depriving CASAC of the needed expertise, this CASAC is not in a credible position to offer judgments regarding causal determinations. In the attached "consensus" response to charge questions, there is language regarding expert judgment which, by the way, was not deliberated at CASAC's December 12-13, 2018 public meeting. However, since CASAC brings up the general issue of expert elicitation, it is important to mention several key points omitted by CASAC in this regard. One is that expert judgment requires judgment by domain experts. Given that this CASAC lacks experts in the appropriate scientific domains, it is unqualified to offer such judgments. Secondly, expert judgment should be based on conditioning of available evidence and inference methods. The conditioning step is substantially more credible when it is based on a larger group of experts with breadth and depth of expertise, and diversity of perspectives. EPA had the larger group in the form of the CASAC PM Review Panel and yet arbitrarily and capriciously dismissed that panel without prior notice and without public consultations with CASAC. Third, there are well known biases in expert elicitation, some of which are cognitive and some of which are motivational. An example of a motivational bias is the so-called "expert bias," which is when people who are not the relevant experts pretend that they are to make themselves appear to be important experts. Another well-known motivational bias is when an "expert" wants to influence the outcome of a scientific review process to achieve a particular policy or regulatory outcome. Such biases might be indicated, for example, when members of a scientific review committee earn their living based on funding from regulated industries, and offer opinions that are consistent with policy outcomes of interest to their funders. Motivational biases also arise when an expert has taken strongly stated public positions previously, as a result of which it becomes more difficult for that person to change their views.

One way to counter-act "expert" bias is to engage experts who have relevant expertise and to make sure that there is breadth and depth of needed expertise, as well multiple experts in key scientific disciplines who have diverse opinions. In contrast, if the goal is to undermine the science review process, efforts could be made to promote and enhance "expert" bias. This can be done, for example, by doing away with

such a group of domain experts, as EPA has done by eliminating the CASAC PM Review Panel, and instead placing the review in the hands of a group that lacks the breadth and depth of expertise, and diversity of perspectives, to properly condition the review. A corollary is that "true" experts are usually the first to admit that they are not qualified to undertake a particular review and to call for the inclusion of additional experts. Persons who are over-confident of their own expertise or who seek to be perceived as an expert in an area for which they are not are unlikely to want to cede their position to other experts. For example, there is diversity of view points on the current CASAC regarding whether to recommend reinstating the disbanded PM review panel. There are also clear differences in the timing by which some members of the panel arrived at a conclusion that more experts are needed, with some members resisting this idea initially much moreso than others. Some members appear inclined to ad hoc and post hoc approaches to cherry-picking additional experts, which is subject to mischief, rather than going with a far less biased approach of simply re-appointing the disbanded panel.

One way to counter-act motivational biases related to experts who want to influence the outcome is, preferably, to not include persons with clear conflicts of interest as part of an expert advisory committee, especially in a regulatory context. This would typically include people with financial ties to regulated industries who have a vested interest in the outcome of the review process, and would also include people who have strongly stated prior positions that imply pre-judgment of the policy-relevant outcomes and people who work at agencies with publicly stated perspectives on issues under deliberation for which there is also a close reporting and line of management relationship. Such persons could still participate in the process as stakeholders via public comments. In contrast, if the goal is to undermine the science review process, efforts could be made to promote and enhance motivational bias. A way to promote and enhance motivational biases is to have fewer experts and include among them persons who are susceptible to such biases. This is what EPA has done in doing away with the CASAC PM Review Panel and with recent changes to the composition of the CASAC.

It is evident that the recent changes to the NAAQS review process have undermined prior measures that were in place to avoid or mitigate motivational biases.

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

This section contains point-by-point responses to some but not all statements in the so-called "consensus" responses to charge questions. A general comment is that, based on observation of the December 12-13, 2018 public meeting, and reading of the minutes of that meeting, it is clear that many of these statements are not based on consensus but represent the opinion of perhaps as few as one member of CASAC. Other members of CASAC should realize that their names are associated with CASAC's report to EPA, and that unless otherwise stated it is assumed by the reader (i.e. the EPA Administrator) that every statement in the letter and "consensus" attachment is agreed to by all members. If this is not the case, individual members must so indicate and the letter and attachment must so indicate.

Page 1, Lines 9-14: "Over the past two decades, an ISA review process has evolved that puts heavy weight on judgments in deciding which health effects should be classified as having a "causal" relationship to exposure and considered further in the context of revising National Ambient Air Quality Standards (NAAQS). This process has not emphasized clear operational definitions of all key terms, or deriving and validating empirically testable and independently verifiable statements and predictions about changes in health effects caused by changing criteria pollutant exposures."

As noted in more detail previously, the process of development of the ISA is based on operational definitions and well-vetted principles. The CASAC appears to misunderstand the role of the ISA. Particularly, the ISA is not about predictions.

Page 1, Lines 14-16: "It has not insisted on, or produced, thorough systematic reviews of relevant high-quality scientific literature using clearly stated, objective, independently reproducible criteria."

This statement is highly debatable on several grounds. The process has demonstrably been based on thorough systematic reviews of policy-relevant scientific literature. Furthermore, such reviews have been proven to be relevant because they have informed policy decisions that have survived judicial review. Criteria (ground rules) for the review have been clearly stated taking into account operational practicality and that the ISA deals with a broad range of scientific disciplines and heterogeneity in the characteristics of policy-relevant studies. There is an explicit role for expert judgment in this process.

Page 1, Lines 16-26: "Evaluations of evidence and conclusions presented in the course of ISA reviews since at least 2009 have also routinely conflated each of the following pairs of importantly distinct quantities: True vs. estimated exposure concentrations; Effects of criteria pollutants vs. effects of factors associated with or modifying effects of criteria pollutants; Shapes of individual-level vs. population average concentration-response (C-R) functions; Observed changes in health effects vs. model-predicted changes in health effects; Assumptions vs. observations about the shapes of C-R functions; Association vs. causation in interpreting C-R observations."

While most of these points are addressed in my comments in previous sections, briefly:

- the Draft ISA distinguishes between true versus estimated concentration;
- the ISA repeatedly deals with potential effect modifiers and confounders;
- the Draft ISA deals mainly with population-based concentration-response functions because these are relevant to the REA and to addressing policy-relevant questions in the PA;
- the ISA is not about making predictions – CASAC members should read the IRP;
- EPA staff replied to CASAC comments about the shape of the C-R functions; and

- the last point about conflation of association and causation is demonstrably inaccurate given that the causal determination framework is concerned with the distinction between the two.

With regard to the last point, the causal determinations are not based on an individual C-R observation from an individual study.

Page 1, Lines 28-29: "Modern techniques for evaluating and improving the validity of expert opinions and judgments under uncertainty have not been systematically applied."

As someone who has conducted expert elicitations of subjective judgments regarding uncertainty, and also served on an EPA Science Advisory Board panel that reviewed EPA's Expert Elicitation Task Force White Paper, I offer the following perspectives on this statement by the CASAC. First, I do not recall delibration on this point that led to a consensus statement in this letter. Secondly, I address motivational biases related to the formulation of expert judgments in my comments in Section 3.22. Third, it is not the role of the ISA to conduct new analyses (read the IRP for a better understanding of the purpose and scope of the ISA).

The comment is ironic given that the current CASAC is poorly constituted to conduct this review given that it has been stripped of the CASAC PM Review Panel and that its members have been appointed in the last two years under recent changes to the NAAQS review process implemented by former Administrator Pruitt that were developed without staff or CASAC input. Among other deficiencies, members of CASAC have been appointed on criteria created in 2017 by Administrator Pruitt without any consultation with EPA staff or CASAC that emphasize geographic diversity, government affiliation, and turnover, not scientific expertise. CASAC lacks scientists and diversity of perspectives in many key disciplines. Thus, this is the least expert of any CASAC in the last four decades.

Page 1, Lines 31-42: "As a result of these practices, the conclusions presented in recent ISAs and in the EPA's Integrated Science Assessment for Particulate Matter (External Review Draft – October 2018), hereafter referred to as the Draft ISA, have uncertain scientific validity as well as unclear meanings. They do not provide clear trustworthy, comprehensive, objective summaries of the scientific evidence and remaining uncertainties about changes in human health and welfare caused by changing exposures that are most essential for informing policy deliberations and decisions. The unknown scientific validity and unclear meanings of its conclusions, its reliance on subjective opinions that cannot necessarily be independently verified, and its failure to objectively and comprehensively address relevant high-quality evidence (especially from studies that conflict with the consensus opinions reached) all show that substantial improvements are needed in both the scientific content and the communication of that content to better inform users of the Draft ISA about human health and welfare effects caused by reducing particulate matter (PM) exposures."

While this statement appears to be the opinion of the current chair of CASAC, it is not evident that this statement is a consensus of the entire CASAC.

To state that the Draft ISA is not "trustworthy" is to imply that EPA staff are lying. This is completely unfounded and unfair to EPA staff.

The Draft ISA is demonstrably comprehensive, as noted in prior sections.

Given that the ISA addresses questions for which cookie-cutter plug-and-chug answers are not available, it is puzzling that CASAC continues to repeatedly use the word "objective" in a manner that is at best naïve. There is an explicit, necessary, and unavoidable role of scientific judgment in the development and review of the ISA.

I have provided comments in earlier sections regarding the challenges of applying strict study "quality" criteria to observational studies. It is not the purpose of the ISA, or even necessary, to rate study "quality." The relevant assessment consideration is regarding the relevance of each study, as already set forth in the Preamble to the ISAs, the IRP, and the Preface to the Draft ISA. It is also clear from the chair's individual comments on page A-76 that an end-game is to throw out as many studies as possible, which is consistent with motivational biases.

The ISA should clearly and transparently explain the basis for its findings that are based on expert scientific judgment.

As noted in my comments in earlier sections, this CASAC is misinterpreting the policy context of the NAAQS review and attempting to redefine the decision context in ways that are not consistent with the Clean Air Act.

Page 2, Lines 2-6: "Overall, the CASAC finds that the Draft ISA does not provide a comprehensive or systematic assessment of the available science relevant to understanding the health impacts of exposure to fine particulate matter, nor does it follow widely accepted scientific methods for deriving sound, independently verifiable, scientific conclusions from available data."

See Sections 2.8, 2.11, 2.12, 3.2, 3.4, 3.6, 3.7, 3.8, 3.11, 3.12, and 3.20 of these comments.

Page 2, Lines 9-21: "Much of the relevant and important scientific literature is not reviewed. For example, in response to follow-up questions from Dr. Tony Cox from the December 12-13 public meeting, the Health Effects Institute (HEI) provided an overview of accountability studies funded by HEI, noting that "we do view accountability research as a valuable opportunity to test causality in real world settings" (Greenbaum, 2019). Table 1 of their overview (entitled "Overview of accountability studies funded by HEI") lists 15 studies. The Draft ISA omits 14 of them. Similarly, the Draft ISA mentions none of the more than a dozen peer-reviewed scientific studies published since 2015 on the roles of inflammasomes in mediating $PM_{2.5}$-induced health effects, including airway hyperresponsiveness, cardiac injury, lung and airway inflammation, atherosclerosis, neurodegenerative diseases, and reproductive toxicity. More generally, the Draft ISA does not provide a comprehensive, systematic assessment of relevant available scientific literature on $PM_{2.5}$ health effects."

The CASAC fails to acknowledge that many of the HEI studies are not policy-relevant. The CASAC fails to explain how not citing 14 studies, many of which are not policy relevant, constitutes lack of a comprehensive review. I have addressed other invalid points of this statement in prior sections – e.g., see Sections 2.8, 2.11, 2.12, 3.2, 3.4, 3.6, 3.7, 3.8, 3.11, 3.12, and 3.20 of these comments, and other sections.

Page 2, Lines 22-35: "Lack of scientific method and of verifiable derivations of conclusions. The standard (hypothetico-deductive) scientific method requires specifying empirically testable generalizations, called hypotheses, from observations; using them to predict outcomes for new situations, typically via hypothetical calculations; comparing these predictions to observations when new situations are encountered in reality (e.g., in designed experiments, controlled trials, or natural experiments); and using discrepancies to modify and improve the initial hypotheses if needed. The scientific method is thus "A method of procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses." (https://en.oxforddictionaries.com/definition/scientific_method). This scientific method is missing from the Draft ISA and its key references. The Draft ISA formulates no testable scientific hypotheses. It presents no validation results comparing hypothetical predictions or calculations for new

situations to observations. No hypothetical analyses are performed or validated in developing the Draft ISA's causality determinations (Vandenberg, 2019)."

This statement is largely a matter of semantics with an element of grandstanding. As noted in prior sections, the ISA is about evaluating hypotheses regarding causality, at risk populations and life stages, and characteristics of concentration response functions.

Page 2, Lines 35-42: "The ISA does not provide clear operational definitions and principles explaining how evidence should be used to draw conclusions; illustrate them with hypothetical examples and calculations to demonstrate their soundness and utility; and then apply them to the particular evidence considered for PM to draw conclusions that can be independently verified by applying the same principles to the same evidence. Thus, the CASAC could not verify and agree on the soundness of the scientific derivations leading to the Draft ISA's major policy-relevant conclusions because no such scientific derivations are presented. They should be included in the ISA."

The Draft ISA does in fact provide operational definitions, such as for causal determination categories, that are based on well-established principles for how evidence should be used to draw conclusions. CASAC would be more credible if it acknowledged in an unbiased, even-handed manner the actual basis of the ISA rather than attempting to broadly over-generalize and exaggerate.

Page 3, Lines 1-10: "Use of unverifiable opinions to draw major policy-relevant conclusions. Instead of applying the scientific method as just described, the Draft ISA relies on judgements about which of five different labels ("causal determination" category names) will be applied to each of a number of associations between PM exposures and adverse health responses. These policy-relevant causal determination labels have no clear operational definitions or empirically testable, potentially falsifiable, implications. For example, the Draft ISA's determination that an exposure-response association is to be labeled "causal" is not defined as implying any particular testable or falsifiable real-world consequences, such as that reducing exposure (but not correlates of exposure such as poverty or extreme temperatures) necessarily reduces risks of adverse health effects in some or all members of the exposed population."

This comment is baffling since the purpose of the causal determinations is to determine whether PM causes an adverse effect independent of other explanations. The causal labels have operational definitions that have been applied to many ISAs in many review cycles. They are based on expert scientific judgment. Given deficiencies identified in other sections of these comments, see especially Section 3.9 and 3.22, this CASAC is poorly positioned to offer relevant or authoritative expert judgments.

Page 3, Lines 11-14: "No rules or procedures for assigning a unique causal determination label to available evidence are stated; indeed, the causal determination categories are not mutually exclusive and collectively exhaustive (Vandenberg, 2019). This makes it logically impossible to independently reproduce or verify assignments of unique causal determination categories to data that fit more than one category (or none)."

This statement is baffling. The causal categories range from not likely to be causal to causal. What additional category does CASAC propose to include? It is clear from the track record of application of the five-level causal framework that a given finding is assigned to one level only (CASAC may want to review every final ISA for the last 10 years to verify this). It is not the case that causal determinations are apportioned among all five categories. The assignment of a causal categorical level is based on weight of evidence from all studies, not data from an individual study.

Page 3, Lines 14-21: "In the absence of clear operational definitions in the Draft ISA, the CASAC could not reach consensus on whether some of the causal determinations in the Draft ISA were implied by or consistent with current scientific knowledge. In this sense, the Draft ISA's major conclusions are not transparently verifiable (or falsifiable) scientific statements that can be determined to be true or false by other independent scientists. Rather, they express the subjective judgments of the authors using ambiguous terms with important policy-relevant consequences but no clearly defined operational meanings."

This is the first time of any mention that CASAC did not reach consensus. Lack of consensus should be communicated in the letter to the Administrator.

Page 3, Lines 22-42: "Lack of scientific support for policy deliberations and decision-making. Sound science can support improved policy and decision-making insofar as it provides trustworthy methods for calculating answers to decision-relevant hypothetical questions (e.g., "If reactants are mixed under stated conditions, what products would result?" or "If we were to reduce exposure concentrations by a stated amount, how would disease risks change?") Sound scientific causal determination and risk assessment calculate and compare risks under alternative hypothetical ("counterfactual") conditions, e.g., with exposures set to different levels; and use data to reject, if possible, "null hypotheses" such as that changes in exposure do not predict changes in health effects. Rational risk management decision-making in the public interest requires comparing the human health and welfare consequences of hypothetical alternative policy decisions and identifying those that achieve desired ends, such as protecting human health and welfare with an adequate margin of safety. Thus, hypothetical calculations are crucial to the application of science to inform rational policy and decision-making to protect human health. However, the Draft ISA omits hypothetical analyses in developing its major conclusions (e.g., causality determinations) (Vandenberg, 2019). It provides no empirically-validated predictions or implications for how or whether possible future changes in PM exposures would change public health risks. It does not discuss whether or to what extent policy makers can be confident that reducing $PM_{2.5}$ alone, without reducing its correlates (such as poverty, co-morbidities, co-exposures, and weather conditions correlated with high $PM_{2.5}$ levels) would reduce adverse health effects. This missing what-if information is crucial for the ISA to fulfill its intended role in supporting policy."

This passage is simply wrong. Here again, the chair of CASAC is attempting to redefine the decision context away from that given by Congress and as interpreted over the decades by EPA and the courts. The decision context is a given, not something to be redefined by a CASAC chair. See Section 2.1 and other sections of these comments for more details. This passage should be deleted.

Page 4, line 42, to Page 4, line 2: "Without it, the ISA provides no empirically-validated or independently verifiable scientific basis for identifying what changes in exposures, if any, would be effective or necessary to protect human health with an adequate margin of safety."

The CASAC has not in any serious way taken on the issue of adequate margin of safety, and thus it is vague and unclear as to the meaning of this statement as intended by CASAC. However, as noted earlier in these comments, the notion of "margin of safety" implies that uncertainties are considered in the context of a risk averse decision making process. The REA, not the ISA, will involve making estimates of health risks associated with air quality at or below the current standard. See other comments for more details.

Page 4, Lines 4-10: "These limitations are unnecessary. Results of both toxicological and accountability studies are available in the peer-reviewed scientific literature that formulate testable predictive hypotheses about health effects of changes in $PM_{2.5}$ exposures, test them with data from natural

experiments and other sources, and draw useful, empirically-grounded conclusions about whether and how much changes in PM exposure affect human health risks (Greenbaum, 2019). Much of this evidence is omitted in the Draft ISA. The ISA should include these and other high-quality scientific studies that emphasize empirical data and test predictions about effects on human health risks of changing PM exposure levels."

The ISA certainly can review studies that include the form of hypothesis testing described here, to the extent that they are policy-relevant. The manner in which hypotheses are tested, and the interpretation of the results, differs among studies and may not always be stated in a standardized manner. Thus, it is overly simplistic and inaccurate to imply that only toxicological studies or accountability studies test hypotheses. Given that this CASAC lacks breadth and depth of expertise, and diversity of perspectives in key disciplines, it is hardly well-positioned to offer such sweeping statements.

Page 4, Lines 14-17: "The CASAC strongly recommends that, throughout the ISA, all key conclusions be supported by independently reproducible and verifiable derivations from stated data and hypotheses. All derivations of conclusions should be explained in enough detail, using standard terms with clear operational definitions, to allow the validity of the reasoning and conclusions to be independently verified."

Does the CASAC actually "strongly" recommend this? It is not clear that all members of CASAC ever expressed concurrence with this statement. The ISA touches on many topics for which judgment is required and that must go beyond data and derivations of individual studies. Is CASAC attempting to argue that EPA may not conduct a systematic review based on weight of evidence, and that the existing framework for causal determination should be thrown out?

What is meant by "independently verified"? In cases where conclusions are reached based on judgment, the goal is to have clarity and transparency in explanations of how those conclusions were reached. Is this part of "verifiable"?

Page 4, Lines 17-22: "High-level explanations of how key conclusions are reached that lack the operational detail needed for independent verification, such as "All causality determinations… are based on the approach of considering the collective body of evidence" (Vandenberg, 2019), are not sufficient to enable the CASAC (or others) to trace and check the steps and logic that lead from stated data and hypotheses to stated conclusions."

This statement makes little sense. A general description of the overall approach is not intended to offer detailed explanation of a particular finding for a particular pollutant and effect. Hence, this seems to be a straw-man argument based on taking a quote out of context. The length of the ISA (over 1,800 pages) is related to the goal of the ISA in identifying policy-relevant scientific information and documenting lines of reasoning from that information that lead to stated conclusions. This process inherently involves scientific judgment. Furthermore, statements from this CASAC repeatedly fail to acknowledge that cookbook procedures that might be applicable in some domains that are based on controlled experiments are not directly applicable to observation-based scientific study for which there is heterogeneity that cannot be controlled in a lab. Thus, causal determination is not just about data and hypothesis testing in individual studies.

Page 4, Lines 26-30: "Results of empirical tests of these assumptions or hypotheses should be provided wherever possible; otherwise, sensitivity and uncertainty analyses should be used to inform readers about the sensitivity of conclusions to untested hypotheses. These best practices for identifying and

communicating hazard information are necessary to enable the CASAC to properly fulfill its duty to provide independent advice to the EPA Administrator on the technical bases for EPA's NAAQS."

As noted in several places in other sections of these comments, the ISA is not about doing analysis, it is about reviewing the existing body of scientific evidence. The CASAC should read the Preamable to the ISAs and the 2016 IRP to obtain a better understanding of the role of the ISA in the review process.

Page 5, Lines 1-6: "The CASAC recommends that it be provided with access to additional technical expertise as needed to thoroughly review a revised version of the Draft ISA. Depending on how the Draft ISA is revised to clarify the detailed derivations of its key conclusions, different sets of detailed expertise may add value in verifying those derivations and in commenting on the plausibility of any remaining untested assumptions and on the sensitivity of conclusions to plausible variations in those assumptions."

Page 5, Lines 6-16: "Likely areas where access to additional expertise may prove useful include the following

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

EPA should reinstate the disbanded CASAC PM Review Panel that was arbitrarily and capriciously disbanded only a few days before the Draft ISA was released. See also other sections of these comments.

Page 5, Lines 18-24: "In addition, the EPA might greatly benefit by seeking and following advice from external experts (e.g., from the Good Judgement Project or related efforts in management science, decision science, and risk analysis) on how to revise the ISA review process to make better use of scientific judgment and diverse sources of scientific evidence and how best to avoid or overcome common pitfalls of consensus judgment processes (e.g., Dhami et al., 2015; Tetlock et al., 2017). Such meta-expertise could help to maximize the value from EPA's investment in expertise and literature reviews of health effects that could be prevented by reducing PM exposures."

I attended both days of the December 12-13, 2018 CASAC meeting. I do not recall any deliberation regaring the "Good Judgment Project" or why that is relevant here, including but not limited to any indication that this issue was raised much less agreed to by all members of the CASAC. This letter may not contain any recommendations that were not deliberated by CASAC in a public meeting. Whether this advice has any merit cannot be ascertained because it was not properly deliberated. Therefore, it must be removed from the letter.

This comment is highly ironic. As noted in Section 3.22, EPA has set the staged for a motivationally-biased review. As recommended by Frey et al. (2018) and many others, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM review panel. Doing so would at least partially address some deficiencies of the current CASAC in terms of making better use of expert judgment and diverse sources of scientific evidence and help avoid or overcome common motivational bias pitfalls in formulating judgments that are symptomatic of the current CASAC.

Page 6, Lines 11-19: "the Draft ISA does not clearly communicate what science has revealed about the real-world effects of changing PM exposures on human health and welfare – and hence about whether or under what conditions changes in PM are needed to protect human health. Substantial discordant and conflicting evidence remains ignored or unresolved, leading to repeated assertions that the literature shows consistent and coherent positive associations when in fact it shows a mixture of positive and negative results. How information was selected for inclusion or exclusion in the Draft ISA is not always clear. How, if at all, its major conclusions would change if other valid selections of information were made and if discrepancies among study results were more adequately resolved has not been described."

Epidemiologic studies are based on observations of relationships between varying PM exposure surrogates on varying metrics of adverse effects surrogates, where variation occurs over time and space, and taking into account to the extent practicable potential confounders and effect modifiers and other sources of possible error. This is generally the best and most practically available information for inferring how changes in air quality affect public health, especially for PM.

The statement "substantial discordant and conflicting evidence remains ignored or unresolved" requires clarification. First of all, what is meant by "substantial"? While there can be discord when comparing studies, that does not mean in every case that the discord is "substantial." Secondly, what is the basis to say that "discordant and conflicting evidence" is "ignored"? In many places throughout the Draft ISA there is acknowledgment of conflicting studies. In some cases, conflicting evidence may be difficult to explain, but also must be considered in the context of factors such as study design, what potential confounders and effect modifiers were quantified, what inference methods were used, and so on. Conflicting evidence may be related to differences in demographics, housing characteristics, and other factors that might lead to differences in the relationship between personal exposure and ambient concentration from one study area to another or over time. Given that CASAC has no experts in this area, CASAC is poorly constituted to delve into these issues. In contrast, the disbanded CASAC PM Review Panel has such expertise. Simply because there is a "mixture of positive and negative results" does not imply that the positive and negative results are equal and offsetting. There may be good reasons to give preference toward one or other direction in making inferences. Furthermore, as noted in Section 2.1 and elsewhere, there is a policy context to this review based on language of the Clean Air Act that requires attention to protection of public health, which is a risk-averse notion. Thus, from a policy-context, evidence of adverse effect, even if not completely definitive or free of uncertainty, can be highly relevant in the context of NAAQS review.

Page 6, Lines 23-25: "The Draft ISA leaves unclear whether or to what extent the human health risks attributed to PM are in fact jointly caused by weather, demographic, socioeconomic, and health variables such as temperature extremes, sex and age, income, and obesity; and whether or to what extent reducing PM exposures alone could reduce risk to human health and welfare."

Much of this is addressed in earlier comments, but it is also self-evident that the Draft ISA does in fact consider these factors in various portions of the document. For example, the ISA specifically touches upon issues of temperature, seasonality, age, sex, socio-economic status (income, education), race, comorbidity, and other factors when such factors were included in policy-relevant studies. The causal determinations are based on whether exposure to PM independently causes the adverse effect (i.e. page P-11, lines 21-22: "this ISA aims to characterize the independent health and welfare effects of PM"). Thus, the wording here by CASAC is misleading in implying that EPA did not account for these factors to the extent that they can be accounted for based on the available literature.

Page 6, Lines 40-43: "The Executive Summary says that "The causality determinations for $PM_{2.5}$ reflect the total body of scientific evidence" but in fact these determinations ignore large bodies of relevant scientific evidence, including 14 of the 15 references tabulated by HEI for accountability studies in Table 1 of Greenbaum (2019)."

Even if EPA "ignored" a dozen or so studies, that hardly negates that EPA has in fact reviewed a very large body of evidence. In fact, in this comment, CASAC has failed to demonstrate that these 14 studies are policy-relevant. CASAC should tone done these types of hyper-critical overly-broad and unfair characterizations that lack accuracy and balance.

Page 7, Lines 1-5: "The Executive Summary states that a causality determination of "causal" or "likely to be causal" reflects "the highest degree to which the evidence reduces chance, confounding, and other biases in the exposure-health effect relationship." In reality, however, these determinations reflect many studies that do not control at all – let alone "to the highest degree" – for important confounders such as poverty and temperature. Examples are given in the individual comments."

The definition is about the overall body of evidence not about an individual study.

Page 7, Lines 6-7, 16-19: "The Executive Summary does not accurately reflect the extent of inconsistent, inconclusive, and ambiguous evidence on PM exposure-response associations in the literature. […] The CASAC finds that this account does not fully represent the mix of evidence in the underlying scientific literature, which includes many individual studies and meta-analyses that do not report consistent, positive associations. Examples are given in the individual comments."

As noted above, the draft ISA addresses inconsistent and inclusive evidence. In fact, this is why some of the causal determinations are weak.

Page 7, Lines 20-24: "The Executive Summary states that "In summary, exposure error tends to produce underestimation of health effects in epidemiologic studies of PM exposure, although bias in either direction can occur." The CASAC finds no justification for this generalization and notes that the underlying scientific literature (not cited in the Draft ISA) discusses the fact that exposure estimation error in many cases tends to produce substantial over-estimates of health effects at low exposure concentrations. References are given in the individual comments."

The statement is correct if caveated to refer to a situation for which there is no threshold. The Draft ISA provides a judgment based on available scientific evidence that there is not a threshold. Thus, the text is internally consistent. CASAC should rephrase. In particular, it is not true that there is "no justification" but rather "The CASAC finds that this statement is justified in cases for which there is no threshold in a concentration-response function, as was the context for this statement. However, in cases for which there is a threshold,…" Such phrasing conveys the point that CASAC wants to make while also acknowledging that there is validity to the point made in the Draft ISA in the context in which that point was originally made.

Page 7, Lines 33-39: "The CASAC finds that these statements do not distinguish between true and estimated concentrations. In this regard, they are not correct as stated. Some of the relevant scientific literature not cited in the Draft ISA shows that exposure estimation errors can conceal exposure-response thresholds if they exist; it is therefore not appropriate to interpret lack of a threshold in estimated exposure-response data as evidence for a lack of threshold in the true exposure-response relationship or as supporting a linear no-threshold relationship."

Here, CASAC is over-generalizing. Just because exposure error "can" conceal thresholds does not mean that estimated exposure-response data always conceal a threshold. Whether a threshold is concealed would depend in part on the extent of the exposure error. Furthermore, CASAC seems to make little distinction between individual and population-based concentration-response relationships in formulating its comments.

Page 8, Lines 24-26: "For example, use "controlled direct effect" or "total effect" to disambiguate importantly different meanings of the ambiguous term "effect." Provide operational definitions for key term."

As stated in the preface, the ISA deals with independence of effect when developing causal determinations. Perhaps this can be explained in other ways, but this concept has been operationally relevant for many years and seems to be interpretable by the various many experts who have served on prior CASACs and CASAC panels.

Page 8, Lines 27-34: "Revise the definitions of causal determination categories for clarity, correctness, and consistency. For example, if the categories are intended to be mutually exclusive, then the words used to define them should not allow more than one category to match the same description of evidence. The definitions should be clear enough so that different people can apply them independently to the same simple test cases and get the same answers. Operational definitions and empirically testable (and potentially falsifiable) implications or predictions for each category should be clearly stated. How to classify uncertain evidence that appears to be consistent with more than one category should be clarified."

In practice, each pollutant/exposure/effect relationship is assigned to only one causal category, as is evident from reviewing a decade of ISAs. This seems to be much ado about nothing.

Page 8, Lines 34-37: "We strongly recommend that the ISA define and use a concept of causation in which exposure is considered to be a cause of an effect if and only if reducing exposure without changing other variables (e.g., income, temperature, or co-pollutants) would reduce the effect. (This is sometimes referred to as "manipulative causation.")"

As a close observer of the December 12-13, 2018 meeting, I do not recall that all members of CASAC agreed to this statement, and I recall specifically (as reflected in the minutes) that at least one stated that creating more definitions is not helpful and obfuscates. Thus, it is not accurate to state "We…" nor can this be a 'strong' recommendation if there is disagreement.

Page 8, Lines 40-Page 9, Line 2: "State and apply explicit inclusion and exclusion criteria for selecting evidence to evaluate. Provide independently reproducible methods or rules for applying the criteria to individual studies and results. Document the results of applying them. For example, if the EPA decides to exclude studies that report PM C-R associations without controlling for well-known potential confounders such as temperature or income, then the results of applying this exclusion criterion to each study should be documented."

It is not appropriate to throw out observational studies for arbitrary reasons and to do so in manner that in effect censors the scientific evidence. Dr. Cox has stated on page A-76 his own comments that excluding studies in this manner "would eliminate most (possibly all) of these numerous studies" given in Table 11-5. See numerous prior sections for comments regarding study selection and systematic review and its application in the context of the ISA.

Page 9, Lines 3-6: "Provide explicit, objective, independently verifiable criteria for how individual studies and evidence are to be evaluated and their results synthesized, reconciled, and summarized. Specify criteria and methods for how results are to be combined or synthesized, resolved when they conflict, and summarized." (and similar types of statements)

This seems like paralysis by analysis and/or censoring. There is a difference between a practical approach that is vetted and demonstrated via established practice versus a hypothetical approach or an subterfuge that is disguised in scientific language but with the end-goal to censor policy-relevant science. Redefining the review methodology at this stage, which is unnecessary and controversial, will also lead to substantial delay in completion of the next ISA, unless of course the goal is to encourage EPA to throw out as much science as possible, in which case the ISA might be short but not consistent with the statutory mandate of the Clean Air Act (see earlier comments).

Page 9, Lines 29-31: "many other reviews of the literature have discussed important inconsistencies or negative findings that are ignored or left unresolved in the Draft ISA and that are not represented in its summary statements."

Here again, CASAC uses broad generalizations such as "many" and "important", yet CASAC fails to establish such. For example, what number of reviews constitutes "many"? Were these reviews policy-relevant? What were their findings? Do their findings provide new insight that is not already included in the Draft ISA? What were the "inconsistencies" or negative findings. Did the Draft ISA actually ignore these inconsistencies and findings? If so, which ones specifically, and were they policy relevant? What advice does CASAC have for how putatively unresolved consistencies might be resolved?

Page 9, Lines 38-43: "p. ES-21 states that "Evidence continues to support a linear, no-threshold concentration-response relationship." However, the evidence referred to comes mainly from studies that do not distinguish between true exposure levels and estimated exposure levels. Such studies typically cannot detect exposure thresholds even if they exist, due to ignored measurement errors in exposure estimates; these flatten out threshold C-R functions and make them appear to be linear (e.g., Cox, 2018). This appearance is therefore not valid evidence for a true linear no-threshold C-R function."

Given that members of CASAC may not advocate for their own studies, CASAC should assure the public that this citation to Cox is not a self-citation. An author of a study cited by EPA or CASAC may not participate in deliberations of their own study. CASAC should ask the DFO for clarifications on these points. Also, for general points, it is generally best to review the overall body of literature and not rely on just one study.

CASAC lacks expertise in air pollution exposure and thus is not qualified to offer much advice in this area. The disbanded CASAC PM Review Panel had such qualifications.

Page 10, Lines 10-15: "The ISA should also carefully reconsider the use and interpretation of conclusions from studies with important uncontrolled confounders (temperature is a prevalent example), untested and unverified modeling assumptions that drive conclusions (such as that unmeasured lagged temperatures are not important confounders), ignored errors and uncertainties in exposure estimates, and data from experiments with species, systems or exposure conditions having no clear relevance to real-world human health effects."

To the extent that the ISA does not already do so, it could discuss these issues. However, it is not self-evident that all "uncontrolled confounders" are "important" – this seems to be a subjective opinion of some CASAC members. This CASAC, which is largely devoid of epidemiologists and other experts, is

not well-constituted to take on these types of issues. CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise.

Of course as a matter of good scientific practice, careful consideration should be given to threats to validity of the findings of observational studies. This is typically routine practice in prior CASAC reviews but requires the appropriate expertise, which is lacking in this CASAC.

Some of the text here is puzzling in that the ground rules of the ISA are to focus on policy-relevant science, which means that exposure conditions relevant to real-world human health effects are in fact taken into account. Given the perplexing nature of this text, its validity is dubious.

Page 10, Lines 23-27: "The EPA and CASAC members should not seek to reach consensus agreements on the causal interpretation of ambiguous data when there is no factual basis for doing so, nor should the ISA assign causal determination categories when doing so requires using personal opinions that go beyond what can be objectively determined from available data."

This statement is consistent with Dr. Cox's individual comments on page A-76 regarding his vision for a Draft ISA stripped of epidemiologic studies.

Given that much of the relevant health effect literature for particulate matter is based on epidemiology, that air pollution epidemiology is based on observation rather than controlled study designs, and there there is heterogeneity in study designs, study populations, exposure condition, and so on among such studies, there is inevitably going to be some degree of "ambiguous data" or, perhaps more accurately, heterogeneous data. There will be varying degrees of uncertainty that differ among studies pertaining to what surrogates for exposure and effect were selected, how they were quantified, what potential confounders were quantified, what potential effect modifiers were quantified, the temporal dimensions of the study, and the methods used to make inferences from the data. Every such study will have limitations and weaknesses. Thus, if one chooses to focus on exclusion criteria based on limitations applied to studies on an individual basis, then perhaps every epidemiologic study would be thrown out. This is "throwing the baby out with the bathwater" in that the evidence from the collection of such studies is useful when appropriately interpreted by the appropriate experts.

This statement clearly implies a major change in the groundrules for the scientific review. Is there some reason why such a change is warranted at this time? Usually, the novel approach of any one investigator is not adopted wholesale. New approaches are adopted as a result of a gradual process in which they eventually are broadly demonstrated, vetted, reviewed, and evaluated. The existing process is not fundamentally broken. Perhaps it can be improved in incremental ways. However, there is no basis for making major, unnecessary, and highly controversial changes to the review process in the middle of a review.

This CASAC is poorly positioned to offer such advice. For example, this CASAC was not selected for its scientific expertise first and foremost but, as revealed by the choices made by EPA that are consistent with an October 31, 2017 memorandum of former Administrator Pruitt, for geographic diversity and representation by state agencies. These latter criteria are not related to scientific expertise.

As noted earlier, this implied approach is inconsistent with the statutory mandate of the Clean Air Act.

Page 10, Lines 27-32: "Extensive research in management science, decision science, and risk analysis has established that scientific judgment is prone to many errors and biases and is not usually a reliable guide to the truth, although initiatives in the intelligence community and decision science, such as the

Good Judgment Project, have developed effective techniques to improve individual and group judgments through extensive practice and feedback using testable, quantitative predictions (e.g., Dhami et al., 2015; 31 Tetlock et al., 2017)."

This point was not deliberated by CASAC and thus cannot be in the letter. See also Section 3.22.

As is typical of many of the comments of the draft letter, the letter focuses on raising doubt after doubt on issue after issue. Certainly, there are limitations to development of scientific judgment. Such judgment could be biased because the group making the judgment does not have the right expertise. Such judgment could be biased because members of the committee have testified to Congress or written op eds in the Wall Street Journal and expressed strongly stated prior views that would now be difficult to contradict. Such judgment could be biased because some members of CASAC work at agencies that have stated strong positions on the subject matter under review. Such judgments could be biased based on the history of co-authorship with others who are funded by regulated industries who have a particular interest in the outcome of these proceedings. However, the Clean Air Act does not allow either EPA or CASAC to side-step a responsibility for making judgments. The Clean Air Act does require that the judgments be "accurate." As noted in elsewhere (see Section 3.22), one way to provide a strong foundation for judgment-based advice is to have the right breadth and depth of expertise, and diversity of perspectives within key disciplines. This is why EPA must reinstated the CASAC PM Review Panel which was arbitrarily and capriciously dismissed only days before the Draft ISA was released.

Furthermore, as a matter of professional credibility, the members of CASAC should more strongly acknowledge the limits of their expertise and that they are not able to offer comments on many aspects of the ISA until such time as the CASAC PM Review Panel is reinstated.

Page 10, Lines 32-35: "Therefore, the ISA should add uncertainty and sensitivity analyses indicating the extent to which causal determinations for C-R relationships are underdetermined by available data and how sensitive conclusions are to uncertainties about modeling assumptions, exposures, unmeasured variables, and residual confounding."

The ISA does not include new analyses. The ISA can review uncertainty and sensitivity analyses that are in the policy-relevant literature.

[note: some statements in the draft "consensus" responses to charge questions on are repetitive of points already address in earlier pages of the draft CASAC letter, so I am not including them below]

Page 11, Lines 13-26: "Chapter 1 repeatedly describes findings as consistent and coherent. This narrative is misleading, insofar as it disregards and leaves unresolved substantial conflicting evidence and findings from high-quality individual studies that present evidence to the contrary. For example, Section 1.4.1.5 states that "Consistent with the conclusions of the 2009 PM ISA, more recently published scientific evidence reaffirms and further strengthens that there is a 'causal relationship' between both short- and long-term $PM_{2.5}$ exposure and total mortality. These causality determinations are based on the consistency of findings across a large body of epidemiologic studies and coherence among evidence from controlled human exposure, epidemiologic, and toxicological studies, as well as biological plausibility for respiratory and cardiovascular morbidity effects by which short- and long-term $PM_{2.5}$ exposure could result in mortality." This statement ignores findings from studies in which neither short-term nor long-term $PM_{2.5}$ exposures are found to be associated with total mortality, and in which changes in $PM_{2.5}$ are not found to affect changes in total (or cardiovascular) mortality rates. A few examples of such discordant evidence include the following (further examples and discussion are provided in Dr. Cox's individual comments):"

Cherry-picking a few studies, which may not be policy-relevant, does not constitute a repudiation of the overall body of evidence.

Page 11, Lines 40 to Page 12, line 1: "The usefulness and effectiveness of the summary presentation in Chapter 1 are undermined by its omission of results from relevant high-quality studies that conflict with the narrative of consistency and coherence. Readers who wish to consider the totality of scientific evidence must look elsewhere for thorough discussions of such conflicting evidence and to understand important factors such as the roles of recent temperature and humidity in causing adverse health effects attributed to $PM_{2.5}$ exposures."

The "elsewhere" where they can look is at the other chapters of the ISA.

Page 12, Lines 1-6: "A thorough scientific understanding of C-R functions for PM and mortality and morbidity that would explain puzzling observations, such as why large reductions in particulate air pollution in Ireland had nodetectable effects on total mortality rates or cardiovascular rates, requires considering the total evidence from all relevant high-quality studies. The Draft ISA does not provide such a comprehensive review and summary of results from relevant scientific literature."

The Irish Coal Ban study is not policy relevant to this ISA. See earlier comments on this point.

NOTE: for many of the points in CASAC's draft "consensus" response to charge questions, CASAC is offering opinions on matters for which it lacks adequate expertise. Each one of these draft comments by CASAC illustrate why the CASAC PM Review Panel should be reinstated.

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines to be able to credibly address these issues. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise.

Page 12, Lines 30-36: "Add to both the ISA and the summary in Chapter 1 a discussion of the role of inflammasomes in mediating effects of $PM_{2.5}$ on respiratory and cardiovascular mortality and morbidity. Discuss the consistency and coherence of available evidence with the existence of exposure thresholds for inducing inflammation-mediated adverse health effects and chronic inflammation in the lung, taking into account that studies that do not find a threshold when exposure estimation error is ignored do not thereby necessarily provide evidence against a threshold."

To partly address this statement, this would depend on the magnitude of the exposure estimation error, would it not?

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines to be able to credibly address these issues. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise.

Page 15, Lines 9-13: "The CASAC should be given ready access to one or more experts in ambient PM measurements and satellite remote sensing AOD analysis to assist in review of the next iteration of the ISA. This would allow for a better understanding of sampling errors and biases associated with integrated and continuous ambient PM measurements and satellite data. This is important since this information will be used to characterize ambient concentrations in the Risk and Exposure Assessment (REA) document."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines to be able to credibly address these issues. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise. EPA should not cherry-pick

experts during the middle of a review process. The proper procedure is to establish the panel BEFORE the start of the review process. That proper procedure was followed and the panel was formed before the draft IRP was provided to CASAC for review.

Page 15, Lines 38-41: "a detailed evaluation of the sampler performance compared to FEM monitors or FRM monitors should be performed before using personal sampling data as the definitive estimate of exposure. In some cases, the data may be better suited for examining gradients in $PM_{2.5}$ exposures rather than directly using the measured $PM_{2.5}$ concentrations."

The ISA does not include new analyses or measurements. Such an evaluation can be based on what is available in the literature, to the extent such information is available.

Page 17, Lines 28-31: "It would be helpful for the CASAC to have ready access to an expert in dispersion modeling and photochemical grid modeling used in health effects analyses. This would allow for a better understanding of errors and biases associated with models that are used to characterize ambient concentrations in the REA document."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise. CASAC should not cherry-pick experts during the middle of a review process. The proper procedure is to establish the panel BEFORE the start of the review process. That proper procedure was followed and the panel was formed before the draft IRP was provided to CASAC for review.

Page 18, Lines 19-21: "It would be helpful for the CASAC to have ready access to an expert in errors-in-variables methods and effects of exposure (and covariate) estimation errors in epidemiology to allow for a better understanding of the impact of exposure errors on epidemiologic study results."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise. CASAC should not cherry-pick experts during the middle of a review process. The proper procedure is to establish the panel BEFORE the start of the review process. That proper procedure was followed and the panel was formed before the draft IRP was provided to CASAC for review.

Page 18, Lines 28-37: "Additional expertise is needed for the CASAC to provide a thorough review of the PM NAAQS documents. The breadth and diversity of evidence to be considered exceeds the expertise of the statutory CASAC members, or indeed of any seven individuals. For example, the chartered CASAC has found it difficult to achieve consensus in some areas (summarized below), and to do so likely requires further scientific expertise from, and discussion with, epidemiologists and additional experts in human clinical studies and toxicology. Some of the proposed changes in causality determinations in the Draft ISA, for example changing the causality designation of long-term exposure to UFP on nervous system outcomes from "inadequate" to "likely", are driven primarily by animal toxicology studies. Therefore, additional expertise is needed in comparative toxicology, dosimetry, and extrapolation of findings in animals to humans."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines to be able to credibly address these issues. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The panel has the needed expertise.

Page 18, Lines 39-42: "Over the past 30 years, CASAC advice to the EPA on NAAQS reviews has been assisted by expert review panels that supplement and expand the scientific expertise brought to bear. Such a review panel was appointed by the EPA for the current PM review. However, the panel was disbanded by the EPA prior to the release of the current ISA."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 19, Lines 1-4: "The CASAC now requests that experts with relevant background, experience, and publications be identified to assist in this PM review, prior to the release of a revised ISA. Experts should be asked to review sections of the revised ISA with relevance to their expertise, provide written comments in advance of CASAC meetings, and participate in those meetings in person."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 19, Lines 8-9: "The CASAC is unable to reach consensus on the causality determination of mortality from $PM_{2.5}$ exposure."

This statement is dumbfounding, given that not only has this determination been in place since the 2009 ISA, but CASAC has offered no rationale for why a weaker determination would be appropriate at this time. CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, before it can credibly address this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 19, Lines 15-18: "The EPA should discuss not just general, possible mechanisms, but specifically how ambient concentrations of $PM_{2.5}$ can move into and through the biological systems in the body to activate a cascade of effects that ultimately lead to a person's death."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 19, Lines 22-32: "In the last PM NAAQS review, the EPA noted that uncertainty remained in the form of unexplained within- and between-city heterogeneity in responses to PM. […] include more discussion of geographic and other types of heterogeneity in this ISA. The implications of unexplained heterogeneity need to be discussed or those endpoints where many potential explanations have been tested, but none have been able to explain the observed heterogeneity (e.g. short-term $PM_{2.5}$ exposure and total mortality). At what point does heterogeneity move from being an uncertainty, to impacting the causality conclusion or other policy-relevant issues such as the use of a single effect estimate for the whole nation?"

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 19, Lines 34-40: "Concentration Concordance" … "whether more serious effects occur at higher, lower, or similar concentrations as more mild effects. This comparison of concentrations of effect should be extended to comparisons between epidemiology, animal, and human controlled exposure studies."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 20, Lines 1-8: "Statistical analysis shows that epidemiology studies cannot determine the true C-R function shape (discussed elsewhere in this document), and the use of linear-no-threshold C-R functions is also inconsistent with human and animal experimental data demonstrating a threshold of $PM_{2.5}$ exposure concentrations below which no health effects are seen. The likely mode of action of $PM_{2.5}$ effects on the body also support a threshold (discussed elsewhere in this document). Therefore, epidemiology studies that draw the conclusion that there is an effect of $PM_{2.5}$ on mortality at concentrations down to zero are not consistent with animal and human data or with our knowledge of adverse effect pathways."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 20, Lines 10-14: "The EPA's mortality causality determination appears to be based almost exclusively on epidemiology studies, which cannot be used in isolation to determine causation. Further integration amongst epidemiology studies showing logical patterns in magnitude and types of health effects, as well as demonstrations of substantial health effects in animals exposed to high concentrations could provide some of the necessary justification for this causality conclusion."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 20, Lines 17-29: "Comparing results between and within studies. The EPA could improve the integration of evidence in this ISA by hypothesis-testing its conclusions by comparing $PM_{2.5}$ effect estimates within and between studies. For example, if one expects that some subset of mortality is more affected by $PM_{2.5}$ (e.g. cardiovascular mortality), then that mortality should have a larger and more significant association with $PM_{2.5}$ than total mortality. Similarly, if all these effects are occurring at the same concentrations, then one would expect more mild effects (e.g. symptom exacerbation) to be more common and more likely to show an association than the more serious effects (e.g. hospital admission or mortality). One would also expect that long-term effects would occur at lower concentrations and would show stronger effects than short-term, because of cumulative exposure (if $PM_{2.5}$ has an impact via cumulative exposure); and that health risks associated with $PM_{2.5}$ would be higher in places with higher $PM_{2.5}$ concentrations. Investigating these types of patterns could be done with the study information that the EPA has already collected for this ISA and would greatly strengthen the conclusions that are drawn."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel. The ISA is based on existing literature and not new analyses.

Page 20, Lines 36-38: "Other members of the CASAC are of the opinion that, although uncertainties remain, the evidence supporting the causal relationship between $PM_{2.5}$ exposure and mortality is robust, diverse, and convincing." [other text follows].

This is an important and valid comment.

Page 21, Lines 3-5: "Indeed, there is new evidence from epidemiological studies supporting the relationship between $PM_{2.5}$ and mortality, and new toxicology studies informing the mechanisms involved and supporting their plausibility."

This is an important and valid comment.

Page 22, Lines 9-17: "Another important addition to this chapter would be a reference to the study by Kendall et al. (2002) in which $PM_{2.5}$ samples were immersed in normal lung lining liquid (surfactant). The small (~35 nm) particles aggregated into larger (>5 um) structures when immersed in lung lining fluid, compared with samples in air or saline, specifically due to interaction with the protein-rich surfactant solution. The probability - and physical possibility - of a particle breaching alveolar epithelial cell membranes is inversely related to the size of the particle. The possibility that small particles aggregate into larger particles upon contact with lung lining liquid could impact the number of particles available for translocation into the circulation. This may impact hypotheses about extra-pulmonary effects of small particles, although how much this aggregation occurs at ambient concentrations in humans is unknown."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 22, Lines 36-41: "Even if there is translocation of UFPs to the brain, it is likely to be a very tiny fraction of particles, as estimated by Garcia et al. (2015), with only 0.001% of 20 nm particles being deposited on the human olfactory mucosa (and presumably far fewer particles actually translocating from the mucosa to the olfactory bulb). Therefore, although these studies show that translocation to the brain may occur at high doses of UFPs, the EPA should note the uncertainty about this translocation, and how much it occurs at ambient concentrations in humans."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 24, Lines 27-34: "In general, the background sections of Chapters 5 and 6 ignore the importance of inter-relationships between respiratory and cardiac function. The mechanistic figures showing potential pathways for PM pulmonary and CV effects should be modified to reflect these considerations. Acute PM-related effects on left ventricular (LV) ischemia or function, or effects on pulmonary artery pressure, could present as respiratory effects, with dyspnea. This is especially true for COPD; many COPD patients have co-existing cardiac disease and/or pulmonary arterial hypertension, and acute exacerbations often have a major cardiac contribution."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 25, Lines 31-34: "this evidence would support a pathway that differs from the current pathways in the biological plausibility figures, suggesting that PM exposure may lead to focal or organ-specific inflammation oxidative stress that could also possibly be mediated by translocated PM or their components."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 26, Lines 9-16: "Page 9-4 - "Inhalation of $PM_{2.5}$ can result in translocation of particles or soluble factors from the lungs (see Chapter 5) which then can increase respiratory tract inflammation…" The sequence is likely wrong here. Particles in contact with airway epithelium initiate airway inflammation, in part via chemokine production by the epithelial cells. That takes a few hours to develop, while transport of particles likely starts before airway inflammation is fully developed. If translocation occurs, it would occur rapidly as the particles enter the pulmonary capillary bed and are quickly transported to the left heart and then the systemic circulation. This sentence seems to make the assumption that translocation causes pulmonary inflammation, which does not accurately represent the pathophysiology."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 26, Lines 18-23: "Figure 10-2 does not accurately reflect the likely pathways for lung cancer. The current emphasis in the figure is on transport of particles and systemic or brain effects. However, the most relevant pathway is direct effects of PM or its components on the airway epithelium. Although airway inflammation may be involved, direct mutagenic, genotoxic, and epigenetic effects on the airway epithelium are likely more important. Systemic inflammation and particle translocation away from the lung are not relevant for lung cancer."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 26, Lines 33-35: "However, Gong et al. (2004b) and Urch et al. (2010), both human controlled exposure studies, investigated effects of fine concentrated ambient particle exposures on lung function in asthmatics." Page 27, Lines 5-9: "Because it is not clear how those studies listed in Table 5-10 do address previously identified uncertainties and limitations, the EPA should provide an explicit list of those criteria used in these sections to include or exclude studies, and/or should provide a list of those studies that were not the focus of this evaluation (perhaps as a sub-category in the HERO database)."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 27, Lines 11-15: "Causality studies - Several studies that conduct causal-type analyses should be included in this ISA: Cox et al. (2017) (for short-term effects of $PM_{2.5}$ on cardiovascular disease), and Greven et al. (2011), Cox and Popken (2015), and Pun et al. (2017) (for long-term effects of $PM_{2.5}$ on mortality). Greven et al. (2011) and Pun et al. (2017) use a method called "a difference-in-differences analysis" that has been used by others to conduct causal-type analyses."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

CASAC members should carefully observe operating procedures that prevent members of CASAC from deliberating on their own studies.

Page 27, Lines 22-26: "For example, if the putative pathway of PM effects on the brain is translocation from the nasal epithelium to the nasal bulb, then how does the difference in percent of nasal deposition and nasal epithelium between rodents and humans impact the interpretation of the animal study results? This discussion should be included when drawing conclusions that rely on extrapolating animal particle translocation results to humans."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 27, Lines 30-42 and Page 28, Lines 1-2: "That appendix indicates that studies are not necessarily excluded from consideration based on quality assessment. What is missing from the current Draft ISA, as well as the preamble and Appendix 1, is a description of how quality assessments are used in the review process. Although the methods for assessing quality appear appropriate, there is currently a gap between study quality assessment and its application in the ISA preparation and subsequent risk assessment process. Are the quality reviews performed by the ISA section author(s) themselves or independently? If independently, are there written quality assessments for each study that are available to the author(s)? The ISA occasionally provides quality-related commentary in the text and/or tables, but this seems to be left up to the individual author of that section, and overall there seems to be little application of study quality considerations in the document. Significant weakness or strengths could be added to the tables listing the studies in each section. Chance, bias, and confounding are all potential reasons for a study to observe an association between two variables (Zaccai, 2004) and therefore should be more explicitly considered when presenting and discussing study results. In addition, more factors than just copollutants should be considered as important confounders in the referenced epidemiology studies."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 28, Lines 4-16: "Effects of chance - Results that are not statistically significant should be indicated as such in the ISA discussion. If there is a reason why statistical significance may not have been achieved (e.g., low sample size), this should be included in the discussion of the study results. An example of the importance of considering statistical significance of results is given on p. 5-118 (Section 5.1.10.2) where the EPA discusses the results of epidemiology studies that used lag -1 as a negative control (i.e., the relationship between asthma ED visits and $PM_{2.5}$ concentrations the day after the ED visit). Strickland et al. (2010) found associations at lag 0-2 RR = 1.05 (1.02, 1.08), and at lag -1 RR = 1.03 (1.00, 1.05); Sarnat et al. (2015) found associations at lag 0-2 RR = 1.04 (1.01, 1.06) and at lag -1 RR = 1.02 (0.99, 1.04). In the absence of statistical significance, the lag -1 results would look like they were providing evidence for a positive association, even though they break the rule that cause must come before effect. In addition to demonstrating the importance of considering statistical significance, the minimal differences between the RR at lag 0-2 compared to lag -1 calls into question the judgement that there is a real association between $PM_{2.5}$ and asthma ED visits in these studies."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 28, Lines 24-27: "If the EPA is drawing a conclusion based on an animal toxicology study, then they should conduct dosimetric adjustments to convert the animal exposure concentrations to human equivalent concentrations, and then determine the likely effects and the relationship to ambient concentrations from those calculated concentrations."

It is not the role of the ISA to conduct new analyses. The ISA reviews existing literature.

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 28, Lines 29-35: "Identifying no- and lowest-observed adverse effect levels - The controlled human exposure studies provide a wealth of information about potential $PM_{2.5}$ effects generated in an experimental setting. urther integration and discussion of this evidence may demonstrate that there are exposure concentrations of effect and no effect (i.e., low- and no-observed (adverse) effect levels – LOEL/LOAELs and NOELs/NOAELs), which would be very informative in determining thresholds of effect and may identify likely mechanistic pathways. Identifying these levels is a standard practice in toxicity factor derivation."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 28, Lines 27-43, Page 29, Lines 1-2: "For example, Ghio et al. (2000) observed an increase in neutrophils in bronchoalveolar lavage (BAL) fluid with exposure to (on average) 120 μg/m3 fine Chapel Hill concentrated ambient particles (CAPs), but Huang et al. (2012) did not observe an increase in neutrophils in BAL fluid with an exposure to (on average) 90 μg/m3 fine Chapel Hill CAPs. Neither observed any change in soluble inflammatory cytokines in BAL fluid or blood. Both studies exposed ~25-year-old healthy adults for 2 hours with 1 hour of exercise and took measurements at 18 hours after exposure. This suggests a NOEL at 90 $\mu g/m^3$, and a LOEL at 120 $\mu g/m^3$ for increased neutrophils in BAL fluid. The question of the adversity of the effect would still need to be discussed."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 29, Lines 3-9: "Animal studies can also provide evidence of NOELs and LOELs. For example, Harkema et al. (2009) exposed rats to Detroit fine CAPS with and without Ovalbumin (OVA)-sensitization. The authors did not observe independent effects of 600 ug/m^3 CAPs (8 hrs per day for 3 days) on pulmonary endpoints but found that fine CAPs enhanced OVA-induced bronchopneumonia. This did not happen with the animals exposed to 356 ug/m^3 CAPs, demonstrating a potential threshold of effects. When modified with a dosimetric adjustment to a human equivalent concentration, and with appropriate uncertainty factors, this information may be relevant to standard setting."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 29, Lines 23-37: "Chapter 5 - The ISA should address possible reasons for the discrepancy in findings from epidemiological and human clinical studies of PM exposure. Despite strong evidence for increased respiratory morbidity and mortality in epidemiology studies, clinical studies that often use PM

concentrations much higher than ambient generally show little or no effects on lung function (Bräuner et al., 2007; Ghio et al., 2000; Gong et al., 2003; Gong et al., 2004a; Huang et al., 2012; Sivagangabalan et al., 2011; or Urch et al., 2010), and somewhat variable findings in terms of airway inflammation (e.g. Holgate et al., 2003; Huang et al., 2012). There may be a number of reasons for this, including the fact that clinical studies involve generally healthy people, or involve those with relatively mild respiratory disease, with brief durations of exposure. The ISA would be strengthened by addressing this, especially considering that the biological plausibility sections repeatedly indicate that airway inflammatory effects may be driving systemic and cardiovascular effects. One possible explanation is that the respiratory effects of ambient PM are enhanced by co-pollutants that are not present in clinical exposure studies, although several controlled human exposure studies that exposed people to fine CAPs + NO_2 or ozone have not shown impacts on airway inflammation, systemic inflammation, or lung function (Gong et al., 2005; Huang et al., 2012; Sivagangabalan et al., 2011; Urch et al., 2010)."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 31, Lines 26-34: "The ISA cites a human clinical study, Liu et al. (2017), as evidence that $PM_{2.5}$ causes perturbation of the blood-brain barrier (BBB). However, the study did not observe a significant change in the BBB biomarkers S100B, NSE, or UCHL1 with exposure to fine, coarse, or UFP CAPs. The p-values in some of these comparisons were less than 0.1, but not less than 0.05. There was a significant relationship between a component of coarse PM and S100B, but this is difficult to interpret in the absence of a total PM effect. There were no effects of concentrated UFP on any marker. Since UFP is the size fraction most capable of transport to the brain, this finding is counter-intuitive. This study should not be interpreted as showing an effect of PM on the BBB, especially considering the many comparisons made in this study."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 32, Lines 13-19: "Chapter 10, Lung Cancer - This chapter reviews new studies addressing lung cancer incidence and mortality in relation to long-term PM exposure. However, the issue of the long lag time that can exist between the inciting exposure and the first clinical signs of cancer is not adequately addressed in the ISA. Most of these studies evaluated $PM_{2.5}$ exposures a few years before cancer diagnosis or death. Over these time frames, it is likely that most of the lung cancer cases already had the disease, albeit in a pre-clinical state, at the time the exposure was assessed. Thus, the findings in these studies may reflect reduced survival of already incident cancer, rather than true increased lung cancer incidence."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 32, Lines 21-25: "The cancer section notes that many studies find the greatest effects of $PM_{2.5}$ in non-smokers. The possible biological reasons for this pattern should be discussed, as well as how it fits in with other information. For example, is it consistent with evidence that animal studies with $PM_{2.5}$ exposure have not shown increased carcinogenesis, except with animals that were pre-initiated with urethane (Pereira et al., 2011)?"

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 33, Lines 32-37: regarding Sato et al. (2003) "The issue with the study in this case is not the exposure to a mixture, but that PM concentrations in the roadside air were not quantified. One could therefore argue that this study should not be included in the ISA, since it does not meet the screening criteria stated in the Preface, page P-14, indicating the focus is on studies that "…(1) include a composite measure of PM or (2) characterize PM and apply some approach to assess the direct effect of PM when the exposure of interest is a source-based mixture…."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 33, Lines 21-31: Regarding $PM_{2.5}$ and CNS - "The toxicology studies have largely been done by a single group. Those animal toxicology studies that were completed by other groups do not provide adequate evidence because the control animals were exposed to gaseous pollutants (Tyler et al., 2016) or were exposed for only two weeks in addition to OVA-sensitization (Campbell et al., 2005). For the brain size epidemiology studies, brain volumes were only measured once in each person and were compared between people. But brain volume can vary up to two-fold between normal people (Reardon et al., 2018), so this seems like an endpoint that could be subject to substantial error. Additionally, the cognitive function epidemiology studies found largely non-statistically significant results (see Figures 8-3, 8-4, and 8-5), including two of the studies that the EPA cited in Table 8-20 (Weuve et al., 2012 and Tonne et al., 2014). Altogether, this evidence does not provide evidence of health effects that are not explained by chance, confounding, or bias, and that have been done by multiple research groups."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 33, Lines 33-38: "Chapter 8, Nervous System Effects - UFP - The ISA does not provide adequate evidence to support the conclusion that there is likely to be a causal association between long-term UFP exposure and nervous system effects. There are no supportive human studies, and the EPA has not considered the appropriate dosimetric adjustments, or rodent-to-human differences in the respiratory tract, that would help extrapolate the animal data to humans. In addition, most of the animal studies that provide coherence were done by a single group in a single location."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 33, Line 42 to page 34, line 3: "There is inadequate evidence for the "likely to be causal" conclusion for long-term $PM_{2.5}$ exposure and cancer. This determination relies largely on epidemiology studies that, as noted above, do not provide exposure time frames that are appropriate for cancer causation. There are no animal studies showing direct effects of $PM_{2.5}$ on cancer formation, with the only positive animal results coming from a group that pre-initiated the animals with urethane."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 34, Lines 11-19, re: conflicting evidence, "In controlled human exposure studies that investigated blood pressure (BP), Bellavia et al. (2013) found increased SBP with exposure to 242 ug/m3 Toronto CAPs; Brook et al. (2009) showed increased DBP (not SBP) with exposure to 148 ug/m3 Toronto CAPs; and Sivagangabalan et al. (2011) showed increased DBP (not SBP) with exposure to 154 ug/m3 Toronto CAPs. No effects on BP were seen with fine CAPs exposure in Brauner et al. (2008), Brook et al. (2002), Gong et al. (2003, 2004, or 2005), Hemmingsen et al. (2015), Huang et al. (2012), or Mills et al. (2008). These studies exposed individuals who were healthy, elderly, overweight, with COPD, asthma, or CHD, to $PM_{2.5}$ CAPs concentrations up to 207 ug/m3."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 34, Line 20-29: "Section 6.1.2.1, ED visits and hospital admissions. This section concludes by saying that recent studies "continue to provide evidence for positive associations between short-term $PM_{2.5}$ exposure and IHD ED visits and HA." However, the preceding text and Figure 6-2 (please note the separate comment about the error in this figure) show considerable heterogeneity in the findings of the studies conducted since the 2009 ISA. There was one study with a positive but not statistically significant result (Bell et al., 2015), one with a positive statistically significant result (Kloog et al., 2014), one with associations only in NYC but not the rest of the state (Hsu et al., 2017), one with associations in 2 of 7 states (Talbot 2014), one with a negative association (Milojevic et al., 2014), and two single city studies with opposite results (Kim et al., 2012, Sarnat et al., 2015). This section should strengthen the rationale for the conclusions."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 34, Lines 31-35: "Section 6.1.12, Coagulation. The statement is made in the second paragraph that "When considered as a whole, these recent studies do provide additional evidence that short-term exposure to $PM_{2.5}$ can promote clot formation." However, the section goes on to describe considerable inconsistency in the findings from epidemiological, human clinical, and toxicology studies. The conclusion drawn in this section should be reconsidered and provided in a summary paragraph at the end of the section."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 34, Lines 37-39: "Section 6.1.1, Short-Term Exposure to $PM_{2.5}$, Biological Plausibility. The results of Langrish et al. (2014) do not support the conclusion that $PM_{2.5}$ has effects on heart conduction abnormalities. The EPA should clarify how they choose biological plausibility endpoints in the presence of conflicting evidence."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 35, Lines 6-17: "Some members of CASAC think that the EPA should do further work on C-R functions. In the Draft ISA, the EPA concludes that the evidence from epidemiology studies largely supports a linear, no-threshold association between $PM_{2.5}$ and various health effects. However, a number of statistical studies have shown that the error (e.g., measurement error) in these types of epidemiology studies lead study authors to the erroneous conclusion that C-R functions are linear with no threshold when that is not, in fact, the case (Rhomberg et al., 2011; Brauer et al., 2002; Cox, 2018; Lipfert and Wyzga, 1996; Watt et al., 1995; Yoshimura, 1990). Therefore, the EPA should not be using these epidemiology studies to draw conclusions about the true shape of the relationship between $PM_{2.5}$ and health effects, unless it can strongly argue (and provide evidence) that the referenced epidemiology studies can produce an unbiased estimate of the true shape of the C-R function. In addition, this conclusion is not consistent with the evidence of a threshold of effects demonstrated in human controlled exposure and animal toxicology studies (discussed above)."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 35, Lines 19-23: "The EPA should consider deriving C-R relationships from animal and human controlled exposure studies, where we can be more certain that the effects are caused by the exposure, and there is less error to bias the shape of the relationship. Interpretation and extrapolation from either epidemiology or experimental C-R relationships is impacted by whether the relationship is quantal or graded, and so the EPA should include this information in their discussion of these responses."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 35, Lines 25-39: "If the EPA does use C-R functions derived from epidemiology studies with binary outcomes (assuming, importantly, that there is a causal relationship between the concentration and the response), they should consider these functions as quantal relationships. Quantal relationships generally have Gaussian distributions and describe a continuum of a population response to an exposure where the response is binary (e.g., percent of population who experienced an asthma attack, or who died). Quantal relationships asymptotically approach a response of 0 percent as the concentration decreases and 100 percent as the concentration increases. The smallest effective concentration of any chemical or substance that causes a pre-determined amount of an all-or-none response may be referred to as a threshold concentration even though it cannot be determined experimentally. Therefore, by their asymptotic Gaussian nature quantal dose responses cannot identify a concentration where 0% of people are responders, and so it is standard practice in toxicology-risk assessment to set an effect level (such as a 10%, 1%, or 0.1% response level) and designate the concentration that causes that effect level to be the threshold dose or concentration. Using this method, the EPA could dictate the threshold response, and therefore concentration, from a type of relationship that otherwise by its nature does not allow the identification of a concentration that causes a response in 0% of the population."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 36, Lines 1-9: Other members of CASAC think that… "In the case of PM, understanding of C-R relationships at low exposure concentrations must come from epidemiology. Toxicological and human clinical studies have a limited role, especially with regard to mortality. For example, mortality and morbidity are not outcomes of human clinical studies, by design. Additionally, clinical studies are generally conducted at concentrations higher than ambient concentrations, in order to provide a contrast with prior ambient exposures of the subjects. Further, clinical studies involve relatively small numbers of subjects and generally do not include individuals with severe disease or frailty that may make them more susceptible to effects from relatively low PM concentrations. For these reasons, clinical studies unfortunately provide little help in informing thresholds of effect for PM."

This is an important and valid point.

Page 36, Lines 24-25: (regarding populations and lifestages potentially at increased risk): "The 4-level grading of the conclusions is logical and reasonable, and parallels the approach taken for causality determinations."

This is an important and valid point.

Page 36, Lines 25-42: "When considering genetic factors such as glutathione polymorphisms, the EPA should look at the effect of the polymorphism (i.e., does it increase or decrease the effectiveness of the glutathione system), and not just whether there is an association with any glutathione polymorphism. Similarly, the EPA should integrate their conclusions between chapters. For example, one would expect that older adults (compared to younger adults) would be more susceptible to the toxic effects of PM (because as a group older people would be frailer and have more diseases). However, the section on older adults (for which there have been many studies) does not find that older age is consistently a risk factor."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 37, Lines 20-21: "It is recommended that the EPA perform more analyses for different size fractions to determine whether various effects on visibility, climate, and materials are observed."

It is not the role of the ISA to perform new analyses. The CASAC is lacking in experts with relevant expertise and experience to this subject matter. CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 37, Lines 26-27: "A "Research Needs" section should be added to the final ISA. In addition, line numbers should be added for pages 13-1 through 13-56."

Research needs are identified in the Policy Assessment, not the ISA. CASAC members should review the IRP.

Page 37, Lines 33-34: "How this distinction can or will be used for setting a secondary standard needs to be included in the document."

This is an inappropriate comment. This is a matter for the Policy Assessment, not the ISA.

Page 37, Lines 38-39: "Setting a secondary standard given such variability will be very difficult."

This is an inappropriate comment. This is a matter for the Policy Assessment, not the ISA.

Page 38, Lines 35-36: "For climate effects, uncertainty in the effects of complex aerosol composition on climate needs to be better resolved."

The CASAC is lacking in experts with relevant expertise and experience to this subject matter. CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 39, Lines 40-42: "For effects on materials, it was difficult to determine from the literature review presented in the ISA at what level damage to materials was unacceptable and how that relates back to PM concentration, size, and mixture."

The CASAC is lacking in experts with relevant expertise and experience to this subject matter. CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.

Page 40, Lines 4-7: "It would be helpful for the CASAC to have ready access to an expert that studies the effects of PM on visibility impairment, climate, and materials. This would allow for additional insight into the non-ecological welfare effects and better inform our recommendations on the appropriate level for the secondary PM standard."

CASAC requires more breadth and depth of expertise, and diversity of perspective within key disciplines, to assess this issue. Thus, EPA should reinstate the arbitrarily and capriciously disbanded CASAC PM Review Panel.