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Dr. Tony Cox
Chair
Clean Air Scientific Advisory Committee

Dr. Cox,

Thank you for your letter of December 17, 2018 providing additional questions following the December 12-13, 2018 meeting of the Clean Air Scientific Advisory Committee (CASAC) on the External Review Draft of the Particulate Matter Integrated Science Assessment (PM ISA). For ease of review, I grouped your questions so that they can be mapped to our overarching approach for developing the ISA and the background documents provided to CASAC. I hope my responses to your questions will be helpful as you finalize your draft peer review report.

The approach EPA uses to develop the ISA is to systematically identify, evaluate and summarize the relevant peer reviewed scientific evidence. This approach is described in the Preamble to the ISAs (EPA, 2015), the Integrated Review Plan for the PM NAAQS (EPA, 2016), and various sections of the draft PM ISA. The ISA focuses on the evaluation of evidence available in the peer reviewed literature and, therefore, utilizes an approach that is not amenable to hypothetical scenarios or ad hoc analyses that might be framed in a thought experiment.

To start, we use the term "independent effect" not to disregard the fact that all the health outcomes we evaluate in the ISA are multi-etiological, but instead to ensure we are operating within the confines of our task of assessing the scientific evidence for each of the criteria pollutants as defined by the Clean Air Act. In the "thought experiments" you outline in your comments you are correct in that other factors besides air pollution can "cause" some health effects, but as I'm sure you are aware, epidemiologic studies go to great pains to identify these factors and to ensure they are controlled for through study design and advanced statistical models. By controlling for these factors (i.e., confounders), researchers are using models in an attempt to identify whether there is an independent association between a health effect and PM exposure. However, it is important to note that in assessing whether there is an independent effect, epidemiologic studies are not used alone, we also consider evidence from experimental studies where animals and subjects have been exposed to one pollutant at a time.

It is important to recognize that EPA does not focus solely on epidemiologic evidence when forming the causality determinations for each of the broad health outcome categories evaluated in the draft PM ISA. Rather, as emphasized in our presentation at the December 12th CASAC meeting, when evaluating health outcomes, the EPA considers multiple studies from multiple lines of evidence including epidemiology, exposure, dosimetry, and experimental evidence (both controlled human exposure and animal toxicological studies) to support determinations as to whether there is an independent effect of PM on health. All causality determinations, whether on human health to support the primary NAAQS or on welfare to support the secondary NAAQS, are based on the approach of considering the collective body of evidence. I am hopeful the information noted above addresses your *Questions on definition of "independent effect"*.

With respect to your 54 wide ranging *Questions on definitions of causal determination categories*, I would note that over the last 10+ years the causal framework developed by EPA has been reviewed by 11 CASAC panels including 138 individual members. The interpretation and application of the causal framework used to make conclusions within ISAs has been informative to decisions on every NAAQS since 2008, hence the structure and content of the ISA has proven to be effective for the identification, evaluation and summarization of the most policy-relevant science to support NAAQS decisions by the EPA Administrator. You identified a series of topics under this heading that are addressed below.

- Your questions on "*Causality and preventability*" and "*Strength of casual relationships and sizes of effects*" include hypothetical aspects and generally seek information on whether reducing PM exposure would reduce response (i.e., risk), and to what extent. The draft PM ISA builds on a long and extensive record of epidemiological and experimental studies and conveys the available evidence on the relationship between exposures and response, including studies that indicate the occurrence and extent of reduction in responses observed with reductions in PM exposures. Such studies, often termed accountability studies, are evaluated and discussed within the ISA (e.g., Section 5.2.11; Section 11.2.2.6) if they fit within the scope of the ISA as detailed in the Preface, i.e., included a composite measure of PM, such as PM_{2.5} mass.
- Regarding your questions on "*Homogeneity of causal relationships*", Chapter 12 on Populations and Lifestyles Potentially at Increased Risk of a Particulate Matter-Related Health Effect, identifies, evaluates and summarizes the evidence on factors that influence inter-individual and inter-population differences in health response from exposures to PM. As detailed in Chapter 12, this information directly supports the role of the NAAQS in protecting public health with an adequate margin of safety, including "protection of the population as a whole and for those groups potentially at increased risk for health effects." Further, the forest plots provided in various chapters demonstrate positive associations for numerous health effects across various factors including age and pre-existing disease with normalized PM exposures.

- Regarding your questions “*Are causal determination categories mutually exclusive and collectively exhaustive*”, the simple answer is no. The EPA and other organizations have supported and conducted extensive research on PM that results in new studies and insights on older studies the EPA considers in the PM ISA. In the draft PM ISA the causality determinations for the various health and welfare outcomes is based on judging the collective body of evidence available at this time (e.g., Table 5-18; Table 6-34). Causality determinations may change over time with the identification and evaluation of new evidence considered in the context of the evidence identified in prior reviews. This is evident in this review with the addition of new causality determinations for Metabolic Effects (Chapter 7) and the change in causality determinations for long-term PM_{2.5} exposure and nervous system effects (Section 8.2.9) and cancer (Section 10.2.2.5). The EPA does not engage in hypothetical analyses such as you describe in the “*Updating evidence categorization*” questions.
- Regarding your questions on “*Operational definitions of ‘adequacy and sufficiency’*” and “*Certainty of causal relationship category*”, the defining conditions are as indicated in the Preamble to the ISAs (EPA, 2015) and Preface to the PM ISA (Section P.3, Table P-2).
- Regarding the conditions you constructed and the questions you posed on “*Categorizing simple cases where all relevant information is known*”, as noted above the purpose of the PM ISA is to effectively identify, evaluate and summarize the available scientific evidence that is published in peer-reviewed literature. The EPA does not conduct hypothetical probability analyses in the ISA.
- Regarding your questions on “*Quantity of evidence needed for a causal determination*”, the EPA identifies, evaluates and summarizes the evidence spanning scientific disciplines, not just epidemiology, that is available in the published peer-reviewed literature and considers this evidence informing causality determinations using a well-established weight-of-evidence framework. The EPA does not count studies nor conduct hypothetical analyses in developing causality determinations.
- Regarding your questions about “*Discordant evidence*”, it is not unusual for studies conducted by different research groups in different locations with varying PM exposures and populations to show differing results. Such evidence is illustrated in the forest plots for the various health endpoints. Careful evaluation of the full range of published findings, whether showing a positive, negative or null response to PM exposure, is important in the weight-of-evidence evaluation. The EPA considers the varying evidence including results from epidemiologic, toxicological and other lines of evidence in developing causality determinations. The EPA does not engage in hypothetical analyses such as you describe.

In closing, we appreciate the time you and the members of CASAC have committed to addressing the Charge questions provided by EPA for the review of the PM ISA. We look forward to receiving your response to the EPA Charge.

Sincerely,

/s/

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