Clean Air Scientific Advisory Committee (CASAC)

A Federal Advisory Committee to the U.S. Environmental Protection Agency

November 22, 2022

EPA-CASAC-23-001

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

Subject: CASAC Review of the EPA's *Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report - April 2020)*

Dear Administrator Regan:

The 2022 Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel, hereafter referred to as the Panel, met on April 29, 2022, to receive a briefing from the EPA on the *Policy Assessment (PA) for the Reconsideration of the Ozone National Ambient Air Quality Standards (External Review Draft – April 2022).* During and after this meeting, several scientific issues were raised by members of the Panel. The Panel met on June 8 and June 10, 2022, and agreed that a fuller discussion of the science was needed before the Panel could review the PA. The CASAC Chair, with input from the Panel, drafted a set of discussion points with specific questions to help focus and guide the Panel's deliberations. The Panel met on August 29, 2022, September 12-16, 2022, and November 14-15, 2022, to discuss the scientific issues from the EPA's *Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report - April 2020)*, hereafter referred to as the 2020 ISA. The Chartered CASAC approved the Panel's report on November 15, 2022.

The responses below reflect the CASAC's evaluation of the scientific issues in the 2020 ISA to inform its future review of the PA. The CASAC is not recommending that the 2020 ISA, which is a final document, be reopened and revised, but does offer advice for consideration in future reviews. Overall, the CASAC finds the ISA to be well written, and offers comments and advice on several issues and areas for improvement in future reviews that are highlighted below. The CASAC acknowledges the accelerated timeline for completion of the 2020 Ozone ISA which may have contributed to several of these issues. The CASAC finds that the existing scientific evidence summarized in the 2020 ISA provides a scientifically sound foundation for the Agency's reconsideration of the 2020 Ozone NAAQS decision. Regarding the Agency's judgements, in some instances the CASAC does have differing opinions, as detailed below.

The ISA does a good job of presenting atmospheric sources, chemistry, meteorology, trends, and background ozone. However, in a future review, it should clearly state whether exceptional events (such as wildfires) have been included or excluded from the ozone design values and ozone concentration

trends presented. Alternatively, the EPA could also present the data both with and without exceptional events. A future ISA should discuss how the treatment of exceptional event designations are handled in the EPA ozone measurement databases used in epidemiology studies and exposure assessments, and whether there is potential for bias.

In the 2020 ISA, evidence from the epidemiology, controlled human exposure (CHE), and animal toxicology studies is considered in a generally thorough and balanced manner. The CASAC finds that the ISA lacks sufficient information to adequately differentiate or differentially weight lines of evidence from observational and CHE studies examining ozone health effects. The scientific evidence suggests that ozone exposures in the ambient environment and CHE study exposures are different since the ambient environment includes photochemical oxidants in addition to ozone. As such, the CASAC advocates a cautious approach when interpreting differences or inconsistencies in health effects associated with ozone, particularly with respect to epidemiological versus CHE studies. The acknowledged differences in laboratory-generated ozone and the ambient photochemical oxidant mix create uncertainty and potential errors for both controlled and observational designs. The ISA provides a thorough discussion on the varying exposure metrics used in observational study designs, with excellent treatment of potential errors from using these various metrics. However, it does not discuss exposure metrics used in controlled settings – a noticeable omission limiting inference. These uncertainties, in both lines of evidence, make differential weighting extremely difficult.

The CASAC suggests that for future ISAs the EPA consider revising its approach to interpreting evidence from CHE and epidemiological studies. Relative weighting of study findings is scientifically more robust when based on individual study details, strengths, design, and infrastructural study planning and execution rather than a more generic up-scaling or weighting of one approach over another. The CASAC suggests consideration of the various study designs on their own merit, to combine the relative strengths of the various design approaches to arrive at the most informed interpretation given study strengths and uncertainties. This approach is relevant when interpreting the evidence for causality determinations and also to help identify and establish exposure levels associated with no adverse health effects. The latter consideration, one particularly relevant for the PA, relates to how CHE studies characterize health effects at low concentrations. The following summarizes the primary reasons why ozone CHE studies may underestimate or miss ozone effects at low concentrations: participants are not representative of the general population; exposures are usually to a single pollutant and of relatively short duration; exposures are to laboratory-generated ozone without other photochemical oxidants; and prior ambient pollutant exposures may affect the CHE ozone responses but are not typically characterized in CHE studies.

The concentrations and health impacts of related photochemical oxidants, relative to ozone alone, are largely unknown, but are relevant to the interpretation of findings from CHE and epidemiology studies. The CASAC recommends that future reviews thoroughly investigate this topic and more fully examine the strengths and weaknesses of CHE and epidemiology in understanding health effects at ambient concentrations. Future reviews should also directly address the differences in concentration-response relationships between CHE and epidemiology studies. Further, when evaluating ozone health effects at low concentrations and in at-risk groups in future reviews, epidemiological findings should be considered just as, or even more, relevant than the CHE findings in determining an exposure level with no adverse effects.

In future reviews, the CASAC recommends that the EPA not restrict the geographic regions considered for health studies in its Population, Exposure, Comparison, Outcome, and Study design (PECOS) statements without an appropriate and strong rationale. The CASAC has concerns about transparent and

uniform application of eligibility criteria for study inclusion and about differential application of geographical location across health endpoints and exposure durations in determining study eligibility for consideration. More transparent and consistent eligibility criteria are preferable for future application.

The CASAC concurs with the EPA that the evidence supports a "causal" relationship between short-term ozone exposure and respiratory effects. Regarding long-term ozone exposure and respiratory effects, a minority of CASAC members concur with the EPA that the evidence supports a "likely causal" relationship due to remaining uncertainties regarding copollutant confounding, failure of some long-term studies to adjust for short-term exposure to ozone, and inconsistent findings with mortality. The majority of CASAC members find that the evidence is more consistent than is indicated in the ISA and that the evidence supports a "causal" relationship. They find that there has been overall increasing evidence and decreasing uncertainty for long-term respiratory effects since the 2013 ISA, studies in primates and rodents provide experimental evidence for long-term airway effects from ozone exposure, and that there are serious limitations in some of the studies cited in the 2020 ISA as supporting a weaker causal determination.

Particularly relevant to providing an adequate scientific basis for consideration of short-term respiratory effects in the PA, there is inadequate discussion of exposure concentrations in the 2020 ISA and previous ozone ISAs, especially with regard to comparing and contrasting the epidemiological and CHE studies. There is no acknowledgement or discussion of the discrepancy between the lowest exposure concentrations at which health effects associations are seen in the epidemiology studies and the lowest effect concentrations in the CHE studies. The latter are substantially higher than the former. This issue is important because prior PAs have interpreted the absence of effects below 60 to 70 ppb in the CHE studies as evidence that adverse effects do not occur below these concentrations, effectively placing less weight on the epidemiological associations of morbidity and even mortality at lower concentrations.

For short-term exposures and cardiovascular effects, the ISA finds that the evidence supports a "suggestive of, but not sufficient to infer, a causal relationship." Some CASAC members concur and put more weight on uncertainties, inconsistent study results, and the relative lack of new studies to address the uncertainties. Other CASAC members do not concur and find that the evidence supports a "likely causal" relationship. They find that the ISA places too much emphasis on the CHE studies over epidemiological studies. For long-term exposures and cardiovascular effects, some CASAC members concur with the EPA that the evidence supports a "suggestive of, but not sufficient to infer, a causal relationship" due to uncertainties from the lack of morbidity findings and somewhat inconsistent findings in animal toxicology studies of long-term exposure and cardiovascular mortality. Other CASAC members find the evidence supports a "likely causal" relationship due to the strength of the cardiovascular mortality epidemiology evidence.

For short-term ozone exposure and mortality, the ISA finds the evidence to support a "suggestive of, but not sufficient to infer, a causal relationship." Some CASAC members concur due to the weakness of the cardiovascular morbidity data. Other CASAC members do not concur and find the evidence supports a "likely causal" relationship due to: consistency of the evidence; overemphasis on CHE studies vs. epidemiological studies; and concerns about transparent and uniform application of eligibility criteria for study inclusion in the evidentiary review. For long-term ozone exposure and mortality, some CASAC members concur with the EPA that the evidence supports a "suggestive of, but not sufficient to infer, a causal relationship." Other CASAC members find that the evidence supports a "likely causal" relationship as there is relatively strong epidemiologic evidence for long-term ozone exposure and increased cardiovascular mortality. They find there to be technical design or analysis issues with some of the studies used to reach the "suggestive" causal determination.

The CASAC finds that the sections characterizing the scientific evidence on the developmental effects from ozone exposure are clear and well written and concurs with the causal determinations. Regarding lung function and development, the CASAC concludes that there is increasing evidence since the 2020 ISA that should be considered in a future review and that likely strengthens the body of evidence. The effects of long-term exposure to ozone on pediatric lung function has accumulated in recent years. This is an important outcome because lung function develops rapidly through childhood and decrements in early life may portend lifelong deficits in maximum attained lung function. Such deficits are associated with chronic disease in adulthood such as chronic obstructive pulmonary disease (COPD). The more recent analyses of long-term exposure on pediatric lung function include addressing copollutants. The consistency and coherence of these findings along with the experimental data in rhesus monkeys suggest that a future review may find the evidence is compelling for reconsideration of the overall causality of long-term effects of ozone on lung function and development.

EPA's treatment of at-risk populations from ozone exposures in the 2020 Ozone ISA is thorough and well structured. Overall, the CASAC concurs with the classifications given in the ISA for the listed at-risk populations. The CASAC suggests the inclusion of pregnant women and developing fetuses in future reviews. A thorough analysis of differences in exposure due to spatial variation that is often associated with sociodemographic factors, especially race/ethnicity, class and income is missing. This type of analysis enables the PA to better assess risk in these communities by understanding the variation in ozone concentrations present over a geographic area. The EPA has made considerable progress in its consideration of at-risk populations and the CASAC looks forward to additional advances in future reviews.

The CASAC finds that the ISA provides a comprehensive and well-written review of the scientific evidence on ozone effects on vegetation and ecosystems. There is a strong consensus by the CASAC that the review of the evidence summarized in the ISA continues to provide robust support for consideration of alternate forms of the secondary standard in the PA. First, it is well established that a cumulative weighted index, such as W126, is the most appropriate for understanding and monitoring ozone impacts on vegetation and ecosystems. Second, research shows that a single year of high ozone exposure can affect plant growth and yield, with longer term, cumulative effects in subsequent years for perennial species. Third, the W126 metric and the primary standard of the 3-year average of the 4th highest 8-hour average ozone concentration capture different features of the ozone distribution. Consequently, the CASAC finds that the scientific evidence supports consideration of a distinct secondary standard (level, form, averaging time) in the PA.

The CASAC concurs with the "causal" determination for tropospheric ozone and radiative forcing. Since global mean surface temperature is directly related to the ozone radiative forcing, the CASAC recommends in future reviews that "temperature" be removed from the "temperature, precipitation, and related climate variables" category and added to the "radiative forcing" category for causal determination. Based on the clear evidence for ozone impacts on radiative forcing and temperature, a "causal" determination for this category is appropriate. Since radiative forcing is not directly measured, global mean surface temperature may serve as a better indicator of the causal effects.

The CASAC appreciates the opportunity to provide advice on the 2020 ISA and looks forward to the agency's response.

Sincerely,

/s/

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

Enclosures

NOTICE

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

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

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Consensus Responses to Discussion Points on the EPA's
Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants
(Final Report, Apr 2020)

Introduction

The 2022 Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel, hereafter referred to as the Panel, met on April 29, 2022, to receive a briefing from the EPA on the *Policy Assessment (PA) for the Reconsideration of the Ozone National Ambient Air Quality Standards (External Review Draft – April 2022).* During and after this meeting, several scientific issues were raised by members of the Panel. The Panel met on June 8 and June 10, 2022, and agreed that a fuller discussion of the science was needed before the Panel could review the PA. The CASAC Chair, with input from the Panel, drafted a set of discussion points with specific questions to help focus and guide the Panel's deliberations on the science. The Panel met on August 29, 2022, September 12-16, 2022, and November 14-15, 2022, to discuss scientific issues from the EPA's *Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report - April 2020)*, hereafter referred to as the 2020 ISA. The Chartered CASAC approved the Panel's report on November 15, 2022.

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Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

Appendix 1 does a good job of presenting atmospheric sources, chemistry, meteorology, trends, and background ozone. The 2020 ISA contains the most recent information that was available at the time it was assembled (e.g., 2014 National Emissions Inventory and ambient air quality concentrations and trends data through 2017). In a future review, the ISA should include a discussion on the significant increase in volatile organic compound (VOC) emissions for "Petroleum & Related Industries" between 2005 (~500 kTons) and 2011 (~2,900 kTons). More recent information on precursor source emissions and ambient ozone concentration trends has been included in the April 2022 Draft Policy Assessment (PA), e.g., 2017 National Emissions Inventory, 2018-2020 design values, and 2000-2020 ozone trends. The more recent information is generally consistent with the trends in the 2020 ISA.

As ozone peak concentrations have shifted from summer to spring in many U.S. areas, warm season ozone monitoring (e.g., May through September) may miss ozone episodes due to spring and fall wildfires. Further, the effects of meteorology and climate events on peak ozone concentrations need additional examination. The global standard for ozone measurement will result in a 1.23% increase in concentration on January 1, 2024 (https://www.bipm.org/en/bipm-workshops/surface-ozone). The National Institute for Standards and Technology (NIST) and EPA standard reference photometers, the basis for calibration of ambient ozone monitors, will be adjusted, resulting in higher reported ambient ozone concentrations. At 70 ppb, the increase would be 0.86 ppb.

In a future review, Appendix 1 should discuss data fusion studies that estimate ozone spatially by combining ozone measurements with model output. Data fusion can accurately fill in the gaps between monitors resulting in more meaningful exposure metrics, such as population-weighted concentrations, or spatial averages over the continental U.S.

The EPA allows the exclusion of high ozone concentrations due to wildfires under the exceptional event rule when calculating official ozone design values. In a future review, the EPA should clearly state if exceptional events have been included or excluded from the ozone design values and ozone concentration trends presented in this Appendix. Alternatively, the EPA could present the data both ways (with and without exceptional events). Also, a future ISA should discuss how exceptional event designations are handled in the EPA ozone measurement databases used in epidemiology studies and exposure assessments, and whether there is potential for bias.

U.S. background (USB) ozone is defined as ambient ozone that would be present at ground level within the U.S. in the absence of all U.S. anthropogenic ozone precursor emissions. Major contributors to USB ozone concentrations are stratospheric exchange, international transport, wildfires, lightning, global methane emissions, and natural biogenic and geogenic precursor emissions. The existing literature on USB trends has focused mainly on monthly or seasonal means. However, USB on days with high ozone concentration (e.g., fourth highest daily max 8-hour average ozone concentration) are the most relevant for the PA. In the western U.S., peak USB ozone concentrations are approaching the current level of the ozone NAAQS (70 ppb) in some locations. Details can be found in Dr. Boylan's individual comments.

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.

For consistency, the same emissions source category break-down presented in Figure 1-2 and Figure 1-3 should be carried forward into the PA. Also, the policy implications of removing exceptional events from official design values and high USB ozone concentrations in the western U.S. should be discussed in the PA.

Ozone and Photochemical oxidants (Appendix 1, 2)

a. What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone?

The CASAC finds that Appendices 1 and 2 are well written and thorough, but lack sufficient information to adequately differentiate or differentially weight lines of evidence from observational and controlled human exposure (CHE) studies examining ozone health effects given the consideration

detailed below. The CASAC agrees that residual uncertainties regarding ozone chemistry and varied human exposure assignments within the available research studies necessitate further investigation to inform these questions and future ISAs.

There is ample evidence to suggest that responses to ozone generated in CHE studies may differ from responses in epidemiology and panel studies, with real-world exposures to complex mixtures of ozone and photochemical oxidants. *Ozone, as noted by the CASAC, should rightly be viewed as the designated indicator of total exposure to photochemical oxidants*, a complex pollutant mixture not replicated in CHE settings which employ ozone alone. Conversely, it is possible that ozone measured at stationary ambient monitoring sites, as a marker of population exposure to total photochemical oxidants, may not fully reflect either total individual-level exposure or biologically-relevant oxidant exposures. The CASAC views that the respective strengths and weaknesses in ozone exposure assignment, by study design, necessitate a balanced consideration of evidence from multiple, complementary study lines.

The scientific evidence in the 2020 ISA suggests that ozone exposures in the ambient atmosphere and CHE study exposures are different since the ambient environment includes photochemical oxidants in addition to ozone. As such, the CASAC advocates a cautious approach when interpreting differences or inconsistencies in health effects associated with ozone, particularly with respect to epidemiological versus CHE studies. (A more detailed discussion of dealing with uncertainty across varying lines of evidence and study designs is provided in the Health Effects – Overarching Comments section below).

The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers.

The acknowledged differences in laboratory-generated ozone and the ambient photochemical oxidant mix create uncertainty and potential errors for both controlled and observational designs. Appendix 1 provides a thorough discussion on the varying exposure metrics used in health effect study designs, with excellent treatment of potential errors from using these various metrics. However, the appendix does not discuss exposure metrics used in controlled settings – a noticeable omission limiting inference related to the discussion question above. These uncertainties, in both lines of evidence, make differential weighing extremely difficult.

Human panel studies employ quasi-controlled protocols and are typically conducted in real-world settings. These research designs, as such, lie at the intersection of observational epidemiology and controlled human exposure studies and may offer unique insights into the similarities and differences reported in epidemiological and CHE studies. While the ISA does include panel study results in its discussion of causal determination status (Appendices 3 and 4), future ISAs may choose to consider, specifically, the results from ozone-related panel studies as they may explain differences in findings among various health effect study designs.

Health Effects – Overarching Comments

The CASAC suggests that for future ISAs the EPA consider revising its approach to interpreting evidence from CHE and epidemiologic studies. Relative weighting of study findings is scientifically more robust when based on individual study details, strengths, design, and infrastructural study planning and execution rather than a more generic up-scaling or weighting of one approach over another.

In the case of CHE and epidemiology studies, both study paradigms (in addition to toxicological investigations involving animals, cellular testing or even *in silico* modeling using computer technologies) have relative strengths and weakness that should be considered when evaluating evidence for the purpose of causality determination. Multiple study designs have and will be developed within each paradigm. Because of the randomized and controlled design, well-conducted CHE studies can provide unique insights regarding mechanisms of effect and concentration-response data that can contribute to causality conclusions. However, CHE studies are routinely performed on a limited number of generally healthy volunteers, include a limited duration of exposure, and with few opportunities for follow-up of more delayed effects. CHE study participants are usually young, healthy, and fit adults. Important segments of the general population (such as children, pregnant women, senior adults, or those with pre-existing severe or unstable respiratory or cardiovascular disease) are usually excluded from study participation for ethical or safety reasons, but this feature limits the potential relevance of any findings to the general population and that may limit the contribution of CHE findings to causality determinations.

Epidemiological studies, like CHE studies, have advantages and limitations for causal determination. Epidemiological studies often include a wider range of study participants, including populations that may not be feasible to study in a CHE design (e.g., fetuses, children, individuals with pre-existing disease) or individuals who may often not be included in CHEs (e.g., individuals from historically marginalized populations, individuals with disadvantaged socioeconomic status). Further, epidemiological studies can evaluate longer-term exposure and exposure to the real-world ambient complex of mixtures as well as outcomes that are more delayed in nature. However, epidemiological studies may be limited in their ability to address and minimize confounding, for example by copollutant exposures, and by potential selection and information bias, which may limit the contribution of results from epidemiological studies to causality determinations.

The CASAC suggests consideration of the various study designs on their own merit, and to combine the relative strengths of the various design approaches to arrive at the most informed interpretation given study strengths and uncertainties. This approach is relevant when interpreting the evidence for causality determinations and also to help identify and establish exposure levels associated with adverse health effects.

The latter consideration, one particularly relevant for the PA, relates to how CHE studies characterize health effects at low concentrations. The following summarizes the primary reasons why ozone CHE studies may underestimate or miss ozone effects at low concentrations:

1. Participants are not representative of the general population. They are most usually young, healthy, and fit. Individuals with severe or unstable respiratory or cardiovascular disease are not studied, for appropriate ethical reasons.

2. Exposures are usually to a single pollutant and of relatively short duration. Few studies include outcome measurements beyond 24 hours after exposure, so delayed effects are missed.
3. Exposures are to laboratory-generated ozone alone: intake air is usually filtered through HEPA and charcoal to virtually eliminate concomitant exposure to particles or ozone reaction products. Ambient exposures may include other oxidants that not only track with ambient ozone concentrations but are also explicitly included as part of this criteria air pollutant.
4. Prior ambient pollutant exposures may affect the CHE ozone responses but are not typically characterized in CHE studies

The concentrations and health impacts of related photochemical oxidants, relative to ozone alone, are unknown, but are relevant to the interpretation of findings from CHE and epidemiology studies. The CASAC recommends that future reviews thoroughly investigate this topic and more fully examine the strengths and weaknesses of CHE and epidemiology in understanding health effects at ambient concentrations. Future reviews should also directly address the differences in concentration-response relationships between CHE and epidemiological studies. Further, when evaluating ozone health effects at low concentrations and in at-risk groups, epidemiological findings should be considered just as, or even more, relevant than the CHE findings in determining an exposure level with no adverse effects.

In future reviews, the CASAC recommends that EPA not restrict the geographic regions considered for health studies in its Population, Exposure, Comparison, Outcome, and Study design (PECOS) statements without an appropriate and strong rationale. The CASAC has concerns about transparent and uniform application of eligibility criteria for study inclusion and about differential application of geographical location across health endpoints and exposure durations in determining study eligibility for consideration. Two examples where the PECOS criteria in the 2020 ISA lack sufficient rationale are:

1. The PECOS structure limited the cardiovascular-relevant studies to North America, Europe, and Australia, which differs from the restriction to the U.S. and Canada for respiratory endpoints; this difference is not justified in the ISA.
2. The PECOS structure excluded considerable research conducted in Asia that would be useful in addressing existing uncertainties without a sufficient rationale.

More transparent and consistent eligibility criteria are preferable for future application.

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

The CASAC finds that the geographical limitations of the studies considered in the 2020 ISA, as indicated in the PECOS framework, are not adequately justified, and may have inappropriately limited the evidence considered, especially for long-term respiratory health effects.

With regard to short-term respiratory health effects, the CASAC agrees with the conclusions of the 2020 ISA, that "…there is a causal relationship between short-term ozone exposure and respiratory health effects." Decades of research involving animal models, epidemiology and panel studies, and CHE

studies have provided consistent and coherent evidence of acute ozone effects on a variety of measures of respiratory health, including respiratory mortality. This conclusion is unchanged from the 2013 ISA.

With regard to long-term respiratory health effects, the 2020 ISA determined that the evidence was "…sufficient to conclude that a likely to be causal relationship exists between long-term ozone exposure and respiratory effects." This conclusion is unchanged from the 2013 ISA.

The CASAC agrees that the evidence is sufficient to support, at least, a "likely causal" relationship for long-term respiratory health effects, and the majority of CASAC members find that the evidence is sufficient to support a "causal" relationship. The minority of CASAC members who agree with the ISA finding of a "likely causal" relationship, cite the remaining uncertainties regarding copollutant confounding, including failure of some long-term studies to adjust for short-term exposure to ozone, and inconsistent findings with mortality.

Among the remaining uncertainties cited in the 2020 ISA is residual copollutant confounding. The CASAC suggests that the EPA, in future reviews, reduce the reliance on multipollutant modeling as a primary means of assessing confounding. The current approach may oversimplify true covariance patterns or biologically-relevant covariance patterns and potentially obscure the presence or absence of confounding in ozone epidemiology. The CASAC suggests that increased consideration be given to the emerging use of novel confounding adjustment methods and accountability studies, such as Yazdi et al. (2021b) and Yazdi et al. (2022).

The majority of CASAC members find that the evidence supports a "causal" relationship, citing the overall increasing evidence and decreasing uncertainty for long-term respiratory effects since the 2013 ISA. Studies in primates and rodents, reviewed in the 2020 ISA and new since the 2013 ISA, provide experimental evidence for long-term airway effects from ozone exposure. Two of the "negative" epidemiological studies cited in the 2020 ISA to support a weaker causal determination had serious limitations, including very low variability of ozone concentrations (Carey et al., 2013) and low number of deaths (Bentayeb et al., 2015). In light of these limitations the majority of CASAC members conclude that there is more consistency in the findings than was characterized in the 2020 ISA. Several studies published since the 2020 ISA further strengthen the evidence for long-term respiratory effects (Lim et al., 2019; Dimakopoulou et al., 2020; Paulin et al., 2020; Wei et al., 2021). There is also increasing evidence, summarized in a 2022 review (Holm and Balmes, 2022), supporting the association between long-term ozone exposure and decreases in both lung function and lung growth in children. Overall, these CASAC members find that the strength of evidence and the minimal uncertainties are sufficient for a causal determination.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

Studies published after the cutoff date for the 2020 ISA have further strengthened the "causal" determination for short-term respiratory health effects, and the CASAC expects that the EPA will incorporate them into its next review and reach the same conclusion.

Additional studies identified above that were published after the cutoff date for the 2020 ISA, are relevant to the causality determinations for long-term respiratory health effects.

Future studies, including CHE, are needed that focus on individuals at increased risk for ozone respiratory health effects.

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

The question of weighting of the CHE studies is perhaps most relevant for the PA. In the 2020 ISA, evidence from the epidemiology, CHE, and animal toxicology studies is considered in a generally thorough and balanced manner. The findings from CHE studies of ozone over recent decades have provided invaluable information about the nature of short-term ozone respiratory health effects, exposure-response relationships, and mechanisms for effects.

However, there is inadequate discussion of exposure concentrations in the 2020 ISA and previous ozone ISAs, especially with regard to the weight of evidence from epidemiological and CHE studies. Exposure concentrations are provided in the study summary tables, and often mentioned in the text. But there is no acknowledgement or discussion of the discrepancy between the lowest exposure concentrations at which health effects associations are seen in the epidemiology studies and the lowest effect concentrations in the CHE studies. The latter are substantially higher than the former. This issue is important because prior PAs have interpreted the absence of effects below 60 to 70 ppb in the CHE studies as evidence that clinically important effects do not occur below these concentrations, effectively placing less weight on the epidemiological associations of morbidity and even mortality at lower concentrations. See also additional discussion in the Health Effects – Overarching Comments section above.

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

<u>Short-term cardiovascular effects</u>

The 2013 ISA concludes that "a likely causal relationship exists between short-term exposure to ozone and cardiovascular effects." This relationship was changed to "suggestive of, but not sufficient to infer, a causal relationship" between short-term ozone exposure and cardiovascular effects in the 2020 ISA.

The short-term epidemiological studies reviewed in the 2020 ISA suggest important associations between ozone exposure and cardiovascular effects but there are uncertainties due to inconsistent study results. Although the underlying pathways/mechanisms linking ozone exposure to cardiovascular effects have not changed since the 2013 ISA, there is a relative lack of new studies in North America and Europe since the 2013 ISA that address these uncertainties. Overall, the uncertainties identified in the 2020 ISA are also reflected in the controlled exposure studies in humans and animals that show inconsistent results. For example, there is reasonably consistent epidemiological evidence for an association between short-term ozone exposure and cardiovascular mortality, but the CASAC agrees that the 2020 ISA presents less consistent evidence for an ozone association with logical underlying mortality factors such as morbidity and physiologic- and bio-markers of cardiovascular effects, in both epidemiological and CHE studies. Given these uncertainties and inconsistencies in the evidence, some CASAC members agree that the EPA's decision to change the short-term ozone cardiovascular effects

causality determination from "likely causal" to "suggestive of, but not sufficient to infer, a causal relationship" is reasonable and appropriate. Other CASAC members do not agree with EPA's decision to change the short-term causality determination from "likely causal" to "suggestive" due to an overemphasis of CHE studies over epidemiological studies. Further details are provided in the Health Effects - Overarching Comments section above.

Long-term cardiovascular effects

The 2020 ISA concludes that the evidence is "suggestive of, but not sufficient to infer, a causal relationship" between long-term ozone exposure and cardiovascular effects and this conclusion is unchanged from the 2013 ISA.

There is relatively strong epidemiological evidence for long-term ozone exposure and increased cardiovascular mortality. The mortality association seems particularly strong given the number of post-2013 studies listed in Figure 4.7. While this mortality association points toward a "likely causal" or possibly a "causal" relationship, the lack of supporting infarction, coagulation, and hospital admission data lends uncertainty. However, a small number of panel studies have reported links between cardiac arrhythmias and short-term ozone exposure and thus support the cardiovascular mortality effect. There are also somewhat inconsistent findings in animal toxicology studies of long-term exposure and cardiovascular mortality.

Some CASAC members believe that the determination of "suggestive of, but not sufficient to infer, a causal relationship" between long-term ozone exposure and cardiovascular effects, which was unchanged from the 2013 determination, is appropriate based on the overall evidence. Other CASAC members find the evidence is strong enough to support a "likely causal" relationship based upon the cardiovascular mortality epidemiology evidence.

b. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

Some CASAC members are concerned with an overweighting of CHE studies over epidemiological studies with regards to the changing of the short-term causality determination. Further details are provided in the Health Effects – Overarching Comments section above.

c. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

Given the lack of applicable CHE studies in recent years (post the 2018 search deadline of the 2020 ISA), there is little evidence to alter the conclusions summarized above for the causal determinations. There is, however, a new panel study (Frampton et al., 2022), a CHE study (Rich et al., 2018), and several epidemiological studies, primarily in Europe and Asia, that add to the knowledge base and reduce uncertainties. More recent studies in Canada, Asia, and elsewhere generally report a positive association (e.g., Bai et al., 2019; Frampton et al., 2022; Guo et al., 2022; Ho et al., 2022; Wu et al., 2022; Zong et al., 2022).

The CASAC also notes that future research that focuses on short- and long-term ambient ozone exposures and cardiovascular effects would help reduce the remaining uncertainties.

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

For short-term ozone exposure and total mortality, the 2020 ISA states that the scientific evidence is "suggestive of, but not sufficient to infer, a causal relationship." This is a change from the 2013 Ozone ISA, which concluded that there was sufficient evidence for a "likely causal" relationship. The 2020 Ozone ISA states that "…inconsistent results from controlled human exposure studies that do not provide evidence of cardiovascular effects in response to short-term ozone exposure…" as well as a paucity of positive evidence from epidemiological studies for more severe cardiovascular morbidity endpoints and potential confounding by copollutants in epidemiological studies combined to increase uncertainties regarding the causal determinations for mortality.

The CASAC does not have consensus on the causality determination for short-term ozone exposure and mortality (the change from "likely causal" in the 2013 ISA to "suggestive" in the 2020 ISA). Consistent with their assessment for short-term cardiovascular effects, some CASAC members agree with 2020 ISA causality determination of "suggestive" for short-term ozone exposure and mortality due to the weakness of the morbidity data. Other CASAC members do not find the change in causality determination from "likely causal" from the 2013 ISA to "suggestive" in the 2020 ISA to be justified due to the overemphasis of CHE studies over epidemiological studies and non-transparent and non-uniform application of study inclusion criteria as detailed in the Health Effects – Overarching Comments section above. They find that there is more consistency in the published evidence than is implied by the "suggestive" determination.

For long-term ozone exposure and total mortality, the 2020 ISA states that the scientific evidence is "suggestive of, but not sufficient to infer a causal relationship." This is comparable to the 2013 Ozone ISA conclusion that the evidence was "suggestive of a causal" relationship.

The CASAC notes that there is relatively strong epidemiologic evidence for long-term ozone exposure and increased cardiovascular mortality. Since cardiovascular mortality is the main driver of total mortality, the CASAC agrees with the EPA that there is good justification to keep these causal determinations consistent with each other.

The 2020 ISA determination for long-term ozone exposure and mortality of "suggestive" seems appropriate to some CASAC members. The CASAC finds that there are technical deficiencies in study design, exposure assessment, and/or analytical approach that call into question three published studies (Bentayeb et al., 2015; Carey et al., 2013; and Kim et al., 2017) that had reported protective effects of ozone exposure. However, the CASAC members that reviewed these studies in detail acknowledge that they did not apply the same level of scrutiny to all references cited in the mortality health outcomes appendix of the 2020 ISA. Concern about these three studies factored into the conclusion by other CASAC members that the "likely causal" determination is more appropriate.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

Since the deadline for published data eligibility for the 2020 Ozone ISA (March 2018), there have been new contributions to the scientific literature that might be germane to the characterizations reached in the 2020 Ozone ISA; panel members have provided these references in their individual comments. The CASAC did not come to consensus on whether the additional information now available warrants a strengthening of the "suggestive" determination to "likely causal."

Health Effects – Developmental Effects (Appendices 3, 4, 7, particularly Section 7.1.4)

a. What are the panel's views regarding the review and characterization of the scientific evidence on developmental effects from ozone exposure?

The CASAC finds that the sections characterizing the scientific evidence on the developmental effects from ozone exposure are clear and well written.

There are several categories falling under the heading of developmental effects, including male and female reproduction and fertility, pregnancy and birth outcomes, and effects of exposure during developmental periods, which itself includes respiratory, cardiovascular, metabolic, and nervous system effects. In the executive summary (Table ES-1), there are determinations provided for long-term exposure to ozone and reproductive effects combined for the 2013 ISA ("suggestive") and separately for fertility and reproduction, and pregnancy and birth outcomes in the 2020 ISA ("suggestive" for both). Appendix 7 of the 2020 ISA provides separate determinations for the same categories. In addition, Section 7,1,4 summarizes the evidence of effects during developmental periods, indicating that this evidence also contributes to the relevant sections (respiratory, cardiovascular, metabolic, nervous system) in the ISA. There is no determination for short-term exposure to ozone for these categories.

Regarding reproductive effects and birth outcomes, the CASAC finds that the evidence is characterized accurately and that there is generally limited evidence for these endpoints, particularly from the epidemiological literature. The evidence is stronger for pregnancy and birth outcomes than for reproduction and fertility, but overall, the CASAC agrees with the causal determination of "suggestive" in the 2020 ISA. The CASAC notes that the available evidence does include studies that observed associations at ozone concentrations below current standards.

The evidence summarized for the neurodevelopmental effects is also fairly limited. Section 7.2 includes broadly the evidence for nervous system effects, including in adults and children. For nervous system effects the determination is "suggestive" in both 2013 and 2020, and the CASAC agrees with this determination.

The development effects evidence summarized in separate sections (Appendices 3, 4, 5) contributes to the causal determinations for respiratory, cardiovascular, and metabolic effects, respectively. As discussed in CASAC's comments on Appendix 3, long-term ozone exposure and respiratory effects, the CASAC agrees with the characterization of the evidence for respiratory disease development (asthma, allergies) and lung function growth in the 2020 ISA, but also notes that the evidence is growing and is significantly strengthening the causal determination, as discussed in more detail below.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

The CASAC notes that there are some newer publications that could be considered in a future review in each of these categories, including the following publications:

- Preterm birth - Bai et al. (2022)
- Birth weight - Wang et al. (2021)
- Respiratory Health – To et al. (2019); Zhu et al. (2022); Sbihi et al. (2016); Holm et al. (2022)
- Neurodevelopment - Ha et al. (2019); Chun et al. (2020)
- Gestational hypertension: Hu (2017); Cao (2020)

Nevertheless, the evidence is likely still limited, with the exception of the evidence discussed in the respiratory section regarding respiratory condition development and lung function growth, as well as potentially for preterm birth / low birth weight. For birth weight, the Wang et al. (2021) study provides additional insight into windows of exposure for effects on term low birth weight.

Regarding Section 3.2.4.2 "Lung Function and Development," the CASAC concludes that there is increasing evidence since the 2020 ISA that should be considered in a future review and that likely strengthens the body of evidence. The newer evidence includes the To et al. (2019) study reporting results from a large Canadian birth cohort, including evidence for both childhood asthma and allergic rhinitis risk increased in relation to birth (proxy for pregnancy) exposure to total oxidants including ozone. Further studies include the Zhu et al. (2022) prospective pregnancy cohort study in Guangzhou, China showing associations with early childhood wheeze and the Sbihi et al. (2016) publication from Vancouver showing increased risk of asthma diagnosis at school age. Notably, there is new and stronger evidence to consider regarding lung function and development. The effects of long-term exposure to ozone on pediatric lung function has accumulated in recent years. This is an important outcome because lung function develops rapidly through childhood and decrements in early life may portend lifelong deficits in maximum attained lung function. Such deficits are associated with chronic disease in adulthood such as COPD. The more recent analyses of long-term exposure on pediatric lung function include addressing copollutants. The Holm & Balmes (2022) article nicely summarizes the state of the evidence in this area. The consistency and coherence of these findings along with the experimental data in rhesus monkeys suggest that a future review may find the evidence is compelling for reconsideration of the overall causality of long-term effects of ozone on lung function and development.

Additional notes

There has been less research emphasis on pregnancy/early life ozone exposure and development of asthma and allergies in the published literature, compared to exposure to PM or NO_2; therefore, future work in this area should be encouraged.

At-Risk Communities

a. Based on the existing scientific record, what are the panel's views regarding the scientific evidence of effects of ozone exposures on at-risk communities?

b. What are the panel's views on how the evidence regarding disparities in exposure and health effects should be brought into the PA?

EPA's treatment of at-risk populations from ozone exposures in the 2020 Ozone ISA is thorough and well structured. The Preamble to the ISA includes a good description of which populations fall into the category of "at-risk." The Preamble specifies that at-risk populations are based on "interindividual variation in both physiological responses, and exposure to ambient air pollution." The framework for including information about at-risk individuals and communities is very nicely presented in the Integrated Summary and clearly depicted in Table IS-9.

The focus of Section IS.4.4 is on whether scientific evidence supports differential or enhanced health risk for at-risk communities. Overall, the CASAC agrees with the classifications given in the ISA for the listed at-risk populations. The following CASAC comments are intended to identify additional at-risk populations and other topics for this section to be considered in a future review.

The 2020 Ozone ISA gives almost exclusive attention to at-risk communities identified by physiological susceptibility. A thorough analysis of differences in exposure due to spatial variation that is often driven by sociodemographic factors, especially race/ethnicity, class, and income, is missing. This type of analysis enables the PA to better assess risk in these communities by understanding the variation in ozone concentrations present over a geographic area.

Residential ventilation is an ozone exposure factor and is correlated with socioeconomic status and other sociodemographic indicators in many locales. While direct evidence related to the influence of ventilation as an effect measure modifier within ozone epidemiologic studies is equivocal (Section 2-4-2, p. 2-21), the current literature does support its inclusion as a potentially important exposure factor that may explain ozone exposure disparities within at-risk communities and possibly added health risk. For future ISAs, the CASAC recommends that the EPA include a discussion of differences in home ventilation as a potential mechanism conferring added ozone risk within specific affected communities.

In addition to the at-risk populations identified in the 2020 ISA the CASAC suggests the inclusion of pregnant women and their developing fetuses in future reviews. Pregnant women are uniquely at risk of pregnancy- related complications (e.g., hypertensive disorders of pregnancy). Exposures experienced in pregnancy have been linked to adverse birth outcomes and other developmental outcomes (e.g., autism spectrum disorder) through these complications as well as via other mechanisms.

Pertinent for the upcoming PA review, it is important to note that most CHE studies do not have sufficient representation of variation by race/ethnicity, socioeconomic levels, age, or comorbidity. This is relevant for considering whether a potential alternative standard has an adequate margin of safety to protect these potentially *at-risk populations*.

<u>Suggestions for future ISAs for at-risk communities:</u>

- The CASAC suggests that the analysis of populations that are at-risk be spread over the entirety of the ISA as relevant outcomes are discussed. Relegating these groups to a single section implies that they are separate from, and secondary to, the main conclusions of the ISA. However, the purpose of setting primary standards for the NAAQS is to "…protect the health of any [sensitive] group of the population."
- The 2020 Ozone ISA includes discussion of only those at-risk communities for which there is new data. Although this may have been done to adhere to a tight timeline, it is more difficult to consider at-risk populations in setting standards when data on that group is in a prior version of

the ISA. The CASAC suggests that future ISAs bring forward analyses and references from previous ISAs that are relevant for the current ISA; especially for those at-risk populations for which there is *adequate* or *suggestive* evidence for increased risk. In the case of the 2020 Ozone ISA these would be outdoor work, genetic factors, diet, sex and SES.

- Consider including "insufficient quantity" to the classification of *suggestive evidence* in Table IS-9. This would allow for an adequate amount of attention and analysis for growing literature addressing potential adverse effects for the identified at-risk communities.
- As is evident from the 2020 Ozone ISA, research exploring adverse effects of ozone on at-risk populations is limited. The number of published studies in this area is smaller than for $PM_{2.5}$. Better characterization requires an increased number of studies specifically designed to explore associations between ozone and at-risk populations. Therefore, increased research in this area is encouraged to enable better evaluation in the future.
- Policymakers are increasingly grappling with the concept of environmental justice (EJ); recognizing exposure to social and environmental stressors are often co-located. This influences disparate health impacts (i.e., effect modification) and perpetuates health disparities. This concept of environmental justice as it relates to ozone does not currently have a place in the ISA and it would be useful to frame the EJ features and EJ-related literature in a future ISA.
- The 2020 ISA lacks studies with an adequate number of participants and data from racial/ethnic minority groups and from a range of income and wealth categories. This should be an area of focus for future research to fully inform and characterize concentration-response functions.

Ecological Effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

The CASAC finds that Appendix 8 on ecological effects provides a comprehensive and well-written review of the scientific evidence on ozone effects on vegetation and ecosystems. Appendix 8 has causality determinations for 12 vegetation and ecosystems effects associated with ozone exposure and the CASAC concurs with all of the causal determinations. Studies newly reviewed in the 2020 ISA as well as studies published after March 2018 (outside the time frame of the ISA review) expand and strengthen the body of evidence for negative impacts of ozone on vegetation and ecosystems. For example, a recent publication (Lee et al., 2022) provides additional exposure-response relationships for 16 tree species native to North America. This study provides updated biomass loss functions for these species with increasing W126. This research needs to be included in the PA and future ISAs. An increasing number of studies also highlight ozone effects on plant phenology, plant reproduction, crop pollinators, pollination, and plant-insect interactions, bolstering new "causal" and "likely causal" determinations for these ecological endpoints. While the literature on ecological effects of ozone exposure continues to grow, these studies are not likely to alter the overall causality determinations presented in Appendix 8. Thus, the CASAC agrees that the summary is adequate to inform the PA.

Areas for additional research include the role of ozone interactions with particulate matter on vegetation and ecosystems, how detoxification processes vary both diurnally and seasonally and their impacts on ozone dose responses in plants, as well as further work on future climate change effects on ozone exposure responses for plants and ecosystems, particularly altered precipitation regimes, rising

atmospheric carbon dioxide concentrations, warming trends, and their interactions. Lastly, a more comprehensive review of ozone impacts on wildlife is needed.

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

There is a strong consensus by the CASAC that the evidence summarized in the ISA continues to provide robust support for alternate forms of the secondary standard in the PA. First, it is well established that a cumulative weighted index, such as W126, is the most appropriate for understanding and monitoring ozone impacts on vegetation and ecosystems. Second, research shows that a single year of high ozone exposure can affect plant growth and yield, with longer term, cumulative effects in subsequent years for perennial species. Third, the W126 metric and the primary standard of the 3-year average of the 4th highest 8-hour average ozone concentration capture different features of the ozone distribution. Consequently, the CASAC finds that the scientific evidence supports consideration of a distinct secondary standard (level, form, averaging time) in the PA. This affirms and repeats previous CASAC advice on the PA on June 26, 2014.

Climate Effects (Appendix 9)

a. What are the panel's views regarding the causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables?

b. Have the effects of warming on ozone production been adequately characterized?

The CASAC concurs with the "causal" determination for tropospheric ozone and radiative forcing. Relative to that reported in the 2020 ISA, which was based on the Fifth Assessment Report of the Intergovernmental Panel on Climate Change (AR5; IPCC, 2014), the role of tropospheric ozone on the climate system is restated with more confidence in the Sixth Assessment Report (AR6) of the Intergovernmental Panel on Climate Change (IPCC, 2021). The global annual mean tropospheric ozone burden increased by ~44% from preindustrial 1850 to the present period (2005-2014), with a projected maximum in 2100 (Griffiths et al., 2021). In AR6, human-caused radiative forcing increased by ~19% relative to the amount reported in AR5 (IPCC, 2014), which served as the basis for the 2020 ISA.

The 2020 ISA, based on IPCC AR5 (2014), notes that the warming effect of tropospheric ozone on global mean surface temperatures is estimated at 0.1 to 0.3 ºC since preindustrial times, and this estimate is consistent with that in IPCC AR6 (IPCC, 2021). This compares with the observed temperature change of about 1.1 ºC over this period, with most of the observed warming occurring since 1980. Since this temperature increase is directly related to the ozone radiative forcing, the CASAC recommends in future reviews that "temperature" be removed from the "temperature, precipitation, and related climate variables" category and added to the "radiative forcing" category for causal determinations. Based on the clear evidence for ozone impacts on radiative forcing and temperature, a "causal" determination for this category is appropriate. Since radiative forcing is not directly measured, global mean surface temperature may serve as a better indicator of the causal effects.

There is strong evidence that radiative forcing and temperature changes affect weather patterns that result in local precipitation changes and other climate variability, such as severe recent droughts in the Western US (IPCC, 2021). Tropospheric ozone, the third-most important anthropogenic climate-forcing agent, contributes to these changes along with other greenhouse gases, aerosols, and other forcing agents. The 2020 ISA focused on a limited set of model simulations for the "likely causal" determination between tropospheric ozone and "temperature, precipitation, and related climate variables." Determining the specific effects of ozone on these variables by model simulations has been extended in AR6 (IPCC, 2021), thereby potentially providing additional support for a "causal" determination in the future. The CASAC recommends that in future ISAs, the EPA should consider the evidence that climate change is influencing precipitation and other climate variables more generally, with ozone contributing to those changes, and weigh that evidence in determining causality for ozone. The influence of ozone on climate via indirect mechanisms, such as suppression of plant growth and related increases in atmospheric CO_2 (Sitch, et al., 2007), needs to be addressed in future reviews.

The 2020 ISA does not elaborate on the effects of atmospheric warming on ozone production. The increasing frequency, intensity, and duration of heat waves in recent years accelerates regional feedbacks and local emissions that increase both average surface ozone and peak ozone concentrations. Over polluted regions, a warmer climate may introduce a surface ozone penalty of 0.2 to 2 ppb per degree Celsius. Positive responses of surface ozone to future climate change through wildfires, soil NO_x emissions, biogenic VOC emissions, and stratospheric-tropospheric exchange also need to be considered (IPCC, 2021).

Future research involving reconstruction of historical ozone concentrations using oxygen isotopes in ice cores (Yeung et al., 2019) would be beneficial. Given the complex climate system, the role/influence of changes in ozone precursor emissions on radiative forcing from ozone, methane, and aerosols may be counter-intuitive (Fry et al., 2012). For example, reductions in NO_x emissions may increase methane and cause a net warming influence (West et al. 2007). Future ISAs could consider presenting the effects of changes in ozone precursor emissions on radiative forcing.

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Appendix A

Individual Comments by the 2022 CASAC Ozone Review Panel Members on the *EPA's Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report - April 2020)*

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Mr. Ed Avol **A-7**
Dr. James Boylan **A-13**
Dr. Judith C. Chow **A-18**
Dr. Mark Frampton **A-26**
Dr. Christina H. Fuller **A-32**
Dr. Terry Gordon **A-35**
Dr. Catherine Karr **A-38**
Dr. Michael T. Kleinman **A-42**
Dr. Danica Lombardozzi **A-45**
Dr. Howard Neufeld **A-47**
Dr. Jennifer Peel **A-49**
Dr. Richard E. Peltier **A-54**
Dr. Alexandra Ponette-González **A-56**
Dr. Jeremy Sarnat **A-59**
Dr. Elizabeth A. (Lianne) Sheppard **A-63**
Dr. Jason West **A-66**

Mr. George A. Allen

Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.

Wildfires can be a large source of ozone precursors, especially VOCs. When wildfire plumes rich in VOC gases are combined with point source or urban NOx emission plumes, elevated O3 can result. The increased frequency of wildfires, especially in the western US, has brought attention to the use of exceptional events to exclude ozone exceedances that may have a wildfire component. Current exceptional event practice allows an exceedance to be excluded from design value calculations if any amount of the event can reasonably be attributed to wildfire smoke, even if the contribution is small. Summaries of O3 exposures and trends should include all valid data, and not exclude data from exceptional events.

In the context of NAAQS compliance, background O3 levels, now called US background or USB O3, are primarily a factor in the US intermountain west and are important to characterize both using observations where possible and through chemical transport modeling with tools like GEOS-Chem, CAMx and CMAQ. Modeled USB "turns off" all O3 precursor sources in the US but leaves all other North American and other international sources on. While it is important to understand to what extent USB could contribute to O3 NAAQS design values, it is my understanding that the process of setting a NAAQS is based on health and welfare effects without regard to contributions of USB, and that USB could be considered as part of implementation of the O3 NAAQS. CASAC does not address implementation, although commenting on economic and social impacts of implementation, adverse or otherwise, is part of the CASAC charter.

The global standard for measurement of ozone is changing by 1.23% on January 1, 2024. NIST and EPA standard reference photometers, the basis for calibration of ambient O3 monitors, will be adjusted to reflect this change. The change is in the direction that will eventually increase reported ambient O3 concentrations once the reference calibration change trickles thru the system. At 70 ppb, the increase would be 0.86 ppb. See: https://www.bipm.org/en/bipm-workshops/surface-ozone . The EPA lead on this is Joann Rice at OAQPS.

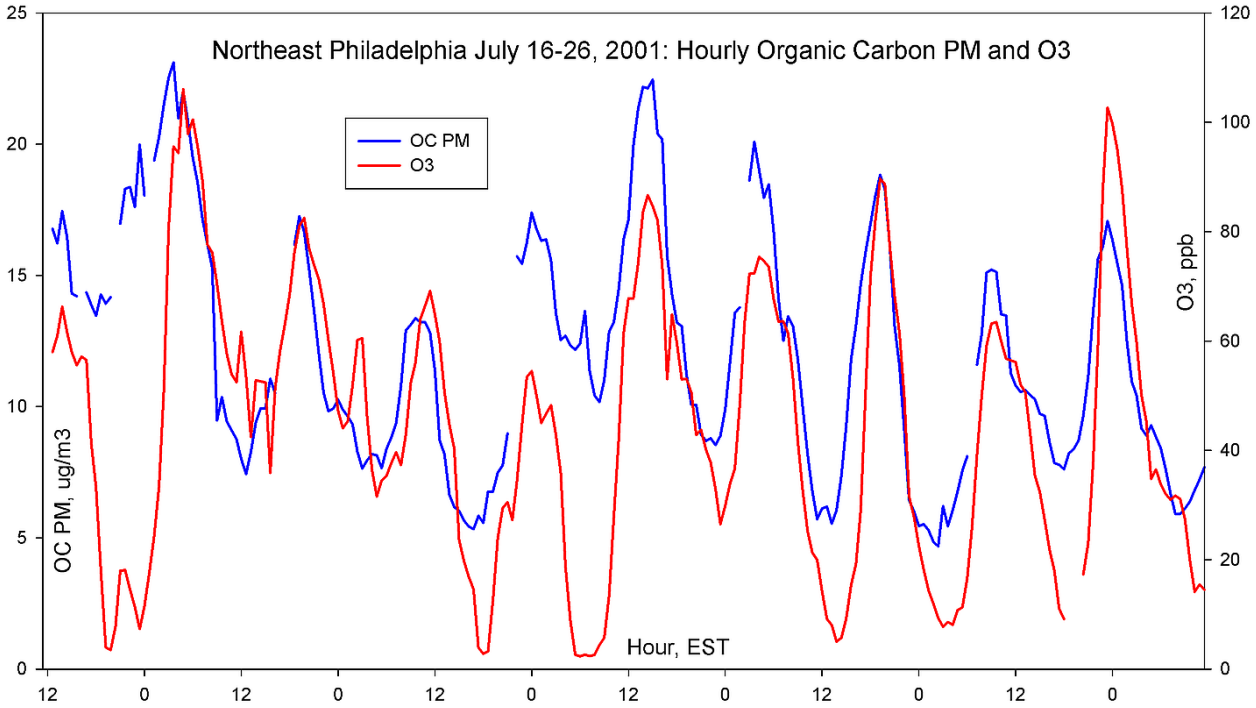
Ozone and Photochemical oxidants (Appendices 1 and 2)

What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone? The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers. These comments are also relevant to Appendices 4 and 6 (cardiovascular and mortality effects).

In the 2020 ISA, the causal determination for short-term cardiovascular and mortality effects was changed from "Likely causal" in the 2013 ISA to "Suggestive but insufficient to infer causality." This was based primarily on the controlled human exposure studies. Laboratory-generated O3 as used in controlled human exposure studies is useful for respiratory health endpoints that are driven by lung tissue inflammation. Although there is value in assessing effects on healthy adults in the absence of confounding pollutants, this approach should not be used to support reduced confidence in short- or long-term ozone cardiovascular or mortality endpoints in the general population. In addition to the exposure issues described below, the value of controlled exposure studies is limited by the use small populations of healthy non-elderly subjects with a single exposure, no accounting for lag time and no follow-up. The NAAQS is for O3, as the indicator for "Ozone and Photochemical oxidants". In practice the non-ozone oxidants portion that is part of the photochemical soup has been ignored because it is more difficult to quantitatively measure. The primary non-O3 oxidants that are present with elevated ambient O3 are peroxyacetyl nitrate (PAN) and hydroxyl radicals (·OH). It has been known for many decades that they may play a role in ambient health effects, co-occurring with ozone. The 1976 EPA-HERL O3 and photochemical oxidants document states: "Because hydroperoxy radicals (HO_2) are free radicals, they may have biologic effects similar to those of ozone and PAN". … "The possibility that free radicals, particularly hydroperoxy, have significant effects on biologic surfaces should be investigated." It is worth noting that between 1971 and 1979, the indicator was "total photochemical oxidants". When the indicator was changed to O3 in 1979, the 1-hour NAAQS was increased, not decreased, from 0.08 to 0.12 ppm.

In additional to the gas-phase oxidants missing from controlled human exposure studies, there can be aerosols that could contribute to O3 cardiovascular health effects. A recent Canadian study by Toyib et al. "Long-Term Exposure to Oxidant Gases and Mortality: Effect Modification by PM2.5 Transition Metals and Oxidative Potential" https://journals.lww.com/epidem/Abstract/9900/Long_Term_Exposure_to_Oxidant_Gases_and_Mortality_.78.aspx states that "Associations between Ox and mortality were consistently stronger in regions with elevated PM2.5 transition metal/sulfur content and oxidative potential."

Some semi-volatile gas phase organic compounds can be temporarily condensed into the aerosol phase by high photochemical oxidant concentrations and result in O3-related increases in PM2.5. The figure below is hourly O3 and organic carbon aerosol from a research site in northeast Philadelphia in 2001 (unpublished data, NARSTO North East Oxidant and Particle Study study, Harvard and Millersville Universities). https://ams.confex.com/ams/annual2002/webprogram/Session12900.html
With southwest winds, this site is down-wind of the core urban area by about 10 miles, parallel to I-95. During this multi-day O3 event the diel cycle of organic carbon PM and O3 is clear, with O3 and OC PM maxima and minima occurring at the same time of day, implying the semi-volatile organic carbon aerosol volatilizes when oxidant concentrations decrease. The combined exposures to photochemical oxidants and fresh (e.g., not photochemically aged) organic carbon aerosol could explain the cardiovascular health effects observed with ambient exposures but not with controlled exposure studies.



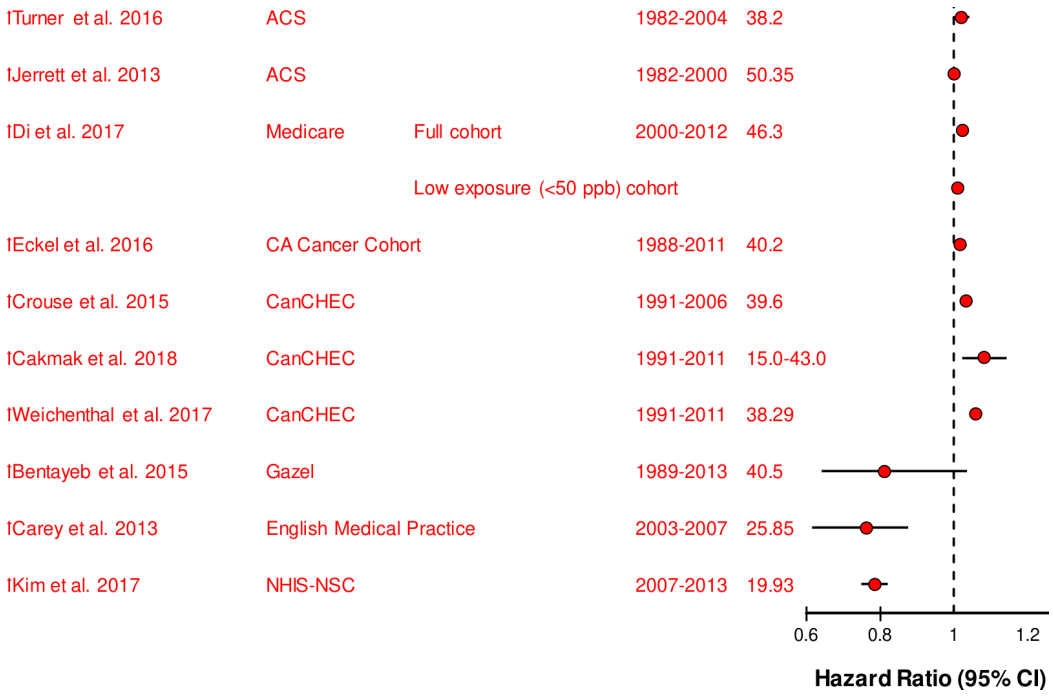
The recent MOSES 2 study (Frampton et al., 2022) that saw almost no cardiovascular effect indicators in the controlled exposures also included a 4-day pre-test ambient O3 assessment of HRV that showed an association between short-term increased ambient ozone and decreased HRV with O3 concentrations lower than used in the controlled exposures. A recent review and meta-analysis of studies on Short-Term Exposure to Ozone and Heart Rate Variability that used ambient O3 as the exposure metric concluded that short-term exposure to O3 was associated with reduced HRV indicators in adults. (Zong et al., Int. J. Environ. Res. Public Health 2022, 19(18) https://www.mdpi.com/1660-4601/19/18/11186)
A parallel to lab-generated versus ambient O3 health effects is the distinction between lab-generated PM for controlled exposure studies and "CAPS" (concentrated ambient particles) PM which is ambient PM that is "concentrated" by use of virtual impactor technology for controlled exposure studies. Controlled human exposures to CAPS PM shows cardiovascular effects consistent with the PM mortality epidemiology, but lab-generated PM usually does not.

In summary, using just O3 to assess short-term health effects of ambient O3 as the indicator for photochemical oxidants may underestimate effects and possibly miss cardiovascular effects. The weighting of health effect evidence from controlled human exposure studies should reflect these limitations, and the lack of evidence for cardiovascular effects in those studies should not be used to discount evidence of short or long-term cardiovascular or mortality effects in the general population exposed to a mixture of ambient photochemical oxidants.

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

In additions to my comments above regarding the limitations of controlled human exposure studies, I want to comment on the long-term mortality studies presented in Figure 6-8 on page 6-29 of the ISA, excerpted here showing the studies new since the 2013 ISA:



The three at the bottom are strikingly different, with HR of about 0.8. This inverse association, indicating that O3 is good for you, seems like it ought to trigger closer scrutiny of these studies beyond the PECOS review, but the ISA has no discussion of this unusual result for these three studies. I can understand a null result, close to 1 in either direction; a HR slightly less than 1 with error bars crossing 1 is not of concern. In a properly done study I cannot understand how a robust HR of 0.8 is possible. Kim was done in S. Korea, Carey in England, and Bentayeb in France. Issues with the Kim analysis have already been discussed by Dr. Sheppard. The other two, both European studies, may have a confounding effect from NOx because automotive diesel is much more common in Europe. Higher diesel emissions result in higher NOx and higher diesel PM (DPM), both which likely have adverse mortality effects. They also result in lower urban O3 due to NOx scavenging. Higher O3 could be due to less diesel PM and NOx, and thus less mortality. If NOx isn't properly controlled for, this could result in an inverse association (O3 is good for you). Looking quickly at these two studies, Carey used annual (not seasonal) O3 as the exposure metric, which was negatively correlated with all other pollutants (Table 1 of that paper), and does not appear to control for NO2 (all other pollutants in the analysis had HR > 1). Bentayeb is not primarily an O3 study – table 5 of bi-pollutant models doesn't include any O3 results (e.g., the O3 results did not control for any other pollutants).

Hvidtfeldt et al. (Environment International 123 (2019) 265–272 https://doi.org/10.1016/j.envint.2018.12.010) also saw a HR < 1 when O3 was negatively correlated

with all other pollutants, and notes "Since a protective effect of O3 on mortality seems little plausible, we consider the lower HRs in association with higher exposure to O3 in our study to be a reflection of the inverse correlation between O3 and truly harmful pollutants." These two papers apparently ignored this artifact. EPA should do a closer assessment of study quality for these two papers, since they play an important role in degrading uncertainty of causality determination. I want to acknowledge that EPA staff were under unusually heavy workloads while the 2020 ISA was being developed, due to the accelerated timeline for completion of both the PM and O3 NAAQS reviews by the end of 2020, and this may have contributed to some of the issues with the ISA discussed here.

Ecological effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

Unlike health effects, the causality determination for all of the ecological effect endpoints are causal or likely causal, and are either new endpoints added in 2020 or have similar determinations since the 2013 ISA. Although the terminology used in the 2006 AQCD for causality was different, O3 effects on plants were well established at that time (Table 2-2 of the 2013 ISA compares 2006 with 2013). Thus while there is some new literature in the last decade on this topic, it does not change any of the conclusions regarding key ecological effects, especially on vegetation, and that a seasonal weighted form such as W126 is appropriate. There is little to no discussion of vegetation effects using a 1-season vs. a multi-year season form, although there is evidence that a single-season form would provide more protection for a given ppm-h W126 exposure level. The ISA is based on research that uses the W126, since "The current secondary standard form of the 4th highest 8-hour max avg over 3 years is rarely reported in the vegetation research." (ISA 8.13.1, pg. 8-181). As such, it cannot provide an assessment of vegetation effects based on the form of the primary (and current secondary) ozone NAAQS. The issue here is that EPA has insisted since 2008 on saying (contrary to consistent CASAC advice) that the primary standard provides adequate ecosystem protection; that is a topic for the CASAC review of the Policy Assessment for the Reconsideration of the O3 NAAQS later this fall.

I had asked about the implementation language for a welfare NAAQS during the meeting. https://www.govinfo.gov/content/pkg/USCODE-2013-title42/html/USCODE-2013-title42-chap85-subchapI-partD.htm says that (unlike the 5- to 10-year timeline for a primary NAAQS) there is no clear deadline requirement for compliance: "(B) The attainment date for an area designated nonattainment with respect to a secondary national ambient air quality standard shall be the date by which attainment can be achieved as expeditiously as practicable after the date such area was designated nonattainment under section 7407(d) of this title."

Mr. Ed Avol

EPA Staff prepared a comprehensive 2020 Ozone ISA on a much-constrained timeframe compared to previous cycles of input, development, and revision. The staff are to be congratulated for the thoughtful and wide-ranging discussions presented and the distillation of data sources available at the time of ISA preparation.

Nevertheless, in my opinion, there were several sections in the 2020 ISA that could be improved upon, that raise issues regarding interpretation of published evidence, or that take a position I respectfully feel is not fully justified by the available information. These sections are discussed in the following sections.

In addition (admittedly with the benefit of 20/20 hindsight from 2022), there have been additional new research placed into the scientific literature that (in my opinion) do have relevant bearing on some of the issues and discussions in the 2020 Ozone ISA.

Below are assorted comments for Staff consideration:

Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.

Substantial understanding of ozone chemistry has accrued through multiple ISAs and build upon each successive cyclical assessment. Nevertheless, there do remain some questions of potential value to consider. The 2020 ISA presentation on atmospheric source chemistry and trends was sweeping and inclusive, but the document presented national emission trends data based on 2014 and 2016 inventory data. Are there more recent inventory data, and do they show substantive differences? For some inventory compounds of importance (VOCs for example) these changes may be of little practical consequence in the overall estimate given that biogenic sources account for 70% of the VOC budget. Alternatively, they could be of significance in near-downwind locales, such as in Southern California east of Los Angeles, where anthropogenic VOCs can be appreciable. Staff should consider and comment on the importance of anthropogenic VOC trend changes downwind of major metropolitan areas (such as Los Angeles) due to the downwind importance of potential shifts in ozone photochemistry equilibria.

Infra-red (IR) monitoring of various oil wells and petroleum piping and transportation operations since 2020 have suggested leakages of CH4 from valves, tanks, and facilities that may have been previously unappreciated or incorporated into inventory projections or assessments (for example, see Cheadle et al, 2022). Are these data now available and accepted for use to improve emissions estimates? Are these large enough to affect the pie-chart distributions for CH4 emission inventory estimates (Fig 1-2 part D, in ISA App1)? Given the observation in the ISA (App1, p1-16, para 2 bullet) that "…there is an approximately linear relationship between anthropogenic methane emissions and tropospheric ozone…", this would seem informative to the PA.

The increased visibility of wildfires and the presence of wildfire smoke across large portions of the US in recent years raises the issue of wildfires as "exceptional events" and the downwind O3 photochemistry that occurs. With increasing frequency and breadth across the US (and world), should wildfires be considered "exceptional events" (they seem to be much more frequent, though not predictable)? Should wildfires somehow be integrated into the annual emissions estimates? They would seem to be common enough, and to potentially generate sufficient downwind NOx/VOC/ozone changes such that inclusion of these emissions would seem important going forward.

(Looking forward to the PA discussions), the scientific evidence tracking O3 trends suggest a compression of the O3 concentration range (reduction of the 95th percentile concentrations and an increase in 5th percentile concentrations). This is positive news for those in areas of high ozone levels (and efforts in those regions should continue to achieve continued reductions), but does this suggest a need for new strategies to address the observed trend in increasing winter O3 levels cross a wider region?

References

Cheadle, LC, Tran T, Nyrarady JF, and Lozo C, "Leak detection and repair data from California's oil and methane regulation show decrease in leaks over two years", Environmental Challenges, volume 8, August 2022, https://doi.org/10.1016/j.envc.2022.100563.

Ozone and Photochemical oxidants (Appendix 1, 2)

a. What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone? The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers.

There has been some discussion during previous public CASAC Ozone Panel meetings regarding the merits of human controlled exposure studies compared to community epi studies for assessing health impacts, but little has been said about the monitoring or generating aspect of the exposure atmospheres in controlled chamber studies compared to the ambient experience of photochemical oxidant exposure. Since ozone is the stipulated marker for photochemical oxidants under the NAAQS, that is the index by which airborne concentrations, community exposures, and pollution trends are tracked…but are there other species that have differentially been measured over time and lumped in as "ozone" (likely not for uv-photometry, but what about for chemiluminescent approaches?)

In previous decades, with differing fuel components and ambient assorted VOCs, the presence of PAN and other aldehydes (such as formaldehyde and acrolein, as well as short-lived but potent photochemical entities) were measured or measurable in ambient air and were identified as being of some health impact. Over the past 20 years in the US, with fuel reformulations and VOC controls/replacements/restrictions, ambient photochemical oxidants have also changed, and (at least in Los Angeles) the days of eyes tearing or chest-burning pain upon inspiration from PAN or acrolein or other oxidants is largely a thing of the past. But do exposure study atmospheres in a chamber where ozone is generated by uv irradiation of otherwise highly filtered air accurately simulate photochemical

oxidants exposure in ambient air? It seems like other short-lived and difficult-to-measure photochemical species in ambient air would make an "ozone-only" chamber exposure an under-estimate of photochemical oxidant effects in ambient air.

On the topic of lab-generated ozone and ambient ozone exposure, an additional aspect of modeling estimation and assignment raises potential issues of over-predicting actual encountered exposures and thus under-predicting toxicity of exposure. In chamber studies, minimal reactive surfaces are typically present to provide for a stabilized and consistent exposure atmosphere. In the "real" world, the surface area and reactivity of ozone with surrounding materials (carpets, furniture materials, fabrics, personal cloud ("pigpen effect"), vegetation surfaces, materials, clothing, etc outdoors potentially leads to diminished levels of actual ozone available for exposure at the personal level (compared to the regionally or remotely monitored concentrations used for modeled exposure assignment). Therefore, there may be measurement mis-classification error and an over-prediction of actual ozone exposure for the public at large, leading to an under-appreciation for any observed health responses in ambient air.

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

I agree with the EPA determination of a causality ranking for short-term respiratory effects of ozone exposure, and while I accept the "likely-to-be-causal" determination for long-term exposure (for the purpose of moving forward to the PA), I do question some of the critical thinking that led to this determination. For decades now, information regarding the respiratory effects of ozone on human health have been researched and characterized in a substantial number of studies, geographic locations, sub-group populations of varying risk, technical approaches, and health endpoints. The combined breadth and coherence of data do seem sufficient to warrant a causal determination for short-term effects. The long-term ozone exposure literature is arguably less robust than the plethora of studies (especially from controlled chamber research) supporting a causal association between exposure and respiratory outcome, but it is substantial.

The assessment and prioritization of chamber studies data over epidemiologic investigations seems to represent a consistent agency perspective throughout the 2020 ISA. However, ethical and moral limitations prevent the actual range of persons (and their respective health status) to participate in controlled chamber research. Caution and care should appropriately govern purposeful exposure of humans to any toxicants, but the demonstration of small or no effects in populations of healthy college-age participants should arguably be seen only as an entrée point to providing confidence for studies to continue in more sensitive or at-risk populations, not a final endpoint for conclusions to be drawn for the population at large. Practical limitations restrict the total number of participants in a controlled chamber

study, including the ethnic, racial, age, and health status range of study participants. This may also limit observed range of response or inclusion of those at increased sensitivity. The necessity for voluntary participation and consent further restricts the potential participant pool. Previous studies (for example, see Linn et al 1988) have demonstrated that seasonal development of tolerance to ozone exposure may blunt the observed responses in controlled-chamber studies for some individuals, so a chamber exposure may not provide adequate "zeroing out" of seasonal or longer-term prior exposures. For all of these reasons, it could be argued that the results of controlled chamber research, while critically necessary and valuable in understanding reversible changes in health status, are likely to underpredict the health impact of the at-large community population. Toxicology, controlled chamber research, and community epi studies each play a critical role in providing the health information necessary to make informed judgements, but each approach offers specific strengths and is limited by inherent weaknesses. Collectively, there are "borrowed" or "shared" strengths, but down-weighting actual real-life exposure studies in favor of short-term, limited-concentration-range-and-time-duration studies involving carefully selected and generally much more healthy individuals than are in the larger "free-living" population, seems an approach destined to under-predict community effects and impacts.

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Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

The 2020 ISA determined that the available evidence for associations between both short-term O3 & total mortality and long-term O3 & total mortality were suggestive but not sufficient to infer causal relationships. This reflects a downgrading of causal determination for short-term O3 and a comparable determination for long-term O3 exposures and health…so what changed from 2013 to 2020?
Staff reported that additional controlled chamber exposures research provided less consistent evidence of cardiovascular changes, epi studies did not provide convincing additional evidence of severe health endpoints, and there were some expressed uncertainties regarding potential confounding by co-pollutants in epi studies. According to the 2020 ISA, the animal toxicity studies did show generally consistent evidence for ozone-induced cardiovascular injury, and for cardiovascular mortality in epi studies, but these results differed somewhat with controlled chamber and other epi studies focusing on cardiovascular morbidity.

(Repeated from above regarding the use of controlled-chamber vs community studies data)

This assessment and prioritization of chamber studies data over epidemiologic investigations represents a consistent agency perspective throughout the 2020 ISA. However, ethical and moral limitations prevent the actual range of persons (and their respective health status) to participate in controlled chamber research. Practical limitations restrict the total number of participants in a controlled chamber study (thereby further restricting the demographic range and distribution of racial, ethnic, age, and health-status in the study population). The necessity for voluntary participation and consent further restricts the potential participant pool. For these reasons, it could be argued that the results of controlled chamber research, while critically necessary and valuable in understanding reversible changes in health status, are likely to underpredict the health impact of the at-large community population. Toxicology, controlled chamber research, and community epi studies each play a critical role in providing the health information necessary to make informed judgements, but each offers specific strengths and are limited by inherent weaknesses.

Since the 2018 deadline for article consideration for the 2020 ISA, a few additional studies have become available. From the epi studies accessible through PubMed, these published investigations were mostly conducted by investigators in and with populations from Canada, China, and South Korea. COPD, hypertension, ischemic heart disease, and stroke were health endpoints identified in short-term cause-specific mortality (For example, see: Shin et al V Chemosphere. 2021 Feb;265:128683. doi: 10.1016/j.chemosphere.2020.128683. Epub 2020 Oct 29; Lin et al, Environ Res. 2022 Aug;211:113098. doi: 10.1016/j.envres.2022.113098. Epub 2022 Mar 12); Bae et al, "Causal association between ambient ozone concentration and mortality in Seoul, Korea", Environ Res. 2020 Mar;182:109098. doi: 10.1016/j.envres.2019.109098. Epub 20,19 Dec 28.

Recently published studies of Asian populations, where ambient ozone exposures appear to be on the rise, report associations between mortality and ozone exposure, (for example, Maji and Namdeo, https://doi.org/10.1016/j.envpol.2020.116183). The application of PECOS and other analogous criteria to assess study quality can potentially qualify additional studies on which to strengthen causal determination. Exclusion of well-designed and performed epidemiological research in non-North American populations limits the thoughtful application of scientific data that could be used to refine and improve understanding of primary and secondary health and material impacts. Undoubtedly, variations in local climate, concurrent exposures, lifestyle issues etc exist and will persist, but the rationale for the current threshold in PECOS for epi studies use (US or Canadian populations) seems unduly restrictive and should be revisited.

At-Risk Communities

a. Based on the existing scientific record, what are the panel's views regarding the scientific evidence of effects of ozone exposures on at-risk communities?

b. What are the panel's views on how the evidence regarding disparities in exposure and health effects should be brought into the PA?

The differential effects of O3 on "at-risk" communities can be substantial but also can be subtle. For those who live in communities with little green space or shaded trees, there may be increased opportunity for sustained and persistent outdoor exposure. For those who live in sub-quality housing, there may be a lesser decrease in indoor O3 exposure due to increased outdoor infiltration or higher air exchange rates due to building leakage through poorly sealed windows or doorframes, or possibly even

an absence of closable windows. For those who constitute an "at-risk" community by virtue of their status as a transient outdoor farmer worker, port dock worker, gardener, or construction worker, extended work hours during the peak of ambient ozone exposure has direct exposure consequences.

Conversely, some at-risk communities may actually be the recipient of decreased localized ozone, due to the over-abundance and presence of other environmental toxicants. Such an outcome could be due to proximity to industrial or chemical operations. Proximity to busy roadways (the plight of many EJ communities with highways or freeways crisscrossing their community) could result in significant vehicle emissions, which would lead to NOx equilibrium shifts and localized reductions of ozone levels. While one can debate the subtleties of ozone photochemistry and the ultimate impact of near-roadway shifts in photochemical equilibria, the fact remains that the chemistry in these regimes is dynamic, complicated, changing, and perhaps not uniformly generalizable.

These issues are therefore both exemplary and subtle and could conceivably shift ozone exposures in either direction. When the agency moves to address these issues in the Policy Assessment (PA) document, this potential bi-directional impact should be addressed and considered.

Ecological Effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

Although I have nothing specifically to add to the discussion in the 2020 ISA or the comments of other Reviewers, I do agree with the oft-repeated comments that there does appear to be sufficient data and justification to argue for a separate secondary standard based on the W126 approach rather than a lumping of the secondary and primary standards into a single value. The 2020 ISA does reach a "causal" or "likely-to-be-causal" determination for seven of the eleven individual categories of consideration for ecological effects (see Table ES-2). The impacts on plants and agriculture do merit, in my opinion, a separate standard based on the data provided and the more appropriate and measurable metrics relevant to ecological impacts.

Dr. James Boylan

Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

Emissions and Ambient Measurements

The 2020 ISA contains the most recent information that was available at the time it was assembled (e.g., 2014 National Emissions Inventory and ambient air quality concentrations & trends data through 2017). More recent information on precursor source emissions and ambient ozone concentration trends has been included in the April 2022 draft ozone PA (e.g., 2017 National Emissions Inventory, 2018-2020 design values, and 2000-2020 ozone trends). The more recent information is largely consistent with the trends in the 2020 ISA.

It is not clear if exceptional events have been included or excluded from the ozone design values and ozone concentration trends presented in this Appendix. EPA should clearly state if exceptional events have been included or excluded and the impact of that decision on the results. Alternatively, EPA could present the data both ways (with and without exceptional events).

Wildfires and Exceptional Events

EPA allows the exclusion of high ozone concentrations due to wildfires under the exceptional event rule when calculating official ozone design values. The ISA should discuss how "Exceptional Events" might bias epidemiology studies and exposure assessments. In general, epidemiology studies and exposure assessments should include all ozone measurements (including those that were flagged as exceptional events) in their study so that study results are not biased toward lower ozone concentrations.

Background

U.S. background (USB) ozone is defined as ambient ozone that would be present at ground level within the U.S. in the absence of all U.S. anthropogenic ozone precursor emissions. Major contributors to USB ozone concentrations are stratospheric exchange, international transport, wildfires, lightning, global methane emissions, and natural biogenic and geogenic precursor emissions. The existing literature on USB trends has focused mainly on monthly or seasonal means. However, USB on days with high ozone concentration (e.g., 4th highest MDA8 ozone concentration) are the most relevant for the PA.

The caption for Figure 1-14 states "Fourth highest daily max 8-hour avg (MDA8) North American background (NAB) ozone concentration…" However, the associated text in the ISA (page 1-59) states "However, poor agreement between air quality models is observed for 4th highest MDA8 USB ozone concentrations in Figure 1-14 (Fiore et al., 2014). The AM3 model predicted that the 4th highest MDA8 USB ozone concentrations for a given site were highest in Colorado early in the year, while the GEOS-Chem model predicted a maximum for 4th highest MDA8 USB ozone concentrations in New Mexico,

much later in the year." After reading the original journal article (Fiore et al., 2014), it has been confirmed that NAB is presented in Figure 1-14, not USB.

Figure 1-14 contains the 4th highest MDA8 NAB ozone concentrations from the AM3 and the GEOS-Chem models. Many NAB values in the western U.S. are between 55-65 ppb. Since NAB does not include the impacts of anthropogenic emissions from Canada and Mexico, NAB is always going to be lower than USB which does include the impacts of anthropogenic emissions from Canada and Mexico. As a result, many USB peak MDA8 O_3 values in the western U.S. will be higher than 55-65 ppb and may approach 70 ppb in some locations.

Figure 1-15 compares modeled 4th highest MDA8 USB ozone concentrations with modeled and measured 4th highest MDA8 ozone concentrations for monitors in the Southeast and the Mountains and Plains regions. In the Mountains and Plains region, the 4th highest MDA8 USB ozone concentrations were only slightly less than 4th highest MDA8 total ozone concentrations, with some USB peak MDA8 O_3 values approaching the current level of the ozone NAAQS (e.g., 64 ppb in 2011 and 66 ppb in 2012).

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.

For consistency, the same source category break-down (see Figure 1-2 and Figure 1-3) should be carried forward into the PA. Also, the policy implications of removing exceptional events from official design values and high USB ozone concentrations in the western U.S. should be discussed in the PA.

Ozone and Photochemical oxidants (Appendix 1, 2)

a. What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone? The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers.

Epidemiology Studies

Exposure measurement error (especially relating to exposure assignment from fixed-site monitors) and copollutant confounding can be important contributors to error in epidemiologic study results. It is stated on page 2-33, "Given that the majority of the copollutant correlation data are low, confounding of the relationship between ambient ozone exposure and a health effect by exposure to CO, SO_2, NO_2, PM_{10}, or $PM_{2.5}$ is less of a concern for studies of the health effects of ambient ozone exposure compared with studies of the health effects related to exposure of other criteria air pollutants. When copollutant correlations are higher during the warm season, greater risk of copollutant confounding exists." However, the summer is the season with the highest ozone concentrations and the highest ozone exposure; therefore, a greater risk of copollutant confounding exists, especially with $PM_{2.5}$ which has many similar health impacts as ozone. In addition, the ISA does not discuss copollutant confounding with noncriteria pollutants such as Hazardous Air Pollutants (e.g., benzene, formaldehyde, acetaldehyde, acrolein, naphthalene, etc., some of which have short-term health impacts and some that have long-term health impacts). Many of these pollutants are associated with the same sources emitting ozone precursor emissions (e.g., mobile sources, industrial sources, and biogenic sources).

Some CASAC panel members have claimed that the differences in reported health effect between CHE and epidemiological studies are due to the additional photochemical oxidants (e.g., hydroxyl radical, PAN, etc.) that are present in the ambient air. However, no information was presented in the ISA or by any CASAC panel members that quantified the concentration or health impacts of these additional photochemical oxidants relative to ozone alone. This would be a good topic for additional future research.

Controlled Human Exposure (CHE) Studies

A section on CHE studies should be added to Appendix 2. This section should discuss both the limitations and advantages of CHE studies. CHE can provide direct evidence for a relationship between exposure and human health effects. These studies allow for the actual individual exposure to be measured along with the resulting health outcomes. They do not have issues with confounding by copollutants. However, CHE studies have limited ability to address more severe outcomes, most at risk groups, and long exposure periods.

The controlled human exposure studies typically involve 6.6 hours of quasi-continuous exercise by healthy adults. However, very few people routinely perform 6.6 hours of outdoor quasi-continuous exercise. The ones that do (construction workers, landscapers, etc.), are typically healthy adults. The ISA should discuss how the health impacts in these studies apply to the general public, specifically to people who don't exercise at all or only exercises 1-2 hours/day.

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?
I agree with EPA's causal determinations for short-term and long-term ozone exposure and respiratory health effects. I have not seen any new compelling evidence that would result in a different conclusion at this time.

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

I agree with EPA's causal determinations for short-term and long-term ozone exposure and cardiovascular effects. EPA's change from "Likely Causal" to "Suggestive" is appropriate due to the lack of cardiovascular effects associated with ozone exposure in the CHE and epidemiological studies. I have not seen any new compelling evidence that would result in a different conclusion at this time.

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

I agree with EPA's causal determinations for short-term and long-term ozone exposure and total mortality. EPA's change from "Likely Causal" to "Suggestive" is appropriate due to the lack of a plausible biological pathway shown in the cardiovascular effects. I have not seen any new compelling evidence that would result in a different conclusion at this time.

Ecological Effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

Yes, the summary is adequate to inform the PA.

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

Yes, the evidence review provides adequate background for consideration of alternate forms of the secondary standard in the PA.

During the CASAC deliberations on September 12, 2022, some members of the CASAC ozone panel commented on the appropriateness of the form, level, and averaging period for the secondary ozone standard. However, that discussion is more appropriate for the PA deliberations, not the ISA discussions. I have not seen any new compelling evidence that would result in different causal determinations at this time.

Climate Effects (Appendix 9)

a. What are the panel's views regarding the causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables?
I agree with EPA's causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables. Also, I agree with the suggestion to include "temperature" in the "radiative forcing" category and keep "precipitation and other related climate variables" in a separate category.

b. Have the effects of warming on ozone production been adequately characterized?

The effects of warming on ozone production have not been discussed.

The CASAC ozone panel was instructed by the Chair to focus on considerations that will directly inform the ozone PA. The April 2022 draft ozone PA does not evaluate the impact of incremental changes in ground-level O_3 concentrations in the U.S. on radiative forcing and subsequent climate effects due to limitations in current climate modeling capabilities for ozone. I have not seen any new compelling evidence in the ISA that would result in a different conclusion at this time.

Dr. Judith C. Chow

Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.

Appendix I presents evidence related to ozone (O_3) in ambient air based on scientific information published before March, 2018. Some recent publications relevant to NAAQS implementation may be considered with respect to emission trends, wildfires and exceptional events, ambient air O_3 concentrations, and background O_3 levels as discussed below:

- Emission Trends

  U.S. anthropogenic O_3 precursor emission trends in Figure 1-2 (Page 1-12) show fluctuating wildfire emissions for CO and VOC from 2002-2014. As the frequency and intensity of wildfires has increased since 2015, an updated emission trend that reflects more recent fire emissions needs to be included to reflect the large increases in CO and VOC from the 2014 to 2017 NEI (U.S.EPA, 2016, 2021). Source types between the 2020 ISA and 2022 PA should be kept consistent for comparison.

- Wildfires and Exceptional Events

  Section 1.3.1.3.3 on "Landscape fires" would benefit from a discussion of exceptional events due to wildland fires (U.S.EPA, 2019). The Exceptional Events Rule (Title 40 of the Code of Federal Regulations, Parts 50.1, 50.14, and 51.930) promulgated in 2007 by U.S.EPA allows state, local, and tribal agencies to demonstrate "uncontrollable air pollution events". After the EPA approves these exceptional events, data are flagged and removed from consideration for NAAQS attainment in the region. As prolonged wildfire events impact large areas (e.g., Brey and Fischer, 2016; Gauthier-Manuel et al., 2022; Rogers et al., 2020; Schill et al., 2020), a larger number of high O_3 values have been designated as exceptional events in recent decades (David et al., 2021). Elimination of these high O_3 levels due to exceptional events does not reduce the fires or protect public health.

  The ISA needs to clarify how "Exceptional Events" might bias exposure assessments. As climate change exacerbates wildfires, smoke, and their health and environmental impacts, the EPA may need to revise the "Exceptional Events Guidance" with a goal to adequately protect public health and the environment. It is desirable for state, local, and tribal agencies to work with other agencies (e.g., US Forest Service, Bureau of Land Management) to improve land management and minimize human-activity-induced fire episodes.

- Ambient Air O_3 Concentrations

There are ~1300 federal, state, local, and tribal ambient air monitors reporting O_3 concentrations. However, there are fewer year-round than warm-season datasets based on monitoring requirement (as shown in Figure 1-7, Page 1-46). May to September warm-season monitoring (e.g., States of Washington and Oregon) may miss O_3 episodes due to wildfires in early spring or late fall. This is especially important as O_3 peak concentrations have shifted from summer to spring and fall in many U.S. regions (Blanchard et al., 2019). Since elevated O_3 concentration may also occur during winter (e.g., Mansfield, 2018), year-round O_3 monitoring is desirable.

The effect of meteorology and climatic events on peak O_3 concentrations needs to be examined and further elaborated (Section 1.5). The fourth highest daily maximum 8-hr (MAD8) O_3 concentration increased from 2014 to 2018 in Los Angeles, CA, despite decreases in estimated NO_x and VOC emissions. Based on the generalized additive model (GAM)-least squares approach, emission variables were found to be the most important predictors; maximum temperature was also important to estimate peak O_3 concentrations (Gao et al., 2022).

- Background O_3 Level

Section 1.8 of the ISA focuses on the use of regional Chemical Transport Models (CTMs, such as CMAQ and CAM_x) to estimate U.S. background (USB) O_3 concentrations. Recent improvements in regional and hemispheric modeling methods estimate U.S. background O_3 levels in the range of 20-50 ppb with 10 ppb uncertainties for seasonal average concentrations. These levels differ from the 54-63 ppb level in rural western states and are more constant (45.8 ± 3 ppb) in northeastern states (Parrish and Ennis, 2019).

Sources of O_3 during high-O_3 events merit additional discussion as large-scale transport processes along with wildfire and stratospheric O_3 intrusion may impact air quality in the southwestern U.S. and intermountain west. The 2017 Fires, Asian, and Stratospheric Transport- Las Vegas Ozone Study (FAST- LVOS) found an elevated O_3 layer above Las Vegas on 35 out of 45 sample days (~78%) and contributions from O_3 aloft to mean 8-hour average surface O_3 of 50-55 ppb (Langford et al., 2022). Multiple modeling coupled with intensive field measurements need to be facilitated to characterize elevated O_3 downmixing events (Zhang et al., 2020). Such intensive studies should be conducted for different regions of the U.S.

The implication of USB O_3 concentrations on NAAQS attainment need to be examined for relevant region. Observation-based baseline O_3 should be considered. Based on Trinidad Head, northern California, ozonesondes, Parrish et al. (2022) found ~45 ppb background O_3 concentrations but increasing to over 60 ppb at 1 km above mean sea level (asl). The northern midlatitudes U.S. baseline O_3 concentrations exhibited a non-linear change, with a rapid increase (~5 ppb/decade) during the 1980s and slowed in the 1990s. It followed a slow decrease (~1 ppb/decade) after the peak mid-2000 to present with transported O_3 into the U.S. varying from -2.8 to +7 ppb/decade (Parrish et al., 2021). These analyses demonstrate the value of using long-term measurements at isolated midlatitude sites to further understand the temporal and spatial variability of the baseline O_3 distributions (Parrish et al., 2020) and their potential impact on O_3 NAAQS in different regions, especially in the intermountain west.

Climate Effects (Appendix 9)

a. What are the panel's views regarding the causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables?

b. Have the effects of warming on ozone production been adequately characterized?

Tropospheric O_3 plays an important role in climate change. The multi-model mean tropospheric O_3 burden increased by ~44% from the pre-industrial 1850 to the present period (2005-2014), with a projected maximum tropospheric O_3 burden of 416 ± 35 Tg in 2100 (Griffiths et al., 2021). This is illustrated in Figure 6.4 of the Intergovernmental Panel on Climate Change (IPCC) Sixth Assessment Report (AR6) (IPCC, 2021), as shown below. The magnitudes of the global positive trend since 1997 are consistent among model ensembles (0.82 ± 0.13 Tg/yr), ozonesonde data (0.70 ±0.15 Tg/yr), and satellite observations (0.83 ± 0.85 Tg/yr) in the Southern hemisphere (Griffiths et al., 2021). However, the O_3 forcing on climate varies by its vertical and latitudinal distribution in the troposphere. Additional vertical O_3 profiles are needed to better understand tropospheric O_3 distribution.

- Causal Determination for Tropospheric O_3 and Radiative Forcing

  Recent studies are consistent with those addressed in Appendix 9 of the ISA 2020 in which tropospheric O_3 plays an important role in the climate system and increases in tropospheric O_3 precursors and O_3 abundance contribute to climate change. However, the 2020 ISA relies on the IPCC AR5 (Myhre et al., 2013) and more recent findings should be consulted to reinforce the causal determination between radiative forcing and tropospheric O_3.

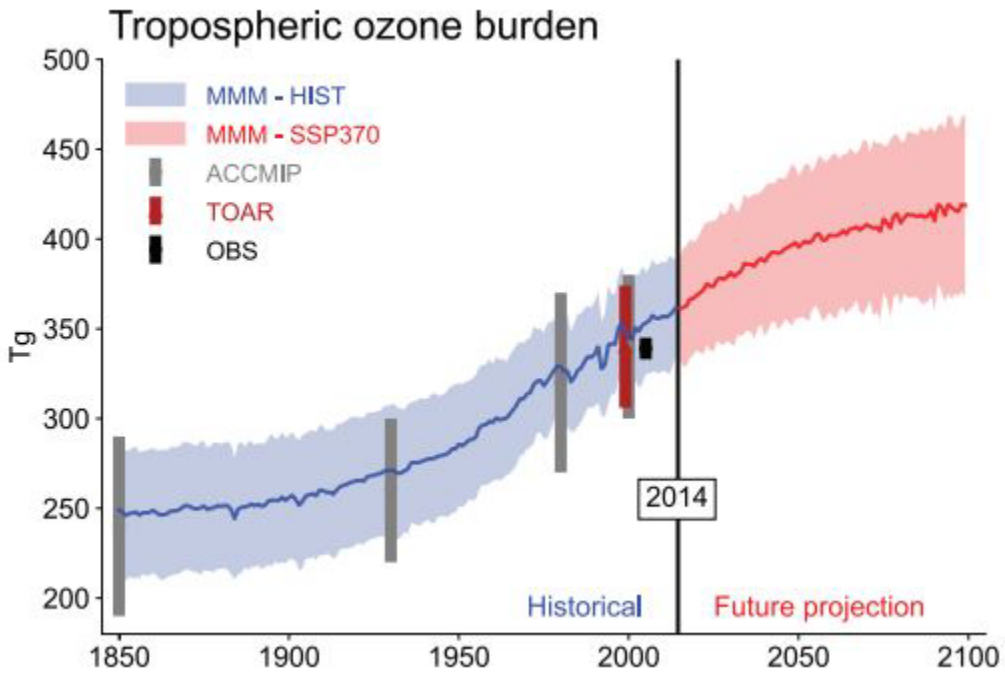

Figure 6.4 | Time evolution of global annual mean tropospheric ozone burden (in Tg) from 1850 to 2100. Multi-model means for CMIP6 historical experiment (1850–2014) from UKESM1-LL-0, CESM2-WACCM, MRI-ESM2-0, GISSE2.1-G and GFDL-ESM4 and for ScenarioMIP SSP3-7.0 experiment (2015–2100) are represented with their inter-model standard deviation (±1 standard deviation, shaded areas). Observation-based global tropospheric ozone burden estimate (from Table 6.3) is for 2010–2014. Tropospheric Ozone Assessment Report (TOAR) multi-model mean value (from Table 6.3) is for 2000 with a ±1 standard deviation error-bar. Atmospheric Chemistry and Climate Model Intercomparison Project (ACCMIP) multi-model means are for 1850, 1930, 1980 and 2000 time slices with ±1 standard deviation error-bars. The troposphere is masked by the tropopause pressure calculated in each model using the WMO thermal tropopause definition. Further details on data sources and processing are available in the chapter data table (Table 6.SM.3).(IPCC, 2021)

AR6 shows continued warming of the climate system in recent decades. Human-caused radiative forcing of 2.72 w/m^2 (ranging 1.96 to 3.48 w/m^2) in 2019 relative to 1750, representing a 19% increase (0.43 w/m^2) relative to those reported in AR5 (IPCC, 2013). This net positive radiative forcing is attributed to the increase in greenhouse gas (GHG) concentrations since 2011 (IPCC, 2021), representing an increase of average heating rate of ~58% from 0.5 w/m^2 (ranging 0.32-0.69 w/m^2) during 1971-2006 to 0.79 w/m^2 (ranging 0.5-1.06 w/m^2) for the period of 2006-2018.

- Likely to be Causal Determination for Tropospheric O_3 and Temperature, Precipitation, and Related Climate Variables

  O_3 is the third largest anthropogenic greenhouse gas contributing to radiative forcing with a total radiative forcing of 0.35 w/m^2 (ranging 0.15-0.55 w/m^2) in 2011 relative to 1750 pre-industrial times based on models with both tropospheric and stratospheric chemistry reported in IPCC (2013). Excluding one model with negative estimates, the predicted present-day total O_3 radiative forcing increased to 0.39 w/m^2 (ranging 0.27- 0.51 w/m^2). Based on the Coupled Model Intercomparison Project Phase 6 (CMIP6), Skeie et al. (2020) estimated O_3 forcing at 0.38 w/m^2. These findings are consistent with those discussed in Appendix 9 of ISA 2020.

- Effect of Warming on O_3 Production

  The frequency, intensity, and duration of heat waves in recent years accelerates regional feedbacks and local emissions to increase surface O_3 and the intensity of peak O_3 concentrations. The effect of climate change (e.g., temperature increases and drought) on surface O_3 needs to be addressed in the 2020 ISA for causal determination. AR6 notes that a warmer climate may reduce surface O_3 in unpolluted regions due to the increased water vapor abundance that accelerates O_3 chemical loss, but introduces a surface O_3 penalty of 0.2-2 ppb/ºC over polluted regions. AR6 reiterates the positive response of surface O_3 to future climate change through wildfires, soil NO_x emissions, and stratosphere-tropospheric exchange (IPCC, 2021).

  Several studies have reported an association between O_3 extremes and heat waves and drought under specific weather patterns coupled with local emissions (e.g., Fu and Tian, 2019; Khomsi et al., 2022; Nolte et al., 2021; Porter and Heald, 2019). Modeling efforts by Pommier et al. (2018) found that

climate change will have distinct effects of surface O_3 in India, with a 4% (2ppb) increase in the north and -3% (-1.4 ppb) decrease in the south by 2050. Phalitnonkiat et al. (2018) notes that the northeastern and southeastern US have the strongest dependence between temperature and extreme level of O_3. More research is needed to better understand the climate change penalty to surface O_3 and its implications for policy making (McNider and Pour-Biazar, 2020).

Given the temperature dependence of surface O_3 concentrations, warmer conditions in the future have potential to increase O_3 levels, with subsequent adverse health effects (Khomsi et al., 2022). Otero et al. (2021) estimated the impacts of NO_x reductions on the O_3-temperature relationship, finding O_3 production rates reduced under NO_x-limited chemistry. VOC changes also influenced O_3 production. As O_3 formation under different environments is complex, multiple pollutants need to be considered to better understand O_3-temperature relationships.

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Dr. Mark Frampton

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

Short-term: I agree with the conclusions of the 2020 ISA as follows:

"Thus, the recent evidence integrated across disciplines, along with the total body of evidence evaluated in previous integrated reviews, is sufficient to conclude that there is a causal relationship between short-term ozone exposure and respiratory health effects."

Long-term: I agree with the conclusions of the 2020 ISA as follows:

"Overall, the collective evidence is sufficient to conclude that a likely to be causal relationship exists between long-term ozone exposure and respiratory effects."

This conclusion is unchanged from the 2013 ISA. While the strength of the evidence has increased in general, and animal studies show airways effects of repeated or longer-term exposures, there are still uncertainties in the epi related to copollutant confounding, and inconsistent findings with mortality.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

Note: Duffney memo incorrectly indicates highest ozone concentration for the MOSES study as 100 ppb; it was 120 ppb.

The following study was identified as relevant to long-term respiratory effects and respiratory mortality, but in itself does not substantially change the conclusions of the ISA with regard to respiratory causal determinations.

Liu, Y., et al. (2019). "Short-Term Exposure to Ambient Air Pollution and Asthma Mortality." American Journal of Respiratory and Critical Care Medicine **200**(1): 24-32.

> Rationale: Short-term exposure to air pollution has been associated with asthma exacerbation and increased healthcare use caused by asthma, but its effect on asthma mortality remains largely unknown.Objectives: To quantitatively assess the association between short-term exposure to air pollution and asthma mortality.Methods: We investigated 4,454 individuals who lived in Hubei province, China, and died from asthma between 2013 and 2018. A case-crossover design and conditional logistic regression models were applied for data analyses. Exposures to particulate matter ≤2.5 μm in aerodynamic diameter (PM2.5), particulate matter ≤10 μm in aerodynamic diameter (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3) were estimated by inverse distance weighted averages of all monitoring stations within 50 km from each case's home address.Measurements and Main Results: Each

interquartile range (IQR) increase of PM2.5 (lag 3; IQR, 47.1 μg/m3), NO2 (lag 03; IQR, 26.3 μg/m3), and O3 (lag 3; IQR, 52.9 μg/m3) were positively associated with asthma mortality, with odds ratios of 1.07 (95% confidence interval, 1.01–1.12), 1.11 (95% confidence interval, 1.01–1.22), and 1.09 (95% confidence interval, 1.01–1.18), respectively. There was no evidence of departure from linearity for these associations. Further adjustment for other pollutants did not change the associations materially. We did not observe significant associations between PM10, SO2, and CO exposures and asthma mortality. Overall, the estimates remained consistent in various sensitivity analyses.Conclusions: Our results provide new evidence that short-term exposures to PM2.5, NO2, and O3 may increase asthma mortality risk. Further studies are needed to confirm our findings in other populations.

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

The question of weighting of the CHE studies is perhaps most relevant for the PA. In the ISA, the epi, CHE, and animal tox studies are all appropriately reviewed and given relatively equal consideration.

What is missing is adequate discussion of exposure concentrations, especially with regard to the epi and CHE studies. Exposure concentrations are provided in the study summary tables, and often mentioned in the text. But there is no acknowledgement or discussion of the discrepancy between lowest exposure concentrations at which health effects associations are seen in the epi studies, and the lowest effect concentrations in the human controlled exposure studies. The latter are several-fold higher than the former. This issue is important because the PA interprets the absence of effects in the CHE below 60 to 70 ppb as evidence that clinically important effects do not occur below these concentrations, effectively ignoring the epi associations of morbidity at much lower concentrations.

The ISA correctly points out that responses in CHE studies are mostly similar between people with and without asthma. But the consequences of a given reduction in lung function, or increase in airway injury, may be greater for people with asthma, because they are already impaired. This does not receive enough emphasis in the 2020 ISA, although it has been acknowledged in previous documents.

Reasons why CHE studies may underestimate ozone effects at low concentrations:

1. Subjects usually young, healthy, and fit.
2. Exposures are usually single and of relatively short duration. Few studies include outcome measurements beyond 24 hours after exposure, so delayed effects would be missed.
3. No other pollutants: intake air is usually filtered through HEPA and charcoal.
4. Ambient exposures may include other oxidants that track with ozone, or ozone reaction products.

Our recently published MOSES 2 study (Frampton et al. 2022, listed with new CV studies below) suggests it is not only a matter of healthy participants. The MOSES CHE study found no significant cardiovascular effects of controlled ozone exposures, up to 120 ppb for 3 hours, on HRV, in healthy older participants. Yet we found that HRV, when measured before each experimental exposure, decreased in association with prior increases in ambient ozone concentrations. Those ambient concentrations were substantially lower than the experimental ozone concentrations.

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

Short-term

There is reasonably consistent epi evidence for short-term ozone CV mortality (4.1.14), but much less consistent evidence for morbidity and markers of CV effects, in both epi and CHE.

Regarding short-term CV causality, the ISA states, "However, the body of controlled human exposure studies evaluating short-term ozone exposure and cardiovascular endpoints has grown, and when evaluated in the context of the controlled human exposure studies available for the 2013 Ozone ISA, the evidence is less consistent and weaker, overall."

"The evidence that supports this change in the causality determination includes: (1) a growing body of controlled human exposure studies providing less evidence for an effect of short-term ozone exposure and cardiovascular health endpoints; (2) a paucity of evidence for more severe cardiovascular morbidity endpoints (i.e., HF, IHD and MI, arrhythmia and cardiac arrest, and thromboembolic disease) to connect the evidence for impaired vascular and cardiac function from animal toxicological studies with the evidence from epidemiologic studies of cardiovascular mortality; and (3) uncertainties and limitations acknowledged in the 2013 Ozone ISA (e.g., lack of control for potential confounding by copollutants in epidemiologic studies) remain in recent evidence…".
The 2013 ISA concluded that "a likely causal relationship exists between short-term exposure to ozone and cardiovascular effects." Given the uncertainties and inconsistencies in the evidence, the EPA's decision to downgrade short-term ozone cardiovascular effects to "suggestive of, but not sufficient to infer, a causal relationship" is reasonable and appropriate.

Long-term

There is increased evidence for long-term exposure and CV mortality (ACS and CanCHEC cohorts), but inconsistent effects on markers and morbidity, and inconsistent findings in animal toxicology studies.

The determination "suggestive of, but not sufficient to infer, a causal relationship", which is unchanged from the 2013 determination, is appropriate based on the overall evidence.

b. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?
This question is relevant here with regard to the causality determination for CV effects. Generally, the ISA gives appropriate and relatively equal consideration of epi, CHE, and toxicology studies in the assessment of short-term effects. Of course, there are no long-term CHE studies.

c. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

See below for a few newer studies, including the recent meta-analysis identified by George Allen (Zong et al., 2022) that found significant inverse relationships between ozone concentrations and markers of HRV. It should be noted that this meta-analysis excluded studies that used maximum 8-hour ozone concentrations, and included only those that used 24 hr averages. The paper did not indicate how many studies were excluded on that basis.

Taken together the newer evidence does not change the causality determination for CV effects that was indicated in the 2020 ISA.

Zong, Z., et al. (2022). "Association between Short-Term Exposure to Ozone and Heart Rate Variability: A Systematic Review and Meta-Analysis." International Journal of Environmental Research and Public Health **19**(18): 11186.

> Abstract: At present, ambient air pollution poses a significant threat to patients with cardiovascular disease (CVD). The heart rate variability (HRV) is a marker of the cardiac autonomic nervous system, and it is related to air pollution and cardiovascular disease. There is, however, considerable disagreement in the literature regarding the association between ozone (O3) and HRV. To further investigate the effects of short-term exposure to O3 on HRV, we conducted the first meta-analysis of relevant studies. The percentage change of HRV indicator(s) is the effect estimate extracted for the quantitative analysis in this study. In our meta-analysis, per 10 ppb increase in O3 was significantly associated with decreases in the time-domain measurements, for standard deviation of the normal-to-normal (NN) interval (SDNN) −1.11% (95%CI: −1.35%, −0.87%) and for root mean square of successive differences (RMSSD) −3.26% (95%CI: −5.42%, −1.09%); in the frequency-domain measurements, for high frequency (HF) −3.01% (95%CI: −4.66%, −1.35%) and for low frequency (LF) −2.14% (95%CI: −3.83%, −0.45%). This study showed short-term exposure to O3 was associated with reduced HRV indicators in adults, which suggested that the cardiac autonomic nervous system might be affected after O3 exposure, contributing to the association between O3 exposure and CVD risk.

Bai, L., et al. (2019). "Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario." Environ Int **132**: 105004.

> Long-term exposure to ambient air pollution has been linked to cardiovascular mortality, but the associations with incidence of major cardiovascular diseases are not fully understood, especially at low concentrations. We aimed to investigate the associations between exposure to fine particulate matter (PM2.5), nitrogen dioxide (NO2), ozone (O3), redox-weighted average of NO2 and O3 (Ox) and incidence of congestive heart failure (CHF) and acute myocardial infarction (AMI). Our study population included all long-term residents aged 35-85years who lived in Ontario, Canada, from 2001 to 2015 (~5.1 million). Incidence of CHF and AMI were ascertained from validated registries. We assigned estimates of annual concentrations of pollutants to the residential postal codes of subjects for each year during follow-up. We estimated hazard ratios (HRs) and 95% CIs for each pollutant separately using Cox proportional hazards models. We examined the shape of concentration-response associations using shape-constrained health impact functions. From 2001 to 2015, there were 422,625 and 197,628 incident cases of CHF and AMI, respectively. In the fully adjusted analyses, the HRs of CHF

corresponding to each interquartile range increase in exposure were 1.05 (95% CI: 1.04-1.05) for PM2.5, 1.02 (95% CI: 1.01-1.04) for NO2, 1.03 (95% CI: 1.02-1.03) for O3, and 1.02 (95% CI: 1.02-1.03) for Ox, respectively. Similarly, exposure to PM2.5, O3, and Ox were positively associated with AMI. The concentration-response relationships were different for individual pollutant and outcome combinations (e.g., for PM2.5 the relationship was supralinear with CHF, and linear with AMI).

Frampton, M., et al. (2022). "Effects of short-term increases in personal and ambient pollutant concentrations on pulmonary and cardiovascular function: a panel study analysis of the Multicenter Ozone Study in oldEr Subjects (MOSES 2)." Environmental Research **205**.

Background: The cardiovascular effects of ozone exposure are unclear. Using measurements from the 87 participants in the Multicenter Ozone Study of oldEr Subjects (MOSES), we examined whether personal and ambient pollutant exposures before the controlled exposure sessions would be associated with adverse changes in pulmonary and cardiovascular function. Methods: We used mixed effects linear regression to evaluate associations between increased personal exposures and ambient pollutant concentrations in the 96 h before the pre-exposure visit, and 1) biomarkers measured at pre-exposure, and 2) changes in biomarkers from pre-to post-exposure. Results: Decreases in pre-exposure forced expiratory volume in 1 s (FEV1) were associated with interquartilerange increases in concentrations of particulate matter ≤2.5 μm (PM2.5) 1 h before the pre-exposure visit (−0.022 L; 95% CI -0.037 to −0.006; p = 0.007), carbon monoxide (CO) in the prior 3 h (−0.046 L; 95% CI -0.076 to −0.016; p = 0.003), and nitrogen dioxide (NO2) in the prior 72 h (−0.030 L; 95% CI -0.052 to −0.008; p = 0.007). From pre-to post-exposure, increases in FEV1 were marginally significantly associated with increases in personal ozone exposure (0.010 L; 95% CI 0.004 to 0.026; p = 0.010), and ambient PM2.5 and CO at all lag times. Ambient ozone concentrations in the prior 96 h were associated with both decreased pre-exposure high frequency (HF) heart rate variability (HRV) and increases in HF HRV from pre-to post-exposure. Conclusions: We observed associations between increased ambient PM2.5, NO2, and CO levels and reduced pulmonary function, and increased ambient ozone concentrations and reduced HRV. Pulmonary function and HRV increased across the exposure sessions in association with these same pollutant increases, suggesting a "recovery" during the exposure sessions. These findings support an association between short term increases in ambient PM2.5, NO2, and CO and decreased pulmonary function, and increased ambient ozone and decreased HRV.

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

Short-term mortality

The 2013 ISA found that short-term ozone exposure was "likely to be causal" for all-cause mortality. In general the epi evidence consistently shows mortality associations. For respiratory mortality, there is

coherence with animal and human studies. However, for CV mortality, the evidence weaker and less consistent. Most telling, the evidence for short-term CV morbidity is weak and inconsistent, reducing the plausibility of a mortality effect.

The 2020 ISA downgrades short-term total mortality to "suggestive of, but not sufficient to infer, a causal relationship … between short-term ozone exposure and total mortality" based on the inconsistency in the more recent CHE studies, and the relative absence of morbidity effects. Too much emphasis is placed on the negative CHE findings here. Some of the previous uncertainties in the mortality findings have been reduced by recent studies, and the total mortality data are quite consistent. But the lack of supporting morbidity evidence remains a substantial source of uncertainty. Even if less weight is placed on the negative CHE studies, the overall evidence falls short of "likely", and "suggestive of" is the appropriate judgement.

Long-term mortality

The determination of "suggestive of", which is unchanged from the 2013 ISA, is appropriate. The geographical inconsistencies in ozone-total mortality relationships is largely unexplained. There are new studies that have strengthened the evidence, but significant uncertainties remain.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

One new study is identified below. This study found positive mortality relationships for PM2.5 and NO2, but inverse effects for ozone.

Hvidtfeldt, U. A., et al. (2019). "Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort." Environ Int **123**: 265-272.

Air pollutants such as NO2 and PM2.5 have consistently been linked to mortality, but only few previous studies have addressed associations with long-term exposure to black carbon (BC) and ozone (O3). We investigated the association between PM2.5, PM10, BC, NO2, and O3 and mortality in a Danish cohort of 49,564 individuals who were followed up from enrollment in 1993-1997 through 2015. Residential address history from 1979 onwards was combined with air pollution exposure obtained by the state-of-the-art, validated, THOR/AirGIS air pollution modelling system, and information on residential traffic noise exposure, lifestyle and socio-demography. We observed higher risks of all-cause as well as cardiovascular disease (CVD) mortality with higher long-term exposure to PM2.5, PM10, BC, and NO2. For PM2.5 and CVD mortality, a hazard ratio (HR) of 1.29 (95% CI: 1.13-1.47) per 5mug/m(3) was observed, and correspondingly HRs of 1.16 (95% CI: 1.05-1.27) and 1.11 (95% CI: 1.04-1.17) were observed for BC (per 1mug/m(3)) and NO2 (per 10mug/m(3)), respectively. Adjustment for noise gave slightly lower estimates for the air pollutants and CVD mortality. Inverse relationships were observed for O3. None of the investigated air pollutants were related to risk of respiratory mortality. Stratified analyses suggested that the elevated risks of CVD and all-cause mortality in relation to long-term PM, NO2 and BC exposure were restricted to males. This study supports a role of PM, BC, and NO2 in all-cause and CVD mortality independent of road traffic noise exposure.

Dr. Christina H. Fuller

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

EPA staff did an incredible job gathering and summarizing the scientific literature on ozone exposure and cardiovascular health impacts.

The 2013 ISA concluded that "a likely causal relationship exists between short-term exposure to ozone and cardiovascular effects." The decision to downgrade the causality determination to "suggestive of, but not sufficient to infer, a causal relationship" in the 2020 ISA requires substantial evidence from new research. The 2020 ISA states that recent epidemiological and animal studies evaluating the association between short-term ozone and cardiovascular effects show a similar pattern and uncertainties as those included in the 2013 ISA. I would expect that a downgrading of the causality determination would be authorized only when there is a clear change in direction in associations. A downgrade could also be justified if newer short-term studies are more accurate and precise in estimation compared to older studies, validating them having a higher weight. However, no evidence of either of these situations is given in the 2020 Ozone ISA. I do not have concerns regarding the causality determination for long-term cardiovascular effects.

b. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

I am concerned with the usage of controlled human exposure (CHE) studies being used as evidence of the need to downgrade the causality determination for short-term effects. CHEs are important, because they can provide information regarding mechanisms of effect, however, they are performed on a healthy population. There may be more pronounced effects in the general population or in a population with co-morbidities. If the basis for causality is relegated only by the healthiest of the population, this does not promote an adequate level of protection for sensitive subgroups. In addition, the very short-term nature of CHEs precludes the evaluation of delayed short-term effects, even those that develop a few days after exposure. In my opinion CHEs should be evaluated with caution if the purpose is to represent associations for the general population or sensitive sub-populations. The ISA makes a similar statement on page 4-41 of the ISA, and I think this applies to the usage of CHEs in causality determinations.

Therefore, I believe that the short-term ozone exposure and cardiovascular determination should be "likely to be causal".

At-Risk Populations (IS 4.4)

a. Based on the existing scientific record, what are the panel's views regarding the scientific evidence of effects of ozone exposures on at-risk communities?

b. What are the panel's views on how the evidence regarding disparities in exposure and health effects should be brought into the PA?

The Preamble to the ISA has a very good description of who falls into the category of "at-risk". The Preamble specifies that at-risk populations selected is based on "interindividual variation in both physiological responses, and exposure to ambient air pollution." However, in the 2020 Ozone ISA almost exclusive attention is paid to interindividual variation. Missing is a thorough analysis of differences in exposure due to spatial variation that is often driven by sociodemographic factors, especially race/ethnicity, class and income. This type of analysis is necessary for the Policy Assessment in order to understand the variation of concentrations present at a given mean level for which a standard may be set.

In future ISAs I suggest that the analysis of populations that are at-risk be spread over the entirety of the ISA as relevant outcomes are discussed. Relegating these groups to a single section implies that they are separate from, and secondary to, the main conclusions of the ISA. This ISA does a good job of evaluating the at-risk populations of children and older adults in other sections, however, the others are fairly absent. The purpose of the NAAQS process is to protect public health for the general population and sensitive sub-populations, so equal attention should be given to both.

The 2020 Ozone ISA includes discussion of only those at-risk communities for which there is new data. Although this may have been done to adhere to a tight timeline, it is more difficult to consider at-risk populations in setting standards when data on that group is in a prior version of the ISA. I suggest that future ISAs bring forward analyses and references from previous ISAs that are relevant for the current ISA; especially for those at-risk populations for which there is *adequate* or *suggestive* evidence for increased risk. In the case of the 2020 Ozone ISA these would be outdoor workers, genetic factors, diet, sex and SES. In addition, at-risk populations based on race/ethnicity should also be included per the Executive Order 12898; *Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations*.

Also, note that most CHEs do not have sufficient representation of variation in race/ethnicity, socioeconomic levels, age, or co-morbidities and therefore, it is possible to draw conclusions from these studies that are not conservative enough to protect *at-risk populations*.

Specific suggestions for future ISAs:

- Consider including "insufficient quantity" to the definition of suggestive evidence.
- Evaluate at-risk groups throughout the ISA and not in a separate section.

As is evident from the 2020 Ozone ISA research exploring adverse effects of ozone on at-risk populations is limited. Published studies in this area are smaller than the number for PM2.5. Better characterization requires an increased number of studies specifically designed to explore associations between ozone and at-risk populations. Therefore, increased research in this area is encouraged to enable better consideration in the future.

Health Effects – Developmental Effects (Appendices 3,4,7)

a. What are the panel's views regarding the review and characterization of the scientific evidence on developmental effects from ozone exposure?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

Overall the 2020 Ozone ISA provides a solid analysis and interpretation of the included studies. It appears that the PECOS protocol focus on studies from U.S., European and Australian regions was waived here. For example, studies from Brazil and China were included on page 7-6 in the discussion of male reproductive function. It is unclear why there is a difference in the regions included for these effects as compared to that of regions included for other effects (e.g. cardiovascular).

What follows are conclusions given in Section 7.

> "Overall, there is consistent evidence for an association between ozone exposures during early to midpregnancy with preterm birth in epidemiologic studies. There are no toxicological studies examining preterm birth in animals or endpoints that are analogous to preterm birth." (p.7-14)
>
> "Overall the evidence is suggestive of, but not sufficient to infer, a causal relationship between ozone exposure and male and female reproduction and fertility." (p. 7-18)
>
> "Overall the evidence is suggestive of, but not sufficient to infer, a causal relationship between ozone exposure and pregnancy and birth outcomes." (p. 7-19)

The statements above are supported by the included studies, and the epidemiological studies are (generally) for exposures lower than the existing standard. Therefore, we should consider this difference in concentration when finalizing the 2020 Ozone Policy Assessment.
Better characterization of the relationships summarized in this chapter requires the inclusion of more studies with greater numbers of racial/ethnic minorities and a broader range of income/wealth categories. In this way there can be a more thorough assessment and inclusion of these at-risk populations (as well as others) into the understanding of associations and concentration-response functions. Increased research in this area is encouraged to enable better consideration in the future.

Dr. Terry Gordon

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

Both the long- and short-term epidemiology studies in the 2020 ISA suggest important causal associations between ozone exposure and respiratory effects with few uncertainties. The underlying pathways/mechanisms linking ozone exposure to respiratory effects have not changed since the last ISA (and strongly overlap with proposed PM pathways). Overall, the uncertainties identified in the 2020 ISA, as reflected in the human and animal controlled exposure studies, are minimal. Again, because the PECOS structure limits (inconsistently) the studies to North America and Canada, the research conducted in Europe and Asia is lost to addressing uncertainties. Ozone, unlike PM, is a pure chemical and its health effects should be the same throughout the world.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

Given the lack of applicable controlled human studies in recent years, there is little evidence to alter these characterizations. Perhaps, within ethical guidelines, EPA should support future studies that focus on the response of susceptible individuals to ozone.

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

When available, epidemiologic studies should be weighted more strongly than controlled human (and animal) exposure studies for the simple reason that susceptible and vulnerable subpopulations are included in the epidemiologic and generally excluded in the control exposure analyses. Importantly, the controlled exposure studies typically have only included healthy and exercising young adults. Moreover, although controlled exposure studies should ideally be used to support epidemiology studies, the short-term controlled ozone exposure studies in human subjects do provide the most convincing concentration-response evidence of an adverse effect of ozone on pulmonary function, airway responsiveness, and inflammation.

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

<u>Information from the existing scientific record reviewed in the 2020 ISA (together with the three technical memos):</u>

Both the long- and short-term epidemiology studies in the 2020 ISA do suggest important associations between ozone exposure and cardiovascular effects but there are uncertainties in both associations due to conflicting study results. The underlying pathways/mechanisms linking ozone exposure to cardiovascular effects have not changed since the last ISA (and strongly overlap with proposed PM pathways) and the relative lack of new studies in North America and Europe since the 2015 ISA is concerning given these uncertainties. Overall, the uncertainties identified in the 2020 ISA are also reflected in the human and animal controlled exposure studies that show conflicting results. If the PECOS structure limits the studies to North America, Europe, and Australia, then research conducted in Asia is lost to addressing these uncertainties. Ozone, unlike PM, is a pure chemical and it's health effects should be the same throughout the world.

Thus, for the most part, it is clear why the 2020 ISA and the current PA conclude that the findings are suggestive but not causal for linking ozone exposure (both short- and long-term) with cardiovascular effects. This uncertain linkage is convincing for some important cardiovascular indices such as short term ozone (i.e., hospital visits/admissions; inflammation; blood pressure; and coagulation factors), but there does appear to be relatively strong epidemiologic evidence for: 1) short-term ozone exposure and ST-elevation myocardial infarction and out of hospital cardiac arrests; and 2) long-term ozone exposure and cardiovascular mortality. The latter mortality association seems particularly strong given the number of post-2013 studies listed in Figure 4.7. This mortality association points toward a 'causal' role although the underlying infarction, coagulation, and hospital admission data do not align well and lend uncertainty. However, while only a small number, panel studies have reported links between arrhythmia results and short-term ozone exposure and thus may support the mortality effect.

Additional pertinent information

The majority of these short- and long-term ozone-health effects uncertainties could be reduced if EPA funded studies directly addressing these issues. Also, it is unclear why the PECOS criteria for 'study location' differs between the short-term and long-term assessments in the 2020 ISA, given the large number of studies conducted in Asia as reported from 2018 to 2022. Similarly, the study location criteria do not seem to be applied consistently in Dr. Vandenberg's "Short-Term Cardiovascular Morbidity and Mortality Studies Excluded from the Draft Ozone ISA Based on Location" memo which 'excludes/lists' many European and North American studies.

b. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

Given the lack of applicable controlled human studies in recent years, there is little evidence to alter these characterizations. There are, however, several epidemiology studies, primarily in Europe and Asia, that can add to the knowledge base and reduce uncertainties. While the more recent studies in Europe are inconsistent in regards to ozone exposure and cardiovascular mortality, studies in Asia generally report a positive association, for example:

Wu H, Lu K, Fu J. A Time-Series Study for Effects of Ozone on Respiratory Mortality and Cardiovascular Mortality in Nanchang, Jiangxi Province, China. Front Public Health. 2022 Apr 26;10:864537. doi: 10.3389/fpubh.2022.864537. PMID: 35558528; PMCID: PMC9087186.

Guo X, Su W, Wang H, Li N, Song Q, Liang Q, Sun C, Liang M, Zhou Z, Song EJ, Sun Y. Short-term exposure to ambient ozone and cardiovascular mortality in China: a systematic review and meta-analysis. Int J Environ Health Res. 2022 Apr 19:1-18. doi: 10.1080/09603123.2022.2066070. Epub ahead of print. PMID: 35438585.

Ho AFW, Tan BY, Zheng H, Leow AS, Pek PP, Liu N, Raju Y, Yeo LL, Sharma VK, Ong ME, Aik J. Association of air pollution with acute ischemic stroke risk in Singapore: a time-stratified case-crossover study. Int J Stroke. 2022 Jan 4:17474930211066745. doi: 10.1177/17474930211066745. Epub ahead of print. PMID: 35974459.

c. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

When available, epidemiologic studies should be weighted more strongly than controlled human (and animal) exposure studies for the simple reason that susceptible and vulnerable subpopulations are included in the analyses. As noted in the ISA and PA, the controlled exposure studies generally include healthy and exercising young adults. Thus, controlled exposure studies would optimally be used to support epidemiology studies.

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

The epidemiology studies in the 2020 ISA suggest important likely to be causal associations between ozone exposure and mortality effects. Overall, the uncertainties identified in the 2020 ISA, as reflected in the human and animal controlled exposure studies, are minimal. Thus, the studies presented in the 2020 ISA suggest a 'likely to be causal' rather than the 'suggestive' causal relationship proposed by the ISA and PA.
Although controlled exposure studies can support the biologic plausibility of the epidemiology mortality studies, in the case of mortality, it may be a stretch to link controlled exposure studies to mortality. Thus, the epidemiology studies provide the strongest evidence of a positive association between ozone and mortality. This reliance on epidemiology is strengthened by the testing for C-R relationships between short- and long-term ozone exposure and mortality.

Dr. Catherine Karr

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

The determination of causality for short-term effects in the 2020 ISA is sound and strengthened based on research conducted in recent years. There are multiple studies revealing mechanistic underpinnings and strong and consistent observational epidemiological studies on a range of respiratory health endpoints. It is noteworthy that the controlled human (CHE) exposure studies demonstrate effects in healthy young adults below the current regulatory standard. Also, noteworthy is that the epidemiological studies are conducted in settings with mean air pollution concentrations that are even further below current regulatory standards compared to the CHEs. For more severe pediatric outcomes, such as pediatric asthma hospitalization, recent studies consistently show effects for school age children in settings with average concentrations in the 30-40 ppb range.

The causal determinant for long- term exposure as "likely to be causal" is also well-supported in the 2020 ISA. However, there have been notable new data since 2013 that significantly bolster the ISA conclusion of: "With respect to long-term ozone exposure, there is strong coherence between animal toxicological studies of changes in lung morphology and epidemiologic studies reporting positive associations between long-term ozone exposures. and new-onset asthma, and respiratory symptoms in children with asthma. Furthermore, the experimental evidence provides biologically plausible pathways through which long-term ozone exposure could lead to the types of respiratory effects reported in epidemiologic studies". Below are some of the newer epidemiologic data that strengthen further the coherence and consistency of long term ozone on respiratory health effects in children.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

In the 2020 ISA Section 3.2.4.2.1 (Lung Function & Development: epi studies), data are summarized as inconsistent evidence for association between long-term exposure and lung development in children. Specifically, Table IS-5 Conclusions from the 2020 ISA read: "A limited number of recent epidemiologic studies continue to provide inconsistent support for an association between long-term ozone exposure and lung function development in children". However, it appears this is no longer an accurate interpretation. Data on the effects of long-term exposure to ozone on pediatric lung function has accumulated in recent years and subsequent to science considered in the 2013 and 2020 ISA. This is an important outcome because lung function develops rapidly through childhood and decrements in early life may portend life-long deficits in maximum attained lung function. Such deficits are associated with chronic disease in adulthood such as COPD. In addition, several of these more recent analyses of long term exposure on pediatric lung function include addressing co-pollutants, one of the identified uncertainties for the causal determination of "likely to be causal" in the 2020 ISA. A review of studies of ozone and pediatric lung function published from 2013-2021 identifies five analyses demonstrating statistically significant reductions in FEV1, with four of these adjusted for co-pollutants (Figure 2 A-C, Holm 2022). Analyses demonstrating statistically significant effects on FVC were observed in four

analyses, three of these were adjusted for co-pollutants (Figure 3 A-C, Holm 2022). The consistency and coherence of these findings along with the experimental data in rhesus monkeys are compelling for re-consideration of the overall causality of long-term effects of ozone on respiratory health. For ethical and practical reasons, there can be no expectation of controlled human exposure data on early life long-term exposure and subsequent development of adverse pediatric respiratory health outcomes such as lung function development to contribute further to this question.

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

The strengths of observational cohort studies (real life exposures, real life co-exposures, diversity of population vulnerability based on genetics, social factors, etc) or panel studies and of controlled human exposures (specific ozone only pollutant exposure) are complementary and should not be viewed hierarchically (one more informative, of higher consequence or weight, than the other). The interpretations in the ISA as written seem to suggest this hierarchy. This is problematic and for some outcomes (early life exposures, long term exposures with subsequent developmental comsequences) data derived from controlled human exposure conditions will not be available. For example, consider this summary statement regarding short-term exposure effects with hierarchical language underlined "In particular, controlled human exposure studies provided evidence of lung function decrements, respiratory symptoms, and increased inflammation in young healthy adults exposed to ozone concentrations as low as 60 to 70 ppb following 6.6-hour exposures with quasi-continuous exercise. Dose-dependent increases in airway responsiveness were also noted after exposures to 0, 80, 100, and 120 ppb ozone. These studies were supported by epidemiologic studies that not only reported ozone-related respiratory effects in healthy populations, but also provided evidence of ozone associations with asthma exacerbation, COPD exacerbation, and hospital admissions and ED visits for combined respiratory disease. Additionally, there was consistent evidence of an association between short-term increases in ambient ozone concentrations and increases in respiratory mortality."

Portrayed this way, it reads as if the CHE studies are upweighted – listing this evidence first and as "in particular", followed by epidemiologic study findings described as supporting the CHE studies. In fact, the large epidemiologic evidence base is more informative for interpretation to protect even the most vulnerable in the population, which is the goal of the primary standard, and perhaps should be highlighted first.

Health Effects – Developmental Effects (Appendices 3, 4, 7, particularly Section 7.1.4)

a. What are the panel's views regarding the review and characterization of the scientific evidence on developmental effects from ozone exposure?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

The review and characterization of reproductive effects are sound. No new notable findings were identified for male reproductive toxicity (sperm toxicity) and female fertility.

The review and characterization for hypertensive disorders of pregnancy is still accurate to be classified as limited although two studies lend further evidence for the previously noted generally positive association of ozone with hypertensive disorders of pregnancy and provide more specific evidence for early pregnancy as the critical window (Hu 2017, Cao 2020).

The ISA concluded there is some evidence for effects on fetal growth and consistent evidence for associations with preterm birth, the latter related most with early to mid-pregnancy exposure windows. While additional studies continue, they do not change this interpretation, although Wang et al 2021 provides additional insight into windows of exposure for effects on term low birth weight. The results from this pregnancy cohort in China observed susceptibility to ozone effects at gestational weeks 15-26.

Regarding respiratory development –In section 7.1.4.1, the ISA notes "Several epidemiologic studies conducted in the U.S., Europe, and Asia report no evidence of an association between long-term exposure to ozone during developmental periods (in utero or early life) and asthma or allergy." One exception (Tetrault et al 2016) is noted.

This is no longer a fair representation of the evidence. For example, To et al conducted an analysis in a large Canadian birth cohort which found evidence for both childhood asthma and allergic rhinitis risk increased in relation to birth (proxy for pregnancy) exposure. Zhu et al 2022 in a prospective pregnancy cohort study in Guangzhou China observed increased exposure to ozone throughout pregnancy and in the second trimester were associated with increased risk of childhood wheezing. These studies were both robust to control for co-pollutants. Sbihi 2016 found higher incident asthma in school-aged children associated with in utero ozone exposure in a cohort of children in Vancouver Canada.

Overall, there has been less research emphasis on pregnancy/early life long term ozone exposure and development of asthma and allergies in the published literature, compared to exposure to PM, NO2 and future work in this area should be encouraged.

The number of epidemiologic studies on autism and early life ozone remains limited as noted in the ISA. A 2019 meta-analysis identified 7 studies, two identifying associations, five showing no effects. (Chun 2019) . A recent multi-site U.S based case control study found evidence for increased ASD risk specifically in relation to third trimester exposure to ozone (McGuinn 2020).

See response to discussion point b for Appendix 3 above regarding increased evidence of long-term exposure to ozone in childhood on lung function and a compelling overall evidence base for early life ozone exposure compromising child lung health.

At-Risk Communities

a. Based on the existing scientific record, what are the panel's views regarding the scientific evidence of effects of ozone exposures on at-risk communities?

Pregnant individuals and their developing fetuses should be considered at risk. Pregnant individuals are uniquely at risk of pregnancy related complications (e.g. hypertensive disorders of pregnancy). Exposures experienced in pregnancy have been linked to adverse birth outcomes and other

developmental outcomes (ASD) through increased risk of pregnancy complications as well as other mechanisms.

b. What are the panel's views on how the evidence regarding disparities in exposure and health effects should be brought into the PA?

Policy makers are increasingly grappling with the concept of environmental justice - recognizing exposure to social and environmental stressors are often co-located. This influences disparate health impacts (effect modification) and perpetuates health disparities. This concept of environmental justice as it relates to ozone does not currently have a place in the ISA and it would be useful to frame the EJ features and EJ related literature in the ISA.

Cited works:

To et al https://erj.ersjournals.com/content/55/2/1900913

Zhu et al 2022 https://www.sciencedirect.com/science/article/abs/pii/S0013935122007538

Sbihi et al 2016 https://erj.ersjournals.com/content/erj/47/4/1062.full.pdf

Holm et al 2022 https://pubmed.ncbi.nlm.nih.gov/34389296/

Hu et al 2017 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5222744/

Cao et al 2020 https://pubmed.ncbi.nlm.nih.gov/32050130/

Wang 2021 https://pubmed.ncbi.nlm.nih.gov/33129003/

Chun 2019 https://pubmed.ncbi.nlm.nih.gov/31733973/

McGuin 2020 https://pubmed.ncbi.nlm.nih.gov/31592868/

Dr. Michael T. Kleinman

Health Effects-Respiratory (Appendix 3)

a. What are the panel's views on the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

i. Short-term respiratory effects: The 2013 Ozone ISA concluded that "*short-term ozone exposure is causally associated with respiratory health effects.*" This was unchanged in the 2020 ISA. Controlled human exposure and toxicological studies demonstrated ozone-induced increases in respiratory symptoms, lung inflammation, airway permeability, and airway responsiveness. The experimental evidence was supported by strong evidence from epidemiologic studies and animal toxicological and controlled human exposure studies demonstrated ozone-induced increases in airway responsiveness, decreased pulmonary function, allergic responses, lung injury, impaired host defense, and airway inflammation which provide biological plausibility for epidemiologic associations of ambient ozone concentrations with lung function and respiratory symptoms.

ii. Long-term respiratory effects: The 2013 Ozone ISA concluded that "*there is likely to be a causal relationship between long-term exposure to ozone and respiratory health effects.*" This is unchanged in the 2020 ISA. However, exposure of infant monkeys to 0.5 ppm O3 delivered in biweekly cycles of alternating filtered air and ozone (i.e., 9 consecutive days of filtered air and 5 consecutive days of 0.5 ppm ozone, 8 hour/day) and to house dust mite allergen (HDMA) for 2 hours per day for 3 days on the last 3 days of ozone exposure, followed by 11 days of filtered air. Exposure altered lung growth and development, altered sensory nerve innervation, increased lung sensitization and promoted an allergic airway phenotype. This, and data from other animal studies is coherent with the generally consistent evidence from epidemiological studies reporting new onset asthma in children and increased severity of respiratory disease. The differentiation between 'causal' and likely to be casual' is based on the presence of uncertainties including "the *potential* for confounding by co-occurring pollutants, the lack of measurement of non-criteria pollutants and exposure measurement error relating to exposure assignment from fixed-site monitors." The uncertainties are perhaps weighted highly since for example, we are dealing with the potential for confounding and not any specific incidence, with 'possible' interference from unmeasured non-criteria pollutants and with possible measurement errors. It may be that the line between causal and likely to be causal is slim and it might be useful to emphasize that ozone is more likely than not to adversely affect respiratory health in children and adults. The potential for developmental changes in the respiratory tract could have serious long term consequences.

b. Does the panel suggest any new scientific evidence that might help strengthen this characterization?

i. Some recent information from urban China might be informative.

ii. If the value of a study is discounted because of potential flaws (unaccounted for co-pollutants) or potential confounding perhaps a biostatistical quantification of the degree to which the study could have been compromised might be worthwhile.

c. What are the panel's views regarding the weighting of controlled human exposures and panel and population based epidemiological studies?

i. Controlled human exposure studies are valuable and can provide causal relationships between short-term O3 exposures and various short-term respiratory outcomes. The method of generating O3 in most studies uses UV irradiation of purified oxygen which reduces risk of contamination by unwanted or unexpected reaction products. In most studies the generated O3 is metered into filtered or purified air. The risk of confounding in these studies is generally low. Epidemiological studies include O3 and to a variable extent other photochemically-generated oxidants. The study populations are relatively healthy adults and group sizes are often small but many study designs use each subject as his or her own control (repeated measures) which improves statistical power and effects are observed at concentrations ≥ 60 ppb for durations of 6 to 7 hours.

ii. Panel studies can include children, people with pre-existing respiratory diseases and breathing real-world atmospheres. The evidence indicates consistent associations for lung function decrements, respiratory symptoms and lung inflammation at levels on the order of 32 to 53 ppb.

iii. Consideration should be given to considering both types of studies in developing a NAAQS with an adequate margin of safety.

Health Effects-Cardiovascular (Appendix 4)

a. What are the panel's views on the causal determinations for short-term and long-term ozone exposure and cardiovascular effects?

i. Short-term cardiovascular effects: The 2013 Ozone ISA concluded that "a likely causal relationship exists between short-term exposure to ozone and cardiovascular effects." This relationship was downgraded to "suggestive" in the 2020 ISA. Appendix 4 documents that there are plausible pathways through which respiratory tract inflammation could exacerbate existing IHD and HF, contribute to the development of a myocardial infarction or stroke, and lead to ED visits and hospital admissions. This is consistent with several new studies that were not included in the previous assessment that relate cardiac arrests, both in and out of the hospital, with short-term O3 exposures.

Health Effects-Mortality (Appendix 6)

i. Short-term mortality effects were downgraded from likely causal to suggestive. The rationale that there "are substantial gaps in the biologically plausible pathways by which short-term O3 exposure could lead to cardiovascular mortality" should be more thoroughly evaluated since there is strong evidence for respiratory mortality, some evidence for cardiovascular mortality and

there appears to be biological plausibility for ozone-related respiratory endpoints as noted in Appendix 3.

ii. Additional studies on mortality –

a. Vicedo-Cabrera et al. (2020) Reviewed data from 406 cities in 20 countries, with overlapping periods between 1985 and 2015, collected from the database of Multi-City Multi-Country Collaborative Research Network. Significant short-term mortality in association with O3 above 70 µg/m3 (~35 ppb). Relationship held when data were restricted to above 100 µg/m3 (50 ppb).
b. Orellano et al. (2020) performed a meta-analysis of 196 articles and found significant associations of short-term all-cause mortality and exposure to O3. In general associations were non-significant when adjusting for a second pollutant but correlations between multiple pollutants were moderate to high (≥ 0.4) which might impair the validity of the co-pollutant models.

Dr. Danica Lombardozzi

Ecological Effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

The scientific evidence on ozone effects on vegetation and ecosystems highlights the deleterious impacts of ozone on vegetation. The initial biomass loss functions with increasing W126 used in the most recent summation of scientific evidence were updated in a recent publication (see Lee et al. 2022) and this new analysis needs to be included in the scientific assessment moving forward. The Lee et al. 2022 publication suggests that a W126 of 9.2 ppm-h over one year or lower should be used to protect sensitive tree seedlings from biomass loss greater than 5% per year. Furthermore, Fig. 8.17 illustrates that trees with higher initial biomass may suffer greater biomass losses, suggesting that the evidence presented by Lee et al. 2022 using seedlings may underestimate the responses in mature forest ecosystems and emphasizes the strong need for protecting forest ecosystems at an annual cumulative W126 of 9.2 ppm-h or lower.

The scientific literature highlights that relationships accounting for stomatal uptake of ozone are typically stronger predictors of plant damage than exposure-based metrics (e.g., Reich et al. 1987). For example, the work by Sanz et al. (2016) presented in this summary highlights that a metric accounting for stomatal uptake of ozone was a stronger predictor of reproductive loss in clover species than a concentration-based metric. A summary of twenty-eight tree responses to ozone illustrates a photosynthetic decrease of 22% per 100 mmol m^{-2} of cumulative ozone uptake per unit of leaf area (Wittig et al. 2007). Several individual studies also illustrate the negative relationship between decreasing photosynthesis and increasing cumulative stomatal uptake of ozone (e.g., Blumenröther et al. 2007, Bortier et al. 2000, Cardoso-Vilhena et al. 2004, Löw et al. 2007). Decreases in photosynthesis affect numerous downstream ecosystem processes including biomass accumulation, reproduction, ecosystem carbon sequestration, and ecosystem hydrology, among others, and should therefore be considered in vegetation risk assessments.

The European Union has considered changing from a concentration-based to a dose-based ozone standard for vegetation that accounts for plant stomatal conductance. The new metric – phytotoxic ozone dose (POD) – accounts for variation in ozone concentrations and stomatal conductance. Recent work led by Anav et al. (2022) illustrates that concentration-based metrics like AOT40 and W126 do not always capture the spatial patterns of cumulative stomatal uptake. In fact, because high ozone concentrations can covary with conditions that coincide with stomatal closure (e.g., drought), estimates of photosynthetic loss can be higher using the concentration-based metrics like W126 than metrics like POD that estimate cumulative stomatal uptake of ozone.

The scientific evidence presented in this analysis and supported by the broader literature illustrates that a single year of high ozone exposure is deleterious to various plant forms, including annual and perennial

species. All evidence supports that a one-year vegetation standard for ozone is required to protect plant health. There is no evidence suggesting that a three-year average sufficiently protects vegetation. This is stated in Section 8.13.1: "The current secondary standard form of the 4th highest 8-hour max avg over 3 years is rarely reported in the vegetation research. The most useful metrics in vegetation research have been differentially weighted hourly concentrations that are cumulative during the growth of plants."

Additionally, the concentration-based W126 metric cannot be confidently met using the 4th highest 8-hour average ozone concentration, as W126 is a cumulative exposure metric and is weighted based on the ozone concentration. Thus, the current implementation of a secondary standard fails to protect vegetation since a three-year averaging timeframe is too long to protect vegetation, especially annual vegetation that only grows for a single year, and that an 8-hour average of ozone concentration does not properly weight the high ozone concentrations that are particularly damaging to vegetation.

Selected References:

Blumenröther, M. C., Löw, M., Matyssek, R. & Oβwald, W. Flux-Based Response of Sucrose and Starch in Leaves of Adult Beech Trees (Fagus sylvatica L.) under Chronic Free-Air O3 Fumigation. *Plant Biology* **9**, 207–214 (2007).

Bortier, K., Vandermeiren, K., Temmerman, L. D. & Ceulemans, R. Growth, photosynthesis and ozone uptake of young beech (Fagus sylvatica L.) in response to different ozone exposures. *Trees* **15**, 75–82 (2000).

Cardoso-Vilhena, J., Balaguer, L., Eamus, D., Ollerenshaw, J. & Barnes, J. Mechanisms underlying the amelioration of O3-induced damage by elevated atmospheric concentrations of CO2. *Journal of Experimental Botany* **55**, 771–781 (2004).

Löw, M., Haeberle, K.-H., Warren, C. R. & Matyssek, R. O3 flux-related responsiveness of photosynthesis, respiration, and stomatal conductance of adult Fagus sylvatica to experimentally enhanced free-air O3 exposure. *Plant Biology* **9**, 197–206 (2007).

Dr. Howard Neufeld

Ecological Effects (Appendix 8)

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

The summaries of causality determinations, and the changes in causality from earlier versions of the ISA, are reasonable given the analyses provided in the 2020 ISA. The new publication by Lee et al. (2022; https://www.sciencedirect.com/science/article/pii/S1352231022002564?via%3Dihub) provides additional exposure-response relationships for 16 tree species native to North America and could be used to update Table 8-5 which lists studies of reductions in growth due to ozone effects on trees.

The variability of outcomes regarding how interactions between climate change and ozone affect plant growth and functioning, coupled with a relatively small amount of literature available on these subjects, leads to difficulties in predicting their impacts. The EPA's conclusion that it is "*difficult to make broad generalizations*" seems justifiable.

I support the reiteration of the conclusions for exposure indices and exposure responses from prior ISAs from 1996 and 2006 (see 8-180 for a list).

In conclusion, the summaries of causalities appear reasonable and sufficient to inform the PA.

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

I support the conclusions of the EPA in section 8.13.3 which states: "*Given the current state of knowledge and the best available data, exposure indices that cumulate and differentially weight the higher hourly average concentrations and also include the midlevel values (e.g., the W126 or AOT40 metrics) continue to offer the most defensible approach for use in developing response functions and comparing studies, as well as for defining future indices for vegetation protection.*"

Figure 4.9 from the 2022 draft PA shows the relationship between the W126 index and the 4th Highest Design Values, either averaged over three years (left panel) or shown for three individual years (right panel). The exposure-response relationships outlined by Lee et al. (2022) indicate that to protect the most sensitive trees to have a 5% or smaller annual growth loss, the W126 should be between 2.5-9.2 ppm*hrs. If the higher value is overlain on the current NAAQS of 70 ppb (0.070 ppm) in Figure 4.9, then a substantial portion of the west and southwest would experience W126 in individual years above this value and hence be unprotective of sensitive trees. Such variation is less visible in the left panel due to averaging over 3 years.

Since plant growth can be affected by a single year of exposure that can have carry-over effects in future years, averaging over three years would not reveal the higher W26 values causing growth decrements shown in the right panel. These graphs would seem to offer strong support for a one-year secondary standard using the W126 metric.

Therefore, I would like to suggest that the PA adopt the W126 metric as the secondary standard for vegetation/welfare, that its summation time be any 92-day period during the growing season, starting April 1 and ending September 30 (the active growing season for most trees, crops and other vegetation types), and that the level be set at 10 ppm*hrs, not to be exceeded once during the year.

Dr. Jennifer Peel

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

The causal determinations for short-term exposure to ozone and respiratory effects was causal in both 2013 and 2020. I agree with this determination based on the evidence included in the 2020 ISA.

The causal determinations for long-term exposure to ozone and respiratory effects was likely causal in both 2013 and 2020. The evidence for this area was bolstered in the 2020 ISA. The primary reasons provided to not move to a determination of causal were the lack of adjustment for short-term exposure to ozone and other potential confounding and lack of consistency across the published studies evaluated. Two of the studies included in the 2020 ISA had serious limitations, including very low variability of ozone concentrations (Carey et al. 2012) and low number of deaths (Bentayeb et al. 2015); further, the Bentayeb et al. study could be reasonably interpreted as null rather an inverse association given the wide confidence intervals.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

For short-term exposure the evidence from articles published since the 2020 ISA are consistent with the causal determination in the 2020 ISA.

Although not only relevant to new evidence, the focus on US and Canadian studies only is not well-justified in the ISA. There are several new studies published for short-term ozone and respiratory effects (e.g., Liu et al. 2019), but the evidence would only be strengthened for an area that is already considered causal.

For long-term exposure, there are several articles published since the 2020 ISA that strengthen the evidence (e.g., a few are listed below):

Dimakapoulou et al. 2020 https://doi.org/10.1016/j.envres.2019.109002

Lim et al. 2019 DOI: 10.1164/rccm.201806-1161OC

Yazdi et al. 2019 DOI: 10.1016/j.envint.2019.05.073

Yazdi et al. 2019 https://doi.org/10.1161/CIRCULATIONAHA.120.050252

Paulin et al. 2019 doi:10.1001/jamainternmed.2019.5498

Wei et al. 2021 https://doi.org/10.1186/s12940-021-00742-x

A 2022 review of evidence of the association between ozone and lung function supports the association for long term exposure and decreases in both lung function and lung growth in children, with studies primary from 2015 – 2021. DOI: 10.1016/j.chest.2021.07.2170

Taken together, my view is that the evidence for long term exposure to ozone and respiratory effects may be more consistent with the rubric described for causal rather than likely causal.

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

In my view the evidence from controlled human exposure studies and epidemiologic studies are complementary in nature. When available, supportive and consistent evidence from controlled human exposure studies can bolster the evidence from the epidemiologic studies. However, particularly when assessing evidence for a regulatory standard for ambient air pollution, the absence of evidence from the controlled human exposure studies should not negate evidence from the epidemiologic studies given the limitations of controlled human exposure studies. These limitations include the lack of representativeness of participants included in the controlled human exposure studies, particularly the lack of participants who may be at higher risk for the adverse effects, as well as the difference in the air pollution composition, the absence of other photochemical pollutants in controlled human exposure studies, the limited sample size of these studies (limiting the ability to evaluate rare and especially serious clinical events), and the form of the exposure (peak vs. exposure).

Health Effects – Cardiovascular (Appendix 4)

Note: https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(22)00093-6/fulltext

Health Effects – Mortality (Appendix 6)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and total mortality?

The determination for short term exposure and mortality was likely causal in 2013 and changed to suggestive in 2020.

I find it challenging to reconcile the causal determination for ST/respiratory (causal), which includes some strong evidence for respiratory mortality, with the mortality determination (suggestive).

The following conclusions paragraph on page 6-21 is more consistent with likely causal than with a suggestive causal determination:
"Overall, the recent multicity studies conducted in the U.S. and Canada provide additional support for the consistent, positive associations reported across multicity studies evaluated in the 2006 Ozone AQCD and 2013 Ozone ISA. These results are supported by studies that further examined uncertainties in the ozone-mortality relationship, such as potential confounding by copollutants and other variables, modification by temperature, and the C-R relationship and whether a threshold exists. Although there

continues to be strong evidence from studies of respiratory morbidity to support respiratory mortality, there remains relatively limited biological plausibility and coherence within and across disciplines to support the relatively strong evidence for cardiovascular mortality, which comprises a large percentage of total (nonaccidental) mortality."

The determination for long term exposure and mortality was suggestive in 2013 and in 2020

My view is that the evidence presented in the ISA is generally consistent, with the notable exception of 3 studies that have some substantial limitations (Figure 6-8 and Figure 6-9): Kim et al. 2017, Carey et al. 2013, Bentayeb et al. 2015.

The following is the conclusion paragraph on page 6-42:

"Overall, recent epidemiologic studies add to the limited body of evidence that formed the basis of the conclusions of in 2013 Ozone ISA for total mortality. This body of evidence is generally inconsistent, with some U.S. and Canadian cohorts reporting modest positive associations between long-term ozone exposure and total mortality, while other recent studies conducted in the U.S, Europe, and Asia report null or negative associations. The strongest evidence for the association between long-term ozone exposure and total (nonaccidental) mortality continues to come from analyses of patients with pre-existing disease from the Medicare cohort, and recent evidence demonstrating positive associations with cardiovascular mortality. The evidence from the assessment of ozone-related respiratory disease, with more limited evidence from cardiovascular and metabolic morbidity, provides biological plausibility for mortality due to long-term ozone exposures. In conclusion, the inconsistent associations observed across both recent and older cohort and cross-sectional studies conducted in various locations provide limited evidence for an association between long-term ozone exposure and mortality."

If you put more weight on the stronger and larger studies, the evidence is more consistent than what is described in this paragraph.

The interpretation of the evidence is further confused by combining across causes of mortality.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

The evidence from articles published since the 2020 ISA further strengthens the overall evidence for both short term and long-term exposure.

Short term exposure:

Wei et al. 2020, https://doi.org/10.1093/aje/kwaa098

Liu et al. 2019, https://doi.org/10.1164/rccm.201810-1823OC

Long term exposure:

Lim et al. 2019 DOI: 10.1164/rccm.201806-1161OC

Niu et al. 2022, https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(22)00093-6/fulltext

In the future could consider separate determinations for respiratory mortality, cvd mortality, total non-accidental, lung cancer, etc., since the evidence is not always the same for each area.

Health Effects – Developmental Effects (Appendices 3, 4, 7, particularly Section 7.1.4)

a. What are the panel's views regarding the review and characterization of the scientific evidence on developmental effects from ozone exposure?

There are several categories falling under the heading of developmental effects, including male and female reproduction and fertility, pregnancy and birth outcomes, and effects of exposure during developmental periods, which itself includes respiratory, cardiovascular, metabolic, nervous system effects. In the executive summary (Table ES-1), there are determinations provided for long term exposure to ozone and reproductive effects combined for the 2013 ISA (suggestive) and separately for fertility and reproduction and pregnancy and birth outcomes in the 2020 ISA (suggestive for both). In Appendix 7 of the 2020 ISA separate determinations are provided for the same categories, but then also summarize the evidence effects of developmental periods in section 7.1.4, and indicate that this evidence also contributes to the relevant sections is the ISA (i.e., respiratory, cardiovascular, metabolic, nervous system). There is no determination for short-term exposure to ozone for these categories.

The summaries for the reproductive effects and birth outcomes is well-written. Although evidence of biologic plausibility is provided, there is limited evidence for these endpoints, particularly from the epidemiologic literature. The evidence is stronger for pregnancy and birth outcomes than for reproduction and fertility, but I agree with the causal determination of suggestive for both in 2013 and 2020. The evidence is growing but still fairly limited.

The evidence summarized for the neurodevelopmental is also fairly limited. Section 7.2 includes broadly the evidence for nervous system effects, including in adults and children. For nervous system effects the determination was suggestive in both 2013 and 2020, and I agree with this determination.

The evidence summarized in separate sections (Appendix 3, 4, 5) contributes to those causal determinations. As discussed related to Appendix 3, Respiratory Effects (long term), the evidence for lung growth and development is growing and is strengthening the current determination of likely to be causal for the respiratory section.

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

There are some newer publications that could be considered in each of these categories.

Preterm birth - Bai et al. 2022 https://doi.org/10.1016/j.envres.2022.113879

Birth weight - Wang et al. 2021 https://doi.org/10.1016/j.envint.2020.106208

Neurodevelopment - Ha et al. https://doi.org/10.1016/j.envres.2019.03.064

Nevertheless, the evidence is likely still limited, with the exception of the evidence discussed in the respiratory section regarding respiratory growth and development and potentially for preterm birth / low birth weight.

For future ISAs, I suggest that EPA consider alternative organization of these sections and categories.

Dr. Richard E. Peltier

Ozone and Photochemical oxidants (Appendix 1, 2)

a. What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone? The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers.

Broadly, Appendix 1 provides only narrow insight into how one might delineate critical differences in complex ambient exposures, and more well-defined controlled human exposure (CHE) studies. While there is very little that is explicitly inaccurate in these sections, they describe a narrow set of chemical formation processes, including precursor emissions. This is more topical for atmospheric chemistry relevance, but less so for ambient human exposures.

The ISA acknowledges remaining uncertainty in emissions inventories (section 1.3.1.1), and this is also likely true for ozone and related photochemical oxidant precursors. This would seem to justify taking more protective approaches to standard setting given that there is remaining uncertainty in ozone and photochemical oxidant formation processes that are still not well characterized.

It would be useful to expand discussion on why petrochemical and industrial emissions (section 1.3.1.1.3) reflect a ~six-fold increase in emissions of anthropogenic VOCs whereas most other sources have decreased, or at least increased and then levelled off, since ~2005. This is a critical ozone precursor that is generally spatially heterogeneous, and disproportionately impacts specific communities near the source of emission. This complex mixture, that includes ozone, unreacted precursors, and other reaction products cannot easily by replicated in controlled exposure chamber studies, and therefore, provide only a limited understanding in how they impact health.

Appendix two is a comprehensive description of the major methods in which exposure studies to ozone and oxidation products are conducted, including panel studies, time series analyses, modelling, personal and microenvironmental monitoring, etc. For most of these study designs, the ISA concludes that significant uncertainty remains, such as under- or over-estimation of effects, poor exposure measurement precision, or bias (of association or effect), and that the magnitude or direction can vary by study type. While imprecision and bias are commonly encountered in epidemiological surveillance, the ISA seems to infer that these epidemiology study designs, because of their remaining uncertainties, are insufficient, or in some way inadequate, to inform EPA in setting standards, even though they are likely to reflect the best possible proxy for ambient exposure effect analysis. They likely capture a more comprehensive, if unmeasured, exposure profile that is linked to concomitant health impacts.

There is no discussion of the value of controlled human exposure research in understanding human exposures. As a result, it remains unclear how these data should be interpreted by EPA in PA development.

Health Effects – Cardiovascular (Appendix 4)

a. What are the panel's views regarding the causal determination for short-term and long-term ozone exposure and cardiovascular effects?

The change in causality determination for short term cardiovascular effects remains poorly justified. The 2013 ISA established 'Likely to be Causal' determination and this was based at least two streams of evidence: animal toxicology and epidemiologic mortality findings. Epidemiologic morbidity was null, as were controlled human exposures, the latter which had very limited evidence at the time of the 2013 ISA. In 2020, the expanded body of evidence remains consistent: animal toxicology and epidemiology mortality show strong evidence for short term cardiovascular effects, and epidemiology morbidity remains null. Approximately eight new CHE studies were published after the 2013 ISA; some report significant effects, other report no effects, and still others report mixed results.

While each approach has strengths and weaknesses, CHE is doubly challenged for two reasons: it involves homogeneous and highly controlled exposures, and the population that is studied is almost always healthy, and skews towards younger populations (except two: Frampton et al 2017, and Rich et al 2018 which evaluated older individuals). These are important mechanistic studies, but, in my view, they are inadequate lines of evidence to revise a causality determination solely because the results are not entirely conclusive. They do not reflect diverse (and more realistic) exposure environments nor do they adequately capture effects for sensitive or susceptible individuals or groups. As a result, they should be viewed as a line of evidence that is supportive to understanding mechanisms of disease in humans, but insufficient to overrule more compelling and diverse evidence from toxicology and epidemiology.

b. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

As noted, CHE provides important insight into disease mechanisms, but it is not a sufficient tool to override compelling and consistent toxicology and epidemiological research findings. A Likely causality was established in the prior ISA and was supported even though the analysis contained limited CHE results; the addition of new CHE findings, which continue to provide mixed conclusions, are inadequate to warrant a change in causality determination from 2013, where the prevailing toxicology and mortality evidence reviewed for the 2020 ISA remains consistently strong. This seems to be an aphorism that the absence of evidence implying the evidence of absence; mixed CHE results simply cannot supersede the long line of convincing epidemiology and toxicology evidence, and should not be the primary driver to change causality determinations.

c. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter any of these characterizations?

None noted.

Dr. Alexandra Ponette-González

Comments on Appendix 8: Ecological Effects

a. What are the panel's views regarding the summarization of the scientific evidence on effects on vegetation and ecosystems from ozone exposure? Is this summary adequate to inform a PA?

Appendix 8 provides a comprehensive and well-written review of the scientific evidence on ozone effects on vegetation and ecosystems. The review is based on an extensive literature search and systematic selection of studies spanning the period January 2011-March 2018. The review process is clearly laid out in Section 10 of the ISA. For ecological effects, studies were primarily identified via topic-specific citation mapping, where references from the 2013 Ozone ISA comprised a "seed set" of references. Major assessments, such as the National Climate Assessment and IPCC AR5, were used to identify additional references.

The summary is adequate to inform the policy assessment. Approximately 4.5 years have elapsed since March 2018. Since then, several studies have been published on ozone effects on plant phenology, plant reproduction, crop pollinators, pollination, and plant-insect interactions (see *References*). However, these studies are not likely to alter the overall causality determinations presented in Appendix 8.

Future ISAs would benefit from improved clarity on which topics are selected for in-depth review and greater consistency among different sections of the text. To the first point, in section 8.7, the ISA indicates that there is likely to be a causal relationship between ozone exposure and changes in plant signaling. A comprehensive review of the literature on this topic was, however, not undertaken. Arguably, extended reviews may be most important in instances where causality determinations are less clear. To the second point, Appendix 8 states that for processes such as ecosystem productivity where ozone effects are considered causal, the synthesis only includes studies conducted in North America. Yet, in section 8.8.1, studies from Sweden and Europe are included as evidence of ozone-induced changes in primary productivity. To be consistent with the earlier text, these could be deleted, or additional text could be added to justify their inclusion.

In terms of future research, the most recent ISA discusses how ozone and nitrogen interact to affect vegetation and ecosystems. Because high ozone and particulate matter concentrations often co-occur during heat waves and stagnation events, future reviews could examine the literature on how ozone interacts with particulate matter to affect vegetation and ecosystem health. For example, occlusion of stomatal pores by particulates could affect rates of ozone deposition, while particulate matter deposition to plant surfaces can lead to stress-induced biogenic VOC emissions, with implications for ozone production. This is an important area for future research and would expand on and strengthen the current body of evidence on "modifying factors". Considering the ISA's acknowledgment that ecosystem functions translate into good and services beneficial to human populations, it would be worthwhile to include some discussion of ozone impacts on urban vegetation as it relates to human well-being.

b. Does the evidence review provide adequate background for consideration of alternate forms of the secondary standard in the PA?

Overall, the summary of available evidence provides adequate background for consideration of alternate forms of the secondary standard in the policy assessment. Throughout Appendix 8, it is clearly stated, in several sections, that cumulative weighted indices are most widely used in the scientific literature and the most appropriate for understanding, and by extension for protecting, vegetation and ecosystems. For example, the text states that "The cumulative weighted indices (w126 and AOTe40) and exposure-response relationships presented in this section continue to be used in analyses in the scientific literature and are the best available approach for studying the effects of ozone exposure on vegetation in the U.S."

Minor comment

- Minor detail – incomplete sentence: page 8-119. While in crops, O3 decreased soil mineral N content".

References

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Brosset, A., Saunier, A., Mofikoya, A. O., Kivimäenpää, M., & Blande, J. D. (2020). The Effects of Ozone on Herbivore-Induced Volatile Emissions of Cultivated and Wild Brassica Rapa. Atmosphere, 11(11), 1213.

Duque, L., Poelman, E. H., & Steffan-Dewenter, I. (2021). Plant age at the time of ozone exposure affects flowering patterns, biotic interactions and reproduction of wild mustard. Scientific reports, 11(1), 1-10.

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Mercado, M., Decoteau, D. R., Marini, R., & Davis, D. D. (2020). Ozone-Sensitivity of Ten Milkweed Species (Asclepias spp.). Northeastern Naturalist, 27(4), 656-668.
Prieto-Benítez, S., Ruiz-Checa, R., Bermejo-Bermejo, V., & Gonzalez-Fernandez, I. (2021). The Effects of Ozone on Visual Attraction Traits of Erodium paularense (Geraniaceae) Flowers: Modelled Perception by Insect Pollinators. Plants, 10(12), 2750

Rollin, O., Aguirre-Gutiérrez, J., Yasrebi-de Kom, I. A., Garratt, M. P., de Groot, G. A., Kleijn, D., ... & Carvalheiro, L. G. (2022). Effects of ozone air pollution on crop pollinators and pollination. Global Environmental Change, 75, 102529.

Comments on Appendix 9: Climate Effects

a. *What are the panel's views regarding the causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables?*

The causal determination for tropospheric ozone and radiative forcing is appropriate, and the evidence to support this determination is bolstered by the most recent IPCC AR6 report. There is a substantial body of literature showing ozone effects on temperature whereas there continue to be relatively few studies on ozone effects on precipitation and climate-related variables. The "likely to be causal" determination for climate-related variables therefore appears to be based more on the unknown effects of ozone on precipitation and other variables than on temperature. Given the current body of evidence, causal determinations for temperature and climate-related variables would be considered separately.

b. Have the effects of warming on ozone production been adequately characterized?

Neither the direct nor the indirect effects of warming on ozone production were adequately characterized in the ISA. Several studies contain observational and model evidence to support the effects of drought, heat waves, and stagnation events on ozone concentrations at regional to global scales (Wang et al. 2017, Hong et al. 2019, Hou and Wu 2016). Moreover, these studies show significant seasonal and spatial variations in changes in air quality resulting from meteorological events over the U.S. and China. Warming-related wildfire increases in surface ozone seem especially appropriate to consider with changing wildfire regimes.

References

Wang, Y., Xie, Y., Dong, W., Ming, Y., Wang, J., & Shen, L. (2017). Adverse effects of increasing drought on air quality via natural processes. *Atmospheric Chemistry and Physics*, *17*(20), 12827-12843.

Hong, C., Zhang, Q., Zhang, Y., Davis, S. J., Tong, D., Zheng, Y., ... & Schellnhuber, H. J. (2019). Impacts of climate change on future air quality and human health in China. *Proceedings of the national academy of sciences*, *116*(35), 17193-17200.

Hou, P., & Wu, S. (2016). Long-term changes in extreme air pollution meteorology and the implications for air quality. *Scientific reports*, *6*(1), 1-9.

Dr. Jeremy Sarnat

Ozone and Photochemical oxidants (Appendix 1, 2)

a. What are the panel's views on evidence pertaining to the distinction between exposure to laboratory-generated ozone and ambient ozone? The panel should focus its attention on aspects of this evidence that will inform consideration of the weighting of health effect evidence from controlled human exposure studies and epidemiologic studies, including summer camp studies and studies of outdoor workers.

Appendices I and II of the 2020 Ozone ISA present a generally good summary of trends, background versus anthropogenic ozone levels, copollutant correlations, and defining numerous exposure-relevant metrics and methods for characterizing ozone. The comments below focus narrowly on Discussion Point 2, and the committee's ability to differentiate or differentially weight lines of evidence from observational and controlled studies examining ozone health effects.

1) Two related questions are moderately neglected, or not well-highlighted, in Appendices I and II of the 2020 Ozone ISA:

- The first concerns discussion on the predominant **modes of action** for ozone toxicity. While there is ample mechanistic discussion for ozone health effects in individual studies and generally, this ISA lacks a section on modes of action for ozone exposures specifically, as has been conducted for previous ISA's (See Chapter 4 of the most recent NOx ISA entitled, 'Dosimetry and Modes of Action for Inhaled Oxides of Nitrogen'). A dedicated discussion of ozone modes of action would, in turn, be a useful starting point for evaluating differences in chemical composition and subsequent internal biochemical response between laboratory-generated or 'pure' ozone versus ozone measured in an ambient pollutant mixture. (I suspect that information regarding some measure of ozone oxidative potential would be the basis of this comparison).

- The second, related omission is the lack of dedicated section explicitly addressing ozone **exposure *assignment* in controlled study settings**. Section 1.2.1 in Appendix I provides a thorough discussion of the concept of Exposure Metrics, with latter sections providing excellent information related to potential errors from using these various metrics in observational study designs. However, this section does not include any mention of exposure assignment approaches or metrics used in controlled settings. As with observational designs, controlled studies also include exposure assignment and should be presented. This, as with the first point above, would provide a key means of comparing the findings and the relative weighting of study findings across the various designs.

Both omissions in the 2020 ISA make it difficult to compare and weigh the respective evidence from observational versus controlled setting (i.e., where laboratory-generated ozone is used).

2) Some ambiguity in discerning differences in health from controlled studies and observational epidemiology also stems from the ISA's treatment of copollutant models in ozone epidemiology. I found two primary ways this appears in Appendix II: First, the presentation of the copollutant model results

focus primarily on confounding (i.e., what is the effect estimate of ozone while controlling for another pollutant), rather than the potential for joint effects or effect measure modification. While Section 2.5 (page 2-33 and subsequent pages) mentions joint effects, the focus on control of confounding creates a misimpression that ozone exposure assignment in epidemiologic studies involves exposure to ozone solely or mainly. This is likely not true, and certainly not intended.

Second, Appendix II simplifies correlation patterns between ozone and its copollutants, which also inadvertently creates an impression of ambient ozone exposure occurring in vacuum and, thus, comparable to controlled ozone chamber or animal studies using laboratory-generated ozone. An example of this point can be found on page 2-33 within Appendix II:

> '*Given that the majority of the copollutant correlation data are low, confounding of the relationship between ambient ozone exposure and a health effect by exposure to CO, SO2, NO2, PM10, or PM2.5 is less of a concern for studies of the health effects of ambient ozone exposure compared with studies of the health effects related to exposure of other criteria air pollutants. When copollutant correlations are higher during the warm season, greater risk of copollutant confounding exists. However, summertime correlations remain relatively low for the majority of ambient monitors*.'

A more thorough comparison of results from single and copollutant epidemiological models with those from joint effects or other advanced mixtures-based approaches to compare ozone effect estimates would be a welcome addition. Differences between those results might help clarify the questions comparability and weighting of health effects from controlled human exposure and observational epidemiology.

3) Finally, panel study designs, of which the summer camp and other outdoor personal exposure assessments belong, are addressed only briefly in Appendix II and don't, in my opinion, provide much insight addressing this specific Discussion Point. Section 2.6.1.2 on Panel Studies does specifically mention this type of design in the context of measurement error. There is considerably more attention given to panel studies and how they contribute towards causal determination (Appendices III and IV), especially with regard to short-term exposures and acute respiratory response, in pediatric asthma and adult panels.

Health Effects – Respiratory (Appendix 3)

a. What are the panel's views regarding the causal determinations for short-term and long-term ozone exposure and respiratory health effects?

b. Does the panel suggest consideration of any new scientific evidence that might strengthen or alter this characterization?

c. What are the panel's views regarding the weighting of controlled human exposure studies and epidemiological studies (i.e., population- and panel-based observational designs)?

I am in general agreement with the rationale and conclusions reached in the 2020 Ozone ISA pertaining to ozone exposures and both short- and long-term respiratory endpoints. My comments below focus primarily on remaining uncertainty associated with confounding alternative methods to address potential confounding, illustrated in two new papers that EPA may consider.

Broadly, Appendix 3 of the 2020 ISA details the state-of-the-science involving ozone and adverse respiratory response. The evidence is extensive and the causal determinations are largely well-justified, in my understanding. The slightly weaker determination of 'likely to be causal' for long-term exposure and respiratory outcomes (rather than 'causal') was reached primarily due to equivocality in the epidemiological findings ('[*r]ecent epidemiologic studies provide some evidence that long-term ozone exposure is associated with respiratory mortality, but the evidence is not consistent across studies'* 3-115) and uncertainties regarding residual copollutant confounding *('…the few studies that include copollutant models examine different outcomes, making it difficult to draw strong conclusions about the nature of potential copollutant confounding for any given outcome'* 3-115). Either: a) confounding was not examined in a multipollutant model setting; or b) there are conflicting or contradictory results from multipollutant models that include ozone, making inference harder across the body of models.

I accept the uncertainties associated with potential confounding in the epidemiology. However, I'd strongly advise the EPA to move away from what I see as an overreliance on multipollutant modeling as a primary means of assessing confounding. Statements such as the following seem, to me, to oversimplify true covariance patterns or biologically-relevant covariance patterns and potentially obscure the presence or absence of confounding in ozone epidemiology (including results presented and interpreted in Appendix 3):

> *Given that the majority of the copollutant correlation data are low, confounding of the relationship between ambient ozone exposure and a health effect by exposure to CO, SO2, NO2, PM10, or PM2.5 is less of a concern for studies of the health effects of ambient ozone exposure compared with studies of the health effects related to exposure of other criteria air pollutants (2-33).*

An emerging area within air pollution epidemiology and biostatics are the use of causal models and accountability studies to address confounding in large cohort studies examining long-term ozone exposure. In Yazdi et al (2022), for example, the authors use causal difference in-difference multipollutant modeling to address confounding. Other approaches, which combine multipollutant and causal methods are also promising. Yazdi et al (2021) uses a doubly robust additive model (DRAM), which uses both exposure weighting and outcome adjustments, to also consider confounding. Both approaches are examples of ways to consider confounding differently than the current approach. A fuller treatment of confounding may, in turn, reduce some of the uncertainties for this exposure-outcome pair, and the weighting used in its causal determination. I'll include the full citations for these recent papers that deal with long term ozone exposure and respiratory outcomes, which might be used to strengthen or alter EPA determinations.

Yazdi, M.D., Wei, Y., Di, Q., Requia, W.J., Shi, L., Sabath, M.B., Dominici, F. and Schwartz, J., 2022. 'The effect of long-term exposure to air pollution and seasonal temperature on hospital admissions with cardiovascular and respiratory disease in the United States: A difference-in-differences analysis'. *Science of The Total Environment*, 843, p.156855.

Danesh Yazdi, M., Wang, Y., Di, Q., Wei, Y., Requia, W.J., Shi, L., Sabath, M.B., Dominici, F., Coull, B.A., Evans, J.S. and Koutrakis, P., 2021. 'Long-term association of air pollution and hospital admissions among Medicare participants using a doubly robust additive model'. *Circulation*, 143(16), pp.1584-1596.

Dr. Elizabeth A. (Lianne) Sheppard

General comments:

- *Evidence used for each human health endpoint*: The lack of consistency in which geographic areas of the world are considered for the various health endpoints is concerning. I don't think there is good scientific justification for geographic restrictions of the evidence considered in the ISA review. I recognize the size of the literature and EPA workload is a factor, particularly for development of the Ozone ISA in 2019, which was rushed. I think the criteria for limiting geographic scope used by the team working on the secondary standard is more defensible: for any determinations that are already causal (and presumably unlikely to be downgraded), it is acceptable to limit the geographic scope for the review. For all other endpoints, the geographic scope of the evidence review should not be restricted.
- *Relative weighting of controlled human exposure (CHE) vs. epidemiologic studies*: At our August 29th meeting Tom Luben noted that EPA equally weights various streams of evidence. I think the weight applied to the CHE studies should depend on the evidence of causality that they provide. Due to their limitations, namely the restricted populations studied, small feasible sample sizes, the limited endpoints and exposure timeframes that can be considered, and the limited exposure (in addition to only a few doses in any given study, more important is that these studies only consider laboratory-generated ozone and not the full photochemical oxidant mixture), I recommend that in general CHE studies should only be used to upgrade the evidence for causal conclusions. In general evidence from CHE studies should not contribute to the downgrading of causal conclusions.
- *Study quality evaluations*: I appreciate Tom Luben's response to my questions about HAWC and its implementation in the Ozone ISA. In addition, it would be helpful for EPA to share the study evaluation protocol(s) they used in their Ozone ISA reviews. There is some limited information in the HAWC 2019 draft ISA documentation, but this seems to be very incomplete. Relative to the study quality documentation that accompanies the IRIS process, it appears to me that more development is needed for the ISA reviews.

Comments on long-term exposure and total mortality:

Summary: I did a careful review of the three studies showing a robustly protective effect of ozone documented in the ISA for total non-accidental mortality (Figure 6-8 and Table 6-6). In conclude that one is certainly flawed, and the remaining two may be flawed, although deeper investigation is warranted. I also note that there are two recently published studies from the Medicare cohort that show long-term ozone exposure is causally related to increased adverse health effects (total mortality, and hospital admissions for cardiovascular and respiratory endpoints). While my ISA study review was selectively driven by the reported results and is thus incomplete, I believe that the questions I raise about these three studies as well as the more recently reported evidence suggests that the conclusions about the causal relationship between long-term ozone exposure and adverse health effects may warrant upgrading in future reviews.
Detailed comments:

- As I previously communicated, the Kim et al 2017 study that showed a protective effect of ozone on total mortality incorrectly quantified exposure in their survival analysis. Thus this study does not meet basic study quality criteria and thus it should not be considered in any policy-relevant reviews for any air pollution exposures.
- The two remaining studies showing protective effects (Bentayeb 2015; Carey 2012) used exposures estimated from chemical transport (Bentayeb) or emissions-based (Carey) models. They also did not document their methods well so it is unclear whether there are biases in the results due to the exposure assessment and/or application of the Cox model in their hazard ratio estimation approach. Details of my review of these features follow:
    - Bentayeb used time since enrollment as the time axis in their survival analysis for a study that enrolled 20,625 participants in 1989 and followed them over a 25-year period (1989-2013). Follow-up ended in 2013 for non-accidental mortality and in 2010 for cardiovascular and respiratory mortality. Their emissions model was grid-based and relied on a deterministic chemical transport model, covering the time period 1989-2008. They used data assimilation to incorporate measurement data based on kriging with external drift (also known as universal kriging). They used 4 different exposure metrics in their survival analyses: "(1) annual mean exposure at baseline (1989) (2) annual mean exposure one year before death or censure (for each participant we assigned mean concentration of the year preceding death or censure) and time dependent exposures as (3) yearly mean exposure during the follow-up before death or censure (for each participant we assigned annual mean concentration of the year of follow-up) and (4) average cumulative exposure before death or censure (for each participant we calculated average pollutant concentrations from baseline to each year of follow-up, ex: exposure in 2005 was calculated as mean of annual concentrations from 1989 to 2005. In 2006, from 1989 to 2006, etc.)." (p. 7) It appears that (1) and (2) are time-constant exposures, where, as I interpret the text as written, (2) has the same problem documented in Kim et al. (Either (2) or (3) appear to be the estimate cited in the ISA, converted to a 10 ppb increment.) The authors state that (3) and (4) are time-varying exposures and presumably the authors correctly implemented a proportional hazards analysis for time-varying exposures, although the documentation in the paper is too sparse to be fully confident this is the case. There was not much attrition from the cohort (95.6% appear to have provided data in the 2007-13 time period). Ozone at the zipcode level was fairly stable over modeling period, though there were two anomalous years (1996 and 2003) which were more dramatic for ozone than for any other pollutant (Bentayeb, 2014 exposure modeling paper). It is strange that the HRs for the ozone effect for a 9 ppb increment for various shorter time periods in models with baseline exposure (exposure (1)) were all elevated (estimates were 1.01 (0.99–1.02) in 1989-94; 1.06 (1.04–1.08)∗ in 1995-2002; 1.11 (1.09–1.13)∗ in 2001-6; 1.20 (1.17–1.23)∗ in 2007-13; Table 4) while the estimate for the entire period was protective (.98 (0.91,1.06); Table 3). This suggests to me that there is some residual confounding in the entire period estimate that is not having the same impact during the shorter time periods. The long duration of this study would lead me to dig into the potential confounding of calendar time, although the authors did use study time as the time axis and the entire cohort started in the same year, so study time should be a reasonable proxy for calendar time.
    - Carey et al followed 836,557 participants from 2003-2007 and estimated the effect of exposure based on a grid-based dispersion model for 2002 that used ozone predictions

based on interpolated data from rural stations adjusted for altitude and NOx emissions. Ozone predictions were further adjusted for an urban decrement using an oxidant partitioning model. The ozone input data were only for data collected between 12:00 and 18:00. Model performance was reported as "good" with R2's of .48-.71, but in addition to omitting the definition for the R2 estimate used, this hides that this range is based on two different validations during 2002-2004 (for the national network vs. verification sites) and that the performance validation was based on agreement in the number of days that exceeded 120 ug/m3, where the mean number of days was in the ballpark of 6-10. Thus, I think there are important reasons to question the ozone exposure model used in this analysis. Regarding the Cox model, the paper did not document the time axis or any adjustment for calendar time. However, the shorter duration of this study means these may not be particularly important concerns.

- There are several new studies using the Medicare cohort written by the Harvard group that suggest that long-term exposure to ozone causes increased mortality. Both of them employ "novel confounding adjustment" methods to account for confounding and allow the effects to be interpreted as causal (assuming their assumptions are valid).
    - Wei et al 2021, *Emulating causal dose-response relations between air pollutants and mortality in the Medicare population*, found higher levels of ozone were associated with a greater risk of mortality. They estimated relative risks by decile of exposure, with the top decile having a mean of 56 ppb. All deciles above the lowest reference decile estimated a relative risk of 1.044 or higher with fairly narrow confidence intervals.
    - Yazdi et al 2022, *The effect of long-term exposure to air pollution and seasonal temperature on hospital admissions with cardiovascular and respiratory disease in the United States: A difference-in-differences analysis*, used a difference in difference approach to estimate exposure effects on the rate of hospital admissions for cardiovascular disease, stroke, myocardial infarction, and respiratory diseases between 2001 and 2016. Ozone exposure had a median of 45.2, IQR of 42.3-48.6, and a range of 19.8-80.4 ppb. Ozone increased rates for all outcomes, with the rate differences per ppb increase in ozone exposure ranging from 1.18 and 2.12 for stroke and myocardial infarction, to 9.08 and 9.51 for cardiovascular and respiratory diseases, respectively, with the lower bounds of the confidence intervals all above 0.

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Dr. Jason West

Atmospheric Source, Chemistry, Meteorology, Trends, and Background Ozone (Appendix 1)

Appendix 1 communicates well the basic science of ozone sources, chemistry, meteorology, trends and background ozone concentrations affecting the US (USB). The EPA did a wonderful job of presenting this information comprehensively. Much of the material there is still current science, not affected in important ways by recently published papers. I will mention that there is now further evidence supporting the downturn in emissions from China over the past decade, that was mentioned here as being important for USB.

The EPA should also be aware that there is now a large number of data fusion studies that estimate ozone spatially by combining ozone measurements with model output, filling in the gaps between monitors. These might be reviewed in future ISAs since they might increasingly be used as input to epidemiological studies, as well as in assessing differential exposure by different racial, ethnic, and socio-economic groups. The EPA tends to analyze trends in ozone by the simple average of many monitors, but these monitors are not distributed uniformly over the US. Data fusion exercises gives the EPA alternatives to represent trends that may be more meaningful, such as population-weighted concentrations, or spatial averages over the continental US.

a. What are the panel's views regarding the scientific evidence on wildfires, exceptional events, precursor emissions, chemistry, and background levels?

There is very strong scientific evidence on the atmospheric chemistry affecting ozone, and on the impacts of precursor emissions on ozone. USB is a model construct and the models are improving and their applications to estimate USB are also improving. Exceptional events can generally be determined well with thorough investigations of ground and satellite measurements of multiple pollutants, analysis of meteorology, and air quality modeling. Wildfires have recently gained much new research attention for their effects on air quality. Clearly wildfires have important influences on both ozone and PM, but there remain important challenges in observing these effects from ground monitors and satellites, since the smoke plumes are often small in scale and chemistry can differ within the plume. Modeling of wildfire impacts is also challenging in estimating the emissions and understanding the movement of the plume spatially. Wildfire effects on the chemistry affecting ozone are has received recent scientific attention in many studies, since this ISA.

b. Please comment on how the evidence reviewed in the ISA should be brought forward into the PA.
Appendix 1 mainly provides background information and there is no statement of causality made here that would directly affect the setting of the NAAQS level. Important questions raised here for the PA have to do with *i*) understanding past trends in ozone as effects of changes in precursor emissions, *ii*) impacts of foreign and natural emissions, and meteorological variability and climate change on USB, *iii*) under what circumstances should appeals for exceptional events be allowed.

Climate Effects (Appendix 9)

The EPA presented a fairly thorough understanding of the effects of ozone on climate. The ISA draws heavily on the IPCC 5th Assessment Report, while the IPCC 6th Assessment Report (2021) is now available. It does not seem that the major conclusions in AR6 concerning ozone climate effects differ strongly from those in AR5 and so the major conclusions of in the ISA still hold, though in some cases now with more confidence.

In addition to affecting climate through absorption of outgoing longwave radiation, ozone affects climate by suppressing plant growth, which has implications for the global carbon cycle; by slowing plant growth, ozone causes CO2 to be elevated in the Earth's atmosphere. This influence is not mentioned in the ISA and could be.

Among the other new science results, the new IPCC report includes new research analyzing the oxygen isotopes from ice cores to infer ozone concentrations in the past. Since radiative forcing is based on a difference in ozone abundance from before the Industrial Revolution to the present, this new research gives an observational constraint on the pre-Industrial ozone levels.

The ISA also mentions briefly that changes in emissions of ozone precursors affect not only ozone but also methane and aerosol concentrations, through atmospheric chemistry. This complex picture is not discussed much here, and future ISAs might discuss this more for its policy relevance. For example, while NOx emissions contribute to ozone formation, it also causes methane's lifetime to decrease and therefore methane concentrations to be lower. Reducing NOx emissions is thought to cause a net warming, because the increase in methane outweighs the decrease in ozone. In contrast, reductions in methane, CO, and VOCs all benefit both ozone air quality and climate (West et al., 2007; Fry et al., 2012). While the ISA focuses on whether ozone affects the climate system for informing the NAAQS, the policy implications of these effects are relevant for EPA decisions generally might be discussed more.

a. What are the panel's views regarding the causal determination for tropospheric ozone and radiative forcing and the causal determinations for tropospheric ozone and temperature, precipitation, and related climate variables?

I agree with the EPA's determination that ozone has a causal effect on radiative forcing. I do not agree with the determination that effects on temperature, precipitation, and related climate variables are "likely to be causal" and suggest that "causal" is justified.

The IPCC AR5 report concluded that global temperature has increased historically by 0.1-0.3 degrees C because of elevations in ozone concentrations from the pre-Industrial period to the present. The new AR6 report also concludes with confidence that historic increases in ozone have a positive radiative forcing and warming influence on climate. Since it is implausible that ozone changes have had a cooling influence on the climate system, it seems that a "causal" determination is warranted for ozone having an effect on global temperature.

The separation of radiative forcing from temperature by the EPA seems a little bit artificial, and goes back to the definition of radiative forcing. While it is fine to say that ozone changes have a positive radiative forcing, therefore a causal effect, radiative forcing itself is not a real measurable quantity but is instead a model construct. Satellites can measure incoming and outgoing radiation, but radiative forcing is defined as a change between different states or time periods. Anthropogenic radiative forcing is taken

as the change in energy flux from the pre-Industrial to the present, based on our understanding of the abundances of climate forcing agents at both points in time, and is therefore not directly observable.

Further, our concept of radiative forcing suggests that a positive radiative forcing would cause a temperature increase, all other factors held constant, by definition. It would also cause changes in the climate system manifest as changes in weather patterns and the distributions of temperature, humidity and precipitation. That is, our concept of the climate system is that an increase in ozone causes a positive radiative forcing, which causes an increase in temperature and causes changes in other climate parameters.

In the ISA, the EPA focused on model simulations to ask whether there is evidence that ozone changes have influenced temperature, precipitation, or other climate patterns. These model simulations control for the change in ozone, separating it from changes in other climate forcing agents that happened concurrently or will happen in the future. Here EPA found a rather small number of studies and poor agreement among those studies, especially for changes in weather and precipitation patters. New modeling studies would strengthen this evidence, but probably still find evidence that isn't particularly strong, especially for changes in weather.

I would encourage the EPA to rethink how the causal determinations are presented for ozone effects on climate change. Instead of making a causal determination for radiative forcing, I suggest making a causal determination for global mean surface temperature. I would suggest that "causal" is justified for an influence of ozone on global temperature, supported by the confidence in ozone having a positive radiative forcing. Ozone is contributing to global warming now, as the 3rd most important greenhouse gas behind CO2 and methane, and is expected to continue to cause warming. As a short-lived forcing agent, reducing ozone can be a key part of the strategy to slow global warming in the coming decades – turning the ship quickly while the world continues to work to bring down CO2.

Then for precipitation and other climate variables, I suggest that changes in weather and precipitation patterns are now being observed that researchers have attributed to anthropogenic global warming, beyond the range of natural variability. Ozone must be contributing to these changes along with other climate forcing agents, even if the effect of ozone alone is difficult to distinguish in modeling studies. I would suggest that this is sufficient to determine causality for ozone effects on precipitation and other climate variables, although others might hold the bar higher and require evidence from modeling studies to uniquely show that ozone has clear influences in patterns supported by multiple models.

This discussion of how EPA could address causality for ozone on climate is likely also relevant for other criteria pollutants including PM, and NO2, SO2 and CO (though changes in ozone and PM).

b. Have the effects of warming on ozone production been adequately characterized?

The ISA focuses on the effects of ozone to affect climate, strengthening the determination of effects on welfare to set the NAAQS. It does not review evidence on how climate change has historically affected ozone concentrations, or is projected to affect ozone in the future. The effect of climate change on ozone air pollution could be added in future ISAs, either in this section or in Appendix 1 where trends are discussed. The policy relevance is that where climate change has or will cause ozone to increase, greater effort will be needed to attain the ozone NAAQS through emission reductions.

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