Responses to CASAC Questions on the Ozone ISA from Consultant Dr. D. Warner North

I begin by reiterating three themes from my earlier response on the Policy Assessment for Particulate Matter.

I. **Causality.** I do not endorse, and am troubled by, EPA's existing Causality framework, Table II, "Weight of evidence for causality determinations," introduced in the Preface at pages lxxix-lxxxx, then again at ES.4 and IS.1.2.4, page IS-6, with determinations set forth in Figure ES-2 and Table IS-1, page IS-7. I support the criticisms of this framework in the two peer-reviewed publications of Dr. Tony Cox referenced in his Questions, ("Modernizing the Bradford Hill criteria," in *Crit. Rev. Tox.* (2018) and "Improving causal determination," in *Global Epidemiology*, 2019). I judge that to deal with these criticisms, much of the ISA would need to be greatly revised – essentially, rewritten. I question whether it is possible to do that on the existing schedule. Ozone causes adverse health impacts on human health at levels at or above 5 parts per million, which is the level listed as "immediately dangerous to life and health" (IDLH) by NIOSH: https://www.cdc.gov/niosh/idlh/10028156.html. The focus of CASAC's review should be on whether there is clear evidence that ozone is a significant partial causal contributor to adverse human health impacts at levels nearly two orders of magnitude lower, that is, at or below 120 parts per billion (the 1979-1997 one hour standard), and especially, in the range between 70 ppb, the existing 8-hour standard, and 60 ppb, a lower standard that might be considered as providing increased protection of public health including susceptible groups, with "an adequate margin of safety."

II. **Concentration- Response relationship.** For both epidemiological studies and human clinical studies, much of the data showing responses above background occurs at levels above this range of 60 to 70 ppb. How should the extrapolation be made to predict changes in mortality, morbidity such as respiratory and cardiovascular disease, or clinical changes such as FEV1 as a measure of lung function? For measures such as lung function, how should responses in healthy volunteers be used to predict adverse health impacts in children, elderly, and members of sensitive groups? Use of linear-to-zero extrapolation should be compared to alternatives, with attention to biological plausibility, variability, and uncertainty.

III. **Regional issues resulting in extreme exposures, such as wildfires.** As a resident of northern California, I am concerned that a large number of the "red circles" in Figure ES-1, page ES-2, (also, Figure 1-8, Appendix 1, p.1-44) of violations of the standard (since it was lowered from 120 ppb in 1997) of 76 to 112 ppb occur in central California. (There are many "orange circles" in California as well, but the majority of orange circles corresponding to small exceedances of the 70 ppb current primary standard are in urban centers in states east of California.) It is not clear in the text whether these "design values" include wildfire episodes, or whether wildfire episodes with even higher ozone observations were removed as "natural disaster" exceptions. Figure 1-12 page 1-48 shows the large number of design values in California, plus a few in other western states, with exceedances of the 70 ppb MDA8 standard and high W126 sigmoidally weighted sums of hourly O3 concentrations.

I urge that CASAC concern itself with wildfire-related ozone exposures and how these high exposures may be reduced by actions that EPA might take, or might advocate to other federal agencies and state agencies that have responsibilities affecting the occurrence and extent of

wildfires. California is experiencing severe wildfires in 2019 as it has several previous years. These wildfires contribute substantially to violations of the existing 8-hour ozone standard of 70 ppb, but under EPA's rules, wildfire exposures may be excluded both from regulation and from including these episodes as data because wildfires are claimed to be "natural disasters." I urge CASAC to tell EPA that the threat of ozone exposure from wildfires should be described in detail in the ISA, and that strategies to reduce wildfires and consequent high PM and ozone levels should be discussed so that the public may be informed on this important cause of NAAQS violations.

More on Theme III, Wildfires and Ozone: Why is there not more discussion of this important source of ozone exposure in the ISA?

Wildfires are mentioned on line 5 of page ES-3 as contributing to "ground-level US background (USB) ozone." But the paragraph, lines 1-17, is quite inadequate in portraying how ozone from a large wildfire can contribute to ozone levels of 70 ppb and above, lasting for multiple days and affecting large areas such as those portions of central California with the red circles in Figure ES-1. And considering ozone from wildfires as "background" seems inappropriate, since the occurrence of wildfires is strongly influenced by human activities, especially land use and vegetation management.

Wildfires are mentioned on line 26 of page IS-13, and then again at IS-14 line 23-24:

> Wildfires have been estimated to contribute a few ppb to seasonal mean ozone concentrations in the U.S., but episodic contributions may be as high as 30 ppb (Section 1.3.1.2). However, estimates of the magnitude of ozone formation from wildfires is highly uncertain with some work showing large overpredictions of modeled wildfire contributions (Section 1.3.1.3). (Note: here is a rare example of a grammatical error in the ISA: "estimates … is")

The statement that "episodic contributions" can be as high as 30 ppb" and that ozone formation "can continue for up to five days following a wildfire event" (page 1-21, lines 38-41) should motivate attention. 30 ppb is a large fraction of a standard now at 70 ppb for a 4th highest maximum 8 hour average in a three year period. What about the magnitude of the uncertainties and the overprediction of modeled wildfire contributions? The reader might conclude that wildfires are not so important as a source of ozone. I believe more disclosure in the ISA would be useful for clarification.

IS Section 1.8, "U.S Background Ozone Concentrations" mentions wildfires as contributing to background, "USB":

> Quantification of USB ozone on days when MDA8 ozone concentrations exceed 70 ppb is more relevant to understanding USB ozone contributions at the upper end of the distribution than are seasonal mean USB ozone estimates because USB varies daily and is a function of season, meteorology, and elevation (Jaffe et al., 2018). (1-49, lines 5-9.)

But the reader is not told that large wildfires can last for weeks, with smoke plumes filled with NOx and VOC transforming into ozone at the "red circle " level in Figure ES-1, and these wildfires happen frequently in California with the plume blowing into the Central Valley.

I now look for sections 1.3.1.2 and 1.3.1.3 in Appendix 1. The section that **should** have been referenced in the Appendix 1 text is 1.3.1.3.3," Landscape Fires," p. 1-21 and 22. I read Jaffe and Wigder (2012),

"Ozone production from wildfires: A critical review," and Jaffe et al. (2018), "Review, scientific assessment of background ozone over the U.S.: Implications for air quality management." Clearly, wildfires are a significant contributor, especially when meteorological conditions such as Santa Ana winds lead to large fire episodes. This pattern has happened for many decades in California, and the past three years – 2017 to 2019 - have been particularly severe.

I also found the Exceptional Events Rule, signed by EPA September 16, 2016: https://www.epa.gov/air-quality-analysis/final-guidance-preparation-exceptional-events-demonstrations-wildfire-events. Under this rule, a state can ask that ozone levels during wildfire episodes not be used for regulatory purposes. Violations of the NAAQS do not count, and these exceedances may be deleted from the data bases. Especially the latter seems to me highly inappropriate. I believe EPA should be calling attention to these exceedances of NAAQS as threats to public health, and NOT excluding them as a part of "natural background!"[1]

Figure A2-1 of this EPA 2016 document shows the increase in ozone over time versus sources of VOC and NOx for several wildfires. In one case the range of projected ozone increase was 60-85 ppb. The two others were in the 8-22 and 24-60 ppb ranges. Figure A2-2 shows the plumes, with ozone increases of 5 to 30 ppb over large area. A good discussion of the complex calculation of how O_3 is formed from VOC and NOX in wildfire plumes is in Jaffe et al. (2018), page 16 of 30. Observations and modeling for 7 urban sites in the western U.S. gave results from negative to 33 ppb, including days with MDA8 values over 70 ppb.

Figure 3 from Jaffe et al. (2018), page 8 of 30, shows observed design values (4th highest MDA8 O3 levels) averaged over 2010-2014, and modeled North American background with North American anthropogenic emissions zeroed out. For most of the American West, the resulting calculation of background levels is in the 61 to 70 ppb range. Natural background - wildfires plus lightning plus pollution from Asia can take the ozone exposure level very close to the current MDA8 standard of 70 ppb! Not only wildfires, but also other aspects of so-called natural background ("USB") are important! The details in Jaffee et al. (2018) are persuasive that so-called natural background varies considerably, and these variations and the uncertainties (of the order of 10 ppb for seasonal average and higher for MDA8 average concentrations; p. 1-53, lines 27-29) ought to be considered carefully, especially in considering how much actions to reduce ozone exposure might actually accomplish in helping areas not now meeting the MDA8 standard to achieve compliance. Yes, this 2016 EPA Rule can help states (e.g., California) achieve compliance. But the exposure above the standard is still happening, and any consequent public health impacts from exposure above the standard are not avoided by EPA's Exceptional Event Exclusion rule.

The Kincaid Fire has burned over 77,700 acres, mostly in Sonoma County in northern California, with full containment achieved November 6, two weeks after the fire started October 23. Fires in southern California have burned many thousands of acres more in the same time period. Many red circles/triangles in the Central Valley might result from these fires. (See Figure ES-1, Figure 1-8, Figure 1-12, and text page 1-56 line 38 to I-59 line 2 plus Figures 1-13a and 14a.) These relationships should be explained to the public in the ISA, and not left to the 2016 EPA Rule document, which I could not find referenced in the ISA. (The Jaffe et al. 2018 paper is referenced in the ISA, in both IS and extensively in

[1] "EE[exceptional event] influenced data can be excluded from the design value calculation if they are identified by the state agency and supported by evidence, which is then evaluated and approved by the EPA. Thus, excluding high O_3 caused by exceptional events may allow an area to be designated in attainment of the NAAQS. … the impact appears to be greatest in the western states where wildfires tend to be greater…" Quote from Jaffe et al, 2018, page 3 of 30.

Appendix 1.) Daniel Jaffe was listed among the authors, contributors, and reviewers in the ISA Preface. Jaffee et al. (2018) describes the EPA guidance on event exclusion in considerable detail. I am not aware how many California fire events have been excluded, but I expect that wildfires such as Tubbs, 2017, Camp, 2018, and Kincaid, 2019, in northern California, and large fires in these same years in southern California, would qualify. Even more of the circles and triangles in the California Central Valley in the equivalents of Figures 1-8 and 1-12 with 2017-2019 data might be red as the result of these large fires.

Other Overall Comments on the ISA. It is a huge document, over 1400 pages. It is generally well written, and the organization is such that a reader can navigate readily from the summary statements to the supporting detail and references. There are remarkably few typos and similar errors. I commend Appendix 1 as excellent support for the ES and IS material. I thought Appendix 2 was overly detailed, with insufficient emphasis on the differences between human exposure indoors, where most people spend most of their time, and ambient levels outdoors. I found weakness with the discussion of inflammation in clinical studies at near-ambient exposure levels in Appendix 3, and I am dissatisfied generally with the discussions of causality and confounding. As far as I can judge, most of the relevant clinical and epidemiological studies are included – but I and others have found other relevant studies not included. There is a deficit of published papers on interpretation of the available studies, especially on uncertainty, variability and severity of health effects. Discussion of inflammation is an example. Non-experts have difficulty understanding the importance of the range of biomarkers for assessing the degree to which these biomarkers indicate a public health impact deserving of protection under the language of the Clean Air Act. I did not find any references to the journal *Risk Analysis*, for which I am an area editor, and which publishes many papers on air pollution health risks. I expect other journals may be neglected as well.

Because there were no questions on this material and my time was limited, I did not read Appendix 8 and the ES and IS sections on welfare relevant to the secondary standard for ozone.

Response to Questions from Dr. Tony Cox

This set of questions, ten pages in length, deals mostly with the causality determination framework developed previously by EPA and used as the organizing framework for this ISA. I am in support of Dr. Cox's criticisms as described in his two referenced papers in *Critical Reviews in Toxicology* and *Global Epidemiology*. I believe the Bradford Hill criteria are out of date, and in particular, strong association is not evidence for causation. But I think emphasizing so heavily the weight of evidence using a five-part hierarchy for causal determination may result in neglect of other areas important for CASAC's review. I urge attention to my Theme II, the shape of the concentration response (C-R) relationship. It seems to me an important issue whether observed mild, apparently reversible effects such as changes in FEV1 (forced expiratory volume in one second) seen in healthy young exercising subjects imply a potential for adverse health effects in the general population. What are the adverse health effects, and how well do FEV1 changes predict them? What is the C-R relationship, not just for FEV1 changes, but for adverse health impacts that are persistent and perhaps cumulative over time, such as scarring of lung tissue so that lung function is permanently lost?

Overarching Questions 1-4: Is the ISA *clear*? I do not find it so to me. Perhaps others would find it so. Is the ISA *sound*? Not in my judgment, because there is little exploration of confounding and too much reliance on strength of association in the Bradford Hill criteria. Is the ISA *scientific*? The classification in the causal categories are judgment calls. Different people might make them differently based on the

same supporting evidence. Is the ISA *policy-relevant*? I believe CASAC is asked to make judgment calls, but this causality framework is not the proper framework to do so. The judgment should be on the change in number people whose health is protected with an adequate margin of safety, and not on the choice among the five causality categories.

Specific Questions:

1. I think this is a clear **NO**. CASAC should be seeking to evaluate manipulative or interventional causation, that is, determining how many people might be added or subtracted from having their health protected with an adequate margin of safety by a change in the primary NAAQS standard. Who will be protected at a 60 ppb MDA8 O_3 standard that was not protected at the current 70 ppb MDA8 standard? How is this number to be estimated? What is the supporting evidence and chain of logic used as the basis for the estimate? What is the uncertainty in the estimate, and what are the sources of this uncertainty? Dr. Cox's *Crit. Rev. Tox.* paper has on the top of p.19, top of col. 2, some excellent insight on the difference between Bradford Hill and manipulative causality. The col. 2 paragraphs following motivate replacing EPA's five part causal categories with a revised framework. But I doubt that a replacement framework can be developed and implemented by EPA in the current cycle for ISA revision without extending the completion data for the NAAS review process.

   O_3 is clearly dangerous to health at high levels. It is much less clear how much risk to public health O_3 poses at current ambient levels. It is CASAC's job to advise the EPA Administrator on whether the existing NAAQS should be revised.

2. (a). No. I agree that the terms are not clearly and unambiguously defined. (b). No. Other factors should be considered, and positive association is not the same as necessary or sufficient. One needs to think in terms of partial causation through examination of multiple factors. Dr. Cox's example in *Crit. Rev. Tox.,* page 3-4 shows how this may be done. (c). No. I do not find that "causal" as used in the ISA implies "a manipulative causal relationship." (d,e,f). yes, no, no. But it seems inappropriate to dispute causality at high O_3 exposure levels such as 5 ppm. CASAC needs to address the extent to which ozone exposure causes health and welfare impairment at ambient levels occurring now and in the future in the United States. There are not obvious, clear answers. Judgment is needed about the uncertainties: how many people might be impaired, and to what extent? (g). No. I do not believe the determination represented by the entries in Table ES-1 can be defended as correct. I think the Administrator, CASAC, and we who are advising CASAC could argue ad nausium about causality, and we would be better off trying to address how to estimate the extent of health response and the severity of the health response for exposures in the 60-70 ppb range. (h). no. See Dr. Cox's example, text in (b). above. (i). no. Let's use probabilities instead of seeking yes-no answers. (j). No. Sensitive subpopulations must be considered. (k). I must respond that the lines between the categories are unclear to me. I cannot attest to mutually exclusivity. Again, I think the level of ozone exposure is critical. CASAC should evaluate the significance to health (and welfare) of ozone exposures in the 60-100 ppb range, in the context of other factors. Causality for adverse health effects seems well established at higher levels in the occupational health literature, for example, the Ozone Material Safety Data Sheets. See https://www.cdc.gov/niosh/idlh/10028156html; www.amsbio.com/images/featureareas/ozilla/Ozilla-MSDS.pdf. Other sites include:

https://www.ozonesolutions.com/knowledge-center/ozone-safety.html.[2] (l). I am not sure I care about "collectively exhaustive." I do not think the framework is useful. (m). I prefer probability statements and partial causation with multiple factors as in Dr. Cox's example. I do not like implied "bright lines," such as greater than 50% means likely. Such conventions need to be agreed to among the users. I do not believe that is the case here.

3. (a).(i) I am concerned that EPA's selection process is leaving out studies with negative findings for ozone. This is evidence against the ISA study selection process being comprehensive, trustworthy, and unbiased. (ii). Including Moore (2008) but not Moore (2013) is further evidence of weakness in study. (iii and iv). I will leave to others specifics on what should be included or excluded. It is my impression that there is a lot of relevant literature on interpretation/evaluation of studies that ought to be included and is not included. (See my earlier general comments on the ISA.) (v). Not clear to me. (vi). I am disappointed that the Executive Summary focuses on the causality determination, rather than a common sense summary of the relevant science including discussion of modeling assumptions, uncertainties and variability in ozone exposure. I did not find the Annex to Appendix 6 useful as a guide to "what should be done." It seemed like a defense of EPA practice as best practice, and I disagree, especially on the use of the Bradford Hill criteria. (b). As I have stated above, EPA's framework does not discuss interventions. How exposures will change with new standards is buried in the details on the draft Policy Assessment for PM, and I expect similar problems with the upcoming draft PA for ozone and related photochemical oxidants. I would like to see possible interventions made explicit at the regional level and evaluated in terms of how much these interventions would reduce exposure, and then, what impacts these would have on health and welfare measures, with results in probabilistic form. Anne Smith's 2019 paper in *Risk Analysis* demonstrates how such an evaluation might be done. On the last sentence of part (b), I judge that Dr. Cox's concern is well justified. I share it, and have serious reservations about basing a risk assessment for health effects on the causal determinations from the framework EPA has used in this draft ISA. I have difficulty interpreting what "likely to be causal" means in connection with possible confounding. What I find informative in Table 3-3 (and other Tables like it) is the summary of ozone levels used in the studies. In my judgment, results obtained at levels of 500 ppb (0.5 ppm) and above have little relevance unless the biological mechanism(s) involved apply at much lower levels, such as 100 ppb. (c). I read the Kai et al. (2018) paper. It demonstrates that confounding by temperature can lead to modification of mortality estimates, and that sophisticated non-linear methods may be needed for both extremes of cold and heat. For the latter, extent of air conditioning can be important, and I did not find that included in comparing US and European cities. I did not find Kai et al. (2018) in the references in ISA Appendix 3, and that concerns me a great deal. Issues of how to deal with confounding by temperature, extent of air conditioning in homes and workplaces, and socioeconomic status – interrelated factors that will differ by location – need to be carefully evaluated in order to get good estimates of mortality and morbidity responses. EPA in this

[2] When I was in my teens I used to experiment with a chemistry set, which was dangerous, and also with a Tesla spark coil. Here is what the website http://donklipstein.com/tcsafe.html says about ozone from a Tesla coil: "The sparks and intense corona easily produced by Tesla coils can produce ozone. Ozone is bad to breathe since it can corrode lung tissue. And if you are going to breathe it a few hours a day, it can be unhealthful to breathe even if the concentration is too weak to smell. Ozone can also oxidize some rubber objects. If you are having corona, you should operate the Tesla coil only in a very well ventilated area, or expose yourself to the ozone for no more than a few minutes a day."

ozone ISA seems far behind evolving "best practices" in how to do such analysis. I did not read through the Tétreault et al. study, but I perceive that the kind of discussion needed on confounding was not present in the ISA, just a judgment of "likely to be causal." And I do not find such judgments useful in the absence of detailed discussion of possible confounding (d). Estimating exposure "according to the centroid of the postal code" is quite crude, and misses all the subtleties whether children are outdoors, indoors in air conditioned space, or indoors in non-air conditioned space, and the extent to which they are exercising in these environments. It also may miss exposure to materials the aggravate asthma, such as pet and cockroach dander. Dr. Cox's quotes from the study persuade me that this study has serious problems of potential confounding. (e). I did not read the sensitivity analysis associated with the Tétrealt et al study. With such crude and aggregated data, it is not clear to me what sensitivity analysis would be useful. Continuing from (d), from the description Dr. Cox has given, I would be inclined to discount the Tétreault et al. study as providing "key evidence." (f). No, I find the discussions of study quality rather superficial, It is clear that some of the recent studies have initiatives for investigating confounding factors. Much more is needed, in the context of learning how to do better estimation of the C-R relationship in the low exposure range. (g). I did not find much discussion on confounding, measurement error, and unverified modeling assumptions. The discussions I did find were often superficial. In a few cases I went to the cited paper and found interesting discussion, similar to that in Kai et al.

4. I read the full text of the Michaudel et al. 2016 paper. Activation of the NLRP3 inflammazome seems important. So I went to the text to find the exposure level. I think there was a misprint: the text reads,

> Chronic ozone exposure such as twice weekly 2-3 part per billion (ppm) for 3 h causes repeated bouts of inflammation with progressive destruction of alveolar epithelial cells and emphysema within 6 weeks, resembling in part to that found in COPD [47,55].

I judge "ppm" is correct rather than "part per billion." Are such mechanisms active in humans at levels of 500 ppb? 100 ppb? It seems to me examination of high occupational exposures might provide some indication, but I have not found studies on occupationally exposed groups. The Abstract of the Xu et al. (2019) paper states that the exposures to mice were single 3-hour exposures at 2.5 ppm. Changes indicating inflammation showed up with bronchoalveolar lavage (BALF). Could such changes be detected in humans as well as mice? Yes, as I learned from reading papers referenced in Appendix 3 for my response for Dr. Packham. I would like to see more evidence in the ISA of the kind in the Michaudel et al. and Xu et al papers, indicating mechanisms for health damage and biomarkers or indicators for biological changes in humans at much lower exposure levels. See my response to Dr. Packham, especially Question 3 and following. It will be important to get expert judgment on which cytokines, neutrophils and other indicators of inflammation are most significant for predicting irreversible damage to lung tissue such as described in the Michaudel et al. quote above. The support in the ISA seems weak for inflammation in humans at 60-80 ppb exposure over 6.6 hours with exercise. This support is from studies done before the last review of the ozone standard.

5. Yes, there is some useful information, and I will consider a series of published papers reporting similar findings as well-validated evidence. But the focus is not on assessing the effects of changing the NAAQS, as should be the case.

6. I will not offer an opinion on Table ES-1 beyond what I have earlier expressed about the causal framework. It seems clear that at 2.5 ppm ozone exposure causes respiratory damage in mice. NIOSH scientists have declared 5 ppm "immediately dangerous to life and health" (IDLH) for short-term exposure. But for all the other categories of causality and for ambient ozone exposure levels, I would like to see projections of what reductions in ambient levels might do to avoid adverse human health impacts, and similarly for welfare effects.

7. The overall answer is yes on all counts. But it would take me a long time to go beyond what I have already said above to describe what those changes should be. I am therefore going on to the other questions.

Responses to Questions from Dr. Mark Frampton

1. Cardiovascular (CV) effects. I have read through section ES 4.1 and Appendix 4, and selected papers included Frampton et al. (2015). I do not dispute EPA's downgrading from "likely" to "suggestive." (My answers to Dr. Cox's questions indicate my difficulty with EPA's causal determination framework.) It is my impression that the available epidemiology has many serious issues of confounding. I think these confounding issues deserve CASAC's attention, and that the ISA discussion on these confounding issues should be improved. I think research such as your own on cardiovascular effects in Frampton et al. (2015) is important, because lung damage and cardiovascular impacts are often linked in subtle ways, as indicated in Figures 4-1 and 4-6. Your 2015 paper indicates oxidative stress as a "fundamental mechanism." I think finding clear evidence of changes such as seen in rodents at 2.5 ppm to occur in humans at levels of 200, 100 ppb, and lower would be extremely important as evidence for risk of adverse CV effects in humans at ambient levels. I wish your success in your ongoing research.

2. Metabolic effects. I have a similar answer for this question. I have read through ES-4.1 and Appendix 5. I will not dispute EPA's ranking of "likely" for metabolic effects. I view potential for confounding as very high, and would like to see other variables included that are causally related to metabolic effects. I have no additional studies to suggest. A search of the epidemiology literature will readily find many studies showing that metabolic effects depend on diet, socioeconomic status and medical care. Ozone at ambient levels might have metabolic effects, but I expect the main risk to public health to be from respiratory effects, and possibly, cardiovascular effects.

3. Total Mortality. Again, my response is similar. I am concerned about confounding, and I would like to see good biological support in clinical studies, such as your have carried out in your career, that there is significant indication of biological damage from ozone exposures in humans at levels of 100 ppb and below. There should be occupational cohorts where exposures of 100 ppb and higher with exercise occur frequently. I am concerned about the confounding with temperature, exercise patterns in indoor air and outdoor air, and air conditioning for indoor air, which reduce exposure levels considerably compared to ambient outdoor levels. Some of the highest ambient U.S. exposures occur in California, where I live. Many agricultural workers in the Central Valley of California are exposed outdoors while exercising, at levels exceeding the current MDA8 standard. I would like to see epidemiology studies carried out on this population and other populations where ozone exposure is high. (I note in Section 3.1.4.4.3, page 3-37, lines 22-23: "There are no recent studies in the U.S. or Canada

that examine the relationship between short-term ozone exposure and pulmonary inflammation in healthy populations." See also 3-38, line 18; 3-47 line 6-7.) And I would like to see wildland fires viewed by EPA (and CASAC) as a major source for ozone as well as for $PM_{2.5}$. I view health risk from air pollution from wildland fires as deserving much more attention than it is receiving at the national level. The large fires California has experienced in the past three years are not natural, but the result of long-standing poor national and local policies that can be changed. It makes no sense to be spending a lot of money controlling mobile and stationary sources of ozone precursors and not spending comparable amounts of money to reduce these ozone precursors by reducing the frequency and extent of large wildland fires. These fires result from wildland fuel-buildup combined with electric power lines and other ignition sources and the dry east wind conditions that California experiences each fall. The climate aspect is getting worse, and we can expect more fires until the electric utilities do better in reducing ignitions from power lines and landowners reduce the large amounts of flammable vegetation.

Questions from Dr. Steven Packham

Question 1

I agree that there is strong evidence that ozone exposure with exercise in the range of 60 to 100 ppb causes a small but statistically significant decrease in FEV1. But whether this should be considered as an adverse health effect motivating lowering the standard from 70 ppb is a judgment call, in my opinion. Ozone exposure at levels of 5 ppm is judged immediately dangerous to life and health in humans, and animal toxicology shows clearly adverse changes at levels of 2-5 ppm. At these levels, causality seems quite clear.

Is a small change in FEV1 after 6.6 hours exposure during exercise predictive of irreversible damage? I am not a medical professional with extensive experience in treating patients, but my information from interacting with medical professionals is that small changes in FEV1 are not considered adverse if there is no lasting change – that is, FEV1 is retested and found to be within variation of earlier measurements within a few days.

A recent publication by Richard Belzer and R. Jeffrey Lewis ("The Practical Significance of Measurement Error in Pulmonary Function Testing Conducted in Research Settings," *Risk Analysis* 39(10):2316-2328) investigates the variability in FEV1 testing and protocols for summarizing data from repeated tests. I quote from the Abstract:

> Measurement error is defined as the difference from between results from the conventional protocol and an unconstrained, eight maneuver alternative. In the default model, average measurement error is shown to be about 5%. The minimum difference necessary for statistical significance is shown to be 16% … Within-day FEV1 differences ≤ 5% among normal subjects are believed to be clinically insignificant. Therefore, many differences reported to be statistically significant may be artifactual.

These statements about clinical significance supported in the main text with statements from the American Thoracic Society and the European Respiratory Society, such as at the bottom of column 2, page 2317 to 2318.

While I have read through this paper, I have not attempted to review its many references, which include the two papers Adams 2006 a and b referenced in your questions, Schelegle et al. 2009 in the ISA, and many papers on spirometry not referenced in the ISA on FEV1 or included in your questions. I urge you to read this Belzer-Lewis (2019) paper and draw your own conclusions about the significance of small FEV1 changes, especially those that are not reported as persistent over time following ozone exposure.

I hope you and others on CASAC will consider the Belzer-Lewis conclusion and recommendation:

> The failure to account for intratest variability is a material limitation of conventional spirometry in research settings. There appears to have been no systematic effort to collect sufficient data to estimate intratest variability, whether for the population, research samples, or subpopulations of interest. All spirometric protocols recognize that intratest variability is important; hence, the universal guidance to conduct multiple maneuvers. But this recognition is abandoned in practice by terminating tests early, thus failing to collect needed data, and discarding all but a single fixed value to represent each test. The result is measurement error and bias.
>
> Measurement error has pernicious effects on research intended to make causal inferences about small changes after treatment or exposure. (p. 2326.)

The authors then list recommendations for collecting further data on variability "to insure that inferences about the statistical significance of observed changes are statistically valid."

Question 2

My understanding impression is that many experts on the toxicology of PM and ozone believe PM at ambient levels poses a greater risk than ozone at ambient levels, and that the mechanisms for toxicity are different: PM is not an oxidative challenge, and ozone is. My own view is that there is considerable uncertainty, and that treating PM as a mixture obscures the possibility that some PM exposures may be considerably more toxic than others, so that concentration response relationships in different regions with differing PM sources may vary. I commented on this for the PM draft PA.

I advocate rewriting of ES4.1 and the entire Integrated Synthesis section with much more discussion of uncertainty and variability, and clear statements of where extrapolations are being made from observations at higher doses to doses at or near ambient levels. I am disappointed that after more than a decade since the publication of the Adams and Schelegle et al. papers, CASAC does not have in the ISA better clinical information about human response to ozone while exercising than these FEV1 data, with the variability problems pointed out by Belzer and Lewis. I will discuss the ISA comments about inflammation below, as an appendix to my response to Question 3.

Question 3

I would be much more impressed by the cumulative dose argument you present with Packham Figure 1 if there were data from subsequent days indicating that significant decrements in FEV1 or in symptoms persisted. I regard FEV1 as a measurement with substantial variability, among subjects and in the responses for each subject. And I do not view transitory changes of less than 10% in FEV1 for healthy subjects as an adverse health effect motivating a national standard. After reading Belzer and Lewis I would ask whether fatigue rather than cumulative ozone dose might have contributed to larger FEV1 decrements in the latter portion of the exposure period.

I did not find Foster et al., 1987, in the ES, IS, or Appendix 4 references, but only in your questions. I note it is over 20 years old. I agree that it and similar, more recent studies in human subjects should be included in the ISA. There are at least two references to Foster's group's later work in Appendix 3, Foster et al. 1997, and Foster et al., 2000. Dr. W.M. Foster was with the Pulmonology Division at Duke University Medical Center in 2011, and his group did a number of studies on human exposure to ozone. It would seem worthwhile looking further into this group's work. Here is the web link for the 2011 paper, which is not referenced in the ISA:
https://www.physiology.org/doi/full/10.1152/japplphysiol.00337.2011.

Toward the end of the period for preparing my response I obtained a copy of the full text of the 1987 paper from Aaron Yeow. The seven healthy male human subjects were exposed to ozone levels of 200 and 400 ppb for two hours, of rest alternated with light exercise. "Mechanical and mucociliary function responses to ozone by lung airways appeared concentration dependent."

I have not been aware of the confounding benefit of 200 ppb ozone exposure in improving PM clearance. I presume this is from Foster et al. 1987. Have these Foster et al., 1987 results been replicated? I looked at titles of Foster papers subsequent to 1987 and then downloaded the "small airways " 1997 paper. Here is what I found (on p.664):

> We suggest that [the observed] response is attributable to O_3-induced alteration in bronchial tone and/or mucus secretions within smaller peripheral airways (Foster, et al., 1987,1993) similar to non-uniform ventilation associated with bronchitis and disease of the small airways. (Other references in the quote have been omitted.)

Foster contributed a book chapter, "Effects of oxidants," in *Air Pollution and the Respiratory Tract*, edited by D.L. Swift and W.M. Foster, New York: Dekker, 1999. That might be a good place to look to ascertain what Foster thought about mucociliary clearance 12 years after his 1987 publication. Without confirmation from other studies, I would hesitate to endorse that ozone exposure induces increased PM clearance, but further investigation might provide support beyond the 1987 paper that ozone exposure has potential benefit in PM clearance via increased mucus secretion.

I have read other, more recent references. Hatch et al. (2013) exposed human volunteers and rats to 400 ppb ozone with a tracer, isotope ^{18}O, and collected samples with bronchcoalveolar lavage (BALF). The authors found that:

> …resting human subjects achieve a much lower alveolar O_3 dose than exercising subjects and that this dose is comparable to that of resting rats. The resting subjects also show fewer detectable O_3-induced cellular, biochemical, and physiological (FEV1) effects than exercising subjects.

You state on page 4, "These studies [by Folinsbee, Adams, Horstman, Kim McDonnell, Schelegle and others} document that the effect of O_3 on reduced FEV1 volumes is temporary, and suggest that hourly mean ambient O_3 concentrations below 70 ppb are not likely to cause FEV1 effects in most healthy adults." I take the "temporary" in this sentence as highly significant. I read Belzer and Lewis as indicating that much is known about FEV1 changes in sensitive subgroups. Are the changes observed in these sensitive groups from modest exposures to ozone while exercising also temporary? I am interpreting your question as motivating more balance and comprehensiveness in including toxicology, clinical human studies, and biomedical research – as well as epidemiology, in order to validate causal

relationships and determine inhalation dose rates for adverse inflammatory responses in pulmonary tissues. As you might infer from my responses to the questions from Dr. Cox, I am concerned about inferences from associations in the variety of currently available epidemiological studies.

Ozone, a potent oxidizing agent, clearly seems causal for adverse inflammatory responses in human pulmonary tissue at exposure levels above 1 ppm. Exposures at or above 5 ppm are judged immediately dangerous to human life and health. But humans can remove most of low or moderate concentrations in the upper respiratory tract, except when their level of exercise requires breathing through the mouth as well as the nose. With exercise, especially vigorous exercise, the material in Hatch et al. (2013) suggests increased O_3 content in BALF cells at 400 ppm might indicate adverse effects such as inflammation. What evidence other than the temporary FEV1 changes do we have for adverse effects in the 60 -100 ppb range? It seems to me that inflammation at near-ambient ozone levels is an obvious place for CASAC to focus its attention and ask EPA for further information and evaluation.

Support for an important statement in the IS Overall Conclusions Table, first bullet, second sentence:

> "The strongest evidence comes from controlled human exposure studies demonstrating ozone-induced decreases in lung function and inflammation in healthy, exercising adults at concentrations as low as 60 ppb after 6.6 hours of exposure."

Has inflammation been demonstrated in healthy exercising adults at concentrations as low as 60 ppb, as stated in this Table, page IS-1? Affirmative answers are in the text at IS-7, lines 5-6, and also 3.1.4.5, page 3-38, lines 27-29 but without listing the exposure level. Similarly in IS 4.3.1, page IS-23, current evidence is summarized as follows:

> There are, however, no new 6.6-hour ozone exposure studies since the 2013 Ozone ISA. Evidence in the 2013 Ozone ISA demonstrated increases in FEV1 decrements, respiratory symptoms, and inflammation following ozone exposures of 6.6 hours, with exercise, as low as 60 to 70 ppb (Section 3.1.4).

A similar statement, lacking the qualification that exposures were with exercise, is found at 3-80, lines 29-32:

> Controlled human exposure studies demonstrate ozone-induced decreases in FEV1 and pulmonary inflammation at concentrations as low as 60 ppb after 6.6 hours of exposure. The combination of lung function decrements and respiratory symptoms has been observed following 70 ppb and greater ozone concentrations following 6.6 hour exposures.

What is in 3.1.4 to support this statement?

Controlled Human studies are discussed in 3.1.4.4.1. Here is the first paragraph:

> As reported in studies reviewed in the 1996 and 2006 ozone AQCDs (U.S. EPA, 2006, 1996a), acute ozone exposure initiates an acute inflammatory response throughout the respiratory tract that has been observed to persist for at least 18−24 hours post-exposure. A single acute exposure (1−4 hours) of humans to moderate concentrations of ozone (200−600 ppb) while exercising at moderate to heavy intensities results in a number of cellular and biochemical changes in the lung,

> including an inflammatory response characterized by increased numbers of PMNs, increased permeability of the epithelial lining of the respiratory tract, cell damage, and production of proinflammatory cytokines and prostaglandins. These changes also occur in humans exposed to 80 and 200 ppb ozone for 6−8 hours.

This paragraph begins by citing EPA documents from 1996 and 2006, based on studies up to that time. Let me focus on the last sentence: "These changes also occur in humans exposed to 80 to 200 ppb ozone for 6-8 hours." Is the support at 80 ppb from old studies or new ones? The following paragraph mentions 200 ppb, but not 80 ppb. The study source of the increases in sputum polymorphic neutrophils (PMNs) in EPA (2013a) is not given. Then the section text has bullet points about specific newer studies.

The first bullet discusses PMNs and shed epithelial cells observed in BALF. Alexis et al. (2013) would appear to be the source for the statement about increased sputum PMNs at 60 ppb. Then comes Arjomandi et al., (2018), the only reference dated after 2013-4. It is a larger study of healthy older adults. Here is what the authors of that paper write about their findings at 70 and 120 ppb exposures in older adults:

> Ozone exposure caused a marginally significant increase in PMN% in a concentration-dependent manner
> (P = 0.012) (Tables 2 and 3, and Figure 3). In the mixed model regression, PMN% increased by an absolute value of 8.16% after 120 ppb compared with 0 ppb ozone (95% CI, 2.84–13.48%; P = 0.003) (Table 3). The 70 ppb effect was not significantly different from 0 ppb (P = 0.134). The absolute PMN count (ln PMN/mg) also showed a positive but nonsignificant increase with increasing ozone concentration (Table 3).

I interpret these statements as indicating a "marginally significant" response at 120 ppb and not supporting a clear finding of an inflammation response at 70 or 60 ppb. However, there is a s statement at 3-30, lines 22-25 that the delivered dose of ozone in the Arjomandi et al study at 120 ppb might have been only 60% of the delivered dose of ozone at 60 ppb in the Kim et al. study. In the Arjomandi et al. study a plasma CC!6 response after exposure at 70 ppb with exercise was not significantly different from control at 0 ppb.

In the second and third bullet, Bosson et al. (2013) measured blood neutrophils for up to 18 hours after ozone exposure, at 200 ppb for 2 hours, compared to filtered air. There was a transient decrease in blood neutrophils. The authors write:

> To date, although numerous groups have examined ozone-induced systemic inflammation in humans by measuring inflammatory mediators and PMN priming, no simple description of the changes in cellularities has been published. … At 18 hours post exposure we found no evidence of blood neutrophilia, though inflammation persisted in the airway lumen at this late time point. No other changes in peripheral blood cell types, or lymphocyte subsets were noted at any of the measured time points." … "We therefore believe that there is merit in further exploring the relationship between systemic neutrophilia and ozone in the real-world setting."

These statements do not indicate strong evidence of inflammation at 70 or 60 ppb, but rather that what is known now motivates further research. It is consistent with a preceding statement in the ISA, at the end of 3.1.4.2.1, page 3-23, line 22-26:

> Although several studies have investigated the effects of 6.6-hour exposures during moderate exercise to 60 ppb ozone, none have observed a statistically significant increase in respiratory symptoms following ozone relative to filtered air. There are no new controlled human exposure studies conflicting with the above or contributing a better characterization of ozone-induced respiratory symptoms.

But on 3.1.4.2.4. page 3-24, lines 18-22, the ISA claims support for an "adverse response," based on a model from 2013:

> A recent model can be used to determine the ozone concentration that would lead to the same FEV1 decrement following an 8-hour exposure (McDonnell et al., 2013). Under the assumption that respiratory symptoms might accompany similar ozone-induced FEV1 decrements, regardless of exposure duration, the model indicates that an 8-hour exposure to 64 ppb ozone concentration might reasonably be expected to cause an adverse response in young healthy adults.

I read McDonnell et al 2013. The model is of about intrasubject variability in FEV1. In the Appendix the authors state:

> One could interpret X to represent the level of oxidant stress resulting from accumulation and removal of ozone or its reactive byproducts, although the validity of the model is not dependent upon this interpretation.

But all the data used is FEV1 data, and X is a dose rate for ozone, concentration times minute ventilation with adjustments for body surface area, age, and body mass index. There is no tie to any measure of inflammation or to respiratory symptoms. The "interpretation" of oxidant stress is in no way confirmed by any data. And I did not find the phrase "adverse response" defined in this paper, which is about modeling between-subject FEV1 response variability. "Adverse response" is not defined in the ISA either, as far as I can determine. There is no support I could find in the McDonnell et al. (2013) paper for the "assumption that respiratory symptoms might accompany similar ozone induced FEV1 decrements."

I return to 3.1.4.4, the fourth bullet point about inflammation and oxidative stress, page 3-29. Here the ISA notes the studies by Fry, et al. (2012) and (2014) and Hernandez (2012) "included no filtered air control arm," and "without an air control it is not possible to assess potential effects of exercise and/or the laboratory procedures on results." The ISA notes (p. 3-29, lines 42-44) regarding comparison of lung function with inflammation indicators, "This is consistent with studies reviewed in the 2006 Ozone AQCD showing spirometric measures and inflammatory responses to ozone are unrelated." (This would seem to contradict the "assumption" from MacDonnell et al. (2013).)

In six years since 2013 the information in the ISA indicates there have not been clinical studies that have confirmed the "predictions" of the 2013 model developed by McConnell et al., or confirmed the findings of inflammation biomarkers with exposures of 60 ppb for adults exercising over a 6.6 hour period from Kim et al. (2011) and Alexis et al (2013). For the second sentence of the "Overall Conclusions" of the ISA, page IS-1, the support seems weak. And this evidentiary support is not new, but was available at the time of the last ozone standard review.

Dr. Packham, you are an expert for pulmonary physiology and inhalation toxicology, and so your understanding of the available published studies should be much better than mine. I hope you will review this material in Appendix 3 plus other relevant clinical studies in detail. These studies seem of

considerable importance in judging whether the current MDA8 ozone standard at 70 ppb is adequately protective of human health.

Questions from Dr. Sabine Lange

1. Statistical significance is useful in epidemiological studies, but in a limited way. These studies use regression to determine the association between a predictor x and a consequence y. This association might be statistically significant, that is, a good predictor, but causality could be absent: There may be a cause z that affects both x and y. Two examples: Children's shoe side predicts the children's reading ability. (Example due to Judea Pearl, in *The Book of Why*). Ice cream sales predict heat stroke cases. (I think Dr. Cox uses this one, which was more accurate before the era of air conditioning.) Progress for better prediction is to consider that there may be other factors that are predictive of y, get the data on these, and use these data on making the prediction. Children's age and high ambient temperature are candidates for the two examples.
2. (and 3). I'm not a fan of these cross-over studies, especially for mortality as the end point. For a good example, consider exposure to wildfires such as we have been experiencing in California. Consider hospital admissions for respiratory distress. What was the level the day before the smoke plume affected the area? What was the level the day the plume arrived? And after the wind blew the smoke away, then what was the level the next day? Yes, one might expect a low response level before the plume, and high levels after the high exposures, perhaps persisting for days after the levels have dropped. For Q3, the response is number of deaths on the exposed day versus the control day, and not the death of an individual person. (With cohort studies, it is more complex.)
3. I read the Di et al. study. Co-authors Schwartz and Zanobetti are among those trying to figure out how to do epidemiology where additional factors are considered. But I am not persuaded that confounding was not a significant issue for the results in the Di et al. study. The data base was all Medicare patients who died in a twelve year period. Most of the deaths occurred on days with ozone and $PM_{2.5}$ levels well below the current standards. The death rates per 10 μg/m3 for $PM_{2.5}$ was 1.45 per million persons at risk per day, and for 10 ppb ozone, 0.66 per million. These are extremely small numbers, but with sample size of nearly a hundred million days, the confidence limits were narrow around these numbers and did not include no increased risk. I looked up reference 9, Maclure (1991), on the study design. The Maclure Abstract begins, "A case-control design involving only cases may be used when brief exposure causes a transient change in risk of a rare acute-onset disease." I don't see the biological plausibility of comparing case days and control days for total mortality – not a rare acute–onset disease, but rather a situation where people who may be already very sick tend to die on days when they have additional stress. I suspect that high temperature may have acted as a confounding variable. Looking at figure 5 in the Di paper, I notice that the exposure response curve seems to flatten out (i.e., is insensitive to exposure level) for the higher 50% of the exposures, both for ozone and for $PM_{2.5}$. If these pollutants were causing the mortality increase, I would expect that the lower half of the exposure levels would be the flatter portion, and at higher exposures there would be more of a positive concentration response relationship. What may be going on is that in the days with higher half of the exposure levels, the pollutant levels are correlated (but rather poorly) with the frequency of very hot days. On such very hot days mortality is significantly elevated. But on the lower pollution half of the days, there is a stronger correlation: a much lower frequency of very hot days. Very hot days can cause stress to an elderly person, especially in non-air conditioned space. Remember, the Di et al response rates

are on the order of a one-in-a-million change. A small number of very hot days correlated with elevated exposure levels might give results such as reported in this paper.

4. I view it as extremely important that ozone concentrations are 2 to 10 (or more) times less indoors, and where the indoor space is air conditioned this has a big influence on 2 versus 10. Who is then at risk with high outdoor exposure during exercise? In California's Central Valley, with high peak ozone exposures, it will be agricultural workers, especially for hand harvesting of crops. In urban areas, we might expect that high exposures will occur for hikers, runners, bicycle riders, garden workers, and children playing outdoors.
5. That is a good question. My impression is that at ppm levels, humans and rodents are about equally sensitive, and that prolonged exposures at 5 ppm or higher are life-threatening to humans. There seems to be some information at lower levels. See my responses to Drs. Cox and Packham.
6. Causality diagrams are still rare. But some epidemiology studies do consider multiple predictive factors, and explain how they do it. I expect we will consider this aspect in the risk assessment in the upcoming Ozone PA.

Questions from Dr. James Boylan

Appendix 1: This is not my area. I would like to see more on wildland fires as an important ozone source. There are references to good papers by Daniel Jaffe. I would like more on the impact of strategies to reduce ozone from fires (wildlland and other) and how background ozone levels combine with ozone from anthropogenic sources in the US. Changing the NAAQS does not change background. Calculating changes in ozone exposure under a revised standard needs to be done, and should be done with realistic rather than simplistic assumptions. Such calculations should be presented in the upcoming Ozone PA.

Appendix 2. Again, it's not my area. Due to time limitations I only skimmed this appendix. It is my impression from reading it that there is an abundance of detail on geographical variation, and not enough emphasis on uncertainty and variability in the patterns of indoor versus outdoor exposure in relation to ambient monitoring, and also exercise patterns, for connecting ozone exposure (especially as measured in epidemiology studies) with human health effects.

Appendix 9. I read Appendix 9 and found it to be generally well done. I chaired the EPA Science Advisory Board's review of the two reports by EPA to Congress on global climate alteration in 1989-1990. I have no specific suggestions regarding accuracy or completeness. While I have followed the extensive literature on climate alteration over the past two decades, I am not familiar with the far smaller number of publications specially addressing tropospheric ozone for radiative forcing, climate alteration, and impacts of UV-B shielding on human health and ecosystems. I believe it is useful to have this chapter included, as I believe it covers important topics for EPA under the provisions of the Clean Air Act.

Questions from Dr. Corey Masuca

1.3.1. It is my impression that volatile organic compounds (VOC) and nitrogen oxides (NOx) are the main precursors of ozone, but that CO and CH4 also contribute. I am not expert in this chemistry. CH4 is an important gas for climate change/greenhouse warming. I do not believe CO is considered to be so,

in part because it is removed from the atmosphere much more quickly than CH4. There is discussion in Appendix 9 on the role of CO and CH4 for radiative forcing and climate alteration that you might wish to read. See page 9-9 line 2 through 9-12 and Figure 9-3, 9-4 on pages 9-11 and 12.

1.3.1.2.1. Repeating my answer above, methane is a minor contributor when VOCs are plentiful, but contributes significantly when VOC levels are low. See 1-23, lines 27-30 and Appendix 9. NOx formed by lightning reacts with CH4 in the atmosphere to make ozone, shortening the atmospheric lifetime of the CH4.

1.3.1.2.2. Transport from Asia is significant for ozone in California and other western states. See the background ("USB") discussion in this section and for more detail, the Jaffe et al. (2018) paper. Regional transport of precursors is important. There is a lot of literature on how to model ozone formation based on precursor emissions. Such modeling is complex, and is not an area in which I have much expertise.

1.3.1.3.2. Biogenic VOC such as terpinoid compounds can be important for ozone formation, especially in the southeast U.S. The Great Smoky Mountain National Park is a classic example, because the name comes from smog formation from the biogenic VOCs. Here is a link to an article you might enjoy reading: https://www.livescience.com/46958-trees-ozone-pollution-map.html. More generally, biogenic VOCs can be the dominant contributors to ozone formation outside urban areas. See page 1-20 lines 9-15. In many urban and suburban areas of the US these biogenic VOCs are less important than the local anthropogenic sources of VOC. One must consider both the VOC and NOx levels, as either can be limiting in ozone formation chemistry. See, for example, the discussion on page 1-52, lines 13-18. In the past highway vehicles were main sources of NOx and VOC, but these emissions have been greatly reduced, as shown in Figure 1-3, page 1-11.

1.4. and continuing on 1.3.1.3.2. Situations occur where ozone forms downwind of an urban area when an air rich in NOx reaches these biogenic VOCs: There was not enough VOC over the urban area to enable the ozone formation to occur earlier. The chemistry and air flow movements from meteorology make the modeling of ozone formation quite complicated. Humidity is one of many important factors. I am not knowledgeable on how well modeling predictions are confirmed via remote sensing and local monitoring. I am doubtful that specialized monitoring of individual chemicals would be very helpful in improving prediction of ozone levels, but my knowledge in this area is quite limited. The ISA at 1-21, lines 21-27 agrees with me for biogenic VOCs. For some anthropogenic source precursor chemicals the ability to predict may be much better.

1.5 Yes, inversion layers are important. We in California have a "mountain bowl" around Los Angeles, and a much bigger one in our Central Valley, where many the highest MDA8 ozone levels in the nation occur.

The discussion of these issues in the ISA Appendix 1 is highly detailed. Based on my limited knowledge the sections you refer to in your questions above seem generally accurate.

Exposure monitoring for ambient and indoor ozone is not an area where I have expertise, and so I am skipping most of your question on Appendix 2. In my judgment this appendix is overloaded with detail, instead of emphasizing the large differences between indoor ozone exposure with and without air conditioning, and ozone exposure in outdoor ambient air. Indoor exposure may be comparable to outdoor exposure on cool days with open windows. On warmer, higher outdoor ozone days, the indoor

levels may be ½ to about 1/20 the outdoor levels, with the lower levels in indoor space with air conditioning and filtration. These big differences for human exposure are not apparent in the text and tables. (The numbers I cite above are roughly consistent with Table 2-4.)

Regarding 2.4.1. Many people will prefer to avoid outdoor exposure and stay indoors in air conditioned space on extremely warm/hot/humid days. For some people, exercise outdoors even in extreme weather is essential. And for many lower income people, including children and elderly people, their homes, workplaces, and schools may not be air conditioned. Heat stress and lack of adequate hydration can bring on additional mortality and morbidity, independent of ozone exposure. I view this potential for confounding as a very important issue for interpreting the epidemiological studies. As one example, Paris, France is a modern city and not known for high levels of air pollution. The heat waves this summer (2019) have reportedly caused nearly 1500 deaths. A heat wave in Paris in 2003 killed about ten times as many (15,000): https://www.bbc.com/news/world-europe-49628275. We should recognize that persistent, stagnant hot air – a "heat wave" - can cause fatalities, independent of the effects of air pollution. And as you point out, such stagnant hot air days are often times of high ozone concentration levels.

Miscellaneous Questions(s)

Yes, continuing from the response above, I think assessing impacts on lower socioeconomic status (SES) populations is very important. Mortality is elevated in lower SES populations. Is this elevation from higher ozone exposure? Or is it from less medical care, poorer housing, and lack of air conditioned space at home and at work? These interacting factors should be examined so that confounding is minimized.

We need to help our lower SES populations, such as those people with lower incomes and their children. We do not want high numbers of deaths in heat waves, such as have occurred in Paris. French authorities claim they were better prepared in 2019 than in 2003 – yet a lot of people still died this year.

References not in the ISA or Questions from CASAC Members:

Richard B. Belzer and R. Jeffrey Lewis (2019), "The Practical Significance of Measurement Error in Pulmonary Function Testing Conducted in Research Settings," *Risk Analysis* **39**(10):2316-2328.