11-27-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC). These preliminary pre-meeting comments are from individual members of the Committee and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Preliminary Comments from Members of the CASAC on

EPA's *Integrated Review Plan for the Review of the Ozone National Ambient Air Quality Standards*

(External Review Draft – October 2018)

Received as of 11-27-18

Dr. James Boylan

Comments on Chapter 1 (Introduction)

The schedule presented on page 1-9 is very aggressive and allows for one draft of the IRP, one draft of the ISA, and one draft of the PA. Also, EPA is planning to incorporate the REA analysis into the PA. EPA should recognize the possibility that second drafts of these documents might be necessary after CASAC and the public review the first draft. In addition, the REA should not be included as part of the PA. Instead, the REA should be a stand-alone document that is reviewed by CASAC and the public prior to the release of the first draft of the PA. This will allow scientific review of risk and exposure metrics prior to developing policy recommendations. This review should not be tied to the schedule in Table 1-1 since getting high quality IRP, ISA, REA, and PA documents is much more important than meeting an arbitrary deadline.

Comments on Chapter 2 (Background)

Figure 2-2 should be updated with 2015-2017 NOx and VOC emissions. It is not clear in Figure 2-4 what the top and bottom black lines represent. Are they the 75/25 or 90/10 percentile values?

Comments on Chapter 3 (Approach for Review of the Primary and Secondary Standards)

Race and obesity should be considered as possible additional at-risk populations. Below is an excerpt from the CASAC review of EPA's "Risk and Exposure Assessment for the Review of the Primary National Ambient Air Quality Standard for Sulfur Oxides (External Review Draft - August 2017)". Although this comment was developed for the primary SO_2 standard, the same comment is appropriate for the primary ozone standard:

> *The prevalence of asthma varies by race/ethnicity and is highest in African-Americans. Asthma prevalence is also higher among obese individuals than in the general population. The CASAC therefore recommends that race and obesity be included as characteristics of the population, and levels of SO_2 exposure and risk of adverse effects associated with the current SO_2 standard be assessed in these sub-groups. The CASAC recognizes that detailed data for African-Americans and obese individuals may not be available, limiting the ability to include them in the risk assessment and exposure models in the manner that was used for other demographic variables. However, it is recommended that the agency use whatever data are available and suitable to assess exposure and risk influence by race and obesity. If it is not possible to include these variables in the analysis, then sensitivity analyses should be considered, and, at a minimum, the possibility*

> *of heterogeneity in associations across population subgroups and uncertainty should be considered as they relate to the margin of safety.*

The current form of the standard is discussed in Section 3.1.2.2.3. For the previous three ozone standards, the form has been the fourth-highest daily maximum 8-hour ozone average concentration, averaged over 3 years. The document discusses the findings that this form better represents the continuum of health effects associated with increasing ozone concentrations compared to the exceedance form of the previous 1-hour ozone standard. Consideration was given to the fifth-highest value and the use of a percentile-based form. In addition, it was recognized that this form of the standard provides stability with regard to implementation of the standard. However, the IRP does not discuss the possible use of an "integrated" form of the standard (e.g., average of 10 highest daily maximum 8-hour ozone average concentrations) which would provide a better representation of the continuum of health effects associated with increasing ozone concentrations. Typically, the higher end of the daily maximum 8-hour ozone average concentration distribution drives health effects at particular locations. The current form of the standard throws away the three highest concentrations (which typically would have the most significant health impacts) and ignores other potentially high concentrations beyond the fourth-highest daily maximum 8-hour ozone average concentration. As a result, a monitor that measures three high ozone values (e.g., 100, 95, 85 ppb) and the fourth-high value is 70 ppb, would have the same fourth-high value as another monitor which measures 70 ppb for each of its four highest concentrations. In addition, the remainder of the higher end of the daily maximum 8-hour ozone average concentration distribution is ignored (i.e., fifth-high, sixth-high, seventh-high, etc). An integrated form of the standard (e.g., 10-day average vs. fourth-highest value) would be able to better account for these higher concentrations as part of multi-day average of daily maximum 8-hour ozone average concentrations. EPA should compare the current form of the standard against various integrated forms of the standard to determine if the relationship is linear and if the current form of the standard is the best way to represent the continuum of health effects associated with increasing ozone concentrations. In addition, an integrated form of the standard would provide greater stability than the current form of the standard with regard to implementation of the standard.

Comments on Chapter 4 (Science Assessment)

For Table 4-2, it is unclear why only U.S. or Canadian populations are considered for short-term exposure and respiratory effects, short-term exposure and mortality, and long-term exposure and respiratory effects. It seems reasonable to include European and Australian populations.

Comments on Chapter 5 (Quantitative Risk and Exposure Assessment)

As stated in comments on Chapter 1, the REA should be a stand-alone document that is reviewed by CASAC and the public prior to the release of the first draft of the PA. This will allow scientific review of risk and exposure metrics prior to developing policy recommendations.

The HREA and WREA presented in the previous review were very comprehensive. The approach of assessing exposure and risks for air quality conditions associated with the existing standard and conditions associated with potential alternative standards is appropriate. The previous HREA included exposure-based analyses (based on controlled human exposure studies) and ambient air concentration-response relationships (based on air quality epidemiological studies). The exposure-based analysis included two approaches: (1) the comparison of estimated population-based ozone exposures experienced while at elevated exertion to benchmark concentrations and (2) lung function decrement (FEV). Both exposure-based risk analyses were performed in a set of 15 urban study areas, while the air quality epidemiologic-based risk analyses were performed for 12 of the 15 urban areas. The use of the APEX model (and CHAD database) is appropriate to simulate the movement of individuals through time and space and their activities. The use of HDDM is an appropriate tool for adjusting air quality to meet current and alternate standards.

In this review, there are newly available ambient air quality data that better reflect concentrations at or near the current standard, updated emissions data and air quality models, and updates to the exposure model to better estimate exposure-based risk. Regarding the epidemiological-based risk approach, EPA states that it is unlikely they will identify any newly available information, models, or tools outside of the updated estimation of ambient air quality. Given the expedited nature of this review, EPA plans to focus new analyses in this review on exposure-based risk analyses. Given the rapid timeline for this review, EPA would expect to focus on a streamlined set of study areas and air quality scenarios compared to the expansive set assessed in the last review. The potential reduction in the number of study areas and scenarios is of concern given that significant changes have occurred in ambient ozone concentrations and spatial patterns of high ozone concentrations (more local and less regional) since the last review. In addition, significant improvements have been made to the photochemical grid models and emission inventories. For these reasons, I believe it is appropriate to include the epidemiological-based risk approach in the current review. In addition, having a new epidemiological-based risk approach with the same ambient air quality monitoring data and modeling results will allow cross-comparison of exposure and risk results across multiple approaches and study areas.

On page 5-2, it is stated that the REA analyses are not generally intended to provide a comprehensive national assessment. However, EPA should make an attempt to estimate the percent and number of adults and children across the county demonstrating adverse health effects at the current standard and potential alternative standards.

Based on page 5-28, it appears that a new WREA will be developed and will focus on two sets of air quality monitoring analyses (Class I areas and monitoring sites nationally). Alternative W126 ozone standards should be evaluated and compared against the current and potential alternative primary ozone standards to determine if the primary standard is protective of the alternative secondary standard. If not, consideration should be given to a separate W126 secondary ozone standard (ppm-hrs).

Additional details for the HREA and WREA should be included in a Planning REA document. Details should include how model performance will be evaluated and how biases in the model will be accounted for in the REA. In addition, the detailed approach for combining modeled concentrations with ambient measurements to estimate exposure should be included.

Dr. Tony Cox

- **Section 4.3.2, p. 4-4, starting at line 20,** enumerates issues on which scientific information will be identified and evaluated. In addition to the issues already listed, the following issues (some of which are discussed later in Chapter 4 and other chapters) should also be included:

(a) Background levels of surface ozone in the US;

(b) Spatiotemporal trends in means and variances of background levels of O3 (both by seasons within years, and over the years);

(c) Spatiotemporal trends and forecasts for means and variances of O3 and of causally related pollutants and precursors in the US and in other relevant air sheds;

(d) Quantitative causal dependence of future O3 concentration distributions in inhaled air on future emissions levels;

(e) Quantitative apportionment of US surface ozone among contributing sources (natural, anthropogenic sources, transport into the US from Asia and elsewhere) to inform understanding of how changing US emissions levels and NAAQS for O3 would change concentrations of ozone in inhaled air in the US;

(f) Quantify dependence of O3 in inhaled air on emissions levels and atmospheric levels of other pollutants such as NOx;

(g) Quantify dependence of health effects of O3 on other causally relevant risk factors and pollutant levels to inform understanding of how changing O3 NAAQS or emissions in the US would change health effects in the US;

(h) Quantify how the concentration-response functions for O3 depends on the levels of other causally relevant factors (e.g., levels of other pollutants, co-morbidities, age, sex, income, and other causally relevant covariates);

(i) Results of accountability studies validating the effects of observed changes in O3 levels on observed health effects.

- **On p. 4-5, starting at line 6,** the IRP discusses EPA's structured frameworks for classifying the weight of available evidence for health and welfare effects using five levels, from causal relationship to not likely to be a causal relationship. The following refinements are needed to provide information essential for scientifically well-informed risk management decision-making and policy making.

(a) Specify the type of causation for which evidence is provided (e.g., associational, attributive, counterfactual/potential outcomes, predictive (e.g., Granger), structural, manipulative, mechanistic, or but-for causation). These are importantly different concepts. (For example, nicotine-stained fingers might be an associational cause and a predictive cause of lung cancer but not a manipulative cause, unless the only way to keep fingers unstained is not to smoke. Even then, they would be a manipulative cause but not a mechanistic causes of lung cancer.) The term "causal" is ambiguous until the specific type of causality being referred to is stated. To provide a sound basis for decision-making, evidence about manipulative causation is typically needed, describing how alternative decisions would affect outcomes over time (or outcome probabilities over time, if the effects are uncertain).

(b) Specify the type of causal effect for which evidence is provided. Epidemiologists distinguish among controlled direct effect (holding other causally relevant factors fixed at specified levels as exposure changes), natural direct effect (holding other causally relevant factors fixed at the levels they currently have as exposure is varied), total effect (allowing other causally relevant factors such as levels of co-pollutants or temperatures to change realistically as exposure is varied), indirect effect, mediated effect, and so forth. References to health "effects" of ozone should specify which types of causal effects are being referred to and what is assumed about the levels of other causally relevant factors as effects of different ozone concentrations are discussed.

(c) Quantify the fraction of each estimated concentration-response function that represents (manipulative) causation rather than other sources of association. Calling an entire exposure-response relationship (typically, an association) "causal" does not inform

decision-makers or the public *how much* or *what fraction* of it is causal, or how much of a specified (e.g., total or natural direct) effect in a population would be prevented by reducing or eliminating the exposure. This is essential information for scientifically well-informed decision-making. It should be provided in the ISA, along with uncertainty characterizations for the answers. Simply classifying the dependency of health or welfare effects on ozone levels as "causal" does not distinguish between situations in which differences in age and income explain 99.99% of observed differences in health effects, and differences in O3 exposures explain only 0.01%; and situations in which differences in O3 explain 100% of the observed differences in health effects. Such quantitative information is needed to support well-informed decisions. The classification system for causal determination should be updated to provide clear quantitative definitions of what the categories mean (e.g., is a relationship to be classified as "causal" if it is 1% explained by manipulative causation and 99% explained by non-causal factors such as confounding or coincident historical trends? What is the cutoff for calling a relationship "causal" if a fraction of it is explained by non-causal factors?) In addition, EPA should provide quantitative information about the fraction of adverse health effects in populations that would be prevented by reducing exposures.

- **On p. 4-18** there is a bullet list of questions considered in in assessing the scientific quality of studies on health and welfare effects. The following questions should also be considered:

(a) For observational studies, were relevant and valid comparison groups used?

(b) For studies based on quasi experimental designs, were threats to internal validity adequately addressed and resolved?

(c) Were plausible non-causal interpretations of concentration-response relationships convincingly refuted using relevant data?

(d) Were threats to external validity (generalizability) adequately addressed and resolved?

(e) Were estimated values of exposures clearly distinguished from true values of exposures throughout the data collection and analysis? Were measurement errors in exposures and covariates quantified and modeled, e.g., using appropriate errors-in-variables techniques?

(f) Were adjustment sets correctly identified and used to obtain unbiased estimates of specified total and direct causal effects of exposures on health?

(g) Do the analytic methods used provide adequate estimates and uncertainty intervals to quantify manipulative causal effects of changes in exposures on changes in health effects over time, given values of causally relevant covariates?

(h) Were causal transport formulas correctly identified and used to generalize the results of individual studies and to synthesize the results of multiple studies so that they can be applied to other populations and conditions?

(i) Do the analytic methods used provide adequate estimates and uncertainty intervals for manipulative causal effects of changes in exposures on changes in health effects over time in exposed populations?

(j) Was a thoroughly developed uncertainty characterization, as well as sensitivity analysis, provided for the analysis as a whole and for each major conclusion?

(k) Did the data analysis and modeling correctly and adequately quantify effects of model uncertainty on conclusions, e.g., using non-parametric model ensembles?

(l) Were potential latent variables adequately accounted for in the data analysis and modeling and addressed in the uncertainty characterization?

(m) Were effects of missing data adequately quantified and included in the uncertainty characterization (e.g., using techniques such as data augmentation or multiple imputation by chained equations)?

- **In addressing causal issues throughout Chapters 4 and 5,** EPA should distinguish clearly between association and causation, being careful not to conflate or combine them. The most valuable scientific information for decision and policy makers is often causal information describing what will happen if exposures levels are changed and how sure

we currently are about the answer. This requires addressing manipulative causation. It is not addressed by describing weaker forms of causation (e.g., associational, attributive, or predictive causation) or by discussing association without causation.

(a) References to an exposure-response "relationship," as in "How do results of recent studies expand understanding of **the relationship** between short term exposure to O3 and cardiovascular effects, such as ischemic heart disease, heart failure, or vascular effects?" (p. 4-27) should clearly specify that the "relationship" of interest is the *manipulative causal* relationship between exposure and health effects, quantifying how changing exposure changes risk of health effects (and how the answer depends on other variables).

(b) The specific causal effects of interest, e.g., total effect vs. natural or controlled direct effects, should also be clearly stated throughout.

(c) It should be made clear throughout that associations are of interest only if they help understand manipulative causation. For example, questions such as "To what extent is short-term exposure to O3 related to **or associated with** the progression of diabetes?" (p. 4-27) can be replaced with causal questions such as "How much do changes in short-term exposures to O3 change risk of progression of diabetes?" or "How would reducing short-term exposure to O3 change risk of progression of diabetes, and how does the answer depend on the levels of other factors?"

(d) The two association questions at the beginning of section 5.1 should be replaced by corresponding causal questions, so that "What are the nature and magnitude of exposures and health risks **associated with** air quality conditions just meeting the current standard?" becomes "What are the nature and magnitude of exposures and health risks **caused by** air quality conditions just meeting the current standard, and how much would they change if the standard were changed?" (Such questions can be answered by showing partial dependence plots and uncertainty intervals for the effect of the standard on exposures and health risks.) Likewise, "To what extent are the estimates of exposures and risks to at-risk populations **associated with** air quality

conditions just meeting the current standard reasonably judged important from a public health perspective?" can be replaced by "To what extent are the estimates of **changes in** exposures and risks to at-risk populations **caused by changes in** air quality conditions just meeting the current standard reasonably judged important from a public health perspective?"

(e) In many places in Chapter 5, the IRP refers to a "concentration-response relationships" without clearly distinguishing between associational and manipulative causal concentration-response relationships. To support sound science-based decisions, it is essential not to conflate these very different concepts. EPA should provide quantitative information specifically on manipulative causal concentration-response functions (and how, if at all, they depend on other direct causes of health effects). For example, p. 5-6 states that "Another type of analysis that has been used is a risk approach based on ambient air **concentration-response relationships** from air quality epidemiological studies." These relationships are usually associational. It is important to consider manipulative causal relationships instead to support scientifically well-informed policy decisions.

(f) Similarly, p. 5-15 notes that "The risk estimates were derived using the EPA's Environmental Benefits Mapping and Analysis Program (BenMAP, version 4.0) for the specified health outcomes and locations with the C-R information from the studies cited for those outcomes and other relevant information for the analysis." However, the BenMAP software does not provide manipulative causal C-R models. The BenMAP documentation (Appendix C: Deriving Health Impact Functions, www.epa.gov/sites/production/files/2015-04/documents/benmap-ce_user_manual_appendices_march_2015.pdf) specifies that it uses associational methods (relative risks and regression equations) for estimated the health impact functions. Different methods are needed to quantify causal functions (Pearl 2009, Causal Inference in Statistics: An Overview. Statistics Surveys Vol. 3 (2009) 96–146 DOI: 10.1214/09-SS057; Cox 2018, Modernizing the Bradford Hill criteria for

assessing causal relationships in observational data. Crit Rev Toxicol. 2018 Nov 15:1-31. doi: 10.1080/10408444.2018.1518404). Indeed, the BenMAP documentation only discusses causality for PM2.5 (Appendix E) and not ozone; for PM.5, it states about causality that "the continuous parametric distributions specified were inconsistent with the causality likelihoods provided by these experts. Because there was no way to reconcile this, we chose to interpret the distributions of these experts as unconditional and ignore the additional information on the likelihood of causality." Thus, it appears useful and important to update BenMAP to include validated manipulative causal health impact functions (e.g., from accountability studies) before using them to generate risk estimates for causal impacts on human health of changes in ozone exposures or standards.

- **Throughout Chapters 4 and 5,** it should be made clear that the causal questions and answers of greatest relevance and value to policy makers are quantitative, not simply qualitative or categorical. For example, the question on p. 4-25, "Does the evidence base from recent studies contain new information to support or call into question the causality determinations made for relationships between O3 exposure and various health and welfare effects in the 2013 ISA?" asks about whether recent studies should lead to reclassifications of the causal labels assigned to exposure-response "relationships" (probably meaning associations). (Here and throughout, wherever "relationship" is used, the specific relationship intended, such as a direct causal relationship or a total causal relationship between changes in O3 exposures and changes in health effects should be stated.) A more quantitative question is: "Does the evidence base from recent studies contain new information that allows updated estimates of the total causal effects of changes in O3 exposures on various health and welfare effects in the 2013 ISA?"

Dr. Mark Frampton

1. Strengths. The draft ozone IRP represents a thorough and detailed review of the approaches and principles that will be applied to the preparation of the ozone ISA, and of the risk and policy assessments. The IRP is logically organized and clearly written. The strategies for literature searches include traditional approaches with broad search terms, and advanced computer algorithms, and is likely to retrieve all data of relevance since the last review. The stages of literature selection and review, and their criteria, are clearly defined.

2. Organization. Section 4.2 of the draft IRP describes a major change from prior NAAQS reviews in the organization of the ISA: The main body of the ISA will now be an "integrated synthesis", with the reviews of the scientific studies that form the basis for the causality and risk assessments relegated to appendices. Appendices traditionally provide supplemental information. Reviews of the relevant literature on ozone health and welfare effects are the "meat" of the ISA, and should not be considered supplemental. The scientific data that form the basis for the NAAQS should remain "front and center" in the main body of the document.

3. Study quality. The IRP includes an excellent and thorough description of the methods to be used for assessing study quality in section 4.3.6. However, there is a need to address how these quality assessments will be utilized in the review process. Will there be any attempt to assign a quality rating to each study? Or will the assessment just be used to highlight strengths and weaknesses in study descriptions? Are studies eliminated from consideration based on the quality assessment? It is admittedly difficult to quantify study quality across a variety of disciplines and approaches, but more needs to be said about how quality will be taken into consideration in the process. These considerations are relevant to all ISAs, and could be incorporated into the ISA Preamble.

4. Divergent effect thresholds in clinical and epidemiological studies. The ISA will use results from clinical, epidemiology, and toxicology studies to determine health risks, as in previous ISAs, and this is clearly described in the IRP. One issue that should be introduced in the IRP, to be considered in the ISA and risk assessments, is the divergence between epidemiology and clinical studies in the ozone concentrations at which health effects are observed. As mentioned in the draft IRP, the concentration threshold for pulmonary function effects in clinical studies appears to be at or near 60 ppb in young healthy subjects exposed for more than 6 hours with extensive exercise. Epidemiology studies show associations between acute lung function decrements and respiratory morbidity at ozone concentrations well below this, with concentration response curves extending through 0 ppb, suggesting no threshold for effects. The reasons for this are debatable and likely diverse, including differences in exposure durations, populations being studied, and effects of co-pollutants. However one important consideration is the possibility that ambient ozone is a surrogate for other ambient oxidant pollutants that track

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with ozone, and therefore cannot be adjusted for in multi-pollutant models. These oxidant
pollutants would not be part of the exposure in clinical studies of ozone. This has important
policy implications, given that the ozone standard applies to "ozone and related oxidants". Thus
relying primarily on ozone clinical studies in the risk assessment could underestimate the risks of
exposure to ambient ozone and the oxidants that track with it. As currently written, the IRP
appears to assume that "ozone" exposures in clinical studies and in ambient air represent the
same entity. It is possible they are not the same, and that the health effects associated with
ambient ozone concentrations include effects from additional oxidant species that are not
measured. These considerations would perhaps be most appropriate for Chapter 5, Quantitative
Risk and Exposure Assessments.

5. Table 4.2. In the PECOS statements for epidemiology studies, it is not clear why the
populations are limited, for example, to US and Canadian for short-term mortality and
respiratory effects.

Minor Comments:

The ATS document, "What constitutes an adverse effect of air pollution?", is referenced
repeatedly in the IRP. This document has been extensively revised and updated, with
considerations of health outcomes beyond lung function, and this should be acknowledged/cited.
[Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. A joint
ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An
analytical framework. Eur Respir J. 2017; 49 https://doi.org/10.1183/13993003.00419-2016]

A list of abbreviations would be helpful, especially for members of the public who may be new
to these processes and their terminology.

Dr. Sabine Lange

Comments on Chapter 6 - Policy Assessment and Chapter 7 - Proposed and Final Decisions

- The EPA's plans to combine the REA and the PA should be reflected in Chapter 6. There is currently no verbiage in this chapter that would tell the reader that the REA and PA will be combined into one document.

- Page 2 of Chapter 6 states "The provisions do not require that standards be set at a zero-risk level, but rather at a level that avoids unacceptable risks to public health, including the health of sensitive groups." A definition or discussion of "unacceptable risks to public health" should be included in this document. This is particularly important because prior ozone reviews have assumed that there are effects down to zero concentrations, even for very serious and potentially "unacceptable" risks like mortality.

- Chapter 7 states that, for the proposed rule, "At the time of publication of the notice of the proposed action, all materials on which the proposal is based are made available in the public docket for the review." There should be more information provided about what is meant by "all the materials on which the proposal is based". Does this refer to the assessment documents, or to the underlying data and studies, or the models, upon which the proposal is based?

- Other than the points above, Chapters 6 and 7 adequately described the role and process for developing the policy assessment, and for EPA's proposed and final rulemakings. The chapters are well organized, clear, and contain appropriate descriptions of explanatory material.

Comments on Chapter 1

- Section 1.1 discusses the CAA's instructions that CASAC should provide advice on adverse health effects from various attainment and maintenance strategies. EPA notes that this may be more relevant to the implementation rather than the standard-setting process. However, footnote 6 describes how some of the information about adverse health effects may be of use for standard setting, as per the supreme court. It would be helpful if EPA clarified their plans for seeking CASAC's advice on adverse health effects.

- The description of the accelerated review of the Ozone NAAQS in Chapter 1 is useful for understanding how the EPA plans to meet the CAA's statutory 5-year deadline. However, the EPA should further discuss how they intend to use previous documents in the review process to inform future documents – i.e. informing the PA/REA with the conclusions

and feedback from the ISA. For example, it seems with this new schedule that the risk modeling would have to take place at the same time as the ISA assessments, but the ISA assessment of aspects like the shape of the C-R function can fundamentally impact the risk modeling.

- Even though the EPA is planning to stream-line the ozone review and the ozone ISA, they should ensure that there is still a thorough review of the literature that accurately reflects the latest scientific knowledge.

Comments on Chapter 2

- This IRP should include explicit, *a priori* details about how the systematic literature review is being conducted, what the exclusion and inclusion criteria are, and what the study quality considerations are. There should be enough detail to replicate the review, as would be expected of any other systematic review. The more methodological detail that is presented *a priori*, the more transparent and objective the review.
- In this IRP, the EPA should provide clear, objective specifications about how they will weigh and integrate evidence for causality determinations. For example, the highest causal determination requires "reasonable confidence" that bias, chance, and confounding have been ruled out of the association. What is the definition for "reasonable confidence"? This requires, at minimum, that statistical significance be taken into account, and that confounders in addition to just copollutants have been considered. What is EPA's plan if there is mixed evidence (ie. Some showing positive effects, some null or negative)?

Comments on Chapter 3

- EPA should provide more detailed information about how the REA will be conducted. There should also be an explicit plan for quantitative uncertainty analysis.

Comments on Chapter 4

- PECOS statements for epidemiologic studies (Table 4-2) – Is every population of interest for the non-respiratory, CV, or mortality effects? Even ones with very different air pollution concentrations and mixtures than the US (e.g. India, China)?
- Evidence integration (4.3.7) – For the endpoints that EPA has already deemed to be causally-related to ozone exposure (e.g. short-term respiratory effects), EPA states that they will focus on those aspects of studies that could decrease uncertainty, such as the shape of the C-R function, copollutant confounding information, etc. For these data-rich endpoints, it would be valuable to move beyond a narrative review of the available data and studies, towards a hypothesis-testing approach for analyzing the data. For example,

the EPA often states that exposure measurement error biases effect estimates towards the null. Therefore, one would hypothesize that studies with better exposure estimates would have larger effect estimates with narrower confidence intervals, and this could be explored across the array of available studies to look for the overall pattern. Another example is total mortality – one would expect that ozone doesn't contribute to every type of mortality, so there should be some cause-specific mortality estimates (supported by biological plausibility) that have higher effect estimates and tighter confidence intervals than the total mortality results. These types of analyses and hypothesis tests would strengthen EPA's conclusions about the strength of the evidence for any particular endpoint.

- Section 4.4 – EPA notes that controlled human exposure and animal toxicology studies that demonstrate similar effects at relevant ozone exposures may demonstrate an independent effect of ozone exposure and provide coherence with epidemiologic evidence. EPA should, when looking for coherence at "relevant O3 exposures", discuss the exposure concentrations used in the controlled human exposure or animal toxicology studies, and determine how they compare to the likely personal exposures of people in epidemiology studies (e.g. using human-equivalent concentrations for the animal studies). Coherence is not necessarily established if a similar effect occurs in an animal toxicology study at 2 ppm, as occurs in an epidemiology study at 20 ppb (and with ozone, the personal exposure is likely to be less than the ambient exposure).

- Specific Science Questions: "Does new evidence confirm or extend biological plausibility of O3-related health effects?" This question doesn't leave open the possibility that a previously identified pathway of biological plausibility has been disproved by new data. The scientific questions that are asked shouldn't assume a pre-determined outcome. Another example: "To what extent does new literature support a biologically plausible relationship between long-term O3 exposures and nervous system effects (e.g., cognitive decline and autism)?" EPA should specify what they will do with the data that does not support a biologically plausible relationship. The same is true for causal determinations.

Comments on the Appendix

- The appendix is labeled as Appendix 5A – it probably should be labeled differently.

Dr. Timothy E. Lewis

Comments on Chapter 3 – Key Policy-Relevant Issues for the Current Review: Approach for the Review of the Primary and Secondary Standards

General

The approach seems reasonable. It may be standard format in all IRP and ISA, but I find that presenting the historical background is very helpful. It's good to know how the Agency got to where they are in their decision making. The historical background was well presented and clear.

Primary Standard

Lowering the standard to 70 ppb was well justified in the previous review. Now the new assessment should present evidence that this new standard is providing the requisite protection to sensitive populations.

Asthma seems to be a major factor that characterizes one of the sensitive populations. I'm not sure of the cause of asthma, whether it is idiopathic or related to allergen exposure or perhaps other air pollutants. It should be explored whether the asthmatic population is created by air pollution of some sort. I seem to recall greater numbers of asthma cases in rural areas near contained animal feeding operations (CAFOs). The ammonia released from CAFOs may be the cause or exacerbate the ailment.

Due to long-range transport and biogenic VOC precursors ozone levels in rural areas could be higher than in urban areas where EPA focused on the asthmatic population. Given that there may be asthmatic populations in rural areas downwind of CAFOs shouldn't the Agency also examine rural areas as well?

It appears that all controlled human exposure studies use ozone alone, if I understand it correctly. Would exposure to the complete mix of total oxidants in the ambient air yield similar exposure thresholds?

Secondary Standard

I'm delighted to read that the Agency will be considering other photochemical oxidants besides ozone.

I did not see mention of ozone effects on materials. Has this been put to rest and no longer considered?

I trust that the Agency will reexamine the validity of using tree seedlings as a surrogate or proxy for the full array of vegetation-related ozone effects.

I thought NCLAN was prima facia evidence that ozone-induced crop loss was firmly established and found to be significant. Footnote on page 3-34 attempts to explain the reasoning.

Comments on Chapter 4 – Science Assessment

The purpose of the ISA is spelled out clearly and the organization of it seems appropriate and logical.

The focus of the ISA and related documents has been on ozone. Footnote on Page 4-4 mentions the paucity of data on other photochemical oxidants as a justification for focusing on ozone. Does that justify not attempting to take a harder look at other oxidants. Perhaps more monitoring sites need to be equipped with instrumentation for measuring other oxidants.

Has the larger body of evidence on welfare effects since the last ISA been due to increased research funded by EPA to gather the information necessary to address uncertainties and limitations found in the last ISA?

Is the funding source considered as a criterion for inclusion or exclusion in the ISA?

Are non-English articles included? How are translations assessed for accuracy?

The development of HERO is a good idea. I registered and am awaiting approval for access.

Search strategies used in the development of the science basis for the ISA have precision and recall targets. How are these set and measured?

Again, in the ISA IRP I see no mention of an assessment of ozone-induced (or other oxidant) effects on materials. Total oxidant concentration may play more of a role on materials rather than just ozone.

Table 4-1 does not present "study design" in the PECOS approach.

In the literature search are aquatic effects picked up? For example, Wayne Swank's finding of higher nitrate being exported out of the Cowetta National Forest watershed in the spring following a high ozone summer. Proposed that ozone decreased photosynthesis, reduced nutrient uptake, and led to excess nitrate in the system during spring rains. Have increased stream temperatures been found after a decrease in riparian canopy cover due to premature leaf senescence from ozone exposure? Disruptions of the thermal regime of aquatic systems can have impacts on the timing of life history events.

The ISA uses secondary data that is integrated or summarized from multiple sources to create new figures, tables, etc. These are subject to rigorous QA/QC measures to ensure accuracy. There is more to QA/QC than just accuracy. Who assesses these products for quality? How are they assessed?

Ecological endpoints are to be reexamined in the next ISA. Are ecosystem goods and services assessed? Are non-monetary values assessed?

Other criterial air pollutants may play a role in background ozone. For example, increased PM can increase atmospheric turbidity and conductivity, which in turn can increase the frequency of cloud-to-ground lightening, which in turn can increase the number of fires.

Dr. Corey Masuca

Comments on Chapter 1 – Introduction and Chapter 2 - Background

Overall organization, clarity and appropriate description of introductory, background and explanatory material:

<u>*Chapters 1 Introduction and 2 Background:*</u>

- *Chapter 1 summarizes the legislative requirements (section 1.1), general NAAQS review process (section 1.2) and specific process and projected timeline for this review (section 1.3).*
- *Chapter 2 summarizes the history of O3 NAAQS reviews (section 2.1), describes the O3 air monitoring requirements (section 2.2.1), and summarizes the data analysis performed for comparison to the standards (section 2.2.2). Section 2.3.4 also provides an overview of current O3 air quality and plans for further characterization in this review.*

Overall, I found the chapters to be well-written and they provided an adequate background for the introductory information and the development of the draft IRP. They cover the basics of what is required, what is expected, and are fairly consistent with previous IRPs.

Comments on Other Chapters

In general, I think that there probably needs to some light discussion around the availability of NO2 Near-Road data and its potential relation(ship) to ozone formation. A significant portion of NO2 data was not available during the previous process of setting the previous 2008 ozone standard. I know many state and local air agencies, including ours, started monitoring for NO2 Near-Road Concentrations back in 2013.

Dr. Steven Packham

These Draft Consultative Comments (Comments) are submitted in preparation for a Clean Air Science Advisory Committee (CASAC) teleconference scheduled for November 29, 2018 with representatives of the U. S. Environmental Protection Agency's (EPA) Office of Air Quality Planning and Standards (OAQPS) and its National Center for Environmental Assessment (NCEA). CASAC chairman, Dr. Anthony Cox, has asked that I lead a discussion in the teleconference on a review of the primary standard.[1]

In this context, it seems appropriate to clarify for teleconference participants what the following comments are; and what they are not. They are not editorial comments, nor are they criticisms of OAQPS or NCEA's work product. The draft IRP is a reasonable and fair representation of the manner in which the Agency undertakes its statutory five-year review of the National Ambient Air Quality Standards (NAAQS).

The draft comments presented here are, however, intended to offer observations on what appears to be certain predicate assumptions that have dominated and defined the Agency's approach to integrating scientific knowledge over the last twenty years, and to introduce facts and opinions that this Member holds to be substantive to a reasonable degree of scientific certainty.

And lastly, it's the intent and hope that the brief comments being submitted here will provide the participants of the November 29th teleconference a glimpse into the submitter's philosophy of science,[2] and how the science of toxicology and a knowledge of human physiology might add regulatory value to the draft IRP and the Integrated Science Assessment (ISA) being planned in the current review-cycle of the ozone NAAQS.

Comments:

Causation, adverse health effects and margin of safety: The draft IRP is generally weak in anticipating contributions that could be made from including the sciences of toxicology and respiratory physiology. The word *toxicology* is only found a total of six (6) times in the draft IRP. There is a wealth of data to be found in textbooks such as Handbook of Human Toxicology by Edward J. Massaro and Hayes Principles and Method of Toxicology. In addition there is a huge body of published literature including the hundreds of studies cited in previous EPA criteria documents, specifically the 1986 criteria.

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[1] *Integrated Review Plan for the Ozone National Ambient Air Quality Standards, External Review Draft* (draft IRP). Chapter 3, Section 3.1.
[2] https://en.m.wikipedia.org/wiki/Karl_Popper

11-27-18 Preliminary Draft Comments from Members of the Clean Air Scientific Advisory Committee (CASAC).
These preliminary pre-meeting comments are from individual members of the Committee and do not represent
CASAC consensus comments nor EPA policy. Do not cite or quote.

The draft IRP also seems to be ignoring what is known about physiological thresholds and known limitations of ozone's oxidative threat to the surface areas of the respiratory airways and pulmonary alveoli. Current science does not suggest that ozone is a threat to making Humans an endangered species; but it does document with absolute certainty that tropospheric ozone is an environmental stressor that in the absence of medical intervention can be lethal to premature infants.

The truth about ozone's mechanisms of causation, its margin of safety and what constitutes an ozone induced adverse health effect must lay somewhere between these two facts.

FEV1[3] and Ozone NAAQS: The first photochemical-ozone primary and secondary standard was promulgated April 30, 1971. It had a 1-hour *Averaging Time*, a concentration *Level* value of 0.08 ppm and a *Form* of "not to exceed more than one hour per year". The 1979 primary standard and secondary standard also featured an *Averaging Time* of 1-hour, but the concentration *Level* was relaxed to 0.12 ppm, and the *Form* became, "an expected number of days per year with a maximum hourly average concentration greater than 0.12 ppm, equal to or less than 1."

The fact that the 1979 standard remained unchanged for eighteen years is interesting.[4] A few details about the Toxicology Effects of Ozone section in the 1986 criteria are worth noting.[5] It had over 500 references. Its Summary Chapter[6] included section on Regional Dosimetry in the respiratory tract,[7] and Effects of ozone on the respiratory tract.[8] It included sub-sections on morphological effects, pulmonary function, biochemical effects, host defense mechanisms, and tolerance. Each section and sub-section presented quantitative dose response information consistent with the existence dose-dependent thresholds at exposure concentrations below 100 ppb.

The 1986 criteria Summary may still represent one of the most valuable sources for the development of experimentally testable research hypotheses for margins of safety, adverse health effects, and dose depended causal mechanisms.

 In considering the need for a revision of the previous standard an array of physiological responses, including FEV1, are characterized as being given primary consideration by the

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[3] FEV1 means Forced Exhalation Volume in one second.
[4] Table of Historical Ozone National Ambient Air Quality Standards (NAAQS)
https://www.epa.gov/ozone-pollution/table-historical-ozone-national-ambient-air-quality-standards-naaqs
[5] U. S. EPA Air Quality Criteria for Ozone and Other Photochemical Oxidants Volume IV of V Toxicological Effects of Ozone and other Photochemical Oxidants. Environmental Criteria and Assessment Office. Washington, D. C. 20460. EPA/600/84/020dF August 1986.
[6] Ibid. (pages 9-217 – 9-256, sans References)
[7] Ibid. (pages 9-218 – 9-220)
[8] Ibid. (pages 9-221 – 9-243)

Administrator.[9] We should keep in mind the historical development of FEV1 and its clinical use in the diagnoses of respiratory disease conditions and to track the progression of respiratory conditions to help guide doctors develop treatment strategies. The ISA typically involves review panels comprised of scientists from a variety of scientific disciplines. Most of these scientists and technical experts may know that FEV1 is a measure of a person's forced exhaled volume in 1-second. But, they may not appreciate the fact that one can't consider the FEV1 in isolation. What's also important is the physiology and anatomy of what the tests are measuring and how one decides what's normal and what's abnormal.

A reduction in FEV1, as used in ozone exposure research involving healthy humans could be an indication of a protective autonomic reflex being exerted on the person's cognitively forced exhalation through the voluntary nervous system. The well documented increase in respiratory rate with an accompanying reduction in tidal volume is consistent with a protective-reflex hypothesis.

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[9] *Integrated Review Plan for the Ozone National Ambient Air Quality Standards, External Review Draft (draft IRP,* Chapter 3, Sub-section 3.1.2.1: Considering the Need for Revision, page 3-10.