UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

December 10, 2018

EPA-CASAC-19-001

The Honorable Andrew R. Wheeler
Acting Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Consultation on the EPA's *Integrated Review Plan for the Review of the Ozone National Ambient Air Quality Standards (External Review Draft – October 2018)*

Dear Acting Administrator Wheeler:

EPA's Clean Air Scientific Advisory Committee (CASAC) held a public teleconference on November 29, 2018, to conduct a consultation with EPA staff on the EPA's *Integrated Review Plan for the Review of the Ozone National Ambient Air Quality Standards (External Review Draft – October 2018).*

The Science Advisory Board Staff Office has developed the consultation as a mechanism to provide individual expert comments for the EPA's consideration early in the implementation of a project or action. A consultation is conducted under the normal requirements of the Federal Advisory Committee Act (FACA), as amended (5 U.S.C., App.), which include advance notice of the public meeting in the Federal Register. No consensus report is provided to the EPA because no consensus advice is given. The individual CASAC members' written comments are provided in Enclosure A.

We thank the EPA for the opportunity to provide advice early in the Agency's review of the Ozone National Ambient Air Quality Standards.

Sincerely,

/s/

Dr. Louis Anthony Cox, Jr., Chair
Clean Air Scientific Advisory Committee

Enclosure

NOTICE

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

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

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Enclosure A

Individual Comments by CASAC Members
on the EPA's *Integrated Review Plan for the Review of the Ozone National Ambient Air Quality Standards (External Review Draft – October 2018)*

Dr. James Boylan

General Comment

I recommend that EPA form an Ozone Review Panel. I believe that an Ozone Review Panel would provide the 7-member chartered CASAC with additional insight and expertise to allow for a more thorough and in-depth review of the relevant science and policy documents. My experience on the most recent SO_2 Review Panel has shown me the importance and value of having multiple independent experts who are at the leading edge of research in their respective fields thoroughly reviewing each Chapter.

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 drafts. 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 strictly tied to the schedule in Table 1-1 since getting high quality IRP, ISA, REA, and PA documents is much more important than meeting the statutory deadline.

Comments on Chapter 2 – Background

Figure 2-2 should be updated to include 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).

Conceptually, an "integrated" form of the standard should 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. 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. This means that the entire ozone season is characterized by a single 8-hour average ozone measurement. 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, eighth-high, ninth-high, and tenth-high). 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 a multi-day average of daily maximum 8-hour ozone average 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.

EPA should compare the current form of the standard against various integrated forms of the standard to determine if the relationship is linear (r^2 near 1.00) and if the current form of the standard is appropriate for representing the continuum of health effects associated with increasing ozone concentrations.

Georgia EPD examined the current form of the standard against various integrated forms of the standard (average of the top 4 and average of the top 10 daily maximum 8-hour ozone average concentrations) at all 23 ozone monitors in the state of Georgia for 2013-2018. Comparisons were made for annual values (2013-2018) and 3-year design values (2015-2018). The ozone design value r^2 for the current form of the standard vs. the average of the top 4 daily maximum 8-hour ozone average concentrations was 0.963 (Figure 1). The ozone design value r^2 for the current form of the standard vs. the average of the top 10 daily maximum 8-hour ozone average concentrations was 0.979 (Figure 2). This indicates that the current form of the standard is appropriate to represent the upper part of the ozone concentration distribution in Georgia. A similar type of analysis should be performed for the entire country (either

state-by-state or region-by-region) to determine if the current form of the ozone standard is appropriate nation-wide.

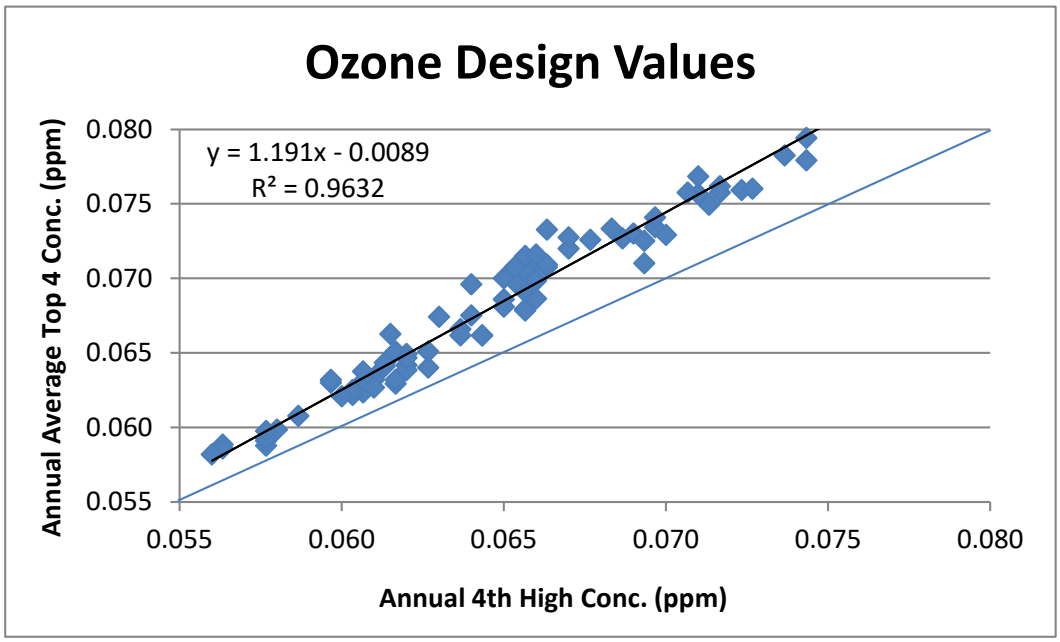

Figure 1. Comparison of the 3-year ozone design values (2015-2018) using the annual 4th high daily maximum 8-hour ozone average concentration vs. the annual average of the top 4 daily maximum 8-hour ozone average concentrations.

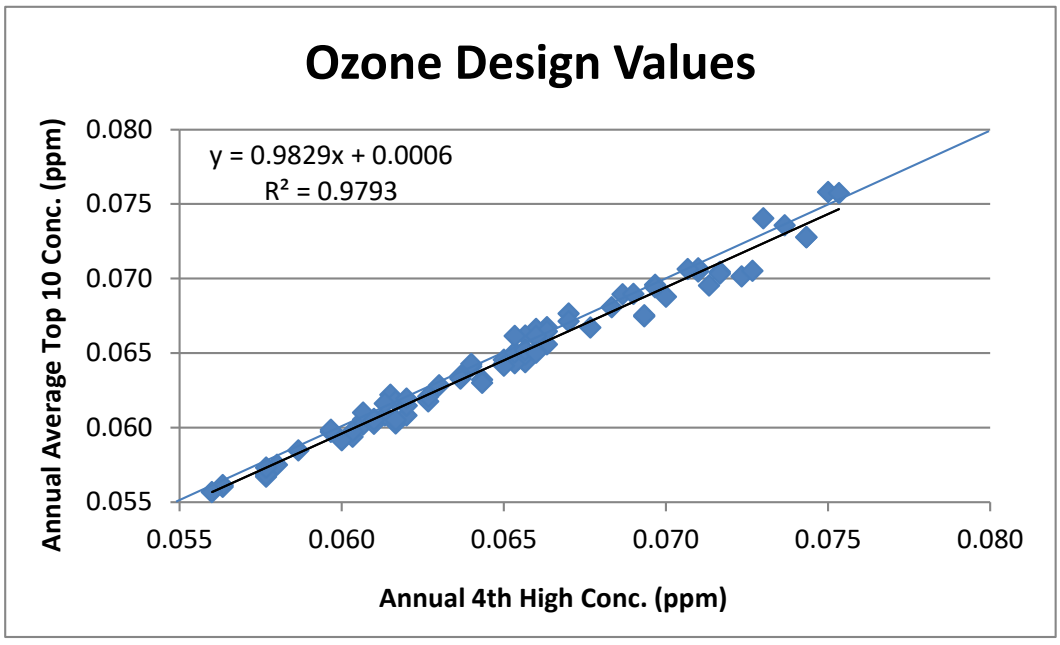

Figure 2. Comparison of the 3-year ozone design values (2015-2018) using the annual 4th high daily maximum 8-hour ozone average concentration vs. the annual average of the top 10 daily maximum 8-hour ozone average concentrations.

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. If not, reasons should be included for excluding these studies.

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 epidemiological-based risk analyses were performed for 12 of the 15 urban areas. The use of the latest version of the CMAQ or CAMx is appropriate for photochemical grid modeling. 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 REA Planning document. Details should include how model performance will be evaluated and how biases in the model and model uncertainty 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.

Editorial Comments

Page 4-2, line 14: "Thus, the integrated synthesis focus will make the ISA more concise than in the past, improve its clarify and also its focus on policy-relevant scientific information and analysis; the ISA scope, as addressed in section 4.3.2 is also more focused than in past ISAs (e.g., as discussed in Pruitt [2018])." Change "clarify" to "clarity".

Page 4-21, line 32: "Therefore, the peer input review is different than what will be provided by the Clean Air Scientific Advisory Committee (CASAC) and the public following the release of the completed 1st draft ISA.," Remove comma at the end of the sentence.

Page 4-29, line 7: "The NAAQS are intended to protect public health with an adequate margin of safety, including protection for the for populations or lifestages potentially at increased risk for O3-related health effects." Change "for the for populations" to "for the populations".

Page 4-30, line 17, "Decreased growth at the plant scale has been well established for several decades and may translate to damages the stand and then ecosystem scales." Add "at" before "the stand and then ecosystem scales."

Page 5-11, line 27, "Exposures at 80 ppb O_3 resulted in larger lung function decrements than following exposures to 60 or 70 ppb, in addition to an increase in airway inflammation, increased respiratory symptoms, increased airway responsiveness, and decreased resistance to other respiratory (section 3.1.2.1, above)." Add "effects" after "respiratory".

- **Section 4.3.2, p. 4-4, starting at line 20,** enumerates issues on which scientific information will be identified and evaluated. Scientific information should also be identified and evaluated on the following issues, some of which are discussed later in the IRP. Explicitly including them in the list of in-scope issues in this part of Section 4.3.2 will help to prepare for discussions in later chapters. The final IRP should address each of these topics. It might be useful to refer in Section 4.3.2 to where each topic is discussed in the rest of the IRP.

(a) 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. This will complement the identification of sources (issue 1 in the current Draft IRP) with quantitative information on source apportionment.

(b) Spatiotemporal trends in means and variances of background levels of O3 (both by seasons within years, and over the years). Note: Some public comments argued that, in Dr. Rizzo's words, "The question on background ozone inappropriately encourages placing it as a factor in the setting of the standard itself." Although inappropriate use of the information should certainly be avoided, understanding how changes in the current NAAQS would change the means and variances (or, more generally, the conditional probability distributions) of exposures received over time is important for assessing the public health consequences of alternative decisions about NAAQS revisions. Quantifying the contributions of background levels of O3 to total O3 exposure remains important insofar as it can help inform understanding of how different changes in the current NAAQS would affect the distributions of exposures.

(c) Spatiotemporal trends and forecasts for means and variances of O3 in the US and of causally related pollutants and precursor.

(d) Quantitative causal dependence of O3 concentration distributions in inhaled air on emissions levels and levels of other causally relevant factors such as precursors and sociodemographic covariates. Quantifying the joint causal dependence of the O3 concentration distributions on multiple causal factors will help to clarify its marginal dependence on each specific factors, such as changes in emissions levels. A directed acyclic graph (DAG) model with a conditional probability table (CPT) or conditional probability model for O3 levels given levels of causally relevant factors is one way to organize and present this multivariate dependence information. Technical references for DAG modeling in epidemiology and risk assessment include the following:

  - Brewer LE, Wright JM, Rice G, Neas L, Teuschler L. Causal inference in cumulative risk assessment: The roles of directed acyclic graphs. Environ Int. 2017 May;102:30-41. doi: 10.1016/j.envint.2016.12.005.
  - Evans D, Chaix B, Lobbedez T, Verger C, Flahault A. Combining directed acyclic graphs and the change-in-estimate procedure as a novel approach to adjustment-variable selection in epidemiology. BMC Med Res Methodol. 2012 Oct 11;12:156. doi: 10.1186/1471-2288-12-156.
  - Fleischer NL, Diez Roux AV. Using directed acyclic graphs to guide analyses of neighbourhood health effects: an introduction. J Epidemiol Community Health. 2008 Sep;62(9):842-6. doi: 10.1136/jech.2007.067371.

- Glymour MM, Greenland S. Causal diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2008:183– 209.
- Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10:37–48.
- Oates CJ, Kasza J, Simpson JA, Forbes AB. Repair of Partly Misspecified Causal Diagrams. Epidemiology. 2017 Jul;28(4):548-552. doi: 10.1097/EDE.0000000000000659.

Technical references for DAG and causal graph modeling in toxicology and systems biology include the following:

- Lagani V, Triantafillou S, Ball G, Tegnér J, Tsamardinos I. (2016) Probabilistic Computational Causal Discovery for Systems Biology. Chapter 2 in L. Geris and D. Gomez-Cabrero (Eds.), Uncertainty in Biology: A Computational Modeling Approach. Springer International Publishing.
- Triantafillou S, Tsamardinos I. Constraint-based causal discovery from multiple interventions over overlapping variable sets. Journal of Machine Learning Research 16 (2015) 2147-2205
- Boué S, Talikka M, Westra JW, et al. Causal biological network database: a comprehensive platform of causal biological network models focused on the pulmonary and vascular systems. Database: The Journal of Biological Databases and Curation. 2015; 2015:bav030. doi:10.1093/database/bav030.
- There are also numerous more specialized methods for causal graph modeling of gene regulatory networks; see e.g., Chang R, Karr JR, Schadt EE. Causal inference in biology networks with integrated belief propagation. Pac Symp Biocomput. 2015:359-70.

(e) Quantitative dependence of O3 in inhaled air on emissions levels and atmospheric levels of other pollutants such as NOx, e.g., using partial dependence plots for their total or direct effects on the conditional probability distribution of O3. Technical references on partial dependence plots include the following:

- Cox LA Jr.(2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. Nov 15:1-31. doi: 10.1080/10408444.2018.1518404
- Greenwell BM. (2017) pdp: An R Package for Constructing Partial Dependence Plots. The R Journal. Jun 9(1): 421-436. ISSN 2073-485.

(f) Quantitative 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.

(g) Definition of "the independent effect of O3 exposure on health and welfare" (issue 5 in the current list) and its relation to standard epidemiological concepts such as pure or natural direct effects and controlled direct effects.

(h) Definition of adverse health effects and clear distinction between harmful and non-harmful (or adverse and non-adverse) physiological responses to O3 exposures.

(i) Relevance of observations of changes in controlled human exposure studies for inferring harmful or adverse effects in people under real-world exposure conditions.

(j) Evidence and mechanisms for exposure concentration thresholds for adverse health effects of exposures to ozone in inhaled air under real-world conditions.
(k) Effects of repeated and prolonged exposures, including cumulative harm and adaptation to repeated or prolonged exposures.
(l) Quantitative dependence of manipulative causal concentration-response functions for O3 on the levels of other causally relevant factors (e.g., levels of other pollutants, co-morbidities, age, sex, income, and other causally relevant covariates). One way to display the results is via causal partial dependence plot for the natural direct effect of O3 on health outcomes, given the joint distribution of other factors in an exposed population or sub-populations defined by specifying levels of other factors.
(m) Characterization of inter-individual variability in causal concentration-response functions. Technical approaches include the following:
    - Individual conditional expectation (ICE) plots (https://cran.r-project.org/web/packages/ICEbox/ICEbox.pdf)
    - Subject-specific causal graph models (e.g., Li X, Xie S, McColgan P, Tabrizi SJ, Scahill RI, Zeng D, Wang Y. Learning Subject-Specific Directed Acyclic Graphs With Mixed Effects Structural Equation Models From Observational Data. Front Genet. 2018 Oct 2;9:430. doi: 10.3389/fgene.2018.00430).
(n) Characterization of uncertainty in causal concentration-response functions and their dependence on other causally relevant variables, such as levels of other pollutants, sociodemographic characteristics, co-morbidities, and gene polymorphisms.
(o) Results of accountability studies for the effects of observed changes in O3 levels on observed health effect. Relevant references for accountability studies include the following:
    - Zigler CM, Kim C, Choirat C, Hansen JB, Wang Y, Hund L, Samet J, King G, Dominici F; HEI Health Review Committee. Causal Inference Methods for Estimating Long-Term Health Effects of Air Quality Regulations. Res Rep Health Eff Inst. 2016 May;(187):5-49.
    - Boogaard H, van Erp AM, Walker KD, Shaikh R. (2017) Accountability Studies on Air Pollution and Health: the HEI Experience. Curr Environ Health Rep. Dec;4(4):514-522. doi: 10.1007/s40572-017-0161-0.
    - Henneman LR, Liu C, Mulholland JA, Russell AG. (2017) Evaluating the effectiveness of air quality regulations: A review of accountability studies and frameworks. J Air Waste Manag Assoc. Feb;67(2):144-172. doi: 10.1080/10962247.2016.1242518.)

- **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 specific type(s) of causation for which evidence is provided. Importantly different types and concepts of causation include associational, attributive, counterfactual/potential outcomes, predictive (e.g., Granger), structural, manipulative, mechanistic, and but-for causation. 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 specified. 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).

Technical references for types of causation include the following:

- Cox LA Jr.(2018). Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol. Nov 15:1-31. doi: 10.1080/10408444.2018.1518404.
- Probabilistic
  i. Suppes P (1970). *A Probabilistic Theory of Causality*. North-Holland Publishing Company. Amsterdam, Holland.
- Associative
  i. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965 May;58:295-300
  ii. IARC (2006). IARC Monographs on the Evaluation of Carcinogenic Risk to Humans: Preamble. International Agency for Research on Cancer (IARC). Lyons, France. http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf. https://www.ncbi.nlm.nih.gov/books/NBK304626/
- Attributive
  i. Murray CJ, Lopez AD. Measuring the global burden of disease.N Engl J Med. 2013 Aug 1;369(5):448-57. doi: 10.1056/NEJMra1201534.
  ii. Lo WC, Shie RH, Chan CC, Lin HH. Burden of disease attributable to ambient fine particulate matter exposure in Taiwan. JFormos Med Assoc. 2016
  iii. Prüss-Üstün A, Mathers C, Corvalán C, Woodward A. (2003). Introduction and methods: Assessing the environmental burden of disease at national and local levels. Environmental burden of disease series No. 1. World Health Organization (WHO). Geneva, Switzerland. www.who.int/quantifying_ehimpacts/publications/en/9241546204chap4.pdf?u a=1
- Counterfactual/potential outcomes
  i. Galles D, Pearl J (1998). An axiomatic characterization of causal counterfactuals. Foundation of Science 3 151–182.
  ii. Glass TA, Goodman SN, Hernán MA, Samet JM. Causal inference in public health.Annu Rev Public Health. 2013;34:61-75. doi: 10.1146/annurev-publhealth-031811-124606.
  iii. Höfler M. The Bradford Hill considerations on causality: a counterfactual perspective.Emerg Themes Epidemiol. 2005 Nov 3;2:11.
  iv. Li J, Ma S, Le T, Liu L, Liu J. (2017) Causal decision trees. IEEE Transactions on Knowledge and Data Engineering. Feb 1. 29(2): 257-271
  v. Lok JJ. (2017) Mimicking counterfactual outcomes to estimate causal effects. Ann Stat. Apr;45(2):461-499. doi: 10.1214/15-AOS1433.
- Predictive
  i. Barnett L, Seth AK. (2014) The MVGC Multivariate Granger Causality Toolbox: A new approach to Granger-causal inference. J. Neurosci. Methods 223: 50-68.
  ii. Kleinberg S, Hripcsak G. (2011) A review of causal inference for biomedical informatics. J Biomed Inform. Dec;44(6):1102-12.

iii. Granger, C. W. J. (1969). Investigating causal relations by econometric models and cross-spectral methods. Econometrica. 37 (3): 424-438.
iv. Papana A, Kyrtsou C, Kugiumtzis D, Diks C. (2017) Assessment of resampling methods for causality testing: A note on the US inflation behavior.PLoS One. Jul 14;12(7): e0180852. doi: 10.1371/journal.pone.0180852.
v. Wiener N. (1956) The theory of prediction. In Modern Mathematics for Engineers, vol. 1 (ed. E. F. Beckenbach). New York: McGraw-Hill.

- Structural
  i. Hoover KD 2012. Causal structure and hierarchies of models. Studies in History and Philosophy of Biological and Biomedical Sciences. Dec 43(4): 778-786. https://doi.org/10.1016/j.shpsc.2012.05.007
  ii. Simon HA. (1953) Causal ordering and identifiability, in: W.C. Hood, T.C. Koopmans (Eds.), Studies in Econometric Method, in: Cowles Commission for Research in Economics Monograph No. 14, John Wiley & Sons, Inc., New York, NY, pp. 49–74, Chapter III.
  iii. Simon HA. Spurious correlation: A causal interpretation. Journal of the American Statistical Association 49 (267) September 1954: 467–479.
  iv. Simon HA and Iwasaki Y (1988). Causal ordering, comparative statics, and near decomposability. Journal of Econometrics 39 (1988) 149-173.
- Manipulative
  i. Hoover KD 2012. Causal structure and hierarchies of models. Studies in History and Philosophy of Biological and Biomedical Sciences. Dec 43(4): 778-786. https://doi.org/10.1016/j.shpsc.2012.05.007
  ii. Spirtes P. (2010). Introduction to causal inference. Journal of Machine Learning Research 11:1643-1662. http://www.jmlr.org/papers/volume11/spirtes10a/spirtes10a.pdf
  iii. Voortman M, Dash D, Druzdzel MJ. (2010) Learning causal models that make correct manipulation predictions with time series data. Proceedings of Machine Learning Research 6:257–266 http://proceedings.mlr.press/v6/voortman10a/voortman10a.pdf
- Mechanistic
  i. Keele L, Tingley D, Yamamoto T. (2015). Identifying mechanisms behind policy interventions via causal mediation analysis. Journal of Policy Analysis and Management, Vol. 34, No. 4, 937–963
  ii. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the black box of causality: learning about causal mechanisms from experimental and observational studies. American Political Science Review Vol. 105, No. 4 November 2011
  iii. Menzies P. The causal structure of mechanisms. Stud Hist Philos Biol Biomed Sci. 2012 Dec; 43(4):796-805. doi: 10.1016/j.shpsc.2012.05.00
  iv. Simon HA and Iwasaki Y (1988). Causal ordering, comparative statics, and near decomposability. Journal of Econometrics 39 (1988) 149-173.
- But-for causation is discussed extensively in tort law.

At present, most of the epidemiological articles that support determinations of causality address associational and attributive causation; some also address counterfactual causation.

Accountability studies typically seek to address manipulative causation. Risk management decisions and policy making should be informed about manipulative causation. Scientific research seeks to understand mechanistic causation, but manipulative causation is necessary and sufficient to provide sound information about consequence probabilities for different decisions or policies, such as revisions in current NAAQS. Mechanistic causation implies manipulative causation, but neither is implied by associative or attributive causation. Therefore, scientific studies that focus on manipulative causation, including recent accountability studies, are particularly valuable for informing decisions and policy.

(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 and welfare "effects" of ozone are ambiguous unless they 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. Technical references on different types of causal effects and how to estimate them from epidemiological data include the following:

- Pearl J. (2001) Direct and Indirect Effects. In Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence, San Francisco, CA: Morgan Kaufmann, 411-420.
- Petersen ML, Sinisi SE, van der Laan MJ. (2006) Estimation of direct causal effects. Epidemiology. May; 17(3):276-84.
- Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology 1992, 3:143-155.
- Tchetgen Tchetgen EJ, Phiri K. Bounds for pure direct effect. Epidemiology. 2014 Sep;25(5):775-6. doi: 10.1097/EDE.0000000000000154.
- VanderWeele TJ. Controlled direct and mediated effects: definition, identification and bounds. Scand Stat Theory Appl. 2011 Sep;38(3):551-563.

(c) Quantify the fraction of each estimated concentration-response function that represents (manipulative) causation rather than other sources of association. A causal determination that labels an entire exposure-response relationship (typically, an association) as "causal" does not inform decision-makers or the public about *how much* or *what fraction* of it is causal. It does not quantify *how much* of a specified (e.g., total or natural direct) effect in a population would be prevented by reducing the exposure by a given amount. Yet, this is essential information for scientifically well-informed decision-making about the public health effects of changes in NAAQS. It should be provided in the ISA, along with uncertainty characterizations for the answers.

(d) Taken together, the two steps of (1) Qualitatively characterizing the statistical dependency of health or welfare effects on ozone levels as "causal" and (2) Providing a quantitative concentration-response relation that is considered to be "causal," do not distinguish between situations that are importantly quantitatively different, and that might have very different implications for what is needed to protect public health. Thus, they fall short of providing policy makers with the information needed to make scientifically well-informed decisions about how to protect public health with an adequate margin of safety. To illustrate, consider the following two simple hypothetical structural equation (causal) models:

- (a) RISK = 0.002*OZONE + 0.01*POVERTY + 0.01*POVERTY*OZONE
- (b) RISK = 0.01*OZONE + 0.002*POVERTY + 0.01*POVERTY*OZONE

Here, RISK is a quantitative measure of risk of adverse health effects; OZONE is a quantitative measure of ozone exposure; and POVERTY is a binary indicator (1 = yes, = no) of poverty. Suppose also that ozone level is positively associated with poverty via the equation

- OZONE = 1*POVERTY

If OZONE is expressed in appropriately chosen units. Then both structural equation models (a) and (b) correspond to the same reduced form (associational) concentration-response model, RISK = 0.012*OZONE + 0.01*$OZONE^2$. But model (b) implies a much larger reduction in RISK from a given exogenous reduction in OZONE than does model (a). Among people not living in poverty (POVERTY = 0), the effect on RISK of a specified reduction in ozone is 5 times greater in model (b) than in model (a). Both models might both warrant a qualitative determination that the association between OZONE and RISK is "causal," and yet they might have opposite implications for whether a proposed reduction in ambient concentrations of ozone will protect public health with an adequate margin of safety. A qualitative determination that there is a "causal relation" between ozone and health risk, even combined with a quantitative estimated statistical concentration-response function (such as RISK = 0.012*OZONE + 0.01*$OZONE^2$ in this example), does not reveal the essential *quantitative* information about how changing exposure affects risk. But this manipulative causal information is what policy makers need to make scientifically well-informed decisions. EPA's system for qualitative causal determination in the draft IRP should be expanded to also 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. (Stating that each unit of reduction in ozone exposure will prevent a specified fraction of adverse health effects per unit time is a useful form for presenting such information, but it should only be used to present manipulative causal information, and not to present associational information, such as from regression models.)

- **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? Threats to internal validity and aspects of study design and analysis for refuting these potential non-causal explanations for observed associations are discussed for social statistics in Campbell DT, Stanley JC. 1963. *Experimental and Quasi-Experimental Designs for Research.* Houghton Mifflin Company. Boston, MA. Very similar considerations apply to quasi-experiments used in epidemiology.

(c) Were plausible non-causal interpretations of concentration-response relationships convincingly refuted using relevant data? (Rothman KJ, Greenland S. 2005. Causation and causal inference in epidemiology. Am J Public Health. 95 Suppl 1:S144–S50.)

(d) Were threats to external validity (generalizability) adequately addressed and resolved? Some relevant technical references on generalizability and external validity are as follows:

- Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing Study Results: A Potential Outcomes Perspective. Epidemiology. 2017 Jul;28(4):553-561. doi: 10.1097/EDE.0000000000000664. Review. Erratum in: Epidemiology. 2018 Mar;29(2):e16.
- Balzer LB."All Generalizations Are Dangerous, Even This One."-Alexandre Dumas.v Epidemiology. 2017 Jul;28(4):562-566. doi: 10.1097/EDE.0000000000000665.
- Pearl J. Generalizing experimental findings. J Causal Inference. 2015; 3(2):259–266.
- Westreich D, Edwards JK, Lesko CR, Cole SR, Stuart EA. Target Validity and the Hierarchy of Study Designs. Am J Epidemiol. 2018 Oct 9. doi: 10.1093/aje/kwy228.

(e) Was a clear distinction made between *estimated* values of exposures and *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? Technical references on measurement error and its effects include the following:

- Rhomberg LR, Chandalia JK, Long CM, Goodman JE. (2011) Measurement error in environmental epidemiology and the shape of exposure-response curves.Crit Rev Toxicol. Sep;41(8):651-71. doi: 10.3109/10408444.2011.563420.
- Cox LAT. Effects of exposure estimation errors on estimated exposure-response relations for PM2.5. Environ Res. 2018 Jul;164:636-646. doi: 10.1016/j.envres.2018.03.038
- https://cran.r-project.org/web/packages/mmc/mmc.pdf ; see also
- https://www.jstatsoft.org/article/view/v048i02,
- https://cran.r-project.org/web/packages/GLSME/GLSME.pdf,
- https://arxiv.org/pdf/1510.07123.pdf

(f) Were adjustment sets correctly identified and used to obtain unbiased estimates of specified total and direct causal effects of exposures on health? Technical references related to adjustment sets for estimating various direct and total causal effects of an exposure variable on a response variables include the following:

- Elwert, F. (2013). Graphical Causal Models. *Handbook of Causal Analysis for Social Research.* 245-273. doi 10.1007/978-94-007-6094-3_13.
- Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10:37–48.
- Glymour MM, Greenland S. Causal diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2008:183–209.
- Knüppel S, Stang A. DAG program: identifying minimal sufficient adjustment sets. Epidemiology. 2010 Jan;21(1):159. doi: 10.1097/EDE.0b013e3181c307ce.
- Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol. 2016 Dec 1;45(6):1887-1894.

(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? Relevant technical references on transportability and transport formulas for generalizing study results include the following:
    - Bareinboim E, Pearl J. Causal transportability with limited experiments. In Proceedings of the 27th AAAI Conference on Artificial Intelligence, pp. 95-101, 2013. http://ftp.cs.ucla.edu/pub/stat_ser/r408.pdf
    - Hernán MA, Vanderweele T. On compound treatments and transportability of causal inference. *Epidemiology*. 2011;22:368.
    - Lee S, Honavar V. (2013) m-Transportability: Transportability of a causal effect from multiple environments. Proceedings of the Twenty-Seventh AAAI Conference on Artificial Intelligence. www.aaai.org/ocs/index.php/AAAI/AAAI13/paper/viewFile/6303/7210
    - Schwartz S, Gatto NM, Campbell UB. Transportabilty and causal generalization. Epidemiology: Sep 2011 22(5): 745-6

(i) Do the study designs and analytic methods used provide valid quantitative estimates and uncertainty intervals for manipulative causal effects of changes in exposures on changes in health effects over time in exposed populations? For relevant aspects of study design and analysis (with an application to estimating ozone health effects in Moore et al.),
    - Moore KL, Neugebauer R, van der Laan MJ, Tager IB. Causal inference in epidemiological studies with strong confounding. Stat Med. 2012 Jun 15;31(13):1380-404. doi: 10.1002/sim.4469.
    - Petersen ML, Porter KE, Gruber S, Wang Y, van der Laan MJ. Diagnosing and responding to violations in the positivity assumption Stat Methods Med Res. Stat Methods Med Res. 2012 Feb; 21(1): 31–54. doi: 10.1177/0962280210386207

(j) Was a thorough 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). The term "relationship" throughout the draft IRP is ambiguous when the specific relationship being referred to (e.g., manipulative causal relationship) is not specified.

(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, emphasis added) should be replaced with clear causal questions. An example might be "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. For example, "What are the nature and magnitude of exposures and health risks **associated with** air quality conditions just meeting the current standard?" could be rewritten as "What are the nature and magnitude of exposures and health risks **preventable by** improving 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 (or between structural equations and reduced-form equations for the "concentration-response relationship.") 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. Ozone Review Panel. The EPA is urged to appoint an expert review panel to assist CASAC in its assessment of the ozone ISA. The perspectives and knowledge of experts actively engaged in various aspects of environmental research will greatly strengthen the ability of CASAC to provide recommendations that will improve the ISA and strengthen the basis for the risk analyses and decision-making. As pointed out in the public commentary, expert review panels have assisted with CASAC reviews for at least 30 years. The decision not to appoint such a panel for this ozone review (and the dissolution of the PM review panel) represents a major departure from prior practice, and can only weaken the scientific quality of the process. Employing an expert panel does not need to slow the review process.

2. 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.

3. 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.

4. Study quality. The IRP includes in section 4.3.6 an excellent and thorough description of the methods to be used for assessing study quality. 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.

5. 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 these differences between epidemiological and clinical studies 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, the concentrations of which track 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.

6. Causality. The comments of Dr. Cox regarding the EPA's causality framework were discussed during the conference call. Dr. Cox brings into consideration more complex and current issues and terminology being used in understanding the concept of causality. These considerations reflect the complex relationships between causal agents and their observed effects, especially when multiple agents and pathways are involved. I agree with Dr. Cox that the IRP should acknowledge this field of study and the "types" of causality that have been introduced in the literature, with references. This could perhaps best be included in the Preamble, since it applies to all criteria pollutants. However, the current causality framework proposed for this ISA, and that has been used for a number of NAAQS reviews with CASAC approval, should be retained. This will foster comparisons and contrasts with causality determinations in the previous ozone ISA.

Minor Comments:

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.
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 1 - Introduction

- Section 1.1 discusses the CAA's instructions about CASAC providing advice on adverse health effects from various attainment and maintenance strategies. EPA notes that this may be more relevant to the implementation of the NAAQS 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, but the ISA conclusions on aspects like the shape of the C-R function can fundamentally impact the risk modeling. A further example is the draft ozone ISA, which is due for EPA management review in mid-December (according to the EPA's discussion during the ozone workshop in Oct/Nov 2018). EPA should provide information about how the comments received on this draft IRP will be integrated into the mostly-finished ozone ISA.
- 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.

Comment on Chapter 4 - Science Assessment

- Including PECOS statements and a defined literature review and study quality parameters is a great step for EPA to be taking in this review. I recommend that EPA take a step further and 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.
- 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)?
- In this IRP the EPA should provide clear, objective specifications about how they will weigh and integrate evidence for causality determinations, including information about study quality. 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 (i.e. If some studies showing positive effects, while other demonstrate null or negative effects)?

- 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 a 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 Chapter 5 - Risk and Exposure Assessment

- The EPA should specifically consider the changes (decreases) in the low daily concentrations of ozone that occur with decreased peak ozone, and how this can impact epidemiology study results that assume effects at daily concentrations below the standard.
- 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 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.

Dr. Timothy E. Lewis

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

- The Agency should reconvene the expert panel on ozone to review all forthcoming documents.
- The Agency should reconsider the timeline for finalizing the ozone review with input from CASAC.

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.

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 2

- unprecedented attainment with current standard across the US - due to reductions in precursor emissions - NOx - Power Plants and VOCs - automobile engines and/or fuels
- availability of new datasets from:
    - NCORE Monitors Sites - 2011 - Co-Pollutants including NO and total reactive nitrogen (NOy), precursor formation - important in correlation determinations with ozone and understanding photolytic chemistry and formation of ozone from precursors; meteorological data
    - PAMS- Photochemical Assessment Monitoring System - enhanced monitoring of ozone, oxides of nitrogen (NOx), and volatile organic compounds (VOC) to obtain more comprehensive and representative data on ozone air pollution - many sites already completing for years; newer sites based on population and NCORE location - delayed until 2020-2021
    - Near-Road Way Monitoring Systems - close association between secondarily-formed NO2 and O3; potential for relatively high correlation
- precursor formation + TRANSPORT (significant in Northeast, New England states) and BACKGROUND

Comments on Chapter 3

- The utilization of controlled human exposure studies (possibly of controlling for health-related conditions vs. epidemiological data, even with uncertainties and potential improvement in exposure misclassification (biasing the hypothesis toward the null);
- controlled exposure human studies - measured decreases in lung functioning; increases in respiratory symptoms, airway inflammation, airway hyperresponsiveness, and impaired lung host defense - smaller universe VS. epidemiological studies - measured respiratory-related emergency room visits and other surrogates – larger universe; which one should more weight be given (to) by the Administrator
- previous CASAC - surrogate for adverse - FEV1 decrements of $\geq$ 15% healthy adults; FEV1 decrements of $\geq$ 10% healthy adults - unhealthy adults; should these be salient indicators of health deficits due to ozone exposure

- **indicator** - ozone routinely monitored; but now NO2 with Near-Road Way sites especially since most of the estimated emissions of NOx (61%) emanating from vehicular emissions
- **form** - evening-out of concentrations, but is this a compromise a less stringent metric is utilized; "thus, the EPA concluded that a form based on the nth-highest maximum ozone concentration would more effectively ensure that people who live in areas with different length ozone seasons received the same degree of public health protection."

Comments on Chapter 4

- systematic literature search and identification of relevant studies
- keyword search terms ozone, O3
- use of SWIFT-AS; best tool?

- peer-reviewed and published or accepted for publication; what about source of research
- why **PECOS** for experimental human studies including toxicological and controlled exposure human studies AND epidemiological studies?
- causality - Weight-of-Evidence - consistent with epidemiological causal determinants? If so, is this sufficient for other non-epidemiological causality research, determinations?
- what is the minimum level of casualty to be considered in evaluating a standard?
- ambient concentrations of ozone – transport important phenomena to discuss
- human exposure -
    - limitations of chemical transport modeling and satellite data
    - personal air sensors
    - biomarkers
    - kriging and other spatial interpolation methods
    - temporal interpolation methods, where applicable
- at-risk lifestages and populations and public health impact
    - lower SES and/or minority populations discussion should be included
- quantitative risk and exposure assessment - purpose? Is the intent to develop a dose-response curve/assessment?

Dr. Steven Packham

A Balanced Review Paradigm for the Ozone IRP[1]

A Table of Historical Ozone NAAQS[2] is presented in Exhibit A. The last three columns present a) the standard's AVERAGING TIME in hours, b) its concentration LEVEL in ppm, and c) its FORM. The FORM is a statement of a specific LEVEL and a specific AVERAGING TIME that must not be exceeded more than a specified number of times in a year, or a specified number of days.

EXHIBIT A

YEAR (Final Rule/Decision)	STANDARD (Primary/Secondary)	INDICATOR (Oxidant)	AVERAGING TIME (Hours)	LEVEL (ppm)	FORM (Descriptive)[3]
1971	Primary and Secondary	Total photochemical oxidants	1 hour	0.08 ppm	
1979	Primary and Secondary	O3	1 hour	0.12 ppm	
1993	EPA decided that revisions to the standard were not warranted at the time				
1997	Primary and Secondary	O3	8 hours	0.08 ppm	
2008	Primary and Secondary	Primary and Secondary	8 hours	0.075 ppm	
2015	Primary and Secondary	Primary and Secondary	8 hours	0.070 ppm	

Risk exposure studies use inferential statistics to rule out the likelihood that an observed temporal association between ambient ozone concentrations and adverse health effects is coincidental. Toxicology studies have shown that the lowest observable effect level (LOEL) and the relative severity of adverse health effects in humans are caused by the dose (i.e., amount) of ozone inhaled and that the inhaled dose is a function of ambient ozone concentrations (C), human respiration (R), and the duration of the exposure (T).[4] This consultative comment presents a toxicologist's rationale for modifying the ozone IRP.

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[1] Integrated Review Plan for the Review of the Ozone National Ambient Air Quality Standard: External Review, EPA-452/P-18-001, October 2018.

[2] NAAQS is an acronym for a National Ambient Air Quality Standard developed and promulgated by the U. S. Environmental Protection Agency (EPA).

[3] Descriptive language can be found at https://www.epa.gov/ground-level-ozone-pollution/table-historical-ozone-national-ambient-air-quality-standards-naaqs.

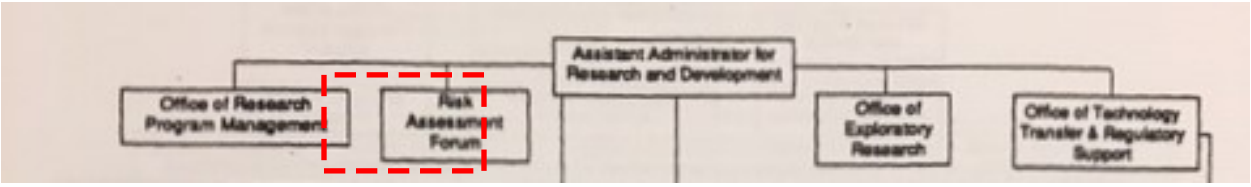
[4] US. Environmental Protection Agency **(1986)** Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vol. I, Report EPA-600/8-84-020aF, pp **1-237, U.S.** Environmental Protection Agency, Research Triangle Park, NC

It proposes that a review of toxicology study results and the status of current scientific knowledge of the causal mechanism and dosage levels at which ozone evokes changes in pulmonary function test results and inflammation induced adverse health effects in human subjects be included when planning for a review of the IRP Integrated Science Assessment; [5] when developing the ISA; [6] when developing the Health Criteria;[7] when constructing the Framework for Causality Determinations in the ISA; [8] and when forming considerations that shape planning for updated or new quantitative analyses[9] and to do this in a manner consistent with the standardized charge questions for CASAC outlined and presented in the May 2018 Memo.[10]

The Rationale: The ozone NAAQS has been changed five times since 1971. Changes most notable are those associated with an increase in reliance on risk exposure assessments and a marked reduction in the weight-of-evidence accorded toxicological study results. Toxicology studies provided an essential basis for the ozone NAAQSs promulgated from 1971 to 1997. The criteria AVERAGING TIME remained constant at 1 hour while the FORM description changed from, "*Not to exceed more than one hour per year,*" when the LEVEL was 0.08 ppm to, "*Attainment is defined when the expected number of days per calendar year, with maximum hourly average concentration greater than 0.12 ppm, is equal to or less than 1,*" in 1979.

The organization chart for the Office of Research and Development (ORD) in 1992 identified a Risk Assessment Forum reporting directly to the Assistant Administrator (EXHIBIT B).

EXHIBIT B[11]



[5] Slide 10 of power point presentation. EPA Integrated Review Plan for Review of the Ozone national Ambient Air Quality Standard.
[6]Ibid. Slide 11
[7] Ibid. Slide 12
[8] Ibid. Slides 13 and 14
[9] Ibid. Slides Ibid. Slide 15 – Planning for this Review: Risk and Exposure Assessment, and Slide 16 – Planning for this Review: Policy Assessment
[10] Ibid. Slide 23
[11] EPA Organization for Environmental Research: The Third Decade. Office of Research and Development U. S. Environmental Protection Agency Washing, D. C. 20460. EPA/600/R-92/246 January 1993, page A-6.

By 1997, with risk assessment elevated to the attention of the ORD Assistant Administrator, the AVERAGING TIME of the ozone NAAQS was changed from 1 hour to 8 hours. This has remained unchanged through the subsequent 2008 and 2015 NAAQS review cycles. The FORM also has remained unchanged since 1997. The LEVEL however did change over this time period from 0.08 ppm, to 0.075 ppm, and to 0.070 ppm; bringing the LEVEL requirement ever-closer to an inevitable natural barrier; i.e., background ozone levels.

Risk exposure assessments have a singular way of reducing health risks associated with exposure to ozone. And that is by lowering the LEVEL concentrations.

EXHIBIT C presents a tabular comparison of independent and dependent variables integral to risk exposure assessments and toxicology study designs. The respective capabilities of these two scientific disciplines to provide scientific information on the adequacy of specific values for AVERAGING TIME, LEVEL, and FORM elements of the ozone NAAQS to protect public health, is shown.

The DOSE column shows the independent variables that can be used in toxicology study designs to provide information on causality, thresholds, the differentiation of homeostatic and adaptive responses from adverse effects, and to quantify margins of safety.

EXHIBIT C

NAAQA	AVERAGING TIME	LEVEL	DOSE	FORM
Risk Exposure Study Design	Independent Variable	Independent Variable	N/A	Dependent Variable
	Exposure duration (T) Daily (8 hours)	Concentration (C) EPA Air Monitoring Data	N/A	Limited to public health outcomes and Limited to EPA Monitoring System
Toxicology Study Design	Independent Variable	Independent Variable	Independent	Dependent
	Exposure duration (T) Hours, days, weeks, Continuous or Episodic	Concentration (C) Controlled clinical, or Uncontrolled, *ad libitum* Uncontrolled ambient unlimited	C, T, and R[12]	Respiration (R) Pulmonary Function Bio markers 2nd Person Observed symptoms 1st Person Recorded Symptoms Doctor-monitored Effects & Conditions Individual or Group Statistics

[12] Respiration can serve as either a Dependent Variable (as in a FEV1 pulmonary function test result) or an Independent Variable (as in RMV, respiratory minute volume). The underlying physiological and neurological nature of this unique quality resides in the afferent and efferent innervation of the respiratory muscles both by the peripheral voluntary and the central-peripheral autonomic nervous systems.

In general, it would appear that results from toxicology studies together with risk exposure assessments would provide stronger scientific information to CASAC and the Administrator during the ozone NAAQS proposal and promulgation processes than the use of risk exposure assessments alone.

The EPA Office of Air Quality Planning and Standards and the EPA National Center for Environmental Assessment should take all reasonable steps to edit and implement pertinent modifications of the External Draft of the Ozone IRP to include a planned review of scientific knowledge obtained through toxicology studies to inform CASAC in its obligation to advise the Administrator on the adequacy of the current ozone NAAQS to protect human and public health requisite with a reasonable margin of safety.

Additional Comments

FORM Options: Providing that a sufficient review and consideration can be made of current and past toxicological studies and included in the ISA, it might be beneficial for the Agency to consider developing new ozone NAAQS having more than one LEVEL and one AVERAGING TIME and one FORM. For instance, a BI-LEVEL NAAQS might be considered with complimentary AVERAGING TIMEs, and scientifically appropriate FORMs.

NAAQS Accreditation v Attainment Designations: Certainly not likely in this current review cycle, but ultimately, the Agency and the States could conceivably agree on developing and adopting an air space accreditation plan using multiple LEVEL, AVERAGING TIME, and FORM strata within the NAAQS to supplement current SIP's. A SIP plus air space accreditation could conceivably be applied in those instances where background ozone levels make it impracticable to meet the 0.070 ppm 8 hour requirement; but could meet a FORM using either a 1 hour max AVERAGING TIME with a 0.08 ppm, or a 0.12 ppm LEVEL requirement. A SIP-Accreditation would retain EPA's role in reducing air pollution and protecting public health while responding to directives in the May 2018 Memo[13] to consider ozone background levels in the development of ozone NAAQS.

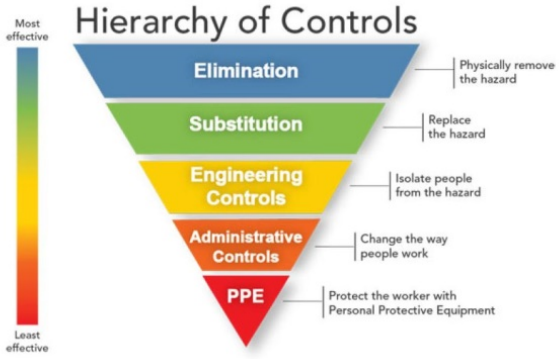
IRP Review Boundaries

Lastly, the universe of scientific knowledge to be include in the present ozone NAAQS review cycle needs to be expanded to include all relevant scientific and medical disciplines and be unlimited in terms of when that knowledge was published or otherwise released and validated in the public domain. There is a genuine reason for concern over the Agency appearing to isolate itself from input and influence from a full complement of relevant scientific disciplines.

[13] Slide 10 of power point presentation. EPA Integrated Review Plan for Review of the Ozone national Ambient Air Quality Standard.

Basic facts must not be overlooked and critical information must not remain unharvest from any body of scientific knowledge that could conceivably guide the CASAC and the Administrator in arriving at a sound, scientifically based decision on the adequacy of a) new and existing concentration LEVELs, b) the adequacy of new or existing AVERAGING TIMES, or c) the adequacy of new or existing FORMs of future ozone NAAQS.

A perfect example of a benefit of thinking outside the box would be to consider the guiding principles underlying the Industrial Hygiene, NIOSH, and OSHA inverted pyramid of Hierarchy of Controls for addressing workers' safety. In many respects, the Agency's NAAQS are analogous to the objective of the first level of the pyramid; i.e., to eliminate as much air pollution as possible.



The promulgation of lower ozone concentration LEVELs over the last three review cycles has established a high expectation and an admirable Agency commitment to maintaining a clean ambient air space for the nation. There is, however, a large number of the nation's population living and working in ozone non-attainment areas. The risk exposure assessment (REA) study design cannot take NAAQS development into the future in terms of the NAAQS requirement to protect public or human health. REA's dependent variable is *totally* dependent on reducing ambient ozone levels. Ultimately, REA's findings will suggest that background levels of ozone should be reduce to provide a requisite margin of safety.

The agency may want to consider Administrative Controls (the orange level) through the development and promulgation of NAAQS Accreditations mention above - using uniquely justified LEVEL, AVERAGING TIMES, and FORM elements within the ozone NAAQS to address adequate margins of safety for at-risk populations in non-attainment areas and for some sensitive groups in general.

<u>Literature search paradigms are insufficient and can result in a failure to preserve scientific knowledge:</u>
The IRP should add the time-proven benefits of assessing the value of a published study on the merits of its entire content. To illustrate, consider the full text of the introduction to just one of Pryor's studies

inserted below.[14,15] Note how the authors not only cite references, they also present insights clarifying how the referenced study added to science's growing body of facts and knowledge. Based on a review of past studies, the authors then explained the reason for conducting the study.

> *"Ozone is the most powerful oxidant to which humans are routinely exposed; it occurs at ppm levels in smog and presents major health problems for urban populations (1). The effects of ozone principally involve the pulmonary system (1-6), but extra pulmonary effects have also been reported in animals exposed to ozone (6-21). Ozone is too reactive to penetrate far into the air/tissue boundary in the lung without reacting (12,231a,n d the non-pulmonary effects of ozone must be due to subsequent reactions of the products that are formed from the reaction of ozone with primary target molecules. The nature of these products has remained unknown.*
>
> *There is a general consensus that unsaturated fatty acids (UFA)' are a primary target for ozone (1,5,6,14-22).* This is *quite reasonable for several reasons. First, while ozone reacts rapidly with many types of organic molecules, it reacts with olefins such as unsaturated fatty acids particularly rapidly (6,12-15,18,23,24). Second, the lungs of rats exposed to 2 ppm ozone in vivo show the presence of low molecular weight acids that clearly result from splitting small molecular fragments from unsaturated fatty acids by cleaving and oxidizing them at their double bonds, just as ozonation is known to do (25). Third, ozone is relatively lipophilic (13). And finally, vitamin E, which is largely confined to the lipid bilayer in cells, protects both in vitro systems and animals against the effects of ozone(6).*
>
> *"The chemistry of the reaction of ozone with olefins has been studied in detail (12,131. The great majority of these studies have utilized aprotic solvents, and in these solvents the Criegee ozonide is the major product and is stable (6, 12,26). Therefore, it is often assumed that the products of the reactions of ozone with UFA in vivo are Criegee ozonides (26-28).*
>
> *"We recently suggested that the UFA in lung lining fluids, including mucus and surfactant, are a primary target for ozone (29-31). Surfactant in different animals contains lipids with from 15% to 40% unsaturated fatty acids (32) and to some degree resembles an aqueous emulsion of fatty acids and other materials (33). If lung lining fluids are an important target for ozone, then the ozonation of unsaturated fatty acids in vivo occurs in the presence of water; this is significant since the ozonation of olefins in water gives carbonyl compounds*

[14] Pryor, W. A., Das, B., and Church, D. F. The Ozonation of Unsaturated Fatty Acids: Aldehydes and Hydrogen Peroxide as Products and Possible Mediators of Ozone Toxicity. (*Chem Res Toxicol*. 1991,4, 341-384.)

[15] References used in the Introduction of Pryor, et.al. are given in an Appendix following the final consultative comment.

and hydrogen peroxide, rather than Criegee ozonides. It also is noteworthy that even if the Criegee ozonides of fatty acids were formed, they are not very toxic (26,27,34a)n d probably cannot explain the non-pulmonary effects of ozone (6).

"The results described here indicate that ozonations of aqueous systems containing unsaturated fatty acids or their methyl or phosphatidylcholine esters produce approximately ***1 mol of hydrogen peroxide and 2 mol of aldehydes per mole of ozone reacted*** [emphasis added] *and of alkene consumed. Under our reaction conditions we observe the formation of very little (about 5% or less) other peroxidic materials (30,31)."*

Modernize the Air Quality Index: One of the most successful instruments of risk communication developed by the Agency has been the Air Quality Index (AQI). The updating of the AQI to include personal health risk alerts and calculated estimates of inhaled dose provided through applications for smart phones and digital watch users is not beyond the current technology horizon.[16] The only factor limiting the Agency's entrance into this inevitable future will be its resistance to embrace the full scope of available scientific knowledge and digital device possibilities.

APPENDIX: Pryor References

(1) US. Environmental Protection Agency (1986) Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vol. I, Report EPA-600/8-84-020aF, pp 1-237, U.S. Environmental Protection Agency, Research Triangle Park, NC.

(2) Lippmann, M. (1989) Health effects of ozone: a critical review. J. Air Pollut. Control Assoc. 39, 672-695.

(3) Nikula, K. J., Wilson, D. W., Giri, S. M., Plopper, C. G., and Dungworth, D. L. (1988) The response of the rat tracheal epithelium to ozone exposure-injury, adaptation and repair. Am. J. Pathol. 131, 373-384.

(4) U.S. Environmental Protection Agency (1986) Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vol. IV, Report EPA/600/8-84/020dF, National Technical Information Service, Springfield, VA.

(5) Menzel, D. B. (1976) The role of free radicals in the toxicity of air pollutants (nitrogen oxides and ozone). In Free Radicals in Biology (Pryor, W. A., Ed.) Vol. 11, pp 181-200, Academic Press, New York, NY.

(6) Pryor, W. A. (1991) Can vitamin E protect us against the pathological effects of ozone in smog? Am. *J.* Clin. Nutr. 53,

[16] https://www.fdanews.com/articles/171476-cohero-health-gains-fda-approval-for-mobile-spirometer

(7) Graham, J. A., Menzel, D. B., Miller, F. J., Illing, J. W., and Gardner, D. E. (1981) Influence of ozone on pentobarbital-induced sleeping time in mice, rats and hamsters. Toxicol. Appl. Pharmacol. 61, 64-73.
(8) Morgan, D. L., Dorsey, A. F., and Menzel, D. B. (1985) Erythrocytes from ozone-exposed mice exhibit decreased deformability. Fundam. Appl. Toxicol. 5, 137-143.
(9) Brinkman, R., Lamberts, H. B., and Veninga, T. S. (1964) Radiomimetic toxicity of ozonised air. Lancet 7325, 133-136.
(10) Skillen, R. G., Thienes, C. H., Cangelosi, J., and Strain, L. (1961) Brain 5-hydroxytryptamine in ozone exposed rats. Proc. SOCE.x p. Biol. Med. 108, 121-122.
(11) Scheel, L. D., Dobrogorski, D. J., Mountain, J. T., Svirbely, J. L., and Stokinger, H. E. (1959) Physiologic, biochemical, immunologic and pathologic changes following ozone exposure. J. Appl. Physiol. 14, 67-80.
(12) Bailey, P. S. (1978) Ozonation in Organic Chemistry, Volume I, Olefinic Compounds, pp 220-237, Academic Press, New York, NY.
(13) Razumovskii, S. D., and Zaikov, *G.* E. (1984) Ozone and Its Reactions with Organic Compounds, pp 1-403, Elsevier, New York, NY.
(14) Giamalva, D. H., Church, D. F., and Pryor, W. A. (1985) A comparison of the rates of ozonation of biological antioxidants and oleate and linoleate esters. Biochem. Biophys. Res. Commun. 133, 773-779.
(15) Giamalva, D. H., Church, D. F., and Pryor, W. A. (1986) Kinetics of ozonation. 4. Reactions of ozone with a-tocopherol and oleate and linoleate esters in carbon tetrachloride and in aqueous micellar solvents. J. Am. Chem. SOC1.0 8, 6646-6651.
(16) Pryor, W. A., Prier, D. G., and Church, D. F. (1981) Radical production from the interaction of ozone and PUFA as demonstrated by electron spin resonance spin-trapping techniques. Environ. Res. 24, 42-52.
(17) Dooley, M. M., and Mudd, J. B. (1982) Reaction of ozone with lysozvme under different exposure conditions. Arch. Biochem. (4) 702-722. Eiopiys. 218, 459-471.
(18) Prvor, W. A., Stanlev, J. P., Blair, E.. and Cullen. G. B. (1976) Autoxidation of polyunsaturated fatty'acids. Part I. Effect of *Chem. Res. Toxicol., Vol. 4, No. 3, 1991* 347 ozone on the autoxidation of neat methyl linoleate and methyl linolenate. Arch. Environ. Health 31, 201-210.
(19) Menzel, D. B. (1970) Toxicity of ozone, oxygen and radiation. Annu. Rev. Pharmacol. Toxicol. 10, 379-394.
(20) Goldstein, B. D., Levine, M. R., Cuzzi-Spada, R., Cardenas, R., Buckley, R. D., and Balchum, 0. J. (1972) p-Aminobenzoic acid as a protective agent in ozone toxicity. Arch. Environ. Health 24,
(21) Goldstein, B. D., Buckley, R. D., Cardenas, R., and Balchum, 0. J. (1970) Ozone and vitamin E. Science 169,605-606.
(22) Pryor, W. A., Prier, D. G., Lightsey, J. W., and Church, D. F. (1980) Initiation of the autoxidation of polyunsaturated fatty acids (PUFA) by ozone and nitrogen dioxide. In Autoxidation in Food and Biological Systems (Simic, M. G., and Karel, M., Eds.) pp 1-16, Plenum Publishing Corp., New York, NY.

(23) Pryor, W. A., Giamalva, D. H., and Church, D. F. (1984) Kinetics of ozonation. 2. Amino acids and model compounds in water and comparisons to rates in nonpolar solvents. J. Am. Chem. SOC1.0 6,7094-7100.
(24) Giamalva, D. H., Church, D. F., and Pryor, W. A. (1988) Effect of bilayer structure on the rates of reaction of ozone with polyunsaturated fatty acids in phosphatidylcholine liposomes. Chem. Res. Toxicol. 1, 144-145.
(25) Rabinowitz, J. L., and Bassett, D. J. P. (1988) Effect of 2 ppm ozone exposure on rat lung lipid fatty acids. Exp. Lung Res. 14,
(26) Ewing, J. W., Cosgrove, J. P., Giamalva, D. H., Church, D. F., and Pryor, W. A. (1989) Autoxidation of methyl linoleate initiated by the ozonide of allylbenzene. Lipids 24,609-615.
(27) Cortesi, R., and Privett, 0. S. (1972) Toxicity of fatty ozonides and peroxides. Lipids 7, 715-721.
(28) Roehm, J. N., Hadley, J. G., and Menzel, D. B. (1972) The influence of vitamin E on the lung fatty acids of rats exposed to ozone. Arch. Environ. Health 24, 237-242.
(29) Pryor, W. A. (1991) The antioxidant nutrients and disease prevention-what do we know and what do we need to find out? Am. J. Clin. Nutr. 53, Suppl., 391s-393s.
(30) Pryor, W. A., and Church, D. F. (1991) Aldehydes, hydrogen peroxide, and organic radicals as mediators of ozone toxicity. Free Radical Biol. Med (in press).
(31) Church, D. F., McAdams, M. L., and Pryor, W. A. (1991) Free radical production from the ozonation of simple alkenes, fatty acid emulsions and phosphatidylcholine liposomes. In Oxidative Damage & Repair: Chemical, Biological, and Medical Aspects (Davies, K. J. A., Ed.) Pergamon Press, NY.
(32) King, R. J. (1984) Isolation and chemical composition of pulmonary surfactant. In Pulmonary Surfactant (Robertson, B.,Van Golde, L. M. G., and Batenburg, J. J., Eds.) pp 1-15, Elsevier, Amsterdam.
(33) Robertson, B., Van Golde, L. M. G., and Batenburg, J. J. (1984) Pulmonary Surfactant, pp 1-582, Elsevier, Amsterdam.
(34) Menzel, D. B., Slaughter, R. J., Bryant, A. M., and Jauregui, H. 0. (1975) Heinz bodies formed in erythrocytes by fatty acid ozonides and ozone. Arch. Enuiron. Health 30,296-301.
(35) Burton, G. W., Ingold, K. U., and Thompson, K. E. (1981) An improved procedure for the isolation of ghost membranes from human red blood cells. Lipids 16, 946.
(36) Bradford, M. M. (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal. Biochem. 72, 248-254.
(37) Bader, H., and Hoigne, J. (1981) Determination of ozone in water by the indigo method. Water Res. 15, 449-456.
(38) Kilpatrick, M. L., Herrick, C. C., and Kilpatrick, M. (1956) The decomposition of ozone in aqueous solution. J. Am. Chem. SOC. 78, 1784-1789.
(39) Heath, R. L., and Tappel, A. L. (1976) A new sensitive assay for the measurement of hydroperoxides. Anal. Biochem. 76,

(40) Sznajder, J. I., Fraiman, A., Hall, J. B., Sanders, W., Schmidt, G., Crawford, G., Nahum, A,, Factor, P., and Wood, L. D. H. (1989) Increased hydrogen peroxide in the expired breath of patients with acute hypoxemic respiratory failure. Chest 96, 606-6 12.
(41) Yamada, K., Terao, J., and Mataushita, S. (1987) Electrochemical detection of phospholipid hydroperoxides in reverse-phase high performance liquid chromatography. Lipids 22, 125-128.
(42) Lappin, G. R., and Clark, L. C. (1951) Colorimetric method for the determination of trances of carbonyl compounds. Anal. Chem. 23, 541-542