Preliminary Comments from Members of the CASAC on EPA's *Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards (External Review Draft – October 2019)*

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Chapter 1 – Introduction

To what extent does the CASAC find that the information in Chapter 1 is clearly presented and that it provides useful context for the review?

The discussions of legislative background and history are clearly, although briefly, presented. They provide useful context for the review.

For the final PA, it might be useful to add a discussion of the exceptional nature of the current CASAC and NAAQS review process. Specifically, relevant background on changes in processes and procedures could include: (a) further details of Administrator Pruitt's "Back to Basics" memorandum (adding to the discussion on p. 1-12); (b) the disbanding of the CASAC Particulate Matter (PM) Review Panel and streamlining of the review process to promote timely advice; (c) the appointment of a pool of non-member consultants to expand the expertise and fields of knowledge used to inform the CASAC's review; and (d) the Administrator's and CASAC's explicit emphasis on sound science throughout the review process, including reexamination of long-standing assumptions and frameworks used in previous reviews.

Relevant background on methodological changes in the current CASAC's scientific and technical approach in this review cycle could be provided in a separate section. These include the following:

(1) Drawing and preserving key conceptual distinctions between
    a. Association vs. causation
        i. Formal quantitative causal inference vs. judgment for drawing causal conclusions from data;
        ii. Manipulative or interventional causation vs. Bradford Hill or weight-of-evidence (WoE) causation;
        iii. Statistical vs. biological (mechanistic) concepts of causation;
    b. Empirically verified evidence vs. unverified assumptions and models;
    c. Estimated vs. actual individual exposures; and
    d. Explicitly derived and independently verifiable scientific conclusions vs. expert judgments.

(2) Emphasis on more effective integration of information from animal toxicology and controlled human exposure studies to:

a. Elucidate and validate potential (i.e., hypothesized) causal biophysical mechanisms underlying epidemiologically suggested health risks; and
b. Better characterize dose-dependent thresholds and causal biological C-R functions for pulmonary inflammation and other physiological responses in other tissues, organs, and systems in response to inhaled ozone.

The stated intentions for the Draft PA presented in Chapter 1 include "to serve as a source of policy-relevant information;" "to be understandable to a broad audience;" and "to facilitate advice to the Agency and recommendations to the Administrator" from the CASAC. The CASAC recommends that these intentions be more fully realized in the PA by undertaking the following measures:

1. *Summarize available empirical evidence on how changes in public health effects depend on changes in ozone levels.* Ideally, this information should be discussed in detail in the final ISA.
2. *Summarize results from a systematic review and critical evaluation and synthesis of relevant studies relied on to reach conclusions*, including negative studies and studies of nonlinear C-R functions for ozone that were omitted in the draft ISA but that should inform the PA.
3. Throughout the PA, *clearly distinguish between causal C-R functions (describing how public health risks change in response to changes in ambient ozone levels) and regression C-R functions* (describing how observed public health risks differ across different observed or estimated ambient ozone levels). These are in general different concepts and different curves. Causal C-R functions are relevant for policy analysis. The draft PA addresses regression C-R functions. The final PA should use validated causal C-R functions to predict effects of alternative policy choices.
4. *Increase transparency and logical soundness in deriving conclusions* by documenting exactly how conclusions were reached and validated, in enough detail so that others can trace and check the logic used. This documentation should provide clear operational definitions of the key quantities and terms used to calculate, validate, and communicate scientific results. Conclusions should address the extent to which changing NAAQS standards for ozone demonstrably causes changes in public health outcomes. Uncertainties and variability in the answers should be quantified.
5. *Distinguish between estimated and actual exposures* throughout the PA.
6. *Discuss in more detail causal biological mechanisms of inflammation-related health effects* preventable by reducing current ozone levels (including, if relevant, roles of the NLRP3 inflammasome in mediating persistent adverse health effects).

7. *Critically discuss the biological realism* of the PA's risk predictions and modeling assumptions, specifically for how public health risks are predicted to change in response to changes in ambient ozone levels.
8. *Present results of empirical validation tests* of the PA's risk predictions and modeling assumptions against observations, specifically for how public health risks have changed in response to changes in ambient ozone levels.
9. *Quantify uncertainty and variability in risk predictions, taking into account epistemic uncertainties (e.g., from model uncertainty and exposure estimation error) as well as sampling variability. Present comprehensive, quantitative uncertainty, sensitivity, and variability analyses* showing how the ISA's conclusions change for variations in selection and weighting of studies, compositions of populations (representing causally relevant interindividual variability and heterogeneity in causal C-R functions), modeling choices and assumptions, interpretations of undefined and vague terms, and subjective judgments on which the conclusions depend. These comprehensive analyses should complement the limited set of uncertainty and variability analyses in Section 3D of the draft PA.

Chapter 3 – Review of the Primary Standard

What are the CASAC views on the approach described in chapter 3 to considering the health effects evidence and the risk assessment in order to inform preliminary conclusions on the primary standard? What are the CASAC views regarding the key considerations for the preliminary conclusions on the current primary standard?

Chapter 3 and its supporting appendixes predict risks using models and assumptions that have not been validated for predicting how changes in ozone affect public health risks. It omits important caveats such as those provided in the 2014 REA (www3.epa.gov/ttn/naaqs/standards/ozone/data/20140829healthrea.pdf). These included the following for the 2012 MSS model (emphases added):

- "Clearly the **intra-individual variability**… in the MSS model is a key parameter and is influential in predicting the proportions of the population with FEV1 decrements > 10 and 15%. **The assumption that the distribution of this term is Gaussian is convenient for fitting the model, but is not accurate**. The extent to which this mis-specification affects the estimates of the parameters of the MSS model and its predictions is not clear."
- "Although **the model does not have good predictive ability** for individuals (psuedo-R2 0.28), it does better at predicting the proportion of individuals with FEV1 decrements. 10, 15, and 20% (psuedo-R2s of 0.78, 0.74, 0.68) (McDonnell et al., 2012). The clinical studies that these model estimates are based on were conducted with young adult

> volunteers rather than randomly selected individuals, so **it may be that selection bias has influenced the model parameter estimates**. The parameter estimates are not very precise, partly as the result of correlations between the parameter estimates… The MSS model is also sensitive to the exposure concentrations, but we have not quantified that sensitivity. … **We are unable to properly estimate the true sensitivities or quantitatively assess the uncertainty of the MSS model**. … As discussed in Section 6.5.3 below, there are uncertainties in extrapolating the MSS model down to age 5 from the age range of 18 to 35 to which the model was fit. …[T]he uncertainty of the extension to children of the MSS model could be substantial." Section 6.5.7 adds that "EPA staff have identified key sources of uncertainty with respect to the lung function risk estimates. These are: the physiological model in APEX for ventilation rates, the O3 exposures estimated by APEX, the MSS model applied to ages 18 to 35, and extrapolation of the MSS model to children ages 5 to 18. … At this time **we do not have quantitative estimates of uncertainty for any of these**."

The Draft PA does state that "We are using this model to estimate lung function decrements for people ages 5 and older. However, this model was developed using only data from individuals aged 18 to 35 and the age adjustment term [$\beta 1 + \beta 2$ (Ageijk – 23.8)] in the numerator of Equation 3D-13 is not appropriate for all ages." However, the fact that the model predictions are based on assumptions that are unlikely to be accurate (e.g., that the parameter alpha 2 in Table 3D-21 quadruples on one's 18th birthday) and that the models and their predictions have not been empirically validated or verified should be emphasized. In effect, the PA selects some specific parametric models and uses them to make risk predictions, but the validity of the models and their predictions is unknown.

The final PA should discuss empirical validation of model predictions for changes in public health risks caused by changes in ambient ozone levels across a variety of settings. It should explicitly address the extent to which the property of invariant causal prediction has been validated for the models used to make predictions of the effects of potential future changes in policies. It should comment on the internal and external validity of the risk models and their predictions, and should present the results of empirical validation tests for the risk models and predictions. Chapter 3 and its appendices should clearly distinguish between *causal* C-R functions (describing how public health risks change in response to changes in ambient ozone levels) and *regression* C-R functions (describing how observed public health risks differ across different observed or estimated ambient ozone levels). These are in general different concepts and different curves. Causal C-R functions are relevant for policy analysis. The draft PA addresses regression C-R functions. The final PA should use validated causal C-R functions (satisfying the property of invariant causal prediction if possible) to predict effects of alternative policy choices.

Dr. Mark Frampton

General Comments

The EPA time-frame and process are inadequate for CASAC to provide a considered and insightful review of this PA. The review of the ISA and the PA are being done simultaneously, when logically the PA depends on the findings of the ISA. CASAC should be provided the opportunity to review, comment on, and receive responses from EPA on the ISA, before any consideration of the PA. The EPA should use CASAC's advice on the ISA to help inform the preparation of the PA. By preparing the PA prior to CASAC's review of the ISA, EPA is short-circuiting the process, and in effect severely limiting CASAC's ability to advise EPA on the ozone NAAQS.

Chapter 3: REVIEW OF THE PRIMARY STANDARD

There are concerns in the approach taken for the ozone risk assessments presented in this PA. The essentially exclusive use of lung function decrements in assessing ozone risk does not adequately consider other respiratory effects that are likely to be important in people with respiratory diseases such as asthma. The analyses do not adequately consider the risks for people with asthma.

The following summary points will be addressed below.

1. Asthma is a complex disease, with several important features beyond airflow limitation.
2. Many of the key features of asthma pathophysiology can be affected by exposure to ozone.
3. The risk assessments are based almost exclusively on studies in healthy adults, and make unverified assumptions about ozone health effects in children with asthma.
4. The current ozone NAAQS level of 70 ppb does not provide an adequate margin of safety for children with asthma.

1. Asthma is a complex disease [1]. It involves airflow limitation, airway inflammation, and nonspecific airways hyperresponsiveness. Injury to, and increased permeability of, the airway epithelium is an increasingly recognized feature of the disease. Remodeling of the airways is also part of asthma, with thickening of the submucosal basement membrane consistently seen in lung biopsies of people with asthma, even in those with normal pulmonary function.

Many people with asthma have normal lung function and are asymptomatic at baseline, but other features of the disease, including airway inflammation and airways hyperresponsiveness, persist even when they are in remission from the symptoms of the disease. Most children with asthma are able to be active and exercise outdoors. They develop problems when something triggers an exacerbation, such as exposure to an allergen to which they are sensitized, a respiratory infection, or air pollutants, among others. Arguably the most important potential adverse effect of acute ozone exposure in a child with asthma is not whether it causes a transient decrement in lung function, but whether it causes an asthma exacerbation.

2. Ozone has respiratory effects beyond its well-described effects on lung function. It increases airway inflammation, a key component in the pathophysiology of asthma. Eosinophilic inflammation is particularly important in allergic asthmatics, and we know from clinical studies that airway eosinophilia is increased in response to ozone exposure in asthmatics. Ozone increases non-specific airways hyperresponsiveness in clinical studies. And ozone exposure causes airway epithelial injury and increases airway epithelial permeability, both cardinal features in asthma pathophysiology. This increases the potential for materials deposited in the distal airways, such as particles or allergens, to access the lung interstitium and vascular space. These effects beyond lung function decrements likely contribute to the risk of an asthma exacerbation. Yet they are not captured or considered in the risk analysis.

EPAs current approach minimizes/ignores the full spectrum of potential ozone airway effects. The human clinical studies indicate that both lung function decrements and increased airway inflammation result from exposures as low as 60 ppb in the 6.6-hr studies. The focus in the risk assessment is solely on FEV_1, because that database is robust. But we know from other studies that the FEV_1 response and the airway inflammatory response occur via different mechanisms [2-4], and some people are more prone to one of these effects than the other. This means that there are individuals who will experience increases in airway inflammation without lung function decrements, or symptoms. The absence of symptoms could result in a failure of the individual to limit exposure, thereby further worsening the airway inflammatory effect of the exposure.

It is reasonable to expect that, in people with asthma, an increase in airway inflammation is an adverse effect, with the potential to increase the risk for an asthma exacerbation. Repeated episodes of airway inflammation may enhance airway remodeling, which occurs in asthma, and leads to irreversible reductions in lung function.

Studies in smokers provide additional evidence that adverse respiratory effects of ozone can occur in the absence of lung function decrements. Current active smokers are generally unresponsive to the lung function decrements of ozone exposure [5], but still may experience airway inflammation [2], and may be at risk for increased oxidative stress effects, because their alveolar macrophages are primed by the smoking [6].

3. The ozone PA makes the following **unverified assumptions**:

a. Lung function decrements in response to 7-8 hour exposures near 70 ppb are the same in asthmatic children as they are in healthy adults.

The clinical data in people with mild to moderate asthma, exposed at higher concentrations than those directly relevant to the standard, suggest that asthmatics do not have markedly increased FEV_1 declines compared with healthy subjects. But it is inappropriate to assume that this extends to lower concentrations, or to people with more severe disease. None of the low-concentration, 6 to 7 hr studies listed in Tables 3A-1 and -2 included asthmatics. And very few clinical studies have included severe or even moderate asthma, let alone asthmatic children. And none have included unstable asthmatics or those prone to exacerbations. This is a key knowledge gap, and raises legitimate questions about whether the current standard provides an adequate margin of safety for people with asthma.

b. Absence of symptoms means less adversity.

The PA seems to suggest that lung function decrements in the absence of symptoms do not represent an adverse health effect. But this should not apply to children with asthma.

c. Lung function and other respiratory effects are rapidly reversible in asthmatic children, similar to healthy adults.

The time course of the pulmonary function response is well established in healthy adults, but less well in children, and especially in children with asthma. We have no data on the persistence of respiratory effects in asthmatics following low-concentration, more prolonged exposures.

4. The current ozone NAAQS level of 70 ppb does not provide an adequate margin of safety for children with asthma.

The EPA focuses almost exclusively on lung function effects in its risk assessment because of the abundant human data on that measurement. The databases for ozone effects on airway inflammation, nonspecific airway hyperresponsiveness, airway epithelial injury, and epithelial permeability are much more limited than for lung function responses, in part because of greater challenges in measurement. However, the current analysis ignores the possibility, and in fact the likelihood, that transient lung function decrements may not be the most adverse effect of ozone exposure, especially for people with abnormal airways at baseline, as in asthma or COPD. We know from the clinical studies, cited in the ISA and the PA, that 0.60 ppb ozone exposure for 6.6 hrs with exercise increases airway inflammation (in addition to causing lung function decrements) in healthy people. Airway inflammation and other effects need to be considered in the risk assessment because of their relevance in chronic lung disease, especially asthma. The

exposure analysis tells us that up to 11% of asthmatic children will experience exposures of this magnitude in areas that just meet the current standard of 70 ppb. We don't know with any certainty how many of those children would/will experience worsening of their asthma as a consequence. But the clinical rationale supporting such a risk is compelling. The epidemiological studies, despite their remaining uncertainties, support this concern. It therefore seems clear that a NAAQS level of 0.70 ppb does not provide an adequate margin of safety, especially for people with airways disease such as asthma.

CASAC recognized this in its advice to the EPA during the 2014 review:

"The CASAC advises that, based on the scientific evidence, a level of 70 ppb provides little margin of safety for the protection of public health, particularly for sensitive subpopulations. In this regard, our advice differs from that offered by EPA staff in the Second Draft PA. At 70 ppb, there is substantial scientific evidence of adverse effects as detailed in the charge question responses, including decrease in lung function, increase in respiratory symptoms, and increase in airway inflammation. Although a level of 70 ppb is more protective of public health than the current standard, it may not meet the statutory requirement to protect public health with an adequate margin of safety." [Letter from H. Christopher Frey, CASAC Chair, to Gina McCarthy, EPA Administrator, dated June 26, 2014, p. ii, https://yosemite.epa.gov/sab/sabproduct.nsf/5EFA320CCAD326E885257D030071531C/%24File/EPA-CASAC-14-004+unsigned.pdf.]

Based on what we know about ozone respiratory effects presented in the ISA, and what we know about the nature of asthma, CASAC's advice in 2014 appears to be relevant for the current review.

Additional Comments

In the MOSES study [7], lung function decrements were not completely resolved (still were statistically significant) 22 hours after exposure.

Repeated exposures: attenuation of lung function decrements, but persistence of markers of lung injury.

Animal tox studies: the PA repeatedly points out that higher concentrations are used in these studies. It should also point out the relevant differences in the efficiency of nasal removal in rodents vs humans. Thus 400 ppb in a rat is the rough equivalent of …

P. 3-50 line 7: Rather than "assessing exposure, ventilation rate, intake dose, and estimated health risk", suggest "estimating exposure, ventilation rate, ozone intake, and health risk".

In the ISA, EPA has established a new health effect category of both short and long-term metabolic effects, each with a "likely" causality categorization, but has not included these effects in the risk assessment. This is most likely due to the difficulties in performing risk assessment without much evidence from human clinical or observational studies. The reasons for the absence of such a risk assessment should be at least briefly addressed in the PA.

3.5.3 Preliminary Conclusions, P. 378, line 8. "With regard to the lowest benchmark concentration of 60 ppb, the percentages are 3%, on average across the three years, and just below 5% in a single year period (Table 3-3)." This sentence appears to be incorrect or misplaced, and contradicts what is stated previously in this section. Table 3-3 indicates that 3 to 9% of asthmatic children will experience one such exposure day per year over 3 years, and 11% in the highest year.

P. 3D-80. For the MSS model, lung function decrements are assumed to be 0 for age >55 yrs. This model does not incorporate newer data on lung function effects in healthy older subjects [7], which demonstrated lung function effects in subjects older than 55 yrs. This should be acknowledged in the PA.

References

1. Fanta CH. Asthma. N Engl J Med. 2009;360(10):1002-14.

2. Torres A, Utell MJ, Morrow PE, Voter KZ, Whitin JC, Cox C, et al. Airway inflammation in smokers and nonsmokers with varying responsiveness to ozone. Am J Respir Crit Care Med. 1997;156:728-36.

3. Frampton MW, Morrow PE, Torres A, Voter KZ, Whitin JC, Cox C, et al. Part II: Airway inflammation and responsiveness to ozone in nonsmokers and smokers. Health Effects Institute Research Report. 1997;78:39-64.

4. Balmes JR, Chen LL, Scannell C, Tager I, Christian D, Hearne PQ, et al. Ozone-induced decrements in FEV_1 and FVC do not correlate with measures of inflammation. Am J Respir Crit Care Med. 1996;153:904-9.

5. Frampton MW, Morrow PE, Torres A, Cox C, Voter KZ, Utell MJ. Ozone responsiveness in smokers and nonsmokers. Am J Respir Crit Care Med. 1997;155:116-21.

6. Voter KZ, Whitin JC, Torres A, Morrow PE, Cox C, Tsai Y, et al. Ozone exposure and the production of reactive oxygen species by bronchoalveolar cells in humans. Inhal Toxicol. 2001;13:465-83.

7. Frampton M, Balmes J, Bromberg P, Stark P, Arjomandi M, Hazucha M, et al. Multicenter Ozone Study in oldEr Subjects (MOSES). Part 1. Health Effects Institute Research Report 2017;No. 192.

Dr. Sabine Lange

A reference list can be found at the bottom of this document for those studies that are not referenced in the ozone PA.

Charge Questions: *Chapter 3 – Review of the Primary Standard: What are the CASAC views on the approach described in chapter 3 to considering the health effects evidence and the risk assessment in order to inform preliminary conclusions on the primary standard? What are the CASAC views regarding the key considerations for the preliminary conclusions on the current primary standard?*

Air Quality

The EPA states in section 3.1.2.2 that "Analyses described in detail in the HREA suggested that reductions in O3 precursors emissions in order to meet a standard with an 8-hour averaging time, coupled with the appropriate form and level, would be expected to reduce O3 concentrations in terms of the metrics reported in epidemiologic studies to be associated with respiratory morbidity and mortality (80 FR 65348, October 26, 2015)."

However, multiple ozone chemistry analyses (e.g. Downey et al., 2015; Simon et al., 2012) have demonstrated that in an area where peak daily ozone concentrations have decreased over time, over the same period of time the lowest daily ozone concentrations have also decreased (due to the NOx disbenefit aspect of ozone chemistry). An example is provided in Figure 1. My general summary from the consultant responses to this is that decreasing peak ozone concentrations will not consistently decrease the mean ozone concentrations and therefore is not necessarily expected to improve the metrics associated with respiratory mortality and morbidity in epidemiology studies.

Health Effects Evidence and Risk Assessment

Accurate & Balanced Reporting

There are a few places in this document that require some editing to ensure fully accurate and balanced reporting of data and analyses.

In several places the EPA summarizes the the causality designations as: "The current evidence primarily continues to support our prior conclusions regarding the key health effects associated with O3 exposure." (Section 3.3.1, Section 3.5.1). This is not an accurate summary statement, because there have been some substantial changes in the causality determinations since the last

review. Those changes are described in the paragraph following this sentence, and so this initial statement needs to be changed to more accurately reflect that.

In section 3.3.1.1 the EPA states that "Evidence regarding respiratory infections and associated effects has been augmented by a number of epidemiologic studies reporting positive associations between short-term O3 concentrations and emergency department visits for a variety of respiratory infection endpoints (draft ISA, Appendix 3, section 3.1.7.4)." Section 3.1.7.4 of the ISA also shows a number of studies that do not report positive associations between ozone and infections - the EPA needs to consider how to report epidemiology results in a more balanced manner.

Fully Justified Conclusions

There are a few places in this document that require some editing to ensure that the EPA has fully supported the conclusions that are being drawn.

In section 3.3.1.2 (Other Effects), the EPA does not adequately explain why the evidence for metabolic effects is likely causal, when they state that the data is mostly from animal studies with high exposure levels and there is limited concordance with human epidemiology studies with some contradictory evidence. Similar with long-term exposure and metabolic effects.

In section 3.3.3, the EPA notes in reference to experimental animal results of respiratory effects that "The exposures eliciting the effects in these studies included multiple 5-day periods with O3 concentrations of 500 ppb over 8-hours per day (draft ISA, section 3.2.4.1.2)." This type of information should be considered for biological plausibility, not just when deciding on relevant concentrations for risk assessment.

Additional Policy-Relevant Information

There are some areas where additional information could be added to help provide information to decision makers. In Section 3.3.2 the EPA could add what fraction of the population (particularly at-risk populations if possible) are expected to spend 6.6 hours or more outdoors at moderate exertion. This information would help decision makers compare the exposure likelihood to the primary CHE studies.

In section 3.5.1 (Evidence-based considerations) the EPA notes that "The current evidence does not alter our understanding of populations at risk from health effects of O3 exposures." However, what about the new metabolism causality determination? Does this suggest that people who are obese or have metabolic syndrome are more susceptible?

Study Limitations

In section 3.3.3 the EPA states that "We have also considered what may be indicated by the epidemiologic studies regarding exposure concentrations associated with health effects, and particularly by such concentrations that might occur in locations when the current standard is met. In so doing, however, we recognize that these studies are generally focused on investigating the existence of a relationship between O3 occurring in ambient air and specific health outcomes, and not on detailing the specific exposure circumstances eliciting such effects" And "these studies generally do not measure personal exposures of the study population or track individuals in the population with a defined exposure to O3 alone. Notwithstanding this, we have considered the epidemiologic studies identified in the draft ISA as to what they might indicate regarding O3 exposure concentrations in this regard." It is good that the EPA acknowledged this limitation with these studies. Consistent with the recommendations from the expert consultants, these caveats should be applied to all similar air pollution epidemiology studies, not just those for ozone.

Clarity of Presentation

There are a few places in this document that require some editing to ensure that data and analyses are clearly reported.

In section 3.4.2 (Population Exposure and Risk Estimates for Air Quality Just Meeting the Current Standard) and elsewhere the EPA refers to the population exposure estimates (i.e. the estimates of percent of the population exposed to certain concentrations of ozone) as a risk estimate. On its surface, these estimates appear to be exposure, rather than risk, estimates. The EPA should clarify their definitions of risk and exposure for readers.

The EPA presents quite different risk estimates from the MSS and E-R models. These are discussed at length in Appendix 3D, with an in-depth justification of the choice of the E-R model risk results over the MSS results. The EPA should add more of this information to the main text to clarify further to the reader why they emphasize the E-R model results over the MSS results.

The EPA states that "The limited evidence that informs our understanding of potential risk to people with asthma is uncertain but indicates the potential for them to experience greater effects or have lesser reserve to protect against such effects than other population groups under similar exposure circumstances, as summarized in section 3.3.4 above." It is not the case that the limited evidence indicates the potential for people with asthma to experience greater effects, although it is true and logical that they may have less reserve. These two aspects need to be discussed separately and the differences noted, because the ways in which they are taken into account are different. For the former, you assume that they are a steeper E-R response, or a lower threshold

(although there is little data to suggest that this is the case). For the latter, you use a lower adverse effect threshold, as the EPA already does with the 10% FEV1 decrement threshold.

In section 3.4.5 (Public Health Implications), I suggest adding a summary of the percent of children with asthma experiencing a 10% FEV1 decrement, with a sentence or two about the adversity of those changes in lung function.

In section 3.6 (Key uncertainties and areas for future research) the EPA states that "In some cases, research in these areas can go beyond aiding standard setting to aiding in the development of more efficient and effective control strategies. We note, however, that a full set of research recommendations to meet standards implementation and strategy development needs is beyond the scope of this discussion. Rather, listed below are key uncertainties, research questions and data gaps that have been thus far highlighted in this review of the primary standard." These statements seem contradictory - stating that the research can go to the level of implementation, but then saying that it doesn't. And in fact the bulleted list includes no implementation guidance. I suggest that these be reworded or removed.

<u>Quantitative Uncertainty Analysis</u>

The EPA does not provide uncertainty bounds on their exposure or risk estimates. The ranges presented represent variability between cities, not uncertainty. There are many ways that some measure of uncertainty can be accounted for in these estimates, some of which are discussed and presented in the Appendix – these should be included in the main text to provide the Administrator with this information for decision making. For example, on page 3D-145, the EPA references Glasgow and Smith 2017 that provides a method for quantitative uncertainty evaluation. There is also an upper bound estimate of the ER function that is presented in Table 3D-64 – if there was an upper and lower bound function provided, then those could simply be used for some quantification of uncertainty.

The EPA discusses uncertainties with air quality analysis in section 3.4.4 (Key Uncertainties) as well as the ways in which they have tried to reduce this uncertainty. However, this type of uncertainty is a prime candidate for a quantitative uncertainty analysis because there are estimates on the uncertainties associated with the air quality estimates.

In section 3.4.4 (Key Uncertainties) of this PA, the EPA notes that "In recognition of the lack of data for some at risk groups and the potential for such groups, such as children with asthma, to experience lung function decrements at lower exposures than healthy adults, both models generate nonzero predictions for 7-hour concentrations below the 6.6-hour concentrations investigated in the controlled human exposure studies." The EPA should provide a rationale for assuming a lack of threshold in an exposure-response relationship as a way of considering potential at-risk populations that may not have been characterized in an exposure-response

assessment. As per the expert consultant responses it is not clear that this is a validated assumption for models based on CHE study data.

The EPA also notes in this section that there is a lack of information about the factors that make people more susceptible to ozone-related effects, and that the risk assessment could therefore be underestimating the risk. However, the exposure-response model used to estimate the risk of lung function decrements uses those people in the health population with a greater response to ozone than the mean response (i.e. that fraction of the people in controlled human exposure studies who had FEV1 responses >10%, 15%, or 20%). Therefore this method already includes some consideration for more susceptible responders in the population and the EPA should address that in their explanations and interpretations from these models.

Risk Threshold

The EPA states in section 3D.2.8.2.2 that the McDonnell-Stewart-Smith (MSS) model has a threshold of accumulated dose built into the model. The EPA notes that this is not a concentration threshold and does not preclude effects at lower concentrations. However, it is a threshold that suggests (as has been suggested by other models (Schelegle et al., 2012) and is consistent with the known MOA of ozone in the respiratory tract) that there are ozone doses below which no effects are expected to occur. This concept of threshold should be discussed by EPA in the main text and should be incorporated into the E-R model.

Other Notes

In the Appendices in a number of locations there is “Error Reference Not Found!” - these need to be located and fixed.

In section 3.3.1.1 Footnote: “As recognized in section 3.3.1.1 above, the single newly available 6.6-hour study is for subjects aged 55 years of age or older, and has a slightly lower target ventilation rate for the exercise periods. The exposure concentrations were 120 ppb and 70 ppb, only the former of which elicited a statistically significant FEV1 decrement in this age group of subjects (draft ISA, Appendix 3, section 3.1.4.1.1.2).” This was a typo I think - the Arjomandi study was a 3-hour exposure, not a 6.6 hour exposure.

The end of the second bullet point on page 3-51 is cut-off mid sentence.

The last sentence of the first paragraph on page 3-82 needs to be edited - there seem to be words missing or juxtaposed.

There is a figure (referenced in page 3D-91) that seems to be labeled as “0”, instead of with the figure name.

Questions to Consultants

1) *Multiple ozone chemistry analyses (e.g. Downey et al., 2015; Simon et al., 2012) have demonstrated that in an area where peak daily ozone concentrations have decreased over time, over the same period of time the lowest daily ozone concentrations have also decreased (due to the NOx disbenefit aspect of ozone chemistry). An example is provided in Figure 1. What are your thoughts about the change of annual average ozone concentrations (which tend to be the focus of epidemiology studies) with decreases in annual peak ozone concentrations?*

Responses:

Dr. Jaffe: "Yes, I agree with your statements: Annual averages have changed much less than the design values due to the NOx disbenefit. How this impacts health is a question for epidemiologists, so I am not able to answer."

Dr. Jansen: "While there may be exceptions, I would expect any changes in the annual averages to be small and could go in either direction. One question I would ask is what the epidemiological studies do when the monitors do not operate for the full year, which is the case of most monitors."

Dr. Lipfert: "I used the data for two frequency distributions from Figure 1 to estimate how cumulative risks could depend on the exposure-response function (ERF) threshold. I postulated a linear ERF so that the contribution to the total risk is the product of the frequency and the midpoint of the O3 concentration bin (Figure 2). With no threshold or up to about 30 ppb, there is no difference in cumulative risk, as is the case with high thresholds (> 80 ppb). In the mid-range (thresholds from 40-80 ppb), the cumulative risk for the higher design value (DV) distribution is about double that of the lower one while the ratio of the 2 DVs is only 1.3, showing the importance of thresholds. Most epi studies have used some measure of peak O3 rather than the annual average. My own studies (see Appendix) have used the 95th percentile of the daily O3 averages."

Dr. North: "I fully agree that the decrease in annual average ozone exposure is significant. I continue to have concerns on whether the epidemiological results imply manipulative causality as opposed to association, and I am pleased to read that EPA is not using these epidemiological results but rather basing its recommendations (for the last round and the present one) mainly on human clinical studies. There are still areas of the US, such as the Sacramento area, that have MDA8 levels well above the current standard of 70 ppb. I would like to see CASAC focus on the public health risk in these areas. See my general comments above regarding asthma. There ought to be more research to see if high ozone episodes in Sacramento (and elsewhere in the Central

Valley and the Los Angeles to San Diego area) have led to increases in hospital admissions and emergency department visits."

Dr. Parrish: "The general situation exemplified in Figure 1 is more or less typical of the temporal evolution of urban ozone concentration distributions, where maximum daily 8-hour average (MDA8) ozone concentrations have decreased, but the minimum MDA8 values have increased. This causes the distribution of MDA8 ozone concentrations to narrow, as shown in the figure. The cause of the increase in the minimum MDA8 ozone concentrations is a reduction in fresh NO emissions in the urban area. The effect of these emissions on days of low photochemical activity is for NO to react with ozone, forming NO2. Thus, between the early 2001-2003 period and the later 2013-2015 period, on days of low photochemical activity the MDA8 ozone concentrations have increased but the NO2 concentrations have decreased. Since the mean and median MDA8 have not changed significantly over this time interval, it may well be that the annual average ozone concentrations have not changed much. The possibility that annual average ozone concentrations have not changed, but that NO2 concentrations have decreased, would be important to consider in the interpretation of epidemiology studies that focus on annual average ozone concentrations."

Dr. Sax: "EPA does acknowledge that "Reductions of NOX emissions are expected to result in a compressed O3 distribution, relative to current conditions" (Draft Ozone PA, pg. 2-4), and it looks like that is what is shown in Dr. Lang's Figure 1. As Figure 1 shows, however, this also means that there will be more days that experience somewhat higher ozone concentrations, although potentially no days with levels that exceed very high concentrations. With regards to how these changes should be interpreted for epidemiology studies, I think the larger issue of how ambient levels relate to actual personal exposures of ozone and how this impacts exposure measurement error in the epidemiology studies is a more critical issue. In the PA, EPA acknowledge this important source of uncertainty, and is one reason provided for not conducting the "epidemiology- based" risk assessment."

2) *Is an epidemiology study with higher statistical power (sample size) innately more protected against problems of confounding, error, and bias, than an epidemiology study with lower statistical power (sample size)?*

<u>Responses:</u>

Dr. Jansen: "I am not a statistician but I do not see how it could "protect against" confounding etc. Confounding exists or it doesn't. If one tests for confounding then maybe the higher statistical power allows it to be demonstrated more reliably."

Dr. Lipfert: "No; sample size only affects random error. Effects of measurement error, incomplete control of confounders, or a miss-specified model are independent of sample size.

Cohort analyses are widely regarded as the best approach to studying long-term effects, but cohort sample size can only be increased by recruiting more subjects or extending follow-up time, which entails aging and loss of the more susceptible subjects."

Dr. North: "No. I responded to a similar question in the O3 ISA. Statistical power comes from having a large sample size, and NOT from having resolved issues of confounding, error, and bias. Consider we have a study of 10 million children showing that shoe size predicts reading ability. Because data were obtained from 10 million children, a very large number, the confidence interval is quite narrow. Does this apparently accurate prediction imply that getting children larger shoes will improve their reading ability? No way!"

Dr. Sax: "The issue of statistical power is separate from issues related to confounding, errors and bias. You can have a very large study that has serious confounding issues if these are not controlled for (or are unmeasured). Similarly, large studies can be prone to selection bias, exposure measurement errors, etc. Sample size (or statistical power) will affect whether you are able to "detect" an effect, and is only one aspect of study quality (larger sample sizes are preferred), but is separate from other issues of study quality, which are associated with the study design, execution, and analyses methodology. That is, poor study design, execution or poor methodology can lead to errors and biases."

Dr. Thomas: "No. Sources of selection, information, and confounding biases could potentially affect any study, irrespective of sample size (or power). That said, very large studies conducted by highly experienced investigators generally make every effort to address such problems in the design and analysis and would discuss these issues in their publications. Also, studies of individual-level data may have access to more information to address bias than meta-analyses or aggregate-level studies."

3) *In section 3.3.3 (Exposure Concentrations Associated with Effects) and section 3.3.4 (Uncertainties in the Health Effects Evidence), the EPA notes that the epidemiology studies are generally assessing the associations between ambient ozone and specific health outcomes and are not investigating the details of the exposure circumstances eliciting these effects (e.g. pg 3-40[1] and pg 3-43[2]). Do you think that this statement is correct? If so, is this statement generally true of air pollution epidemiology studies, or is it peculiarly specific to ozone? If it is not specific to ozone, then should this caveat always be considered when evaluating exposure concentrations associated with these types of epidemiology studies?*

Responses:

Dr. Jansen: "Yes, I believe those statements to be correct. I believe the statements are generally true and the caveat should apply generally, not to just ozone. I suspect the reason it is highlighted here in the ozone proceeding is because ozone concentrations may be more variable than, say, PM among micro-environments. Exposure is very dependent on the integrated levels of ozone in those micro-environments, thus the use of the highly complex and data intensive APEX model. That said, it is not clear that why similar efforts are not done for PM and the other NAAQS. Studies have shown differences in PM and their species between the ambient and homes, restaurants, groceries, etc. In many cases PM is higher indoors due to numerous sources (e.g., cooking, dust, pet dander). Note that indoor sources of ozone (e.g., air purifiers) were explicitly excluded in this assessment. I find it curious that EPA expends so much effort with APEX on ozone and not PM. Finally, the whole APEX discussion implies but does not demonstrate that the complexities added to APEX result in a more accurate exposure estimate."

Dr. Lipfert: "Yes, this is correct in all cases. Epidemiology deals only in numbers, not rationales. Reduced lung function may lead to hospitalization and then to death, but individual longitudinal analyses would be required to follow such a path. Each of these processes would require its own long-term analysis with its own confounders to be controlled and it is possible, perhaps likely, that different pollutants could be involved in each process (except for smoking). I know of no epidemiology studies that link sequential long-term effects. The time-series model of Murray and

[1] "We have also considered what may be indicated by the epidemiologic studies regarding exposure concentrations associated with health effects, and particularly by such concentrations that might occur in locations when the current standard is met. In so doing, however, we recognize that these studies are generally focused on investigating the existence of a relationship between O3 occurring in ambient air and specific health outcomes, and not on detailing the specific exposure circumstances eliciting such effects."

[2] "As associations reported in the epidemiologic analyses are associated with air quality concentration metrics as surrogates for the actual pattern of exposures experienced by study population individuals over the period of a particular study, the studies are limited in what they can convey regarding the specific patterns of exposure circumstances (e.g., magnitude of concentrations over specific duration and frequency) that might be eliciting reported health outcomes."

colleagues (see Appendix) postulates a frail subpopulation from which all daily deaths emanate in response to spikes in air pollution and/or temperature. An advanced version of this model solves for prior relationships with air pollution or temperature but the corresponding time scales are uncertain. This model decouples the causes of frailty from the causes of daily mortality which are likely to differ. Studies of daily mortality and hospital admissions have indicated similar relationships with ozone, but longer-term studies have not."

Dr. North: "I am inclined to think that the problem is a general one that will only be resolved by getting data on potential confounders such as income (more generally, socioeconomic status), and extremes of temperature, which have large impacts on mortality and morbidity via mechanisms independent of air pollutants. However, we should understand that at VERY high exposure levels, air pollutants such as ozone and fine particulate matter (e.g., smoke) can cause illness and death. The shape of the exposure-response relationship is critical for assessing the risks. Extrapolation over orders of magnitude is readily done with available mathematics. But how this extrapolation is done should reflect judgment on the biological mechanisms underlying damage to health."

Dr. Sax: "I agree with this statement – the ambient data, whether from fixed-site monitors or from modeling data are only surrogates of the actual personal exposures and any differences contribute to exposure measurement errors. This statement is true for all air pollution studies, not only ozone, and this caveat should be included for other air pollution epidemiology studies."

Dr. Thomas: "The two statements cited are generally correct and apply broadly to air pollution epidemiology studies, not just ozone. Most epidemiologic studies are based on measurements of ambient pollution levels, which are readily available. For some pollutants, indoor sources or penetration from outdoor sources, local variation in pollutant concentrations, time-activity patterns, etc., can be important sources of inter-individual variation, which some studies have attempted to quantify by, for example, personal monitoring, microenvironmental measurements, exposure modeling, GPS or accelerometer instruments, etc., but such studies are expensive and may be infeasible for large-scale epidemiologic studies. Since the statements queried do apply to ozone studies, I don't see than any particular caveats are needed to point out the generality of this issue."

<u>Exposure-Response Modeling</u>

4) *In section 3.4.4 (Key Uncertainties) of this PA, the EPA notes that "In recognition of the lack of data for some at risk groups and the potential for such groups, such as children with asthma, to experience lung function decrements at lower exposures than healthy adults, both models generate nonzero predictions for 7-hour concentrations below the 6.6-hour concentrations investigated in the controlled human exposure studies." Is assuming a lack of threshold in an exposure-response relationship a standard method for*

considering potential at-risk populations that may not have been characterized in an exposure-response assessment?

Responses:

Dr. Lipfert: "I'm not aware of any "standard methods" for dealing with thresholds, aside from controlled (clinical) experiments that are sensitive to selection of subjects. A linear relationship may be the default option with noisy data for which the lowest concentrations may be the least reliable. However, there are good reasons to accept the concept of (essentially) zero threshold, that differ between long- and short-term analyses. The time-series model of Murray and colleagues analyzes daily mortality relationships in terms of the combination of subject frailty and air pollution. Death may result from excess frailty or excess pollution or both. As a result, in a sufficiently large population there will likely always be someone sick enough to succumb to a small air pollution perturbation; the threshold depends on the population at risk. The situation with long-term effects is more complicated. They result from cumulative or repeated exposures after a period of latency, so that effects of pollution abatement will be delayed and it becomes difficult to define the appropriate exposure over the periods involved. Background ozone will also play a role. Here the threshold depends on the characteristics of exposure. Finally, health responses during a year will be the result of both long-and short-term exposures, so that even in the absence of long-term effects there may be pollution-related mortality at any outdoor concentration level. Also, different pollutants may be involved at different time scales."

Dr. North: "Yes, assuming a lack of threshold has become a standard method in many areas of EPA's risk assessment practice. Many of us old-timers believe this practice is questionable, because absence of evidence is not evidence of absence. The biological mechanisms underlying the adverse health response should be assessed based on available information including judgment. Traditional toxicology has used a sigmoid shaped exposure-response function, on the basis that very small exposures (episodic or cumulative) are unlikely to trigger an adverse response but as the exposure increases, the body's defenses and repair mechanisms can become inadequate, so the adverse effect becomes common in an exposed population. And the response may saturate with most or all of those who are susceptible to it having the adverse response – e.g., given enough bacteria in the spoiled food, nearly everyone gets sick from eating it. But linearity to zero became common in cancer risk assessment. This assumption was originated as a health-protective default assumption for screening: a plausible upper bound for identifying chemicals deserving more detailed risk analysis, and not for estimating the incidence of human cancer. But linear to zero is often used for the latter purpose."

Dr. Sax: "This approach does not make sense to me. If asthmatics are truly more susceptible to the effects of ozone, then it might be that the threshold for effects might be lower, but not zero. Although data are limited, the data that are available do not indicate that asthmatics are more susceptible than non-asthmatics to the effects of ozone. In fact, data are inconsistent, with some

studies indicating effects in asthmatics at elevated ozone exposures, but others showing no effects. For example, no effects on lung function were observed in asthmatics compared to non-asthmatics at exposures to 400 ppb for 2 hours (Alexis et al., 2000) and 200 ppb for 2 hours (Mudway et al., 2001)."

Dr. Thomas: "As I pointed out in earlier rounds of questions, the exact shape of a dose-response relationship at low doses, including the existence or not of a threshold, is difficult if not impossible to determine from feasible-sized epidemiologic studies. Hence, the default analysis model generally assumes low-dose linearity (or log-linearity depending on the form of the outcome variable); see for example the classic paper by Crump, Hoel, Langley, and Peto (1976) I previously cited. This would be true for either main effects in the whole population or for effect modification in potentially sensitive subpopulations, to the extent that the necessary data on individuals are available. The question of effects below the current standard is particularly important, and especially for highly sensitive groups; to the extent that such data exist, any demonstrable low-dose associations should be considered in revising the standard, whether or not the assumption of low-dose linearity or thresholds can be tested."

5) *The EPA also notes in this section that there is a lack of information about the factors that make people more susceptible to ozone-related effects, and that the risk assessment could therefore be underestimating the risk. However, the exposure-response model used to estimate the risk of lung function decrements uses those people in the health population with a greater response to ozone than the mean response (i.e. that fraction of the people in controlled human exposure studies who had FEV1 responses >10%, 15%, or 20%). Does this method already include consideration for more susceptible people in the population?*

<u>Responses:</u>

Dr. Lipfert: "Most epidemiology studies assume a homogeneous population at risk which may be convenient but is unrealistic. The remaining life expectancies of those aged 65 and over range from one day to 35 y or more with a median around 15 y. (This situation pertains for populations but not necessarily cohorts, depending on subject selection.) Many air pollution epidemiology studies have shown higher risks for subjects with pre-existing conditions. Lung cancer mortality rates are proportional to the cumulative cigarettes smoked, even though not all smokers get lung cancer. Following this model, we would expect air pollution-related mortality to respond to cumulative exposures from a few days to decades, depending on many other variables including preexisting disease. The answer to this question is thus: Yes, air pollution epidemiology includes all degrees of susceptibility but the most highly susceptible subjects may dominate the group response."

Dr. North: "I am concerned that FEV1 decrements are not a good indicator for adverse health impacts in sensitive populations. (See my general comments at the beginning of this response. FEV1 measurements vary a good deal. The Belzer-Lewis paper mentioned in my O3 ISA response has perceptive criticism about using FEV1 data in research.) It seems to me that lack of information, referring to the words you use in your first sentence, (1) should motivate detailed studies of the people that are judged to be at highest risk, and (2) leaders of agencies such as EPA should think beyond legally required standard setting to the bigger issue of how to protect public health with an adequate margin of safety. If adverse health effects are judged to be essentially absent for much of the United States (a reasonable inference from Figure ES-1 in the ISA and Figure 2-5, page 2-12 in the PA), then attention should be focused on the remaining areas where such adverse health effects may still be occurring. Are these adverse health impacts really there in these remaining areas, or are our government officials being overly precautionary and protective in setting standards, but ignoring major public health protection needs by assuming that some causes, such as wildfires, are "natural background?" EPA should be using common sense and not be trapped in traditions that violate common sense. The levels of ozone and fine particulate matters that millions of people in California have experienced from wildfire smoke plumes in 2017, 2018, and 2019 are far above the NAAQS standards and pose serious health effects, especially to members of sensitive subgroups. Some of these people are among my family, my friends, and my neighbors. The costs involved in reducing these risks to health from wildfire plumes are very large. So are the costs of bringing ozone levels in Sacramento into compliance with a 70 ppb MDA8 standard, even if with wildfire periods are exempted. (In my humble judgment, the former activity makes much more sense than the latter.) EPA staff and CASAC should acknowledge these facts in their written documents, as part of advising the EPA Administrator on strategy with respect to criteria air pollutants. I believe giving such advice is within the legal mandate of CASAC under the Clean Air Act."

Dr. Sax: "The controlled human exposure studies that form the basis of the exposure-response model are based on exposure circumstances that are highly unlikely to occur in the general population, and in particular in susceptible population groups (i.e., heavily exercising individuals exposed to elevated concentrations of ozone over extended periods of time). Only outdoor workers are likely to experience the exposure conditions in these studies. In addition, the results clearly indicate that only a small percentage of the study volunteers (although generally healthy adults) had a statistically significant response to ozone, and as noted by Dr. Lange, these responders likely represent people that are more susceptible to ozone (particularly at lower ozone concentrations). Therefore, I agree that the model already represents a very conservative estimation of ozone effects that are likely to be protective of sensitive population groups."

Dr. Thomas: "This question appears to relate more to controlled human exposure studies than to epidemiologic studies but does seem to be a reasonable approach for getting a handle on inter-individual variability in susceptibility in that context. Obviously, the slope of an exposure-response relationship in the general population will underestimate risk for more sensitive

individuals, or more importantly, for identifiable subgroups. Of course, there are other characteristics than lung function (e.g., genetic variants, age/gender, baseline health status, etc.) that could influence sensitivity of ozone or other pollutants. To the extent that the necessary data are available, most epidemiologic studies have reported variation across quantifiable subgroups, and given EPA's mandate to provide adequate protection to such groups as well as to the entire population should be taken into consideration in revising standards."

References

Downey, N., Emery, C., Jung, J., Sakulyanontvittaya, T., Hebert, L., Blewitt, D., Yarwood, G., 2015. Emission reductions and urban ozone responses under more stringent US standards. Atmos. Environ. 101, 209–216. https://doi.org/10.1016/j.atmosenv.2014.11.018

Schelegle, E.S., Adams, W.C., Walby, W.F., Marion, M.S., 2012. Modelling of individual subject ozone exposure response kinetics. Inhal. Toxicol. 24, 401–15. https://doi.org/10.3109/08958378.2012.683891

Simon, H., Baker, K., Phillips, S., 2012. Compilation and interpretation of photochemical model performance statistics published between 2006 and 2012. Atmos. Environ. 61, 124–139.

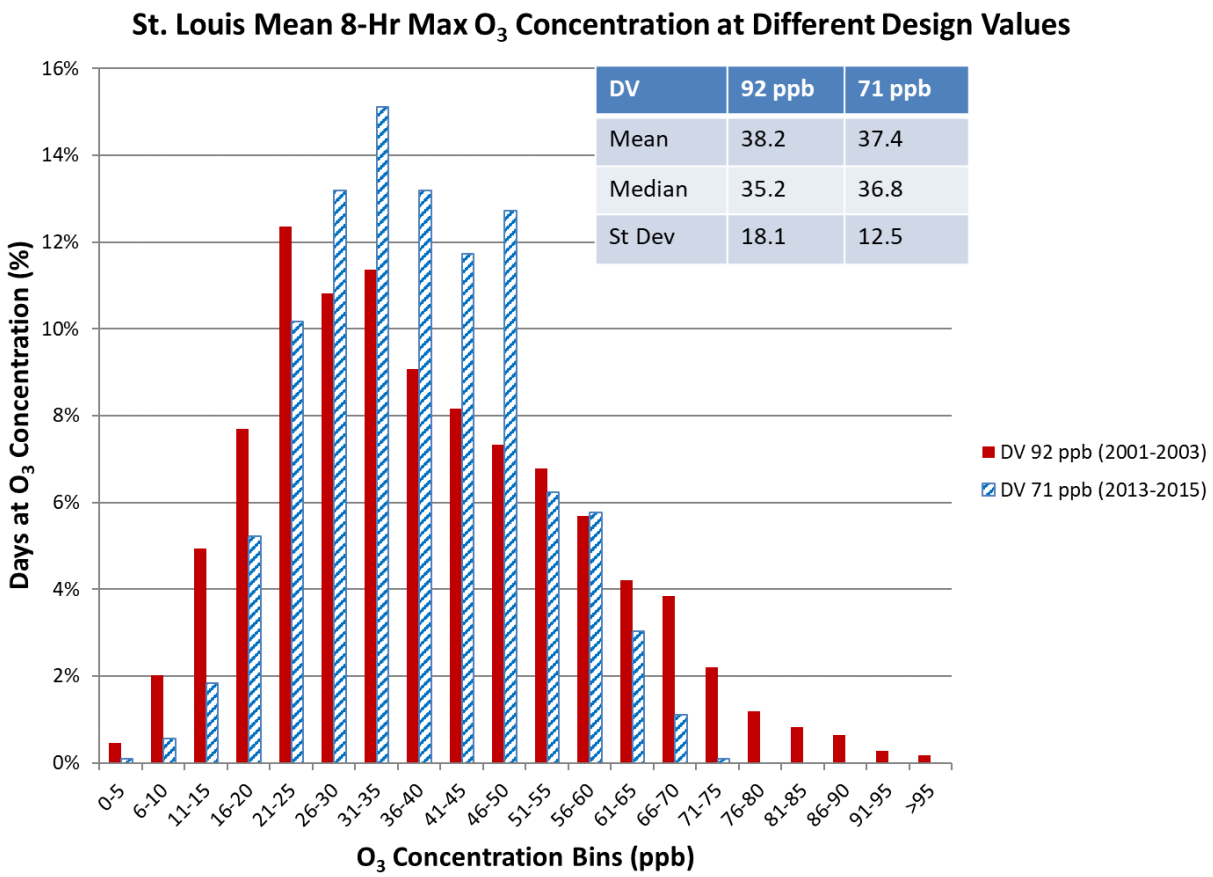


Figure 1. Distribution of Daily 8-Hr maximum ozone concentrations in St. Louis (averaged over all monitors in the city) for the 3-year period of 2001-2003 (red bars) or 2013-2015 (hatched blue bars); DV – design value.

Dr. Ronald J. Kendall

The Clean Air Scientific Advisory Committee (CASAC) has been asked to review the document, "Policy Assessment for the Ozone National Ambient Air Quality Standards, External Review Draft" submitted October 31, 2019. The document will be referred to as 2019 Draft IRP and Ronald J. Kendall was assigned Chapter 4 – Review of the Secondary Standard and the charge was as follows:

> *Chapter 4 – Review of the Secondary Standard: What are CASAC views on the approach described in Chapter 4 to considering the evidence for welfare effects in order to inform preliminary conclusions on the Secondary Standard? What are the CASAC views regarding the key considerations for the preliminary conclusions on the Secondary Standard?*

<u>Background on the Current Standard</u>

The current Standard was set in 2015 based on the scientific and technical information available at that time as well as the Administrator's judgements regarding the available welfare effects evidence, the appropriate degree of public welfare protection for the revised Standard, and available air quality information on seasonal cumulative exposures that may be allowed by such a Standard (80 FR 65292, October 26, 2015). With the 2015 decision, the Administrator revised the level of the Secondary Standard for photochemical oxidants, including ozone (O_3) to 0.070 ppm (70 ppb) in conjunction with retaining the indicator (O_3), averaging time (8 hours), and form (4th-highest annual daily maximum 8-hour average concentration, averaged across three years).

The welfare effects evidence base available in the 2015 Review included decades of extensive research on the phytotoxic effects of O_3, conducted both in and outside of the U.S. that documents the impacts of ozone on plants and their associated ecosystems (U.S. EPA, 1978, 1986, 1996, 2006, 2013).

In light of the extensive evidence base, the 2013 Integrated Science Assessment (ISA) concluded there was a causal relationship between ozone and visible foliar injury, reduced vegetation growth, reduced productivity in terrestrial ecosystems, reduced yield and quality of agricultural crops, and alteration of belowground biogeochemical cycles. In addition, the 2013 ISA concluded there was likely to be a causal relationship between O_3 and reduced carbon sequestration in terrestrial ecosystems, alteration of terrestrial ecosystem water cycling, and alteration of terrestrial community composition (2013 ISA). Further, based on the then available evidence with regard to O_3 effects on climate, the 2013 ISA also found there to be a causal

relationship between changes in tropospheric ozone concentrations and radiative forcing, found there likely to be a causal relationship between tropospheric ozone concentrations and effects on climate as quantified through surface temperature response, and found the evidence to be inadequate to determine if a causal relationship exists between tropospheric ozone concentrations and health and welfare effects related to UV-B shielding (2013 ISA).

The 2015 Decision was a public welfare policy judgment made by the Administrator, which drew upon the available scientific evidence for O_3-attributable welfare effects and on analyses of exposures and public welfare risks based on impacts to vegetation, ecosystems and their associated services, as well as judgements about the appropriate weight to place on the range of uncertainties inherent in the evidence and analyses.

Considerations Regarding Adequacy of the Prior Standard

The Administrator's conclusion in the 2015 Review regarding the adequacy of the Secondary Standard that was set in 2008 (0.075 ppm, as annual 4th-highest daily maximum 8 hour average concentration averaged over three consecutive years) gave primary consideration to the evidence of growth affects in well-studied tree species and information in cumulative seasonal ozone exposures in certain study areas. In doing so, the exposure information for Class I areas was evaluated in terms of the W126 Cumulative Seasonal Exposure Index, an index recognized by the 2013 ISA as a mathematical approach "for summarizing ambient air quality information in a biologically meaningful form for ozone vegetation effects purposes" (2013 ISA). The EPA focused on the W126 index for this purpose consistent with the evidence of the 2013 ISA and advice from the Clean Air Scientific Advisory Committee (CASAC). The Administrator gave particular weight to analysis with focus on exposures in Class I areas, which are lands that Congress set aside for specific uses intended to provide benefits to the public welfare, including lands that are to be protected so as to conserve the scenic value and the natural vegetation and wildlife within such areas and to leave them unimpaired for the enjoyment of future generations. This emphasis on lands afforded special government protections such as national parks and forests, wildlife refuges, and wilderness areas, some of which are designated as Class I areas under the Clean Air Act, was consistent with a similar emphasis in the 2008 Review of the Standard (73 FR 16485, March 27, 2008).

As noted across past reviews of the Ozone Secondary Standard, Administrator's judgments regarding effects that are adverse to public welfare consider the intended use of the ecological receptors, resources, and ecosystems affected. Thus, in the 2015 Review, the Administrator utilized the median RBL estimate for the studied species as a quantitative tool within a larger framework of considerations pertaining to the public welfare significance of O_3 effects. The Administrator recognized such considerations to include effects that are associated with effects on growth and that the 2013 ISA determined to be causally or likely causally related to ozone and ambient air, yet for which there are greater uncertainties affecting estimates of impacts on

public welfare. These other effects included reduced productivity in terrestrial ecosystems, reduced carbon sequestration in terrestrial ecosystems, alteration of terrestrial community composition, alteration of below ground biogeochemical cycles, and alteration of terrestrial ecosystem water cycles. The Administrator in considering the revised lower standard, noted that a revised Standard would provide increased protection for other growth-related effects, including for relative yield loss (RYL) of crops, reduced carbon storage and for types of effects for which it is more difficult to determine public welfare significance, as well as for other welfare effects of ozone, such as visible foliar injury (80 FR 65390, October 26, 2015).

In reaching a conclusion in the amount of public welfare protection from the presence of ozone and ambient air that is appropriate to be afforded by a revised Secondary Standard, the Administrator gave particular consideration to the following:

1. The nature and degree of effects of O_3 on vegetation,
2. The strength and limitations of the available and relevant information,
3. Comments from the public on the Administrator's proposed decision, and
4. The CASAC reviews regarding the strength of the evidence and its adequacy to inform judgements on public welfare protection.

It was also noted that the Clean Air Act does not require that a Secondary Standard be protective of all effects associated with a pollutant in the ambient air, but rather those known or anticipated effects judged "adverse to the public welfare" (CAA Section 109).

<u>Does the Current Evidence Alter Conclusions from the Last Review Regarding the Nature of Welfare Effects Attributable to O_3 in Ambient Air?</u>

The evidence newly available in this Review supports, sharpens, and expands on the conclusions reached in the last Review (Draft Ozone ISA, Appendices 8 and 9). Consistent with the evidence in the last Review, the currently available evidence describes an array of ozone effects on vegetation and related ecosystem effects as well as the role of ozone in radiative forcing and effects on temperature, precipitation, and related climate variables. Evidence newly available in this review augments more limited previously available evidence related to insect interaction with vegetation, contributing to conclusions regarding ozone effects on plant-insect signaling (Draft Ozone ISA, Appendix 8) and on insect herbivores (Draft Ozone ISA, Appendix 8). Thus, the conclusions reached by EPA in the last Review are supported by the current evidence base and conclusions are reached in a few new areas based on the now expanded evidence. The 2019 Ozone PA details of effects of ozone on vegetation and ecosystem processes are reviewed in detail and updated with newly available evidence.

Public Welfare Implications

The public welfare implications of the evidence regarding ozone welfare effects are dependent on the type and severity of the effects, as well as the extent of the effect at a particular biological or ecological level of organization. In the Draft Ozone PA, EPA discusses such factors in light of judgements and conclusions made in prior reviews regarding effects on the public welfare. As provided in Section 109 (b) (2) of the Clean Air Act, the Secondary Standard is to "specify a level of air quality the attainment and maintenance of which in the judgement of the Administrator…is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of such air pollutant in the ambient air". The Secondary Standard is not meant to protect against all known or anticipated ozone related welfare effects, but rather those that are judged to be adverse to the public welfare in a bright line determination of adversity it is not required in judging what is requisite. Thus, the level of protection from known or anticipated adverse effects to public welfare that is requisite for the Secondary Standard is a public welfare policy judgement to be made by the Administrator.

Is There Information Newly Available in this Review Relevant to Consideration of the Public Welfare Implications of Ozone Related Welfare Effects?

The categories of effects identified in the Clean Air Act to be included among welfare effects are quite diverse and, among these categories, any single category includes many different types of effects that are of broadly varying specificity and level of resolution. For instance, effects on vegetation is a category identified in the Clean Air Act Section 302 (h), and the 2019 Ozone ISA recognized numerous vegetation related effects of ozone at the organism, population, community, and ecosystem level (Draft ISA, Appendix 8). In the decisions to revise the Secondary Standard in the last two reviews (2008, 2015) the Administrator recognized that by providing protection based on consideration of effects in natural ecosystems in areas afforded special protection, the revised Secondary Standard would also "provide a level of protection for other vegetation that is used by the public and potentially affected by ozone including timber, produce grown for consumption and horticultural plants used for landscaping" (80 FR 65403, October 26, 2015). EPA provides in the Ozone PA figure 4-2. Potential effects of O_3 on the public welfare, which does an excellent job at summarizing the potential effects of causal or likely to be causal impact of ozone on vegetation at the organism, population, community, and ecosystems levels.

Exposures Associated with Effects

The types of effects identified in Figure 4-2 of the Ozone PA vary widely with regard to the extent and level of detail of the available information that describes the ozone exposure circumstances that may elicit them. Therefore, EPA organized a section in the 2019 Ozone

PA to address first, effects of ozone exposure on growth and yield effects, a category of effects for which information on exposure metrics and E-R relationships is most advanced. In addition, EPA discusses the current information available regarding exposure metrics and relationships between exposure and the occurrence and severity of visible foliar injury.

Growth Related Effects

The longstanding body of vegetation effects evidence includes a wealth of information on aspects of ozone exposure that are important in influencing effects on plant growth and yield (Draft 2019 ISA). A variety of factors have been investigated, including "concentration, time of day, respite time, frequency of peak occurrence, plant phenology, predisposition, etc.," (2013 Ozone ISA). In the last several reviews, based on the then available evidence, as well as advice from the CASAC, the EPA has focused on the use of cumulative, seasonal concentration-weighted index for considering the growth related effects evidence and in quantitative exposure analyses for purposes of reaching conclusions on the Secondary Standard. More specifically, the EPA used the W126-based cumulative, seasonal metric (Draft 2019 ISA). This metric, commonly called the W126 Index, is a non-threshold approach described as the sigmoidally weighted sum of all hourly ozone concentrations observed during a specified daily and seasonal time window, where each hourly ozone concentration is given a weight that increased from 0-1 within increasing concentration (2013 ISA). The most well studied data sets in this regard are those for 11 tree species seedlings and ten crops referenced and described by Lee and Hogsett (1996) and Hogsett et al (1997). These datasets include 1) for growth effects on seedlings of a set of tree species and 2) for quality and yield effects of a set of crops. These datasets, which include growth and yield response information across a range of multiple seasonal cumulative exposures, were used to develop robust, quantitative, E-R functions for reduced growth (termed Relative Biomass Loss or RBL). In seedlings of the tree species and E-R functions for RYL for a set of common crops (Draft 2019 ISA, Appendix 8) the EPA's conclusions regarding exposure levels of ozone associated with vegetation related effects at the time of the last review were based primarily on these established E-R functions. The 2019 Ozone Draft ISA concludes that "the cumulative exposure indices, including the W126 Index, "are the best available approach for studying the effects of ozone exposure on the vegetation in the U.S." (Draft 2019 Ozone ISA, Appendix 8). Accordingly, in this review, the EPA as in the last two reviews used the seasonal W126-based cumulative, concentration-weighted metric for consideration of the effects evidence in quantitative exposure analyses, particularly related to growth effects, which appears reasonable and scientifically sound. This information for the tree species, in combination with air quality analysis was a key consideration in the 2015 EPA decision on the level for the revised Secondary Standard (80 FR 65292, October 26, 2015).

Other Effects

With regard to climate related effects, including radiative forcing, the newly available evidence in this review does not provide more detailed quantitative information regarding ozone concentrations at the national scale. Although ozone continues to be recognized as having a causal relationship with radiative forcing and a likely causal relationship with effects on temperature, precipitation, and related climate variables, the non-uniform distribution of ozone (spatially and temporally) makes the development of quantitative relationships between the magnitude of such effects in differing ozone concentrations in the U.S. challenging (Draft 2019 Ozone ISA, Appendix 9). Thus, the Draft 2019 Ozone ISA recognizes that "current limitations in climate modeling tools, variation across models, and the need for more comprehensive observational data on these effects represents sources of uncertainty in quantifying the precise magnitude of climate responses to ozone changes, particularly at regional scales (Draft 2019 Ozone ISA). While these complexities affect EPA's ability to consider specific ozone concentrations associated with differing magnitudes of climate-related effects, it does give EPA the ability to estimate growth-related impacts of trees that can inform their consideration of the sequestration of carbon in terrestrial ecosystems, a process that can reduce tropospheric abundance of the pollutant (CO2) ranked first in importance as a greenhouse gas and radiative forcing agent.

What Are Important Uncertainties in the Evidence?

Among the categories of effects identified in past reviews, key uncertainties remain in the current evidence (Draft Ozone PA 2019). The category of ozone welfare effects for which current understanding of quantitative relationships is strongest is reduced plant growth. As a result, this category was the focus of the Administrator's decision making in the last review, with RBL in tree seedlings playing the role of surrogate for the broader array of vegetation related effects that range from the individual plant level to ecosystem services. Limitations in the evidence base and associated uncertainties recognized in the last review remain and include a number of uncertainties that affect characterization of the magnitude of cumulative exposure conditions eliciting growth reductions in U.S. forests.

As recognized in the last review, there are uncertainties in the extent to which the 11 tree species for which there are established E-R functions encompass the range of ozone sensitive species in the U.S. and also the extent to which they represent U.S. vegetation as a whole. Therefore, it should not be assumed that species of unknown sensitivity are tolerant to ozone.

EPA recognized important uncertainties in extent to which the E-R functions for reduced growth in tree seedlings are also descriptive of such relationships during later life stages for which there is a paucity of established E-R relationships. In addition, EPA recognizes

limitations and their ability to estimate growth effects of tree lifetimes of year to year variation in ozone concentrations. For example, the studies on which the established E-R functions for 11 tree species are based vary in duration (such as 82 days in a single year to 555 days spanning more than one year). In the 2019 Draft Ozone PA, EPA goes to great lengths in walking through uncertainties and recognizing limitations and data interpretation with a number of studies that they have considered. This is not unexpected due to the biological variability in response to a pollutant such as ozone in ecological systems.

Exposure and Air Quality Information

In general EPA decision making in the last review placed greatest weight on estimates of cumulative exposures to vegetation based on ambient air monitoring data for ozone and consideration of those estimates in light of E-R relationships for ozone related reduction in tree seedling growth. These analyses supported the consideration of the potential for ozone effects on tree growth and productivity as well as its associated impacts on a range of ecosystem services, including forests, ecosystem productivity, and community composition (80 FR 65292, October 26, 2015).

In revising the Standard in 2015 to the now current Standard, the Administrator concluded that with revision of the Standard level, the existing form and averaging time provided the control needed to achieve the cumulative seasonal exposure circumstances identified for the Secondary Standard. The focus of cumulative seasonal exposure primarily reflects the evidence of E-R relationships for plant growth. The 2015 conclusion was supported by the air quality data analyzed at that time. Analysis in the 2019 current review of the still more expanded set of air monitoring data, which includes 1,545 monitoring sites with sufficient data for variation of design values, documents similar findings as from the analysis of data from 2000 -2013 described in the last review.

Monitoring sites with lower ozone concentrations as measured by the design value metric (based on the current form and averaging time of the Secondary Standard) also have lower cumulative seasonal exposures, as quantified by the W126 Index. As the form and averaging time of the Secondary Standard have not changed since 1997, the analyses performed have been able to assess the control exerted by these aspects of the standard in combinations with reductions in the level (i.e., from 80 ppb in 1997 to 75 ppb in 2008 to 70 ppb in 2015) on cumulative seasonal exposures in terms of the W126 Index.

In the 2019 Draft Ozone PA in Figure 4-7, W126 Index values at monitoring sites with valid design values (2015-2017) the evidence currently available leads EPA to conclusions regarding exposure levels associated with effects as similar conclusions in the last review. Based largely on this evidence in combination with use of RBL as a surrogate, for vegetation related effects, the value of 17 ppm–hrs was the average W126 Index (over three years) was identified in the 2015 decision (80 FR 65393; October 26, 2015). As summarized above, the

information available in the present review continues to indicate that cumulative seasonal exposure levels at virtually all sites with air quality meeting the current standard fall below the level of 17 ppm-hrs that was identified when the current standard was established (80 FR 65393; October 26, 2015). Additionally, the average W126 Index in Class I areas that meet the current standard for the most recent three year period is below 17 and at or below 13 ppm-hrs in 44 of those of 46 Class I areas. In addition, in the current draft 2019 Ozone PA, table 4-2 summarizes distribution of W126 Index values in/near Class I areas. In summary, as is the case at all monitoring sites nationally, sites in or near Class I areas with design values at or below 70 ppb in the most recent three year period have had a seasonal W126 Index (based on three year average) at or below 17 ppm-hrs. As was the case at the time the current standard was established, with the exception of four values that occurred nearly a decade ago in the southwest region, cumulative seasonal exposures in all Class I areas during periods that met the current standard were no higher than 17 ppm-hrs which reflects a protective level in the standard.

Based on established E-R functions for tree seedling growth reductions in 11 species, the tree seedling RBL for the median tree species is 5.3% for a W126 Index of 17 ppm-hrs, rising to 5.7% for 18 ppm-hrs, 6% for 19 ppm-hrs and 6.4% for 20 ppm-hrs. Below 17 ppm-hrs, median estimates include 4.9% for 16 ppm-hrs, 4.5% for 15 ppm-hrs, 4.2% for 14 ppm-hrs, and 3.8% for 13 ppm-hrs. These estimates are unchanged from what was indicated by the evidence in the last review.

EPA has focused in the current review on the E-R relationships available in the last review for purposes of considering ozone exposure levels associated with growth-related impacts. Currently available evidence, including the newly available in the 2019 Ozone Draft ISA does not indicate the occurrence of ozone-related effects attributable to cumulative ozone exposures lower than was established at the time of the last review (.07 ppm). As in the last review, the currently available evidence continues to support a cumulative, seasonal exposure index as a biologically-relevant and appropriate metric for assessment of the evidence of exposure/risk information for vegetation, most particularly for growth related effects. This is reasonable, responsible, and reflects good use of scientific information by the EPA. The evidence continues to support important roles for cumulative exposure and for weighting higher concentrations over lower concentrations of ozone and ambient air. Thus, among the various such indices considered in the literature the cumulative, concentration-weighted W126 function continues to be best supported for purposes of relating ozone air quality to growth-related effects.

The RBL appears to be appropriately considered as a surrogate for an array of adverse welfare effects and based on consideration of ecosystem services and potential for impacts to the public as well as conceptual relationships between vegetation growth effects and ecosystem scale effects. Biomass loss is a scientifically sound surrogate of a variety of

adverse effects that could be exerted to public welfare. In the previous review, the Administrator used RBL as a surrogate for consideration of the broader array of vegetation related effects of potential welfare significance that included effects of growth of individual sensitive species and extended to ecosystem level effects such as community composition in natural forests, particularly in protected public lands (80 FR 65406, October 26, 2015). EPA believes, and I concur, that information available in the present review does not call into question this approach, indicating there continues to be support for the use of tree seedling RBL as a proxy for the broader array of vegetation-related effects, most particularly those related to growth.

<u>To What Extend Does the Available Information Alter Our Understanding of the Magnitude of Growth Reductions Expected to be of Public Welfare Significance?</u>

It was recommended in the last review that a 6% RBL was "unacceptably high" and endeavored to identify a Secondary Standard that would limit three year average ozone exposures somewhat below W126 Index values associated with a 6% RBL in the median species. This led to identification of a seasonal W126 Index value of 17 ppm-hrs that the Administrator concluded appropriate as a target at or below which the new Standard would generally restrict cumulative seasonal exposures (80 FR 65407, October 26, 2015). The currently available evidence continues to indicate conceptual relationships between reduced growth and the broader array of vegetation-related effects of ambient ozone exposure.

<u>What Does the Information Available in the Current Review Indicate with Regards to Support for Use of a Three Year Average Seasonal W126 Index as the Cumulative Exposure Metric (Associated with a Value of 17 ppm-hrs) for Describing the Requisite Level of Protection for the Secondary Standard?</u>

In the setting of the current Standard, the EPA focused on control of seasonal cumulative exposures in terms of a three year average W126 Index metric. The evaluations in the PA for the last review recognized there to be limited information to discern differences in the level of protection afforded for cumulative growth related effects by a Standard focused on a single year W126 as compared to a three year W126 Index (80 FR 65390, October 26, 2015). Accordingly, the identification of the three year average for considering the seasonal W126 Index recognized that there was year-to-year variability, not just in ozone concentrations, but also in environmental factors, including rainfall and meteorological factors, that influences the occurrence and magnitude of ozone related effects in any year and contribute uncertainties to interpretation of the potential for harm to public welfare over the longer term. Based on this recognition, as well as other considerations, the Administrator expressed greater confidence in judgements related to public welfare impacts based on seasonal W126 Index estimated by a three year average and accordingly relied on that metric, which appears of reasonable thought and scientifically sound.

Does the Currently Available Scientific Evidence in Air Quality and Exposure Analyses Support or Call into Question the Adequacy of the Protection Afforded by the Current Secondary Ozone Standard?

As delineated by the Clean Air Act, the Secondary Standard is meant to protect against ozone related welfare effects that are judged to be adverse to the public welfare. The EPA in development of the Draft 2019 Ozone PA considered the currently available information regarding welfare effects of ozone in this context, while recognizing that the level of protection from known or anticipated adverse effects to public welfare that is requisite for the Secondary Standard is a public welfare policy judgement made by the Administrator. EPA considered the quantitative analyses, including associated limitations and uncertainties and the extent to which they indicate differing conclusions regarding the level of protection indicated to be provided by the current Standard from adverse effects. EPA additionally considered the key aspects of the evidence in air quality/exposure information emphasized in establishing the now current Standard and the associated public welfare policy judgements and judgements about inherent uncertainties that are integral to decisions on the adequacy of the current Secondary Ozone Standard. In considering the currently available evidence, EPA recognized the long-standing evidence base of the vegetation-related effects of ozone, augmented in some aspects since the last review. Consistent with the evidence in the last review, the currently available evidence describes an array of ozone effects on vegetation and related ecosystem effects as well as the role of ozone in radiative forcing with effects on climate related variables. The current evidence base supports conclusions of causal relationships between, particularly, vegetation and other endpoints and likely to be causal relationships between other endpoints that EPA thoroughly discussed in the 2019 Draft ISA. EPA appropriately recognized uncertainties in categories of effects newly identified that could limit consideration of the protection that might be provided by the current Standard against these effects.

As was the case in the last review, a category of effects for which the evidence supports quantitative description of relationships between air quality conditions and response is plant growth or yield. The evidence base continues to indicate growth-related effects as sensitive welfare effects, with the potential for ecosystem scale ramifications. For this category of effects, there are established E-R functions that relate cumulative seasonal exposure of varying magnitudes to various incremental reductions in expected tree seedling growth (in terms of RBL) and in expected crop yield. Decades of research also recognizes visible foliar injury as an effect of ozone, although uncertainties continue to hamper efforts to quantitatively characterize the relationship of its occurrence and relative severity with ozone exposures.

Reviews of NAAQS also required judgements on the extent to which particular welfare effects (such as with regard to type, magnitude/severity, or extend) are important from a

public welfare perspective. In the case of ozone, such a judgement includes consideration of the public welfare significance of small estimates of RBL and associated unquantified potential for larger scale effects. With regard to public welfare significance of 5-6% RBL, the EPA notes CASAC characterization of 6% RBL (in seedlings of median tree species) in the last review. The rationale provided by the CASAC with this characterization was primarily conceptual and qualitative rather than quantitative. The conceptual characterization recognized linkages between effects on the plant level scale and broader ecosystem impacts, and this facilitated the Administrator consider RBL as a surrogate for the broader impacts that could be elicited by ozone. In the 2015 decision, the Administrator took note of CASAC advice regarding use of RBL as a proxy and set the Standard with "underlying objective of a revised Secondary Standard that would limit cumulative exposures in nearly all instances to those for which the median RBL estimate would be somewhat lower than 6%" (80 FR 65407, October 26, 2015). The 2015 decision noted that "the Administrator does not judge RBL estimates associated with marginal higher exposures [at or above 19 ppm-hrs] in isolated rare instances to be indicative of adverse effects to the public welfare" (80 FR 65407, October 26, 2015).

In considering the quantitative analyses available in the draft 2019 Ozone PA, EPA noted the findings from the analysis of recent air quality at sites across the U.S., including in or near 64 Class I areas and also analysis of historical air quality. Findings from the analysis of air quality data from the most recent period and from the larger analysis of historical air quality data extended back to 2000 are consistent with the air quality analysis findings that were part of the basis for the current Standard. That is, in virtually all design value periods and in all locations at which the current Standard was met, the three year average W126 metric was at or below 17 ppm-hrs, the target identified by the Administrator in establishing the current Standard (80 FR 65404-65410, October 26, 2015).

EPA summarized in the draft 2019 Ozone PA there is little in the information available in the current review that differs from that in the last review that relate to key aspects of the judgments and associated decision that established the current Standard in 2015. The new information available is consistent with that available in the last review for the principle effects for which the evidence is strongest (such as growth, reproduction, and related larger scale effects, as well as visible foliar injury).

<u>General Comments</u>

1. I compliment the United States Environmental Protection Agency on a very thorough and well-written Chapter 4 contributing to the draft 2019 Ozone Policy Assessment.
2. The foundation upon which scientific data was utilized while also incorporating concepts of judgement on behalf of the EPA with input from various entities lays a strong and

clear scientific process of considerations for the preliminary conclusions on the current Secondary Standard.

3. The preliminary conclusion by the U.S. EPA that the 2015 decision to revise the level of the Secondary Standard for photochemical oxidants, including ozone to .07 ppm (70 ppb) in conjunction with retaining the indicator (O_3), averaging time (8 hours) and form (4th highest annual daily maximum 8-hour average concentration, averaged across three years) appears to be working in maintaining ambient air concentrations of ozone across the United States at levels that are protective for the public welfare, particularly as related to vegetation.
4. EPA recommends the RBL appears to be appropriately considered as a surrogate for an array of adverse welfare effects and based on consideration of ecosystem services and potential for impact to the public as well as conceptual relationships between vegetation growth effects and ecosystem scale effects. I agree that biomass loss, as reported in RBL, is a scientifically sound surrogate of a variety of adverse effects that could be exerted to public welfare.
5. EPA believes, and I concur, that information available in the present review does not call in to question this RBL approach, indicating there continues to be support for the use of tree seedling RBL as a proxy for the broader array of vegetation related effects, most particularly those related to growth that could be impacted by ozone.
6. It was recommend in the last review that a 6% RBL was "unacceptably high" and endeavored to identify a Secondary Standard that would limit three year average ozone exposure somewhat below W126 Index values associated with a 6% RBL in the median species, and I concur that this strategy is still scientifically reasonable. The identification of a seasonal W126 Index value of 17 ppm-hrs that EPA concludes appropriate as a target at or below which the Secondary Standard would generally restrict cumulative seasonal exposure. I believe that this target is still effective in particularly protecting the public welfare in light of vegetation impacts from ozone.
7. The approach described in Chapter 4 to considering the evidence for welfare effects is laid out very clearly, thoroughly discussed and documented, and provided a solid scientific underpinning for the preliminary conclusions leaving the current Secondary Standard in place.

Dr. Corey Masuca

Chapter 2 – Air Quality

2.3.1 Ambient Air Monitoring Requirements and Monitoring Networks

There is a noticeable absence of discussions about Near Road monitoring sites, especially for NOy, as an ozone precursor.

2.3.2 Data Handling Conventions and Computations for Determining Whether the Standards Are Met

More elucidation needs as to why the selection of the ozone design value as the 3-year average of the annual 4th highest daily 8-hour maximum concentration.

2.5 Background Ozone

While this section focuses on background concentrations, expressed as concentrations that would exist in the absence of US anthropogenic emissions and ozone concentrations from global natural sources and from anthropogenic sources transports from sources outside of the US, what localized, interstate and/or intercity transport of anthropogenic ozone and/or precursors?

Chapter 3 - Review of the Primary Standard

3.3.1.2 – Other Effects

With respect to the determination that metabolic effects have been determined to have likely causal relationship with ozone exposures, should this finding stand even though the evidence the most salient evidence is from animal studies at exposure conditions much higher than those commonly occurring?

3.3.2 Public Health Implications and At-Risk Populations

With respect to at-risk populations, there appears to be a noticeable absence of discussion about greater susceptibility for minority and/or lower SES populations.

3.3.3 Exposure Concentrations Associated with Effects

This section indicates that otherwise valid epidemiological studies (US and Canada) which found positive associations between ozone and respiratory outcomes were deemed to be less useful since the studies were conducted in areas and during time periods that would not have met the current standard.

When evaluating epidemiological health effects, should this limitation be placed on study and study result effectiveness? In other words, should epidemiological evidence **only** be limited to those areas that meet the current standard with disregard for effects noted as both higher and lower concentrations that those of the current standard?

3.4 Exposure and Risk Information

General Questions

What is the inherent purpose of the risk assessment in the policy assessment evaluation? Are the results from the risk assessment viewed to be more substantive than controlled human and epidemiological studies? Even given the extensive list of uncertainties highlighted in 3.4.4

3.4.1 Conceptual Model and Assessment Approach

For the risk assessment, why the utilization of ambient air monitoring data consisting of concentrations at or near the current standards? Why not consider ozone concentrations well above and below the current standard also?

3.4.2 Population Exposure and Risk Estimates for Air Quality Just Meeting the Current Standard

While not totally invalid, some concern with developing risk estimates from concentrations from eight (8) representative cities.

Greater explanation and concern with 'simulated children with asthma.'

While the focus has been on areas just meeting the current standard, how would the percentages change for each benchmark (i.e., 60 ppb, 70 ppb, 80 ppm) for concentrations below the current standard? For concentrations above the current standard?

3.5.2 Exposure/Risk-Based Considerations

While not totally invalid, some concern with developing risk estimates from concentrations from eight (8) representative cities.

While the focus has been on areas just meeting the current standard, how would the number of days and lung function decrement changes for concentrations below the current standard? For concentrations above the current standard?

Dr. Steven Packham

Preliminary Comment. Empirical observations and pulmonary function data from controlled human exposures are sufficient to conclude that a causal biological mechanism exists between objectively measured decrements in FEV1 and subjective symptoms in healthy human adults.

1. The shape of the biologically mediated FEV1 dose-response curve is a function of the inhaled hourly dosage rate and the cumulative dose inhaled over several hours immediately prior to the onset of the effect.
2. The threshold for these biologically mediated FEV1 responses in healthy adult humans exposed for 6.6 hours to ozone concentrations from 60 to 87 ppb is estimated to be 1,362 µg. (Schelegle et al. 2009)
3. This is equivalent to a cumulative dose of millions of trillions of highly reactive oxidizing molecular moieties.

Formula 1. $\frac{1362\mu g}{48gm} \cdot \text{AvogadroN} = 1.709 \times 10^{19}$

4. The threshold doses for ozone induced FEV1 and reports of symptomatic effects are lower than for clinical signs of pulmonary inflammation.
5. Ozone induced FEV1 decrement is most probably one of several specific protective biological responses.
6. Ozone exposures have been shown to stimulate peripheral mucus flow into central bronchi thereby enhancing particle transport from peripheral to central airways and mucociliary clearance of inhaled particulate matter.
7. This beneficial dose-dependent response to ozone "…is of interest since it characterizes the reaction of a primary defense mechanism essential to the protection of mucosal surfaces of the tracheobronchial tree." (Forster et al. 1987)

Recommendations. In order to present a review of key scientific studies and an integration of current scientific evidence and knowledge, future O3 ISA and PA documents MUST present a clear description of all the known biological mechanisms underlying the O3-FEV1 effect and further validate and refine the dose response functions for FEV1 and pulmonary inflammation derivable from controlled human exposure studies.

In response to the Question,
"When a causal relationship is conclusive to a high degree of scientific certainty as it is in this case, should this take precedence over causal inference when drafting a NAAQS ISA?" Dr. Parrish Responded:

> I have no relevant expertise, so I cannot respond to this question as an expert; however, to a non-expert the answer is obviously, Yes.

Substantive-bases for these Recommendations. Figure ES-3 in the Ozone ISA External Review Draft (shown below) is adapted from the 2013 Ozone ISA which was based on eight human studies published between 1988 and 2013. The 2009 study by Schelegle et al. specifically played a decisive role in the 2015 revision of the O3 NAAQS from 75 to 70 ppb (80 FR 65292 Oct 26, 2015).

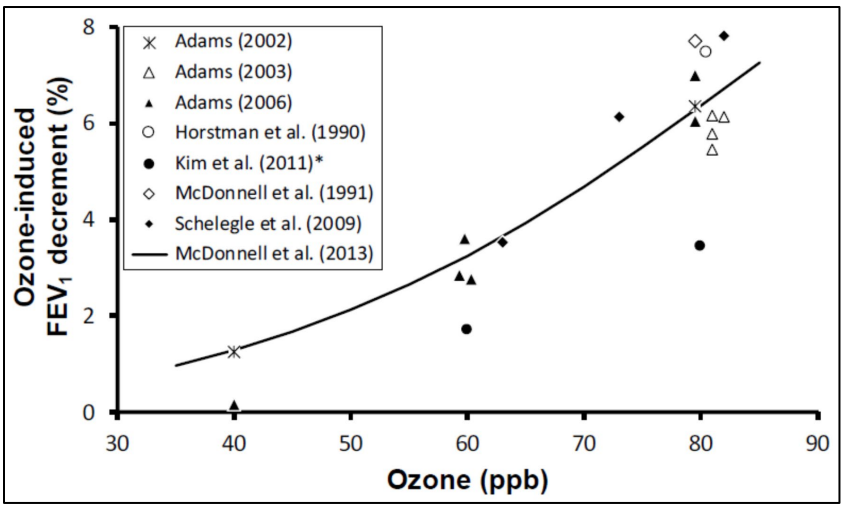


Figure ES-3 was adapted from **Figure 6-1 of 2013 Ozone ISA (U.S. EPA, 2013)** which was based on studies by Adams (2006), Adams (2003), Adams (2002), Folinsbee et al. (1988), Horstman et al. (1990), Kim et al. (2011), McDonnell et al. (2013), McDonnell et al. (1991), and Schelegle et al. (2009).

In contrast to **Figure ES-3**, the original figure (***Figure 1***) shown below from Schelegle et al. 2009, depicts the actual sigmoid curvilinear relationships and mean accumulative doses of the 31 healthy adult human subjects who completed the four 6.6-hour chamber exposures to target mean O_3 concentrations of 60,70, 80, and 87 ppb.

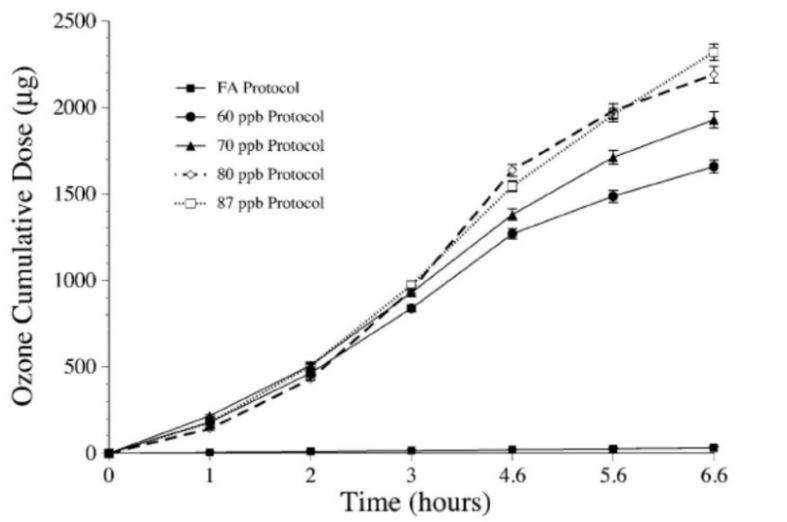
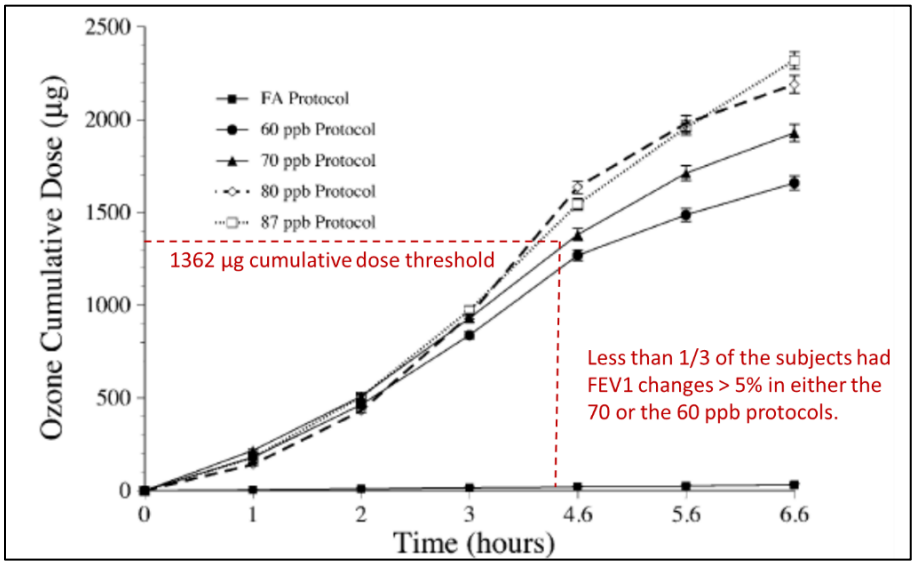


Figure 1. Diagram of mean group values for cumulative dose of ozone (micrograms) against time of exposure for each of the five protocols. Values represent means ± SEM.

The original data presented *in this way* conveys critical information to toxicologists and biomedical researchers that is "lost in translation/integration" in the concentration/risk-effect picture presented in Figure ES-3. To quote Schelegle et al. (2009), "*We were able to obtain reliable estimates of a Dose of Onset [i.e., a threshold for the FEV1 effect], using the pooled FEV1from the 80 and 87 ppb ozone exposure protocols, …but not from the pooled FEV1 data from the 60 and 70 ppb ozone exposure protocols. The inability to estimate [a threshold] using the FEV1 data from the 60 and 70 ppb ozone exposure protocols is most likely because* <u>*less than one third*</u> *of the subjects had changes in FEV1* <u>*greater than 5%*</u> *in either of these protocols.* (Emphasis added)



Packham Figure 1. Adapted from Schelegle et al. (2009) with toxicological annotations by author, 2019.

The notable differences between **Figure ES-3** compared with **Packham Figure 1** are driven by how data are interpreted by different scientific disciplines. By superimposing Schelegle's descriptive narrative of conclusions onto the sigmoid shaped dose-response curves, one sees the beginning of an increased trend of dose-response curve separation between hour 3 and hour 4: Indicative of the cumulative Dose of Onset threshold between the respective exposure protocols.

Figure ES-3 is the product of imposing a *quantal* risk-assessment mindset upon data collected from ***continuously graded biological responses*** characteristic of the ongoing physical events integral to the nature of living organisms.

The narrative associated with **Figure ES-3** (found on page ES-7) is grossly misleading and completely overlooks the positive confounding health benefit of enhanced PM clearance stimulated by 200 ppb ozone exposures mentioned above.

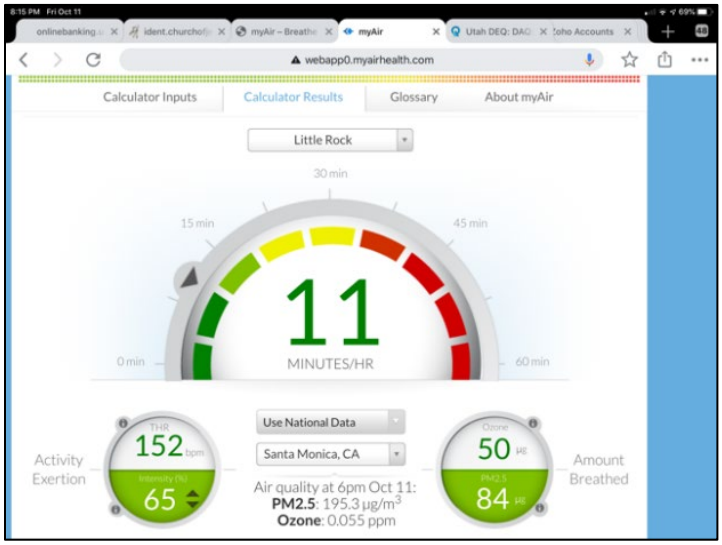
The controlled human studies by Folinsbee, Adams, Horstman, Kim, McDonnell and Schelegle, and others cited below in the References and Reading List, provide the empirical bases of testable hypotheses that exposures to elevated ambient levels of O3 can cause measurable decrements in FEV1 in healthy adults. These studies document that the effect of O3 on reduced FEV1 volumes is temporary and suggest that hourly mean ambient O3 concentrations below 70 ppb are most likely incapable of causing FEV1 effects in most healthy adults.

Pulmonary Physiology and Inhalation Toxicology:
Several nonmember consultants have expressed reluctance to comment on certain questions because of limited familiarity with pulmonary physiology and inhalation toxicology. Here are few facts to keep in mind.

1. Lungs have an evolutionary history in which surfactant was key to the evolution of all air breathing species on the surface of the planet, (Daniels and Orgeig (2003.)
2. Antioxidant secretions from epithelial Type II cells into the liquid lining of the lungs is one of most important natural defenses the human organism has against naturally occurring ozone levels in the atmosphere near the earth's surface.
3. All known effects of ozone on the human respiratory system are dose dependent.
4. Ozone stimulation of the respiratory airways evokes a number of defensive and adaptive physiological responses in humans.

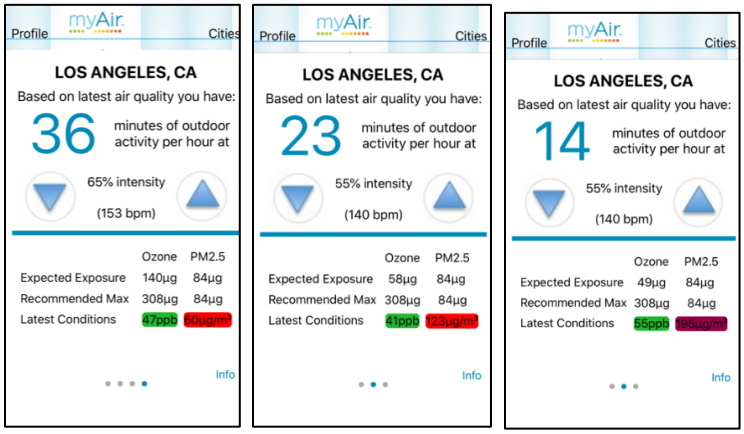
Overarching Health Benefits from Regulations Based on Sound Science: An accurate understanding of the causal dose-response relationship between ambient ozone exposure and responses elicited in the human organism opens up a number of important options that could be considered in reviewing and setting NAAQS standards and in how those standards might be used to protect, and even promote, public health. For instance, the realization that the ozone-induced FEV1 effects are temporary, reversible, and occur at a lower inhaled dose than a potential adverse health effect (such as a pulmonary inflammatory response) could be considered a tenable rationale for classifying them as natural benchmark margin-of-safety indicators.

Another application of minute respiratory volume and hourly MSS inhalation dosage models and thresholds would be for the EPA to imbed them into web and mobile platform applications for public education and personal risk management. Shown here, as proof-of-concept, is a screen shot of such a web application that can be found at http://webapp0.myairhealth.com/# giving an individual (user name Little Rock) in Santa Monica California who is being exposed to 193 µg/m3 of PM2.5 on October 11, 2019 during the Saddleridge wild fire episode the useful information that they should limit any outdoor activity to 11 minutes or less if that activity



necessitates a physical exertion intensity level of 65% corresponding to an average heart rate of 152 beats-per-minute or higher.

A free iPhone app is also in the public domain https://apps.apple.com/us/app/myair-health/id790049340. By way of full disclosure, friends and I in Utah developed these web and mobile applications on our own dime and have made them available free to the public since 2013. Here are a few screen shots representative of similar guidance being offered to folks in the Los Angeles area during this same Saddleridge fire episode.



References to these applications in these comments are not being made to announce, promote, or advocate these particular apps; but, to illustrate the power and potential of using sound scientific methods and fundamental principles of toxicology and human respiratory physiology together with current mobile technology to promote public health and demonstrate the public health value inherent in the EPA O3 and PM NAAQS and their associated Air Quality Index Health Advisories when risk assessment and scientific knowledge from controlled human exposure studies are fully integrated.

References and Reading List

Adams WC, Savin WM, Christo AE. (1981). Detection of ozone toxicity during continuous exercise via the effective dose concept. J Appl Physiol 51:415–422.

Adams WC. (2002). Comparison of chamber and face-mask 6.6-hour exposures to ozone on pulmonary function and symptoms responses. Inhal Toxicol 14:745–764.

Adams WC. (2003). Comparison of chamber and face mask 6.6-hour exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal Toxicol 15:265–281.

Adams WC. (2003). Comparison of chamber and face mask 6.6-hour exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal Toxicol. 15(3):265-81

Adams WC. (2006a). Comparison of chamber 6.6-h exposures to 0.04-0.08 PPM ozone via square-wave and triangular profiles on pulmonary responses. Inhal Toxicol 18:127–136.

Adams WC. (2006b). Human pulmonary responses with 30-minute time intervals of exercise and rest when exposed for 8 hours to 0.12 ppm ozone via square-wave and acute triangular profiles. Inhal Toxicol 18:413–422.

Bennett WD, Hazucha MJ, Folinsbee LJ, Bromberg PA, Kissling GE, London SJ. (2007). Acute pulmonary function response to ozone in young adults as a function of body mass index. Inhal Toxicol 19:1147–1154.

Bush ML, Asplund PT, Miles KA, Ben-Jebria A, Ultman JS. (1996). Longitudinal distribution of O3 absorption in the lung: gender differences and intersubject variability. J Appl Physiol 81:1651–1657.

Chadha TS, Birch S, Sackner MA. (1987). Oronasal distribution of ventilation during exercise in normal subjects and patients with asthma and rhinitis. Chest 92:1037–1041.

Colucci AV. (1983). Pulmonary dose/effect relationships in ozone exposure. In: Lee SD, Mustafa MG, Mehlman MA, ed. International Symposium on the Biomedical Effects of Ozone and Related Photochemical Oxidants. Princeton, NJ: Princeton Scientific, vol. V, 21–44.

Daniels CB, Orgeig S. (2003). Pulmonary Surfactant: Key to the Evolution of Air Breathing. 0886-1714/03 5.00 © 2003 Int. Union Physiol. Sci./Am. Physiol. Soc. www.nips.org. News Physiol Sci 18:151-157.

Drechsler-Parks DM, Bedi JF, Horvath SM. (1987). Pulmonary function responses of older men and women to ozone exposure. Exp Gerontol 22:91–101.

Folinsbee LJ, Drinkwater BL, Bedi JF, Horvath SM. (1978). The influence of exercise on the pulmonary function changes due to low concentrations of ozone. In: Folinsbee LJ, Wagner J A, Borgia JF Drinkwater BL, Gliner JA, Bedi JF, eds. Environmental Stress. New York: Academic Press, 125–145.

Forster WF, Costa DL, Langenback EG. (1987) Ozone exposure alters tracheobronchial mucociliary function in humans. J Appl Physiol 63:996-1002.

Hazucha MJ. (1987). Relationship between ozone exposure and pulmonary function changes. J Appl Physiol 62:1671–1680.

Hazucha MJ, Folinsbee LJ, Bromberg PA. (2003). Distribution and reproducibility of spirometric response to ozone by gender and age. J Appl Physiol 95:1917–1925.

Horstman DH, Folinsbee LJ, Ives PJ, Abdul-Salaam S, McDonnell WF. (1990). Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. Am Rev Respir Dis 142:1158–1163.

Kim CS, Alexis NE, Rappold AG, Kehrl H, Hazucha MJ, Lay JC, Schmitt MT, Case M, Devlin RB, Peden DB, Diaz-Sanchez D. (2011). Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. Am J Respir Crit Care Med 183:1215–1221.

Kriebel D, Smith TJ. (1990). A nonlinear pharmacologic model of the acute effects of ozone on the human lungs. Environ Res 51:120–146.

Larsen RI, McDonnell WF, Horstman DH, Folinsbee LJ. (1991). An air quality data analysis system for interrelating effects, standards, and needed source reductions: Part 11. A lognormal model relating human lung function decrease to O3 exposure. J Air Waste Manage Assoc 41:455–459.

McDonnell WF, Stewart PW, Smith MV. (2010). Prediction of ozone induced lung function responses in humans. Inhal Toxicol 22:160–168.

McDonnell WF, Stewart PW, Smith MV. (2007). The temporal dynamics of ozone-induced FEV1 changes in humans: an exposure-response model. Inhal Toxicol 19:483–494.

McDonnell WF, Smith MV. (1994). Description of acute ozone response as a function of exposure rate and total inhaled dose. J Appl Physiol 76:2776–2784.

McDonnell WF, Kehrl HR, Abdul-Salaam S, Ives PJ, Folinsbee LJ, Devlin RB, O'Neil JJ, Horstman DH. (1991). Respiratory response of humans exposed to low levels of ozone for 6.6 hours. Arch Environ Health 46:145–150.

McDonnell WF, Horstman DH, Abdul-Salaam S, Raggio LJ, Green JA. (1987). The respiratory responses of subjects with allergic rhinitis to ozone exposure and their relationship to nonspecific airway reactivity. Toxicol Ind Health 3:507–517.

McDonnell, WF; Stewart, PW; Smith, MV; Kim, CS; Schelegle, ES. (2012). Prediction of lung function response for populations exposed to a wide range of ozone conditions. Inhal Toxicol 24: 619-633. http://dx.doi.org/10.3109/08958378.2012.705919.

McGregor M, Adam W, Sekelj P. (1961). Influence of posture on cardiac output and minute ventilation during exercise. Circ Res 9:1089–1092.

Messineo TD, Adams WC. (1990). Ozone inhalation effects in females varying widely in lung size: comparison with males. J Appl Physiol 69:96–103.

Pryor WA, Das B, Church DF. (1991). The Ozonation of Unsaturated Fatty Acids: Aldehydes and Hydrogen Peroxide as Products and Possible Mediators of Ozone Toxicity. Chem Res Toxicol 4:341-384.

Schelegle, ES; Morales, CA; Walby, WF; Marion, S; Allen, RP. (2009). 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. Am J Respir Crit Care Med 180: 265-272. http://dx.doi.org/10.1164/rccm.200809-1484OC.

Schelegle ES, Adams WC, Walby WF, Marion MS. 2012. Modelling of individual subject ozone exposure response kinetics. Inhal Toxicol 24:401–415.

Seal E Jr, McDonnell WF, House DE, Salaam SA, Dewitt PJ, Butler SO, Green J, Raggio L. (1993). The pulmonary response of white and black adults to six concentrations of ozone. Am Rev Respir Dis 147:804–810.

Silverman F, Folinsbee LJ, Barnard J, Shephard RJ. (1976). Pulmonary function changes in ozone-interaction of concentration and ventilation. J Appl Physiol 41:859–864.

Smith MV, McDonnell WF. (1999). A statistical model for FEV1 response to arbitrary dynamic ozone exposure conditions. J Air Waste Manag Assoc 49:289–298.

Weinmann GG, Weidenbach-Gerbase M, Foster WM, Zacur H, Frank R. (1995). Evidence for ozone-induced small-airway dysfunction: lack of menstrual-cycle and gender effects. Am J Respir Crit Care Med 152:988–996.