Responses to CASAC Questions on the Ozone PA from Consultant Dr. Frederick W. Lipfert

General Comments

Most of my concerns involve human health effects, definitions of exposures, and the form of the NAAQS (averaging time). Some of them arise from recent literature; see below for example. Others relate to the failure of the O_3 ISA to consider all of the relevant epidemiology studies, notably those of my own and colleagues, listed in the Appendix. I regard premature mortality as the most important health endpoint because of its high assigned monetary values, its role in cost-benefit analyses, and the focus on the primary standard (Chapter 3).

That discussion focuses on respiratory effects, primarily morbidity, and delegates the more common and serious cardiovascular effects to a footnote. Shapes of dose-response functions and thresholds are not mentioned nor are residual risks at exposures below 70 ppb. I regard the most important exposure issue as that of indoor air quality and personal exposures, which are much lower than 70 ppb. The PA considers indoor exposures in great detail but they are ignored in the epidemiology. I find Chapter 3 to be inadequate.

A new long-term study of hospital admissions by Yazdi et al. (2019) deserves consideration. They created Medicare cohorts of admissions for stroke, heart attacks, and pneumonia and plotted exposure-response functions (ERFs) for annual average O_3 and $PM_{2.5}$ This is one of very few studies to consider long-term rather than daily hospitalization rates and to use annual average ozone rather than 8-h max. Ozone was statistically significant for all 3 outcomes. I extrapolated the ERFs and found ozone thresholds from 21-28 ppb. The extrapolated $PM_{2.5}$ ERFs showed a threshold of 4.5 μg/m3 for pneumonia admissions but residual risks for stroke and heart attack admissions. These results demand that ozone epidemiology be further considered as well as the form of the NAAQS. Below I list some relevant papers based on annual average ozone levels.

Questions remain about potential mechanisms for long-term health effects of ozone. Ozone is a powerful irritant to the respiratory system, but can it also initiate new cases of disease as hypothesized for PM? It is reasonable to expect cumulative vegetation damage from repeated exposures to O_3, lacking a repair mechanism between episodes, but some human respiratory effects are reversible. Given seasonal variability and the strong adsorption of ozone on indoor surfaces, it is hard to identify health effect mechanisms other than acute responses. Purported long-term effects may thus comprise the sums of short-term effects over the periods in question. None of the four new long-term studies listed below include the terms “cumulative” or “repeated exposure”, for example. Also, it is difficult if not impossible to conduct sufficiently long-term animal or human clinical testing that could support the long-term epidemiology.

Comments on the bulleted items in PA Section 3.6, "Key Uncertainties"

1. *Emphasis on at-risk populations in moderate exercise.* It would not be possible to clinically test the most susceptible individuals to improve the general understanding of the exposure- response relationship (ERF). The most important uncertainties in clinical experiments are selection of subjects, the shape of the ERF, the importance of ambient temperature in this regard, the roles of co- pollutants.
2. *Exposures in epidemiology.* Consideration of indoor-outdoor exposure

relationships in epidemiology is perhaps the most important issue, followed by timing of exposures including frequencies, latency, cumulative effects, and repeated exposures. In the absence of personal exposure information, ambient air quality must be considered as descriptive of the places where it is monitored rather than the exposures of inhabitants. Other examples of such descriptives include green spaces and traffic density, which was a highly significant predictor of mortality in the Veterans Cohort (see Appendix references).

3. *Different population groups.* Frailty of those at risk should be considered. Specific cohorts may be selected but would have limited applicability. Populations should be studied by age group.
4. *Co-pollutants.* Ozone never exists in isolation; co-pollutant effects must be considered with different exposure models, including indoors and time scales.
5. *Other photochemical oxidants.* The first consideration must be distribution in the atmosphere, thus requiring ambient monitoring. Clinical testing could then indicate which species are both hazardous and prevalent. My personal opinion is that improving our knowledge of ozone should take precedence over new species having poorly defined properties.
6. *Epidemiology with co-pollutants and temperature.* Temperature, ozone, and other pollutants such as PM comprise a 3-way system. Outdoors, ambient temperature strongly affects ozone formation but not PM, and all 3 may affect health over various time scales. Ozone is always reduced indoors, residential air conditioning (RAC) reduces temperature effects, but PM concentrations from indoor sources will increase when the house is closed up. The importance of RAC invokes socioeconomic factors in epidemiology.
7. *Ambient and indoor exposure considerations.* Spatial heterogeneity is a source of exposure error but indoor/outdoor differences are much more important. The likelihood of peak ozone levels in suburban or rural areas may require ambient monitoring networks denser than those now in place. Indoor ozone levels may only ~30% of outdoors.
8. *Exposure timing.* Short-term effects, especially mortality, must be summed over lag periods up to a week. Longer term exposures such as annual include the short-term effects experienced over the same period. More information, such as from clinical testing, is needed to understand repeated exposures, especially the timing between peaks.

9, 10. Personal exposure by season; activity levels. Time-activity levels must first be considered in epidemiology before those data could be used in predicting subsequent health effects including benefits from abatement. Clinical ERF data can be used for morbidity such as respiratory effects but not for mortality or hospital admissions.

<u>Recent epidemiology papers using annual average ozone concentrations</u>.

Lim CC, Hayes RB, Ahn J et al. Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. Am J Respir Crit Care Med. 2019 200(8):1022-1031.

Danesh Yazdi M, Wang Y, Di Q etal. Long-term exposure to PM(2.5) and ozone and hospital admissions of Medicare participants in the Southeast USA. Environ Int. 2019 ep;130:104879.

Rhee J, Dominici F, Zanobetti A et al. Impact of Long-Term Exposures to Ambient PM(2.5) and Ozone on ARDS Risk for Older Adults in the United States. Chest. 2019 Jul;156(1):71-79.

Hernandez AM, Gimeno Ruiz de Porras D, Marko D, Whitworth KW. The Association Between PM2.5 and Ozone and the Prevalence of Diabetes Mellitus in the United States, 2002 to 2008. J Occup Environ Med. 2018 Jul;60(7):594-602.

Questions from Dr. James Boylan

Chapter 2 – Air Quality

- *Is the discussion on O_3 and Photochemical Oxidants in the Atmosphere (Section 2.1) accurate and complete? If not, what additional information needs to be included?*

  Yes, it's adequate for this purpose.

- *Is the discussion on Sources and Emissions of O_3 Precursors (Section 2.2) accurate and complete? If not, what additional information needs to be included?*

  Yes.

- *Is the discussion on Ambient Air Monitoring and Data Handling Conventions (Section 2.3) accurate and complete? If not, what additional information needs to be included?*

  No. Indoor air quality information should be added.

- *Is the discussion on Ozone in Ambient Air (Section 2.4) accurate and complete? If not, what additional information needs to be included?*

  Urban-suburban-rural concentration profiles for various averaging times would be of interest.

- *Is the discussion on Background O_3 (Section 2.5) accurate and complete? If not, what additional information needs to be included?*

  It would be useful to have historical trend data on background levels.

Chapter 3 – Review of the Primary Standard

- *Is the discussion on Exposure and Risk Conceptual Model and Assessment Approach (Section 3.4.1) accurate and complete? If not, what additional information needs to be included?*

  I would like to see comparisons of risks by O_3 averaging times (annual, 24-h, 8-h, daily max) by season and health endpoint.

- *Is the discussion on Population Exposure and Risk Estimates for Air Quality Just Meeting the Current Standard (Section 3.4.2) accurate and complete? If not, what additional information needs to be included?*

  Indoor infiltration and attenuation should be included.

- *Is the discussion on Population Exposure and Risk Estimates for Additional Air Quality Scenarios (Section 3.4.3) accurate and complete? If not, what additional information needs to be included?*

  Personal exposures by age group.

- *Is the discussion on Key Uncertainties (Section 3.4.4) accurate and complete? If not, what additional information needs to be included?*

  No. See the discussion of Section 3.6 above.

- *Is the discussion on Public Health Implications (Section 3.4.5) accurate and complete? If not, what additional information needs to be included?*

  This section should include considerations of health risks at background ozone levels for various averaging times.

Appendix 3C – Air Quality Data Used in Population Exposure and Risk Analyses

- *Is the discussion on Urban Study Areas (Section 3C.2) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Ambient Air Ozone Monitoring Data (Section 3C.3) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Comprehensive Air Quality Model with Extensions (CAMx) (Section 3C.4.1) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Evaluation of Modeled Ozone Concentrations (Section 3C.4.2) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Air Quality Adjustment to Meet Current and Alternative Air Quality Scenarios (Section 3C.5) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Interpolation of Adjusted Air Quality using Voronoi Neighbor Averaging (Section 3C.6) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Results for Urban Study Areas (Section 3C.7) accurate and complete? If not, what additional information needs to be included?*

  I have no comments on this Appendix.

Questions from Dr. Sabine Lange

<u>Air Quality</u>

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?*

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 O_3 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 O_3 rather than the annual average. My own studies (see Appendix) have used the 95^{th} percentile of the daily O_3 averages.

Epidemiology

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)?*

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.

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 and pg 3-43). 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?*

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 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.

Exposure-Response Modeling

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?*

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.

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?*

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.

Questions from Dr. Corey Masuca

1) **2.1. Ozone and Photochemical Oxidants in the Atmosphere**

How sound science is this mechanism of ozone transfer between the stratosphere and the troposphere?

I don't see this as relevant to the setting of NAAQS levels.

2) **2.3.1 Ambient Air Monitoring Requirements and Monitoring Networks**

While a number of types of sites are mentioned in this section such as PAMS, NCore, CASTNET, National Park Service (NPS), and Special Purpose Monitors (SPMs), what about Near Road Monitoring Sites, especially for NOy?

I'm not familiar with these networks.

3) **2.3.2 Data Handling Conventions and Comparisons for Determining Whether Standards Are Met**

There is a reference to the hourly concentrations being utilized to compute 8-hour averages. Is this short-term 8-hour rolling average consistent with short-term actual and scientific studies?

I believe so.

4) **2.4.3 Diurnal Patterns**

While this section refers diurnal patterns of relative ozone concentrations between day and night, are these diurnal patterns solely (although mostly are) attributable to temperature? What about stagnant weather conditions? What about the effects on topography/geography in determining diurnal patterns?

It's my understanding that the mechanism is controlled by UV light and that temperature accelerates the reactions. To sort out these interactions, I would like to see clinical health effect experiments using ozone exposures at various temperature levels. Los Angeles and the Utah Valley offer examples of topographic influences on ozone photochemistry.

5) **Background Ozone**

There, in general appears to be a lot of discussion about background ozone concentrations from transport and natural sources. However, are most salient ozone concentrations more localized and from anthropogenic sources?

This depends on what is meant by "salient" and may depend on contributions of other photochemical oxidants.

This section references the utilization of photochemical grid models due to the lack of ability to characterize the origins of ozone and the ability to estimate the magnitude of background ozone.

However, how predictable are these photochemical models, especially given the highly photolytic and relative instability of ozone in the atmosphere?

This is a question for the modelers. Relevant questions concern indoor, outdoor, and background temporal patterns and diurnal cycles.

This section mentions that international emissions sources via transport mostly originate from anthropogenic sources. However, is there a possibility that there can be international transports from non-anthropogenic/biogenic sources?

I suppose so.

Also, this section noticeably leaves out non-international, interstate transport of ozone.

Interstate transport should be accounted for by the usual photochemical grid models that don't recognize political boundaries.

6) 2.5.1.6 Pre-Industrial Methane

There is a whole section devoted to long-lasting atmospheric methane. However, what is the importance of methane with respect to the formation of and consideration of ozone? Is a discussion on methane warranted?

I don't think so. It's up to the PA to provide linkage.

Relevant Publications by Lipfert and Colleagues Not Cited in ISAs or PAs

Daily Mortality Publications

Murray CJ, Lipfert FW. Revisiting a Population-Dynamic Model of Air Pollution and Daily Mortality of the Elderly Population in Philadelphia. J Air Waste Manag Assoc. 2010 60:611-629.

Murray CJ, Lipfert FW. A new time-series methodology for estimating relationships between elderly frailty, remaining life expectancy, and ambient air quality. Inhalation Toxicology 2012 24:89-98.

Lipfert FW, Murray CJ. Air pollution and daily mortality: A new approach to an old problem. Atmos Environ 55; 467-74 (2012).

Murray CJ, Lipfert FW. Inferring frail life expectancies in Chicago from daily fluctuations in elderly mortality. Inhal Toxicol. 2013 Jul;25(8):461-79.

Long-term Cohort Mortality Publications

Lipfert FW, Perry, H.M. Jr., Miller, J.P., Baty, J.D., Wyzga, R.E., Carmody, S.E. (2000) The Washington University-EPRI Veterans' Cohort Mortality Study: Preliminary Results, Inhalation Toxicology 12 (Suppl 4):41-73.

Lipfert FW, Perry, H.M. Jr., Miller, J.P., et al., 2003. Air Pollution, Blood Pressure, and Their Long-Term Associations with Mortality. Inhalation Toxicology 15, 493-512.

Lipfert FW, Wyzga, R.E., Baty, J.D., Miller, J.P., 2006a. Traffic Density as a Surrogate Measure of Environmental Exposures in Studies of Air Pollution Health Effects: Long-term Mortality in a Cohort of U.S. Veterans, Atmospheric Environment 40, 154-169.

Lipfert FW, Wyzga, R.E., Baty, J.D., Miller, J.P., 2006b. $PM_{2.5}$ Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans, Inhalation Toxicology 18:645-57.

Lipfert FW, R.E. Wyzga, Jack D. Baty, J. Philip Miller. Vehicular Traffic Effects on Survival within the Washington University - EPRI Veterans Cohort: New Estimates and Sensitivity Studies, Inhalation Toxicology 20:949-960 (2008).

Lipfert FW, R.E. Wyzga. On Exposure and Response Relationships for Health Effects Associated with Exposure to Vehicular Traffic. J Expos Sci Environ Epidem 18: 588-599 (2008).

Lipfert FW, Wyzga RE, Baty JD, Miller JP. Air pollution and survival within the Washington University-EPRI Veterans Cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J Air Waste Manag Assoc. 2009 59:473-89.

Lipfert FW, Wyzga RE. Revisiting the Veterans Cohort Mortality Study: New results and synthesis. J Air Waste Manag Assoc. 2018 Nov;68(11):1248-1268.

Lipfert FW, Wyzga RE. Environmental Predictors of Survival in a Cohort of U.S. Military Veterans: A Multi-level Spatio-temporal Analysis Stratified by Race. Envir Res (in press 2019)**.**