Comments on the Draft Letter to be Discussed on the July 6, 2011 Teleconference of the CASAC Ozone Review Panel

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Gradient

Below are comments on the deliberative draft letter that will be discussed on the July 6, 2011 teleconference of the CASAC Ozone Review Panel. Page and line numbers and statements from the draft dated June 17, 2011 are in bold and my comments follow in plain text.

Cover Letter

page 1, line 20: "EPA's adoption of this framework has greatly improved the consistency and transparency of its assessment as compared to the approach of past reviews."

While the framework is an improvement over the approach of past reviews, there is still an issue with the application of the framework in the ISA, most notably a lack of information regarding study selection criteria, inconsistent methods for evaluating the strengths and weaknesses of individual studies, and the lack of a clear framework for weighing evidence. In addition, the same study is often reviewed differently in different NAAQS publications (*e.g.*, some studies that analyze both O_3 and PM are assessed differently in O_3 and PM documents).

page 1, line 31: "The PRB calculation is critical because it defines the extent to which ozone concentrations can be reduced by U.S. regulations or through international agreements with neighboring countries."

The PRB as defined is not a representation of "the extent to which ozone concentrations can be reduced by U.S. regulations or international agreements with neighboring countries." Rather, it is an estimate of the level of ozone that might occur with zero man-made emissions of O_3 precursors. The PRB as defined by EPA is a level that cannot be reached. There is no U.S. policy approach or international agreement that can result in zero emissions.

page 2, line 1: "The ISA provided useful information on human exposures to ozone and the evidence relating human exposure to ambient ozone concentration and the errors associated with exposure assessment; however, the characterization of the temporal and spatial variability of ozone could be improved."

CASAC should go a step further and suggest that the impact of exposure measurement error on the results of epidemiology studies and the determination of a threshold must be considered. It is well known that exposure measurement error can bias regression results, which tends to flatten and apparently linearize a

steeper and perhaps even threshold-bearing curve, producing a false linear result (Rhomberg *et al*., 2011a,b). In the ISA, EPA does not present the conclusions from the study by Brauer *et al.* (2002), in which exposure misclassification and threshold concentrations in time-series analyses of air pollution health effects were evaluated. For pollutants such as ozone, which exhibit a very low correlation between ambient and personal exposure, Brauer *et al* (2002) reported that it is not possible to determine whether or not a threshold exists. The authors reported that the use of poorly correlated ambient air measurements as a surrogate for personal exposure obscures the ability to detect thresholds. Another issue is that heterogeneity across cities makes it difficult to identify a threshold (Rhomberg *et al*., 2011b), and EPA acknowledges this throughout the concentration-response section of the ISA.

page 2, line 21: "This ISA covered the new evidence on the relationship between ozone and all-cause (non-accidental) mortality and concluded that there is "likely to be a causal relationship" between ozone and all-cause mortality. This is an elevation of the classification of the evidence over the previous conclusion from the 2006 Air Quality Criteria Document that the evidence was "highly suggestive" of ozone contributing to all-cause mortality. This upgrading was well justified by new multi-city studies and new studies examining potential confounders (co-pollutants and seasonality) of the ozone-mortality relationship."

This upgrade is not justified by new studies. In the 2006 AQCD, EPA stated that there was strong evidence for associations between short-term ozone exposure and all-cause mortality and that consistently positive associations were reported for ozone-related CV mortality. The few positive, statistically significant risk estimates reported in mortality studies in the 2006 AQCD were very weak and susceptible to confounding and bias, however. EPA acknowledged that multiple uncertainties remained in the assessment of the ozone-mortality relationship (US EPA, 2006), and studies that address these uncertainties are the main focus of the short-term mortality section of the ISA. Some of these studies reported positive associations (e.g., Bell and Dominici, 2008; Zanobetti and Schwartz, 2008), whereas other studies that reported no association between ozone and mortality are not included (Dominici et al., 2005; Goldberg et al., 2006), even though these studies were mentioned in EPA's provisional assessment of recent ozone data (US EPA, 2009). The omission of studies with null results in the ISA without a clear presentation of the criteria for study inclusion and exclusion indicates a lack of transparency in the assessment.

In the ISA, EPA cites recent studies that focused primarily on three areas of uncertainty: confounding, effect modification (i.e., sources of heterogeneity across cities and the ozone-mortality concentration-

response function), and model specification. Overall, the results of these studies indicate that important uncertainties remain for the association between short-term ozone exposure and mortality, and these are not adequately addressed in the ISA. Specifically, the new studies indicate that the ozone-mortality association is significantly confounded by various forms of PM, the currently used ozone time-series models are very sensitive to model specification, and the mortality association varies greatly by region and, thus, is not consistent.

page 2, line 37: " In this ISA, evidence from new epidemiologic and toxicology studies supports the finding that the effects of ozone on long-term respiratory effects are "likely to be causal"…

The 2006 AQCD concluded that the evidence was inconclusive regarding the association between long-term ozone exposure and respiratory morbidity. In the ISA, EPA states that recent studies report consistent associations with new-onset asthma related to genotype, and provide evidence for associations with respiratory symptoms in asthmatics and for first asthma hospitalization. Recent evidence does not provide support to strengthen this association to a "likely to be causal relationship" as concluded in the ISA, however.

The long-term studies of respiratory morbidity suffer from several limitations that are not adequately addressed in the ISA, including exposure measurement error from the use of central monitors and confounding by other pollutants..

A few studies are cited in which associations are reported between ozone exposure and new-onset asthma or respiratory symptoms in children with certain gene variants. These data are limited, however, in that essentially only one study of each specific gene variant is discussed. In addition, while some of these studies report reduced risks for these outcomes in children with a specific, "protective" variant in low ozone communities compared to high ozone communities, it is not demonstrated that children with the alternative variant actually have an increased risk for these outcomes with ozone exposure. For example, the study by Islam et al. (2008) reports an interaction p-value of 0.003 for the effect of gene variation on the risk of new-onset asthma in children by community-specific ozone level (continuous). This interaction is inconsistent with the fact that Islam et al. (2008) also reported null risk estimates for all children (with or without the protective gene variant) in communities with higher ozone concentrations, suggesting that none of the children in the study have an increased risk of new-onset asthma with increasing ozone exposure.

Overall, the determination of the relationship between long-term ozone exposure and respiratory morbidity as "likely to be causal" is questionable. The recent evidence cited for this causal determination mainly comes from studies of asthma-related outcomes in children with specific gene variants, but these studies do not demonstrate any consistent associations between ozone exposure and these outcomes. It is unclear how this evidence is more compelling than that of other health outcomes for which the evidence was determined by EPA to only be "suggestive" of a causal relationship.

ISA Length

page 5, line 22: "The text should focus on findings, only discussing methods and models when necessary to support or describe the findings."

The weight of findings in a weight-of-evidence analysis is completely dependent on the methods used to determine those findings. Omitting the methods will not allow the reader to judge whether the relative weights placed on study results are appropriate, or if a weight-of-evidence analysis was even done. This results in a lack of transparency of how the evidence was evaluated.

Chapter 1, Framework

page 5, line 43: "The separation between old and new studies causes duplication and restricts cohesive understanding. Furthermore, this distinction is artificial because the NAAQS is based on all pertinent information, independent of what year it was published. Having tables and utilizing them optimally would avoid this problem…"

This is very important. It is crucial that the weight of each study is not dependent on when that study was published with respect to artificial cut-off dates. All available and relevant data should be considered in a weight-of-evidence analysis.

Question 2 asks if the framework is appropriately applied.

While the framework is an improvement over the approach of past reviews, there is still an issue with the application of the framework in the ISA, most notably a lack of information regarding study selection criteria, inconsistent methods for evaluating the strengths and weaknesses of individual studies, and the lack of a clear framework for weighting evidence.

page 6, line 16: "'Cause' is a significant, effectual relationship between an agent and an effect on health or public welfare."

CASAC stressed that the effect is on "health or public welfare," not merely a biological change. We have discussed this at length in a recent manuscript: Goodman *et al*. (2010). This is a particular issue with the controlled human O_3 exposure studies, for which statistically significant effects on lung function at exposures below the current NAAQS are not considered adverse according to clinical guidelines, and should be given more consideration.

page 7, line 33: "The shape of the exposure-response relationship is influenced by the degree of measurement error, as touched on (1-23, line 8). Specifically, measurement error at lower concentrations can obscure a threshold and make it appear that a linear relationship extends to lower concentrations (Brauer M et al. Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects. Risk Anal 2002; 22: 1183-1193). This might be a particularly important issue for interpreting risks of pollutants, such as ozone, that exhibit large degrees of measurement error.

In concept, a population threshold should be equal to the lowest of all individual thresholds in the population under study. Thus, it does not require that the population-wide data, taken alone, present a clear signal about thresholds if other kinds of data, e.g., human exposure studies, show that some person or group has lower individual thresholds than inferred at the population level. If the ISA is to use a different conceptual framework for interpreting analyses directed at thresholds, that framework and related definitions should be presented here and defended."

The ISA does a poor job of considering and incorporating thresholds in its analyses. In addition to the Brauer *et al*. paper, the ISA should consider: Rhomberg *et al*. (2011a). This manuscript reviews several studies, including that of Brauer *et al*., that address this topic. The ISA should also consider that thresholds in controlled exposure studies are higher than exposure levels in many of the observational studies, and must determine how to incorporate this information.

Chapter 4, Human O_3 Exposures

page 10, line 25 "Historical placement of central site monitors away from local sources has potentially resulted in a buffered view from the monitoring network regarding ozone variability, given the considerable variation induced by NOx titration near or immediately downwind from busy roadways or other substantive sources of NOx. Further, studies have shown central site monitors to be relatively poor proxies of personal ozone exposures, especially for individuals living in poorly ventilated environments or who spend little time outdoors. Thus, the chapter should more critically address the adequacy of central site monitors for use in epidemiological studies and be more forthcoming about potential biases that could result from assuming central site data are representative of spatial homogeneity, temporal trends, and personal exposures. Discussion is provided about models and factors affecting various microenvironmental relationships, but a focused, decisive, and succinct summary of the results of applying the models is lacking."

This is a very important point, but it should go further. This issue should be discussed in the health effects sections of the ISA when the epidemiology study results are discussed. Specifically, the impact of exposure measurement error on results and the ability to detect a threshold should be stressed. As discussed above, this is described by Rhomberg *et al*. (2011).

Chapter 6, Health Effects Evidence for Short-Term O_3 Exposures

Pages 13-14 discuss controlled exposure studies.

CASAC should recommend that EPA include a more balanced discussion of statistics, as much has been made of the results of the Adams (2006) study. It has been argued recently by some CASAC members that Adams (2006) only found statistically non-significant results because the statistical test, specifically the Scheffe *post hoc* test, was not sufficiently powerful to detect the effect. The Scheffe test used by Adams (2006) is a commonly used statistical test to compare mean values that minimizes false positives, but may be more likely to produce false negatives. Some CASAC members suggested that this test is overly conservative and had other statistical tests been used, results would have been statistically significant (Allen *et al*., 2011).

Brown (2007) and Brown *et al*. (2008) claim to address this by analyzing only the 6.6-hour response at 60 ppb ozone *vs*. FA in the Adams (2006) study. This approach excluded all pulmonary function data at other interim hourly time points and exposure levels within the 6.6-hour exposure pattern. This approach is also at variance with those of other research groups that have performed prolonged ozone exposures and published their results in the scientific literature prior to the Brown reanalysis, including those by researchers at the University of Rochester (Torres *et al*., 1997), the University of Toronto (Liu *et al*., 1999), the University of California, Los Angeles (Gong *et al*., 1998), and EPA (Gong *et al*., 2004). In a presentation to CASAC, Professor William Adams expressed concerns with EPA's reanalysis of selected data from his study and its conclusions, which are very different from those in the published paper (Adams, 2007). While the approach used by Brown (2007) and Brown *et al*. (2008) produced statistically significant results, this can be attributed to the majority of the data being selectively omitted from the analysis.

Dr. Mark Nicolich conducted an analysis of the full data set from Adams using a mixed model analysis of variance and Dunnett's *post hoc* test instead of the Scheffe test (Deason, 2007). This re-analysis, using a technique that is less likely to produce false negatives, was consistent with the original finding by Adams (2006) that there was no statistically significant decrement in group FEV_1 after exposure to 60 ppb ozone *versus* filtered air after 6.6 hours of exercise. In addition, Lefohn *et al*. (2010) re-analyzed five controlled ozone exposure studies, including those by Adams (2006) and Schelegle *et al*. (2009), using two-factor ANOVA and evaluating statistical significance using the Tukey's studentized range approach to account for multiple comparisons for least square means. Although they did not subtract the FA FEV_1 from the

ozone-treatment responses, their methodology can still be considered conservative in that it minimizes Type II errors. They did not find any statistically significant changes in FEV_1 at any measurement time associated with the 40 ppb and 60 ppb profiles. In addition, they found that in four out of five studies, exposures to FA substantially improved FEV_1 response over the exposure period, which means that analyses using FA controls likely overestimated FEV_1 changes.

EPA has provided no scientifically acceptable justification for relying on the Brown statistical analyses over the original analyses conducted by the authors or those of Nicolich or Lefohn *et al*. (2010). While each statistical method has strengths and limitations, several scientifically accepted statistical methods indicate that there is no statistically significant association between exposure to 60 ppb ozone and lung function decrements. We recommend that in the ISA, EPA recognize and give equal or greater weight to analyses using these methods.

page 14, line 19: "The epidemiologic results of increased mortality (overall) are quite consistent in direction (not in severity) over space, time, and a range of circumstances and study designs, although there are some exceptions for single cities or other subgroups. Possible flaws in the evidence being presented are adequately discussed. However, the discussion misses the point that a remarkable combination of factors would have to affect the reported studies, each in different ways, to decrease the estimated effect to be no more than 'likely'."

While there are differences in study design, the same set of issues can affect all studies, leading to consistent results, but results that are consistently biased. The majority of risk estimates are so close to unity, it would actually take very few factors to push them to null. These factors include, but are not limited to, confounding by co-pollutants and exposure measurement error, which are major limitations in all of the epidemiology studies using measurements from central monitors as surrogates for personal ozone exposure.

page 14, line 41: "The discussion of severity of effects observed in humans should be expanded. The ATS guidance on pulmonary function is referenced, but not explained. The document should make clear what it means to have a certain percentage change in pulmonary function or an increase in lung inflammatory markers in a healthy human or in an asthmatic child. This chapter would also benefit from more integration with mechanisms of action and animal toxicology studies."

As discussed above, EPA should only consider effects on "health or public welfare," not merely a biological change. We have discussed this at length in a recent manuscript: Goodman *et al*. (2010). A mere change in a controlled human exposure study does not indicate what will happen in the general population.

Chapter 7, Health Effects Evidence for Long-Term O_3 Exposures

page 15, line 33: "Overall, the panel agreed with the causality conclusions in this chapter. The strength of evidence for causality is perhaps weakest for mortality, for which EPA concluded a "suggestive" relationship. This conclusion is largely based on a single epidemiological study, with consistent supporting evidence from other lines of research, including toxicological research. Further description of the mortality study, including its limitations, is needed. The conclusion for evidence on all-cause mortality is appropriate, given the single study's evidence that the all-cause relationship is not robust to inclusion of PM. There is stronger evidence for respiratory mortality.

The 2006 AQCD concluded that an insufficient amount of evidence existed to suggest a causal relationship between long-term ozone exposure and mortality. In the ISA, EPA cites multiple ozone-mortality studies that reported null results, and cites two studies conducted since the last review (one of which reported null results) as new evidence. EPA also states that results of short- and long-term respiratory morbidity studies provide biological plausibility for mortality due to respiratory disease, but then concludes that the collective evidence is suggestive of a causal relationship between long-term ozone exposure and *all-cause* mortality, not just respiratory mortality. Multiple studies reporting no association between long-term ozone exposure and mortality, with one study providing weak evidence for respiratory-specific mortality (as discussed further below), do not provide suggestive evidence for a causal relationship, however.

Several large studies that examined long-term ozone exposure and respiratory or cardio-pulmonary mortality have not reported positive associations. No associations were reported for cardio-pulmonary mortality in the Harvard Six Cities Study by Dockery *et al*. (1993), the American Cancer Society (ACS) study by Pope *et al*. (2002), or the Adventist Health Study of Smog (AHSMOG) by Abbey *et al*. (1999). Abbey *et al*. (1999) also reported no association between long-term ozone exposure and non-malignant respiratory mortality. A recent study by Wang *et al*. (2009) examined cardio-respiratory mortality in Australia and found that long-term exposure to SO_2, but not ozone, was associated with this endpoint. In the ISA, EPA describes these studies and acknowledges that the available data regarding long-term ambient ozone exposure and either respiratory or cardio-pulmonary mortality, with the exception of one study by Jerrett *et al*. (2009), show no association.

In the ISA, EPA focuses on the follow-up analysis of the ACS cohort by Jerrett *et al*. (2009) in its assessment of the association between long-term ozone exposure and respiratory mortality. No other

studies of the ACS cohort have reported associations with cardio-pulmonary mortality that were robust to inclusion of co-pollutants, and the Jerrett *et al*. (2009) study does not provide clear evidence of an association for several reasons. Jerrett *et al*. (2009) reported a weakly positive risk estimate in a multi-pollutant model with $PM_{2.5}$. The authors did not adequately control for the potential confounding effects of co-pollutants, however. Although the study examined ozone air concentrations from 1977 to 2000, only two years of data on $PM_{2.5}$ (1999-2000) were considered because of limited availability of data prior to 1999. Because the levels of ozone and $PM_{2.5}$ decreased considerably between 1977 and 2000, the analysis of ozone included higher levels observed in the past, whereas the analysis of potential confounding by $PM_{2.5}$ considered the more recent, lower levels observed in 1999 and 2000. Furthermore, the exposure metric for ozone focused on daily maximum hourly levels in the warm seasons, whereas for $PM_{2.5}$ the annual average concentration was used. Thus, this approach increased the potential to observe an association between ozone and mortality and decreased the potential to observe $PM_{2.5}$ as a confounder of this association. The authors noted this limitation, stating, "Since particulate air pollution has probably decreased in most metropolitan areas during the follow-up interval of our study, it is likely that we have underestimated the effect of $PM_{2.5}$ in our analysis." Another limitation of the study is that confounding by other pollutants, such as SO_2, was not examined. In an earlier study of the ACS cohort, SO_2 demonstrated a stronger association with mortality than $PM_{2.5}$ (Krewski *et al*., 2000). Because of this, as well as the likely underestimation of confounding by $PM_{2.5}$, the study by Jerrett *et al*. (2009) does not demonstrate an association between ozone and respiratory mortality that is independent of other co-pollutants.

Other aspects of the Jerrett *et al*. (2009) study that are not consistent with a positive association between long-term ambient ozone exposure and mortality include a small inverse association between ozone and mortality from CV disease, ischemic heart disease, and all causes combined, as risk estimates for these outcomes were less than one and statistically significant in two-pollutant models with $PM_{2.5}$. The magnitude of these risk estimates was similar to that of the positive risk estimate for respiratory mortality, and it is not biologically plausible that ozone exposure would be protective of mortality; thus, it is likely that both positive and negative associations of this magnitude, even if they are statistically significant, are not reliable. There is also high regional heterogeneity in risk estimates, as positive associations were only reported in two of the seven regions examined. Because of this high geographic heterogeneity, it was inappropriate for Jerrett *et al*. (2009) to combine data across cities for a US national risk estimate. Finally, socioeconomic data was collected for the ACS study in 1982-1983 but was never updated, so this potential confounder was not fully accounted for in the analysis.

Although several studies have been conducted, only the study by Jerrett *et al*. (2009) has reported an association with long-term respiratory mortality, and this study had many limitations that weakened the evidence for causality. A casual relationship is also not coherent with the overall inconsistent evidence for respiratory morbidity and the almost exclusively null evidence for short-term effects on respiratory mortality, as described above. Together, the evidence for an association between long-term exposure to ozone and mortality is overwhelmingly null, and one weakly positive study with many limitations is not sufficient to suggest a causal relationship.

page 15, line 42: "The text on evidence for causality of long-term exposure to O3 could be made stronger by drawing on literature from other chapters that found consistent evidence for similar health outcomes, albeit for a different timeframe of exposure. Specific examples are the findings from epidemiology, toxicological, and human experimental studies on respiratory morbidity for a range of health endpoints. These findings provide evidence of plausibility for the conclusions in the long-term exposure chapter. The chapter could explicitly state the ways in which there is and is not evidence for causality, such as whether the limitations relate to sample size, lack of variability in study designs, etc. This should be done in the context of evidence for causality, not research needs."

The findings from studies on short-term respiratory morbidity are not consistent and thus do not provide evidence of plausibility for long-term respiratory morbidity. The evidence for short-term effects on other health outcomes, such as cardiovascular morbidity and mortality, are also not consistent and do not support the plausibility of long-term effects of ozone on these outcomes. The controlled human exposure studies show respiratory effects that are less adverse and occur at higher exposure levels than those in the epidemiology studies. Overall, there is no consistency or coherence for health outcomes at exposure levels below the current NAAQS. CASAC should stress the last two sentences in the above quote, in that these limitations have large impacts on determinations of causality.

Other

There are several references that are not in the peer-reviewed literature in the ISA. These references may be difficult for the public to obtain. EPA should make these references available to the general public, perhaps through HERO.

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