Comments to the CASAC Ozone Review Panel on the Ozone Scope and Methods Plan for Health Risk and Exposure Assessment

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1 Introduction

In April, 2011, the United States Environmental Protection Agency (EPA) released the *Ozone National Ambient Air Quality Standards: Scope and Methods Plan for Health Risk and Exposure Assessment* (US EPA, 2011a), hereafter referred to as the "REA Plan." The REA Plan describes EPA's intended scope and methods for conducting the human health risk and exposure assessments to support the review of the primary ozone National Ambient Air Quality Standard (NAAQS). According to the REA Plan, the human health risk assessment for ozone will include risk estimates based on both controlled human exposure studies (US EPA, 2011a, Chapter 4) and epidemiology/field studies (US EPA, 2011a, Chapter 5). The REA Plan relies heavily on information assessed in the first draft Integrated Science Assessment (ISA) for ozone (US EPA, 2011b), but there are many issues with EPA's approach for evaluating human data in the ISA. These issues are described below, in the context of a critical review of Chapters 4 and 5 of the REA Plan.

2 The Use of Controlled Exposure Study Data in the REA Plan

In Chapter 4 of the REA Plan, EPA stated that, if possible, it would use a model that estimates forced expiratory volume in one second (FEV_1) responses associated with short-term exposures to ozone discussed by McDonnell *et al*. (2010) to determine exposure levels at which FEV_1 decrements of 10, 15, and 20% will occur. In this publication, the authors evaluated an earlier model by McDonnell *et al*. (2007) and then expanded it to include body mass index (BMI) as a covariate. The model is based on 15 studies conducted by EPA between 1981 and 1992, none of which evaluated exposures less than 80 parts per billion (ppb). McDonnell *et al.* (2010) concluded that their FEV_1 model over-predicts low concentration (< 80 ppb) values from the more recent studies by an average of one percentage point. FEV_1 decrements are so low at 60 ppb – ranging from 1.7% to 3.5% in some of the recent exposure studies (Adams, 1998, 2006; Kim *et al.*, 2011; Schelegle *et al.*, 2009) – that this one percentage point could have a large effect on the predicted FEV_1 decrement.

The model also does not include a threshold. Because the biological mechanism of ozone-induced lung function decrements is known to have a threshold [*e.g.*, see Schelegle *et al*. (2007], the statistical model used should reflect this.

It is not clear how EPA intends to use this model to determine at what exposure levels decrements of 10, 15, and 20% will occur. These values are all at the high end of the curve and inherently unstable. As stated in an earlier risk assessment funded by EPA and the Department of Energy:

> One particularly bothersome case involved the lung function endpoints for 6.6-h exposures of subjects engaged in moderate exertion (the combined data of the studies by Folinsbee *et al.* 1988, Horstman *et al*. 1990, and McDonnell *et al*. 1991). The observed response rate at 0.12 ppm for the FEV_1 decrement $\geq$ 15% endpoint was judged to be unreasonable and was not used in the regression. (Whitfield *et al*., 1996)

It should also be noted that, although not stated in the REA Plan, EPA and CASAC have suggested in the past that FEV_1 decrements of a certain level for *individual* study subjects are a result of ozone, even if the average FEV_1 decrements at that exposure level are not statistically different than filtered air. This is not an appropriate way to interpret these data, and this type of analysis should not be incorporated in the REA.

Overall, because of the limitations with the McDonnell *et al*. (2007) model, EPA should construct a new statistical model based on all of the available controlled ozone exposure studies that incorporates a threshold, with FEV_1 decrements associated with exposures $\leq$ 60 ppb no different than those with filtered air.

3 The Use of Epidemiology Data in the REA Plan

In the REA Plan, EPA states that the human health risk assessment will focus on health endpoints for which the weight of the evidence, as assessed in the ISA, supports a causal or likely causal relationship. These endpoints are short-term respiratory morbidity and mortality, as well as long-term respiratory morbidity. EPA will also consider using two health outcomes judged in the ISA to have a "suggestive" causal association with ozone. Long-term birth outcome effects will be considered for the sensitivity analyses, whereas long-term respiratory mortality will be considered for inclusion as part of the core risk assessment. EPA did not consistently apply its framework for causal determination across studies or health outcomes in the ISA, however, and causal relationships determined in the ISA are not a reliable basis for determining the health endpoints to focus on in the risk assessment.

3.1 Only Studies of Respiratory Morbidity Associated with Short-Term Ozone Exposure Should Be Considered for the Core Risk Assessment

EPA's approach to assessing the epidemiology evidence in the ISA was inappropriate and did not consider many of the limitations and uncertainties associated with the underlying studies. EPA focused on the positive associations reported in the studies, whether they were statistically significant or not, and often discounted null results. This led to the consistency of the results being routinely overstated in the ISA. EPA also did not appear to appropriately weigh the evidence for causality, and instead provided summarizing statements that emphasized only the few positive associations that may have been reported for a given outcome, with no discussion of the strengths and weaknesses of the studies to support the summary. Furthermore, EPA did not adequately consider the factors that can bias study results and often understated these uncertainties – including confounders, measurement error, exposure misclassification, and model uncertainty – and did not give them consistent or sufficient weight in the evaluation of epidemiology studies. Most of the reported risk estimates were very small, and many of the statistically significant associations were found to be non-significant when confounders were accounted for; thus, it is likely that residual, unmeasured, and/or unknown confounders could have accounted for many of the observed associations. For these reasons, conclusions of "causal" or "likely to be causal" relationships are generally overstated in the ISA, as there is a high possibility that the actual risk for a given endpoint is, or approaches, zero. This possibility must be included for the core set of risk estimates.

Only the health endpoints that have been shown to have a causal association with ozone exposure after a thorough weight-of-evidence evaluation should be included in the core risk assessment. As noted above, EPA's approach for evaluating studies in the ISA emphasized only the positive associations for each endpoint, and this essentially ignores the weight of the evidence. Given the degree of uncertainty associated with the "causal" relationships in the ISA, and even greater uncertainty associated with the other causal classifications, only health endpoints for which ozone is deemed "causal" by EPA's definition should be considered in the core risk assessment. In the ISA, EPA identified short-term respiratory morbidity as the only health effect endpoint for which ozone exposure has a "causal" relationship. Thus, only studies of respiratory morbidity associated with short-term exposure to ozone should be considered in the core risk assessment, and only "likely causal" health endpoints can be considered in the sensitivity analyses.

3.2 EPA Should Not Evaluate Long-Term Respiratory Mortality in the Risk Assessment

EPA's consideration of including long-term respiratory mortality as part of the core risk assessment is not justified. Several large studies have examined long-term ozone exposure and respiratory or cardio-pulmonary mortality and have not reported positive associations. In the ISA, EPA described these studies and acknowledged 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.

EPA focused on the follow-up analysis of the American Cancer Society (ACS) cohort by Jerrett *et al*. (2009) in the ISA. 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 $PM_{2.5}$, but the authors did not adequately control for the potential confounding effects of co-pollutants. 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 sulfur dioxide (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 cardiovascular (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. 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 or to be used in a risk assessment. Thus, this endpoint should not be evaluated in the core risk assessment or sensitivity analyses.

3.3 The REA Plan Does Not Address how Non-Statistically Significant or Negative Results will be Accounted for in the Risk Assessment

Many of the studies relied on for the causal associations in the ISA reported results that did not achieve statistical significance, and it is assumed that these results will be used in the risk assessment. If so, the core set of risk estimates must include the case that the possible risk is zero. In addition, the choice of which concentration-response (C-R) functions to use in the risk assessment should not be guided by the identification of the highest or most statistically significant function, as this could lead to bias. Instead, one should choose the most plausible model, such as the model most consistent with the hypothesized mechanism of action (Rhomberg *et al*., 2011a). If the results of the most plausible model indicate no statistically significant risk, the risk assessment should reflect this lower-bound, no-risk scenario.

An additional point for consideration is that some of the multi-city studies reported decreases in community-specific mortality for certain cities of interest. If EPA does include the endpoint of short-term mortality in the risk assessment, it must address how these community-specific, negative effect estimates will be used.

3.4 EPA Should Not Use Single-Pollutant Models in the Risk Assessment

In the REA Plan, EPA states that the risk assessment will include C-R functions based on both single- and multi-pollutant models, noting that both have their advantages and disadvantages. While this is true, it does not mean that an approach using findings from both types of models is justified. Because both modeling approaches have limitations, the results from both are of uncertain confidence. Given that a number of air pollution epidemiology studies report statistically significant positive associations for most pollutants that are analyzed, it is clear that an approach for disentangling the effects of specific pollutants is necessary. Single-pollutant model results likely bias risk estimates away from the null, resulting in an overestimate of risk. Even though multi-pollutant models may underestimate risks in some circumstances, they offer the only way to identify the effects of the pollutant under consideration *vs.* potential confounding pollutants, so only these models should be used in the risk assessment. If the inclusion of potentially confounding pollutants markedly reduces the risks of a particular endpoint to levels that are no longer statistically significant, EPA should consider that it is not possible to separate out the risks for the pollutant of concern for this endpoint, even if the risks are still above 1.00.

3.5 There is Biological Justification to Use a Threshold Model for the Core Set of Risk Estimates

The REA Plan indicates that EPA will not consider a threshold C-R model in the short-term core analysis or the sensitivity analyses because the ISA concludes there is little support in the literature for a population threshold for short-term ozone exposure-related effects. This is not true, however, as the controlled ozone exposure studies clearly show a threshold effect. Statistically significant effects on lung function have not been consistently observed at controlled ozone exposures below 72 ppb (Adams, 2002, 2006; Schelegle *et al*., 2009; Kim *et al*., 2011), and adverse lung function effects have only been observed with exposures above 81 ppb ozone (Adams, 2002, 2003; Folinsbee *et al*., 1988; Horstman *et al*., 1990; McDonnell *et al*., 1991; Schelegle *et al*., 2009).

A short-term exposure threshold for effects on lung function in response to ozone is also consistent with biological data that support a mode of action related to antioxidant defenses. Antioxidants may provide the first line of defense against ozone exposure by reacting with ozone in the airway lining fluid (Avissar *et al.*, 2000; Ballinger *et al.*, 2005; Cross *et al.*, 1994; Mudway *et al.*, 1996; Samet *et al.*, 2001). Ozone exposure of a sufficient duration and concentration can overwhelm the antioxidants, allowing oxidative damage to occur in airway epithelial cells (Schelegle *et al*., 2007). Thus, antioxidants react with ozone in a time- and concentration-dependent manner, and ozone can cause adverse effects only when these defenses are saturated. This indicates that a threshold exists below which these antioxidant defenses are sufficient to protect against adverse effects from ozone.

The conclusion in the ISA that there is no evidence to support a threshold for short-term health effects of ozone indicates that EPA is overstating the limited ability to detect a threshold as a lack of evidence to support one. There are several factors that limit the ability of studies to assess ozone C-R thresholds. 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*., 2011b,c). 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*., 2011c), and EPA acknowledges this throughout the C-R section of the ISA. Even if a non-threshold model best described the reported data for ozone, it is likely that a threshold model would have better described the data were these uncertainties taken into account.

The available ozone epidemiology data are not robust enough to determine whether a non-threshold model best describes the association between ozone exposure and health effects. Because the controlled human exposure studies and proposed modes of action for respiratory morbidity support the existence of a threshold, however, a threshold C-R model should be used for the core set of risk estimates, and other models can be assessed in the sensitivity analyses.

3.6 EPA Should Not Use Different Lag Periods for Different Cities Without Biological Justification

In selecting C-R functions from the epidemiology studies for the risk assessment, EPA plans to use distributed lag models, if information is available for this type of model. If there are multiple lags presented, but a distributed lag model is not included, EPA plans to consider information in the ISA to determine if there is biological support for selecting a specific lag period for a given health effect. EPA appears to be open to using different lag periods for different cities, however, as supported by the statement on page 5-24 of the REA Plan that it "plan[s] to consider this source of variability by using effect estimates and lag structures specific to each urban study location." The use of different lag periods for different cities raises questions regarding the biological plausibility of the reported associations. If there is no biological justification, lag periods should not differ by city for any given endpoint. Instead, EPA should decide *a priori* which lag model has the most biological plausibility for each health endpoint and then use that model in the risk assessment.

4 Conclusions

EPA's plan for an ozone risk assessment relies heavily on information assessed in the first draft ozone ISA, but many of the conclusions presented in the ISA are not a reliable basis for determining the health endpoints to focus on in the risk assessment. The core set of risk estimates must be based on factors that are most likely indicative of the true risk of individuals in the population. To achieve this, EPA should consider the following in carrying out the ozone risk assessment:

- EPA should construct a new statistical model based on all of the available controlled ozone exposure studies that incorporates a threshold, with FEV_1 decrements associated with exposures ≤ 60 ppb no different than those with filtered air.
- Only health endpoints for which ozone is deemed "causal" by EPA's definition should be considered in the core risk assessment (*i.e.*, respiratory morbidity association with short-term exposure), and other health endpoints deemed "likely causal" can be considered in the sensitivity analyses.
- Long-term ozone mortality should not be evaluated in the core risk assessment or sensitivity analyses because the evidence for an association is overwhelmingly null and is not sufficient to even suggest a causal relationship.
- Non-statistically significant and negative results should be accounted for in the risk assessment.
- Only multi-pollutant models should be used in the risk assessment.
- A threshold C-R model is biologically justified and should be used in the core risk assessment.
- A decision should be made *a priori* as to what type of lag model has the most biological plausibility for a given endpoint, and this model should be used in the risk assessment.

These recommendations would increase the likelihood that the core set of risk estimates for ozone-related health effects will be based on the most biologically plausible methods and robust data, and the sensitivity analyses can address more conservative scenarios.

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