Comments to the CASAC Ozone Review Panel for the Reconsideration of the 2008 NAAQS

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Gradient

1 Introduction

US EPA is in the process of reaching a final decision on the reconsideration of the 2008 ozone NAAQS and seeks to ensure that this decision is based on the most appropriate interpretation of the scientific evidence. These comments will focus on issues related to epidemiology studies that examined the association between short-term ambient ozone exposure and respiratory effects, particularly in asthmatics, and are relevant to charge questions 5 and 6 that US EPA (Wegman, 2011) has provided to CASAC to solicit advice on the strengths and limitations of the scientific evidence for the reconsideration of the 2008 primary ozone NAAQS.

> *Charge question 5: "…how can we appropriately use the results of…epidemiological studies of susceptible groups to inform a judgment on the effects of ozone exposure on susceptible populations?"*
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> *Charge question 6: "To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O_3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?"*

The epidemiology studies relied on by US EPA as evidence for respiratory effects in the 2008 rulemaking examined associations between short-term exposure to ambient ozone and (1) lung function deficits; (2) asthma symptoms and/or medication use; and (3) respiratory-related emergency department (ED) visits and hospital admissions. These studies do not report robust associations, as the US EPA (Wegman, 2011) memorandum states, and the many issues inherent to these studies still remain in the proposed reconsideration.

Most of the epidemiology studies of short-term respiratory effects of ozone were conducted in asthmatics, and they do not provide robust evidence that ambient ozone exposures below the current standard are associated with adverse effects in this population. Regarding charge question 5, the inconsistency of results within and among the studies and their inherent methodological issues preclude their use as a reliable basis to inform a judgment on the effects of ozone in asthmatics. Regarding question 6, there should be little confidence that any of the associations between short-term ozone exposure and respiratory effects are attributable specifically to ozone, regardless of whether they were observed in areas with ozone levels near the lower or higher end of the proposed range. The uncertainty surrounding the proposed ozone range has not been clearly stated. The majority of positive associations were observed in single-pollutant models, and thus cannot be attributed specifically to ozone. Exposure measurement error, from the use of central ambient monitors as a surrogate for personal ozone exposure

in almost every study, obscures the actual ozone levels at which any individual is exposed to, which can bias the results in either direction.

Arguments supporting these responses to the charge questions that are specifically related to the general methodological limitations of the epidemiology studies and US EPA's inappropriate assessment of the findings in documents related to the 2008 rulemaking are described in more detail below.

2 Methodological limitations

2.1 Confounding by other pollutants

Confounding by particulate matter is a major issue in studies of ozone health effects, particularly in the summer, when outdoor ozone and $PM_{2.5}$ concentrations are correlated, so outdoor ozone measurements may be a surrogate for personal $PM_{2.5}$ exposure. Indeed, most studies report stronger associations in summer, when ozone levels are higher, and usually null or negative associations in winter. Most studies of short-term exposure to ozone and respiratory morbidity evaluated in the 2006 AQCD (US EPA, 2006) and 2007 Staff Paper (US EPA, 2007) used single pollutant models, so any reported associations cannot be attributed specifically to ozone. For those that used multi-pollutant models, associations were not robust and were often confounded by PM or sulfates.

2.2 Exposure measurement error

An assessment of the epidemiology evidence must consider the inadequacy of using ambient ozone measurements from central monitors as a surrogate for personal exposure to ambient ozone. Many studies have been published that confirm a very weak correlation between ambient and personal ozone exposure (Sarnat *et al*., 2001, 2005, 2006). Reasons for this include: (1) uneven distribution of ozone attributable to local sources; (2) monitoring sites may represent a nearby source and not human exposures a small distance away; (3) pollution patterns can be affected by terrain features and weather; and (4) daily variations in ozone concentrations at a central monitoring site may differ from variations experienced by individuals. These factors may bias the results of an epidemiological analysis in either direction. Some individuals in the population will have greater exposures than others for any given central-site ambient concentration. Brauer *et al*. (2002) noted that for pollutants with poor personal-ambient correlations, it is not possible to accurately assess C-R relationships and thresholds in observational studies, particularly at

low levels where the presence of other pollutants will confound the findings for ozone. The possibility that exposure measurement error obscures thresholds limits the ability to draw conclusions about effects of ozone at low exposure levels.

All of the epidemiology studies of respiratory morbidity relied on ambient ozone measurements as a surrogate for personal exposure to ambient ozone, which could have biased results in either direction. This exposure measurement error has profound implications for assessing both causality and ozone concentration-response considerations.

2.3 Lag times are often not based on biological plausibility

The extensive human clinical and mechanistic data do not support a long lag between ozone exposure and pulmonary function changes; rather, they indicate that the respiratory effects of ozone occur soon after exposure; therefore, findings for 0-1 day lags or for cumulative ozone exposure over a few days should carry more weight in an assessment of the evidence. In many cases, studies that examined multiple lag times reported positive associations only from one or a few biologically implausible lag times, but not from plausible lag times. These studies should carry less weight in an assessment.

2.4 Unreliability of self-reported effects

Many published studies have documented the general unreliability and inaccuracy of self-reported peak expiratory flow (PEF) measurements, as discussed in detail by ExxonMobil (2007) in comments on the 2008 ozone NAAQS review. Some of the key studies from the last review used PEF measurements as the outcome, including those by Mortimer *et al*. (2002), Ross *et al*. (2002), Neas *et al*. (1999), and Naeher *et al*. (1999). Because of the unreliability of PEF measurement, studies using this method to assess pulmonary function should be given less weight when evaluating the evidence. There are also several limitations of symptom reports used in studies of self-reported respiratory symptoms and medication use, including recall error, biased reporting, and small sample sizes.

3 Assessment of the epidemiology evidence

3.1 Studies of lung function

The 2006 AQCD evaluated acute ozone-related lung function effects in panel studies of asthmatics and healthy individuals and stated that these studies provide "clear evidence of causality for the association observed between acute ozone exposure and relatively small, but statistically significant declines in lung function" (US EPA, 2006). The majority of studies reported no association between frequently-studied measures of lung function and short-term ozone exposure, however, even in asthmatic children. Studies that did report a positive association generally used only single pollutant models and calculated estimates over a broad number of lag and ozone exposure metrics and found mixed results.

The Staff Paper states that the most representative data for lung function effects comes from the panel study of hikers by Korrick *et al*. (1998). This study reported small, albeit statistically significant, declines in pulmonary function tests (FEV_1 and FVC), and noted that hikers with asthma or a history of wheeze had four-fold greater responsiveness to ozone than others. There are several concerns that weaken the results of this study, however. The authors used five different statistical models to assess the relationship between ozone and pulmonary function changes, which increases the possibility of chance findings from the issue of multiple comparisons. In addition, the mean FEV_1 change attributed to 50 ppb ozone in this study is a 2.6% decrement, a very small change that is not considered clinically significant by both the ATS (2000) and the ERS (Pellegrino *et al*., 2005). Using the normal convention of change per 10 ppb ozone, this FEV_1 change is reduced to 0.5%, which is even further below the accepted criteria for clinical significance. When adjustment for $PM_{2.5}$ and aerosol acidity were included in the models, the pulmonary function changes attributed to ozone were not statistically significant. Thus, this study provides no evidence for an ozone-specific change in pulmonary function.

It is noteworthy that US EPA did not cite the study of lung function in hikers by Girardot *et al*. (2006) as a key study in the Staff Paper, as it has a similar study design to that of Korrick *et al*. (1998). Girardot *et al*. (2006) reported no statistically significant associations between ozone exposure and changes in FEV_1 or FVC and, thus, does not confirm the small, statistically significant changes reported by Korrick *et al*. (1998). Consideration of these results provides greater confidence that the small changes reported in the study by Korrick *et al*. (1998) were not likely attributable to ozone.

In studies examining the effects of ozone on PEF measurements, most reported null results, with the few positive associations being reported almost exclusively with single pollutant models. The AQCD states that results from the study of asthmatic children by Mortimer *et al*. (2002) provide key evidence for a significant relationship between ozone and PEF changes among asthmatics. Mortimer *et al*. (2002) did not present multi-pollutant models for ozone-associated PEF changes, however, so it cannot be ascertained whether those changes are attributable to ozone or another pollutant. In addition, the reported PEF changes are small and clinically insignificant, as the group changes in PEF are less than 1%. Furthermore, the authors used multiple lag times with no biologic justification. For a decline of ≥ 10 % in PEF, null associations with ozone were reported for 1, 2, 3, 5, or 6 day lags, and statistically significant associations were reported only for a 4-day lag and the average of 1-5 day lags. Choosing one day with a positive association among the various lags examined increases the likelihood of false positive effects.

The panel studies of ozone exposure and lung function effects do not provide clear evidence of causality, as US EPA suggests. Conclusions about these studies should reflect the evidence cited, which demonstrates no association with lung function in asthmatics or healthy individuals, in most cases.

3.2 Studies of respiratory symptoms or asthma medication use

In the 2006 AQCD, US EPA reviewed several panel studies of the association between short-term ambient ozone exposure and respiratory symptoms or asthma medication use, mostly conducted with children. Overall, a number of studies found no association, with those reporting an association often using only single pollutant models, reporting very small associations, and having mixed findings across respiratory symptom effect measures, ozone exposure metrics, subpopulations, and lag times. US EPA cites the studies by Mortimer *et al*. (2002) and Gent *et al*. (2003) as key studies providing evidence of robust associations between acute ozone exposure and respiratory symptoms in asthmatics. The associations reported in this study were not statistically significant in multi-pollutant models, however. The study by Gent *et al*. (2003) relied on subjective reporting of symptoms by mothers, whereas associations with more objective symptoms were not generally statistically significant and do not support the more subjective respiratory symptom findings. US EPA did not cite the large, multi-city study by Schildcrout *et al*. (2006) that reported no associations between short-term ozone exposure and daily asthma symptoms and rescue inhaler use in asthmatic children across the various lag periods examined.

Although the AQCD notes that a number of well-conducted, small studies have not reported associations with asthma symptoms, the Staff Paper discounts these studies as having less statistical power than the multi-city study by Mortimer *et al*. (2002) or because they are conducted in areas with relatively low ozone levels, and concludes that the panel studies, as a group, indicate a positive association with respiratory symptoms. Because of the inconsistent results across studies and the limited number of associations that are statistically significant in multi-pollutant models, the evidence does not support a positive association between ozone and respiratory symptoms.

3.3 Studies of respiratory-related ED visits and hospital admissions

In the 2006 AQCD, US EPA evaluated a number of studies of respiratory hospital admissions and emergency department (ED) visits and concluded that "the overall evidence supports a causal relationship between acute ambient ozone exposures and increased respiratory morbidity resulting in increased ED visits and [hospital admissions] during the warm season" (US EPA, 2006). Studies cited in the 2006 AQCD in support of this conclusion often reported very small associations and did not appropriately control for confounders and had many other limitations, and in some cases included positive but non-statistically significant risk coefficients. In the 2006 AQCD, US EPA stated that positive but inconsistent associations were observed between ozone and respiratory-related ED visits. The results of studies regarding respiratory-related hospital admissions are also generally inconsistent, with many reporting no association. Study results were often mixed within and across effect measures, and varied depending upon the model parameters selected, including lag time.

Regarding respiratory-related ED visits, the AQCD states that of the studies reporting positive associations, three key studies reported effects that were robust to adjustment for other pollutants, including PM_{10} (Lin *et al*., 1999; Peel *et al*., 2005; Tenias *et al*., 1998). The AQCD also states that several studies reported at least one positive association with ozone, but these associations were inconsistent and depended upon the model specifications and analysis approach, the length of the study period, or the methods to control confounding by seasonal patterns and co-pollutants. In addition, several studies reported null associations, but the AQCD erroneously stated that overall, the studies report generally positive associations for asthma-related ED visits in the warm season.

Regarding respiratory-related hospital admissions, the AQCD notes some positive associations, some inconsistent effects, and some null studies, and concludes that the evidence generally supports findings of significant and robust effects. The AQCD also states that co-pollutants do not generally

confound the reported associations, particularly in the key, multi-city study conducted in Canada by Burnett *et al*. (1997), which reported statistically significant associations in models including PM_{10} and $PM_{2.5}$. Not all studies examining effects in multi-pollutant models reported statistically significant associations, however, and another key, multi-city study reporting positive associations only used single-pollutant models (Anderson *et al*., 1997).

Overall, studies of short-term exposure to ozone and respiratory-related ED visits and hospital admissions provide inconsistent findings that do not support a causal relationship. US EPA should not interpret null results from these studies as positive associations.

4 US EPA's assessment of the evidence

As described above, the epidemiological evidence for short-term effects of ozone exposure is generally weak and inconsistent. US EPA's assessment of this evidence in the 2006 AQCD and 2007 Staff Paper is not scientifically appropriate, however, and does not adequately consider the various uncertainties associated with epidemiological data of air pollutants.

US EPA uses risk estimates that are above null but not statistically significant as evidence for an overall positive association. This is inappropriate because only statistically significant results should be used as evidence for a positive association. The few positive and statistically significant associations that are cited in the AQCD are in many cases from studies that calculated risk estimates across multiple lag time and ozone exposure metric combinations. Often, these same studies also reported negative and/or null risk estimates, thus providing inconsistent, rather than overall positive, results. US EPA also ignored certain negative studies in favor of those with positive results. An example of this can be seen in the review of the panel studies. The key studies cited by US EPA (Mortimer *et al.*, 2002; Gent *et al.*, 2003; Korrick *et al.*, 1998) reported small respiratory effects but other studies of similar design (Schildcrout *et al.*, 2006; Girardot *et al.*, 2006) reporting no association between ozone exposure and respiratory effects were not cited as key studies. These latter studies were not included by US EPA in their 2008 review; rather, they were cited by the public in their comments on the proposed ozone NAAQS. Thus, it is unclear if US EPA considers them as "new" studies or part of the 2008 review.

US EPA did not adequately take into account the biological plausibility of lag times for effects on pulmonary function, as the long lag periods used in many of these studies are not biologically plausible.

Instead of basing the "best" estimates for lag times on biological plausibility, US EPA often emphasizes the largest positive association, particularly for the panel studies.

US EPA did not appropriately take into consideration the uncertainties associated with flaws in the time-series and panel studies, such as their use of ambient ozone measurements as a surrogate of personal ozone exposures in spite of the weak correlation between ambient and personal ozone exposures. Most studies of short-term exposure to ozone and respiratory morbidity evaluated in the 2006 AQCD used single pollutant models. For those that used multi-pollutant models, associations were usually not robust and were often confounded by PM or sulfates. Single pollutant estimates were often cited by US EPA as support of an association even though it has been demonstrated that co-pollutants can be significant confounders of the relationship between ozone and health effects. In addition, many of the panel studies, including the study by Mortimer *et al.* (2002) on which US EPA places high reliance, used self-reported peak expiratory flow rate (PEFR) measurements which, as noted above, have been demonstrated to be highly unreliable. Because of this unreliability, studies using PEFR data to assess pulmonary function should be given less weight when evaluating the evidence.

While US EPA has requested that CASAC consider only the data available at the time of the 2008 ozone NAAQS review, CASAC should at least be aware of the general results of highly relevant studies that have been recently published in the peer-reviewed scientific literature. US EPA is aware of these studies, as they have been summarized in a rough draft Integrated Science Assessment document for the next ozone review (US EPA, 2010). CASAC should recognize that these new studies cast further uncertainty on US EPA's conclusion that current levels of ozone cause respiratory morbidity. For example, in a study sponsored by the National Institute of Allergy and Infectious Disease (NIAID), the National Institute for Environmental Health and Safety (NIEHS), and US EPA, O'Connor *et al.* (2008) reported no consistent associations between ambient ozone exposure and pulmonary function, asthma symptoms, or school absences in 861 inner-city children with persistent asthma. In contrast to previous studies that relied on PEF measurements, this study assessed pulmonary function using FEV_1, a more reliable measurement technique.

Other studies not included in the last review that evaluated the potential for ambient ozone to exacerbate symptoms in asthmatics reported no association between ozone exposure and asthma exacerbations. These include a study reporting no association between ozone exposure and asthma exacerbation in children and adults in Toronto (Burra *et al.*, 2009), and a study reporting no associations between ozone exposure and a wide variety of effect measures, including nighttime symptoms, asthma

exacerbations, symptom scores, PEF measurements, and bronchodilator use, a more objective measure of effect (Rabinovitch *et al*., 2004).

All three studies not included in the last review that evaluated the potential association between ambient ozone and airway inflammation also reported no associations. These include studies in elderly individuals (Adamkiewicz *et al.*, 2004), nonsmoking high school athletes evaluated after exercising (Ferdinands *et al.*, 2008), and asthmatic children (Liu *et al.*, 2009).

Three of the four new studies that evaluated the association between short-term ambient ozone exposure and lung function, as measured by changes in FEV_1 and FVC, reported no associations. These include studies of highly-exposed outdoor groups such as lifeguards (Thaller *et al.*, 2008) and healthy hikers, as noted above (Girardot *et al.*, 2006), as well as potentially susceptible subjects with COPD, asthma, or ischemic heart disease (Lagorio *et al.*, 2006). Together, many of the studies not included in the previous ozone NAAQS review provide significant evidence that current levels of ambient ozone do not cause respiratory morbidity.

5 Conclusions

The epidemiological evidence for short-term respiratory effects of ozone in asthmatics and healthy individuals is methodologically flawed and was not appropriately assessed by US EPA in the most recent review of the ozone NAAQS. Confounding by particulate matter (PM) is a common issue among studies of ozone health effects, but the vast majority of studies used only single pollutant models. Almost every study also used ambient monitors as surrogates of personal ozone exposures in spite of the weak correlation between ambient and personal ozone exposures. Because of these and other limitations noted above, two of the charge questions that US EPA (Wegman, 2011) provided to CASAC regarding the strengths and limitations of the scientific evidence for ozone-related health effects can be addressed as follows:

> *5. "…how can we appropriately use the results of…epidemiological studies of susceptible groups to inform a judgment on the effects of ozone exposure on susceptible populations?"*

Most of the epidemiology studies of short-term respiratory effects of ozone were conducted in asthmatics, and they do not provide robust evidence that ambient ozone exposures below the current standard are associated with adverse effects in this population. The inconsistency of results within and

among the studies and their inherent methodological issues preclude their use as a reliable basis to inform a judgment on the effects of ozone in asthmatics.

> *6. "To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O_3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?"*

There should be little confidence that any of the associations between short-term ozone exposure and respiratory effects are attributable specifically to ozone, regardless of whether they were observed in areas with ozone levels near the lower or higher end of the proposed range. The uncertainty surrounding the proposed ozone range has not been clearly stated. The majority of positive associations were observed in single-pollutant models, and thus cannot be attributed specifically to ozone. Exposure measurement error, from the use of central ambient monitors as a surrogate for personal ozone exposure in almost every study, obscures the actual ozone levels at which any individual is exposed to, which can bias the results in either direction. Only the controlled ozone exposure studies can address effects that are specifically attributable to ozone. These studies indicate transient and minor lung function changes that are not likely to be responsible for more serious morbidity effects, such as increases in respiratory-related ED visits or hospital admissions, at least not at very low ambient ozone levels.

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