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

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Gradient

Background

In reconsidering the 2008 ozone standard, the United States Environmental Protection Agency (US EPA) proposed the primary 8-hour ozone National Ambient Air Quality Standard (NAAQS) be set in the range of 0.060 to 0.070 parts per million (ppm). In its deliberations, the agency is weighing the evidence favoring the upper or lower ends of this range with respect to the uncertainties and limitations in the data available at the time of the 2008 ozone NAAQS review. These comments address the body of evidence comprising controlled exposure studies of young, healthy adults at an ozone concentration at 0.060 ppm for 6.6 hours. Specifically, this evidence was reported in three studies by Adams (1998, 2002, 2006). Below, this evidence is discussed in relation to charge questions 2, 3, and 4 that were attached to the January 26, 2011 memorandum, in which US EPA solicited the CASAC's advice on the reconsideration of the primary ozone NAAQS (Wegman, 2011). Overall, this evidence supports maintaining the existing primary ozone 8-hour NAAQS pending a thorough review of scientific evidence that has become available since the 2008 review of the primary ozone NAAQS.

CASAC Charge Question 2. Recognizing that controlled human exposure studies at 0.080 ppm O_3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?

Human exposure studies with exposures of ≥0.080 ppm ozone have provided valuable evidence of the exposure-response relationship for respiratory health effects. At lower ozone concentrations, particularly ≤0.060 ppm, similar studies have yielded only limited evidence of adverse respiratory effects, specifically of decrements in forced expiratory volume in one second (FEV_1). Indeed, there appears to be a threshold below 0.070 ppm ozone where there are no significant effects of ozone exposure. Because of this discontinuity in the exposure-response relationship, FEV_1 decrements at exposures ≥0.080 ppm ozone may not be appropriate for inferring effects at the lower end of the proposed ozone range of 0.060 to 0.070 ppm. Regarding respiratory health endpoints of interest other than FEV_1 at ozone concentrations <0.080 ppm, there were no data available at the time of the 2008 ozone NAAQS review, but a recent study (Kim *et al*., 2011) may shed some light on inflammatory responses at a lower concentration. Kim *et al*. (2011) reported elevated polymorphonuclear neutrophils (PMNs) in the induced sputum of 24 subjects at a time point of 16-18 hours after exposure to 0.060 ppm ozone for 6.6 hours, and, although the elevation was statistically significant, it is not clear whether this effect is clinically significant. Thus, studies of elevations in this outcome at higher exposures should not be used to infer lung function responses, especially at relatively low ozone levels in the range of 0.060 to 0.070 ppm.

CASAC Charge Question 3. How should the results of the controlled human exposure studies at 0.060 ppm O_3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?

Although the controlled chamber experiments by Adams (2006) demonstrated statistically significant decrements in FEV_1 at 0.080 ppm ozone for 6.6 hours relative to fresh air exposure, statistically significant decrements were not demonstrated at 0.060 ppm ozone. Dr. Adams reiterated this result in the March 5, 2007 CASAC teleconference, when he affirmed that data from Adams (2006) should not be interpreted as demonstrating respiratory effects at ozone exposures of 0.060 ppm. Moreover, the FEV_1 decrement reported in Adams (2006) was only 3.52%, which was attributable in part to FEV_1 reductions of >10% in only two of the 30 study subjects. Similarly, two face-mask exposure studies by Adams (1998, 2002) did not report statistically significant decrements in pulmonary function at or below 0.060 ppm ozone after 6.6 hours of exposure, although it was noted that six of 30 subjects had an FEV_1 decrement greater than 10%.

The null results at 0.060 ppm ozone in the Adams (2006) study are not necessarily due to small sample size or lack of statistical power. In reality, one cannot know whether a lack of effect is the result of small sample size or because there is actually no association. Using non-statistically significant results as evidence for an association essentially ignores the results obtained using statistics. If future studies demonstrate an association at 0.060 ppm ozone that is both statistically significant and clinically relevant, they would contribute to the weight of evidence in favor of the lower end of the proposed range of the 8-hour primary ozone standard. In the absence of such evidence, CASAC should conclude that the available data do not support an association between lung function effects and 0.060 ppm ozone.

US EPA conducted an internal reanalysis (Brown, 2007) of a small portion of the data reported in Adams (2006), which, in contrast to the original published results, found a statistically significant decrement in FEV_1 at 0.060 ppm ozone. This was primarily based on a t-test of FEV_1 applied to the 6.6 hour data only from the square wave profile *versus* that of controls. This is inappropriate because it was based on only a small subset of the available FEV_1 data (*i.e.*, the analysis excluded all measurements taken at 1, 2, 3, 4.6, and 5.6 hours) and did not account for all the other responses from different exposure scenarios.

Given the choice between discarding data *versus* using all available data, the general preference should be to use the most information with the most powerful statistical technique suitable for the study design. Hence, the statistical approach by Brown (2007) is curious because the data were discarded rather than being analyzed in a more powerful, albeit more complex, statistical model, such as mixed effects models. Discarding data is not only inefficient, but is generally inappropriate because such *post hoc* selection of a data subset when valid and otherwise non-problematic observations exist calls into question the rationale for such action. The primary rationale for Brown (2007) to remove data from other experimental conditions was apparently to avoid stringent reductions in the critical p-value for statistical significance due to multiple comparisons procedures. The intention of multiple comparisons procedures, however, should not be to deter researchers from analyzing available data. Or, as Rothman (1990) noted in questioning the general necessity of multiple comparisons procedures, "The more that one observes, the stiffer the penalty exacted for the privilege of observing." It is also notable that US EPA investigators, as well as other research groups who perform human clinical studies of prolonged ozone exposure, do not routinely exclude time-varying pulmonary function data in order to focus their analysis on only the final data point. Rather, these research groups use statistical procedures that utilize all of the data, similar to the approach used by Adams (2006) (*e.g.*, McDonnell *et al*., 1997; Liu *et al*., 1999; Gong *et al*., 1998; Vincent *et al*., 1997; Torres *et al*., 1997; Wang and Petsonk, 2004).

Even though the observed effects for lung function were not statistically significant, it is also worth considering whether the decrements were clinically relevant with respect to broadly recognized clinical guidelines (Goodman *et al*., 2010). The American Thoracic Society (ATS) judges a reversible loss of lung function *in combination with symptoms* to be adverse (ATS, 2000). Although Adams (2006) reported a statistically significant increase in total symptom severity (TSS) after 6.6 hours of exposure to 0.060 ppm ozone compared to pre-exposure baseline, there was no significant difference when compared to filtered air exposure (in contrast to US EPA's claims that this difference was statistically significant). Hence, not only was the decrement in lung function not statistically significant at 0.060 ppm ozone for 6.6 hours, but also symptom scores were not statistically different from those for filtered air exposure, indicating that the observations at 0.060 ppm ozone by Adams (2006) were not clinically adverse according to ATS guidelines. The European Respiratory Society (ERS) suggests that only short-term changes in FEV_1 exceeding 12% "may be clinically important," and that changes in FEV_1 measurements should exceed 5% to overcome the intra-day variability of FEV_1 in normal subjects (Pellegrino *et al*., 2005). The FEV_1 decrement of 3.52% reported in Adams (2006) is below potential clinical relevance, and, according to ERS guidelines, is within the bounds of intra-individual variability for daily FEV_1.

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 recently published in the peer-reviewed scientific literature, which US EPA has summarized in the draft Integrated Science Assessment document for the next review of the primary ozone NAAQS (US EPA, 2010). In particular, CASAC should recognize that these studies cast further uncertainty on the existence of clinically relevant decrements in FEV_1 at 0.060 ppm. Schelegle *et al*. (2009) conducted a series of controlled exposure chamber studies on 31 healthy young adults at mean ambient ozone concentrations of 0.063, 0.072, 0.081, and 0.088 ppm (Schelegle *et al*., 2009, Table 2), as well as filtered air (control), with FEV_1 measurements at multiple time points up to 6.6 hours of exposure and four hours post-exposure. Subjects exercised during the exposure, with periodic breaks. The researchers' stated goal was to identify the lowest ozone concentration that induced a statistically significant decrement in FEV_1. Their findings indicate that the lowest mean ambient ozone concentration associated with a statistically significant decrease in FEV_1 from filtered air control after 6.6 hours of exposure was 0.072 ppm. The researchers, however, were clearly mindful of the interest in FEV_1 effects at 0.063 ppm ozone, as they discussed with particular attention the statistical analyses of data at this concentration (Schelegle *et al*., 2009, Table 4). The researchers used no less than three different statistical techniques to address different analytic issues, such as repeated measurements, multiple comparisons, and non-normally distributed data. These techniques were mixed effects two-way (with ozone concentration and time as factors) ANOVA with Tukey's adjustment for multiple comparisons (also known as the Tukey-Kramer adjustment), mixed effects one-way (with ozone concentration as the factor) ANOVA with Dunnett's adjustment for multiple comparisons against a single control (fresh air), and Friedman's nonparametric test with Dunnett's adjustment. For the latter two techniques, in order to avoid stringent reductions in the critical value for statistical significance due to excessive multiple comparisons, the researchers restricted statistical analysis to the FEV_1 decrements at 6.6 hours, ignoring data collected at other time points. None of these techniques yielded a statistically significant FEV_1 decrement at an exposure of 0.063 ppm ozone for 6.6 hours, yet all were statistically significant at 0.072 ppm. After 6.6 hours of exposure at 0.063 ppm ozone, the researchers observed a mean FEV_1 decrement from baseline of 2.72% (standard error: 0.27) *versus* 5.34% (0.25) at 0.072 ppm ozone. For comparison, the mean percent-change in FEV_1 for filtered air after 6.6 hours was 0.80% (0.16).

Kim *et al*. (2011) exposed 59 healthy, exercising young adults to 0.060 ppm ozone for 6.6 hours under controlled chamber conditions and observed a statistically significant mean percent-change in FEV_1 (clean-air adjusted) of -1.75 (95% CI: -3.0, -0.5) and an increase in neutrophilic inflammation of the airways, with no statistically significant increase in total symptom score. The decrement reported by Kim

et al. (2011) is much smaller than the ATS and ERS clinical guidelines reported above, and is also smaller than the previously reported decrements of Adams (2006) and Schelegle *et al*. (2009), neither of which were statistically significant. Hence, the results of Kim *et al*. (2011) are consistent with earlier reports that the effect of 0.06 ppm ozone exposure for 6.6 hours is not clinically adverse. In view of the lack of clinically significant lung function effects at 0.060 ppm for 6.6 hours demonstrated by these recent studies, the weight of evidence clearly favors maintaining the existing primary ozone NAAQS.

Results from controlled human exposure studies at 0.060 ppm ozone (Adams 1998, 2002, 2006) provide the best evidence for whether respiratory health effects in healthy adults are associated with ozone exposures at the lower end of the range proposed for the primary ozone NAAQS. Clearly, the data do not support adverse health effects at 0.060 ppm ozone. As a consequence, the available evidence for health effects in healthy adults from relatively low ozone exposure levels supports maintaining the existing primary ozone NAAQS pending a thorough review of the scientific evidence that has become available since the 2008 review of the primary ozone NAAQS.

CASAC Charge Question 4. With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean FEV_1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV_1 decrements ≥10%? Please consider this question from both a public health and a clinical perspective.

In the charge questions attached to the January 26, 2011 memorandum soliciting the CASAC's advice on the primary ozone NAAQS, US EPA writes:

> The CASAC panel indicated that a focus on the lower end of the range of moderate levels of functional responses (*e.g.*, FEV_1 decrements ≥ 10%) is most appropriate for estimating potentially adverse lung function decrements in people with lung disease. (Wegman, 2011)

As already noted above, ERS considers a decrement of at least 12% in FEV_1 as only potentially clinically important. In addition, clinical studies have often used a cut-off value of at least 20% for a decline in FEV_1 as the definition of a "mild" asthma exacerbation (Reddel *et al*., 2009). CASAC's suggested cut-off of 10% would appear to be overly conservative with respect to clinical guidelines.

CASAC also seems to be suggesting that, because a proportion of subjects in the studies by Adams (2002, 2006) had an FEV_1 decrement >10%, a similar proportion of the healthy young adult population and a larger proportion of the population with lung disease will have comparable FEV_1 decrements at 0.060 ppm ozone. Not only is the number of subjects far too small to support such generalizations, but the study sample (young, healthy adults) is not suitable for extrapolation to the population with lung disease (*e.g.*, asthmatics may not be able to achieve the total cumulative ozone doses in Adams, 2006 because of the inability to exercise strenuously for long durations). Thus, the proportion of subjects with FEV_1 decrements ≥10% is an inappropriate estimate of the decrements that would be faced by the population with lung disease at 0.060 ppm ozone.

The findings of small, group mean FEV_1 decrements and the observation that 7 to 20% of subjects experienced FEV_1 decrements ≥10% are related insofar as they represent two characteristics of the distribution of FEV_1 decrements in healthy subjects exposed to 0.060 ppm ozone. The mean FEV_1 decrements represent the central tendency of the distribution and are only significant — both from public health and clinical standpoints — if they exceed clinically relevant levels, which they do not at 0.060 ppm ozone. In contrast, the proportion of subjects with FEV_1 decrements ≥10% represent the extreme lower tail of the distribution, and hence are associated with the degree of variation and are not necessarily attributable to ozone exposure. In the case of FEV_1 measurements, it has been well-established that there

is substantial inter-individual variation that is largely unexplained (McDonnell *et al*., 1993, 1997), except for its dependence on age and elevated ozone exposure. In fact, at such relatively low levels of ozone exposure, it is likely that the apparent variation is attributable to a substantial intra-individual variation, which ERS estimates to be about 5% for intra-day variation (Pellegrino *et al*., 2005). It is therefore inappropriate to ascribe to the entire population with lung disease the results from a relatively small number of healthy adults at the lower tail of the distribution.

Conclusions

In his experimental chamber study, Adams (2006) analyzed the data using accepted statistical methods and found that FEV_1 decrements in young, healthy adults exposed to ozone were not statistically significantly different from those in subjects exposed to fresh air at 0.060 ppm ozone. Although this non-statistically significant finding has been the subject of some debate, it is also important to consider whether the observed decrements in lung function are significant with respect to broadly recognized clinical guidelines (Goodman *et al*., 2010). ATS judges a reversible loss of lung function *in combination with symptoms* to be adverse (ATS, 2000). Adams (2006) found no statistically significant increase in TSS after 6.6 hours of exposure to 0.060 ppm ozone compared to fresh air exposure. Hence, the observations at 0.060 ppm ozone in Adams (2006) were not clinically adverse according to ATS guidelines. In addition, ERS suggests that only short-term changes in FEV_1 exceeding 12% "may be clinically important," and that changes in FEV_1 measurements should exceed 5% to overcome the intra-day variability of FEV_1 in normal subjects (Pellegrino *et al*., 2005). The FEV_1 decrement of 3.52% reported in Adams (2006) is below potential clinical relevance, and, according to ERS guidelines, is within the bounds of intra-individual variability for daily FEV_1.

Adams (2002, 2006) also noted that a proportion of subjects — 20% and 7%, respectively — had an FEV_1 decrement greater than 10%. CASAC has suggested that a similar proportion of the healthy young adult population will have comparable FEV_1 decrements at 0.060 ppm ozone, but the number of subjects is far too small (*i.e.*, 30) for such a generalization. Hence, the proportion of subjects with FEV_1 decrements greater than 10% should not be the basis for claims about the population-wide risks of exposure to 0.060 ppm ozone.

Because lung function effects at 0.060 ppm ozone were neither statistically nor clinically significant (Adams 2006), and effects at 0.040 ppm ozone were clearly not significant (Adams, 2002), the exposure-response curve for FEV_1 flattens out in the 0.040 to 0.060 ppm ozone range. This is suggestive of a threshold for a clinically adverse response. Hence, effects at 0.080 ppm ozone and above may not be appropriate for inferring effects at the lower end of the proposed 0.060 to 0.070 ppm ozone range.

In view of the evidence, and, in particular, the uncertainties surrounding possible decrements in lung function at 0.060 ppm ozone, the primary ozone 8-hour NAAQS should be maintained pending a

thorough review of scientific evidence that has become available since the 2008 review of the primary ozone NAAQS.

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