Response to CASAC Ozone Review Panel Regarding the Reconsideration of the 2008 NAAQS

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The American Petroleum Institute
1220 L Street NW
Washington DC 20005-4070

February 28, 2011

Gradient

During the February 18, 2011 CASAC teleconference regarding the reconsideration of the ozone standard, Dr. Frederick Miller made a comment regarding the Adams (2006) data. In the Adams (2006) study, lung function was measured in 30 study subjects seven times, including before and after 6.6 hours of intermittent exercise, under exposure scenarios of filtered air and respective average ozone concentrations of 0.04, 0.06, and 0.08 ppm. In the 0.06 ppm ozone scenario, two of the subjects had lung function decrements, as measured by forced expiratory volume in one second (FEV_1), of greater than 10%. Dr. Miller commented that these two subjects were above their individual thresholds for ozone sensitivity at this exposure. In other words, he claimed that of the 30 people studied, 0.06 ppm ozone adversely affected two of them, and he interpreted this finding as pertaining to the greater population exposed to ozone. Dr. Miller's interpretation is incorrect for several reasons. When scientifically accepted statistical methods are used, it is evident that: (1) one cannot conclude that ozone caused the lung function decrements in those two study subjects and (2) lung function decrements at 0.06 ppm ozone with exercise are neither statistically significant nor clinically relevant.

While one's longer term lung function does not change greatly in the absence of progressive health conditions, there are many causes, both known and unknown, of lung function variability in a given person on a single day or among people in a group (McDonnell *et al.*, 1993, 1997). Adams (2006) was interested in whether lung function decrements after exercise while being exposed to 0.04, 0.06, or 0.08 ppm ozone were different than those after exercise in filtered air. If there were no statistical differences between groups of individuals exposed to ozone at a given concentration *versus* filtered air, then one could not conclude that ozone at that concentration caused the lung function decrements. It is important to note that Adams (2006) designed his study specifically to examine whether ozone affected *groups* of people who were exposed to various concentrations differently, not whether ozone affected any particular *individual*. That is, it was not designed to account for intra-individual variability, or how ozone affected any individual study subject. Although there were two people with decrements in lung function greater than 10% when exposed to 0.06 ppm ozone, the lack of a statistically significant difference between the 0.06 ppm ozone and filtered air groups overall indicates that one cannot conclude that the decrements in these two people were due to ozone rather than some other source of variability that hasn't been accounted for.

The Adams (2006) study also showed an apparent "improvement" in lung function in 6 of the 30 subjects exposed to 0.06 ppm ozone. Just as lung function "improvements" in individual study subjects do not signify a beneficial effect of ozone, lung function decrements after exposure to 0.06 ppm ozone should not be interpreted as an effect from ozone. Indeed, it is well-established that there is substantial

inter-individual variation in FEV_1 measurements that is largely unexplained (McDonnell *et al.*, 1993, 1997), which shows that lung function, as assessed by paired filtered air *versus* test exposures, can vary appreciably due to factors unrelated to ozone. Particularly at low ozone concentrations, this variability must be carefully considered because it can lead to relatively large apparent decrements after ozone exposure that may be completely unrelated to the exposure.

The limitation of looking solely at two individual's results for the 0.06 ppm exposure scenario is also exemplified by looking further at their lung function decrements after exposure to 0.08 ppm ozone. When compared to the 0.06 ppm exposure, after being exposed to 0.08 ppm ozone, one subject's FEV_1 decrement increased from 12.76% to 14.29% and the other decreased from 14.52% to 12.36%. Had 0.06 ppm ozone affected lung function in these two individuals, one would have expected substantially worse FEV_1 decrements at 0.08 ppm ozone, and certainly not an improvement. Either way, Adams would have needed to take repeated measures from these individuals at these exposures to assess each one's individual sensitivity to ozone.

It is also notable that when subjects were exposed to filtered air, after 6.6 hours of exercise, lung function changes ranged from a decrease of 5.02% to an increase of 8.62%. This means that lung function changes varied by 13.64% among subjects with no ozone exposure at all. While the source of these lung function changes is unknown, based on the lack of statistically significant differences between the 0.06 ppm exposure and the filtered air exposures, the decrements noted in the two individuals with FEV_1 changes greater than 10% at 0.06 ppm was likely at least partially due to this variability.

It should be evident at this point that the lung function decrements observed in the two individuals in the Adams (2006) study that were greater than 10% at 0.06 ppm ozone cannot be attributed to ozone. Even if this were so, however, their absorbed ozone dose was much higher than that which would be achievable by sensitive people in the population (*e.g.*, asthmatics). While the nominal ambient ozone concentration in the Adams (2006) study at issue is 0.06 ppm ozone, the subjects were exercising vigorously (V_e = ~20 L/min/m^2) over 6.6 hours, so the absorbed dose of ozone was substantially higher than it would have been if the subjects had been at rest. Indeed, the absorbed dose can probably be safely said to be much higher than that of sensitive populations exerting even moderate physical effort. Because this is the case, Adams (2006) has a bias toward overestimating the effect on lung function response. Thus, this provides a "margin of safety" for sensitive individuals in the population.

It has been argued 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). This conclusion is incorrect. Dr. Nicolich conducted an analysis of the full data 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, upheld the original finding in Adams (2006) that there was no statistically significant decrement in group FEV_1 after exposure to 0.06 ppm ozone *versus* filtered air after 6.6 hours of exercise.

Brown (2007) and Brown *et al*. (2008) claim to address the issue of multiple comparisons by only analyzing the 6.6 hour exposure data at 0.06 ppm ozone *vs*. filtered air. This approach excluded all pulmonary function data at other time points and exposure levels. In addition, this approach is 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*., 1997), and US EPA (Gong *et al*., 2004). We also note that in a presentation to CASAC, Professor William Adams expressed concerns with US 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 omitted from the analysis.

As per my previous comments (Goodman, 2011), it is important to consider whether small decrements in lung function are clinically relevant with respect to broadly recognized clinical guidelines (Goodman *et al.*, 2010). For changes in lung function, the American Thoracic Society judges a reversible loss of lung function in combination with symptoms to be adverse (ATS, 2000), while the European Respiratory Society suggests that only short-term changes in FEV_1 exceeding 12% are of potential clinical relevance (Pellegrino, *et al*. 2005). The FEV_1 decrement of 3.52% at 0.06 ppm ozone reported by Adams (2006) is below potential clinical relevance. In addition, Adams (2006) did not find a statistically significant increase in total symptom severity (TSS) at 0.06 ppm ozone compared to filtered air. Hence,

the observations at 0.06 ppm ozone by Adams (2006) were not statistically significant or clinically adverse according to ATS guidelines.

In conclusion, the use of appropriate, scientifically accepted statistics does not demonstrate that 0.06 ppm ozone results in lung function decrements overall or in specific individuals at the extremes.

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