COMMENTS ON MEMORANDUM FROM LYDIA N. WEGMAN TO HOLLY STALLWORTH: SOLICITATION OF CASAC ADVICE ON EPA'S RECONSIDERATION OF THE 2008 PRIMARY OZONE NATIONAL AMBIENT AIR QUALITY STANDARD. JANUARY 25, 2011

After reconsidering the scientific literature supporting the current 8-hour primary ozone National Ambient Air Quality Standard (NAAQS) level of 0.075 ppm, EPA in January 2010 proposed to lower the level to within the range of 0.060 to 0.070 ppm in order to provide increased protection for children and other ''at risk'' populations.

On January 25, 2010, EPA sent a memorandum to the CASAC Ozone Reconsideration Panel soliciting additional advice preparatory to EPA's decision on a final primary ozone standard (the "Memorandum"). The American Petroleum Institute asked Exponent, Inc. to review and comment on important issues raised by the Memorandum.

We find that the Memorandum is deficient in a number of ways. It asks CASAC for guidance on matters that are not within CASAC's purview, namely on policy judgments that should be made at the sole discretion of the EPA Administrator. It asks CASAC to provide assistance in areas in which CASAC has already taken unequivocal positions and in which its responses are predictable. Perhaps most importantly, it asks CASAC to base its response to the charge questions posed in the Memorandum to literature that appeared before 2006, despite the fact that much directly relevant peer-reviewed new literature has appeared after that cut-off date. Overall, the purpose of the Memorandum appears to be to ask CASAC to rubber-stamp decisions that EPA has already made.

Our further thoughts on each of these items are given below.

CASAC is being asked to comment on policy decisions that should made by the EPA Administrator

EPA's Memorandum makes clear that the upper and lower bounds on the range of levels on an ozone standard that EPA proposed in its January 2010 reconsideration reflect two approaches to judging the scientific data available on the health effects of ozone. The upper end of the range places significant weight on the uncertainties and limitations inherent in the scientific information while the lower end places less weight on the strength of the information, with more concern shown for the need to avoid underestimating adverse effects on the public health. Another way of viewing these approaches is as follows. An ozone level set at the upper end is consistent with one of the fundamental tenets of scientific inquiry, namely the need to embrace a theory only if the evidence for it is extremely strong in the face of competing theories. A level set at the lower level, on the other hand, acknowledges the existence of data limitations but recognizes that EPA's mission under the Clean Air Act to protect the public health with an adequate margin of safety may require it to accept scientific information of questionable certainty in order to avoid the possibility of subjecting a portion of the population to adverse health effects.

Thus, in deciding on the final form of the ozone standard, EPA will have to judge the weight to place on information that is characterized by a high degree of scientific certainty and the weight to give to information that is marked by a greater degree of uncertainty and is perhaps subject to additional limitations. The significance of the role that subjective judgment plays is clearly shown by the fact that although both the NAAQS current level of 0.075 ppm set in 2008 and the range of levels of 0.060 to 0.070 ppm proposed in EPA's reconsideration of 2010 were based upon identical scientific information embodied in the ozone Criteria Document of 2006. The difference in the levels were simply a reflection of the policy judgments made by different Administrators on interpretation of the data, with their uncertainties and limitations, which in turn reflected different understandings of EPA's mission. In 2008, the Administrator apparently

gave more weight to data with a greater degree of certainty while in 2010 a new Administrator decided to give more weight to data with more uncertainty.

Given the large role played in the decision-making process by subjective judgment, it is questionable what EPA can hope to gain from soliciting further advice from CASAC, a committee that was established to provide independent advice to the EPA Administrator on the technical basis for EPA's NAAQS. The charge questions in large part extend beyond a solicitation for advice on the technical basis for an ozone NAAQS; they ask CASAC to respond to questions that can be answered only by making policy judgments on the weight to be given to studies that are marked by varying degrees of uncertainty. For example, charge questions 2 and 3 in the Memorandum ask whether results of controlled human studies at ozone levels at 0.080 and 0.060 ppm can contribute to an understanding of the effects from exposure levels to healthy adults between 0.060 and 0.080 ppm. As we discuss below, the significance of the results at the 0.060 ppm level are uncertain. These questions can only be answered on the basis of policy judgments on the weights to apply to the studies, judgments that must be left to the EPA Administrator, and not to CASAC.

<u>The Memorandum asks CASAC to respond to questions on which CASAC has already taken strong and unequivocal positions.</u>

In the past, CASAC has made abundantly clear its position on the range in which the ozone primary NAAQS level should be set. In commenting on the 2007 2nd draft EPA Staff Paper, the 2007 Final Rule and the 2010 proposed reconsideration, CASAC has consistently and forcefully let EPA know that an ozone level in the of 0.060 to 0.070 ppm was appropriate. In fact, EPA has made clear that it relied heavily upon this series of recommendations by CASAC to propose changing the 2008 primary standard to a level within those limits. One can only question whether CASAC can render an unbiased opinion on the charge questions, especially if they were to lead the Administrator to consider an ozone 8-hour primary NAAQS that is outside the 0.060 to 0.070 ppm level range.

This is put into sharp focus by the first "overall" charge question, by which EPA solicits advice from CASAC on "the overall strengths and limitations of the evidence from controlled human exposure and epidemiological studies and the results of the exposure and risk assessments, in the context of EPA's selection of a standard level within the proposed range that would be requisite to protect public health with an adequate margin of safety, including the need to protect susceptible populations, such as children and people with asthma." Certainly both EPA, as stated in its proposed reconsideration, and CASAC, as stated in its series of advisory letters to the EPA Administrator, already believe that the evidence is sufficient to establish a level within the range of 0.060 to 0.070 ppm. Beyond that, however, the precise nature of advice that EPA is requesting from CASAC is not at all clear. Does EPA expect CASAC to offer an opinion on whether the evidence is strong enough to support a specific level within that range? As indicated above that subjective decision must be left to the Administrator and not an outside scientific advisory panel. Other than endorsing decisions already made, the only purpose that we can see in such a charge question is to paint a veneer of scientific respectability on any final ozone primary NAAQS set by the Administrator.

<u>CASAC is asked to respond to charge questions on the basis of literature appearing before 2006 despite the fact that highly relevant literature has appeared since then.</u>

The Memorandum explicitly asks CASAC "to consider only the information that has become available in the record of the 2008 O_3 NAAQS review, as information that has become available since the 2008 is not relevant to EPA's reconsideration of the 2008 O_3 standard." Since the 2008 NAAQS review was based on the scientific literature compiled in the March 2006 Criteria Document, CASAC is being asked to confine its response to the charge questions to literature published not later than early 2006. We are puzzled by EPA's imposition of a restriction on CASAC to provide advice without benefit of information that appeared in the scientific literature beyond that date. As we point out in our comments below, new and highly relevant literature is available that calls into question some of the results of studies that appeared before 2006. Since any new standard that EPA may decide upon will presumably remain in

place during the next five-year NAAQS review cycle, EPA runs the serious risk of imposing a standard based upon outdated scientific information.

Our further comments below review EPA's line of reasoning that led to its proposed range of 0.060 to 0.070 ppm. We point out areas where EPA either glossed over or misinterpreted results of studies it relied upon, with an emphasis on how new published data can lead to a deeper understanding of the technical basis for an ozone standard.

Basis for EPA's Proposed Decision on a Range of Primary Ozone NAAQS Levels

Upon reconsidering the data available through 2006, EPA proposed to reduce the 2008 standard based on the following evidence:

1. Two controlled exposure studies (Adams 2002, 2006), in which healthy subjects were exposed to ozone for 6.6 hours down to a level of 0.060 ppm. Pulmonary function decrements were observed at 0.080 ppm and some subjects showed moderate decrements at 0.060 ppm.

2. EPA's understanding that the evidence from controlled human exposure and epidemiological studies indicate that "people with asthma are likely to experience larger and more serious effects than healthy people."

3. A body of epidemiological evidence indicating associations for a wide range of serious health effects across distributions of ambient ozone concentrations that extend beyond 0.075 ppm

In addition, EPA took into account the results of exposure and risk assessments it conducted to arrive at its proposed range on the levels of a primary ozone standard. The remainder of this section focuses on the evidence-based information relied upon by EPA.

The Adams Studies

Three of the eight charge questions in the Memorandum deal with the interpretation of results of controlled human exposure studies, with particular attention paid to two studies conducted by Adams in 2002 and 2006. The importance of these latter studies stems from the low ozone levels to which subjects were exposed. They are the only controlled exposure studies that examined respiratory effects associated with ozone exposures less than 0.080 ppm.

EPA states in its 2010 reconsideration that the Adams studies provide "limited but important evidence" of the range of levels defining where a primary ozone standard should be set. Despite EPA's contention that the evidence provided by the Adams studies was "limited," EPA relied on the studies to recommend that the primary ozone standard should be set in the range of 0.070 to 0.060 ppm. In fact, the 2007 Staff Paper concluded that the Adams papers "provide evidence of a lowest-observed effect of 0.060 ppm for potentially adverse lung function decrements and respiratory symptoms in some healthy adults wile at prolonged moderate exertion." EPA cited this conclusion numerous times in its proposed reconsideration. The charge questions EPA poses to CASAC in this regard are at least partially directed to what weight the Administrator should ultimately give to the Adams studies.

A number of issues have already been raised by commenters on EPA's interpretation of the results of the Adam's studies, two of which are especially relevant. The first issue relates to the response of subjects to ozone at a level of 0.060 ppm. Although Adams observed a group mean $FEV_{1.0}$ decrement of 1.5% at the 0.06 ppm level, his paper concluded that this decrement was not statistically different from the mean $FEV_{1.0}$ increase of 1.5% in those exposed to filtered air. Based on a reevaluation of the data by Brown using a different statistical method than Adams, EPA concluded to the contrary that a statistically significant group mean decrease in $FEV_{1.0}$ occurred at the 0.060 ppm level.

Brown et al. (2008) have now published their reanalyses of the Adams data. The Adams studies were designed as longitudinal studies with repeated measures. As such, that is how they should be analyzed. An appropriate approach would be to use mixed effects models for longitudinal studies. Neither Adams nor Brown et al. (2008) used this approach. In fact, Brown et al. used only the data points at the end of the study at 6.6 hours after examining the data. A glance at their figure 1 shows that, while there is a clear difference in the response at 0.08 ppm ozone and filtered air over the entire period of the study, this is not true of 0.06 ppm group. For this group only the results at 6.6 hours are significantly different from the filtered air group. Brown et al. do not report whether the difference at 5.6 hours reached significance. Because Brown et al. (2008) did not analyze the entire data and because of the post-hoc nature of their analyses, their result should at best be thought of as a hypothesis requiring further investigation. In particular, a chamber study in which exposure extends beyond 6.6 hours would be needed to see whether the apparent trend in 0.06 ppm group starting at 5.6 hours continued beyond 6.6 hours.

The second issue revolves about whether decrements ≥ 10 ppm in $FEV_{1.0}$ should be considered adverse in the absence of symptoms. Adams found that 7 to 20 % of the subjects experienced $FEV_{1.0}$ decrements ≥ 10% without accompanying symptoms and concluded that these were adverse, contrary to the American Thoracic Society guidelines that stipulated that such a response should not be considered adverse.

Numerous comments were submitted in response to EPA's proposed reconsideration, which among other things questioned the validity of EPA's interpretation of the Adams' studies. The comments of the National Association of Manufacturers in particular provide an extensive review of the relevant scientific issues including a detailed critique of the Brown study showing that a large number of prominent researchers in the field favored Adams' method of statistical analysis over Brown's method of analysis. Yet EPA's solicitation memorandum does not discuss any of these contrary comments in its discussion of the charge questions. Admittedly, CASAC

had the opportunity to review public comments at the time they were submitted about one year ago, but a summary of the arguments that were taken opposing the position advocated by EPA would have presented a more balanced view of this important subject. At the very least, if CASAC agrees with EPA's on its interpretation of the results of the Adams studies, it is obligated to address in detail the questions raised by commenters, specifically on the validity of the statistical methods used by Brown and on the definition of pulmonary system adversity that EPA relied upon.

The Gent et al. (2003), Mortimer et al. (2002), Schildcrout et al. (2006) and O'Connor et al. (2008) studies

The Gent et al. (2003) and Mortimer et al. (2002) studies were viewed by EPA as providing substantial evidence that people with asthma are among those that are at increased risk from ozone exposure. EPA ignored the results of the Schildcrout (2006) study, which found no associations with ozone. A new study by O'Connor et al. (2008), cosponsored by EPA, likewise finds no associations with ozone.

The Gent et al. (2003) study includes a number of significant limitations. It investigated the association of ambient fine particles and ozone with respiratory symptoms in children with asthma. The study included 271 children (<12 years old) in southern New England. Daily respiratory symptoms and medication use were prospectively recorded over the six-month study period of April 1, 2001 to September 30, 2001. The authors stratified the subjects into a group of 130 that used maintenance asthma medications during the follow-up period and 141 who did not use asthma medications. In joint pollutant modeling with $PM_{2.5}$, risks for ozone were elevated and sometimes statistically significant while $PM_{2.5}$ risks were generally not elevated and not significant. As noted below, Schildcrout et al. (2006) found that the highest risks were attributable to carbon monoxide and nitrogen dioxide, not ozone.

Another limitation of the Gent et al. (2003) study is its treatment of potential meteorological confounders. Although limited control for temperature is reported in the paper, relative humidity

does not appear to have been controlled. Additionally, it is puzzling that while the results clearly suggest a dose related increase in respiratory symptoms, there is little indication of increased use of bronchodilators, which would have been expected. In this regard, EPA's summary of this study in the Staff Paper (p. 3-10) is misleading. The Staff Paper states:

> "Effects of O_3, but not $PM_{2.5}$, remained significant and even increased in magnitude in two-pollutant models. Some of the associations were noted at 1-hr max O_3 levels below 60 ppb. In contrast, no effects were observed among asthmatics not using maintenance medication."

The odds ratios in Table 5 of the Gent et al. study, which show that results for maintenance medication users for wheeze, persistent cough, chest tightness, shortness of breath and bronchodilator use, are quite similar in magnitude to the results in Table 6 for those who did not use maintenance medication. However, the confidence intervals are wider for the later group. Also, only a handful of the odds ratios for maintenance medication users were statistically significant. A more judicious interpretation of these results would be that the odd ratios were similar in magnitude for users and non-users of maintenance medication, but that the odd ratios were sometimes statistically significant for maintenance medication users. The Staff Paper should be more balanced in its discussion of these results.

The second study relied on by the Staff Paper was conducted by Mortimer et al. (2002). This study examined the effects of summer air pollution on 846 asthmatic children residing in eight urban areas in the U.S. EPA uses this study not only as evidence that exposure to ozone results in decreased lung function among asthmatics, but also suggests that this study provides evidence of increased symptoms and medication use associated with exposure to ozone. However, ozone was not the only pollutant associated with health effects. The authors state, "In conclusion, summertime air pollution is associated with increased asthma morbidity and decreased pulmonary function among inner-city children with asthma in the USA … Nitrogen dioxide, sulfur dioxide, and particles with a 50% cut-off aerodynamic diameter of 10 μm were associated with increases in symptoms, with nitrogen dioxide exhibiting the strongest influence. Ozone

was most influential in peak expiratory flow rate." Moreover, the peak expiratory flow rate (PEFR) results are inconsistent in the study. For an incidence of greater than or equal to a 10% decline in PEFR, the associations for ozone were not significant for 1, 2, and 3-day lags, but were significant for a 4-day lag, a result for which there is no plausible biological explanation. More significantly, when SO_2, NO_2, PM_{10}, and O_3 were included in multi-pollutant modeling for morning asthma symptoms, ozone was not elevated (RR=1.00; CI, 0.75-1.34). The risks for SO_2, NO_2, and PM_{10} were not significant; but, in contrast to O_3, were all elevated. This result contradicts EPA's conclusion that the ozone effects were "robust" in this study. If the ozone effects vanish in a multi-pollutant analysis, the ozone effects were, by definition, not robust. The Staff Paper should add a discussion of the multi-pollutant modeling results in Mortimer et al. (2002) and discuss how their results cast doubt on the associations with ozone.

The Schildcrout et al. (2006) study included 990 children in eight North American cities during the pre-randomization phase of the Childhood Asthma Management Program (CAMP). The authors evaluated associations with CO, NO_2, PM_{10}, SO_2, and warm season O_3 during the period November 1993 – September 1995. The cities consisted of Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; and Toronto, Canada. Many of these cities would have likely exceeded the current O_3 standard, particularly back in the early to mid-1990s. The endpoints in the study included asthma symptoms and rescue inhaler uses. The authors concluded: "Lags in carbon monoxide and nitrogen dioxide were positively associated with both measures of asthma exacerbation, and the 3-day moving sum of sulfur dioxide levels was marginally related to asthma symptoms. PM_{10} and ozone were unrelated to exacerbations." The results were particularly clear for rescue inhaler uses. For ozone, the relative risks ranged from 0.99-1.01 depending on the lag and none were close to statistical significance. However, the relative risks were 1.06 (1.01-1.10) and 1.04 (1.01-1.07) for CO for a 2-day lag and a 3-day moving average lag, respectively. They were 1.05 (1.01-1.09) and 1.03 (1.01-1.05) for NO_2 for a 2-day lag and a 3-day moving average lag, respectively.

The O'Connor et al. (2008) study examined the association between air pollutants and pulmonary functions (specifically FEV_1 and PEFR) and asthma symptoms among 861 inner-city

children with "persistent asthma." They report their results thus, "In single-pollutant models, higher 5-day average concentrations of NO_2, sulfur dioxide, and particles smaller than 2.5 µm were associated with significantly lower pulmonary function. Higher pollutant levels were independently associated with reduced lung function in a 3-pollutant model. Higher concentrations of NO_2 and particles smaller than 2.5 µm were associated with asthma-related missed school days, and higher NO_2 concentrations were associated with asthma symptoms." Most relevant, no associations with ozone were reported.

Taken together, the longitudinal studies evaluating asthma effects are inconsistent and not robust. There were associations with ozone in the Gent et al. and the Mortimer et al. studies but not the Schildcrout et al. and O'Connor studies using single-pollutant models. For the Mortimer et al. (2002) study, the association of ozone with the incidence of morning asthma symptoms disappeared in multi-pollutant modeling. Across the studies, there were associations of asthma-related variables with SO_2, NO_2, particles and CO for different endpoints, but these associations were inconsistent, as they were with ozone. Therefore, these studies do not provide a clear picture of how air pollution affects asthmatics and which pollutants are responsible.

Other epidemiological evidence

Other substantial epidemiological studies of the health impacts of ambient ozone have appeared as well after 2006 that are highly relevant to the setting of an ozone standard. In particular there are two comprehensive time-series studies by Smith et al. (2009) and Katsouyanni et al. (2009) that should certainly be considered in the setting of revised standards. For example, in a reanalysis of the NMMAPS data, Smith et al. (2009) reported strong effect modification of the short-term impact of ozone on mortality by a number of factors. This finding raises questions regarding the estimation of a national effect estimate for ozone in the US. The Katsouyanni et al. (2009) study reported that the association of ozone with mortality in NMMAPS was sensitive to the model used, particularly the degrees of freedom used for smoothing of trends and the inclusion of co-pollutants.

Conclusions

EPA has already proposed to replace the current primary ozone standard of 0.075 ppm with a standard in the range of 0.060 to 0.070 ppm. Rather than asking CASAC to provide advice on whether this range is supported by the available scientific literature, EPA appears to be looking to CASAC to support a decision that EPA has already made. The nature of the charge questions is inappropriate given CASAC's mandate to provide technical guidance only. Moreover, CASAC is being asked to provide fresh insight on matters in which its stance has been made very clear since 2006. Finally, EPA's placement of restrictions on the new information that can be considered threatens to result in the setting of an ozone NAAQS that has limited scientific validity.

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