Comments on the CASAC Response to the Agency's Charge Questions in the Ozone NAAQS Reconsideration

By
Jon M. Heuss
Air Improvement Resource, Inc.
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These comments are written to provide additional input to the CASAC Panel as it prepares its written response to the Administrator. Having participated in previous ozone NAAAQS reviews, having listened to the two teleconferences held so far, and having carefully read the draft CASAC letter discussed on the March 3 call, I want to offer several suggestions concerning the letter to the Administrator. Clearly from listening to the myriad of public comments, there is a wide range of opinion as to whether the current 0.075 ppm standard or a standard set as low as 0.060 ppm is requisite to protect the public health. These comments are meant to help assure that the advice provided by CASAC includes consideration of all the factors that the Administrator should weigh in evaluating the evidence.

At the outset, it is acknowledged that the choice of the ozone NAAQS, whether by the Administrator or as expressed as a preference by either an individual CASAC panelist or the panel as a whole, is a policy decision that is informed by and based on the science. However, the science alone cannot determine the standard, which is why the Clean Air Act leaves the decision to the Administrator acting on the latest science as presented in the criteria document with advice from CASAC and informed by public comment.

With the issuance of the first draft of the next ISA, we now have comparisons in time of the relevant science (the 1996 CD, the 2006 CD, and the 2011 draft ISA) and the relevant policy considerations (the 1996 Staff Paper, 1995 CASAC closure letter and the Administrator's 1997 decision and the 2006 CD, 2007 Staff Paper, several CASAC letters and now two Administrator's views of the science and policy).

My comments are presented on three relevant topics -- the estimates of policy relevant background, the interpretation of the human clinical studies, and the interpretation of the epidemiological studies.

I begin with a summary of pertinent CASAC views[1] from the review completed in 1997 when the first 8-hour standard of 0.08 ppm was established. In the 1997 review, the CASAC panel assumed that there was no threshold for biological effects of ozone above background and that, therefore, the risk assessment must play a central role in the choice of standard. However, the panel also indicated that because of the myriad of assumptions that are made to estimate population

[1] CASAC letter to Administrator Browner, EPA-SAB-CASAC-LTR-96-002, November 30, 1995.

exposure and risk, large uncertainties exist in the risk estimates. In the 1997 review, the panel considered 8-hour standards in the range of 0.07 to 0.09 with a range of allowable exceedances. Importantly, the Panel concluded that there is no "bright line" which distinguishes any of the proposed standards (either the level or the number of allowable exceedences) as being significantly more protective of public health. The consensus of the Panel was that the ranges of concentrations and allowable exceedences proposed by the Agency were appropriate. However, a number of Panel members expressed "personal" preferences for the level and number of allowable exceedences. Of the ten panel members who expressed their opinions, all ten favored multiple allowable exceedences, and their personal preferences for the level ranged from 0.08 to 0.09. The Administrator set the standard at 0.08 ppm with multiple exceedances. With this history in mind, I will discuss the 2008 review and the current re-consideration with respect to changes in the science or changes in the interpretation of the data for the three relevant issues noted above.

Estimates of Background Ozone

One of the reasons that 0.07 ppm was not favored in 1997 was that it was very close to the extremes of background as reported in the 1996 CD and SP. In fact, the Administrator found that a standard set at a level of 0.07 ppm was not requisite to protect public health in part because an 8–hour standard set at 0.07 ppm would be closer to peak background levels that infrequently occur in some areas due to non-anthropogenic sources of ozone. In the 2008 Review, EPA changed the way background was evaluated, relying solely on the use of a global atmospheric model to calculate monthly mean background. EPA also neglected to estimate the extreme values of background even though the statistical form of the ozone NAAQS is an extreme value. This is an important omission that led the Agency and CASAC to assume, incorrectly in my view, that a standard in the range of 0.06 to 0.07 ppm was substantially higher than background. CASAC needs to provide the Administrator with additional advice concerning the limitations of the method used to estimate background ozone in the letter - as discussed during the March 3 call and in individual panelist's comments.

The Interpretation of Human Clinical Studies

A number of the charge questions and much of the text of the CASAC draft letter involves discussion of the human clinical studies and their interpretation with regard to public health. I have a number of concerns with the explanation of the Panel's position.

First, the draft text in the answer to charge question #2 indicates that chamber studies of asthmatic and non-asthmatic subjects exposed to O_3 at relatively high concentrations showed that the changes in FEV1 were significantly greater in the asthmatic than in the non-asthmatic subjects. In contrast, the discussion of clinical studies in Section 6.3.2 of the 2006 CD indicates that there are some studies

that report slightly higher functional responses in asthmatics compared to normal subjects, some studies that report similar responses, and one new study that reports lesser responses in asthmatics. The conclusion drawn in the 1996 CD, the 2006 CD and now in the 2011 draft ISA[2] is that "asthmatic subjects appear to be at least as sensitive to acute effects of O3 as healthy nonasthmatic subjects."

Second, the draft text in the answer to charge question #3, in discussing the individual subject responses in the Adams 2006 study, refers to lung function test decrements >10% as a decrease in lung function determined to be clinically relevant by the American Thoracic Society (ATS). In contrast, the 1999 ATS guidelines[3] indicate that:

> The committee recommends that a small, transient loss of lung function, by itself should not automatically be designated as adverse. In drawing the distinction between adverse and nonadverse reversible effects, this committee recommended that reversible loss of lung function in combination with the presence of symptoms should be considered adverse.

In the Adams 2006 study, the total mean symptom scores were only 2-4 units at 0.04 and 0.06 ppm out of a possible total score of 160. Adams indicated that the differences in the symptoms between the 0.04 and 0.06 ppm exposures and the filtered air control were not statistically significant. Thus, according to the ATS guidelines, the functional changes at 0.06 ppm would not be considered as adverse.

Third, the draft CASAC letter indicates in response to charge question #5 that "while FEV1 changes > 10% may still allow healthy individuals to go about their normal daily activities, individuals with compromised lungs, such as asthmatics, incur significant health impacts with such lung function changes." In contrast to this statement, the 1997 review drew other conclusions regarding the public health significance of > 10 % FEV1 changes. In the 1997 review, the Agency considered the issue of clinical and public health significance and developed separate guidelines for evaluating the adversity of respiratory effects for healthy individuals and those with impaired respiratory systems. The CASAC closure letter[4] at the time indicated "After considerable debate, it was the consensus of the Panel that the Agency's criteria for the determination of an adverse physiological response was reasonable." The Panel went on to caution "Nevertheless, there was considerable concern that the criteria for grading physiological and clinical responses to ozone was confusing if not misleading."

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[2] U. S. Environmental Protection Agency, Integrated Science Assessment for Ozone and Related Photochemical Oxidants, EPA/600/R-10/076A, March 2011, at page 6-11.

[3] What Constitutes an Adverse Health Effect of Air Pollution? Official Statement of the American Thoracic Society Adopted by the ATS Board of Directors, July 1999, Am J Respir Crit Care Med, **161**, 665-673, 2000.

[4] November 30, 1995 CASAC letter, supra note 1.

One of the concerns with the guidelines is that is that the "moderate" category includes both functional changes of between 10 and 20 % decrements in FEV1 and moderate symptomatic responses. For considering the public health significance, the guidelines refer to "moderate functional and/or symptomatic responses." Thus, the category of moderate functional changes without symptoms is not specifically addressed.

In addition to the guidelines tables, the 1996 SP included extensive discussion of how to interpret the guidelines in terms of public health.[5] Large functional changes, > 20 % FEV1 decrements, and severe symptomatic responses were indicated as clearly adverse. Moderate functional changes and symptoms were discussed in relation to interference with normal activity for both healthy and asthmatic individuals. For asthmatics, the Agency and CASAC concluded that moderate responses, when repeated, should be considered adverse. After considerable discussion there was consensus on CASAC that single, acute moderate functional responses should <u>not</u> be considered adverse for healthy individuals. Rather the staff indicated that the number of exposures resulting in moderate responses should be considered a factor in determining adversity for healthy individuals. Thus, the current draft letter characterizes the adversity of single, acute >10 % FEV1 changes differently from the consensus view in 1996.

To fully inform the Administrator, the current panel should carefully explain the rationale for its view on the adversity of single, acute transient and reversible lung function test decrements without symptoms at or below the current ozone standard. That discussion should take into account that:

- The same guidelines used in the 1996 SP are included in the 2006 SP.
- The overall risk of exposures of concern below 0.08 ppm for both healthy individuals and asthmatics is lower in the Risk Assessment for the 2008 Review than was calculated in the Risk Assessment for the 1997 review.[6]
- As indicated in the draft CASAC letter, for ethical reasons, controlled exposure studies involve effects that are relatively mild and reversible, including changes in pulmonary function and increased evidence of inflammatory changes.

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[5] U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Ozone: Assessment of the Scientific and Technical Information, OAQPS Staff Paper, EPA-452/R-96-007, June 1996, at pages 62 to 72.

[6] U.S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information, OAQPS Staff Paper - Second Draft, EPA-452/D-05-002, July 2006, at pages 5-71 and 6-27.

- Controlled studies of asthmatics and COPD patients have been conducted with intermittent exercise at substantially higher ozone exposures than at issue in the current review, resulting in group-mean FEV1 decrements as high as 20 to 25 %, suggesting that such effects are relatively mild with regard to clinical or public health significance. [7]

- Since 1996, there is substantial evidence that the lung function decrements observed in clinical and field studies are involuntary neural reflexes - the body's reflexive reaction to the presence of an irritant gas.

Fourth, the draft letter notes that ethical issues with carrying out experimental studies in diseased individuals precludes extension of these studies to what are likely to be more sensitive groups. This is followed by a statement indicating that without having specific studies among asthmatics and children at these levels of exposure, prudence would indicate choosing a level closer to 0.06 ppm. These statements are confusing. They appear to mix up the issue of studying the very most sensitive and vulnerable groups and the kind of asthmatics and children that have been studied in the past at considerably higher ozone exposures. For the very most sensitive, they are very unlikely to be outside exercising for 6 to 8 hours so that their more sedentary lifestyle provides protection since the first effects when sedentary occur at 0.50 ppm. With regard to children and asthmatic's responses at 0.06 to 0.08 ppm, those studies have not been done but there is no ethical reason they could not be done since such groups have been studied at higher exposures in the past.

Fifth, the draft letter indicates that, as CASAC has noted in the past to the Agency, evidence is accumulating that persons with asthma, the elderly, and particularly children, are more sensitive and experience larger decrements in lung function due to O_3 exposure than do healthy volunteers. In contrast, the 2011 draft ISA summarizes the available data, noting that children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O_3, but have greater responses than middle-aged and older adults when exposed to comparable O_3 doses.[8] The ISA goes on to indicate that symptomatic responses to O_3 exposure, however, appear to increase with age until early adulthood and then gradually decrease with increasing age. This was the state of the evidence in 1996 and is still the state of the evidence in 2011. Noting that the ISA also indicates that asthmatics are at least as sensitive as healthy subjects, studies of healthy young adults are likely the most sensitive means to evaluate lung function test decrements with symptoms, the physiological changes ATS views as adverse.

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[7] See Table AX6-3 in Vol. II of 2006 Ozone CD.
[8] Draft 2011 ISA, supra note 2, at page 6-13.

The Interpretation of Epidemiological Studies

In contrast to the science regarding human clinical studies which, while refined, has not changed substantively since the 1997 review, the available epidemiological evidence has increased dramatically. However, along with an outpouring of studies has come increased understanding of the limitations of the epidemiological evidence, particularly for time series studies. For example, the issue of publication bias exaggerating the apparent strength of association, the issue of model selection adding substantial uncertainty, and the issue of stochastic variability adding substantial uncertainty have all arisen along with the increase in the number of studies. In addition, the issue of confounding raises the possibility that a positive association for ozone or any other pollutant in a single-pollutant model may be an indicator of some other pollutant rather than evidence of an independent effect of that pollutant. While the draft letter notes that ozone may be an indicator of the mix of photochemical oxidants, other possibilities also need to be acknowledged.

There are two specific points in the discussion of epidemiology in the draft letter that warrant comment. The first is the discussion of the Friedman et al., 2001 study of health care utilization for asthma during the Summer Olympic Games in Atlanta in 1996 as evidence specifically supporting an 0.06 ppm standard. Because of concerns raised that the Friedman et al. 2001 study had not corrected for seasonal trends, the Health Effects Institute (HEI) sponsored a more detailed analysis of the available data surrounding the Atlanta Olympics.[9] The April 2010 HEI report by Peel et al. was not able to reproduce the Friedman et al. pediatric asthma findings. This is an example of how the reliance on the record available in the 2008 review can be misleading.

The second point is the discussion of the fact that mortality effects for ozone have been found at concentrations well below the proposed range, both in single communities where the community mean ambient concentrations are well below the proposed range and in a multi-city study where high ozone days have been excluded, Bell et al. (2006). However, there is a follow-on study by Bell et al. (2007)[10] that is not included in the record for the re-consideration that illuminates this issue.

When Bell et al., 2007 restricted the analysis to days with low ozone, in order to see if the small combined association persisted, the range in individual-community associations widened. For example, when the data was restricted to days with

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[9] J. L. Peel, M. Klein, W. D. Flanders, J. A. Mulholland, and P. E. Tolbert, Impact of Improved Air Quality During the 1996 Summer Olympic Games in Atlanta on Multiple Cardiovascular and Respiratory Outcomes, Health Effects Institute, Research Report 148, Health Effects Institute, Boston, Massachusetts, April 2010.
[10] M. L. Bell, J. Y. Kim, and F. Dominici, Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies, Environ Health Perspect, 115, 1591-1595 (2007).

ozone less than 0.02 ppm, the range in individual city mortality associations for a 0.01 ppm increase in ozone was from – 20 % to + 30 %. It is inconceivable that such low ozone exposures would be causing a dramatic increase in mortality in one city and protecting against mortality in another. With such wide variation, the interpretation of a small combined association as a health effect is highly questionable, especially in light of the fact that ozone indoors, where people spend about 90 % of their time is reduced about half by deposition to building surfaces. With such a wide range in individual-city associations, it is not surprising that there are some positive associations in single city studies with low ozone concentrations such as Vedal, et al. (2003). I note also that the authors of that study do not implicate ozone as the direct cause of mortality in their study.

In addition to these specific comments, it is useful to compare the science available in the 1997 review with that available now. During the 1997 Review, an early study of the association of ozone with asthma hospital admissions was included in the risk assessment. Thus, the CASAC Panel in that review considered both the human clinical and the epidemiological data when rendering their judgments. In addition, there were a substantial number of epidemiological studies of lung function in setting such as summer camps at the time of the 1997 review. The 2011 draft ISA notes that newer data on children attending camps, outdoor workers, and other healthy populations were limited, and across these studies, ambient O_3 exposure was associated with both decreases and increases in lung function.[11] It goes on to note that a large number of older studies comprise a majority of the supporting evidence from epidemiology regarding lung function test effects, whereas recent studies, which were far fewer in number, provide less compelling evidence. Whether this is due to reduced ozone exposures, differences in study design, or other factor should be considered.

Closure

As noted above, these comments are provided to help assure that the advice provided by CASAC includes consideration of all the factors that the Administrator should weigh in evaluating the evidence.

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[11] Draft 2011 ISA, supra note 2, at page 6-17.