

01-09-12 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

Preliminary Comments from Dr. Sverre Vedal on

EPA's Integrated Science Assessment for Ozone and Related Photochemical Oxidants

(Second External Review Draft – September 2011)

Comments on the Preamble

The Preamble serves its purpose. I have only minor points:

p. lvii, line 17. It's not clear from what is written how multicity studies provide insight into confounding.

p. lx, Table 1. Specificity. This "criterion" is more intended to refer to a cause having a specific effect rather than an effect having a specific cause, as written. It has become clear that this "criterion" is not very applicable to the air pollution setting where there is evidence that a single pollutant, such as ozone, causes a myriad of effects.

p. lxiv. Much of this section seems repetitious of points made earlier: dose-response, coherence across study designs and different fields of enquiry. Also, I wouldn't single out life stage as somehow distinct from subpopulations. Each life stage is simply a subpopulation that may have increased sensitivity.

Comments on the Executive Summary

This executive summary is reasonably faithful to the information provided in the body of the ISA, with the rare exception. First, in Table 1-1, the claim that findings on CNS effects are "not available" is not correct. If so, the causal assignment would be "inadequate." In fact, there are reported findings (section 1.6.3 and p. 2-19, Table 2-1), which is consistent with the causal assignment of "suggestive." Parenthetically, this table should be moved to the next page so that it comes after the reference to it in the text. The same issue surfaces in the Integrative Summary (Table 2-3, p. 2-49). Second, it seems that it is being claimed that UV-B radiation causes no health effects (Table 1-3), when these are clearly present (and documented on p. 2-48).

Some points need to be clarified. First, ozone exposure has only been relatively consistently associated with total and cardiopulmonary mortality in the setting of short-term exposure. This is not the case for long-term exposure. The reference to consistent associations in Section 1.6.1 therefore needs to be qualified. Second, the lack of a discernible threshold in the concentration-response relationship is an often-repeated refrain. The evidence for this is largely based on epidemiological findings. Even though the human clinical findings, specifically on level of lung function, have demonstrated effects at lower exposure concentrations, there is evidence that effects do not occur at a concentration of 40 ppb, implying a threshold.

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Section 1.6.5. Ozone Concentration-Response Relationships. Here, as elsewhere in the ISA, we find the statement that there is “no indication of a threshold for O₃ concentrations greater than 30 or 40 ppb.” This ignores the findings from human clinical studies showing not effects at 40 ppb.

Section 1.9. Conclusion. The statement that “populations identified as being at most risk for O₃-related health effects are individuals with influenza/infection, individuals with asthma, and older age groups” is too strong. Preferable wording would be something like there are some subpopulations that exhibit “potentially increased sensitivity” to ozone (eg, p. 6-139, line 25 and as used in the Integrative Summary).

Fig. 1-1 (also shown as Fig. 2-1, p. 2-7) takes some figuring out. The role of VOCs in potentiating NO₂ formation is here, as is O₃ quenching, but both take some searching to identify.

Comments on Chapter 2 - Integrative Summary

This Summary is generally well done. I have a few issues:

1. I would have thought that one very policy-relevant question for welfare effects (p. 2-3) is that of time period of effects. This information is critical to distinguishing the averaging period and form of the secondary standard as distinct from those of the primary standard.
2. I like the attempt at including both 2006 conclusions and current conclusions in Table 2-1 (p. 2-18). However, some 2011 concluding points are uninformative, eg, “suggestive of a causal relationship” and some are not correct (see point 4 on respiratory symptoms [Where newer findings weaken earlier conclusions] below).
3. I also like Fig. 2-3 (p. 2-22) with the incorporation of evidence from studies and the types of studies (eg, tox, epi, clinical) being identified.
4. The statement on “asthma as a factor affecting risk” to ozone (p. 2-32, line 10) ignores evidence from human clinical studies that largely shows no difference in effects on asthmatics and non-asthmatics.
5. The statement on threshold is misleading (p. 2-33, line 23). The data referred to show an effect at 60 ppb, but not at 40 ppb. This is not the same as saying “Recent studies provide evidence for a smooth C-R curve without indication of a threshold in young healthy adults exposed . . . to O₃ concentrations between 40 and 120 ppb.”
6. Table 2-3, p. 2-49. Again, as in Table 1-1 of the Executive Summary, the claim that findings on CNS effects are “not available” is not correct. If so, the causal assignment would be “inadequate.” In fact, there are reported findings (section 1.6.3 and p. 2-19, Table 2-1), which is consistent with the causal assignment of “suggestive.”

Comments on Chapter 6 - Short-term exposure effects

Respiratory:

Arguably, the most important new findings relating to respiratory effects of short-term ozone exposures are from more recent human clinical studies of lung function responses showing effects at 0.60 ppm, but not at 0.40 ppm.

1. Pulmonary function responses.

i) It seems clear that there is likely some bronchoconstriction from ozone exposure, possibly only small airways effects, but that this must be a relatively trivial effect, and has not been demonstrated using the low concentration protocols. The reduction in FEV1 is neither prevented nor helped by inhalation of a bronchodilator or treatment with corticosteroids, suggesting that bronchoconstriction does not contribute, or is possibly just affecting small airways. My sense is that prominent reference to the contribution of bronchoconstriction to the acute lung function response (eg, in the Summary, p. 6-22, line 20; p. 6-4, line 1) reflects the difficulty the research and policy community has in accepting that this effect of ozone is entirely, or predominantly, due to triggering of airway receptors and neural responses.

ii) I somewhat reluctantly agree that one needs to use the post-filtered air exposure with exercise in assessing acute ozone effects on lung function (p. 6-4, lines 30-37). The result, however, is that the effect of ozone exposure is then essentially one of causing less improvement in FEV1 with exercise. This naturally brings up issues as to the adversity of this response.

iii) Ozone has been the “poster child” for the [concentration x time x minute volume] unifying exposure concept for a long time. It’s confusing here when this point (p. 6-8, line 19) is followed closely by a discussion of the differential effects of a triangular vs. square wave exposure protocol. Both can’t be completely true.

iv) I wonder whether there shouldn’t be more discussion of the relevance of the acute lung function response in the chamber studies. There’s a drop in level of lung function that occurs during a 6.6-hr exposure with moderate exercise when exposed to 0.60 ppm. These are conditions that are not often experienced by those for whom such a drop might be meaningful, ie, those with severe asthma or with COPD. Motivation for the relevance might be provided by the panel studies. Better linkage is perhaps warranted.

2. Sensitive (or less sensitive) subpopulations.

i) The evidence that asthmatics are particularly sensitive to the respiratory effects of ozone exposure is pretty weak. Studies that only examined subjects with asthma do not address the question of enhanced sensitivity (section “Children with asthma, p. 6-33).

ii) I think the correct characterization at this time is that there are some subpopulations that exhibit “potentially increased sensitivity” to ozone (p. 6-139, line 25). The inclusion in the list of sensitive

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subgroups in the Summary section (6.2.9), such as those using corticosteroids, those with current URI, older adults with bronchial hyperresponsiveness, and those with elevated BMI or certain genetic polymorphisms, largely on the basis of studies in Mexico City, is not warranted.

iii) The identification of healthy children as an at risk population is a little weird (p. 6-46, line 10).

3. Selective reporting and highlighting of positive findings and studies.

While this style has been much more prominent in previous ISAs, there remain some vestiges in this latest incarnation. Examples:

i) The multi-city Canadian study by Stieb et al (p. 6-126) on COPD and asthma ED visits only highlight lag 2 findings;

ii) What is the justification for dedicating a figure to the Seattle findings on asthma ED visits (p.6-130)? This is a very selective highlighting of results.

4. Where newer findings weaken earlier conclusions.

The one instance where newer study findings weaken conclusions that were drawn previously is, somewhat surprisingly, that relating to respiratory symptoms and medication use in asthmatic children (p. 6-86). Multi-city studies of symptoms in asthmatic children, which should carry the most weight (and do in every other part of the ISA), are not convincing or show no effects. I therefore question the conclusion on p. 6-100, lines 8-10, regarding respiratory symptoms and medication use in asthmatic children, and in the corresponding part (Respiratory symptoms and medication use – 2011 conclusions) of Table 2-1.

5. Miscellaneous.

i) I'm not sure that describing a 5% within-day variability in lung function as clinically meaningful is correct (p. 6-14). Such variability may indicate some disease state, or may be outside normal variability, but the actual variability itself is unlikely to be of clinical significance.

ii) Figure 6-6 (p. 6-35) shows little support for the statement regarding decrements in FEV1 in children with asthma (p.6-33, line 18).

iii) The description of the APHENA findings (pp. 6-114 to 6-117) is complex; admittedly, the study itself and its findings are complex. Some bottom line conclusions are needed.

iv) The attempt to explain absence of associations in outpatient/doctor visit data (p. 6-131, lines 34-35 and p. 6-132, lines 24-27) is unconvincing. It is not clear whether these studies are restricted to unscheduled visits? If not, that is a more likely explanation.

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Non-respiratory:

- i) Highlighting a French study on ischemic stroke with positive findings with a plot demonstrating dose-response (Fig. 6-21, p. 6-153) puts more emphasis on these findings than is merited.
- ii) The Gong 1998 study (p.6-143) did show controlled human exposure effects on increasing heart rate, not just on blood gases.
- iii) The claim that “there is no apparent biological mechanism to explain the association observed for short-term O₃ exposure with cardiovascular mortality (p. 6-183, line 21). I would argue that neural autonomic effects could be one mechanism for CV effects, as could pulmonary inflammation, just as it is in the PM setting.

Mortality:

p. 6-215, line 1. The point about the distinction between effect modification and interaction is not necessary, subtle and not widely acknowledged.

Minor:

- p. 6-13, line15. Adams footnote should be 1 instead of 5?
- p. 6-15, line 35. The inflammation discussion should not be in this lung function section.
- p. 6-92. Table 6-120 and Figure 6-12. The Rabinovitch 2004 study should be included here.
- p. 6-123. Edit title “Averting Behavior”
- p. 6-14, line 2. editing needed.

Comments on Chapter 7 - Long-term exposure effects

1. Introductory. There are largely two new important observational study findings that have been reported since the previous review that potentially modify the previous conclusions: 1) new-onset asthma in children and long-term ozone exposure in the CHS cohort and 2) respiratory mortality and long-term ozone exposure in the ACS cohort. Findings from the recent toxicological study on atherosclerotic plaque size in hyperlipidemic mice are also important.

2. The CHS cohort findings. The CHS cohort still provides the most definitive data on long-term ozone exposure and longitudinal lung function growth, finding no association with ozone as opposed to the other pollutants considered. Regarding new-onset asthma, the earlier finding from this cohort was that number of outdoor sports was associated with new-onset asthma, but only in high ozone communities. This finding was only moderately compelling, being hampered by the relatively small number of cases, and by the observation that participation in tennis drove most of the association. The new findings on new-onset asthma take a gene-environment interaction approach to a larger number of cases (n=160). The emphasis is on gene main effects, somewhat unfortunately, rather than on the ozone exposure main effect, which ignores the fact that modification of ozone effects by genetic polymorphisms does not require a gene main effect. That is, genes that influence new-onset asthma may have nothing to do with how ozone might cause new-onset asthma. Having said that, the genes assessed (reported) in the CHS

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study (HMOX-1 and GSTP1/GSTM1) might well be of interest in influencing ozone effects. The primary finding is that the protective gene main effect is lost in the higher ozone communities (Figure 7-1, p. 7-5), a finding that was replicated in another part of the cohort. The more important finding, from the perspective of usefulness in this setting relating to policy, would have been a demonstration of an ozone main effect, with secondary modification of the ozone effect by genetic polymorphisms. Effect modification, it can be argued, should only be explored when a main effect is first observed, although in the gene-environment setting, strong modifying effects of a relatively unusual polymorphism, it could be argued, might not be reflected in an exposure main effect. Also, in the study of traffic effects on new-onset asthma, no effects of ozone were observed (p. 7-6, lines 23-29). The bottom line, however, is that I nevertheless agree with the causal assignment for respiratory effects.

3. The ACS Study. The ACS study played a central role in setting the annual standard for PM_{2.5}, so findings on ozone effects in this cohort need to be considered seriously. Given that this is the only evidence at this point, I agree with the causal determination of “suggestive.”

4. Endpoints caused by both short- and long-term exposure. Some endpoints, such as ED visits or hospitalizations, can be caused by both short-term and long-term exposure. Studies typically identify an exposure metric, and conclusions are drawn relative to that metric. When associations are observed, this results in a type of self-fulfilling prophesy regarding the temporal features of exposure, but unfortunately provides little insight into the temporal features that are most critical into producing the associations. Specifically, when it is claimed that long-term exposure to ozone is associated with increased ED visits or hospitalization, and only long-term exposure metrics are employed, it is not known whether short-term or long-term exposures are responsible. Control for short-term exposures would implicate long-term exposure.