

March 13, 2014

Dr. H. Christopher Frey
Chair, Clean Air Scientific Advisory Committee
Science Advisory Board
US Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Dr. Frey:

We urge CASAC to consider the following comments, presenting our recommendations for improvements to the 2014 *Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards* (PA; US EPA, 2014a). We received funding from the American Petroleum Institute (API) to prepare these comments, but the recommendations are based on our own independent evaluation of the PA and do not necessarily reflect the views of API.

We have a number of concerns with the United States Environmental Protection Agency's (EPA's) evaluation of the scientific evidence and overall recommendation to lower the ozone standard. Specifically, we found that EPA's approach is overly conservative at each level of its analysis. Despite this, both the scientific evidence and risk assessment show that the current standard is health protective and lower standards are unlikely to lead to increased benefits. We urge CASAC to consider our comments and recommend EPA to present maintaining the current level of the ozone standard as an option to the Administrator.

The PA presents an evaluation of the available evidence and conclusions regarding the adequacy of the current ozone standard based on the ozone *Integrated Science Assessment* (ISA), referred to in the PA as the evidence-based considerations; and *Health Risk and Exposure Assessment* (REA) which are referred to in the PA as the exposure and risk-based considerations.

EPA's approach to the consideration of scientific evidence for ozone-related health effects is based on the causal framework used in the ISA (US EPA, 2013), which has serious limitations (Goodman *et al.*, 2013a). The framework does not include specific guidance for several aspects that are critical for a rigorous WoE evaluation, which led to an inconsistent evaluation of the evidence. The ISA should have evaluated all relevant data in a consistent manner using well-specified criteria and determined whether, as a whole, they constitute evidence for causation or are more likely indicative of an alternative hypothesis. Based on the inadequate evaluation of evidence in the ISA, the PA cannot soundly conclude that there is sufficient evidence for any causal relationships at ozone exposures below the current standard. Below, we discuss additional issues with EPA's evaluation and presentation of the evidence in the PA in response to specific CASAC charge questions.

Evidence-based considerations

With regard to the evidence-based considerations, EPA posed the following question to CASAC:

To what extent does section 3.1 (Evidence-based Considerations) capture and appropriately characterize the key aspects of the evidence assessed and integrated in the ISA?

In its consideration of the available evidence regarding potential modes of action by which ozone could cause health effects, EPA should evaluate mechanistic and biomarker studies using a WoE approach to adequately assess the consistency and coherence of results within and across disciplines in relation to respiratory and extrapulmonary effects of ozone. In addition, the PA should include a discussion of the clinical relevance of biomarkers and their relation to adverse apical effects to support the usefulness of such data.

The PA considers the evidence for respiratory effects associated with short- and long-term ozone exposure. The key epidemiology studies on which EPA relied in the ISA to support its causality determinations for short-term ozone exposure and respiratory effects reported small changes in respiratory function and have numerous limitations that undermine many of the results. These limitations were also present in studies evaluated in previous ozone reviews; thus, the evidence for respiratory-related effects of ozone is not strengthened by the availability of more recent evidence. A critical evaluation of controlled human exposure studies demonstrates that lung function effects in humans exposed to ozone at concentrations below 72 ppb are independent and not statistically different in participants exposed to filtered air, indicating a lack of causation (Goodman *et al.*, 2013b). In addition, broadly recognized clinical guidelines do not consider reported lung function effects at ozone concentrations below 88 ppb to be adverse (Goodman *et al.*, 2013b). The PA should acknowledge that the currently available evidence does not support a causal relationship between short-term ozone exposure at concentrations below the current standard and adverse respiratory effects.

With regard to respiratory effects associated with long-term ozone exposure, EPA's classification of a likely to be causal relationship is unsubstantiated. The recent evidence EPA cites to support this classification does not demonstrate any consistent associations with ozone exposure, and EPA does not adequately address the limitations of the available studies. Importantly, the evidence is no more compelling than for other health outcomes that EPA determined to be only "suggestive" of a causal relationship. The same uncertainties remain since the last review of the respiratory effects associated with long-term ozone exposure (US EPA, 2006), and this should be reflected in the PA.

The consideration of the evidence for total mortality associated with short-term ozone exposure in the PA does not consider the numerous inconsistencies across recent multi-city studies, including those that use similar datasets and modeling assumptions. The risk estimates reported in these studies are likely heavily biased as a result of unresolved between-city heterogeneity and numerous uncertainties associated with confounding effects, model selection, and the shape of the ozone-mortality concentration-response function (CRF). EPA should discuss these considerations in the PA, and it should eliminate statements describing the evidence as "consistent." The results for cardiovascular (CV)- and respiratory-related mortality are even less consistent, with most studies reporting results that are not statistically significant. Overall, the available data do not support a causal relationship between short-term ozone exposure and mortality at exposures equal to or below the current National Ambient Air Quality Standards for ozone, and this should be reflected in the PA.

Many new studies of the potential effects of short-term ozone exposure on the CV system have become available since the last ozone review (US EPA, 2006), which concluded that the body of evidence for CV effects of ozone was limited. A systematic WoE analysis of the available data indicates that the results of these studies do not provide stronger evidence of a causal relationship (Goodman *et al.*, 2014); this should be reflected in the PA.

With regard to the evaluation and discussion of adversity, EPA posed the following question to CASAC:

To what extent is staff's consideration of the health effects evidence, including the adversity of reported respiratory effects and public health implications technically sound and clearly communicated at an appropriate level of detail? In the Panel's view has the information been appropriately interpreted for the purpose of assessing the adequacy of the current standard?

In its discussion of the potential adversity of the effects of ozone, EPA indicates that evidence since the last review supports a relationship between ozone exposure below the current standard and adverse effects on lung function. As discussed above, a critical review of the controlled human exposure studies of the effects of ozone at concentrations near or below the current standard indicates that lung function effects are within the range of intra-individual variability in normal subjects, however, and not considered adverse with respect to clinical guidelines (Goodman *et al.*, 2013b). The lowest ozone concentration associated with both a lung function decrement >10% and increased respiratory symptoms, which is considered an adverse effect based on clinical guidelines, is 88 ppb (Goodman *et al.*, 2013b). Thus, the available data indicate that ozone induces adverse effects on lung function only at levels above those that are protected by current standards, and the PA should acknowledge this.

Exposure and risk-based considerations

With regard to the exposure and risk-based considerations, EPA posed the following question to CASAC:

With regard to the presentation of the exposure and risk information for the purpose of assessing the adequacy of the current standard, to what extent is the information, including associated limitations and uncertainties, sufficiently characterized, appropriately interpreted and clearly communicated?

The discussion in the PA regarding the health exposure and risk assessment does not fully consider the significant uncertainties in model estimates; EPA describes uncertainty qualitatively and separately from the risk evaluation. This is not useful from a policy perspective because it can lead to misinterpretation of the estimated risks. In addition, the discussion of risk estimates in the PA does not consider the conservative assumptions that EPA makes at various levels in the analysis. These conservatisms compound and lead to scenarios that are unrealistic. For example, in the exposure evaluation, EPA not only considers the most highly exposed individuals (*i.e.*, children) but also uses benchmark levels below those that are considered to be associated with adverse effects, and it highlights single occurrences in a year or ozone season above these levels. While we agree that being conservative is important, the use of conservative assumptions at all levels is not appropriate, particularly given the significant amount of unquantified uncertainty. Also, in the REA (US EPA, 2014b), EPA conducted no statistical tests to determine whether there are significant differences in risk estimates at the current level of the standard *vs.* alternative levels. This is critical for determining whether additional gains will be obtained from lowering the standard. Our evaluation of the REA indicates that there would not likely be a significant decrease in risks from lower ozone standards.

Consideration of "at-risk" populations

In the PA, EPA discusses "at-risk" populations using a classification framework introduced in the ISA to identify and understand effect modifiers that cause an increased risk of ozone-related health effects in these populations. EPA concludes that factors such as asthma, lifestage (children and older adults), dietary factors, and working outdoors increase the risk of health effects of ozone exposure. The classification framework used to evaluate the evidence for these factors has many of the same issues as EPA's framework for causal determination. In addition, the evidence is inconsistent and incoherent within and across disciplines. The PA should discuss this lack of consistent evidence and highlight areas where the evidence is stronger and may benefit from further research. Specifically, because there is little support for increased adverse effects from ozone exposure in children (vs. adults), EPA should highlight results for the general population.

Conclusion

Overall, the evidence presented in the PA does not support EPA's conclusions regarding the adequacy of the current ozone standard. A critical review of the evidence indicates that the current ozone primary standard is health protective, and lowering it will not decrease risks of ozone-related health effects in the general population or susceptible populations. We urge CASAC to recommend that EPA present maintaining the current level of the ozone standard as an option to the Administrator.

Sincerely,

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