Comments on the "Policy Assessment for the Review of Ozone National Ambient Air Quality Standards (External Review Draft)"
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Executive Summary

The "Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards, External Review Draft" (hereafter, the draft Ozone PA) addresses whether newly available scientific evidence and risk-based information support or call into question the adequacy of the public health protection afforded by the current annual primary ozone National Ambient Air Quality Standard (NAAQS).

The draft Ozone PA concludes that new scientific evidence and results from the exposure and risk analyses do not call into question the adequacy of the standard. However, a review of the evidence and risk-based information indicates that the current standard may be more conservative than necessary to protect public health.

The 2013 Ozone Integrated Science Assessment (ISA) and 2019 draft Ozone ISA concluded that there are causal and likely to be causal relationships between short- and long-term ozone exposure, respectively, and respiratory effects. The 2019 draft Ozone ISA concluded that there is a likely causal relationship between short- and long-term ozone exposure and metabolic effects. Based on these causal determinations, the draft Ozone PA focuses its risk assessment on respiratory effects following short-term exposure to ozone, as it concludes that the strongest scientific evidence regarding ozone and adverse health effects comes from studies of respiratory endpoints and, in particular, lung function.

The draft Ozone PA indicates that evidence from controlled human exposure studies suggests adverse respiratory effects at concentrations as low as 60 ppb ozone. However, the observed effects are not statistically significant or adverse at this concentration. As such, the inclusion of 60 ppb as a benchmark concentration in the exposure and risk assessment is extremely conservative.

Considering that the draft Ozone PA evaluated risks of exposures to 60 ppb ozone, and did so in the most sensitive population (children with asthma breathing at an elevated rate), its conclusion that the current primary ozone standard is adequate to protect public health is warranted. In fact, the overly conservative nature of this assessment indicates that the current standard may be more stringent than necessary to protect public health.

1 Introduction

The "Policy Assessment for the Review of Ozone National Ambient Air Quality Standards (External Review Draft)" (hereafter, the draft Ozone PA) reviews the currently available scientific literature pertaining to the human health effects associated with ozone exposure and evaluates the potential policy implications of the body of scientific evidence. The draft PA takes into account the scientific evidence presented in the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants (External Review Draft)" (hereafter the draft Ozone ISA; US EPA, 2019) and ultimately evaluates the adequacy of the current ozone primary National Ambient Air Quality Standard (NAAQS). The draft Ozone PA concludes that new scientific evidence and results from the exposure and risk analyses do not call into question the adequacy of the current ozone primary NAAQS.

The draft Ozone PA indicates that the strongest scientific evidence regarding ozone risks to human health comes from studies of respiratory endpoints; this consists of controlled human exposure and epidemiology studies, as well as animal toxicity studies. The draft Ozone PA concludes that currently available scientific evidence and risk-based information do not call into question the adequacy of the public health protection afforded by the current primary NAAQS. While this is true, it should also be noted that this evidence and information also indicate that the current standard may be more stringent than necessary to protect public health.

2 The general approach for reviewing evidence is inadequate (3.1.2).

The draft Ozone PA expanded on previous assessments and considered new scientific evidence discussed in the draft Ozone ISA to assess the adequacy of the current ozone primary NAAQS. As discussed in our comments on the draft Ozone ISA (Gradient, 2019), there are several issues with the evaluation of evidence in this document.

Briefly, study quality information is limited and presented in an unclear manner in an online database, and in the draft Ozone ISA, study quality is not fully or consistently considered. Furthermore, while the draft Ozone ISA emphasizes biological plausibility for each health outcome with regard to ozone exposure, the evidence presented does not demonstrate a complete pathway from exposure to downstream health endpoints. As a result, causal determinations are not based on a transparent, systematic, balanced review of the available evidence.

The NAAQS systematic review and causal determination framework should be updated to allow for conclusions that are reflective of the weight of scientific evidence, and this framework should be followed and described in a transparent manner in the ISA. Suggestions for an updated framework are described in Gradient's comments on the draft Ozone ISA (Gradient, 2019).

3 Nature of Health Effects (3.3.1)

The draft Ozone PA cites the draft Ozone ISA's conclusions that the current evidence supports causal and likely to be causal relationships between short- and long-term ozone exposure, respectively, and respiratory effects. In addition, the draft Ozone ISA states that newly available evidence indicates a likely causal relationship between ozone and metabolic effects. Below, we demonstrate that the evidence presented in the draft Ozone ISA for respiratory and metabolic effects does not support EPA's causal determinations at ambient ozone concentrations.

3.1 Short-term exposure evidence does not support a causal classification for respiratory effects (3.3.1.1).

The draft Ozone PA states that the strongest evidence for ozone-induced health effects comes from the scientific literature on short-term ozone and transient decrements in pulmonary function and respiratory symptoms (*i.e.*, coughing and pain on deep inspiration). The draft Ozone PA cites findings from controlled human exposure studies discussed in the 2013 Ozone ISA as the primary evidence for these effects.

As discussed below, the evidence for respiratory effects does not support EPA's conclusion that there is a causal relationship between short-term ozone exposure and respiratory morbidity and mortality at relevant concentrations. The controlled human exposure studies indicate that there are no statistically significant adverse respiratory effects associated with ozone exposures below 70 ppb. Effects reported at 60 ppb are also not adverse. In addition, the 2013 Ozone ISA did not properly consider key limitations in the epidemiology evidence, and new studies have the same critical issues that impact the validity of the results. Furthermore, key toxicity studies on which EPA relied to support the epidemiology data were conducted at very high exposure levels that are not relevant for assessing the health effects of ambient ozone.

3.1.1 Evidence from controlled human exposure studies does not support respiratory effects following short-term exposure to ozone at ambient levels.

In the 2013 Ozone ISA, EPA reviewed controlled human exposure studies of ozone in healthy adults, focusing on four studies that assessed the association between ozone and lung function at exposures below 80 ppb (Adams, 2002, 2006; Schelegle *et al*., 2009; Kim *et al*., 2011). In addition, EPA presented a cross-study analysis of controlled ozone exposures between 40 and 120 ppb and lung function in the 2013 Ozone ISA (Folinsbee *et al*., 1988; Horstman *et al*., 1990; McDonnell *et al*., 1991, 2007; Adams, 2002, 2003, 2006) with a smooth curve that represented a linear relationship between ozone and forced expiratory volume in the 1 second (FEV_1).

As discussed in Gradient's comments on the draft Ozone ISA (Gradient, 2019), we evaluated the same data. We estimated the group mean decrease in ΔFEV_1 for a given ozone concentration and fit both linear and sigmoid models across the studies. The linear model suggests a protective effect of ozone below ~50 ppb, which is biologically implausible. However, the sigmoid model fits the data and indicates that there is a likely threshold. This is consistent with biological data that support a threshold mode of action. EPA should consider a chemical agent's mode of action when choosing a statistical model for dose-response data.

Based on evidence presented in the 2013 Ozone ISA, the draft Ozone PA claims that young adults experience statistically significant decreases in group mean pulmonary function after 6.6 hours of 60 ppb ozone exposure with moderate exertion. This conclusion is based on studies by Kim *et al.* (2011), Schelegle *et al*. (2009), and Adams (2006), as well as a re-analysis of Adams (2006) by Brown *et al.* (2008); yet, only the findings by Kim *et al*. (2011) were statistically significant.

In the re-analysis of Adams (2006), Brown (2008) reported a statistically significant decrement in FEV_1 at a 60 ppb square-wave mean ozone concentration using a t-test applied to the 6.6 hour data. This analysis excluded all other time points (*i.e*., 1, 2, 3, 4.6, and 5.6 hours) and did not account for other responses from different exposure scenarios (*i.e*., triangular mean 40, 60, and 80 ppb and square-wave 80 ppb ozone). Thus, this statistically significant finding can be attributed to the majority of the data being selectively omitted from the analysis.

Discarding data is inappropriate, especially in light of more powerful and complex statistical models (*e.g*., mixed effect models) that can be employed (Gradient, 2011). Such post hoc selection of a data subset when valid and otherwise non-problematic observations exist calls into question the rationale for such action. The primary rationale for Brown (2008) to remove data from other experimental conditions was apparently to avoid stringent reductions in the critical *p*-value for statistical significance due to multiple comparisons procedures. These other data still exist, so leaving them out of the analysis does not eliminate the issue. In addition, Nicolich (2007,) conducted a reanalysis of the full dataset from Adams (2006); the findings were consistent with the findings of Adams (2006), confirming that there was no statistically significant decrement in group mean FEV_1 following 60 ppb ozone exposure.

Finally, effects at 60 ppb are not clinically adverse. The American Thoracic Society (ATS) stated that transient loss of lung function could be considered adverse if the loss is accompanied by respiratory symptoms (ATS, 2000). In a more recent statement, ATS expressed that small changes in lung function without symptoms should only be considered adverse in individuals with pre-existing compromised function, such as asthma (Thurston *et al*., 2017). The controlled human exposure studies focused on young, healthy adults and decrements in lung function were not accompanied by respiratory symptoms.

3.1.2 Animal toxicity studies are not informative regarding ambient ozone exposures.

In studies that investigated the effects of ozone in animals with asthma or airway hyperresponsiveness, the asthmatic phenotype has been modeled by allergic sensitization of the respiratory tract. There are only a limited number of studies that have observed airway hyperresponsiveness in rodents and guinea pigs at less than 300 ppb ozone. Studies discussed in the 2013 Ozone ISA and new studies discussed in the draft Ozone ISA do not provide evidence for human respiratory effects at ambient concentrations. Many of the cited studies in the draft Ozone ISA reported effects only at concentrations as high as 1,000 or 2,000 ppb. For example, the 2013 Ozone ISA included a study by Funabashi *et al*. (2004; US EPA, 2013); the authors reported changes in pulmonary function (increased respiratory resistance and decreased dynamic compliance) in mice exposed to 1,000 ppb ozone. More recent studies reviewed in the draft Ozone ISA report increased airway responsiveness at exposure concentrations as high as 2,000 ppb (*e.g*., Kasahara *et al*., 2015; Stober *et al*., 2017; Cho *et al*., 2018 US EPA, 2019). The draft Ozone ISA noted that 800 ppb was the lowest ozone dose that increased airway responsiveness. Furthermore, setting aside the issue of high ozone exposure doses, there is also uncertainty regarding the relevance of the evidence because of the differences in airway morphology in rodents compared with humans. While evidence of ozone-induced respiratory effects has been documented in non-human primates, a more biologically relevant species, the effects occurred following episodic exposure to 500 ppb ozone. These findings do not provide evidence of ozone-induced respiratory effects in humans at ambient concentrations, as mechanisms of biological effects may differ at high *vs.* low ozone concentrations.

3.1.3 Epidemiology studies are insufficient to provide evidence on short-term ozone exposure and respiratory effects.

The draft Ozone ISA cites new studies and previously reviewed studies from the 2013 Ozone ISA as evidence of ozone-induced respiratory effects. As discussed in Gradient's previous comments on the 2013 Ozone ISA, there are several key limitations of the epidemiology studies (Goodman and Sax, 2012). Furthermore, the EPA Administrator indicated in 2014 proposed rule that these limitations precluded their use in risk assessment, and they are not considered in the risk assessment in the draft Ozone PA (US EPA, 2014; Gradient, 2015). These same issues that make these studies inadequate for use in risk assessment also create uncertainty regarding the interpretation of their results and their application to causal determinations.

For example, many of the studies cited as key evidence for short-term ozone exposure and respiratory endpoints estimate personal exposure based on data from central ambient monitoring sites. However, the lack of agreement between ambient and personal exposures is a source of exposure measurement error and has been highlighted in previous Clean Air Science Advisory Committee (CASAC) reviews (CASAC, 2006) and other more recent studies (Avery *et al*., 2010a,b). Personal ozone exposures are often lower than ambient ones and are rarely correlated with concentrations at ambient sites (CASAC, 2006).

Also, many studies presented in the draft Ozone ISA do not analyze the role of copollutants in statistical models, so it is unclear whether the reported adverse effects are attributed to ozone. Although the draft Ozone ISA acknowledges the complexity of determining the effects of ozone alone due to its high correlation with other copollutants, it is not clear whether findings that did consider copollutants were deemed "higher quality" and given more weight that others in the evidence evaluation.

Similarly, the draft Ozone ISA appears to downplay studies with null results. In many instances, null results are discounted or assumed to be "positive," without a full consideration of study quality. For example, the draft Ozone ISA mentioned the potential exposure measurement error in the study by Sarnat *et al*. (2015) but states that the positive yet null findings are likely a result of "the short length of the time-series" (US EPA, 2019) and does not consider that the association could be truly null. Furthermore, an evaluation of the draft Ozone ISA's study review process suggests that studies with positive results are not subject to the same level of scrutiny.

3.2 Long-term exposure evidence does not support a likely causal classification for respiratory effects (3.3.1.1).

The draft Ozone PA also discusses long-term respiratory effects evidence discussed in the draft Ozone ISA. The draft Ozone ISA states that new evidence supports the 2013 Ozone ISA's conclusion that there is a likely causal relationship between long-term ozone exposure and respiratory effects. Furthermore, the draft Ozone ISA states that animal toxicity studies and human epidemiology studies support the effects of ozone on new-onset asthma in nonhuman primates and children, respectively.

As discussed below, the evidence does not support EPA's conclusion that there is a likely causal relationship between long-term ozone exposure and respiratory morbidity and mortality at ambient concentrations. The animal toxicity studies often report effects at high ozone concentrations that are not relevant to ambient exposure levels; different mechanisms may be involved at high ozone exposures. New epidemiology studies have the same critical issues as older ones that impact the validity of their results. Furthermore, in

many instances, the draft Ozone ISA appears to make definitive conclusions regarding causality from a limited number of animal toxicity or human epidemiology studies.

3.2.1 Animal toxicity evidence is limited and not relevant to ambient ozone concentrations.

Several studies evaluated the effects of long-term ozone exposure in both rodents and infant rhesus monkeys. Infant rhesus monkeys are ideal animal models because their lung branching pattern and airway distribution are more closely related than other animals' to those of humans. Recent studies cited in the draft Ozone ISA report statistically significant changes in airway growth and development, airway responsiveness, and the immune system in infant monkeys that suggest that long-term ozone exposure may lead to the development of asthma. Yet, these conditions all occurred following exposure to 500 ppb ozone (Chou *et al*., 2011; Moore *et al*., 2012; Murphy *et al*., 2013; Clay *et al*., 2014; Crowley *et al*., 2017). Studies in rodents also report statistically significant effects at only high concentrations (*e.g*., 500 or 2,000 ppb), which may involve different mechanisms that are not relevant to ambient concentrations. The findings from these studies are not informative regarding human health effects at ambient ozone concentrations.

3.2.2 Evidence from epidemiology studies is limited.

Many of the epidemiology studies cited as key evidence for the effects of long-term ozone exposure and respiratory effects suffer from the same limitations as discussed in Section 3.1.3. The draft Ozone ISA acknowledges that recent epidemiology studies have issues with exposure measurement error due to the use of fixed-site air monitors and confounding by copollutants.

Despite this, the draft Ozone ISA appears to make causal conclusions regarding the effects of long-term ozone on specific respiratory endpoints using limited epidemiology evidence. For example, according to the draft Ozone ISA, there were no studies in the 2013 Ozone ISA that examined the association between ozone and chronic obstructive pulmonary disease (COPD); one new study is discussed in the 2019 draft Ozone ISA (To *et al*., 2016). To *et al*. (2016) investigated the association between long-term ozone exposure and COPD incidence in adults with incident asthma. Notably, the authors included multiple individual- and ecological-level covariates and information on other comorbidities in both single- and two-pollutant models (*i.e*., ozone and $PM_{2.5}$). The authors reported a statistically significant association between ozone and COPD incidence in asthmatics; however, the results were attenuated, albeit positive, in the two-pollutant model, which suggests confounding by $PM_{2.5}$. There is also potential for exposure measurement error, because air pollution data were collected from fixed monitoring sites. In addition, a majority of the health risk factor data (*e.g*., smoking, body mass index) were collected at baseline from surveys and likely changed over the course of the study. Setting aside these issues, one study is not sufficient evidence to suggest an association.

Finally, the draft Ozone ISA cites several cross-sectional studies as evidence of long-term ozone's effects on allergic responses. This evidence base includes a new cross-sectional study by Weir *et al*. (2013) that is evaluated in the draft Ozone ISA. Causal conclusions cannot be determined from cross-sectional studies.

3.3 Evidence for other health effects following ozone exposure is inadequate (3.3.1.2).

3.3.1 Evidence for metabolic effects is inadequate.

The evidence for metabolic effects does not support EPA's conclusion that there is a likely causal relationship between such effects and short- and long-term ozone exposure at relevant concentrations. The draft Ozone ISA acknowledges that there is limited evidence from epidemiology and controlled human exposure studies, but indicates that animal toxicity studies provide robust evidence of the impact of short-term ozone exposure on metabolic effects. While key animal toxicity studies may support the effects of short-term ozone on glucose impairment at 500-1,000 ppb, the evidence for other metabolic endpoints is not consistent, and most studies only evaluated ozone exposure concentrations that are far higher than ambient levels. Also, animal toxicity and human epidemiology studies are limited regarding the long-term effects of ozone on metabolic endpoints. Overall, the evidence presented is inadequate to classify causation for ozone exposure and metabolic effects in humans at ambient concentrations.

3.3.2 Evidence for other endpoints is inadequate.

As indicated in the 2019 draft Ozone ISA, evidence for short-term ozone exposure and cardiovascular effects and total mortality does not support a likely causal relationship. However, it also is not suggestive of a causal relationship; rather, it remains inadequate to address causality, if not suggestive of a lack of an association. Similarly, while the draft Ozone ISA concludes that the evidence for other endpoints does not support causal or likely causal associations, like the evidence for short-term ozone exposure and cardiovascular effects and total mortality, this evidence falls short of being suggestive.

3.4 Exposure concentrations associated with health effects are not evaluated properly (3.3.3).

The draft Ozone PA states that the current evidence does not alter the previous conclusions regarding the ozone exposure duration and concentration associated with health effects. However, the 2013 and 2019 draft Ozone ISAs and the draft Ozone PA all indicate that adverse respiratory effects (particularly lung function decrements) occur at lower exposure concentrations than the evidence supports.

3.4.1 Controlled human exposures studies do not support effects at 70 ppb or lower.

The draft Ozone PA states that "[t]he lowest concentration for which lung function decrements have been found to be statistically significantly increased over responses to filtered air remains approximately 60 ppb" (US EPA, 2019). Evidence from 6.6-hour controlled human exposure studies do not support ozone-induced respiratory effects at concentrations below 70 ppb; effects at 60 ppb are neither statistically significant nor adverse. As discussed in Section 3.1.1, the evidence does not support decrements in lung function at 70 ppb or lower.

3.4.2 Epidemiology evidence is insufficient for determining exposure circumstances that can elicit health effects.

With regard to epidemiology evidence, the draft Ozone PA states:

> We recognize that these studies are generally focused on investigating the existence of a relationship between O_3 occurring in ambient air and specific health outcomes, and not on detailing the specific exposure circumstances eliciting such effects. While the evidence base of epidemiologic studies of associations between O_3 and respiratory effects and health outcomes (e.g., asthma-related hospital admission and emergency department visits), as a whole, provides strong support for the conclusions of causality, as summarized in section 3.3.1 above these studies generally do not measure personal exposures of the study population or track individuals in the population with a defined exposure to O_3 alone. (US EPA, 2019)

It is appropriate to recognize that the epidemiology evidence cannot provide accurate information on ozone exposure to be considered in the exposure analyses. In addition, as discussed in Gradient's comments on the draft Ozone ISA (Gradient, 2019), there are considerable limitations in the epidemiology evidence that create uncertainty regarding the interpretation of these studies' results. In fact, the draft Ozone PA states that, during the "last review, the Administrator placed relatively less weight on the air quality epidemiologic-based risk estimates, in recognition of an array of uncertainties, including, for example, those related to exposure measurement error (80 FR 65346, October 26, 2015)" (US EPA, 2019). It is appropriate that the draft Ozone PA does not consider these studies in the risk assessment.

4 Using a benchmark concentration of 60 ppb in the exposure and risk assessment is conservative (3.4).

The draft Ozone PA used air monitoring data and the Comprehensive Air Quality Model with Extensions (CAMx) instrumented with the higher order decoupled direct method (HDDM) in conjunction with EPA's Air Pollutant Exposure (APEX) model to estimate percentages of the population in eight key study areas that will experience days with elevated ozone exposure at or above benchmark concentrations and decrements in lung function. The draft Ozone PA indicates that the benchmark concentrations chosen (*i.e.*, 60, 70, and 80 ppb) represent the concentrations associated with effects in controlled human exposure studies. In addition, exposure analyses focused on populations breathing at an elevated rate. Risk was characterized for both children aged 5-18 years and adults with and without asthma; ultimately, children with asthma were chosen as the focus of the assessment. The results presented are numbers and percentages of individuals in simulated populations estimated to experience one or more days with 7-hour average exposure at or above benchmark concentrations or a lung function decrement at or above 10%, 15%, or 20%, all while breathing at an elevated rate. In addition, results for adjusted air quality conditions scenarios in which monitors had a design value equal to 65 or 75 ppb are also presented.

The use of the most sensitive population (children with asthma breathing at an elevated rate) is appropriate. However, a benchmark of 60 ppb is extremely conservative, because effects at this exposure concentration were not statistically significant or adverse. As such, this analysis indicates that the current standard is more than adequate to protect public health.

5 Evidence indicates that the standard may be more protective than necessary (3.5).

The draft Ozone PA states that "[t]he currently available evidence regarding O_3 exposures associated with health effects is largely similar to that available at the time of the last review and does not indicate effects attributable to exposures of shorter duration or lower concentrations than previously understood" (US EPA, 2019). However, as discussed above, this evidence indicates that the current standard may be more stringent than necessary to protect public health.

The draft Ozone PA indicates that the epidemiology studies reporting positive associations between ozone and respiratory health outcomes, such as asthma-related hospital admissions and physician and emergency department visits, are not helpful for understanding the health effects associated with the current standards. Only a few of these studies were conducted in areas that met the current annual standards; as the draft Ozone PA states, these studies should not be used in the exposure and risk analyses. In addition, as discussed in Sections 3.2.2 and 3.1.4, these same limitations make them insufficient to provide evidence for causal determinations for ozone and respiratory effects.

The draft Ozone PA states that the current primary NAAQS of 70 ppb ozone is protective of the public health. This conclusion is based on the draft Ozone PA's exposure and risk analyses, which is based on evidence from the 6.6-hour controlled human exposure studies that were evaluated in the 2013 Ozone ISA. As a result, no alternative standards for the primary ozone NAAQS have been proposed. While it is true that new evidence does not support an alternative, lower standard, it also indicates that the current standard is more stringent than necessary to protect public health.

6 Conclusions

The draft Ozone PA indicates that the strongest scientific evidence regarding ozone and adverse health effects comes from studies of respiratory endpoints. Furthermore, the draft Ozone PA indicates that evidence from controlled human exposures studies suggests adverse respiratory effects at concentrations as low as 60 ppb ozone. However, the observed effects are not statistically significant or adverse at this concentration. As such, the exposure and risk assessment should not have included 60 ppb as a benchmark concentration.

Even so, because the draft Ozone PA evaluated risks of exposures to 60 ppb in the most sensitive population (children with asthma breathing at an elevated rate), its conclusion that the current primary ozone NAAQS is adequate to protect public health is certainly warranted. However, it should be noted that the overly conservative nature of this assessment indicates that the current standard is in fact likely more stringent than necessary to protect public health.

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