Comments on the Draft Report on the Clean Air Scientific Advisory Committee (CASAC) Review of EPA's Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document

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Abbreviations

AHR	Airway Hyper-responsiveness
CASAC	Clean Air Scientific Advisory Committee
CBSA	Core-based Statistical Area
CRF	Concentration-response Function
DM1H	Daily Maximum 1-hour
EPA	United States Environmental Protection Agency
ISA	Integrated Science Assessment
MoA	Mode of Action
NO_2	Nitrogen Dioxide
ppb	Parts Per Billion
REA PD	Risk and Exposure Assessment Planning Document
TRP	Traffic-related Pollutants

Executive Summary

While the Clean Air Scientific Advisory Committee (CASAC) discussed several important points in the "Draft Report on the Clean Air Scientific Advisory Committee (CASAC) Review of EPA's Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document" (US EPA, 2015a), there are a few key issues that were not sufficiently addressed:

- More information is needed on how core-based statistical areas (CBSAs) will be selected and how quantitative uncertainty analyses will be conducted for an updated air quality analysis;
- The analysis should focus on results for exposure benchmarks above 100 parts per billion (ppb); and
- An epidemiology-based risk assessment of respiratory effects from long-term nitrogen dioxide (NO_2) exposures is not feasible.

1 More information is needed on how CBSAs will be selected and how quantitative uncertainty analyses will be conducted for an updated air quality analysis.

The Clean Air Scientific Advisory Committee (CASAC) should ask the United States Environmental Protection Agency (EPA) to provide more documentation of the analysis plan for an updated air quality assessment. As we discussed in our comments on the Risk and Exposure Assessment Planning Document (REA PD) (Gradient, 2015a), EPA should provide more information in its analysis plan to include the following:

- A clear explanation for how this analysis will be used to inform the decision to conduct updated exposure and risk assessments;
- An increased emphasis on results at exposure benchmarks where evidence indicates that adverse health effects could occur;
- Improved documentation of the method used to weight the criteria for selecting core-based statistical areas (CBSAs);
- An elimination of the high-nitrogen dioxide (NO_2) concentration criterion from the list of primary criteria used to select CBSAs;
- An evaluation of the uncertainty in the adjustment factors for NO_2 daily maximum 1-hour (DM1H) concentrations above the 98^{th} percentile; and
- Clarification of the use of near-road and on-road NO_2 concentrations and their uncertainties in informing a decision as to whether a new exposure assessment is needed.

2 The analysis should focus on results for exposure benchmarks above 100 ppb.

CASAC should acknowledge that there is a lack of evidence for effects at 100 parts per billion (ppb) and below. As the REA PD noted, "important uncertainties" are associated with evidence regarding increased airway hyper-responsiveness (AHR) following exposure to 100 ppb NO_2, including "the general lack of statistically significant results in individual studies at 100 ppb and the lack of an exposure-response relationship based on individual studies" (US EPA, 2015b).

Gradient has discussed this issue in detail in comments on the second draft Integrated Science Assessment for Oxides of Nitrogen - Health Criteria (Gradient, 2015a). Importantly, when considering the fraction of individuals experiencing increased AHR following exposure to NO_2 across all studies and concentrations, this was statistically significant only for non-specific airway challenges following exposure at rest. This fraction was not significant at any NO_2 concentration for non-specific airway challenges following exposure while exercising, or for specific airway challenges following exposure either at rest or while exercising. Considering the uncertainties associated with the AHR data following exposure to 100 ppb, the paradoxical lack of an effect following exercise, and the lack of an effect on AHR for specific airway challenges (which are more representative of plausible exposure scenarios than non-specific airway challenges), CASAC should recommend that EPA focus on benchmarks above 100 ppb.

3 An epidemiology-based risk assessment of respiratory effects from long-term NO_2 exposures is not feasible.

CASAC strongly encourages EPA to assess the feasibility of conducting an epidemiology-based risk assessment using asthma incidence in children as the critical health effect. As Gradient discussed in comments on the REA PD (Gradient, 2015b), such a quantitative risk assessment is neither warranted nor feasible.

A critical review of long-term NO_2 exposure/respiratory effects epidemiology studies shows that results are inconsistent within and across studies. There is a large degree of heterogeneity in exposure windows evaluated in the studies with positive findings. In addition, there are considerable uncertainties in the study findings with regard to confounding by traffic-related pollutants (TRP). Further, the evidence of new-onset asthma associated with long-term NO_2 exposure in animal studies is not robust, and the evidence regarding effects associated with the mode of action (MoA) for asthma development is not compelling. Considering the significant limitations of and uncertainties in the epidemiology studies, the inconsistency and lack of coherence across the epidemiology studies, and the lack of robust, compelling evidence from animal toxicity and MoA studies, CASAC should acknowledge that the evidence is not sufficient to support a likely causal relationship.

Setting aside uncertainties about a likely causal relationship between long-term NO_2 exposure and respiratory effects, a quantitative epidemiology-based risk assessment requires robust data sufficient for deriving a concentration-response function (CRF). However, available epidemiology studies of long-term NO_2 exposure and asthma development in children do not provide such data. A critical limitation of most of the long-term epidemiology studies is the uncertainty regarding potential confounding by TRP. McConnell *et al*. (2010) conducted the only longitudinal cohort study of asthma development in children that adjusted for TRP in multi-pollutant analyses, but they relied on central site monitoring for NO_2 exposure assessment, likely resulting in substantial exposure measurement error.

In addition, the presence of a threshold may radically affect the results of a risk assessment (Rhomberg *et al*., 2011), and the available epidemiology studies provide very little data appropriate for assessing whether a threshold likely exists. EPA would require more robust epidemiology data evaluating the shape of the CRF to conduct a defensible epidemiology-based risk assessment.

Finally, the available epidemiology studies evaluated diverse populations in various countries, and there is considerable heterogeneity in the methods of exposure assessment, the exposure window evaluated, the methods of outcome ascertainment, and the ways analyses were adjusted for TRP and other confounders. Therefore, it is not appropriate to pool the CRF data from multiple studies for quantitative risk assessments.

Based on these arguments, CASAC should not recommend an assessment of the feasibility of an epidemiology-based risk assessment.

4 Conclusions

CASAC should recommend that EPA provide more information on CBSA selection and quantitative uncertainty analyses, and emphasize exposures above 100 ppb for an updated air quality analysis. CASAC should not recommend that EPA evaluate the feasibility of an epidemiology-based risk assessment for long-term respiratory effects, as such a risk assessment is neither warranted nor feasible.

References

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