

April 30, 2014

H. Christopher Frey, Ph.D.
Chairman
Clean Air Scientific Advisory Committee and Ozone Review Panel
Science Advisory Board
US Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-0001

via email to Aaron Yeow, Designated Federal Officer, at yeow.aaron@epa.gov

Re: Comments on US EPA's Integrated Science Assessment for the Primary National Ambient Air Quality Standards (NAAQS) for Nitrogen Dioxide (External Review Draft) for the Public Teleconference of the Chartered Clean Air Scientific Advisory Committee (CASAC) and the CASAC Oxides of Nitrogen Primary NAAQS Review Panel

Dear Dr. Frey:

The Clean Air Scientific Advisory Committee (CASAC) identified several important issues regarding how the United States Environmental Protection Agency (EPA) applied its causal framework to the *Integrated Science Assessment for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft)* (NO₂ ISA). Specifically, CASAC noted it "[did] not find the application of the causal framework to be transparent," and there was "no clear consensus about the [ISA's] causal determinations." These conclusions were based on several considerations, including: 1) there was no discussion regarding the impact of measurement error on inferences from epidemiology studies, and EPA did not connect specific modes of action (MoAs) it discussed in Chapter 3 to specific health effects in Chapter 4; 2) EPA often evaluated subclinical outcomes (*e.g.*, QT interval changes, circulating inflammatory biomarkers) as primary evidence of cardiovascular effects (*e.g.*, cardiovascular hospital admissions) due to NO₂ when they are, at most, supportive of such findings; 3) there was an overall lack of consideration of confounding by co-pollutants in the incorporation of epidemiology studies as evidence for causal determination; and 4) EPA applied the causal framework inconsistently across various health endpoints. Below, I identify additional points CASAC should consider asking EPA to address in the second draft ISA.

CASAC's letter provides helpful guidance to improve the ISA's discussion of MoA, specifically recommending MoAs be linked to health outcomes of interest in the second draft ISA. I encourage CASAC to further ask EPA to discuss whether there is sufficient detail to show the proposed MoAs are likely occur in humans, particularly at relevant exposure levels, and how MoA studies should influence the interpretation of epidemiology and controlled exposure studies. CASAC should also consider recommending that EPA address the major data gaps regarding the proposed MoAs and identify what future studies would establish that these MoAs occur in humans at ambient exposure levels.

A major and mostly unresolved criticism of the ISA is the lack of consistent and transparent criteria for identifying the level of evidence needed to make causal determinations across various health endpoints, particularly with respect to the treatment of confounding in epidemiology studies. CASAC provided several suggestions to address this issue in the second draft ISA; I urge CASAC to consider expanding these recommendations to address criteria for evaluating the robustness of study results incorporated as evidence in the causal framework, as well as criteria for evaluating evidence that suggest a lack of causal

effect (*e.g.*, see Goodman *et al.*, 2013).¹ Another issue that CASAC could expand on in its letter to the Administrator is whether potential confounding by traffic related pollutants has been sufficiently addressed in studies published since the last nitrogen oxide review (*i.e.*, the 2008 ISA) to now conclude that NO₂ *per se* is a causal factor for respiratory effects.

I further encourage CASAC to consider why the framework for evaluating at-risk factors (*i.e.*, effect modifiers) detailed in Chapter 6 differs from the causal determination framework. The four-level hierarchy EPA uses to evaluate effect modifiers is much more appropriate than the five levels in the causal framework; in any case, there is no reason they should not be the same. Also, CASAC should consider asking EPA to clarify how analyses of effect modifiers will be applied in the NAAQS review process.

In closing, I urge CASAC to more fully consider these issues both in its comments on the ISA and as the NAAQS process moves forward.

Thank you for your consideration.

Sincerely,

GRADIENT

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Principal

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¹ Goodman, JE; Prueitt, RL; Sax, SN; Bailey, LA; Rhomberg, LR. 2013. "Evaluation of the causal framework used for setting National Ambient Air Quality Standards." *Crit. Rev. Toxicol.* 43(10):829-849.