

April 30, 2014

H. Christopher Frey, Ph.D.
Chair
Clean Air Scientific Advisory Committee and Oxides of Nitrogen Review Panel
Science Advisory Board
U.S. 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 Review Plan 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:

In its draft letter to the United States Environmental Protection Agency (EPA), the Clean Air Scientific Advisory Committee (CASAC) made recommendations to improve the *Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft)* (NO₂ IRP). Regarding plans for the Integrated Science Assessment (ISA), these include improving the criteria for including and evaluating studies in the literature review; expanding the discussion of measurement error; and developing a framework for distinguishing effects associated with NO₂ from effects associated with copollutants. CASAC also identified several important issues relevant to the Risk and Exposure Assessment (REA), specifically regarding consideration of uncertainty in EPA's proposed concentration-response functions. In its charge questions to CASAC, EPA did not ask whether the National Ambient Air Quality Standards (NAAQS) causal framework is adequate for judging causality or applied consistently across studies within the same health effect categories, and CASAC did not opine on this issue. Below, I identify additional points that could be made regarding some of the important issues that CASAC did address.

An overarching issue is the adequacy of EPA's causal framework. As my colleagues and I discussed in a recent publication (Goodman *et al.*, 2013),¹ the weight-of-evidence framework for causal determinations presented in the IRP and used in the ISA should be more specific. This is particularly true for the determination of individual study quality; the selection, evaluation, and integration of studies, including those reviewed in the 2008 ISA as well as newer studies; consideration of the modified Bradford Hill aspects; and the criteria for causal judgments. Because EPA's causal framework is not explicit on these topics, the ISA's conclusions tend to be biased toward causation. I encourage CASAC to evaluate the overall strength of EPA's causal framework, including whether it is sufficiently explicit and, in its current form, can be applied in a consistent manner across studies.

I also urge CASAC to strengthen its comments regarding evaluation of study quality. In addition to Dr. Sheppard's recommended application of the ARRIVE framework for evaluating quality of animal

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.

toxicology studies, for example, there are guidelines for other types of studies, such as the STROBE guidelines (<http://www.strobe-statement.org/>) for evaluating epidemiology studies. To ensure a more balanced assessment, CASAC could also suggest that EPA consider reviewing and incorporating additional guidelines for other types of studies. For example, specific criteria that should guide evaluating study quality include an evaluation of how studies address specific confounders and their likely impacts on study results, as well as the adequacy of methods for evaluating and accounting for bias, measurement precision, replicability of observations, data reliability, outliers, and selective outcome reporting. My colleagues and I discussed several of these guidelines in another recent paper (Rhombert *et al.*, 2013),² and incorporated them in our recommendations on the NAAQS causal framework (Goodman *et al.*, 2013).¹

I further encourage CASAC to consider additional issues related to the IRP's discussion of how the ISA will address measurement error and incorporate results from null studies. Specifically, it is important to consider how measurement error impacts the interpretation of results of individual epidemiology studies and the body of literature as a whole. CASAC should also consider recommending that EPA develop criteria for evaluating and accounting for the robustness of the statistical methods used in studies provided as evidence for causality. Finally, CASAC should consider whether the IRP provides sufficient guidance for incorporating evidence from null studies in its causal framework and determining when a lack of causal association becomes as likely as a causal association.

With regard to the REA, I urge CASAC to consider the evaluation of threshold concentration-response functions and the relative magnitude and direction of uncertainty associated with risk estimates for each potential source if the specific magnitude of uncertainty cannot be calculated. Although these issues will be further explored by EPA in planning documents for the REA, addressing these issues at this stage of the process could help ensure a more balanced analysis in the REA.

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

Thank you for your consideration.

Sincerely,

GRADIENT

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Principal

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² Rhombert, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A survey of frameworks for best practices in weight-of-evidence analyses." *Crit. Rev. Toxicol.* 43(9):753-784.