Comments on US EPA's Integrated Science Assessment for Oxides of Nitrogen - Health Criteria (First External Review Draft)

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Thank you for the opportunity to speak on behalf of the American Petroleum Institute on the first draft NO_x Integrated Science Assessment (ISA) (US EPA, 2013).

For most outcomes, the ISA concludes that evidence is stronger than it was in 2008 (US EPA, 2008). The ISA indicates that this conclusion is based on an evaluation using the National Ambient Air Quality Standards (NAAQS) causal framework, which is largely based on the modified Bradford Hill aspects. However, it does not appear that these aspects were considered fully or in a consistent fashion.

Many of the studies cited in the draft ISA as providing evidence of either a causal or likely causal relationship reported associations that were null or close to null and more likely explained by chance, bias (such as exposure or outcome misclassification), and/or confounding (such as by co-pollutants, smoking, or socioeconomic status). In some cases, associations were not consistent within or among epidemiology studies or coherent with controlled exposure studies.

For example, epidemiology studies do not provide robust evidence of an association between nitrogen dioxide (NO_2) and either hospital admissions or emergency department visits for asthma. Most studies estimated exposures based on central-site monitors, which likely resulted in exposure measurement error. Effect estimates in all studies were small (with increases of 7% or less). Some studies (such as those by Son *et al*., 2013; Strickland *et al*., 2010; and Li *et al*., 2011) did not fully evaluate effects in co-pollutant models, despite fairly high correlations with NO_2 or stronger associations between other pollutants and health outcomes. In studies that evaluated associations in models with co-pollutants (such as those by Ko *et al*. 2007; Samoli *et al*., 2011; and Jalaludin *et al*., 2008), NO_2 effect estimates were substantially reduced compared to single-pollutant models and, in most cases, no longer statistically significant. Biological plausibility was an issue in several studies, such as those by Ko *et al*. (2007) and Villenueve *et al*. (2007), where associations were stronger for exposures occurring several days prior to a hospital admission or emergency department visit than for same-day exposures. Finally, it is not clear whether NO_2 *per se* is causally associated with the outcomes evaluated in these studies or whether NO_2 is a surrogate for other pollutants or mixtures of pollutants.

On this last point, there is considerable uncertainty regarding whether NO_2 is a surrogate for traffic-related pollution (TRP). The ISA indicates that this issue has been sufficiently addressed, but it only reviewed a limited number of potential TRP indicators. Even so, of the studies reviewed, few have reported statistically significant or clinically relevant associations with NO_2, and many investigators have concluded co-pollutant confounders are an important source of uncertainty. For example, Jerret *et al.* (2008) conducted a study of new-onset asthma in the Children's Health Study cohort of Southern California communities, concluding, "Although some toxicologic evidence supports the potential for NO_2 as a direct causative agent for respiratory health effects at high concentrations…the more likely

interpretation is that NO_2 was a proxy for other components of the local air pollution mixture with high toxic potential." McConnell *et al*. (2010) and Oftedal *et al*. (2009) also questioned whether associations were due to NO_2 or TRP. The ISA concludes that there is a causal relationship between short-term NO_2 exposure and respiratory effects, specifically asthma morbidity in children, but this is not supported by studies that have evaluated both NO_2 and TRP.

Finally, the ISA reviews several possible modes of action for NO_2, but none of them have been demonstrated to occur in humans at ambient exposures. At this point, the data neither support nor contradict potential associations, and the ISA should reflect what studies should be conducted to help interpret the epidemiology evidence and evaluate the overall weight of evidence regarding causation.

In conclusion, EPA strengthened its causal determinations in the draft ISA compared to 2008 for several endpoints; however, the evidence it presented does not support an increased confidence in causality. The second draft ISA should evaluate studies using the modified Bradford Hill aspects in a systematic fashion and, in particular, consider mode of action and cofounding by TRP more fully.

References

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