Comments on US EPA's Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft)

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Thank you for the opportunity to speak on behalf of the American Petroleum Institute. Overall, the draft Integrated Review Plan (IRP) presents a reasonable approach for conducting the nitrogen oxides (NO_x) review, but there are several instances where the IRP should be more explicit. Also, in some cases, the draft Integrated Science Assessment (ISA) did not follow the approach outlined in the draft NO_x IRP (US EPA, 2014). This includes the ISA's (US EPA, 2013) evaluation of 1) key considerations for determining causality; 2) whether studies conducted at high exposure concentrations are informative regarding biological plausibility and modes of action (MoAs); and 3) whether nitrogen dioxide (NO_2) is a surrogate for traffic-related pollution (TRP).

As my colleagues and I discussed in a 2013 paper (Goodman *et al.*, 2013), the weight-of-evidence framework for causal determination EPA discussed in the IRP and used in the ISA needs to be more specific. This is particularly true for several factors: individual study quality determination; 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 criteria for causal judgments. Because the framework is not explicit on these topics, the ISA's conclusions tend to be biased toward causation.

For instance, the draft IRP states that the ISA will consider the consistency of findings across studies, coherence of evidence across disciplines, and biological plausibility. In practice, these considerations do not always factor prominently in the causal determinations EPA presented. For example, evidence regarding lung function decrements in school children, much of which is inconsistent, as well as controlled human exposure studies, which show no effects on pulmonary function at concentrations below 100 ppb, is not coherent with evidence for respiratory-related hospital admissions and emergency department visits, which show effects at ambient NO_2 levels. In addition, findings from animal toxicological and *in vitro* studies do not provide support for a biologically plausible MoA for these short-term respiratory effects. Despite this, the ISA concludes that evidence supports a causal relationship.

The draft IRP states that findings from studies using high exposure concentrations may be considered if they are informative regarding biological plausibility or potential MoAs. MoA studies cited in the first draft ISA as providing support for causation were invariably conducted at exposure concentrations much higher than ambient concentrations. The ISA did not discuss whether these MoAs are biologically plausible in humans at ambient concentrations. The IRP should be revised to indicate that the ISA will discuss the extent to which findings at higher exposure concentrations are predictive of responses at lower concentrations, specifically in light of potential MoAs for NO_2. If these MoAs involve a threshold response, such as saturation of anti-oxidants in the airway extracellular lining fluid, the ISA should consider the likelihood that findings at higher exposure concentrations may have exceeded such a threshold and are thus not relevant.

The first draft ISA also did not fully evaluate whether NO_2 is a surrogate for TRP, even though the draft IRP states that this would be considered. In fact, the ISA cited studies as supporting an association between NO_2 and specific health effects despite study authors concluding that associations were more likely due to other pollutants (*e.g.*, Jerrett *et al.*, 2008; McConnell *et al.*, 2010; Oftedal, 2009). The IRP should indicate that the ISA must clearly articulate why it concluded the effects were instead due to NO_2. Also, the draft ISA evaluated the influence of TRP only for a very limited number of compounds, primarily particulate matter or some of its constituents (*e.g.*, black, elemental, and organic carbon), but it should have considered other TRP (such as from volatile organic compounds) that could contribute to adverse health effects (*e.g.*, HEI, 2010).

With regard to the Risk and Exposure Assessment (REA), considering that NO_2 likely acts *via* a threshold MoA, the IRP should be revised to indicate that the REA will evaluate threshold concentration-response functions (CRFs). Also, the IRP should indicate that the REA should only calculate quantitative risk estimates for endpoints with strong evidence of a causal association, including robust data for both air quality evaluations and CRFs. The IRP should also require confidence bounds around risk estimates to include quantitative estimates of uncertainty or, at the very least, the REA should provide the magnitude and direction of uncertainty associated with each potential source.

Overall, the draft IRP presents a reasonable approach for conducting the NO_x review; however, there are several places where the IRP could be more explicit. Also, there are several additional issues that should be considered or evaluated more fully in the ISA and REA, following the general approach outlined in the IRP.

References

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