

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

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Thank you for the opportunity to speak today on behalf of the American Petroleum Institute. Overall, the draft Integrated Review Plan (IRP; US EPA, 2014) presents a reasonable approach for conducting the sulfur dioxide (SO₂) reviews. However, there are several instances where the IRP should be more explicit regarding the analyses to be conducted in the forthcoming Integrated Science Assessment (ISA) and Health Risk and Exposure Assessment (REA).

First, the IRP states that the ISA will address the question of whether new information provides evidence of SO₂ effects at concentrations lower than those EPA identified previously (US EPA, 2008). If EPA conducts the ISA evaluation in this manner it will be biased; rather than evaluate the weight of evidence (WoE), it will only focus on whether the situation is worse than EPA previously thought.

In this vein, EPA needs to describe how it will determine when evidence calls a causal association into question. For example, it is often the case that evidence indicates a lack of causation to be as likely, or even more likely, than causation (*e.g.*, if confounders cannot be totally accounted for or if exposure misclassification causes false positive results). There is a tendency to conclude that because of the *possibility* for causation, the data supports causality. Instead, in this case, one should conclude that the evidence is non-informative.

Similarly, the IRP indicates that the ISA will include *in vitro* studies if they provide mechanistic insight into the *in vivo* results. The ISA should consider results from all relevant *in vitro* studies along with other lines of evidence, and it should determine whether the studies support or refute findings from epidemiology, controlled human exposure, or animal studies.

To accomplish this, the IRP should revise the NAAQS causal framework so that it more fully represents Bradford Hill's "aspects of association." As discussed in Goodman *et al.* (2013), EPA's application of the causal framework is not congruent with the judgments based on the original or modified Bradford Hill aspects. For example, the framework claims to rely heavily on the aspect of consistency across studies in its categorization scheme, but, in practice, it does not always fully evaluate consistency or incorporate aspects such as coherence, biological plausibility, biological gradient, and strength of association. Moreover, it is notable that the causal framework requires only one high-quality study for evidence of a causal relationship to be deemed suggestive. Using this definition, high-quality studies that are inconsistent with evidence of an association may exist but one high-quality study demonstrating an effect would still provide enough evidence to constitute a suggestive relationship. All studies should be reviewed using the same criteria and one should conclude a suggestive causal association exists *only* if the WoE indicates that a causal association is more likely than not, based on all the data combined. Because of this issue, we recommend eliminating the suggestive category, similar to the effect modifier ("at-risk" factor) framework.

The IRP should also indicate that the ISA will fully evaluate whether observed effects in controlled human exposure studies are caused by SO₂ or other factors. The ISA should consider that human lung function is highly variable, as evidenced by the appreciable differences in intra-human baseline lung function measures. Variability in baseline values can lead to large percentage changes post-exposure, even if the exposure had no effect. This calls into question whether perceived decrements in lung function in a few individuals at low SO₂ concentrations represent effects of SO₂ or are simply artifacts of human variability. Also, while it seems intuitive that severe asthmatics would be more susceptible to effects of SO₂ than the mild-to-moderate asthmatic participants in the controlled human exposure studies, the ISA should evaluate whether the limited data available to address this issue support that asthma severity and SO₂ responsiveness are closely related. The IRP should state that these uncertainties are important issues that the ISA needs to address.

Overall, the draft IRP presents a reasonable approach for conducting the SO₂ review; however, the issues I discussed and submitted in written comments must be addressed for the ISA to be balanced and unbiased.

References

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.

US EPA. 2008. "Integrated Science Assessment for Sulfur Oxides - Health Criteria." Office of Research and Development, EPA/600/R-08/047F. September.

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