Comments on the Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (Second External Review Draft)

Kirsten Zu, Ph.D., Sc.D., M.P.H.
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Thank you for the opportunity to speak today. My opinions are my own, but I received funding from the American Petroleum Institute to attend this meeting.

The second draft Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (ISA; US EPA, 2015) evaluated evidence from epidemiology, controlled human exposure, animal toxicity, and mode-of-action (MoA) studies of short- and long-term NO_2 exposures. It strengthened the causal determinations for several health effects compared to the 2008 ISA (US EPA, 2008). Over the next few minutes, I will discuss problems with the way that EPA applied its causal framework and assessed individual studies, the lack of consistency and coherence in the available data, and the uncertainties regarding the independent effects of NO_2, to show that the weight of the evidence does not support strengthening any causal determination.

With regard to the causal framework, I find that it does not provide enough guidance for studies to be evaluated in a systematic manner using well-specified criteria, and therefore, EPA's analyses cannot be replicated by other investigators. It also does not require a determination of whether, as a whole, the evidence more likely indicates causation or alternative hypotheses. In addition, the framework is not applied using a true weight-of-evidence (WoE) approach.

In the second draft ISA, EPA developed study quality criteria based on various methodological characteristics that can affect the validity of results. These characteristics are presented in Table 5-1 of the ISA. Although adding these criteria provides a major improvement over the first draft, the evaluation of study quality was not transparent. I prepared a table of epidemiology studies of short-term NO_2 exposure and hospital admissions (HAs) and emergency department (ED) visits for asthma, to demonstrate that EPA did not apply study quality criteria in a consistent and systematic manner (Table 1). This table includes, in each row, the 23 epidemiology studies cited in the ISA to support a causal association between short-term NO_2 exposure and asthma exacerbation. In each column is a study quality criterion that EPA defines in Table 5-1 of the ISA. If a study meets a criterion, the cell is shaded green; otherwise, the cell is shaded red. EPA considered the shaded studies to be of overall higher quality than the others. This table provides a systematic perspective on overall and comparative study quality. As you can see, the studies designated as "high quality" in the ISA do not appear to be of higher quality than others.

With respect to the interpretation of study findings in the ISA, in general, associations deemed to be causal (short-term NO_2 exposure and respiratory effects) and likely to be causal (long-term NO_2 exposure and respiratory effects) were close to null and more likely the result of chance, bias, and/or confounding. In some cases, associations between NO_2 exposure and health effects were not consistent either within or among epidemiology studies or were not coherent with controlled exposure studies. For several reported short-term health effects, associations were found at lag times that do not appear to be biologically plausible. For numerous endpoints, the MoAs were not established; in cases in which the ISA hypothesized a potential MoA, the MoA lacked biological plausibility.

As the ISA acknowledges, there is also uncertainty regarding whether some observed associations are attributable to NO_2 *per se* or whether NO_2 is a surrogate for another pollutant or pollutant mixture. For example, EPA primarily relied on longitudinal cohort studies of asthma development in children and concluded a likely causal relationship between long-term exposure to NO_2 and respiratory effects. However, most of the studies evaluated multiple traffic-related air pollutants, such as $PM_{2.5}$ and carbon black, and often found similar positive associations with asthma for these co-pollutants in single-pollutant analyses. None of the studies conducted multi-pollutant analyses, so there is considerable uncertainty with regard to potential confounding by traffic-related co-pollutants. Also, in several instances, the ISA cites the results of multi-pollutant models as evidence that traffic-related pollutants do not appear to confound associations between health and NO_2; however, in other instances, the ISA states that the results of multi-pollutant models are unreliable.

Overall, while I do not necessarily agree with each causal classification in the 2008 ISA (US EPA, 2008), I find that the current ISA does not provide evidence that the classifications should be strengthened for any of the endpoints reviewed because of considerable inconsistency and uncertainty in available evidence.

References

US EPA. 2015. "Integrated Science Assessment for Oxides of Nitrogen–Health Criteria (Second External Review Draft)." National Center for Environmental Assessment (NCEA), EPA/600/R-14/006. 1,135p., January.

US EPA. 2008. "Integrated Science Assessment for Oxides of Nitrogen." National Center for Environmental Assessment (NCEA) - RTP Division, EPA/600/R-08/071. 260p., July.

Table 1: Asthma HA/ED Visit Study Quality Characteristics

Citation	Study Design			Pollutant		Exposure Assessment			Outcome Assessment		Confounding by Co-pollutants			Other Confounders				Statistical Methods	
	Design	Single *vs.* Multi-city	Size/ Duration[1]	NO, NO_2, NO_x	Comparisons Between Oxides	Central Site Monitoring	Spatial Variability Assessed	Comparison of Exposure Assessment Methods	Type of Outcome	Exclusion of Children < 2 Years Old	Traffic-related Pollutants Assessed	Correlations Reported	Relative Measurement Error in Co-pollutants Discussed	Meteorology	Day of Week	Season	Allergens	Cautious Interpretation of Multi-pollutant Models	Sensitivity Analysis: Alternate Model Specification
Strickland *et al.* (2010)																			
Villeneuve *et al.* (2007)																			
Jalaludin *et al.* (2008)																			
Ito *et al.* (2007)																			
Iskandar *et al*. (2012)																			
ATSDR and NYSDOH (2006)																			
Stieb *et al.* (2009)																			
Samoli *et al.* (2011)																			
Peel *et al*. (2005)																			
Son *et al.* (2013)																			
Ko *et al.* (2007)																			
Sarnat et al. (2013b)																			
Orazzo *et al.* (2009)																			
Strickland *et al.* (2011)																			
Li *et al.* (2011)																			
Gass *et al.* (2014)																			
Winquist *et al.* (2014)																			
Burnett *et al.* (1999)																			
Linn *et al.* (2000)																			
Burra *et al.* (2009)																			
Sinclair *et al.* (2010)																			
Tolbert *et al.* (2000)																			
Jaffe *et al.* (2003)																			

Legend	
	Criterion Met
	Criterion Not Met
	Listed in ISA as a High Quality Study