

March 17, 2014

H. Christopher Frey, Ph.D.
Chairman
Clean Air Scientific Advisory Committee and Oxides of Nitrogen Review Panel
Science Advisory Board
US Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Clarifying Comments on the Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (First External Review Draft)

Dear Dr. Frey:

In my clarifying comments at the Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen Review Panel Public Meeting, I pointed out that there seemed to be agreement among CASAC members about the serious limitations of epidemiology studies (*e.g.*, exposure measurement error from central monitors, confounding by traffic-related pollution and other factors). The committee also discussed how data should be evaluated endpoint-by-endpoint in a systematic fashion, how all studies should not be weighted equally, and how inconsistent results should be considered. Yet, despite this excellent discussion, many committee members supported US EPA's causal classifications. This is likely because study quality and the weight of evidence (WoE) was not fully considered in a systematic fashion at the time that the committee evaluated the data as a whole. If these factors are more clearly defined in US EPA's causal framework, and shown endpoint-by-endpoint and study-by-study in tables, this would facilitate a balanced analysis based on the WoE.

I provided several tables at the CASAC meeting, which I am also attaching to this letter. It should be emphasized that the purpose of these tables is to present all the evidence as part of a systematic review, not simply to provide a summary of the data. Laying out all of the data in tables (as opposed to only discussing it in the text) can facilitate a WoE evaluation. Thus, an important part of the analysis method is deciding what to include in the tables. In this vein, a series of tables that each focus on a specific strand of the pertinent information is more useful than a single table with information from all studies. It is critical that tables be constructed in such a way that the data are abstracted the same way from each study. Having columns with a lot of information in each is likely to result in inconsistent reporting across studies. Study results should be laid out separately by outcome to ensure that all data on each endpoint are reported in a consistent manner, regardless of whether findings are positive or null.

In the hypothetical examples presented in the attachment, you will find separate tables for (1) basic information about the individual studies (different epidemiology study designs [*e.g.*, cohort *vs.* case-control] and experimental animal studies with different exposure routes and different types of toxicity have different features to consider when assessing quality, so it is often desirable to have separate tables for each study type); (2) the outcomes examined across studies;¹ (3) study quality; and (4) study results by outcome, with each outcome in its own table (or, alternatively, each outcome could be in a separate section of a larger table of related outcomes). Please note that the outcome table I provided does not

¹ This table might be redundant with one that shows not only what the studies evaluated, but also the results. Having only the latter would likely serve both purposes.

show study quality. However, study quality could be indicated by using arrows of different sizes, colors, or weights, for example. It may also be desirable to indicate statistical significance or clinical relevance.

Although there is no perfect way to tabulate data from a large number of studies with many differences among them, it is important to present all data (regardless of whether findings are positive or negative) in a way that facilitates assessment of the consistency and coherence of results and considers study strengths and limitations. This is best accomplished by providing focused tables in which the number of columns is maximized and the amount of information in each column is minimized. Compiling tables in this manner can facilitate a balanced, unbiased analysis of the WoE for hazard identification.

I also strongly urge the committee to review the following two papers before making recommendations to US EPA, as they provide details on WoE best practices and recommendations for systematic evaluation of evidence:

Rhomberg, 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):753-784.²

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):829-849.³

Thank you very much for your consideration.

Sincerely,

GRADIENT

Julie E. Goodman, Ph.D., DABT
Principal

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Attachments

² This article is available as an "eprint." Please use the link, <http://articleworks.cadmus.com/doc/1532194>, to download a program that will let you save a copy on one computer. You can then print hard copies, but you cannot save as a pdf.

³ Available here: <http://informahealthcare.com/eprint/p9enFgeQniJhxxUE5t4r/full>.

NOx ISA Clarifying Comments

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Causal Framework

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in Toxicology**

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REVIEW

A survey of frameworks for best practices in weight-of-evidence analyses

Lorenz R. Rhomberg¹, Julie E. Goodman¹, Lisa A. Bailey¹, Robyn L. Prueitt¹, Nancy B. Beck², Christopher Bevan³, Michael Honeycutt⁴, Norbert E. Kaminski⁵, Greg Paoli⁶, Lynn H. Pottenger⁷, Roberta W. Scherer⁸, Kimberly C. Wise², and Richard A. Becker²

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REVIEW ARTICLE

Evaluation of the causal framework used for setting National Ambient Air Quality Standards

Julie E. Goodman, Robyn L. Prueitt, Sonja N. Sax, Lisa A. Bailey, and Lorenz R. Rhomberg

Study Info Table

Reference, Location, Study size, Population, Age, Exposure info

Outcomes Examined Table

| | Hospital Admissions | ED Visits | Asthma Med. Use | <i>Etc.</i> |
|---------|---------------------|-----------|-----------------|-------------|
| Study 1 | | | | X |
| Study 2 | X | X | X | |
| Study 3 | X | | | |
| Study 4 | | X | | X |
| Study 5 | | | | X |

Study Quality

- Reference
- Study Design
- Potential for Selection Bias
- Study Size
- Exposure Measurement
- Outcome Assessment
- Statistical Modeling
 - Model type
 - Single pollutant models
 - Multi-pollutant
- Confounders/Effect Modifiers Adequately Considered
- Sensitivity Analysis
 - Yes/No
 - Multiple lag periods examined

Study Quality

| Reference | Study Design | Potential for Selection Bias | Study Size | Exposure Measurement | Outcome Assessment | Statistical Modeling | Control for Confounders | Sensitivity Analysis | Study Quality Rating |
|-----------|--------------|------------------------------|------------|----------------------|--------------------|----------------------|-------------------------|----------------------|----------------------|
| A | 1 | 1 | 1 | -1 | -1 | -1 | 1 | 1 | 2 |
| B | 1 | 1 | 1 | -1 | 1 | 1 | 1 | 1 | 6 |

Note: A table like this can allow one to divide studies into categories based on overall study quality.

Detailed Results

| Endpoint | Reference | Seasonal Analysis | Unit of Measure | Exposure Metric | Covariates | Lag Period (Days) | Result | 95% CI | p-value |
|----------|--------------|-------------------|----------------------------------|-----------------|-------------------|-------------------|--------|---------------|---------|
| A | Author, Year | NA | Change (mg/dL) per 1 SD (17 ppb) | 8-hr average | None | 0 | 1.5 | -2.6 to 5.6 | > 0.05 |
| | | | | | | 1 | 2.7 | -1.3 to 6.8 | > 0.05 |
| | | | | | | 2 | -3.2 | -6.2 to -1.1 | < 0.05 |
| | | | | | | 3 | -3.4 | -6.8 to 0.1 | > 0.05 |
| | Author, Year | Summer only | % change per IQR (NR) | 24-hr average | Men | 0 | 2.7 | -1.3 to 6.8 | NS |
| | | | | | Women | 0 | 2.7 | -1.3 to 6.8 | NS |
| B | Author, Year | NA | % change per IQR (12 ppb) | 2-hr average | None | 0 | -7.7 | -12.1 to -3.3 | < 0.01 |
| | | | | | PM _{2.5} | 0 | 2.7 | -1.3 to 6.8 | > 0.05 |
| | | | | | PM ₁₀ | 0 | -3.4 | -6.8 to 0.1 | > 0.05 |
| | | | | | NO ₂ | 0 | 2.7 | -1.3 to 6.8 | > 0.05 |
| | | | | 8-hr average | None | 0 | -8.7 | -16.1 to -1.3 | < 0.05 |
| | | | | | PM _{2.5} | 0 | -3.4 | -6.8 to 0.1 | > 0.05 |
| | | | | | PM ₁₀ | 0 | -3.4 | -6.8 to 0.1 | > 0.05 |
| | | | | | NO ₂ | 0 | -9.5 | -13.4 to -5.7 | < 0.05 |

Results Overview

| | HA | ED Visits | Asthma Med. Use | <i>Etc.</i> |
|---------|----|-----------|-----------------|-------------|
| Study 1 | | | | ↑ |
| Study 2 | ↓ | ↑ | ↓ | |
| Study 3 | ↓ | | | |
| Study 4 | | ↓ | | ↑ |
| Study 5 | | | | ↓ |

Note: Although this sample table does not show study quality, one could incorporate this by using arrows of different sizes, colors, or weights, for example. It may also be desirable to indicate statistical significance or clinical relevance on this type of table.