

05-29-15 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

**Preliminary Comments from Members of the CASAC Oxides of Nitrogen Review Panel on
EPA’s Integrated Science Assessment for Oxides of Nitrogen – Health Criteria
(Second External Review Draft – January 2015)**

Received as of 05-29-15

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Mr. George A. Allen

A key component of the new material in this review is the availability of early data from the new near-road monitoring network. For the near-road NO₂ data presented in this draft of the ISA, none of these sites show an exceedance of the NO₂ hourly NAAQS (e.g., any 1-hour average over 100 ppb). 98th percentile values of daily 1-hour NO₂ maximums are well below the 100 ppb NAAQS.

There is at least one long-term site that can be used to show trends of near-road NO₂. The Elizabeth Lab site at interchange 13 of the New Jersey Turnpike is not considered a near-road site by EPA's criteria; the NYC CBSA phase 1 near-road site is in Fort Lee, NJ. Although the Elizabeth Lab site does not technically meet EPA's siting criteria, it is representative of near-road NO₂ and has NO₂ data going back to 1980.

For context regarding the Elizabeth Lab site's value for looking at long-term near-road NO₂ trends, a significant inversion/stagnation NO₂ event occurred March 10, 2015 in the NYC metro area that resulted in exceedances (> 100 ppb NO₂ 1-hour average) at two sites. The Fort Lee near-road site did not have an exceedance during this event. A partial list of daily max NO₂ for this date at metro NYC sites follows.

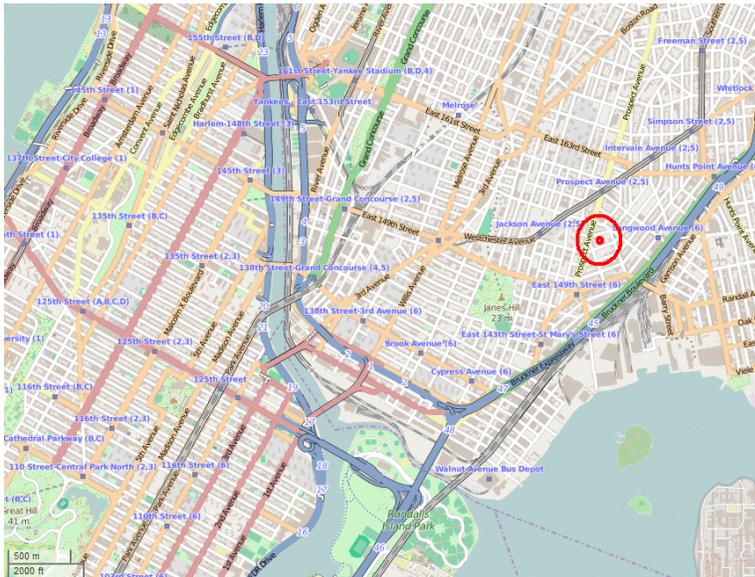
<u>Site</u>	<u>NO₂ (1-h max)</u>	<u>AQS ID</u>	<u>Notes</u>
Elizabeth Lab	137 (NO _x =618)	34-039-0004	also known as "Elizabeth Trailer"
NYC IS-52	122	36-005-0110	NATTS site
Jersey City	100	34-017-1002	not in AQS - urban canyon
Queens Coll. NYC	98	36-081-0124	NCore site
Ft. Lee NJ	81	34-003-0010	NYC phase 1 near-road site

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The Elizabeth Lab site location (circled):

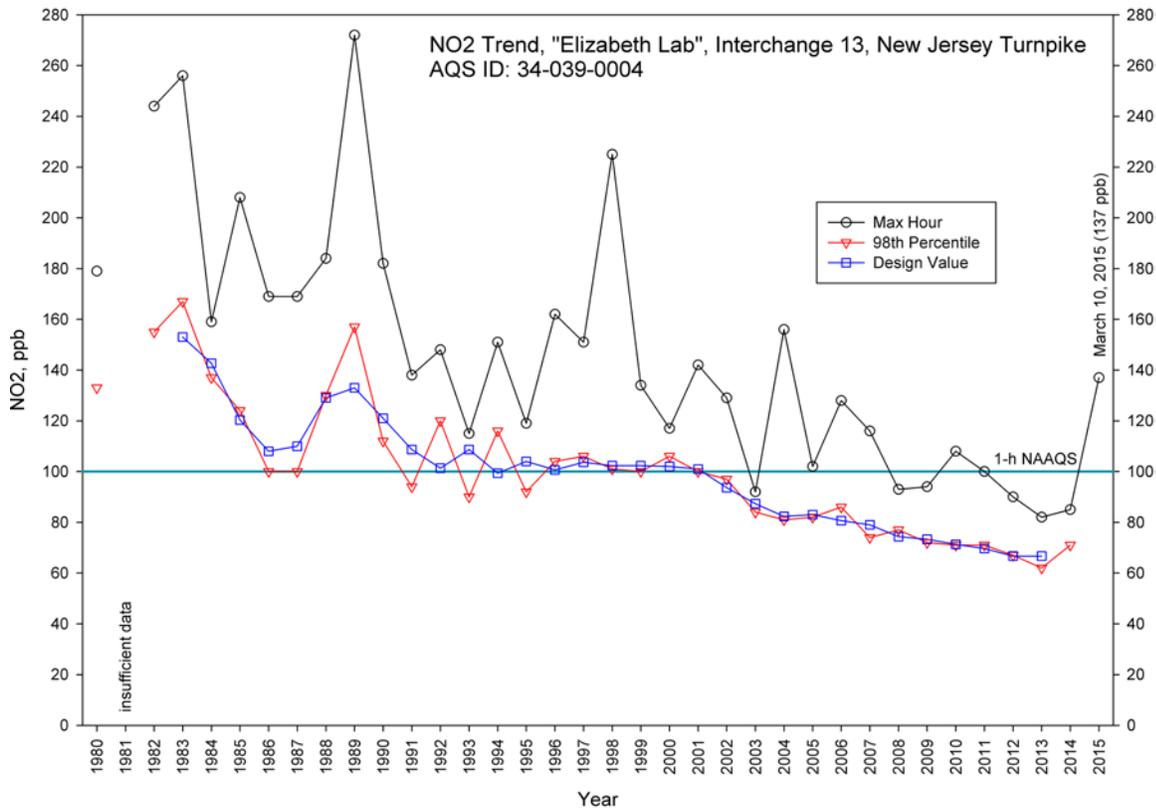


The 2nd site with an exceedance on this day is a neighborhood-scale site (681 Kelly St.) at a school in the Bronx, circled below, approximately 420 meters northwest of I-278/895, the Bruckner Expressway.



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The 34-year trend of hourly NO₂ for the Elizabeth Lab site provides valuable context for near-road NO₂ concentrations. I encourage EPA to include this site in their near-road analysis.



EPA/OAQPS released an update to the status of the near-road network build-out on May 20, 2015, posted on their Near-Road Monitoring web page at www.epa.gov/ttn/amtic/nearroad.html. This list of active sites includes meta-data about the sites and their target roads:

<http://www.epa.gov/ttn/amtic/files/nearroad/nearroadsites.xlsx>

54 Near-Road sites are now operational out of an expected 75 phase 1 and 2 NO₂ sites. Two Phase 3 sites are operational, for a total of 56 sites. 36 NO₂ sites were operational by July 1, 2014. For the final ISA, I encourage EPA to include as much of the near-road data as possible in their analysis.

Dr. Timothy Larson

Comments on the Executive Summary and Chapter 1

Communication to a non-technical audience

The Summary is generally well written and for the most part is understandable to an interested audience. Table ES-1 is an accurate summary of the ISA conclusions. Figure ES-1 is a good way to show the thinking on short term causality, although words such as “mast cell degranulation” and “epithelial barrier function” seem a bit too technical for a general audience.

The one section of the Summary that needs improvement is the “Summary of Major Findings”. Many of the bulleted summaries of the major findings are awkwardly worded and frequently combine several concepts into a single bullet. It is hard to follow. In addition, the sub-bullets on page 89 (starting on line 1) contain too much detail for a non-technical audience.

Linking of major exposure issues relevant to causality

In general, this is a good summary of the important issues as they relate to causality. A few issues still remain. In Section 1.4.2 the reader is left with the impression that there is potentially a lot of exposure estimate error for long-term exposure estimates that vary over space. Further perspective on this uncertainty in the context of key studies would be helpful, especially given that long-term respiratory effects are likely causal. Most of the important long term epi studies cited in Table 6-5 have exposure estimates that are based on measurements taken near subject locations. Given the relative similarity in the results across these studies, it would seem that this measurement error is not as large as it theoretically could have been. Any context here would be helpful.

In Section 1.4.3 the issue of confounding is discussed in sufficient detail to follow the logic. The key issue of confounding by traffic related pollutants is identified. The discussion of the weight of evidence for each causal determination is easy to follow.

Of concern to this reader is the “suggestive” classification for NO₂ and lung cancer. It could just as reasonably kept its original classification of “inadequate” given that diesel engine emissions are a major source of not only NO₂ but also other co-pollutants and that diesel exhaust is classified as a known human carcinogen by IARC . It would seem that for this outcome the confounding issue for diesel exhaust is greater than that for general traffic related pollutants. Most of the studies listed in Table ES-1 and 6-20 either did not assess confounding in this way, or found no association with NO₂ in the presence of other co-pollutants such as UFP or BC known to be present in diesel exhaust. The rationale for the “suggestive” category needs more

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clarification. If one good epidemiological study (one of the criteria for this category) points to lung cancer, it should be identified. It is not clear which one that would be. From studies cited in the text and Table, Villeneuve et al 2014 measured NO₂, benzene, hydrocarbons but did not assess confounding by diesel exhaust. Raaschou-Nielsen 2010,2011 used a traffic marker NO_x, not NO₂. Jerret et al 2013 refers to NO₂ as a marker of traffic. Amigou et al 2011 looked at leukemia and used proximity metrics and traffic volume surrogates for exposure assessment, but did not measure NO₂ nor base their exposures on contemporaneous monitoring data; rather, they used a 4km² smoothed spatial map to estimate background NO₂. Hystad refers to NO₂ as a traffic exposure indicator. Both Nyberg et al and

Nafstad et al used a traffic emissions model as input to a dispersion model validated with measurements of NO₂ to predict NO₂ at subject locations, but these same model predictions could also represent other traffic pollutants.

Specific Comments:

- P84 line 21 EC/BC, metals, or UFP are not obvious: one should not have to refer to the glossary
- P85 line 1 this wording implies that results from controlled human exposures of other traffic related pollutants were also summarized and considered. But that is not true. Improve the wording for clarification.
- P87 line 13 should “pattern” be “temporal pattern” ?
- P89 line 16 not true: some studies report null effect of BC
- P104 line 2 which studies of importance to long term effects as listed in Table 6-5 assessed the independent effects of residential proximity to roads? Asthma exacerbation or pulmonary function? It is certainly not the case for asthma incidence (p110, line 25). Needs clarification.
- P109 line 19 few epidemiological findings..
- P101 line 34 define “spatial misalignment” more specifically, presumably with subject locations vs LUR based monitoring sites
- P122, Table 1-1 the link to Tables 6-1 and 6-5 indicates that the confounding potential of traffic related pollutants in some of these studies is seemingly higher than others. The Vancouver cohort has much lower co-pollutant correlations than those from Gehring et al 2010. The summary statement in Table 6-5 is somewhat misleading in that regard. In the same Table 6-5, why do the findings of Shima et al 2002 have higher potential for exposure measurement error than the other studies? In that study, children went to school near both their home and their assigned monitor.

Comments on Chapter 3 – Exposure to Oxides of Nitrogen Measurements and Models

Page 3-4 line 30: Ross et al did not sample at all 150 sites simultaneously, only up to 25 in a given two week period. See also Allen et al Environ Res 2009 109(3), 334-342 for another extensive NO₂ passive sampling campaign.

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Page 3-10 line 33: The model of Lindstrom et al 2013 is fundamentally different from that of Wilton et al. They are not directly comparable. Lindstrom predicted two week average measurements spatiotemporal framework that included static covariates and added the inherently spatiotemporal dispersion model as a separate term. Therefore the model even without the dispersion predictions captures some temporal variability. Wilton simply added the dispersion model prediction as an additional covariate in the standard multi-linear LUR regression model so that the other covariates did not capture any temporal variability.

Page 3-11 line 21: Lindstrom's model (Lindstrom et al, 2013) should be discussed in either the Spatiotemporal Interpolation Model section or the Hybrid Models. It is a different category of model than the others discussed here. In addition to terms for the deterministic model predictions, it includes temporal basis functions that are combined with the static spatial covariates.

Page 3-18 line 29: OSPM predictions were compared with 2-week average NO₂ concentrations at > 200 sites at different times in 2006 in New York City with relatively low R² =0.28 (Jensen et al Atmospheric Environment 43(2009) 4544-4556).

Page 3-19 Line 13 This discussion refers to hybrid dispersion models, not to be confused with other hybrid models that combine deterministic models with measurements. It might help to clarify this distinction in this entire section of the document. Maybe some number of subsections would help in this regard.

Connections between exposure assessment method and study design:

Table 3-1 is an important summary of the connection between a particular exposure assessment method and epidemiologic study designs. Below are specific comments regarding this important table.

- The table implies that the passive monitor method does not suffer from decreased correlation with distance from the monitor. Perhaps the Application column could be more specific, e.g., "short-term panel" could clarify a maximum spatial range of subject locations based on Figure 3-4.
- In this document, more weight is given to studies with measurements taken at subject residences than taken at central sites, but it is not clear if "short term panel" is referring to just personal sampling or also fixed site sampling at residences.
- The accompanying text also discusses the potential for exposure error if the passive samples are averaged over a week or more, even though this time scale is defined as "short-term".
- Are there examples of the CTM alone or the CTM-based Hybrid Method that show improved predictions of NO₂ with smaller scale CTM grid resolution? The Table implies

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this, but it is not clear if any of the cited studies actually show this. Perhaps the wording in the Table needs revision.

- The difference between the dispersion modeling and CTM methods needs to be clarified in the Table. Perhaps including “(e.g. Gaussian plume modeling)”
- The conclusions summarized in Table 3-1 regarding exposure errors should be clearly stated in the different subsections of 3.4.3.

Implications of exposure error for epidemiological studies

Community Time Series Study

The relevant literature addressing exposure error in time series studies by spatiotemporal interaction is discussed in detail. Table 3-13 summarizes the important results of Goldman et al (2012) who examined this issue in Atlanta. The text refers on line 11 on page 313 to a large negative exposure measurement bias of the area weighted average, but it must be referring to NO_x not NO₂. The latter has a small negative bias according to the Table, a presumably important result given that the exposures are assigned to the total population. The original reference additionally cautions that there are relatively few monitors for a given pollutant (5 for NO₂), and that these tend to be located in more heavily populated areas (three of them).

The study by Butland (2013) looked at modeled urban background NO₂ versus measured NO₂. The UK monitoring network emphasizes near-road monitors compared to the U.S. emphasis on monitors located further from the roadway. Thus the exposure assignment error is qualitatively different in this study than in the U.S. studies.

The interpretation by EPA of the study results from Dionisio et al 2014 regarding the bias introduced by variable indoor depositional loss seems reasonable but it was not discussed explicitly by the authors. Another factor that can decrease the correlation with outdoor monitors is the differences in sunlight and thus the NO₂/NO_x ratio indoors versus outdoors.

Longitudinal Cohort Studies

The Szpiro and Paciorek (2013) paper seems important to this discussion of bias in chronic health effects studies. It would be useful to provide some context for those cases that are biased toward the null vs those that are biased away from the null. Specifically please clarify how their insights apply to long-term average NO₂?

Page 321, Line 17: This conclusion is important but it is stated awkwardly. Suggest eliminating the clause “...,such that the average total personal NO₂ exposure would necessarily be equal to or greater than the average personal exposure to ambient NO₂, ..” for clarity.

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Panel Studies

Page 322 Line 21 This concluding sentence needs further clarification. I interpret this statement as referring to the variation in the NO_y concentrations (as well as the NO_y/NO_z ratios) across the urban area. Is this correct?

Confounding by Co-Pollutants and Noise

The discussion of potential confounding has been extensively improved from the last draft. It is an important part of the information relevant to the causality argument.

The Panel studies based on personal exposure measurements or outdoor residential measurements do not appear to have co-pollutant confounding, especially for subjects living far from busy roads. This result is not mentioned in the final summary paragraph on page 325. Given the extensive analysis of this issue in the main body of this Chapter, it deserves some concluding statement.

Dr. Jeremy Sarnat

General Comments

The Second External Draft of the NO_x ISA is a coherent, extensive, and well-written report on the state-of-the-science regarding NO_x health effects. EPA staff involved in preparing this draft deserve considerable credit for their clear responsiveness to the previous comments from the Review Panel and the public. The changes, both in structure and substance, are evident in the current version. The Second Draft ISA is transparent in addressing limitations, uncertainties, and methods used to inform causal determination.

There is notable, added attention in the current draft to issues of confounding and the assessment of NO₂ independent effects in both Chapters 3 and 5, which was lacking in the previous draft.

Chapter 1

- The strongest basis for causal determination in the association between short-term exposure and respiratory response are the few, controlled exposure studies involving airway responsiveness at environmentally realistic levels. These studies should, therefore, be presented first in this chapter, as they are in Chapter 5, as the rationale for proposing to strengthen causal determination status, rather than the additional results from observational studies which include NO₂ co-pollutants in multivariate model settings (See P1-17 through 1-19).
- While not specifically relevant for NO_x, I question the designation of concentrations within two orders of magnitude from peak observed levels as being ‘ambient relevant’. Even for controlled designs, studies of 5,000 ppb of NO₂, seem exceedingly high and not relevant to any realistic exposure scenario (Figure 3-1 on P3-22, clearly shows this). Even a one order of magnitude benchmark is high. Again, most of the science within this ISA involves concentrations/exposures far below the two orders of magnitude cutoff, but I think this ambient-relevant designation is worth reconsidering; especially as we move towards identifying potential risks associated with very low pollutants levels, including exposures well below the current NAAQS.

Chapter 3

- *Response to charge questions:* The Second Draft does a thorough job of summarizing and, more importantly, contextualizing NO_x exposure science within broader discussions of health effects (Section 3.4), appropriate study design (e.g., Section 3.4.5), and

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measurement error and its implications (Section 3.4.3). The current structure of the NO_x ISA represents a pronounced improvement over previous drafts.

- There is a critical assertion made within this chapter and repeated throughout the ISA, regarding observed correlation patterns between NO₂ and its copollutants, and their implications for assessing potential confounding. Specifically, instances of weak correlation between NO₂ and its copollutants, especially within indoor environments and as personal exposures, are presented as opportunities to disaggregate potential independent NO₂ effects. As stated in the Second Draft:
 - “[l]ow correlations between ambient NO₂ and personal measures of copollutants could support inferences regarding the independent effects of NO₂.” (P3-79)

For me, two main questions exist concerning observed weak correlations between indoor/personal NO₂ and its copollutants, including CO, UFP, EC, and VOCs.

- The first question is whether or not they are indeed real. As noted in the ISA, citing work by Meng et al. (2012) (P5-31), measurements of indoor and personal NO₂ [and here I would also include many of its copollutants] are frequently below detection and quantitated with increased analytical uncertainty, resulting in attenuated strengths of correlation between these non-ambient measurements and corresponding ambient NO₂ concentrations. For some of the studies reporting weak correlations, I suspect what we see are truly ‘Type II-like’ findings and that actual correlations between NO₂ and its copollutants, especially those from traffic sources, are likely stronger.
- A second question is whether appropriate correlation pairs are being examined. The Draft states that,
 - *“These observations [of weak correlations between personal NO₂ and its copollutants] provide further evidence that nonambient sources of NO₂ provide noise to the ambient NO₂ signal. At the same time, the weaker correlations between total personal NO₂ exposures and copollutant exposures indicate that for panel studies of total NO₂ exposure, ambient copollutants would be unlikely to confound health effect estimates for NO₂ exposure.” (P3-78).*

To me, the greatest source of uncertainty regarding causal inference is the specific role of NO₂ within a broader mixture of primary traffic emissions. To examine NO₂ as a potential marker for this mixture, therefore, then correlations should focus on associations between *Ca from traffic sources* and *Ea from traffic sources*. Since none of the exposure or measurement studies included within this ISA, even those where personal NO₂ exposures were conducted, are able to resolve source attribution on this level, this issue remains unanswered and central for defining the role of NO₂ in epidemiologic models, as either a contributing causal agent among a multiplicity of agents or a confounder (i.e., a non-causal surrogate of a true causal agent or mixture).

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- Given the role of oxidative stress as a mediator of NO₂-related acute response, it would be useful to include a discussion of pollutant oxidative potential (OP) (i.e., its ability to generate reactive oxygen species), relative to its other copollutants. Clarifying NO₂ OP, particularly on a per mass basis, might be especially helpful addressing the plausibility of NO₂ independent effects at ambient-relevant levels.
- P3-20. Rate ratios from APEX models estimating associations between NO_x and asthma ED were significant, but not significantly higher than corresponding rate ratios from models using alternative exposure assignment approaches.
- P3-56. In the Goldman et al (2010) paper, the authors report that, “instrument precision error increased with increasing concentration.” It should be stressed that this trend is not consistent for all methods for measuring NO_x or NO₂. Methods based on passive diffusion, for example, typically have greater precision error at low concentrations. This is relevant for the discussion of NO₂ correlation and potential confounding.
- P3-83, Line 18. To be clear, differences between health effect estimates from models using C instead of E is not technically a form of epidemiologic bias. (A more accurate discussion of this concept can be found on P3-87, Lines 27 – 35.)

Chapter 5

- Much like Chapter 3, the revised chapter on health effects is much improved compared to the First Draft and is clearly responsive to the Panel’s previous comments and discussions. I especially appreciate the careful attention given to the issue of potential copollutant confounding and the role of NO₂ within a traffic mixture, and am comfortable with most of the interpretations and conclusions made within this chapter (and within this ISA Draft, in general). The comments below mainly focus on one area of disagreement in my interpretation of the results and conclusion in the current Draft, relating to the recommendation to change the causal determination status of the association between short-term exposure and respiratory response.
- In general, much is made in the Second Draft of the consistency and coherence between the observational and controlled human studies for short-term exposure to NO₂ and respiratory response. Fundamentally, I still believe there are meaningful questions concerning the role of NO₂ as an indicator of a traffic pollution mixture. Although controlled exposure studies demonstrate the biological plausibility of independent, clinically-relevant NO₂ effects at stages along an asthma exacerbation pathway, I am not convinced of its primary and independent role in driving the corresponding responses in the real-world, observational findings. Based on this lingering uncertainty, I struggle with whether these epidemiologic

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findings provide convincing evidence of NO₂ independent effects that sufficiently ‘*rule out chance, confounding, and other biases with reasonable confidence.*’

There seems to be some dissonance between conclusions in Chapter 3 and 5 regarding the potential for confounding of NO₂ independent effects. Throughout Chapter 5, short-term exposures to NO₂ are shown to be associated with respiratory morbidity ‘alone and in combination with other pollutants’ (P5-97). Chapter 3, however, seems clear in suggesting that it may be difficult to separate NO₂ exposures from general exposure to traffic pollution and corresponding health response:

“Section 3.4.4 concludes that NO₂ concentration generally correlates spatially with other traffic- related pollutants in urban areas... With respect to exposure, these observations make it hard to distinguish NO₂ from other pollutants when considering the health impacts potentially attributable to each.” (P3-25)

“As a surrogate for traffic-related exposure, NO₂ concentration may do an adequate job of capturing spatial and temporal trends of traffic pollution.” (P3-25).

“For traffic, NO (reacting to NO₂), CO, EC, UFP, and benzene are commonly coemitted and can be highly correlated with NO₂ in time and space.” (P3-97).

Uncertainty on this question is also related to statistical or modelling limitations. The main approach used in epidemiology and within the ISA to assess confounding, namely to model pollutants together within a co-pollutant or multivariate setting, is rightly acknowledged within the ISA to be lacking (P5-11, Line 20). Co-pollutant models are based on numerous assumptions, including linear associations among the independent terms, non-differential measurement errors among the copollutants, and other distributional assumptions that seem unlikely in most of the models conducted.

Taken together, the findings seem to point to the inability of observational designs, even those with excellent exposure assessment components, to conclusively disaggregate whether NO₂ is serving as a confounder or a marker of a source-specific mixture. Given these uncertainties, I feel that the degree of coherence among study designs examining short-term NO₂ exposure and respiratory response is overstated, and the existing determination status between short-term exposures and acute respiratory response, namely that NO_x are likely to be causally associated with acute response, appears to be a more accurate summary of the science.

- P5-77. An example of a finding from a panel study that includes NO₂ and traffic-related VOCs that contradicts the interpretation of independent NO₂ effects is Greenwald et al. (2012). This paper showed that the outdoor and indoor BTEX VOCs were predictive of both increased pulmonary inflammation and decrements in lung function in a pediatric asthma

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cohort, where outdoor or indoor NO₂ concentrations were not significantly associated with either endpoint.

- The Second Draft presents limited results from alternative modeling approaches, in an attempt to consider whether NO₂ is acting multiplicatively, within a mixture, in eliciting acute respiratory response. Examples of these approaches are those in Gast et al. (2014), who used a C&RT approach and Winquist et al. (2014), who used a broad joint effects approach. The interpretation of finding from these studies is generally fair, although I'm not sure if either really strengthens inferences regarding NO₂ independent effects. Given the degree of concordance between the single-pollutant and joint effects models, for example, I would interpret the Winquist et al. (2014) paper as indicating NO₂ as a surrogate of a traffic pollutant mixture.

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Dr. Ronald Wyzga

Charge Questions 1-3:

By and large these sections reflect the overall policy of the Agency and the content of the remaining Chapters. In several areas a little more detail or clarification would be helpful. See my detailed comments below.

Detailed comments on Preface and Chapter 1.

p. xlvii: ll. 17-19: Information on mechanisms can aid in the interpretation of these results.

ll. 29-33: It should be pointed out that there are generally fewer degrees of freedom on cross-sectional study, which makes consideration of an extensive set of confounders difficult

p. lii: Table 1 - Consistency: I'm not sure what is meant by the sentence: "Elevated risks are not defined by statistical significance." This sentence need be clarified.

Strength of the observed association: "may or may not"

p. liii: ll. 6-12: but statistical significance is nevertheless informative and should be indicated.

l. 33: insert "can" before represent.

p. lv: Table II - Causal relationship: Is two orders of magnitude too high? Some discussion would be welcome.

p. lix, l. 4: or a different threshold.

p. lxi, ll. 5-9: The ATS definition also has a statement about the concurrent occurrence of symptoms. This discussion need be modified.

l. 15: change would to could.

The bottom line is that there is no clear definition of what is adverse. It reflects considerable judgment.

p. lvi, l. 30: is two too high? Discussion please.

p. lxxvii, ll. 16-21: It should be clarified that many emissions are of NO which converts to NO₂. This can impact the gradient with respect to difference from roadside emissions.

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p. lxxix, ll. 20-33: This issue is complicated by the simultaneous presence of confounding by other pollutants. This need be discussed.

l. 38: The other traffic-related pollutants should be indicated.

p. lxx, ll. 14-19: Averaging time need be stated. Also some mention of current levels would also be helpful here.

p. lxxxiii: figure ES-1: should “asthma attack” be replaced by “asthmatic response”?

p. lxxxvii, ll. 4-7: Error can also change the shape of the dose-response function.

p. 1-01, ll. 15-33: I urge the Agency to present any available results from the near-road network. Results for the contemporary US would be particularly valuable.

p. 1-11, ll. 19-30: It would be worth mentioning that indoor sources of NO_x can be important and influence personal exposures.

p. 1-12: The potential emissions of NO and their conversion to NO₂ should be mentioned as influencing the results.

p. 1-13, l. 16: Are these correlations for personal or for ambient measures?

p. 1-18, ll. 14-20: The most important co-pollutants to consider should be highlighted.

p. 1-23, ll. 12-17: See above comment.

p. 1-37, ll. 27-29: The high correlation between 1-h max and 24-hr ave Nos should be noted.

p. 1-41, l. 8: may or may not; on-road exposures, if high, could not be reflected in these averages.

ll. 31-38: The correlations between NO₂ and co-pollutants may differ by concentration level (and place of measurement).

p. 1-44, l. 10: How does EPA interpret this definition?

ll. 12-17: I believe the ATS definition also mentions the co-occurrence of symptoms. This should be stated.

Comments on Chapter 2

Charge Questions 1-3: I would urge the Agency to present all available on-road measurements that are currently available. These data should then be contrasted with the data from London.

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Detailed comments:

p. 2-71, Figure 2-21: Given the concerns about long-term effects, including cancer, it would be important to have some indication of trends in NO₂ levels from 1975. Any information about these trends should be included.

Comments on Chapter 3

Charge questions 1-2: I appreciate the detailed information presented here, and I compliment the Agency for its organization of this extensive material. There should be greater discussion about the implications of the relatively weak correlations between ambient and personal NO₂ measures. The differences by season would be highlighted and revisited again when the epidemiology results are presented.

Detailed comments:

p. 3-25, l. 34: When the on-road measurements become available this should be updated.

p. 3-26, Figure 3-2: what is the difference between VOCD1 and VOC2?

p. 3-31, Table 3-3: Define what is meant by Reference Site and by Regulatory Site? Should the reference be Matte et al or Ross et al (2013)?

p. 3-47, Table 3-5: The Personal-Ambient Slope for Sahsuvaroglu results are strange. Why is the total so much more highly correlated than the temporal subsets.

p. 3-49, Table 3-6: clarify the difference between outdoor and ambient monitors?

p. 3-50, ll. 2-7: This has serious implications for epidemiology studies.

p. 3-52, Table 3-7: The averaging time is not clear. Ideally results should be presented for both hourly and annual concentrations given that the NAAQS utilize these averaging times.

p. 3-83, l. 32: Is there a sign missing for NO_x?

p. 3-84, ll. 19-22: but if the correlation between ambient and personal measures of NO₂ is very low, we have a greater problem than measurement error.

p. 3-85, ll. 8-11: See above comment.

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Comments on Chapters 5 and 6

Charge Questions:

1. The organization is helpful. My concern is that greater weight should be given to analyses that considered relevant co-pollutants and studies that considered personal (and possibly indoor) exposures. The text need to explain why such studies need to be emphasized; it also tends to ignore the relatively low correlations between personal and ambient exposures presented in Chapter 3. Chapter 5 does not to my mind adequately summarize the results from human clinical studies. The results are often poorly summarized; moreover emphasis should be given to those studies with exposures near contemporary ambient levels. There should be greater integration of results from clinical studies with alternative definitions of “adverse” or “clinically significance”.
2. I need to carefully read the Brown (2015) paper before commenting. By and large the document does a good job of summarizing and presenting the results.
3. I believe that Chapters 5 and 6 need to do a better job in utilizing exposure information presented in Chapter 3. Ambient-personal correlations are generally small – so small that exposure misclassification is likely of greater importance than exposure error. There should be some discussion of this issue in the Chapter. I believe that this small correlation, as well as seasonal differences in this association, are not adequately addressed in the conclusions.
4. The co-pollutant issue is certainly well-addressed with two exceptions. There needs to be more emphasis given to studies that consider this issue. This is not always the case. Also, clearer distinction must be made between the more relevant co-pollutants of concern and those of lessor concern. Seasonal differences could also play a role here.
5. The rationale are reasonably laid out. I think the discreteness of categories bothers me. So often we see the terms “limited” and “inconsistent”. These generally translate into “suggestive” because the only alternative appears to be “inadequate”. I frankly would like to see a category between these two because so many of the endpoints considered fall in between these two. I am particularly troubled by the carcinogenicity classification.

Detailed Comments:

Section 5.2.2.1, p. 5-15: how important is the dose of the challenge type? I frankly don't know, but some discussion of this would be helpful.

p. 5-23, Table 5-3, Tiedl et al 2012: is this results protective?

p. 5-34, l. 8: How was “clinically relevant” determined?

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p. 5-41, ll. 15-36: A recapitulation of time averages would be helpful.

Section 5.2.2.2.: There should be some discussion of what is considered adverse or clinically relevant as was presented in the previous section.

p. 5-47, Figure 5-3: the dose level should be included here.

p. 5-57, ll. 1-3: This finding is of concern and raises a red flag.

l. 10: delete the word “strong”

ll. 26-28: given the weak associations between personal and ambient monitors this result is not surprising.

p. 5-61, Table 5-10: Where are the results for these studies?

p. 5-59, Table 5-12: Spita-Cohem et al. The odds ratios are not statistically significant, but it is reported that the personal EC measurements were associated; was this association statistically significant?

p. 5-70, Table 5-12: Delfino et al (2003): Were the co-pollutant results statistically significant?

p. 5-75: Several of the results represented here are not statistically significant. This should be explicitly indicated.

p. 5-78, l. 4: “consistency” alone is misleading. “Some consistency” would be better.

p. 5-79, Table 5-13: Present results.

p. 5-87, l. 12: “positive” but not statistically significant.

ll. 19-22: but these are not the correct co-pollutants

p. 5-92, l 11: Were they statistically significant?

Section on Seasonal Differences; Note that the correlation between personal and ambient measures also differ by season.

P. 5-93, ll. 24-34: It should be noted that measurement error will also affect the shape of the dose-response curve.

p. 5-99, ll. 9-12: See above comment.

p. 5-103, Experimental Studies: This section should also discuss alternative measures/definitions of adversity.

p. 5-108: More attention should be given to studies with exposures near the current NNAQS.

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p. 5-110, Table 5-19: Were any measures of personal exposure available for any of these studies?

p. 5-14, Table 5-20: Delfino et al (20206) are NO₂ results in models with co-pollutants statistically significant?

p. 5-123, ll. 24: Here is where there should be some discussion of adversity or clinical relevance.

pp. 5-164-165: I would like to see results presented when they were considered with co-pollutants as well.

p. 5-239, line 6; delete "several"

p. 5-250: I would like to see the argument give emphasis to those studies that considered relevant co-pollutants and to those studies that made use of personal and indoor measurements of NO₂. Among human clinical studies and panel studies, I would like to see emphasis to those with exposures near ambient levels.

p. 5-303, l. 12: a result is or is not statistically significant.

p. 5-304: ll. 14-15: given this disparity can we make any inference from the results?

p. 5-305: Table 5-5: Was there any consideration of co-pollutants?"

p. 5-313, ll. 5-15: can we say anything about the clinical significance of these results?

p. 5-234, l. 15 and l. 19: Are these results statistically significant?

p. 5-328: Table 5-58: I would like to see the argument give emphasis to those studies that considered relevant co-pollutants and to those studies that made use of personal and indoor measurements of NO₂. Among human clinical studies and panel studies, I would like to see emphasis to those with exposures near ambient levels. Statistical significance should also be indicated,

p. 5-338, Table 5-60: %Increase should indicate per 20ppb increment.

P. 5-343, Table 5-62: These are not the most relevant co-pollutants.

p. 6-7, Table 6-1: Please indicate results with co-pollutants.

p. 6-18, Figure 6-2: what is meant by soot? PM_{2.5}, EC, BC?

p. 6-46, Table 6-4: Please indicate results with co-pollutants.

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p. 6-155, l. 9: statistically significant?

p. 6-173, Table 6-18: what exposure metric is the correct one? It would be useful here to see how NO₂ levels have changed since 1975. See my comments for Chapter 2.

p. 6-192. Table 6-20: I am particularly concerned by this table. Given the long latency for cancer, the reported NO₂ or NO_x concentrations are probably irrelevant. Long term trends of NO₂ are needed. See my comments for Chapter 2. In addition, ambient NO₂ is associated with known carcinogens (e.g., benzo(a)pyrene); the concentrations and associations were likely much greater 20-30 years ago. Given the lack of information mentioned above, I am troubled by the “suggestive” label.