Preliminary Comments from Members of the CASAC Oxides of Nitrogen Review Panel on EPA's Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft – September 2016)

Received as of 11-04-16

Mr. George Allen 2
Dr. Judith C. Chow 3
Dr. Douglas W. Dockery 7
Dr. Philip M. Fine 11
Dr. Jack Harkema 13
Dr. Timothy Larson 15
Dr. Jeremy Sarnat 19
Dr. Richard Schlesinger 22
Dr. Ronald Wyzga 24

Mr. George Allen

Chapter 2: NO2 Air Quality

General comments

This chapter appropriately summarizes chemistry and emissions, monitoring, and trends for NO2, with a focus on the new near-road NO2 network. In terms of monitoring data, the relatively new near-road network plays a key role in assessing exposures to NO2 at the upper end of the ambient concentration range, as summarized in section 2.3.2. As always, data summaries in the final version of this document should reflect the most recently available monitoring data.

Other comments

Most of the text on page 2-2, section 2.1.2 (Emissions) is also in footnote 31 on the next page. Thus footnote 31 should be removed.

Figures 2-7, 8, and 9 are difficult to read. The dark background should be removed, and the size of the figures made larger.

Chapter 5: Preliminary Conclusions on the adequacy of the current primary NO2 standards

This chapter clearly explains the rationale behind staff's conclusion that the current primary NO2 standards do not need to be revised. The introduction's explanation of the Clean Air Act's (and court's) requirements regarding setting a primary NAAQS is well written.

I agree with EPA's decision not to conduct a "more complex NO2 exposure and risk assessment" in this review, as noted in footnote 114 on page 5-12 given the limited newly available information for NO2 health effects. Ambient exposures from fixed site monitors (both area and near-road) would require a roll-up (not roll-back) at nearly all monitoring sites to reflect potential health risks from just meeting the current standards. This chapter's focus on using data from the near-road monitors (page 5-12, lines 12-15) is appropriate.

I agree with staff's conclusions regarding the adequacy of all elements (level and form) of the current primary NO2 NAAQS, and to retain them in this review (page 5-15, lines 1-3).

Section 5.4 appropriately summarizes key uncertainties and areas for future research.

Dr. Judith C. Chow

Chapter 2 – NO_2 Air Quality:

1. To what extent does the Panel find this information to provide useful context for the review and to be clearly presented?

Chapter 2 adequately documents NO_2 chemistry, emissions sources, and air quality trends. However, there are inconsistencies across the various chapters. Clarification is needed for the following subcategories:

2.1.1 Atmospheric Chemistry

The complexity of NO_2 pathways based on its relationship with NO and O_3 seems to be oversimplified. The term "total oxides of nitrogen", NO_y, was briefly noted in Section 1.3 (Lines 22-23, Page 1-9) and defined in Footnote 16 (Page 1-10). As non-NO_2 oxidized nitrogen can be an important interferent for NO_2 measurement, a schematic diagram (see Chart 1 below) like Figure 2-1 from the NO_x ISA (Page 2-3, U.S. EPA, 2016) might be included to illustrate the reactive and oxidized nitrogen compounds.

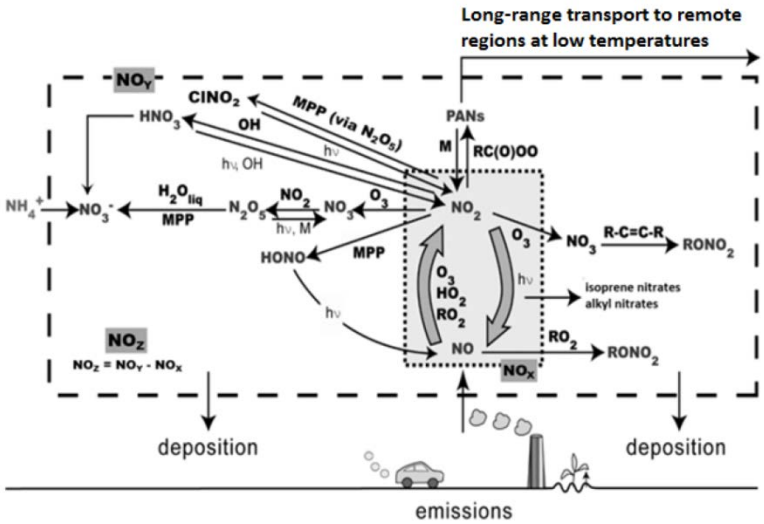

Figure 2-1, Schematic diagram of the cycle of reactive, oxidized nitrogen species in the atmosphere
Source: National Center for Environmental Assessment.

Chart 1- Diagram illustrating nitrogen species reaction pathways (U.S. EPA, 2016)

2.1.2 Emissions

Figure 2-1 (Page 2-3) shows decreasing trends in NO_x emissions as a result of multiple regulatory programs. It would be informative to provide the calendar year that each regulatory program was implemented. A chronological timeline denoting the types of regulatory programs may also be helpful to demonstrate the effectiveness of emission control measures.
The shape of Figure 2-1 differs from those shown in the 2016 NO_x ISA (Figure 2-2, Page 2-9; see Chart 2 below for comparison). As emissions are expressed in different units (i.e., 'thousands of short tons' versus 'millions of tons'), cross comparison is difficult. It is important to denote that tons of NO_x are expressed as equivalent NO_2 (assuming that is the case). Why were the largest NO_x emissions reduction found during the 2005 – 2010 period? In addition, the sharp reduction from 2000 – 2001 found in Chart 2b is not found in Chart 2a.

2a.) Draft NO_2 PA:

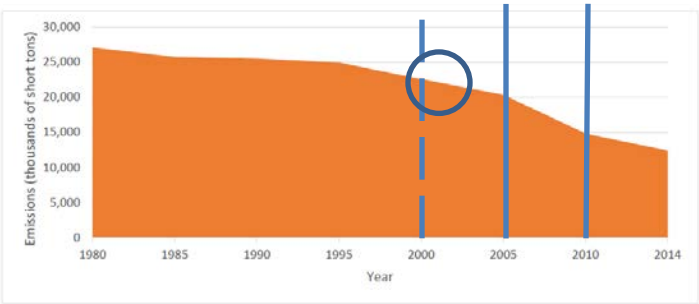

Figure 2-1 U.S. national average NO_X emissions from 1980 to 2014.
Source**:** http://www.epa.gov/air-emissions-inventories/air-pollutant-emissions-trends-data

2b.) NO_x ISA:

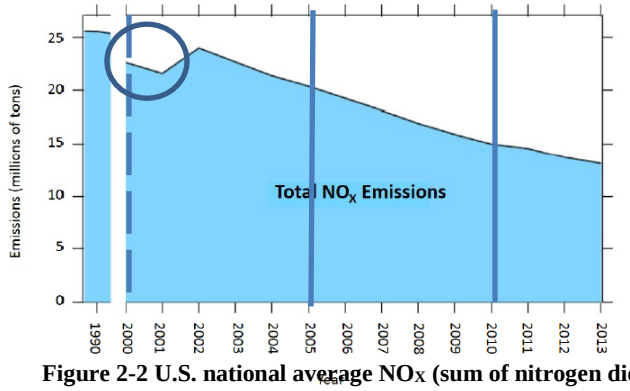

Figure 2-2 U.S. national average NO_X (sum of nitrogen dioxide and nitric oxide) emissions from 1990 to 2013.
Source: National Center for Environmental Assessment 2014 analysis of 2011 National Emissions Inventory data

Chart 2- Comparison of NO_x emission trends for: a.) 2016 draft NO_2 PA and b.) 2016 NO_x ISA

2.2.1 NO_2 Methods

Although measurement methods for NO_2 were documented in Section 2.4 of the NO_x ISA (U.S. EPA, 2016), the potential positive and negative interferences for the chemiluminescence-based FRM, such as presence of other nitrogen species (e.g., nitric acid and peroxyacetyle nitrate [PAN]), conversion efficiencies, and duration of the measurement cycles should be acknowledged as measurement uncertainties that may result in exposure errors. The statement (Lines 18-20, Page 5-4) in Section 5.1 under Evidence-Based Considerations, that "…the degree to which monitored NO_2 reflects actual NO_2 levels, as opposed to NO_2 plus other gaseous oxides of nitrogen, can vary (Section 2.2)," is incorrect as this issue was not addressed in Section 2.2.

2.2.2 NO_x Ambient Monitoring Network

A. Number of NO_2 Sites

The number of monitoring sites needs to be clarified. Section 2.2.2 notes that as of 2015, ~462 NO_2 monitors were in operation and reporting to AQS (Line 2, Page 2-5) with the addition of 65 near-road monitors. These numbers are much lower than the 2,099 NO_2 sites across the continental US (Line 3, Page 2-10) as well as the 647/433 monitors used to determine annual/hourly design values, respectively. The number of sites shown in Figures 2-5 and 2-6 (Pages 2-13 and 2-14) seem high. Added together it represents over 1,500 sites, far more than the 647 and 433 sites used to determine design values.

B. Site Zone of Representations

Most compliance monitoring sites (i.e., central site) represent urban-scale (4 - 50 km), whereas near-road monitors characterize a micro-scale (<100 m) zone of representation. However, Section 2.2.2 (Lines 16-17, Page 2-6) says that: "At the time of the last review of the primary NO_2 NAAQS, the majority of NO_2 monitors were sited to represent the neighborhood scale". However, the 2016 NO_x ISA (U.S. EPA, 2016) shows that the ~500 NO_2 sites include SLAMS, NCORE, CASTNET, and SEARCH network. These are primarily urban- and regional-scale sites, not neighborhood-scale sites (Section 2.4.5, Page 2-34, U.S. EPA, 2016).

Section 1.4.1 (Lines 14-18, Page 1-11) noted that "area-wide" monitors intend to characterize the highest expected NO_2 concentrations at the neighborhood- and large spatial-scales. Although near-road monitors may capture some elevated NO_2 peaks, the highest NO_2 concentrations may be higher in street canyons during traffic congestion and while vehicle engines are idling. The criteria to select sites with highest expected NO_2 concentrations should be documented.

As EPA has proposed to rescind the third phase of near-road monitoring for core-based statistical areas (CBSAs) with populations ranging from 500,000 to 1,000,000 (Footnote 35 on Page 2-7), it is wise to locate NO_2 monitors to areas with potentially high NO_2 concentrations to address

human exposure. The statement (Lines 24-26, Page 4-17) in Section 4.2.1 (Updated Analyses Comparing NO_2 Air Quality with Health-Based Benchmarks) that "…we anticipate that the near-road NO_2 monitoring network, with monitors sited from 2 to 50 m away from heavily trafficked roads, effectively captures the types of locations around roads where the highest NO_2 concentrations can occur", needs to be verified with additional spatial monitoring in street canyons.

2.3.2 Near-Road NO_2 Air Quality

Distributions of daily maximum 1-hour near-road and non-road NO_2 concentrations for 2015 in Figure 2-9 (Page 2-18) show relatively low NO_2 concentrations (e.g., ~35 ppb, 98th percentile) at the Atlanta-Sandy Springs-Roswell, GA, site. This does not reflect the statement (Footnote 109, Page 5-8) that "…we note that 1-hour NO_2 concentrations in 2015 in Atlanta were higher than concentrations at all of the non-near-road monitors in the area (Figure 2-9)". Table B2-7 in Appendix B (Page B2-24) attributes this to the design value (DV) adjustment factors (AFs), noting that "Preliminary results show on-road estimation (2015) unusually higher than expected, likely a function of the DV-based AFs". Which site does this refer to? Figure B5-1 of Appendix B (Page B5-13) shows that the area design value monitor was close to the near-road monitors in the Atlanta study area. Other examples may be more appropriate than those in Figure 2-9.

Appendix A

While Appendix A provided historical design values for the selected epidemiologic studies, no perspective was given on the study outcome and Appendix A is not cited in the text.

References

U.S. EPA, 2016. Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, North Carolina. EPA/600/R-15/068

Dr. Douglas W. Dockery

3. CONSIDERATION OF EVIDENCE FOR NO2-RELATED HEALTH EFFECTS

3.2 Effects of Short-Term NO2 Exposures

To what extent does the evidence indicate adverse respiratory effects attributable to short-term exposures to NO2 concentrations lower than previously identified or that would be allowed by the current standards?

The shift to a "causal relationship" for asthma exacerbation produced by short-term NO2 exposure is driven by evidence from controlled human exposure studies. These studies were almost all done earlier, and were considered in the previous review. However, meta-analyses of these studies, and specifically the Brown (2015) meta-analysis is central to this chance in causal determination.

Given the influence of the Brown (2015) meta-analysis, it is interesting to compare these results to the earlier meta-analysis by Goodman et al (2009) of the same studies. Both meta-analyses reported effectively the same fraction of subjects with NO2-induced increased airway responsiveness (see table below) for All Exposures and also separating by Exposure During Exercise and Exposure At Rest. Both found this fraction to be significantly increased for All Exposures and for Exposures At Rest, but not for Exposures During Exercise.

	All Exposures	During Exercise	At Rest
Brown (2015) *Table 5*	0.59 (P<0.001)	0.53 (n.s.)	0.67 (P<0.001)
Goodman (2009) *Table 3*	0.58 (0.52,0.63)	0.52 (0.43,0.60)	0.64 (0.58,0.71)

Likewise both meta-analyses found no evidence of an exposure-response in airway responsiveness with increasing NO2 exposures.

The Goodman et al (2009) meta-analysis further examined the quantitative measures of airway responsiveness, that is the provocative dose of a challenge agent necessary to cause a specified change in lung function (PD), and the change in FEV1 after an airway challenge. While these

combined changes were statistically significant and consistent with an adverse effect of NO2 among these asthmatic subjects, Goodman and colleagues concluded the average magnitude of AR changes was too small to be clinically significant. However, they did not examine the fraction of the asthmatic subjects experiencing a clinically significant change.

On the other hand, the Brown (2015) meta-analysis examined the fraction of the asthmatic subjects who experienced a doubling of provocative dose following short-term NO2 exposure. The use of this doubling measure is consistent with ATS and ERS statements of clinically significant AR changes. Statistically significant increased fractions were found in the Brown meta-analyses although only for non-specific challenge. AR changes were minimal for NO2 exposure during exercise.

The controlled exposure studies of asthmatic subjects provide evidence for a specific effect of NO2, which is not confounded by other traffic related air pollutants. However, the lack of an exposure response, and the restriction to effects only at rest with non-specific challenges diminishes confidence that this is a causal association.

The evidence from epidemiologic studies of the associations of short term NO2 exposures with asthma admissions and emergency room visits is suggestive but also not compelling. As noted, there is the issue of potential confounding with traffic related co-pollutants. In addition, there is inconsistency in the cited studies from the United States and Canada. The argument is made (page 3-24) that ”asthma-related ED visits are not consistently or strongly associated with NO2 concentrations in locations that could have met the current standard.” My interpretation of Figure 3-1 is that studies in such cities are positive but imprecise. I would not hang my hat on the lack of statistical significance in these studies to defend the current standard. On the other hand the multi-city Canadian study by Stieb et al (2009) was clearly null, even though two cities (Ottawa and Edmonton) had elevated maximum and mean hourly DVs . It is unfortunate that Stieb and colleagues do not present city specific associations for NO2 and asthma similar to those for NO2 and angina/myocardial infarction as in their Figure 1, reproduced below.

It is interesting that Stieb et al (2009) found that cardiovascular ED visits were most strongly (and most statistically) associated with NO2 and CO in their multicity study. This study was very informative in changing the cardiovascular finding from “inadequate” to “suggestive”.

Overall, the Policy Assessment makes a cogent case for the causal determination regarding short-term NO2 exposures.

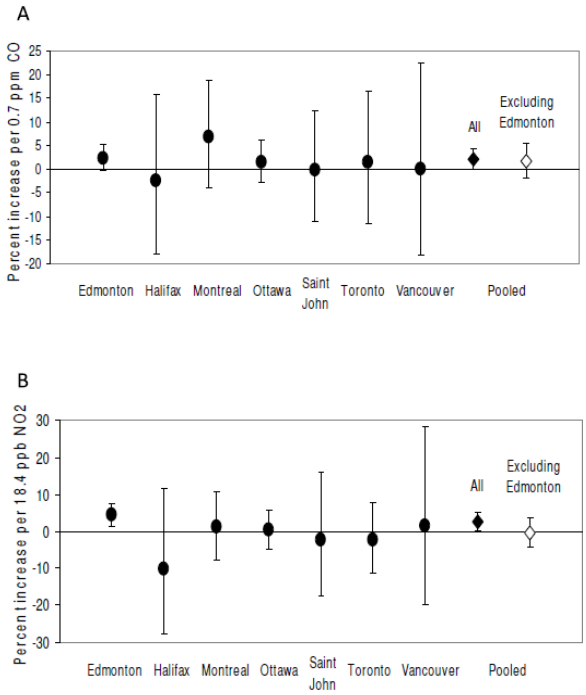

Figure 1
Percent increase in emergency department visits for angina/myocardial infarction by center. (Point estimates and 95% confidence intervals are shown, for CO (panel A) and NO2 (panel B)).

3.3 EFFECTS OF LONG-TERM NO2 EXPOSURES

To what extent does the currently available scientific evidence alter or strengthen our conclusions from the last review regarding health effects attributable to long-term NO2 exposures? Have previously identified uncertainties been reduced? What important uncertainties remain and have new uncertainties been identified?

In this review, there has been a general shift in the causal determination for the effects of long-term NO2 exposures from "inadequate" to "suggestive" (*Cardiovascular and Diabetes, Total Mortality, Birth Outcomes, and Cancer*) or from "suggestive" to "likely" (*Respiratory*). In large part, these changes in causal determination reflect new epidemiologic evidence since the last review. In particular, there have been a substantial number of new epidemiologic studies using improved exposure methods (such as incorporating LUR) to estimate individual exposures and participants residences. These studies are providing much stronger evidence of health effects with long term estimated exposures to traffic-related (or roadway related) air pollutants such as NO2. However, these studies have limited ability to separate the specific effects of NO2 from other traffic related co-pollutants. Thus, while the evidence base is stronger, without supporting

evidence from experimental studies, the most appropriate causal characterization is "suggestive". The only health effect with such supporting experimental evidence is Respiratory (specifically the development of asthma or reactive airways disease), where the designation of "likely" is appropriate.

3.4 POTENTIAL PUBLIC HEALTH IMPLICATIONS

To what extent does the currently available scientific evidence expand our understanding of populations and/or lifestages that may be at greater risk for NO2-related health effects?

The ISA and this document present a cogent and compelling argument that children and the elderly are at increased risk for health effects from short and long term NO2 exposures. One might add those living in proximity to heavily trafficked roadways.

In addition, the ISA and this document argue that people with asthma are at increased risk of exacerbation of their condition from short-term NO2 exposures. It follows that people with COPD, the 3rd leading cause of death in the US, may also be at increased risk. COPD includes chronic bronchitis which has a prevalence of about 6% in those 65+ years, and emphysema which also has a prevalence of about 6% in this older age group. In addition, the "suggestive" evidence of cardiovascular effects for short and long term NO2 exposures, suggest that those with chronic cardiovascular conditions and the elderly may be a particular at risk population. The elderly are the fastest growing age-group in the population and have highest prevalence of these chronic respiratory and cardiovascular conditions. Consideration of the elderly as a special at-risk group for cardiovascular effects is warranted.

Dr. Philip M. Fine

Chapter 2 – NO2 Air Quality

To what extent does the Panel find this information to provide useful context for the review and to be clearly presented

A description of the NOx emission sources, atmospheric chemistry, and ambient data trends provides critical context for the review. Chapter 2 generally provides this information succinctly and clearly, with the Appendices providing additional details. However, the chapter could be improved by the addition of some additional information and some other changes for clarity and consistency. These are provided below

Page 2-1, line 30. It is stated that "…the highest concentrations do not always occur immediately adjacent to those sources." It is unclear if this statement refers to the concentrations as measured by the existing monitoring network, or in general based on where highest concentrations would be expected. It is also unclear as to the spatial scale being referred to (locally, state-wide, nationally). One would generally expect higher NO2 near sources, as any time needed for conversion from NO to NO2 would be overwhelmed by atmospheric dispersion, and studies have demonstrated this. Even at larger scales, in areas with high regional NO2, higher levels would still be expected near sources in that area. Stationary sources with tall stacks may be an exception, but that is not the argument being made here. This statement should be clarified and cite references if, in fact, higher levels of NO2 occur away from sources relative to adjacent to sources.

Page 2-2, line 6. The statement that the timing of ozone availability to convert NO to NO2 leads to higher near-road NO2 in the early morning hours conflicts with the previous statements that peak ozone concentrations occur in the late morning to early evenings. The lack of atmospheric mixing and direct NO2 emissions from morning commute traffic are likely the primary factors, and not ozone chemistry as suggested.

Page 2-2, lines 11-27. This paragraph provides data on national NOx emissions from various categories of sources, and also described what these categories include. The categories correspond to the categories in Figure 2-2. But without a reference to Figure 2-2, or a statement that "the NEI divides sources into various categories as follows", it is awkward for the reader to understand why these distinctions are being made into esoteric category names. Furthermore, most of the paragraph is repeated verbatim in footnote 31 on the next page. Suggested improvements include a reference to Figure 2-2 early in the paragraph to inform the reader why these categories are being described (i.e. to clarify the figure), put the information in the foot note or the text, but not both, or described more clearly the purpose of the categories and the

paragraph itself. In addition, it would be helpful in Figure 2-2 and/or in the text to mention the contribution to NOx of diesel vs. gasoline powered vehicles, given the policy relevance of that information.

Page 2-9, Figure 2-3. It may be illustrative to include an indication of the current standard levels on both charts with a horizontal line. It might also be interesting to include the maximum and minimum design values for each year nationally, showing whether and by how much the highest site in the nation attains or does not attain.

Page 2-10, lines 4-11. The criterion for including a site in this analysis is at least 5 valid DV over the period 1980 – 2015. It seems like that in comparing trends at sites to one another, it would make a big difference whether the site had valid design values between 1980 and 1984, 1980 and 2015, or 2011 and 2015. For example, for the 3.9% and 1.8% of sites that trending upward for annual and hourly DVs respectively, was that a 5 year trend in the 1980s, in the last five years, or was it a 35 year trend upward? Perhaps the criterion could be reconsidered to provide a more consistent long-term comparison.

Page 2-13, Figure 2-5. The figure effectively conveys the general relationship between NO2 DVs and distance from road. However, pooling the data from 1980 through 2015 does not recognize the effects of a shifting national monitoring network. Including more near-road monitors in the later years, when NO2 levels are generally lower across all sites, will bias the (0,50) bin low relative to other distance bins that include data over a 35 year period. Figure 2-6, which presents the relationship by decade, better accounts for the effects of this long term trend. The need for Figure 2-5 should be reconsidered given that Figure 2-6 presents the same information while minimizing any biases from temporal trends.

Page 2-19, line 18. The sentence would be clearer with the following addition: "these data indicate that 1-hour DVs **near 100 ppb** correspond to annual DVs of about 35 ppb or below."

Chapter 5 – Preliminary Conclusions on Adequacy of the Current Primary NO2 Standards

Given that staff's summaries and preliminary conclusions in this chapter are based on the information presented in Chapters 2 through 4, I will defer potential individual comments on Chapter 5 until after the Panel discussion on the previous chapters.

Dr. Jack Harkema

Comments on Chapter 1 – Introduction

Chapter 1 provides introductory information including a summary of the legislative requirements for the NAAQS, an overview of the history of the NO_2 NAAQS and the decisions made in the last review, and a summary of the scope and approach for the current review.

To what extent does the Panel find this information to provide useful context for the review and to be clearly presented?

This chapter is well crafted in terms of format and content. In the *Background* section, the authors have provided a thorough and necessary history of the previous NO_2 NAAQS Reviews (1.2.2) and the substantive basis of the Administrator's previous policy decisions. This importantly sets the stage for the current review process described in the rest of the chapter.

Most importantly, the authors have nicely explained the background (including evidence-based considerations, risk and exposure assessments) regarding the addition of the 1-hour NO_2 standard and the continuation of the annual NO_2 standard in 2010.

The information in Table 1-1 is certainly important and clearly presented in this section (1-5), but why is it entitled Primary national ambient air quality standards *for oxides of nitrogen* rather than . . . .*for nitrogen dioxide*? Throughout the rest of the document (and in the document title) NO_2 is used as the indicator that has been adequately described and defended in the text.

The scope and approach for the current review are also well presented in this chapter. Most importantly the four basic elements of the NAAQS (indicator, averaging time, level and form) are clearly explained concerning their use in the last review and the current review process.

<u>Minor Comments/Questions</u>

p. 1-16, line 1. Delete ". . . more serious . . . "and replace with ". . . important . . ."

p. 1-17, line 31. A brief description of the form for the annual standard should be added to the end of this paragraph.

p. 1-18, lines 16-19. The key policy-relevant questions should be concisely stated in the text or the reader should be referred to Figure 1-1.

p. 1-19, lines 3-6, and Figure 1-1. I would suggest that this paragraph and figure be moved to the beginning of 1.4.2, rather than ending this section.

Comments on the Executive Summary

In general, the *Executive Summary* is clearly and concisely written with an appropriate format and informative content highlighting the key information and recommendations more completely described in the remainder of the document.

Comments and Questions

p. ES-1, line 24. Change to read ". . . the staff's preliminary conclusion that it is appropriate to retain the current primary NO2 standards, without revision , . . . This paragraph needs to clearly and concisely stated along with a brief statement on what this conclusion was based. The paragraph on p. ES-6, lines 19-23, better states the staff's conclusions and preliminary recommendations.

p. ES-2, line 20 and 21. How many near-road monitors still need to be placed into operation? - 65 monitors represent what percentage of the goal?

p. ES-5, line 5. What does "asthma incidence" actually refer to – development (new onset) and/or asthma exacerbation?

p. ES-5, lines 11 and 12. Are there actual data on repeated short-term NO_2 exposures that indicate the development of asthma (experimental or epidemiologic)? Or is this sentence referring to repeated exposures to other gaseous air pollutants (e.g., ozone).

p. ES-5, line 27. In regards to asthma development, does "long-term exposures" also include repeated short-term NO_2 exposures as stated previously on lines 11 and 12?

Dr. Timothy Larson

Chapter 1

To what extent does the Panel find this information to provide useful context for the review and to be clearly presented?

This chapter is clearly written and provides context for the document as a whole. Figure 1-1 is a useful summary of the overall approach for reviewing the Primary NO_2 standard. The history of the rationale for reaching the previous decision on the existing standard is helpful, including the following important conclusions by EPA at that time:

1. NO_2 is the indicator species for oxides of nitrogen.
2. Reducing NO_2 will also reduce exposures to other oxides of nitrogen.
3. Short-term exposures (minutes to hours) to NO_2 leads to respiratory morbidity.
4. Effects associated with long-term exposures to NO_2 are suggestive but not sufficient to infer a causal relationship.
5. A 1-hour averaging time could also be effective at protecting against effects associated with 24-hour NO_2 exposures.
6. The existing annual standard should be retained to protect against effects potentially associated with long-term exposures.
7. Evidence from controlled human exposure studies supports the conclusion that short-term exposures at or above 100 ppbv increases airway responsiveness for some asthmatics, especially those with more serious asthma.
8. The 3-year average of the 98th percentile provides an appropriate balance between limiting peak concentrations and reducing the potential for instability in the higher percentiles.
9. Protecting against maximum 1-hr NO_2 concentrations anywhere in an area with a given level at or near 100 ppbv and a 98th percentile form would be expected to limit area-wide NO_2 concentrations to below those levels at locations where epidemiologic studies report associations with respiratory-related hospital admissions or emergency department visits.
10. A 1-hour standard with a level lower than 100 ppbv would *only* result in further public health protection if there is a continuum of serious adverse effects caused by short-term exposure to NO_2 concentrations below 100 ppb, and/or if area-wide NO_2 concentrations are well below those in locations where key epidemiologic studies have reported associations with respiratory-related hospital admissions or emergency department visits.

The chapter also identifies areas of uncertainty at that time, as follows:

1. The role of NO_2 in complex ambient mixtures including a range of co-occurring pollutants

2. The extent to which monitored NO_2 concentrations used in epidemiological studies reflect true exposures in study populations
3. The magnitude and potential adversity of NO_2- induced respiratory effects in controlled human exposure studies
4. The relationship between near-road NO_2 spatial gradients and their relationship to broader ambient monitoring concentrations

This history of the rationale for setting the existing standard, including identified uncertainties, provides an excellent introduction to the conclusions arrived at in subsequent chapters.

Chapter 4

What are the Panel's views on staff's conclusions regarding support for new or updated quantitative analyses?

Figure 4-2 clearly summarizes the rationale for doing updated quantitative analysis. There is substantially more near-road air quality monitoring data than there was a few years ago. These measurements substantially reduce the uncertainties associated with estimating the near-road exposures to NO_2.

What are the Panel's views on the technical approach taken to conduct updated analyses comparing NO2 air quality to health-based benchmarks?

EPA has made a reasonable choice in looking both at the number of exceedances of the unadjusted data as well as the level of exceedance of the adjusted data. Reliance on either one alone weakens the overall conclusion that there are not any days with levels much above the current standard. In my view, the adjusted data overstate the problem because the proportionality assumption may not strictly hold.

The two-step approach used to adjust the NO2 concentration distributions to simulate just meeting the current standards is an improvement over the previous single-step approach. This two-step approach recognizes that the extreme values above the 98th percentile have a different distribution than those below this percentile. It is an improvement over the single-step approach used in the 2008 REA. I agree that there is relatively little data at these higher levels, and as such, the approach in section 2.4.1 in Appendix B is reasonable. 'as is"

One key to the simulation is the proportionality assumption discussed in Section 2.4.1 in Appendix B. The results shown in Figure B2-9 show that this assumption is justified for all values (0 to 100th percentile) based on the results shown in Figure B2-9. Given that all monitors are currently in compliance with the current standard, EPA intends to make such an assumption with existing data only up to the 98th percentile. It would be nice to see a few examples such as

those shown in Figure B2-9 for other locations to further support the proportionality assumption. The data in Figure B2-9 were from an area-wide monitor in Chester, N.J. located relatively far from NYC. Do other area-wide monitors located in more built up areas exhibit this proportionality up to the 98th percentile? Do near-road monitors also show this proportionality (there are a handful of near-road sites whose data was considered in the previous review and whose NO2 concentrations have decreased in recent years). If so, it would strengthen the proportionality argument.

The reference to Rizzo (2008) in Figure B2-9 is not included at the end of the section.

To what extent does the draft PA accurately and clearly communicate the results of these analyses?

The concentration adjustment procedures are relatively complicated. The pooling of hourly data over 3 years vs. the year to year comparisons gets a bit confusing. It might help to provide a figure that shows the procedure for a simple example of a few sites over a few years of data. The relationship between different sites and different years might be better appreciated.

The example shown in Figure B2-10 for Philadelphia raises as many questions as it answers. Why is it that the adjusted concentration distribution has 98th percentile values that exceed the current standard? I assume that this monitor is not the design monitor. That fact that its 'as is' distribution adjusted upwards will exceed the current standard, but that it currently is not the design monitor, i.e., the highest monitor in the area currently seems odd. It would be good to test the proportionality assumption at this monitor to check that its distribution has not changed over time. It might actually strengthen the argument that, in fact, the proportionality assumption can be a 'worst case' assumption in areas where the distributions at design monitors are actually less variable than at other sites.

In any case, as described in Table B2-7, the issues associated with estimating adjustment ratios in the Philadelphia example seems more complex than at other locations described in this same table. Perhaps a more straightforward example, such as Boston, could also be shown.

What are the Panel's views on staff's interpretation of these results for the purpose of evaluating the adequacy of the current standards?

I am limiting my remarks at the moment to the exposure assessments. The summary on page 4-14 is a reasonable interpretation of these results. I agree with the following important points about the uncertainties associated with these assessments:

1. This is a hypothetical scenario and not a projection of future air quality trends
2. If ambient NO_2 concentrations were to increase to the point of just meeting the existing 1-hour standard, the resulting air quality patterns may not be similar to those estimated using these adjustment methods.

3. The inclusion of additional years of near-road monitoring information in the determination of updated air quality adjustments could result in fewer estimated 1-hour NO2 concentrations at or above benchmarks in some study areas.
4. The near-road monitoring network effectively captures the types of locations around roads where the highest NO2 concentrations can occur.
5. There is almost no potential for 1-hour exposures to NO2 concentrations above the benchmarks, even at the lowest benchmark of 100 ppbv.
6. Compared to the on/near road simulations in the last review, there is substantially less potential for 1-hour exposures to near-road values above the benchmarks

The issue of potential confounding in the assessment of long-term studies of asthma incidence (c.f. Table 4-3) is important. However, the following statement in Table 4-3 seems a bit too general: "If an NO_2 risk assessment were conducted based on studies of long-term NO_2, there would be particular uncertainty regarding the extent to which NO_2 risk estimates reflect the magnitude of NO_2 health impacts rather than the health impacts of traffic related pollutants as a whole". One can imagine studies using personal monitors where these correlations could be broken. One could also imagine a study design that chooses a study population to maximize the spatial variation in the relative concentrations of the co-pollutants of interest, thereby minimizing the confounding.

Dr. Jeremy Sarnat

Chapter 4

What are the Panel's views on staff's conclusions regarding support for new or updated quantitative analyses?

- I feel the recommendation against conducting additional, extensive model- or epidemiology-based risk analyses based is largely justified based on two primary considerations: 1) As demonstrated in the benchmark air quality estimates, present-day NO_2 ambient concentrations are historically low; well below any current empiric health-based benchmarks of response. Moreover, in many US locales, nitrogen oxide and NO_2 levels continue to decline – with little evidence that reverse trends are likely in the future; and 2) observational studies have still have not been able to adequately disaggregate NO_2 independent effects and/or cumulative effects associated with exposures to pollutant mixtures. I feel these uncertainties would substantially inhibit our ability to properly interpret output from the quantitative analyses. Given both these considerations, conducting additional extensive quantitative analyses seem to be of limited benefit, at this time.

- I am curious about the decision not to conduct limited, model-based analyses similar to what was done for the 2008 ISA, as a form of sensitivity analysis. Basing the benchmark on controlled short-term-AR associations, which serve as the primary driver of causal determination in the present ISA, is appropriate. The numerous population- and panel-based epidemiologic studies recently published and included in the present ISA draft do, however, provide plausible support for causal association between short-term NO_2 and other health endpoints (e.g., emergency department visits, lung function decrements, pulmonary inflammation). I agree with staff that the epidemiologic evidence is equivocal, yet conducting a health-based benchmark analysis with at least one of these other endpoints, at a benchmark that would presumably be < 100 ppb, would be informative.

What are the Panel's views on the technical approach taken to conduct updated analyses comparing NO_2 air quality to health-based benchmarks?

- The technical approach for the health-based benchmark analysis is mostly consistent with the approach used for the 2008 PA and seems reasonable here, too. Inclusion of data from the roadside monitoring network in the current benchmark assessment represents a real improvement over previous air quality estimates. While these data are still limited and not sufficient for generating formal DV's, the roadside levels do contribute to our understanding of declining NO_2 levels and trends at locations expected to be 'hotspots'.

- I may have missed this, but were the roadway measurements also spatially adjusted based on the proximity of the monitoring to the source?

- It is possible that daily commuters comprise a potentially vulnerable sub-population based upon their repeated exposures to elevated primary traffic pollution. I appreciate the (brief) discussion of on-road exposures and acknowledge the uncertainties involved in estimated on-road NO_2 using upward adjustment factors (Appendix B2.4.2). I was, however, moderately surprised that the factors listed in Appendix B, from Kimbrough (2013), were so low. (Parenthetically, at the time of this review, neither the Richmond-Bryant et al. nor the Kimbrough (2016) were published or readily available). Although still few in number, there have been studies measuring in-vehicle NO_2 and it could be useful to consider a range of adjustment factors along with those presented in Appendix B from the Las Vegas location (Riediker et al., 2003, for one example that quickly comes to mind). There is also a potential to use on-road primary emission factors as input parameters for estimating in-vehicle exposures.

  Perhaps a semi-quantitative discussion of the potential exposures among commuters could serve to underscore the potential vulnerability of commuters as well as uncertainties in what we currently know about on-road exposures? This discussion could include the number of Americans commuters that experience high NO_x/NO_2 conditions daily; how variable these exposures are likely to be; how this affects the overall benchmark estimates. Additionally, the Panel, in previous comments on the REA, raised questions regarding the use of exposure models (e.g., APEX) for estimates of population exposure. Could targeted estimates of commuters' exposures be generated using this type of modeled analysis as a straightforward means of discussing incremental exposure and risk from exposure to on-road concentrations?

To what extent does the draft PA accurately and clearly communicate the results of these analyses? What are the Panel's views on staff's interpretation of these results for the purpose of evaluating the adequacy of the current standards?

- I think the draft PA generally does a good job of highlighting areas of uncertainty in conducting the revised benchmark analysis and the other quantitative analyses. These uncertainties, and their impact on interpretation of analysis results, are a key factor in not conducting additional quantitative analyses. I also agree that this decision is well-aligned with the EPA staff recommendation of not proposing a new standard. It is worth stressing, however, that this recommendation does not preclude the likelihood that quantitative health risk analyses be conducted in future revisions of the NO_2 NAAQS and this should be stated, clearly, in the PA. Many of the uncertainties which currently limit the utility of these analyses could, for example, be resolved with additional research.

Chapter 5

General comment on Section 5.3: EPA staff have done an admirable job compiling, summarizing, and presenting the evidence and existing uncertainties of NO_2 health effects and the adequacy of the current NAAQS. Based on the current scientific evidence outlined in the ISA, REA, and draft PA, I support the staff recommendation to retain the current NO_2 standard in both level and form.

Dr. Richard Schlesinger

Overall this is a well written document that generally clearly summarizes the key issues related to NO2 exposure and public health. While there is evidence that NO2 does result in some biological effects at some level, the conclusion that the current standards are protective is well supported. The only comment in this regard is that it is not clearly noted from sections 3.41-3.44 whether or not these groups are also expected to b protected by the current standard since they are highlighted as sensitive. This should be made clearer.

p.3.2, line 6. Change "ventilation rates" to "ventilation conditions."

p. 3-2, line 13. Move the fragment, "…are not subject to uncertainties related to inter-species variation" to line 4 after "…and human health effects."

p.3-2, line 15. Change "…particularly the biological action of a pollutant" to "including mechanism of action"

p.3-3. line 22. It is noted herein that in the PA, the focus is only on potential at risk populations and lifestyles for which there is adequate evidence. Why not also look at those for which there is suggestive evidence as well to assure protection of all potentially susceptible populations or lifestyles. This would be more consistent with the "likely causal" criteria noted on page 3.2

p.3-7, line 1. Are these controlled human exposure studies in normals or in asthmatics?

p.3-7, line 30. By personal exposures do you mean using personal monitors?

p.3-8, lines 3-9. What is the difference between the confounding with SO2 and O3 in line 5 and the statement that recent studies also find persistent effects with adjustment for key co-pollutants as noted on line 7. These seem to say the same thing.

p.3-8, line 15. After synergistic, suggest insert "or additive"

p3-9, line 7. In this sentence, it is stated that the most relevant co-pollutants are those from traffic. However, this seems to contradict statements about other relevant co-pollutants noted on page 3.8 such as in line 7.

p.3-9, lines 24-27. If the current ISA review does not substantially alter our understanding of CV effects, then what is the justification for changing the causal determination in the current ISA from the 2010 review as noted in Table 3-1. In fact, the rationale presented on page 3-10 for not

changing the causal determination for mortality is basically the same as the rationale used for CV effects but which in the latter case did result in a change in conclusion.

Dr. Ronald Wyzga

Chapter 3: Consideration of the Evidence for NOx-Related Health Effects

1. *To what extent does Chapter 3 capture and appropriately characterize the key aspects of the evidence assessed and integrated in the ISA?*

By and large this chapter does an excellent job in characterizing the key results of the ISA. I have two specific issues to raise, however, that could improve the content of this chapter. First of all, this chapter could provide a more detailed and focused discussion about what determines an adverse effect, especially as it relates to airway responsiveness. There are elements of such a discussion in Chapter 3, but they need to be more clearly articulated. Footnotes 57 on p. 3-6 and 62 on p.3-18 provide the clearest statements, but further discussion of this could be helpful. I am unclear whether "clinical relevance" equates to "adversity"; a more forthright discussion of this would be helpful.

Secondly, the chamber studies are key in informing in informing the choice of a NAAQS. Among these studies, the airway responsiveness (AR) response appears to be the most relevant. This measure is basically a continuous variable but the results of the human clinical studies are often characterized as a dichotomous variable indicating whether these is an increase or decrease in AR. The discussion about adversity of AR should indicate whether this dichotomy should be expanded into a trichotomy, which includes frankly adverse or even "clinically relevant" responses. I realize that the much of the discussion here is based upon the recent meta-analysis of Brown (2015), but the document could indicate the need to revise/expand results presented in Tables 3-2 and 3-3 if possible.

2. *To what extent is staff's consideration of the evidence from epidemiologic and controlled human exposure studies, including important uncertainties, technically sound and clearly communicated? What are the Panel's views on staff's interpretation of the health evidence for short-term (section 3.2) and long-term (section 3.3) NO_2 exposures for the purpose of evaluating the adequacy of the current standards?*

See comments to the above question. Overall the Chapter does an excellent job, but the content could be improved along the lines indicated above. One minor addition would be the indication of co-pollutants studied in the studies listed in Figure 3-1.

With respect to the long-term studies, the document notes that the uncertainty of such effects is reduced by the coherence of findings from experimental studies and epidemiologic studies. (p.3-27) It would be particularly helpful if the document were to indicate whether the changes

observed in experimental studies were transient or extended temporally. Greater articulation of this issue would be welcome.

Detailed comments:

p. 3-5, ll. 14 and 16: I would replace "attacks" with "responses"

p. 3-6, l 24: Does "some" refer to the "about a quarter of the volunteers"; if so, a more quantitative phrase would be helpful as opposed to "some."

p. 3-6:ll. 26-27: There should more discussion of the definition of "clinically relevant" as well as "adverse".

p. 3-10, ll. 26-29: Is there a minimum cutoff point to define increased AR; i,e., is any increase in AR, even if slight included here?
Table 3-2: Should there be an intermediate category for Changes in AR to indicate when there are small changes that are not deemed to be clinically relevant.

p. 3-14, l. 11: what is "marginal statistical significance"?

p. 3-17, ll. 12-14: Does this imply that 52% experienced NO_2-induced decreases in AR? If there were no effects, given a simple dichotomy, wouldn't we expect 50% of study subjects to experience NO_2-induceced increases in AR.
ll.16-34: Good discussion

p. 3-34: It is also important to factor in the activity patterns and mobility of individuals; how long are they near roadways?

p.3-35: Since many of us do not want to print out a color version if this document, I suggest some other key other than color be used in the final document.

p.4-8, ll. 1-17: This should be presented as clearly in Chapter 3.