



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

March 7, 2017

EPA-CASAC-17-001

The Honorable E. Scott Pruitt
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft – September 2016)*

Dear Administrator Pruitt:

The Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen Primary National Ambient Air Quality Standards (NAAQS) Review Panel met on November 9-10, 2016, and January 24, 2017, to peer review the EPA's *Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft – September 2016)*, hereafter referred to as the Draft PA. The Chartered CASAC approved the report on January 24, 2017. The CASAC's consensus responses to the agency's charge questions and the individual review comments from members of the CASAC Oxides of Nitrogen Panel are enclosed.

Overall, the CASAC finds that the Draft PA provides an appropriate summary of the science and technical information for the review of the primary National Ambient Air Quality Standards (NAAQS) for nitrogen dioxide (NO₂). The CASAC has additional comments and recommendations on improving the PA. With the completion of the recommended revisions outlined below and in the consensus responses, the PA will serve its intended purpose and another CASAC review of the document is not needed. The CASAC concurs with the EPA that the current scientific literature does not support a revision to the primary NAAQS for nitrogen dioxide.

The Draft PA summarizes and updates material from the Integrated Science Assessment (ISA) on NO₂ chemistry and emissions, monitoring, and trends, with a focus on the new near-road network. The final PA should use the most recently available data from the near-road network. The CASAC notes that there is a future research need for more data from micro-scale environments such as on-road or sidewalk urban canyons, which may have some of the highest ambient NO₂ concentrations. There is a discrepancy in the number of monitoring sites reported and this should be clarified. The draft PA attributes decreasing trends in NO_x emissions to multiple regulatory programs. It would be informative to provide

a chronological timeline of regulatory programs to demonstrate the effectiveness of emission control measures.

Although the Draft PA generally does a good job in characterizing the key health effects from the ISA, there are several areas that would benefit from more elucidation. There should be a more detailed discussion of what an adverse effect is, especially with respect to airway responsiveness (AR). The strongest evidence for short-term effects is from human clinical studies, but it should be noted that these studies do not consider the most sensitive subpopulations.

The CASAC is satisfied with the short-term exposure health-based benchmark analysis presented in the Draft PA and agrees with the decision to not conduct any new model-based or epidemiologic-based analyses. The decision to set the lowest benchmark analyses at 100 ppb NO₂ is reasonable as it reflects the lowest level, with sufficient scientific certainty, where acute NO₂ health effects have been shown to occur. There is, nonetheless, limited and uncertain evidence of possible adverse effects at lower NO₂ concentrations, such as 85 to 90 ppb. The conclusiveness of such evidence may improve in the future, beyond the current review cycle, and the CASAC suggests that the EPA consider sensitivity analyses of the extent of potential exposures at a benchmark in this lower range. The CASAC also supports the decision not to conduct any new or updated quantitative risk analyses related to long-term exposure to NO₂. Although it is plausible that long-term NO₂ exposure is associated with adverse respiratory outcomes, specifically excess asthma incidence, the CASAC believes that existing uncertainties in the epidemiologic literature limit the ability to properly estimate and interpret population risk associated with NO₂, specifically within a formal risk assessment framework. The PA should include a statement that the decision not to conduct any new epidemiologic-based or model-based analyses does not preclude conducting quantitative health risk analyses in future reviews of the NAAQS. This is especially true as new observational and controlled findings on NO₂ health risk emerge and potentially address existing uncertainties.

The Draft PA provides an appropriate and sufficient rationale to support retaining the current primary NAAQS for short-term exposures to NO₂. The draft appropriately summarizes the current state of science. The main difference in the state of science since the last review is that there is a more mechanistic understanding of effects. The current scientific evidence supports the choice of NO₂ as the indicator for ambient gaseous oxides of nitrogen. The CASAC concurs with the EPA finding that short-term exposures to NO₂ are causal for respiratory effects, based on evidence for asthma exacerbation. The strongest evidence is for an increase in airway responsiveness based on controlled human exposure studies, with supporting evidence from epidemiologic studies. The CASAC concurs that long-term exposures to NO₂ are likely to be causal for respiratory effects, based on asthma development. The strongest evidence is for asthma incidence in children in epidemiologic studies, with supporting evidence from experimental animal studies.

The existing 1-hour and annual averaging times address short-term and long-term exposures to NO₂, respectively. Controlled human and animal studies provide scientific support for a 1-hour averaging time as being representative of an exposure duration that can lead to adverse effects. Epidemiologic evidence provides support for the annual averaging time.

The CASAC concurs with the EPA that the available scientific evidence, based on controlled human studies, indicates adverse effects from short-term (1-hour average) exposures at concentrations as low as 100 ppb NO₂. There is insufficient evidence to support a level lower than 100 ppb NO₂ at this time. The

CASAC finds that the suite of the current 1-hour standard and the current annual standard, taken together, imply that attainment of the 1-hour standard corresponds with annual design value averages of 30 ppb NO₂. Therefore, the combination of the 1-hour standard and annual standard is more protective of annual exposures compared to the annual standard by itself. There is insufficient evidence to make a scientific judgment that adverse effects occur at annual design values less than 30 ppb NO₂. Therefore, the CASAC recommends retaining, and not changing the existing suite of standards. The recommendation to retain the current suite of standards is not an endorsement that the current annual 53 ppb NO₂ standard, by itself, is protective of public health. Rather, it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects.

Although the CASAC findings regarding the indicator, averaging time, and level of the standard are based on scientific evidence, the CASAC's advice regarding the form of the standard entails the policy consideration of "programmatic stability." For the current 1-hour standard, the form is based on the 98th percentile of daily maximum 1-hour concentrations, which corresponds to the 7th or 8th highest daily maximum 1-hour concentration in a year. This form limits, but does not eliminate, exposures at or above 100 ppb NO₂. Changing the form to a higher percentile of daily maximum 1-hour concentrations would be more protective of public health, but would entail less programmatic stability. Changing the form to a lower percentile of daily maximum 1-hour concentrations would be less protective of public health, but would provide more programmatic stability. The CASAC recommends retaining the current form.

The CASAC has identified areas for additional research that should be considered by the EPA in setting its own research priorities, in promoting collaborations with research sponsors and partners, and in developing the literature review for the next review cycle. The key research areas include multipollutant exposure and epidemiology to attempt to distinguish the contribution of NO₂ exposure to human health risk, identification and evaluation of additional health effect endpoints (e.g., multiple asthma phenotypes, cardiovascular disease, premature mortality), implications of effects for adversity and clinically significant outcomes, improved mechanistic understanding of modes of action, ongoing need for meta-analysis of existing and new studies, temporal and spatial variability in NO₂ concentration, and better characterization of at-risk populations. These and other research recommendations are detailed in the response to charge questions. In addition, for future reviews, the CASAC encourages the EPA to consider expanding their approach to evaluating the weight of evidence to include additional consideration of consistency and coherence across multiple health effect categories.

The CASAC appreciates the opportunity to provide advice on the Draft PA and looks forward to the agency's response.

Sincerely,

/s/

Dr. Ana Diez Roux, Chair
Clean Air Scientific Advisory Committee

/s/

Dr. Elizabeth A. (Lianne) Sheppard, Chair
CASAC Oxides of Nitrogen Primary NAAQS
Review Panel

Enclosures

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: <http://www.epa.gov/casac>.

**U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Oxides of Nitrogen Primary NAAQS Review Panel**

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**Consensus Responses to Charge Questions on the EPA's
Policy Assessment for the Review of the National Ambient Air Quality Standards
for Nitrogen Dioxide (External Review Draft – September 2016)**

Chapter 1 – Introduction

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. The Background section (1.2.2) provides a thorough and necessary history of the previous Nitrogen Dioxide (NO₂) NAAQS reviews and the substantive basis of the Administrator's previous policy decisions.

The background (including evidence-based considerations, risk and exposure assessments) provides a good explanation for the addition of the 1-hour NO₂ standard and the continuation of the annual NO₂ standard in 2010. The EPA has also explained the important uncertainties associated with that decision, including those associated with co-occurring pollutants, exposure misclassification, adversity of acute effects, and the role of near-road and on-road exposures.

Although the information in Table 1-1 is important and clearly presented, it is unclear why its title refers to oxides of nitrogen as opposed to NO₂. Throughout the rest of the document (and in the document title) NO₂ 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. The four basic elements of the NAAQS (indicator, averaging time, level and form) and their roles are clearly explained.

Comments on Executive Summary

In general, the Executive Summary is clearly and concisely written, appropriate in format, with informative content that highlights the key information. The Executive Summary should be revised to capture any key changes made in the individual chapters of the final PA document.

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?

Chapter 2 summarizes chemistry and emissions, monitoring, and trends for NO₂, with a focus on the new near-road NO₂ network. It is largely a summary and update of material presented in the Integrated Science Assessment (ISA). 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. The final version of this document should reflect data summaries of the most recently available monitoring data.

In Section 2.1.1, the complexity of NO₂ pathways based on its relationship with NO and O₃ seems to be oversimplified. The term “total oxides of nitrogen”, NO_y, was briefly noted in Section 1.3 and defined in Footnote 16. As non-NO₂ oxidized nitrogen can be an important interferent for NO₂ measurement, a schematic diagram like Figure 2-1 from the NO_x ISA (see also Dr. Chow’s individual comments) might be included to illustrate the reactive and oxidized nitrogen compounds.

Section 2.1.1 also states that “...while ambient NO₂ concentrations are often elevated near important sources of NO_x emissions, such as major roadways, 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 the highest concentrations would be expected, and the spatial scale referred to (i.e., is it local, state-wide, or national?). This statement should be clarified and references cited as to where the highest concentrations of NO₂ are occurring.

Figure 2-1 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 of the PA differs from Figure 2-2 of the ISA (see Dr. Chow’s individual comments for this comparison). Emissions in Figure 2-1 should be expressed in the same units as the figure in the ISA (i.e., ‘thousands of short tons’ instead of ‘millions of tons’) for consistency. It is important to note here that tons of NO_x are expressed as equivalent NO₂ (assuming that is the case). This figure shows the largest NO_x emissions reductions occurring during the 2005 – 2010 period; regulatory programs driving these reductions should be noted. The sharp reduction in NO_x emissions from 2000 – 2001 is mentioned in the ISA, but not here; this should be carried forward into this chapter.

Although measurement methods for NO₂ were documented in the ISA (Section 2.4), the potential positive and negative interferences for the chemiluminescence-based Federal Reference Method (FRM), such as presence of other nitrogen species (e.g., nitric acid and peroxyacetylene nitrate [PAN]), conversion efficiencies, and duration of the measurement cycles should be acknowledged as measurement uncertainties that may result in exposure errors. In Section 5.1, it makes mention that “...the degree to which monitored NO₂ reflects actual NO₂ levels, as opposed to NO₂ plus other gaseous oxides of nitrogen, can vary (Section 2.2).” However, this issue is not discussed in Section 2.2.

The number of monitoring sites needs to be clarified. Section 2.2.2 notes that as of 2015, 462 NO₂ monitors were in operation and reporting to Air Quality System (AQS). These numbers are fewer than the 2,099 NO₂ sites across the continental U.S. that have been sampled since 1980 and this difference should be clearly explained. Figures 2-5 and 2-6 show the distribution of NO₂ design values (DVs), but the number of sites shown in these figures seem to be more than the number of sites used to determine the annual and hourly DVs (647 and 433 respectively). This difference should also be clearly explained.

Distributions of daily maximum 1-hour near-road and non-road NO₂ concentrations for 2015 in Figure 2-9 show relatively low NO₂ concentrations (e.g., ~35 ppb, 98th percentile) at the Atlanta-Sandy Springs-Roswell, GA site. This does not reflect the statement (Footnote 109) that “...we note that 1-hour NO₂ 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 attributes this to the 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.” It is unclear which site this refers to. Figure B5-1 of Appendix B 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.

On-road NO₂ exposures may be the highest of all micro-scale environments. Appendix B includes results of estimates of those exposures based primarily on near-road NO₂ measurements. A brief summary of this appendix should be brought into the body of Chapter 2.

In the Section 2.3.1 analysis of national trends, the criterion for including a site is that there are at least 5 valid DVs over the period of 1980 – 2015. When comparing site-specific trends to one another, it could make a big difference whether a site had valid design values between 1980 and 1984, 1980 and 2015, or 2011 and 2015. In particular, for the 3.9% and 1.8% of sites that trend upward for annual and hourly DVs respectively, it is unclear whether these represent a 5-year trend in the 1980s, a 5-year trend in the last 5 years, or a 35-year trend upward; it would be useful to list the DV years used for these sites. The criterion of 5 valid DVs for inclusion could be larger (at least 15) to provide a more consistent long-term comparison, or the time period could be constrained to more recent years when more of the sites had more complete data (1990 to 2015 for example). Figure 2-4 shows some monitoring sites trending upward, counter to overall emission trends. It is unclear whether the upward trend is due to local activities such as hydraulic fracturing, fuel changes, or due to limited data. A discussion of upward trend would be helpful.

In Section 2.3.2 (near road air quality), Figure 2-5 effectively conveys the general relationship between NO₂ DVs and distance from road. However, pooling the data from 1980 through 2015 masks the effects of a shifting national monitoring network. Because there are more near-road monitors in the later years, when NO₂ levels are generally lower, the (0,50) distance bin will be biased low, relative to other distance bins (which did not have a similar increase in sites in later years). Figure 2-6 presents the relationship by decade and 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.

There is a lack of monitoring in some areas such as street canyons that could have some of the highest ambient NO₂ concentrations in urban areas. When CO concentrations were of concern in a compliance context, some “sidewalk” monitoring was done. Passive NO₂ sampling in these environments may be a practical approach to provide some information on the potential for hotspots. The CASAC encourages more research on NO₂ hotspots (additional detail is provided in the consensus response to the Chapter 5 charge questions).

Figure 2-10 in Section 2.3.3, Relationships between hourly and annual NO₂ concentrations, is very helpful in assessing the utility of the current annual standards. The 2011-2015 graph does not include any near-road sites; although this is noted (Footnote 50), it would be helpful also to mention this information in the body of the document.

Chapter 3 – Consideration of the Evidence for NO₂-Related Health Effects

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

The chapter generally does a good job in characterizing the key results of the ISA. There are, however, several areas that would benefit from more elucidation.

- There should be a more detailed discussion of what is an adverse effect, especially with respect to airway responsiveness (AR). Some elements of such a discussion are given in parts of Chapter 3, such as the footnotes on p. 3-6 and footnote 62 on p. 3-8, but they need to be more clearly articulated and they should support the statement in slide 10 of the EPA presentation (U.S. EPA, 2016) about uncertainty of adversity.
- The chapter needs to note that the evidence of health effects associated with long-term exposure is stronger than in the previous ISA; it should also be noted that some of the epidemiological studies of long-term effects consider co-pollutants.
- The strongest evidence for short-term effects is from human clinical studies, but it should be noted that these studies do not consider the most sensitive individuals or all potentially sensitive subgroups. The controlled exposures considered in these studies are also far less complex than those to which people are exposed. These studies do, however, provide causal evidence of NO₂-specific health effects.
- There should be more discussion about of the potential health responses for cardiovascular disease and diabetes.
- It would be useful to clearly indicate the levels of exposure to NO₂ in the various studies cited in the Tables of Chapter 3.

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) NO₂ exposures for the purpose of evaluating the adequacy of the current standards?

There is some concern that the discussion about the influence of correlations between NO₂ and co-pollutants is emphasized too strongly. Correlations from monitoring data should be presented to help address this issue. More detailed discussion of how this issue impacts the setting of a standard could be included.

The chapter does not present the results of long-term studies in a way that adequately allows any consideration of the proposed 53 ppb NO₂ long-term standard. This is discussed in further detail in the consensus response to Chapter 5.

There needs to be more discussion of the difference between new onset of asthma and exacerbation of existing disease. There needs to be a more detailed discussion about the relationship between the results of short-term studies and long-term studies. In particular, the issues of transient vs. persistent or repeated responses to repeated acute exposures needs to be addressed. Scientific evidence to date does not help us determine whether the time averaging methods are correct. It is unclear whether there is any evidence that shorter exposures (less than one hour) or longer exposures (more than one year) are of concern.

Chapters 4 – Consideration of NO₂ Exposures and Health Risks:

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

The CASAC is satisfied with the short-term exposure health-based benchmark analysis presented in the Draft PA and agrees with the decision to not conduct any new model-based or epidemiologic-based analyses. The decision to base the lowest benchmark analyses at 100 ppb NO₂ is reasonable as it reflects the lowest level, with sufficient scientific certainty, where acute NO₂ health effects have been shown to occur. There is, nonetheless, limited and uncertain evidence of possible adverse effects at lower concentrations, such as 85 to 90 ppb NO₂ (see Figure 3-1). The conclusiveness of such evidence may improve in the future, beyond the current review cycle. Therefore, the CASAC suggests that the EPA consider sensitivity analyses of the extent of potential exposures at a benchmark in this lower range. If the analysis indicates that the number of potential exposures above the lower benchmark does not significantly increase as the benchmark decreases, then there is increased confidence that the 100 ppb NO₂ 1-hour benchmark is sufficiently protective of potential exposure near, but below the 100 ppb NO₂ DV.

Conversely, future decisions in the next review cycle to conduct additional model-based or epidemiologic-based risk assessments may be necessitated if the number of exposures above a lower benchmark is substantially greater than those at 100 ppb NO₂, indicative of population exposures at levels that may possibly be associated with acute adverse response.

The CASAC supports the decision not to conduct any new or updated quantitative risk analyses related to long-term exposure to NO₂. Several epidemiologic studies have indicated that long-term NO₂ exposure is associated with adverse respiratory outcomes, specifically excess asthma incidence (See Figure 3-2). Emerging epidemiologic evidence suggests that there may also be associations between long-term NO₂ exposure and adverse cardiovascular and reproductive outcomes. Despite these findings, the CASAC believes that existing uncertainties in the epidemiologic literature limit the ability to properly estimate and interpret population risk associated with NO₂, specifically within a formal risk assessment framework.

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

The 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. 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. For future reviews, the CASAC suggests adding a few additional examples, beyond the New York/New Jersey example in Figure B2-9, to provide further support for the proportionality assumption shown in Appendix B.

Exposures to NO₂ occurring in-vehicle during commuting, during active commuting (e.g. bicycling, walking, etc.), and within urban street canyons should be given greater attention as examples of exposure scenarios where elevated exposures to ambient NO₂ may occur, potentially above hourly NAAQS levels. The CASAC suggests including, within the body of Chapter 4, a formal discussion of these types of exposure scenarios, the processes used for deriving adjustment factors to account for

exposures within these microenvironments, and their potential scope of influence within the U.S. population at-large.

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?

Generally, the draft PA accurately and clearly communicates the results analyses. However, the CASAC has recommendations for improving the discussion:

- The CASAC recommends adding a figure to more clearly demonstrate the concentration adjustment procedures for comparison with health-based benchmarks.
- The chapter should include a statement that the decision not to conduct any new epidemiologic-based or model-based analyses does not preclude conducting quantitative health risk analyses in future reviews of the NAAQS. This is especially true as new observational and controlled findings on NO₂ health risk emerge and potentially address existing uncertainties.

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

What are the Panel's views on staff's preliminary conclusions regarding adequacy of the current standards and on the public health policy judgments that support those preliminary conclusions? Does the discussion provide an appropriate and sufficient rationale to support staff's preliminary conclusion that it is appropriate to consider retaining the current standards, without revision, in this review?

Chapter 5 provides an appropriate and sufficient rationale to support a recommendation to the Administrator that it is appropriate to retain and not change the current primary NAAQS for short-term exposures to NO₂. The draft PA appropriately summarizes the current state of science. The main difference in the state of science since the last review is that there is a more mechanistic understanding of effects. A recent meta-analysis (Brown, 2015) that looked at controlled short-term exposures of NO₂ alone, provides confirmation of causality for short-term effects. The controlled human experiments do not include the most sensitive subpopulations. The CASAC concludes that with regard to short-term exposure, there is evidence for airway responsiveness (AR) and includes exacerbation of asthma. Evidence for short-term effects includes controlled human studies and epidemiologic studies. Although the latter are confounded by traffic-related co-pollutants, the body of evidence taken as a whole supports the conclusions of the draft policy assessment. Animal studies and epidemiologic studies provide an adequate basis for inferences regarding long-term effects, as further described below.

Findings based on scientific evidence:

Indicator

- The current scientific evidence supports the choice of NO₂ as the indicator for ambient gaseous oxides of nitrogen. For example, controlled human and animal exposure studies provide specific evidence for health effects following exposure to NO₂. Epidemiologic studies also provide support for NO₂ as associated with adverse effects. NO₂ also serves as a good indicator of exposures to oxides of nitrogen, since reductions in exposures to NO₂ would reasonably be related to reductions in exposures to oxides of nitrogen more broadly.

Causality

- The CASAC concurs with the finding that short-term exposures to NO₂ are causal for respiratory effects based on evidence for asthma exacerbation. The strongest evidence is for an increase in airway responsiveness based on controlled human exposure studies, with supporting evidence from epidemiologic studies.
- Long-term exposures to NO₂ are likely to be causal for respiratory effects, based on asthma development. The strongest evidence is for asthma incidence in children in epidemiologic studies, with supporting evidence from experimental animal studies. Current scientific evidence for respiratory effects related to long-term exposures is stronger since the last review, although uncertainties remain related to the influence of co-pollutants on the association between NO₂ and asthma incidence.

Averaging Time

- Current scientific evidence, including evidence for asthma exacerbation related to short-term exposures based on controlled-human exposure studies, strengthens the conclusions reached in the last review. The strengthening of the conclusions is based on more specific integration of evidence, rather than new evidence.
- Epidemiologic studies provide support for the annual averaging time, representative of likely to be causal associations between long-term exposures, or repeated short-term exposures, and asthma development.
- Thus, with regard to averaging time, the existing 1-hour and annual averaging times address short-term and long-term exposures to NO₂, respectively. Controlled human and animal studies provide scientific support for a 1-hour averaging time as being representative of an exposure duration that can lead to adverse effects. Epidemiologic evidence provides support for the annual averaging time.

Levels

- *Short-Term Exposures (1-Hour Average)*
 - Controlled human exposure studies provide evidence of adverse effect at one-hour average exposures of 100 ppb NO₂ and higher. At the lowest evaluated exposure concentration of 100 ppb NO₂, a “marginally significant majority of participants experienced increased AR.” Based on a recent meta-analysis (Brown, 2015) of multiple studies, significant majorities of study participants experienced increased AR at levels from 100 ppb NO₂ to 530 ppb NO₂.
 - Short-term epidemiological studies provide some evidence of the possibility of adverse effects at 1-hour concentrations as low as 85 ppb NO₂ to 90 ppb NO₂. However, given uncertainties in epidemiologic studies related to relevance to the design values that will account for near-road monitoring in the future and related to co-pollutant confounding, the scientific judgment of the CASAC is that the controlled human studies provide a stronger basis for quantification of the level of the standard. Thus, the CASAC advises that, based on review of the scientific evidence, 100 ppb NO₂ is associated with adverse effects found in both controlled human studies and epidemiologic studies, and is the lowest level at which there is scientific confidence in such adverse effects.
 - The CASAC’s scientific judgment is that the controlled human experiments did not include human subjects who likely have more sensitivity to NO₂ at concentrations equal to or potentially lower than those measured. Thus, there is uncertainty regarding the potential for adverse effects at levels below 100 ppb NO₂. However, the lack of a clear

- dose-response model based on available data is another source of uncertainty that makes it difficult to extrapolate a dose-response relationship at levels lower than those measured in the controlled human studies.
- Available epidemiologic studies based on short-term averages, such as 1-hour averages, typically represent air quality scenarios that would not have met the current standard, taking into account the higher exposures near roads. Existing epidemiologic studies are typically based on monitors that do not represent the near-road environment. Furthermore, epidemiologic studies suffer from confounding with pollutants other than NO₂. The uncertainties related to co-pollutant confounding, exposure measurement error, and lack of representativeness of near-road concentrations in quantifying design values limit the applicability of epidemiologic studies to infer a suitable level or levels for a 1-hour averaging time.
 - The CASAC concurs with the EPA that the available scientific evidence, based on controlled human studies, indicates adverse effects from short-term (1-hour average) exposures at concentrations as low as 100 ppb NO₂. There is insufficient evidence to support a level lower than 100 ppb NO₂ at this time.
- *Long-Term Exposure (annual)*
 - The level of the existing annual average standard is 53 ppb NO₂.
 - The existing standard was set to protect children from NO₂-associated respiratory disease. Animal toxicology studies provide scientific support for a relationship and mode of action between exposure to NO₂ and adverse effect. The weight of evidence for causality of long-term exposure and adverse respiratory effect has been strengthened in this review to “likely to be causal,” based primarily on epidemiologic studies of asthma development in children coupled with evidence regarding mode of action from animal toxicological studies. Long-term epidemiologic studies are also subject to uncertainty, including possible confounding with other traffic-related pollutants. Epidemiologic studies may also have uncertainty related to exposure error. However, despite these uncertainties, it is the judgment of the CASAC that the available long-term epidemiological evidence is informative in reaching a conclusion regarding the level of the current standard.
 - Risk ratios from long-term epidemiologic studies shown in Figure 3-2 illustrate that there are significant associations based on several studies. These studies include annual average DVs ranging from 11 ppb NO₂ to over 100 ppb NO₂. These studies imply the possibility of adverse effects at levels below that of the current annual standard. However, these DVs are based on available monitors at the time that the studies were conducted. Because near-road monitors were very limited in number and have only been implemented more extensively in recent years, the design values of these epidemiologic studies do not account for near-road monitoring. Because near-road monitors are likely to measure concentrations higher than those of the legacy monitoring network, the DVs may increase. The epidemiologic studies also have uncertainty related to confounding from co-pollutants.
 - The current air quality standard DV can be influenced by near-road monitors, which typically are expected to measure higher ambient NO₂ concentrations than other monitors. However, at this time, there is not a good estimate of a mean ratio in annual concentrations between near-road and other monitors. Furthermore, such ratios may be complicated by proximity of some near-road monitors to other sources (e.g., major point sources). As more monitoring data are acquired, it will be possible to appropriately

- categorize the near road monitors with regard to whether they are influenced only by near-road sources and to quantify these ratios in the next review cycle.
- Figure 2-10 illustrates that there is a statistical association in annual DVs versus hourly DVs. This figure provides support for a finding that an hourly DV of 100 ppb NO₂ is associated with DV values that average approximately 30 ppb NO₂ (e.g., based on the 1980-1990, 1991-2000, and 2001-2010 charts).
 - The CASAC finds that the suite of the current 1-hour standard and the current annual standard, taken together, imply that attainment of the 1-hour standard also implies that the annual DV averages 30 ppb NO₂. Therefore, the current suite of standards is more protective of annual exposures compared to the annual standard by itself.
 - Thus, the scientific question is whether there is evidence of adverse effects for annual exposures with design values averaging less than 30 ppb NO₂.
 - Given uncertainties in the epidemiologic evidence related to lack of near road monitoring and potential confounding of traffic-related co-pollutants, there is insufficient evidence to make a scientific judgment that adverse effects occur at annual DVs less than 30 ppb NO₂. Therefore, the CASAC recommends retaining the existing suite of standards.
 - Based on EPA's analysis of recent air quality, current DVs for the 1-hour standard are typically at or below 70 ppb NO₂, which correspond to average annual DVs at or below approximately 20 ppb NO₂. Thus, there is evidence that the daily standard would typically be protective against annual concentrations at which there is insufficient scientific evidence to reliably quantify long-term adverse effects.
 - The recommendation to retain the current suite of standards is not an endorsement that the current annual 53 ppb NO₂ standard, by itself, is protective of public health. Rather, it is the suite of the current 1-hour and annual standards, together, that provide protection against adverse effects. In the next review cycle for oxides of nitrogen, the CASAC recommends that EPA should review the annual standard to determine if there is need for revision or revocation.

Summary of the **indicator, averaging time, and levels**: Thus, there is a scientific basis to state that there is strong evidence for the selection of NO₂ as the **indicator** of oxides of nitrogen, for the selection of 1-hour and annual **averaging times** to represent short-term and long-term exposures, respectively. For the one-hour averaging time, there are notable adverse effects at **levels** that exceed the current standard, but not at the level of the current standard. Thus, the CASAC advises that the current 1-hour standard is protective of adverse effects and that there is not a scientific basis for a standard lower than the current 1-hour standard. For the annual standard, there is epidemiological evidence that is suggestive of the possibility of adverse effects below the level of the current annual standard but not below an annual average of 30 ppb NO₂. However, the suite of 1-hour and annual standards is protective of annual levels that average 30 ppb NO₂ or lower when air quality is at the 1-hour design value. Thus, the suite of the 1-hour and annual standards is protective against adverse effects.

Policy advice separate from findings based on scientific evidence:

- The **form** of the standard is the most difficult to assess scientifically. A key factor in making a decision regarding the form is often “programmatically stability” which is intended to avoid situations in which compliance with the standard is subject to highly stochastic variable factors that are beyond human control, such as meteorological variability. For the 1-hour current standard, the form is based on the 98th percentile of daily maximum 1-hour concentrations,

which corresponds to the 7th or 8th highest daily maximum 1-hour concentration in a year. This form limits but does not eliminate exposures at or above 100 ppb NO₂. A scientific rationale for this form is there is uncertainty regarding the severity of adverse effects at a level of 100 ppb NO₂, and thus some potential for maximum daily levels to exceed this benchmark with limited frequency may nonetheless be protective of public health. As such, however, the choice of form appears to be more of a policy than scientific judgment. The policy judgment regarding protecting public health with an adequate margin of safety is at the discretion of the Administrator.

What are the Panel's views on the areas for additional research that are identified in Chapter 5? Are there additional areas that should be highlighted?

Key areas of uncertainty that have come up during the current review cycle for the Nitrogen Oxides Primary NAAQS have included:

- In a letter from CASAC to the Administrator of September 9, 2015 (CASAC, 2015b), CASAC stated that “quantitative risk assessment based on the epidemiologic evidence would be challenged by considerable uncertainty due to the inability to distinguish the contributions of NO₂ from the contributions of other highly correlated pollutants.” There is an ongoing need for research in multipollutant exposure and epidemiology to attempt to distinguish the contribution of NO₂ exposure to human health risk.
- A related point is that co-pollutant exposures may have the potential to enhance the severity of adverse effects related to NO₂, at least for some pollutants (e.g., black carbon)
- There are many phenotypes of asthma. Future work should evaluate whether it is useful to categorize studies, causality, and health effects by phenotype.
- Research regarding averaging time would be beneficial, such as evaluating the latency period for development of new asthma.
- There is generally a need to continue to characterize “adverse” and “clinically” significant outcomes when interpreting the results of controlled exposure and epidemiologic studies (e.g., see also CASAC, 2015a).
- There is a growing body of evidence on the effects of NO₂ exposure on mortality, cardiovascular disease, and other outcomes. Research to synthesize this evidence through meta-analysis will help inform and reduce uncertainty in causal determinations of these outcomes. In addition, research that broadly examines the coherence of evidence across multiple outcomes will better inform causal determinations.
- More scientific evidence regarding “triggering” events, related to better understanding of mode of action, would be helpful, and would require experiments aimed at further mechanistic understanding.
- Issues of seasonal differences in NO₂ exposures, and distinguishing between ambient and indoor exposures, need to be addressed to improve inferences of health effects (e.g., see CASAC, 2015a). As noted in the CASAC response to charge questions regarding the second draft of the ISA, “There can be more interpretation from studies of indoor exposure and for studies undertaken in different seasons. The indoor exposure studies can be informative because they do not have the same mix of co-pollutants as the outdoor exposure studies. More consideration of the modes of action associated with the various co-pollutants would also be of use.”
- Information that helps explain variability in ambient NO₂ concentrations is an ongoing need, including air quality monitor site characteristics (e.g., location in a street canyon), available

traffic counts, fleet mix data, and historical emissions information and trends. The representativeness of the available ambient data should be determined. New information on near-road oxides of nitrogen levels is critical for better quantifying near-road impacts. The amount of data from near-road monitoring will increase between now and the next review cycle and should be analyzed and evaluated. Additional issues to consider would be the locations of peak exposure occurrences (e.g., on-road in vehicles, roadside for active commuters, in street canyons, near other non-road facilities such as rail yards or industrial facilities). Any additional characterization of peak NO₂ exposure locations should also include measurements of other traffic-related pollutants such as ultra-fine particles (number concentration), black carbon, PM, and CO. Another issue to consider would be the role for wide deployment of low-cost sensors to help answer these questions.

- The body of epidemiologic studies reporting associations of NO₂ with cardiovascular disease, cardio-metabolic disease, birth outcomes, and cancer is growing rapidly. Indeed, in terms of total public health impact, these health outcomes are likely much larger than asthmatic exacerbation. The weakness in the evidence for a causal association is the specific link to NO₂. Controlled human NO₂ exposure studies would be most informative, but are unlikely to be feasible for most of these outcomes. However, controlled animal NO₂ exposure and other mechanistic studies would be particularly informative for the next NO₂ NAAQS review. Such studies would foster greater understanding of mode of action for a wider range of endpoints. There is ongoing need for experimental confirmation of mechanistic understanding related to effects of exposure to multiple traffic-related air pollutants, and their effect not just on asthma but also on cardiovascular disease and premature mortality.
- Commuting exposure and health studies would be helpful to assessing higher ambient exposures, inhaled dose, and dose-response relationships.
- There is also a need to continue to address issues of equity and environmental justice related to the distribution of exposures among and between communities of varying socioeconomic status. Such distributions may also be highly related to identification of groups at higher risk for adverse effects as a result of combinations of exposure scenarios, populations, lifestages, and socioeconomic factors. More research on effect modification with regard to such factors (as well as psychosocial stress) is an ongoing need. For example, as noted in CASAC (2015a), “There is substantial evidence that groups in poverty or who are non-white experience higher exposures to NO₂, but the epidemiological evidence is still lacking. It is important to clearly show how the exposure differences follow socioeconomic status (SES) or racial gradients, because for those that are considered causal or likely to be causal, there is high potential for larger health effects even if the epidemiological evidence of a direct effect modification is lacking.”
- Sensitivity of exposures to NO₂ may be enhanced for persons who have other conditions, such as diabetes, cardiovascular disease (e.g., COPD), or psychosocial stress. Furthermore, some asthma onset may be related to atopy. These and other potentially relevant sensitivities should be investigated. Cardiovascular effects may also be associated with NO₂ exposures, but controlled experimental studies are lacking to support a causality determination for such endpoints. Thus, further research in these areas would be useful.
- Scientific information to support quantification of ambient concentration and exposure benchmarks is an ongoing need. As noted in CASAC (2015b), “EPA should evaluate whether there is a basis for positing a benchmark lower than 100 ppb for use in interpreting the short-term exposure estimates.”

- As stated in CASAC (2015b), “quantitative uncertainty analysis methods are recommended for characterizing and comparing these potential sources of uncertainty.” There will be an ongoing need to quantify uncertainties.
- EPA should continue to explore ways to improve quantitative methods for estimating exposure and develop or collect data needed to support such methods.
- As noted in CASAC (2015b), “The available controlled human exposure data do not rule out that adverse effects could occur at NO₂ concentrations below that of the current 1-hour standard. Therefore, other means for inferring concentrations that may be associated with adverse effects at 1-hour average NO₂ concentrations below 100 ppb (such as based on epidemiologic data) should be explored and taken into account when considering benchmark concentrations and interpreting results from the exposure assessment.” This is an ongoing need.
- Although in this review there was not sufficient new scientific information to support a substantial update of previously conducted risk assessments, it is possible that the state of science could further develop between now and the next review cycle. Thus, there may be an ongoing need to develop exposure quantification methods, models, and data to make use of information that may arise, or new interpretations of existing information.

In addition to advice relevant to the review of the NO₂ NAAQS, for future reviews, the CASAC encourages the EPA to consider expanding their approach to evaluating the weight of evidence to include additional consideration of consistency and coherence across health effect categories. For example, if the weight of evidence becomes stronger for multiple health effect categories, consideration of consistency and coherence across these categories could provide important information that would not be evident when evaluating evidence for individual health effect categories alone. This type of integration might logically be raised in the ISA and carried forward, as appropriate, to a subsequent Risk and Exposure Assessment (REA) and PA.

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Appendix A

Individual Comments by CASAC Oxides of Nitrogen Primary NAAQS Review Panel Members on the EPA’s *Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft – September 2016)*

| | |
|--------------------------------------|-------------|
| Mr. George Allen | A-2 |
| Dr. Judith C. Chow..... | A-3 |
| Dr. Douglas W. Dockery..... | A-7 |
| Dr. Philip M. Fine | A-13 |
| Dr. H. Christopher Frey..... | A-15 |
| Dr. Jack Harkema..... | A-18 |
| Dr. Michael Jerrett | A-20 |
| Dr. Michael Kleinman | A-24 |
| Dr. Timothy Larson..... | A-26 |
| Dr. Jeremy Sarnat..... | A-30 |
| Dr. Richard Schlesinger | A-32 |
| Dr. Ronald Wyzga..... | A-33 |

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.

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 NO₂ (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 NO₂ PA:

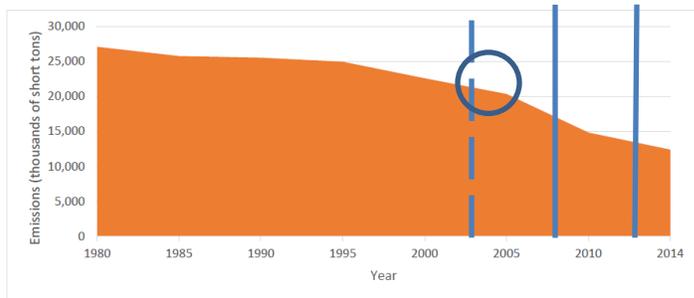


Figure 2-1 U.S. national average NO_x emissions from 1980 to 2014.
 Source: <http://www.epa.gov/air-emissions-inventories/air-pollutant-emissions-trends-data>

2b.) NO_x ISA:

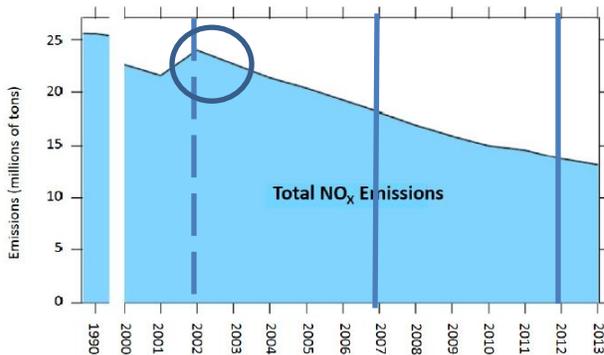


Figure 2-2 U.S. national average NO_x (sum of nitrogen dioxide and nitric oxide) emissions from 1990 to 2013.
 Source: National Center for Environmental Assessment 2014 analysis of 2011 National Emissions Inventory data

Chart 2- Comparison of NO_x emission trends for: a.) 2016 draft NO₂ PA and b.) 2016 NO_x ISA
2.2.1 NO₂ Methods

Although measurement methods for NO₂ 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 peroxyacetylene 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 NO₂ reflects actual NO₂

levels, as opposed to NO₂ 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 NO₂ Sites

The number of monitoring sites needs to be clarified. Section 2.2.2 notes that as of 2015, ~462 NO₂ 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 NO₂ 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 NO₂ NAAQS, the majority of NO₂ monitors were sited to represent the neighborhood scale”. However, the 2016 NO_x ISA (U.S. EPA, 2016) shows that the ~500 NO₂ 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). Several articles examine the zones of representation in source dominated environments (Kourtidis et al., 2002; Lazic et al., 2016; Pirjola et al., 2012; Zoras et al., 2008).

Section 1.4.1 (Lines 14-18, Page 1-11) noted that “area-wide” monitors intend to characterize the highest expected NO₂ concentrations at the neighborhood- and large spatial-scales. Although near-road monitors may capture some elevated NO₂ peaks, the highest NO₂ concentrations may be higher in street canyons during traffic congestion and while vehicle engines are idling. The criteria to select sites with highest expected NO₂ 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 people (Footnote 35 on Page 2-7), it is wise to locate NO₂ monitors to areas with potentially high NO₂ concentrations to address human exposure. The statement (Lines 24-26, Page 4-17) in Section 4.2.1 (Updated Analyses Comparing NO₂ Air Quality with Health-Based Benchmarks) that “...we anticipate that the near-road NO₂ monitoring network, with monitors sited from 2 to 50 meters away from heavily trafficked roads, effectively captures the types of locations around roads where the highest NO₂ concentrations can occur”, needs to be verified with additional spatial monitoring in street canyons.

2.3.2 Near-Road NO₂ Air Quality

Distributions of daily maximum 1-hour near-road and non-road NO₂ concentrations for 2015 in Figure 2-9 (Page 2-18) show relatively low NO₂ 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 NO₂ 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.

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Kourtidis, K.A., Ziomas, I., Zerefos, C., Kosmidis, E., Symeonidis, P., Christophilopoulos, E., Karathanassis, S., Mploutsos, A., (2002). Benzene, toluene, ozone, NO₂ and SO₂ measurements in an urban street canyon in Thessaloniki, Greece. *Atmos. Environ.* 36, 5355-5364.

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Zoras, S., Triantafyllou, A.G., Evagelopoulos, V., (2008). Aspects of year-long differential optical absorption spectroscopy and ground station measurements in an urban street canyon near industrial pollution sources. *Atmos. Environ.* 42, 4293-4303. <Go to ISI>://000257498700022

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 change 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) <i>Table 5</i> | 0.59 (P<0.001) | 0.53 (n.s.) | 0.67 (P<0.001) |
| Goodman (2009) <i>Table 3</i> | 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 (AR) with increasing NO₂ exposures.

The Goodman et al (2009) meta-analysis further examined the quantitative measures of AR, 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.

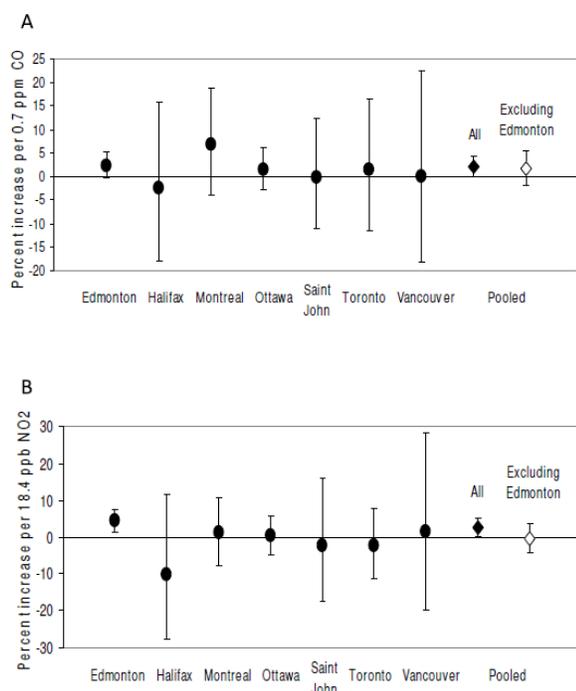


Figure 1
Percent increase in emergency department visits for angina/myocardial infarction by center. (Point estimates and 95% confidence intervals are shown, for CO (panel A) and NO₂ (panel B)).

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 lifestyles 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 particularly at risk. The elderly are the fastest growing age-group in the population and have the highest prevalence of these chronic respiratory and cardiovascular conditions. Consideration of the elderly as a special at-risk group for cardiovascular effects is warranted.

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

- 1. What are the Panel’s views on staff’s preliminary conclusions regarding adequacy of the current standards and on the public health policy judgments that support those preliminary conclusions? Does the discussion provide an appropriate and sufficient rationale to support staff’s preliminary conclusion that it is appropriate to consider retaining the current standards, without revision, in this review?*

The PA provides a clear synthesis of the basis for the determination of a “causal” relationship between short-term NO₂ exposure and respiratory effects, specifically asthma exacerbation. There is growing epidemiologic evidence for this relationship, but the correlation between NO₂ and other traffic-related co-pollutants in real world settings makes it impossible to separate the specific effect of NO₂ in existing epidemiologic studies. Thus the available controlled short-term NO₂ exposure studies of asthmatic subjects provides confirming experimental evidence of the specific effect of NO₂. The Brown (2009) meta-analysis provides an important synthesis of the effects on a recognized clinical indicator, halving of provocative dose. While these controlled exposure studies are at concentrations above the standard or commonly observed NO₂ concentrations in the US, and they do not show an exposure response, they provide experimental confirmation of clinical asthma exacerbation in asthmatic subjects. Note, that while the subjects in these studies were asthmatics, there is a range of response in the population even among asthmatics, and these study participants were no doubt not the most sensitive.

The evidence for a “suggestive” relationship of short-term NO₂ exposure and triggering of acute cardiovascular events in epidemiologic studies is growing. However, this body of epidemiologic evidence lacks confirmation by understanding of mechanisms and by experimental studies. Thus the PA appropriately has not characterized this relationship as “causal” yet, but informative further studies could quickly change that evaluation.

- Given the body of evidence in the ISA, I would agree that there is not a basis for modifying the level or averaging time of the short-term NO₂ standard.

The PA also provides a clear synthesis of the evidence for the determination that there is “likely to be a causal relationship” between long-term NO₂ exposures and respiratory effects, that is development of asthma in children. The development of improved home-specific estimates of exposures to NO₂ and correlated traffic-related co-pollutants has led to multiple epidemiologic studies showing such associations in children. Mechanistic studies in animals support this evidence, but extrapolating from these animal models to children is tenuous. Thus the characterization remains “likely” until more informative animal models are found.

Similarly there is developing epidemiologic evidence of associations of long-term exposures to NO₂ and other traffic-related co-pollutants with incidence of a number of health outcomes including total mortality, cardiovascular disease, diabetes, birth outcomes, and cancer. However, this body of epidemiologic evidence is weaker, and lacks confirmation of specific links to NO₂ by mechanistic or experimental studies.

- Given the body of evidence in the ISA, I would agree that there is not a basis for modifying the level or averaging time of the long-term NO₂ standard.

2. What are the Panel’s views on the areas for additional research that are identified in Chapter 5? Are there additional areas that should be highlighted?

The PA describes the need for future research and data collection in three areas. Let me comment on each in turn.

Interpretation of Epidemiologic Evidence

With the development of improved exposure assessment methods for traffic related pollution, the epidemiologic body of evidence for health effects of these exposures is growing rapidly, both for short-term and long-term exposures. In addition, a much wider array of health outcomes is being investigated, including not only respiratory, but also cardiovascular, cardio-metabolic, birth outcomes, cancer, and others not considered in the ISA. The correlation of NO₂ with other traffic-related co-pollutants will continue to be problematic in these studies. This is a constraint on epidemiologic studies by the nature of exposures in the real world, and will not be solved by improved analytic methods.

We can examine the specific effects in epidemiologic studies if we can find populations or situations in which NO₂ exposures are not predominately from traffic sources. (A historical example would be the epidemiologic studies of ambient nitrogen dioxide exposures from TNT and fertilizer production in Chattanooga in the 1970’s.) In that sense, examination of the epidemiologic evidence from studies of indoor NO₂ exposures could be informative.

The other option would be to examine ambient exposures with varying levels and correlations of NO₂ with other traffic-related co-pollutants. As noted, the multi-city studies of short-term effects have been very informative. Combining data across the US and Canada, where we see substantial differences in

ambient NO₂ exposures should be considered. The body of epidemiologic evidence for NO₂ and traffic related co-pollutants is growing even faster in Europe. The focus on US and Canadian studies is missing this body of evidence, but more importantly missing the opportunity to examine the contrasts in the mixtures of NO₂ with other traffic-related pollutants across populations in the US, Canada, and Europe.

Data Collection and Methods Development

The PA highlights the value of the near-road monitoring network for improving NO₂ exposure for health effects assessment. Improved exposure models which will be informed by near-road monitoring of traffic-related air pollution will improve epidemiologic studies and risk assessment. However, current epidemiologic studies have used short term monitoring programs to develop such city-specific models. The residential or population oriented monitoring network will remain the essential part of long-term epidemiologic studies.

As noted above, the advances in the epidemiology of NO₂ exposures will come from multi-city or multi-location with contrasting mixtures of NO₂ and other traffic-related co-pollutants. Thus effort to provide comparable data across a wider range of different climatic zones in North America, and different cities in the developed world more broadly would be more informative.

Again as noted above, development of low-cost sensors to characterize the short-term exposures to NO₂ and co-pollutants indoors would also be informative for advancing the epidemiology.

Airways Responsiveness in Controlled Human Exposure Studies

The controlled human NO₂ exposure studies conducted in the 1980's and 1990's, and recently synthesized in meta-analyses, were critical to identifying NO₂ as having a "causal relationship" with asthma exacerbation. While sensitive subjects (asthmatics) were studied, they were not the most sensitive. The value contributed by these studies was not in identifying a safe level, or in showing (or not showing) exposure response. Rather it was in demonstrating experimentally a clinically relevant response to specifically NO₂. There is value in further examination of this NO₂-asthma exacerbation pathway, however, I would suggest that there is more value in examining pathways for other health outcomes.

As noted earlier, given the improved exposure assessment methods, the body of epidemiologic studies reporting associations of NO₂ with cardiovascular disease, cardio-metabolic disease, birth outcomes, and cancer is growing rapidly. Indeed, in terms of total public health impact, these health outcomes are likely much larger than asthmatic exacerbation. The weakness in the evidence for a causal association is the specific link to NO₂. Controlled human NO₂ exposure studies would be most informative, but are unlikely to be feasible for most of these outcomes. However, controlled animal NO₂ exposure and other mechanistic studies would be particularly informative for the next NO₂ NAAQS review.

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 NO_x 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 NO_x 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 footnote 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 NO_x 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. H. Christopher Frey

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

1. *What are the Panel's views on staff's preliminary conclusions regarding adequacy of the current standards and on the public health policy judgments that support those preliminary conclusions? Does the discussion provide an appropriate and sufficient rationale to support staff's preliminary conclusion that it is appropriate to consider retaining the current standards, without revision, in this review?*

Chapter 5 provides an appropriate and sufficient rationale to support a recommendation to the Administrator that it is appropriate to retain the current primary NAAQS for nitrogen dioxide.

- Current scientific evidence, including evidence for asthma exacerbation related to short-term exposures based on controlled-human exposure studies, strengthens conclusions reached in the last review. The strengthening is based on more specific integration of evidence, rather than new evidence. Supporting evidence is available from epidemiologic studies, including some studies conducted since the last review. With regard to epidemiology, uncertainty remains as to the potential for confounding by traffic-related air pollutants.
- Current scientific evidence for respiratory effects related to long-term exposures is stronger since the last review, although there are uncertainties related to the potential role of co-pollutants.
- The current scientific evidence supports the choice of NO₂ as the **indicator** for ambient gaseous oxides of nitrogen. For example, controlled human and animal exposure studies provide specific evidence for health effects following exposure to NO₂. Epidemiologic studies also provide support for NO₂ as associated with adverse effects. NO₂ also serves as a good indicator of exposures to oxides of nitrogen, since reductions in exposures to NO₂ would reasonably be related to reductions in exposures to oxides of nitrogen more broadly.
- With regard to **averaging time**, the existing 1-hour and annual averaging times address short-term and long-term exposures to NO₂. Controlled human and animal studies provide scientific support for a 1-hour averaging time as being representative of an exposure duration that can lead to adverse effects. Epidemiologic evidence provides further support for the 1-hour averaging time.
- Epidemiologic studies provide support for a longer average time representative of an association between long-term exposures, or repeated short-term exposures, and asthma development.
- There is very limited support for adverse effects at **levels** below the current standards for either the 1-hour or annual averages. Available epidemiologic studies that might provide such support suffer from two key problems: (a) they are subject to uncertainty regarding copollutant confounding; and (b) they represent air quality situations that would likely violate the current standard.
- Thus, there is a scientific basis to state that there is strong evidence for the selection of NO₂ as the **indicator** of oxides of nitrogen, for the selection of 1-hour and annual **averaging times** to represent short-term and long-term exposures, respectively, and that there are notable adverse

effects at **levels** that exceed the current standard, but not at levels that are below the current standard.

- The **form** of the standard is the most difficult to assess scientifically. A key factor in making a decision regarding the form is often “programmatically stability” which is intended to avoid situations in which compliance with the standard is subject to highly stochastic variable factors that are beyond human control, such as meteorological variability. For the 1-hour current standard, the form is based on the 98th percentile of daily maximum 1-hour concentrations, which corresponds to the 7th or 8th highest daily maximum 1-hour concentration in a year. This form limits but does not eliminate exposures at or above 100 ppb NO₂. A scientific rationale for this form is there is uncertainty regarding the severity of adverse effects at a level of 100 ppb, and thus some potential for maximum daily levels to exceed this benchmark with limited frequency may nonetheless be protective of public health. As such, however, the choice of form appears to be more of a policy judgment rather than a scientific judgment. The policy judgment regarding protecting public health with an adequate margin of safety is at the discretion of the Administrator.

2. *What are the Panel’s views on the areas for additional research that are identified in Chapter 5? Are there additional areas that should be highlighted?*

Key areas of uncertainty that have come up during the current review cycle for the Nitrogen Oxides Primary NAAQS have included:

- In a letter from CASAC to the Administrator dated September 9, 2015 (EPA-CASAC-15-002), CASAC stated that “quantitative risk assessment based on the epidemiologic evidence would be challenged by considerable uncertainty due to the inability to distinguish the contributions of NO₂ from the contributions of other highly correlated pollutants.” There is an ongoing need for research in multipollutant exposure and epidemiology to attempt to distinguish the contribution of NO₂ exposure to human health risk.
- There is generally a need to continue to characterize “adversity” and “clinically” significant outcomes when interpreting the results of controlled exposure and epidemiologic studies (e.g., see also EPA-CASAC-15-001)
- There is very likely to be an ongoing need for meta-analysis of multiple studies, to incorporate possible future studies.
- Issues of seasonal differences in NO₂ exposures, and distinguishing between ambient and indoor exposures, need to be addressed to aid in better inferences of health effects (e.g., see EPA-CASAC-15-001). As noted in the CASAC response to charge questions regarding the second draft of the ISA, “There can be more interpretation from studies of indoor exposure and for studies undertaken in different seasons. The indoor exposure studies can be informative because they do not have the same mix of copollutants as the outdoor exposure studies. More consideration of the modes of action associated with the various copollutants would also be of use.”
- Information that helps explain variability in ambient NO₂ concentrations is an ongoing need, including air quality monitor site characteristics (e.g., location in a street canyon), available traffic counts, fleet mix data, and historical emissions information and trends. The representativeness of the available ambient data should be determined. New information on near-

road oxides of nitrogen levels is critical for better quantifying near-road impacts. The time series of near-road monitoring data will increase between now and the next review cycle and should be analyzed and evaluated.

- There is also a need to continue to address issues of equity and environmental justice related to the distribution of exposures among and between communities of varying socioeconomic status. Such distributions may also be highly related to identification of groups at higher risk for adverse effects as a result of combinations of exposure scenarios, populations, lifestages, and socioeconomic factors. More research on effect modification with regard to such factors is an ongoing need. For example, as noted in EPA-CASAC-15-001, “There is substantial evidence that groups in poverty or who are non-white experience higher exposures to NO₂, but the epidemiological evidence is still lacking. It is important to clearly show how the exposure differences follow socioeconomic status (SES) or racial gradients, because for those that are considered causal or likely to be causal, there is high potential for larger health effects even if the epidemiological evidence of a direct effect modification is lacking.”
- Scientific information to support quantification of ambient concentration and exposure benchmarks is an ongoing need. As noted in EPA-CASAC-15-002, “EPA should evaluate whether there is a basis for positing a benchmark lower than 100 ppb for use in interpreting the short-term exposure estimates.”
- As stated in EPA-CASAC-15-002, “quantitative uncertainty analysis methods are recommended for characterizing and comparing these potential sources of uncertainty.” There will be an ongoing need to quantify uncertainties.
- EPA should continue to explore ways to improve quantitative methods for estimating exposure and develop or collect data needed to support such methods.
- As noted in EPA-CASAC-15-002, “The available controlled human exposure data do not rule out that adverse effects could occur at NO₂ concentrations below that of the current 1-hour standard. Therefore, other means for inferring concentrations that may be associated with adverse effects at 1-hour average NO₂ concentrations below 100 ppb (such as based on epidemiologic data) should be explored and taken into account when considering benchmark concentrations and interpreting results from the exposure assessment.” This is an ongoing need.
- Although in this review there was not sufficient new scientific information to support a substantial update of previously conducted risk assessments, it is possible that the state of science could further develop between now and the next review cycle. Thus, there may be an ongoing need to develop exposure quantification methods, models, and data to make use of information that may arise, or new interpretations of existing information.

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 NO₂ 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 NO₂ 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 NO₂ standard and the continuation of the annual NO₂ standard in 2010.

The information in Table 1-1 is certainly important and clearly presented in this section (1-5), but why is it titled 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) NO₂ 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.

Minor Comments/Questions

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 NO₂ 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 NO₂ exposures as stated previously on lines 11 and 12?

Dr. Michael Jerrett

Comments on Chapter 3

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

For the short-term effects on respiratory, cardiovascular and mortality outcomes, Chapter 3 accurately conveys the science and key aspects of the evidence base used in the ISA. The chapter also does a good job of presenting the human chamber studies and the *in vitro* and *in vivo* toxicological evidence. The upgrading of the relationship between short-term effects and respiratory outcomes to “causal relationship” is well supported by the science and the EPA has correctly characterized the science in reaching this conclusion. For the most part, with the exception of children’s respiratory health and long-term exposures, all other conclusions about the causal determinations for other outcomes appear well-supported by the science and appear to have been correctly interpreted by the EPA.

On the longer-term effects, particularly with respect to children’s respiratory health, especially asthma incidence, the document does not always accurately capture the science as presented in the original articles. There are issues with the interpretation of the McConnell study. In particular, the EPA notes that there is not adequate control for confounding by PM_{2.5} or other pollutants related to traffic. The McConnell study did control for confounding by PM_{2.5} and other pollutants through the central site monitor, and the relationships remained largely the same after control for co-pollutants. Much of the PM_{2.5} in Southern California forms as a secondary pollutant, with the direct contribution from traffic being relatively small. The authors were unable to control for other constituents of traffic because they were using a dispersion model that resulted in extraordinarily high correlations among the estimated pollutants, which were not likely indicative of the actual correlations that would be observed between NO₂ and some of the other pollutants.

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) NO₂ exposures for the purpose of evaluating the adequacy of the current standards?

Overall the interpretations of the evidence from controlled human studies and epidemiological findings are sound and well presented, with, as mentioned, the exception of childhood respiratory health.

My major concern is with the presentation and conclusions regarding the long-term effects of NO₂ on children’s respiratory health, particularly asthma. The primary argument against taking any further action appears to hinge on the difficulty of separating out the effects of NO₂ from other pollutants in the complex mixture and lack of control for confounding pollutants.

The argument about co-pollutants is potentially an argument that could be used against making regulatory changes for any criteria pollutant, as there are other pollutants, which depending on the

spatiotemporal scale and means of assessing exposure, have moderate to high correlations with other criteria pollutants. Regionally, PM_{2.5} and ozone, for example, often have moderate to high correlations ($r \sim 0.7$).

I would like the EPA to clarify whether they have even taken action to tighten (meaning lower the standard) for any pollutant based on a “likely to be causal” determination. Have they ever recommended against adopting more stringent standards primarily on the basis of co-pollutants have moderate to high correlations with the pollutant in question?

Correlations with black carbon would be less problematic—this pollutant is at least on its own – has weak toxicological plausibility – but it too could be a marker for diesel exhaust. The correlations noted between NO₂ and other traffic pollutants appear to be partly artifacts of the similarities in model structure (e.g., dispersion or land use models), which have likely increased the correlations observed beyond what would be expected if multiple measurements had been made in the field.

On the second question in Charge Question 2, it is concerning that so many of the long-term studies have concentrations well below the annual average of the current standard of 53 ppb. Many of the communities in the Southern California studies, which likely had influence on the results, were well below the design values for the annual average.

Comments on Chapter 4

- 1. What are the Panel’s views on staff’s conclusions regarding support for new or updated quantitative analyses?*
- 2. What are the Panel’s views on the technical approach taken to conduct updated analyses comparing NO₂ air quality to health-based benchmarks?*
- 3. 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?*

On Chapter 4, with respect to charge question 1, the EPA staff have made appropriate conclusions with respect to the determinations related to short-term exposures. The current standards appear to be unlikely to be violated in most instances and show decreasing trends in most places. The decision not to update the short-term quantitative risk assessment appears justified.

For the long-term quantitative assessment, there may have been misinterpretations of some of the original studies, particularly the McConnell study. For example, the authors note that McConnell et al. use only the central site monitors, but they also used estimates of NO_x on local streets from a dispersion model. The dispersion model had high correlations among estimates of all pollutants, but other studies have suggested that these dispersion models are strong predictors of ambient NO₂ concentrations and probably weaker predictors of other confounders such as PM_{2.5}. Thus, some large portion of the NO_x prediction used in the McConnell study is likely due to NO₂, and not other pollutants.

On the linearity of this effect, McConnell et al. state it is unlikely to be non-linear, so for the purpose of quantitative risk assessment, the EPA could use a linear estimate.

“There was little evidence of nonlinearity in the exposure–response relationship based on sensitivity analyses comparing the fit of a smoothed cubic spline model of asthma with a linear model (p -value > 0.80) for the partial likelihood ratio test for models with 3 and 5 knots compared with the linear model.”

The EPA could examine Gauderman et al. 2005 paper for correlations between the NO₂ measures and other predictors used in the McConnell study. A subsequent Gauderman study used data from 900 locations for NO₂, NO_x, NO. It found the biggest determinant of NO₂ was traffic.

On the absence of exposure metrics, there are published land use regression models for the entire US (Marshall et al.) and for the state of California (Beckerman et al.). While these might over smooth the resulting surfaces because the models rely on government monitoring networks before the installation of the near road networks, they could potentially give a reasonable lower-end approximation of NO₂ variability.

It would also be instructive to examine the correlation between PM_{2.5} and NO₂ at the near road monitors or in high traffic areas? Ozone should not be a major issue because it is likely to be negatively correlated with NO₂ and if anything this would positively confound the association. But it would be useful to examine this association as well.

On the McConnell results from the central monitors, none of the other central site exposures (PM and ozone) was significantly related to the outcome; therefore the chance that these pollutants would confound empirically would be quite low as they would not meet the definition of a confounder which must be related to both the exposure and the outcome of interest. PM_{2.5} was close. Much depends on how the EPA defines a likely confounder.

Thus, arguably the central site NO₂ monitors could be used to assess exposures for the quantitative risk assessment.

If the EPA is concerned about lack of control for confounding co-pollutants, they could conduct sensitivity analyses that would have NO₂ effects with no confounding, with 50% confounding, and 25% confounding – in calculating the likely risks to the population.

There is concern about incidence rates not being available. These rates are clearly given in the McConnell article or they can be derived from other secondary sources that give prevalence rates (which can be used to back out incidence rates).

The size of effects in the Jerrett et al. vs. McConnell et al. studies are fairly similar. Rescaling the Jerrett et al. results to the 8 ppb contrast used in the McConnell study would result in an HR of 1.39, versus the 1.51 in the McConnell study and the confidence intervals would almost certainly overlap. Thus the consistency in effects across different age groups further builds the case for causality for NO₂ and suggests that the dispersion model comes close to producing the results of the individually measured home estimates.

On road estimates – more than 110,000,000 people commute distances greater than 30 minutes per day.

Recent Reference that may be Useful

Kreis, H., et al., Exposure to traffic-related air pollution and risk of development of childhood asthma: A systemic review and meta-analysis, Environ Int (2016), <http://dx.doi.org/10.1016/j.envint.2016.11.012>

Dr. Michael Kleinman

Chapter 3 – Consideration of the Evidence for NO₂-Related Health Effects:

Chapter 3 summarizes key aspects of the health effects evidence that are particularly relevant to considering the adequacy of the current primary standards and describes staff's consideration of this evidence to inform preliminary conclusions regarding the adequacy of the current standards.

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

Chapter 3 provides an excellent overview of the evidence summarized in the ISA. The discussion of the Brown (2015) meta-analysis was provided in clear detail and was used to, in part, substantiate the increased causality category for Respiratory effects from 'sufficient to infer a causal relationship' to 'Causal relationship.' It might be useful to consider that another recent meta-analysis (Shah et al., 2015) which used lags and reported a significant acute effect of NO₂ on morbidity and mortality from stroke, with regard to causality for cardiovascular disease. The Shah study examined 238 articles and found 103 suitable for inclusion in their analysis. They found that NO₂ was the most commonly measured gaseous pollutant and that NO₂ exposure showed a consistent association with both ischemic and hemorrhagic stroke (1.024 (95% confidence interval 1.010 to 1.038; I² =56%) and 1.024 (1.003 to 1.045; I² =42%). Associations persisted when data were stratified by outcome, age, and study design. (See Figure 1 on next page).

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) NO₂ exposures for the purpose of evaluating the adequacy of the current standards?

In general the epidemiologic and controlled human exposure studies are clearly presented as are many of the important uncertainties and caveats. One additional caveat that might be considered is that the subject pool for controlled human exposures are, for ethical reasons, not selected from among the most susceptible individuals, even when the subjects are drawn from among those with respiratory or cardiologic diseases. Thus it might be fair to say that dose-response relationships derived from these studies might underestimate risks for the most sensitive subjects in the population. Another caveat is that exposures are almost always to atmospheres that are much less complex than ambient air and might not fully represent interactions with co-pollutants that could alter the dose, dose distribution and potential toxicity of NO₂ when present in mixtures with other pollutants. For example, in the atmosphere NO₂ and O₃ could react together to form nitric acid vapor which could enhance irritant effects but few, if any studies of this mixture have been performed.

Specific Comment:

P 3-24 do not indicate *excess* NO₂-associated...?

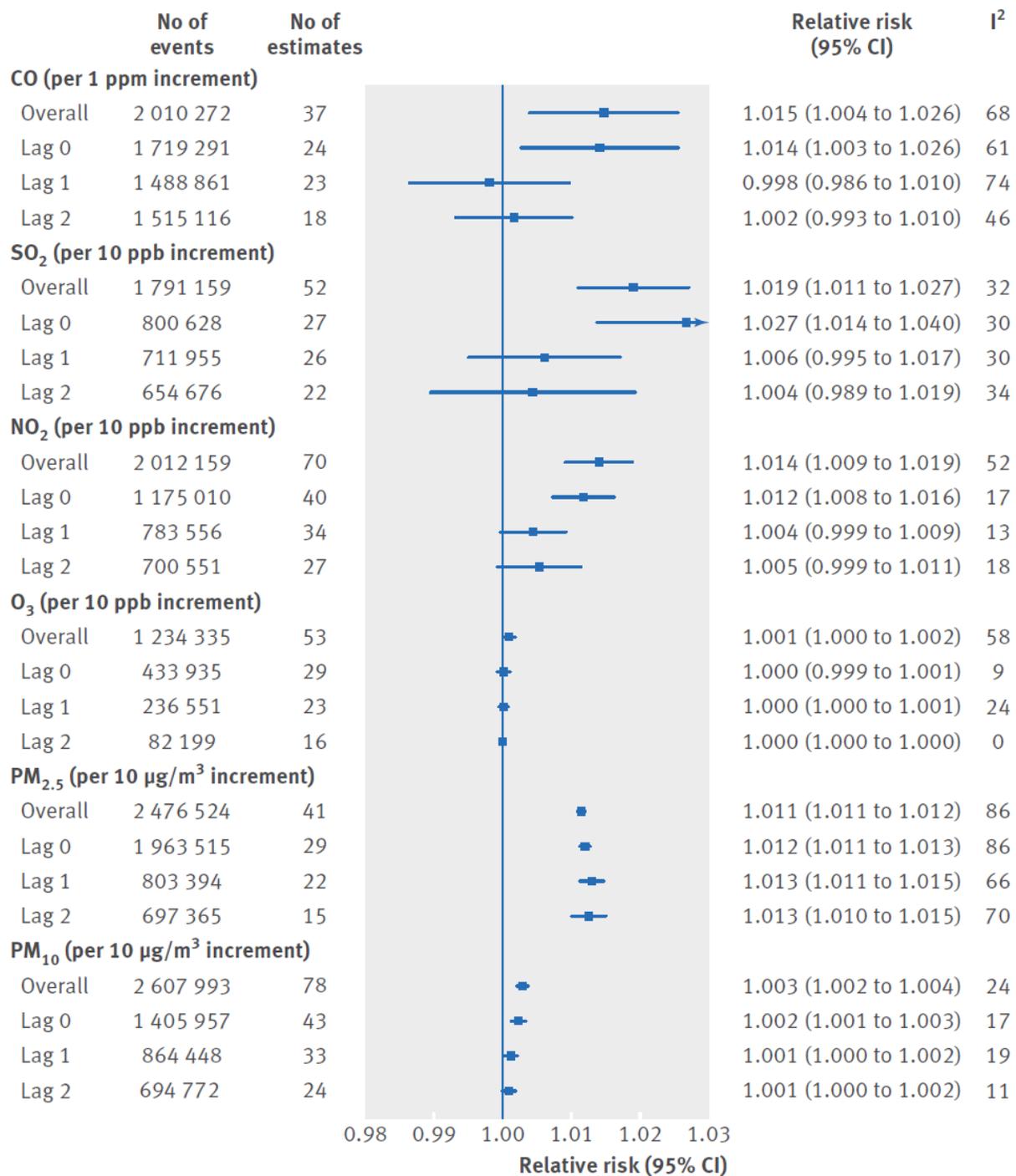


Fig 1 | Association between gaseous and particulate air pollutants and admission for stroke or mortality from stroke stratified by time lag (days)

Shah, A. S. V., Lee, K. K., McAllister, D. A., Hunter, A., Nair, H., Whiteley, W., Langrish, J. P., Newby, D. E., and Mills, N. L. (2015). Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ*, 350:h1295 (doi:10.1136/bmj.h1295).

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 NO₂ 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. NO₂ is the indicator species for oxides of nitrogen.
2. Reducing NO₂ will also reduce exposures to other oxides of nitrogen.
3. Short-term exposures (minutes to hours) to NO₂ leads to respiratory morbidity.
4. Effects associated with long-term exposures to NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ concentrations below 100 ppb, and/or if area-wide NO₂ 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 NO₂ in complex ambient mixtures including a range of co-occurring pollutants
2. The extent to which monitored NO₂ concentrations used in epidemiological studies reflect true exposures in study populations
3. The magnitude and potential adversity of NO₂- induced respiratory effects in controlled human exposure studies
4. The relationship between near-road NO₂ 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 NO₂.

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, NJ, 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 NO₂ 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 ppb.
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 NO₂ risk assessment were conducted based on studies of long-term NO₂, there would be particular uncertainty regarding the extent to which NO₂ risk estimates reflect the magnitude of NO₂ 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 NO₂ ambient concentrations are historically low; well below any current empiric health-based benchmarks of response. Moreover, in many US locales, nitrogen oxide and NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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/NO₂ 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 Risk and Exposure Assessment, 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 NO₂ 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 NO₂ 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 NO₂ 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 be 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 NO_x-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. Further discussion about the protocols and nature of responses in these studies could help facilitate a reader’s understanding of the significance of these studies.

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) NO₂ 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 persistent. Greater articulation of this issue would be welcome.

The Tables which summarize the results of the epidemiologic studies should also include the co-pollutants considered in these studies as well as the range of NO₂ levels in the communities where these studies were undertaken.

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. 3-14, l. 11: what is “marginal statistical significance”?

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