UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

DATE

EPA-CASAC-15-XXX

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document*

Dear Administrator McCarthy:

The Clean Air Scientific Advisory Committee (CASAC) Oxides of Nitrogen Primary National Ambient Air Quality Standards (NAAQS) Review Panel met on June 3, 2015, to peer review the EPA's *Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document*, hereafter referred to as the REA Planning Document. The CASAC's consensus responses to the agency's charge questions and the individual review comments from the CASAC Oxides of Nitrogen Review Panel are enclosed and the major comments and recommendations are highlighted below. The CASAC understands that EPA staff have not yet reached a decision regarding whether to prepare a stand-alone draft Risk and Exposure Assessment (REA) document or to incorporate a risk and exposure assessment into the forthcoming draft Policy Assessment (PA) document. The latter approach was used, for example, in the most recent review of the Lead NAAQS. For brevity, the CASAC offers advice regarding the risk and exposure assessment using the term "REA" with the understanding that it may be later communicated in a stand-alone REA document or as part of the draft PA.

Overall the CASAC finds that the approach in the REA Planning Document to consider support for an updated quantitative analysis is suitable and appropriate. The CASAC concurs that quantitative risk assessments for respiratory health effects from short-term NO_2 exposures would be unlikely to substantially improve the understanding of NO_2-attributable health risks or to increase the confidence in risk estimates. However, the CASAC urges the agency to explore the feasibility of performing a quantitative risk assessment of respiratory health effects from long-term NO_2 exposures, particularly due to the strengthening of the causal determination to "likely to be a causal relationship" in the Integrated Science Assessment (ISA).

The REA Planning Document identifies the most important and relevant information available to inform updated analyses of ambient NO_2 concentrations. However, the REA will benefit from inclusion and consideration of additional information that would help explain variability in ambient NO_2 concentrations, such as 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 REA should include as much of the available near-road sites and data as possible.

The EPA staff conclusion supporting updated analyses comparing ambient NO_2 concentrations to health benchmarks is sound, given the large amount of new information available from near- and on-road monitoring since the last analysis. The choice of benchmarks for the 1-hour NO_2 standard is supported by the information in the ISA and the CASAC recommends that the lower short-term exposure concentration benchmarks (e.g., 100 ppb) should be emphasized.

The CASAC is generally supportive of the model-based exposure assessment outlined in the REA Planning Document. The EPA should carefully consider the method used to estimate population exposure. The CASAC appreciates the qualitative presentation of potential model uncertainties among several relevant exposure factors. For transparency and prioritization of data gaps, quantitative uncertainty analysis methods are recommended for characterizing and comparing these potential sources of uncertainty. Sensitivity analyses are also recommended to account for uncertainties in input parameters (i.e., exposure factors) that are unknown or particularly influential. The EPA should examine the possibility of using a hybrid or blended approach for estimating the spatial and temporal variability of oxides of nitrogen concentrations that integrates across chemical transport models, land use regression, and ambient monitoring data and that address uncertainties in the current AERMOD approach for estimating exposures.

The EPA has done a commendable job to assemble the data from controlled human exposure in a manner that takes into consideration variability in the key study design factors between studies. The CASAC concurs that a new quantitative risk and exposure assessment based on information from controlled human exposure studies is not warranted given the lack of compelling new evidence available in the current review compared to the previous review. However, the available controlled human exposure data do not rule out that adverse effects could occur at NO_2 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 NO_2 concentrations below 100 pbb (such as based on epidemiologic data) should be explored and taken into account when considering benchmark concentrations and interpreting results from the exposure assessment.

With regard to an updated epidemiology-based risk assessment estimating respiratory related endpoints attributable to short-term NO_2 exposures, the CASAC concurs that an updated epidemiology-based risk assessment would be unlikely to substantially improve our understanding of NO_2-attributable health risks, or to increase our confidence in risk estimates, beyond the assessment from the last review.

For respiratory endpoints associated with long-term NO_2 exposures, the CASAC concurs with the EPA staff conclusion that a quantitative risk assessment based on the epidemiologic evidence would be challenged by considerable uncertainty due to the inability to distinguish the contributions of NO_2 from the contributions of other highly correlated pollutants. However, due to the strengthening of the causal determination to "likely to be a causal relationship" in the ISA, even in the face of these uncertainties, the CASAC recommends that the EPA explore the feasibility of a quantitative risk assessment based on the long-term epidemiology. The agency may find that such an REA is not feasible or that it may not substantially improve the understanding of health risk attributable to long-term NO_2 exposures, in which case the CASAC would request a clear explanation for this finding. However, if the EPA determines such a quantitative risk assessment based on the epidemiologic evidence is feasible and potentially informative, the CASAC looks forward to reviewing it.

The CASAC appreciates the opportunity to provide advice on the REA Planning Document and looks forward to the EPA's response.

Sincerely,

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

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Clean Air Scientific Advisory Committee
Oxides of Nitrogen Primary NAAQS Review Panel

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Consensus Responses to Charge Questions on EPA's Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document

Chapter 1 – Introduction

1. Chapter 1 provides introductory and background information to provide perspective on the role of the REA planning document within the broader context of the review of the primary NO_2 *NAAQS. To what extent is the information in this chapter appropriate for this purpose and clearly communicated?*

Chapter 1 provides a clear introduction and appropriate background information giving an adequate perspective on the role of the REA Planning Document in regards to the review of the primary NAAQS for NO_2.

2. Section 1.3 outlines the approach to informing staff's preliminary conclusions on the extent to which updated quantitative analyses are supported in the current review. Key components of this approach include consideration of the available health evidence; consideration of the available technical information, tools, and methods; and judgments as to the likelihood for particular quantitative analyses to provide substantial insights into NO_2 *exposures or health risks, beyond the insights gained from the analyses conducted in the last review. What are the Panel's views on this approach to considering support for updated quantitative analyses?*

Overall the CASAC finds that the approach in the REA Planning Document to consider support for an updated quantitative analysis is suitable and appropriate. The CASAC concurs that quantitative risk assessments for respiratory health effects from short-term NO_2 exposures would be unlikely to substantially improve the understanding of NO_2-attributable health risks, or to increase the confidence in risk estimates. However, the CASAC urges the agency to explore the feasibility of performing a quantitative risk assessment of respiratory health effects from long-term NO_2 exposures, particularly due to the strengthening of the causal determination to "likely to be a causal relationship" in the Integrated Science Assessment (ISA).

Chapter 2 – Air Quality and Health Benchmark Comparisons

1. Section 2.1 provides an overview of the NO_2 *air quality characterization and health effect benchmark comparisons from the last review of the primary* NO_2 *NAAQS. To what extent is the information in this section clearly presented, and to what extent does it provide useful context for the subsequent discussions in Chapter 2?*

Information in this section is generally clear and provides essential background for the following sections, but inclusion of more plain language would improve readability. The references to the adjustments of ambient concentrations to "just meet" the standard are a little confusing without the

proper background on the rationale and methodology. Although it is explained in detail later in the chapter, a little more background in this section would be useful.

2. Section 2.2 provides an overview of the information available in the current review that could inform updated analyses comparing NO_2 *air quality and health effect benchmarks. Section 2.2.1 discusses the data available to inform the characterization of ambient* NO_2 *concentrations, including concentrations on and near roads. Section 2.2.2 provides an overview of the health information assessed in the 2nd draft ISA that could inform the identification of* NO_2 *health effect benchmarks in the current review.*

a. To what extent does section 2.2.1 identify the most important and relevant information available to inform updated analyses of ambient NO_2 *concentrations? What are the Panel's views on the extent to which this new information could reduce important uncertainties identified in the last review, particularly with regard to characterizing ambient* NO_2 *concentrations on or near roads?*

Section 2.2.1 provides much of the information needed, but the REA Planning Document would benefit by also considering and including additional information on available traffic counts, fleet mix data, historical emissions information and trends. There is a need to determine the representativeness of the available ambient data. Perhaps modeling or satellite data could be used to assess this issue. The new information on near-road oxides of nitrogen levels is critical for better quantifying near road impacts, since the last NAAQS review had very little near-road monitoring data available. Since September of 2014, additional near-road NO_2 sites and additional data have become available. Table 2-1 and the corresponding analyses in the REA Planning Document should include as much of the available near-road sites and data as possible.

b. To what extent does section 2.2.2 appropriately characterize the health evidence from the 2nd draft ISA that could inform the identification of NO_2 *health effect benchmarks in the current review?*

Section 2.2.2 appropriately characterizes the health evidence from the ISA with regard to the short-term impacts of NO_2 exposures.

3. Section 2.2.3 presents staff's preliminary conclusion that updated analyses comparing ambient NO_2 *concentrations to health effect benchmarks are supported in the current review, with a particular focus on updating analyses of concentrations on and near roads. What are the Panel's views on this preliminary conclusion?*

The conclusion supporting updated analyses is sound, given the large amount of new information available from near- and on-road monitoring since the last analysis. Given that the health effect benchmarks proposed are much higher than current ambient levels, and given the expected further decline in emissions and ambient levels, there may be some opportunities for a more limited analysis, at least for the higher benchmarks.

4. Section 2.3 describes the technical approach staff is proposing to use in the current review for updated analyses comparing NO_2 *air quality to health effect benchmarks (section 2.3.1) and presents preliminary results for a single urban study area (section 2.3.2).*

a. Section 2.3.1.1 identifies the NO_2 *health effect benchmarks to be evaluated, based on the ISA's assessment of the evidence for* NO_2*-induced increases in airway responsiveness. What are the Panel's views on these benchmarks, and on the extent to which particular benchmarks should be emphasized?*

The choice of benchmarks for the 1-hour NO_2 standard is supported by the information in the ISA. The CASAC recommends that the lower short-term exposure concentration benchmark (i.e. 100 ppb) should be emphasized. As described in the Chapter 4 charge question response, 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.

b. Section 2.3.1.2 describes staff's planned approach for selecting urban study areas, based on consideration of diversity and availability of ambient monitoring data, representativeness of the highest measured daily maximum 1-hour concentrations, having large populations residing in the study area, and overall U.S. geographic coverage. What are the panel's views on these factors and their proposed use in selecting urban study areas?

These factors are appropriate, but the consideration of additional factors would also be useful. These include diversity and variation of the mobile source fleet mix in different areas, the presence or absence of large stationary or non-road sources, and additional sites near concentrated mobile source emissions that are not part of the "near-road" network (e.g., El Paso, TX; Elizabeth Lab, NJ) that may have a longer historical data record.

c. Section 2.3.1.3.1 presents staff's planned approach to adjusting ambient NO_2 *concentrations to just meet the existing primary* NO_2 *NAAQS, and any potential alternative standards judged appropriate. What are the Panel's views on this adjustment approach?*

The two-step adjustment approach that accounts for the different relationships above the 98th percentile is reasonable, but there will be additional uncertainties since the adjustment will necessarily be large in magnitude in most areas. A bracketing of the magnitude of the adjustments into different ranges may help to track the level of uncertainty in the analyses.

d. Section 2.3.1.3.2 presents staff's consideration of potential approaches to simulating NO_2 *concentrations on roads in the selected study areas. To what extent does this section identify the most relevant evidence to inform our understanding of roadway* NO_2 *concentrations? What are the Panel's views on the various potential approaches to simulating* NO_2 *concentrations on roads?*

All the potential approaches appear to be reasonable, and the CASAC does not express a preference for one approach over another. The analysis should consider opportunities where published on-road data can be used in conjunction with near-road monitoring locations, or even other high traffic locations that are

not near freeways where such data may exist. The units in Figure 2-4 should be changed to be consistent with the other figures and tables in the chapter.

e. Section 2.3.2 presents an illustrative example of the proposed approach for the air quality and health benchmark comparisons, using air quality data from the Philadelphia CBSA. To what extent does the Panel find the analyses and results to be clearly presented, informative, and appropriately characterized?

The illustrative example is extremely helpful and informative and the CASAC looks forward to additional analyses in other cities that may have different analysis challenges. However, the Principal Component analysis was not persuasive or useful in this example.

Chapter 3 – Exposure Assessment

1. Chapter 3 presents the proposed approach to reaching staff conclusions on support for an updated model-based assessment of human exposures in the current review. This proposed approach is based in large part on considering the implications of results from the air quality and health benchmark comparisons described in Chapter 2. What are the Panel's views on this proposed approach?

The CASAC is generally supportive of the model-based exposure assessment outlined in the REA Planning Document. The EPA should carefully consider the method used to estimate population exposure to NO_2 for the NAAQS averaging time of greatest concern. Specifically, there are questions concerning the suitability of the exposure modeling approach given the understanding that the long-term oxides of nitrogen standard will effectively become the controlling standard. If true, a hybrid or blended approach should be used for estimating oxides of nitrogen that integrates across chemical transport models (CTM), land use regression (LUR), and ambient monitoring data.

The CASAC appreciates the qualitative presentation of potential model uncertainties among several relevant exposure factors. For transparency and prioritization of data gaps, quantitative uncertainty analysis methods are recommended for characterizing and comparing these potential sources of uncertainty. Sensitivity analyses are also recommended to account for uncertainties in input parameters (i.e., exposure factors) that are unknown or particularly influential.

2. Chapter 3 also provides overviews of the exposure assessment conducted in the last review (section 3.1) and the new information that could potentially inform an updated exposure assessment in the current review, should one be judged appropriate (section 3.2). To what extent does the Panel find this information to be clearly presented and appropriately characterized? Is there additional new information that staff should consider?

There are numerous hybrid or blended approaches that have been published for estimating oxides of nitrogen that integrate across CTM, LUR, and ambient monitoring data. The EPA should examine the possibility of using one of these hybrid methods to address uncertainties in the current AERMOD

approach for estimating exposures. This is particularly pertinent given the shortcomings of AERMOD algorithms in accurately modeling oxides of nitrogen photochemistry (see Dr. Timothy Larson's comments for further detail).

Chapters 4 – Human Health Risk Assessment

1. Section 4.1 presents staff's preliminary conclusion that a quantitative risk assessment based on information from controlled human exposure studies is not supported by the evidence available in the current review. What are the Panel's views regarding this preliminary conclusion?

The EPA has done a commendable job to assemble the data from controlled human exposures in a manner that appreciates variability in the key study design factors – concentration, exposure, provocation agent, etc. In the ISA (and in Brown et al., 2015), the meta-analysis incorporates studies conducted from 10-40 years ago. These studies show consistent respiratory effects (a reduction in the dose of provocation agent needed) at concentrations at and above the 1-hour standard. As such, there is strong evidence that NO_2 at 100 ppb can induce a biological effect. However, the general pattern of response is independent of the concentration of NO_2 from 100 to 500 ppb.

There are no controlled human exposure data below 100 ppb to consider and, given the lack of compelling new evidence in the current review compared to the previous review, it would be difficult to quantifiably derive any number lower than 100 ppb that would represent a scientifically justifiable estimate of a threshold for adverse effect, a bound on lowest observable adverse effect or highest observable no effect level, or a level judged to pose *de minimus* adverse effect. Therefore, using controlled human exposure data for the quantitative risk assessment is difficult to justify. However, the controlled human exposure data do not rule out the possibility that 1-hour NO_2 concentrations less than 100 ppb could pose adverse effects. Thus, the EPA is encouraged to explore whether benchmark concentrations of less than 100 ppb could be justifiable based on joint consideration of the controlled exposure studies and epidemiological data or other data.

2. Section 4.2 discusses the extent to which the available evidence and information could support an updated quantitative risk assessment based on information from epidemiology studies. Section 4.2.1 provides an overview of the epidemiology-based risk assessment from the last review. Section 4.2.2 presents staff's consideration of the newly available evidence in the current review.

a. Section 4.2.2.1 presents the basis for staff's preliminary conclusions that (1) an updated epidemiology-based risk assessment estimating respiratory-related endpoints attributable to short-term NO_2 *exposures would be subject to uncertainties that are essentially the same as those identified in the 2008 REA and (2) an updated epidemiology-based risk assessment in the current review would be unlikely to substantially improve our understanding of* NO_2*-attributable health risks, or increase our confidence in risk estimates, beyond the assessment from the last review. What are the Panel's views on these preliminary conclusions?*

b. Section 4.2.2.2 presents staff's preliminary conclusions that (1) a risk assessment quantifying the development of asthma attributable to long-term NO_2 *exposures would be subject to considerable uncertainty due to the inability to distinguish the contributions of* NO_2 *from the contributions of other highly correlated pollutants and (2) that such a risk assessment would be of limited value in informing decisions in the current review. What are the Panel's views on these preliminary conclusions?*

Section 4.2 of the document discusses the extent to which the available evidence and information could support an updated quantitative risk assessment based on information from epidemiology studies. With regard to an updated epidemiology-based risk assessment estimating respiratory related endpoints attributable to short-term NO_2 exposures (Section 4.2.2.1), the CASAC concurs that an updated epidemiology-based risk assessment in the current review would be unlikely to substantially improve our understanding of NO_2-attributable health risks, or to increase our confidence in risk estimates, beyond the assessment from the last review.

With regard to the risk assessment quantifying the development of asthma attributable to long-term NO_2 exposures (Section 4.2.2.2), the CASAC agrees with the assessment in the ISA that the evidence for long-term exposure to oxides of nitrogen contributing to development of respiratory conditions (e.g., asthma) is "likely to be a causal relationship," which is an increase in confidence from the prior review. The CASAC concurs with the assessment that a quantitative risk assessment based on the epidemiologic evidence would be challenged by "considerable uncertainty due to the inability to distinguish the contributions of NO_2 from the contributions of other highly correlated pollutants." Nevertheless the finding that the evidence for these relationships is likely to be causal dictates a thoughtful consideration of an updated risk assessment, even in the face of these uncertainties. The CASAC encourages the EPA to explore the feasibility of a quantitative risk assessment based on the long-term epidemiology. The agency may find that such an REA is not feasible or that it may not substantially improve the understanding of health risk attributable to long-term NO_2 exposures, in which case the CASAC would request a clear explanation for this finding. However, if the EPA determines such a quantitative risk assessment based on the epidemiologic evidence is feasible and potentially informative, the CASAC is confident the EPA is qualified and prepared to undertake such an assessment and looks forward to reviewing it.

References

Brown, J. S. (2015). Nitrogen dioxide exposure and airway responsiveness in individuals with asthma. *Inhalation Toxicology*, 27(1):1-14.

Appendix A

Individual Comments by CASAC Oxides of Nitrogen Primary NAAQS Review Panel Members on EPA's Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide: Risk and Exposure Assessment Planning Document

Mr. George A. Allen

Comments on Chapter 2

Section 2.1 provides a useful overview of the REA process and results from the last review of the NO_2 NAAQS. Section 2.2.1, Characterizing Ambient NO_2 Concentrations, appropriately focuses on data from the new near-road monitoring network. Table 2-1 lists active near-road NO_2 sites as of September 2014; EPA just released an updated list of current and planned near-road site meta-data, available at http://www.epa.gov/ttn/amtic/files/nearroad/nearroadsites.xlsx . Of the 70 sites on this updated list with information on distance to the roadway, 11 are within 10 meters, and another 29 are within 20 meters. As data from these sites becomes available, it could be used to improve estimates of on-road or curbside NO_2 concentrations. Sites within 10 to 20 meters of the road would be more useful for this purpose than sites further away.

Section 2.2.2, Evidence Informing Health Effect Benchmarks, notes that the lowest benchmark concentration was 100 ppb in the last review, and there is no substantial new information to change that value in this review. The summary of health evidence from the second draft ISA is appropriately characterized. As section 2.2.3 notes, ambient NO_2 concentrations at or above this benchmark concentration are likely to be found on or (very) near roadways; data so far from the near-road monitors show almost no exceedances of the 100 ppb NO_2 1-hour NAAQS.

Section 2.3.1.1 identifies health benchmarks to be evaluated, from 100 to 400 ppb. Given the range of concentrations reported and expected on or near-roadways, the lower end of this benchmark range should be emphasized.

Section 2.3.1.2 presents the approach for selection of urban study areas. The criteria are appropriate, but I would encourage consideration of additional sites that may reflect near-road NO_2 concentrations but are not technically part of the near-road network, as noted in footnote 34 on pg. 2-19. As this section states on pg. 2-19 line 21-22, the less upward adjustment needed to meet the current standard, the less potential uncertainty in this adjustment. Lines 1-8 on pg. 2-21 appropriately emphasize the need for historical NO_2 data (back to the 1980's) that reflect changes in emissions over a long time period.

Table 2-3 on pg. 2-25 should include the NJ Elizabeth Lab site as a near-road monitor for the NYC CBSA with a very long measurement history (see my ISA comments regarding this site).

Section 2.3.1.3.1 clearly explains the need to focus on the upper end of DM1H NO_2 concentrations when adjusting existing data upwards to just meet the current NAAQS or other health benchmark concentrations (pg. 2-31, lines 33-36). The 2-step proportional approach is appropriate given the observed non-linear distribution relationship observed between high and low years, using Chester NJ (NYC CBSA) as an example (Figure 2-2, pg. 2-32). This section should clearly ID the site; it is described as "NY" in the text and in figure 2-2, but is not in an urbanized area. It would be helpful if this section would explain why this site is used as an example.

Section 2.3.1.3.2 presents approaches for adjusting data from the new near-road network to reflect NO_2 concentrations at or on the road. The description of possible approaches is appropriate. The conclusions presented on pg. 2-41 suggest modest increases (6 to 35%) of measured NO_2 at sites 10 to 20 meters from the road. Limiting inputs of on-road simulations to sites in this range will minimize uncertainty in these adjustments relative to use of near-road sites more than 20 meters from the road. For the existing and planned near-road sites listed in EPA's recently updated meta-data, 11 sites are < 10 meters from the road, and 29 are between 10 and 20 meters.

Section 2.3.2, Philadelphia CBSA example. This example is very helpful in understanding the adjustment process. Figure 2-9 on pg. 2-57 clearly shows the nature of the adjustment and the effect of the non-linear adjustment to the highest values. Data for all of 2014 should now be available for use here and in subsequent sections of this chapter.

Typo, Page 2-56, line 3: "monitor ID 421010002". Should this be 420450002?

Dr. Philip Fine

Chapter 2 – Air Quality and Health Benchmark Comparisons

1. Section 2.1 provides an overview of the NO_2 *air quality characterization and health effect benchmark comparisons from the last review of the primary* NO_2 *NAAQS. To what extent is the information in this section clearly presented, and to what extent does it provide useful context for the subsequent discussions in Chapter 2?*

The information in this section generally clear and provides very useful background for the following sections. The references to adjusting ambient concentrations is a little confusing without the proper background, and although it is explained in detail later in the Chapter, a little more background in this section would be useful.

2. Section 2.2 provides an overview of the information available in the current review that could inform updated analyses comparing NO_2 *air quality and health effect benchmarks. Section 2.2.1 discusses the data available to inform the characterization of ambient* NO_2 *concentrations, including concentrations on and near roads. Section 2.2.2 provides an overview of the health information assessed in the 2nd draft ISA that could inform the identification of* NO_2 *health effect benchmarks in the current review.*

a. To what extent does section 2.2.1 identify the most important and relevant information available to inform updated analyses of ambient NO_2 *concentrations? What are the Panel's views on the extent to which this new information could reduce important uncertainties identified in the last review, particularly with regard to characterizing ambient* NO_2 *concentrations on or near roads?*

The section provides much of the information needed, but would benefit by including additional information on available traffic count and fleet mix data, as well as historical emissions data and trends. The new information is critical for better quantifying near road impacts, since the last review had very little data available.

b. To what extent does section 2.2.2 appropriately characterize the health evidence from the 2nd draft ISA that could inform the identification of NO_2 *health effect benchmarks in the current review?*

The section appropriately characterizes the health evidence from the ISA.

3. Section 2.2.3 presents staff's preliminary conclusion that updated analyses comparing ambient NO_2 *concentrations to health effect benchmarks are supported in the current review, with a particular focus on updating analyses of concentrations on and near roads. What are the Panel's views on this preliminary conclusion?*

The conclusion supporting an updated analyses is sound, given the new information available from near and on road monitoring. But since the health effect benchmarks proposed are much higher than current

ambient levels, and given the expected further decline in emissions and ambient levels, there may be some opportunities for a more limited analysis.

4. Section 2.3 describes the technical approach staff is proposing to use in the current review for updated analyses comparing NO_2 *air quality to health effect benchmarks (section 2.3.1) and presents preliminary results for a single urban study area (section 2.3.2).*

a. Section 2.3.1.1 identifies the NO_2 *health effect benchmarks to be evaluated, based on the ISA's assessment of the evidence for* NO_2*-induced increases in airway responsiveness. What are the Panel's views on these benchmarks, and on the extent to which particular benchmarks should be emphasized?*

The choice of benchmarks is supported by the information presented.

b. Section 2.3.1.2 describes staff's planned approach for selecting urban study areas, based on consideration of diversity and availability of ambient monitoring data, representativeness of the highest measured daily maximum 1-hour concentrations, having large populations residing in the study area, and overall U.S. geographic coverage. What are the panel's views on these factors and their proposed use in selecting urban study areas?

These factors are appropriate, but the addition of an additional factor looking at diversity and variation of the mobile source fleet mix and CA vs. EPA emissions standards would also be useful.

c. Section 2.3.1.3.1 presents staff's planned approach to adjusting ambient NO_2 *concentrations to just meet the existing primary* NO_2 *NAAQS, and any potential alternative standards judged appropriate. What are the Panel's views on this adjustment approach?*

The adjustment approach is reasonable, but there will be additional uncertainties since the adjustment will necessarily be large in magnitude in most areas.

d. Section 2.3.1.3.2 presents staff's consideration of potential approaches to simulating NO_2 *concentrations on roads in the selected study areas. To what extent does this section identify the most relevant evidence to inform our understanding of roadway* NO_2 *concentrations? What are the Panel's views on the various potential approaches to simulating* NO_2 *concentrations on roads?*

All the potential approaches appear to be reasonable.

e. Section 2.3.2 presents an illustrative example of the proposed approach for the air quality and health benchmark comparisons, using air quality data from the Philadelphia CBSA. To what extent does the Panel find the analyses and results to be clearly presented, informative, and appropriately characterized?

The illustrative example is extremely helpful and informative. An additional example in another city with different analysis challenges might also be helpful.

Dr. Jack Harkema

Comments on Chapter 1 - Introduction

1. Chapter 1 provides introductory and background information to provide perspective on the role of the REA planning document within the broader context of the review of the primary NO_2 *NAAQS. To what extent is the information in this chapter appropriate for this purpose and clearly communicated?*

Chapter 1 provides a clear introduction and appropriate background information giving an adequate perspective on the role of the REA Planning Document in regards to the review of the primary NAAQS for NO_2.

2. Section 1.3 outlines the approach to informing staff's preliminary conclusions on the extent to which updated quantitative analyses are supported in the current review. Key components of this approach include consideration of the available health evidence; consideration of the available technical information, tools, and methods; and judgments as to the likelihood for particular quantitative analyses to provide substantial insights into NO_2 *exposures or health risks, beyond the insights gained from the analyses conducted in the last review. What are the Panel's views on this approach to considering support for updated quantitative analyses?*

Approach appears to be suitable to consider support for updated quantitative analyses.

Dr. Joel Kaufman

Comments on Chapter 4 – Human Health Risk Assessment

Section 4.1 of the document presents the staff's preliminary conclusion that a quantitative risk assessment based on information from controlled human exposure studies is not supported by the evidence available in the current review. This strikes me as an unexpected conclusion to reach, and I would recommend a more complete assessment of this. Since the ISA has made a compelling case that there is a relationship between short-term exposures to NO_2 (as low as 100 ppb for one hour) on the risk of exacerbation of asthma in individuals with asthma, and since this concentration and duration matches the form of the current standard, it raises a substantial question of whether the standard provides a sufficient margin of safety. I would expect this question to be addressed by the agency in this review process. There is a very large population of existing asthmatics in the U.S. The ISA appears to conclude that the controlled exposure studies should be interpreted to mean that we can expect approximately 70% of them to have worsened/increased nonspecific airway reactivity at this concentration of NO_2. Increased nonspecific airway reactivity is considered a laboratory surrogate for worsening asthma. Hence 100 ppb for one hour can be seen as analogous to a "lowest observed adverse effect level" in the appropriate sensitive population and species. I would anticipate that staff should be able to use this as a starting point for consideration of risk assessment procedures.

Section 4.2 of the document discusses the extent to which the available evidence and information could support an updated quantitative risk assessment based on information from epidemiology studies. I note and agree with the assessment in the ISA that the evidence for long-term exposure to oxides of nitrogen contributing to development of respiratory conditions (e.g., asthma) can be considered consistent with (i.e., "likely to be") causal, which is an increase in confidence from the prior review. However, in the REA, staff have not changed their assessment from the last review that the current review does not provide a basis for quantitative risk assessment. I do agree with the REA's conclusion that such a process would be challenged by "considerable uncertainty due to the inability to distinguish the contributions of NO_2 from the contributions of other highly correlated pollutants." Nevertheless the likelihood of these relationships being causal is sufficiently high—and supported by the results of toxicological studies and the human controlled exposure studies—to use the epidemiological studies even with these uncertainties. I would argue that even in the face of these uncertainties the evidence for a relationship between long-term exposure to oxides of nitrogen and respiratory disease is sufficiently strong to move forward with consideration of quantitative risk assessment. The fact there are correlated co-pollutants is an argument for additional research to disentangle these correlated exposures' relationships with health effects, but not a compelling argument for not moving forward with quantitative risk assessment.

Dr. Michael Kleinman

Comments on Chapter 4

1. Section 4.1 presents staff's preliminary conclusion that a quantitative risk assessment based on information from controlled human exposure studies is not supported by the evidence available in the current review. What are the Panel's views regarding this preliminary conclusion?

"With regard to the health benchmarks appropriate for evaluation in this review, 100 ppb is the lowest NO_2 exposure concentration for which the evidence indicates the potential for NO_2-induced increases in airway responsiveness. Given this, we reach the preliminary conclusion that 100 ppb is an appropriate health effect benchmark to evaluate. However, we also recognize the important uncertainties associated with the evidence for increased airway responsiveness following exposures to 100 ppb NO_2. These include the general lack of statistically significant results in individual studies at 100 ppb and the lack of an exposure-response relationship based on available studies. Such uncertainties will be taken into consideration when interpreting the potential public health implications of NO_2 air quality concentrations that equal or exceed the 100 ppb health effect benchmark."

The Brown meta-analysis for resting exposures (Table 1) cites several cases with significant indications of increased airway reactivity. Out of 16 studies listed 12 showed more than 50% of the participating subjects evidencing increased AR after 1 hr or less exposure at 100 ppb or above. There was a broad spectrum of challenge agents. Given this the above statement in the document about lack of significance could be tempered. There should be more specificity about how the agency will "interpret the public health implications," i.e. is a 1 hr 100 ppb standard protective with a reasonable margin of safety.

2. Section 4.2 discusses the extent to which the available evidence and information could support an updated quantitative risk assessment based on information from epidemiology studies. Section 4.2.1 provides an overview of the epidemiology based risk assessment from the last review. Section 4.2.2 presents staff's consideration of the newly available evidence in the current review.

a. Section 4.2.2.1 presents the basis for staff's preliminary conclusions that (1) an updated epidemiology-based risk assessment estimating respiratory related endpoints attributable to short-term NO_2 *exposures would be subject to uncertainties that are essentially the same as those identified in the 2008 REA and (2) an updated epidemiology-based risk assessment in the current review would be unlikely to substantially improve our understanding of* NO_2*-attributable health risks, or increase our confidence in risk estimates, beyond the assessment from the last review. What are the Panel's views on these preliminary conclusions?*

The increase in the agency's stated level of causality for short term effects suggests the possibility that adverse effects are being induced at exposures below the current standard. If so the agency might want to expand on how the appropriateness of the annual and 1 hr standard will be addressed.

b. Section 4.2.2.2 presents staff's preliminary conclusions that (1) a risk assessment quantifying the development of asthma attributable to longterm NO_2 *exposures would be subject to considerable uncertainty due to the inability to distinguish the contributions of* NO_2 *from the contributions of other highly correlated pollutants and (2) that such a risk assessment would be of limited value in informing decisions in the current review. What are the Panel's views on these preliminary conclusions?*

Mixture issues are difficult to interpret but they remain important areas where new policies could be helpful.

Dr. Timothy Larson

Chapter 1 Introduction

1. Chapter 1 provides introductory and background information to provide perspective on the role of the REA planning document within the broader context of the review of the primary NO_2 *NAAQS. To what extent is the information in this chapter appropriate for this purpose and clearly communicated?*

The key considerations for doing updated quantitative risk and exposure assessments is clearly stated and summarized in Figure 1-3. The choice of doing this for both causal as well as likely to be causal effects is reasonable.

2. Section 1.3 outlines the approach to informing staff's preliminary conclusions on the extent to which updated quantitative analyses are supported in the current review. Key components of this approach include consideration of the available health evidence; consideration of the available technical information, tools, and methods; and judgments as to the likelihood for particular quantitative analyses to provide substantial insights into NO_2 *exposures or health risks, beyond the insights gained from the analyses conducted in the last review. What are the Panel's views on this approach to considering support for updated quantitative analyses?*

There is a lot of emphasis on the short-term standard, given that this was the "controlling" standard in the 2008 REA . However, the conclusion from epidemiological evidence that long- term exposures are likely to be causally related to selected respiratory effects would appear to make a newly revised long-term standard the "controlling" standard. Specifically, as listed in Table 2-2, there are a number of CBSAs that have 2013 annual averages associated with long- term respiratory effects. Therefore, it might very well be the case that adjusting the short term concentrations to just meet the current standard will lead to annual average values in these same CBSAs that exceed the ranges observed in the selected epidemiological studies. That would imply exceedances of any newly proposed long-term standard value.

Chapter 3 – Exposure Assessment

1. Chapter 3 presents the proposed approach to reaching staff conclusions on support for an updated model-based assessment of human exposures in the current review. This proposed approach is based in large part on considering the implications of results from the air quality and health benchmark comparisons described in Chapter 2. What are the Panel's views on this proposed approach?

The approach is reasonable, but if the long-term standard becomes the controlling standard, it will be necessary to rely on a combination of deterministic meteorologically based models as well as measurements with spatial interpolation (possibly universal kriging based on additional spatial covariates) in order to produce a defensible set of exposure surfaces for use in a exposure model.

2. Chapter 3 also provides overviews of the exposure assessment conducted in the last review (section 3.1) and the new information that could potentially inform an updated exposure assessment in the current review, should one be judged appropriate (section 3.2). To what extent does the Panel find this information to be clearly presented and appropriately characterized? Is there additional new information that staff should consider?

If a new quantitative REA is therefore required, it is worth noting that the CBSAs with the most NO_2 monitors are, for the most part, those whose annual average concentrations are the highest. Note however that the number of monitors in the CBSAs highlighted in Table 2-2 have been decreasing dramatically in the past few years.

The use of AERMOD may not be able to accurately capture the relevant atmospheric transformations of NO_2. The algorithms in AERMOD do not include the concept of a photochemical steady state ratio of NO_2 to NO, nor to the ultimate conversion of NO_2 to NOy. Some of the highest annual averages of NO_2 are found in photo-chemically active urban areas (LA, Houston, Riverside). This suggests the need for a combination of a chemical transport model coupled with a relatively dense monitoring network, a requirement that may limit the choice of cities for any newly proposed REA.

CTM models alone are not able to capture small scale spatial variability. Therefore a hybrid approach such as described in Dionisio et al (2014) is seemingly required if the long-term average becomes the controlling standard. This approach may limit the available urban areas, however, given the relatively few published studies.

Dr. Jeremy Sarnat

1. *Chapter 3 presents the proposed approach to reaching staff conclusions on support for an updated model-based assessment of human exposures in the current review. This proposed approach is based in large part on considering the implications of results from the air quality and health benchmark comparisons described in Chapter 2. What are the Panel's views on this proposed approach?*

   I am generally supportive of the model-based exposure assessment outlined in the Draft REA, although details about the specific approach are lacking (see second bullet below). I also understand that the utility of conducting this assessment is in large part dependent on the outcomes of the air quality assessment. Below are a several, relatively minor comments and questions, on this chapter.

   - Table 3-1 is a useful qualitative presentation of potential model uncertainties among several relevant exposure factors. How was the characterization of uncertainty magnitudes determined? For transparency and prioritization of data gaps, I recommend using quantitative uncertainty analysis methods for characterizing and comparing these potential sources of uncertainty.

   - It's unclear whether a similar exposure assessment, using a single city as an intensive case study, is being proposed for a future REA. I understand why the APEX study area was limited to one city in the 2008 REA, Atlanta, but I'd like to see another city included within a future REA, if possible, along with the broad national air quality characterization. From an exposure factor standpoint, specifically with regard to city-wide building infiltration factors, I am guessing that Atlanta is fairly non-representative of the US population at-large.

2. *Chapter 3 also provides overviews of the exposure assessment conducted in the last review (section 3.1) and the new information that could potentially inform an updated exposure assessment in the current review, should one be judged appropriate (section 3.2). To what extent does the Panel find this information to be clearly presented and appropriately characterized? Is there additional new information that staff should consider?*

   - New information is presented clearly, albeit in a cursory manner. There is a lot of cross-referencing to external documents, including the previous 2008 REA.

   - Since the 2008 ISA, numerous hybrid or blended approaches for estimating NOx have been published that integrate across CTM, LUR, and ambient monitoring data. One promising method, developed within EPA, is built around a hierarchical Bayesian approach that uses AERMOD dispersion output (Crooks and Isakov, 2013). Is there a possibility of using one of these hybrid methods to address uncertainties in the current AERMOD approach for estimating exposures? Although I have not used the most recent AERMOD version, I am

encouraged by the options that allow for inclusion of ambient monitoring data, which gets closer to being able to use all available data to generate exposure output.

Dr. Ronald E. Wyzga

Chapter 4 – Human Health Risk Assessment

1. Section 4.1 presents staff's preliminary conclusion that a quantitative risk assessment based on information from controlled human exposure studies is not supported by the evidence available in the current review. What are the Panel's views regarding this preliminary conclusion?

Given the lack of new information, I support the staff's conclusion; a new quantitative risk assessment is not needed.

2. Section 4.2 discusses the extent to which the available evidence and information could support an updated quantitative risk assessment based on information from epidemiology studies. Section 4.2.1 provides an overview of the epidemiology-based risk assessment from the last review. Section 4.2.2 presents staff's consideration of the newly available evidence in the current review.
a. Section 4.2.2.1 presents the basis for staff's preliminary conclusions that (1) an updated epidemiology-based risk assessment estimating respiratory-related endpoints attributable to short-term NO_2 *exposures would be subject to uncertainties that are essentially the same as those identified in the 2008 REA and (2) an updated epidemiology-based risk assessment in the current review would be unlikely to substantially improve our understanding of* NO_2*-attributable health risks, or increase our confidence in risk estimates, beyond the assessment from the last review. What are the Panel's views on these preliminary conclusions?*

I agree with the staff's conclusions; an updated risk assessment is not needed.

b. Section 4.2.2.2. presents staff's preliminary conclusions that (1) a risk assessment quantifying the development of asthma attributable to long-term NO_2 *exposures would be subject to considerable uncertainty due to the inability to distinguish the contributions of* NO_2 *from the contributions of other highly correlated pollutants and (2) that such a risk assessment would be of limited value in informing decisions in the current review. What are the Panel's views on these preliminary conclusions?*

The Panel identified some additional studies that merit more careful examination by EPA Staff before any decision can be made about the need for a new risk assessment. I would urge the EPA Staff to review all of the relevant literature carefully and to make a decision about the need for a risk assessment. If there does not appear to be a need, the Staff need provide a detailed rationale on why such an assessment is not needed. If such a risk assessment is to be undertaken, the Staff need carefully outline the uncertainties associated with any risk assessment and clearly state caveats associated with such an assessment. My concern is that attention be given to other likely co-pollutants that could provoke responses that are associated with NO_2. In particular, I would hope the Staff would address the possibilities of EC and OC being associated with the development of asthma.