

**Summary Minutes of the
U.S. Environmental Protection Agency (EPA)
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
Oxides of Nitrogen Primary NAAQS Review Panel
Public Teleconference
December 5, 2008**

Committee Members: (See Roster – Attachment A)

Scheduled Date and Time: From 1:00 p.m. to 3:00 p.m. (Eastern Time) on December 5, 2008.
(See Federal Register Notice, Attachment B)

Location: By Teleconference

Purpose: To review EPA's completed Risk and Exposure Assessment (REA) to Support the Review of the NO₂ Primary National Ambient Air Quality Standard (NAAQS)

Participants:

Dr. Jonathan M. Samet, Chair
Prof. Ed Avol
Dr. John R Balmes
Dr. Joseph Brain
Dr. Ellis Cowling
Dr. James Crapo
Dr. H. Christopher Frey
Dr. Terry Gordon
Dr. Dale Hattis
Dr. Rogene Henderson
Dr. Donna Kenski
Dr. Patrick Kinney
Dr. Steven Kleeberger
Dr. Timothy Larson
Dr. Edward Postlethwait
Dr. Armistead Russell
Dr. Richard Schlesinger
Dr. Elizabeth A. (Lianne) Sheppard
Dr. Frank Speizer
Dr. George Thurston
Dr. James Ultman
Dr. Ronald Wyzga

SAB Staff Office: Dr. Angela Nugent, EPA SAB Staff Office,
Designated Federal Officer (DFO)

EPA Participants Listed on the Agenda
Dr. Scott Jenkins (EPA OAR)

Teleconference Summary – December 4, 2008

The discussion addressed the topics included in the Proposed Meeting Agenda (See Meeting Agenda - Attachment C) and followed the sequence summarized below.

Opening of Public Teleconference

Dr. Angela Nugent, Designated Federal Officer (DFO) for the CASAC Oxides of Nitrogen Primary NAAQS Review Panel, opened the public teleconference. She noted that the panel complied with the requirements of the Federal Advisory Committee Act. She noted that there had been two requests for oral public comment and three sets of written comments provided. Dr. Samet introduced the agenda. He noted that CASAC had requested the opportunity to review the completed REA and that there were no Agency-provided charge questions. He noted that the review was important because the NO₂ REA was the first REA developed after introduction of EPA's new NAAQS process. It offers a template for future NAAQS. Panel comments on the REA will offer input for EPA's Advance Notice of Proposed Rulemaking (ANPR). He acknowledged the contributions of a workgroup that had developed a straw review letter as a starting point for CASAC discussion. He noted that the letter will be edited to presents the major substantive points more succinctly, with details included as an appendix or enclosure.

REA Chapter 10 Overview and NAAQS Update

Dr. Scott Jenkins provided an update on the NAAQS schedule for the NAAQS (Attachment D) and noted that the REA had been issued in final form. He noted that EPA would be able to factor CASAC comments on the REA Chapter 10 into the ANPR, planned for publication by January 20, 2009.

Public Comment

The DFO introduced two members of the public who requested the opportunity to provide public comment.

The first commenter was Ms. Deborah Shprentz, speaking on behalf of the American Lung Association. Her written comments are included in Attachment E. The second commenter was Dr. Julie E. Goodman, speaking on behalf of the Gradient Corporation American Petroleum Institute. Her written comments are included in Attachment F.

Report from panel workgroup on exposure

Dr. Samet briefly summarized the draft review letter prepared by the panel workgroup, since Dr. Douglas Crawford-Brown, who had led the effort, was not available for the teleconference. Dr. Samet noted that the body of the letter would be shortened and revised to make the following points briefly:

- Chapter 10 is important as a generic model for bringing for integrating information in the Integrated Science Assessment (ISA)
- The importance of characterizing uncertainties and recommendations regarding tabular presentation.

He noted that many specific issues in the straw document were more technical and could be discussed in an appendix or enclosure. Drs. John Balmes and Ronald Wyzga, who also participated in the panel workgroup, agreed with this suggestion.

CASAC Panel Discussion

Dr. Samet requested panel discussion of chapter 10 as a model for the type of synthesis CASAC desired for NAAQS reviews generally. CASAC members agreed that the NO₂ REA offered a very useful model. One member advised that the CASAC letter convey a strong positive message that Chapter 10 provided an effective synthesis of scientific information needed to set the NAAQS for NO₂. Members also noted that they would prefer a chance to review such a synthesis chapter before the REA was finalized. EPA staff responded that EPA planned synthesis chapters for future REAs and intended to provide them in draft to CASAC for review before the documents are finalized. One member noted that, according to the Deputy Administrator's letter of September 2008, policy interpretations do not belong in the REA as they appear in Chapter 10 of the NO₂ REA. She noted, however, that CASAC found such a summary valuable.

The panel then discussed the chapter 10's discussion of uncertainty. Members noted that the text was largely qualitatively but comprehensive. A member noted that EPA should have discussed the Clean Air Act's mandate to provide a margin of safety as a point of departure for discussion of uncertainties in chapter 10. Uncertainties should be viewed through the lens of how available information can inform a "health protective" strategy. Another member acknowledged the appropriateness of the qualitative uncertainty approach in the current document, but argued that CASAC should advise EPA to provide a more robust quantitative approach in future documents. Yet another member noted that EPA should conclude its discussion of uncertainty with identification of research needs to guide research supporting future NAAQS. As a final comment, a member noted that although chapter 10 provided a full discussion of uncertainties, it was less successful in identifying biases associated with the uncertainties and the studies chosen.

The panel then discussed the four elements of the NAAQS for NO₂. The panel generally agreed that the level should not go above 0.1 ppm or 100 ppb to provide a margin of safety for asthmatics. The REA describes a meta-analysis that showed adverse effects for mild asthmatics at that level. The panel discussed modeling issues related to setting the limit and agreed that the upper range should be 0.1 ppm or 100 ppb. The panel agreed that NO₂ should be the indicator. They then discussed the averaging time, with general support for a one-hour standard to protect asthmatics from exacerbations. Panel members, noted however, that it would be desirable also to retain the current annual average to protect against potential threats to lung function growth. The panel briefly discussed the form, but noted that a decision about form was directly linked to the decision about level. Several members noted that a percentile decision about form provided a stability that assisted states in measuring for attainment. Members agreed that EPA should provide analysis in the ANPR to demonstrate that the combination of level and averaging time chosen was health protective.

The panel turned to discussion of additional general issues. The Chair noted that it was important for the letter to inform the Administrator that Chapter 10 was not reviewed by

CASAC. EPA staff observed that EPA could reissue the REA with the CASAC letter attached so that readers would know that EPA's REA was finalized before CASAC had the opportunity to review Chapter 10, the final summary chapter. The chair of the CASAC Oxides of Nitrogen (NO_x) and Sulfur Oxides (SO_x) Secondary Review Panel suggested that the REA letter also mention that CASAC was advising EPA on its review of the secondary NAAQS concurrently with the review of the primary NO₂ standard. Setting the primary standard will affect secondary effects, as well as health effects from other pollutants.

CASAC Review/Acceptance of panel report and identification of next steps

The panel, including chartered CASAC Members, accepted the draft report with the changes discussed during the teleconference. The Chair noted that a revised draft would be circulated to panel members with the goal of providing a final advisory letter to the Administrator by December 15, 2008.

At the chair's request, the Designated Federal Officer adjourned the meeting at 2:45 p.m.

Respectfully Submitted:

/s/

Angela Nugent
Designated Federal Officer

Certified as True:

/s/

Jonathan M. Samet
Chair

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Attachments

Attachment A	Roster
Attachment B	Federal Register Notice
Attachment C	Meeting Agenda
Attachment D	Presentation: REA Chapter 10 Overview and NAAQS Update
Attachment E	Comments of Ms. Deborah Shprentz, speaking on behalf of the American Lung Association
Attachment F	Dr. Julie E. Goodman, speaking on behalf of the Gradient Corporation American Petroleum Institute

Attachment A: Roster

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

CHAIR

Dr. Jonathan M. Samet, Professor and Chair of the Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

CASAC MEMBERS

Dr. Joseph Brain, Philip Drinker Professor of Environmental Physiology, Department of Environmental Health, Harvard School of Public Health, Harvard University, Boston, MA

Dr. Ellis B. Cowling, University Distinguished Professor At-Large, Emeritus, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, Raleigh, NC

Dr. James Crapo, Professor of Medicine, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. H. Christopher Frey, Professor, Department of Civil, Construction and Environmental Engineering, College of Engineering, North Carolina State University, Raleigh, NC, USA

Dr. Donna Kenski, Data Analyst, Lake Michigan Air Directors Consortium, Des Plaines, IL

Dr. Armistead (Ted) Russell, Professor, Department of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

CONSULTANTS

Professor Ed Avol, Professor, Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

Dr. John R. Balmes, Professor, Department of Medicine, Division of Occupational and Environmental Medicine, University of California, San Francisco, CA

Dr. Douglas Crawford-Brown, Professor and Director, Department of Environmental Sciences and Engineering, Carolina Environmental Program, University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. Terry Gordon, Professor, Environmental Medicine, NYU School of Medicine, Tuxedo, NY

Dr. Dale Hattis, Research Professor, Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University, Worcester, MA

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

Dr. Patrick Kinney, Associate Professor, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY

Dr. Steven Kleeberger, Professor, Lab Chief, Laboratory of Respiratory Biology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC

Dr. Timothy V. Larson, Professor, Department of Civil and Environmental Engineering, University of Washington, Seattle, WA, USA

Dr. Kent Pinkerton, Professor, Regents of the University of California, Center for Health and the Environment, University of California, Davis, CA

Dr. Edward Postlethwait, Professor and Chair, Department of Environmental Health Sciences, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

Dr. Richard Schlesinger, Associate Dean, Department of Biology, Dyson College, Pace University, New York, NY

Dr. Christian Seigneur, Director, Atmospheric Environment Center, Université Paris-Est, Champs-sur-Marne, France

Dr. Elizabeth A. (Lianne) Sheppard, Research Professor, Biostatistics and Environmental & Occupational Health Sciences, Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. Frank Speizer, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. George Thurston, Professor, Environmental Medicine, NYU School of Medicine, New York University, Tuxedo, NY

Dr. James Ultman, Professor, Chemical Engineering, Bioengineering Program, Pennsylvania State University, University Park, PA

Dr. Ronald Wyzga, Technical Executive, Air Quality Health and Risk, Electric Power Research Institute, Palo Alto, CA

SCIENCE ADVISORY BOARD STAFF

Dr. Angela Nugent, Designated Federal Officer, 1200 Pennsylvania Avenue, NW 1400F, Washington, DC, Phone: 202-343-9981, Fax: 202-233-0643, (nugent.angela@epa.gov)

Attachment B: Federal Register Notice

Science Advisory Board Staff Office; Clean Air Scientific Advisory Committee (CASAC);
Notification of a Public Advisory Committee Teleconference of the
CASAC Oxides of Nitrogen Primary NAAQS Review Panel

[Federal Register: November 12, 2008 (Volume 73, Number 219)]

[Notices]

[Page 66895-66896]

From the Federal Register Online via GPO Access [wais.access.gpo.gov]

[DOCID:fr12no08-85]

ENVIRONMENTAL PROTECTION AGENCY

[FRL-8739-8]

Science Advisory Board Staff Office; Clean Air Scientific Advisory
Committee (CASAC); Notification of a Public Advisory Committee
Teleconference of the CASAC Oxides of Nitrogen Primary NAAQS Review Panel

AGENCY: Environmental Protection Agency (EPA).

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ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Science Advisory Board (SAB) Staff Office announces a public teleconference of the Clean Air Scientific Advisory Committee's (CASAC) Oxides of Nitrogen Primary NAAQS Review Panel (Panel) to review EPA's completed Risk and Exposure Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard and to provide advice for EPA to consider as it develops its Advance Notice for Proposed Rulemaking for nitrogen dioxide.

DATES: The teleconference will be held on December 5, 2008 from 1 p.m. to 3 p.m. (Eastern Daylight Time).

Location: The public teleconference will be conducted by telephone only.

FOR FURTHER INFORMATION CONTACT: Members of the public who wish to obtain the call-in number and access code to participate in the teleconference may contact Dr. Angela Nugent, Designated Federal Officer (DFO), EPA Science Advisory Board (1400F), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460;

via telephone/voice mail (202) 343-9981; fax (202) 233-0643; or e-mail at nugent.angela@epa.gov. General information concerning the CASAC and the CASAC documents cited below can be found on the EPA Web site at <http://www.epa.gov/casac>.

SUPPLEMENTARY INFORMATION:

Background: The Clean Air Scientific Advisory Committee (CASAC) was established under section 109(d)(2) of the Clean Air Act (CAA or Act) (42 U.S.C. 7409) as an independent scientific advisory committee. CASAC provides advice, information, and recommendations on the scientific and technical aspects of air quality criteria and national ambient air quality standards (NAAQS) under sections 108 and 109 of the Act. The CASAC is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The Panel will comply with the provisions of FACA and all appropriate SAB Staff Office procedural policies.

Section 109(d)(1) of the CAA requires that the Agency periodically review and revise, as appropriate, the air quality criteria and the NAAQS for the six "criteria" air pollutants, including oxides of nitrogen (NOX). EPA is in the process of reviewing the primary NAAQS for nitrogen dioxide (NO₂), an indicator for NOX. Primary standards set limits to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly.

As part of its scientific advice to support EPA's review of the primary NAAQS for nitrogen dioxide (NO₂), CASAC met on September 9-10, 2008 to conduct a peer review of the Risk and Exposure Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard: Second Draft (73 FR 43444-43445). At that time, EPA had not completed chapter eight of the draft assessment entitled "Exposure and Health Risk Characterization." CASAC also held a public teleconference on October 22, 2008 to conduct a peer review of the draft chapter 8 (73 FR 55074-55075).

The public may access completed CASAC advisory reports related to the primary NO₂ NAAQS, including the CASAC reports on the Risk and Exposure Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard: Second Draft, on the EPA Web site at <http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyTopicCASAC!OpenView>.

EPA now plans that the final document will include an additional chapter (chapter 10) that considers the scientific evidence and exposure-risk-based information specifically as it relates to the current and potential alternative standards. At the December 5, 2008 teleconference, the CASAC will review EPA's completed Risk and Exposure Assessment and provide advice for EPA to consider as it develops its Advance Notice for Proposed Rulemaking for nitrogen dioxide.

Technical Contact: Any questions concerning Risk and Exposure

Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard should be directed to Dr. Scott Jenkins, OAR (by telephone (919) 541-1167 or e-mail jenkins.scott@epa.gov).

Availability of Meeting Materials: EPA's Risk and Exposure Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard will be accessible via the Agency's Office of Air Quality Planning and Standards Web site at http://www.epa.gov/ttn/naaqs/standards/nox/s_nox_cr_rea.html on or about November 21, 2008. Agendas and materials supporting the teleconference will be placed on the EPA Web site before the meeting on the CASAC meeting page, accessible through the calendar link on the blue navigation bar at <http://www.epa.gov/casac>.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral information for the CASAC Panel to consider during the advisory process. Oral Statements: Interested members of the public may submit relevant written or oral information for the SAB Panel to consider during the advisory process. Oral Statements: In general, individuals or groups requesting an oral presentation at a public teleconference will be limited to three minutes per speaker, with no more than a total of 30 minutes for all speakers. Interested parties should contact Dr. Angela Nugent, DFO, in writing (preferably via e-mail) by December 1, 2008 at the contact information noted above to be placed on the public speaker list for this meeting. Written Statements: Written statements for the public meeting should be received by Dr. Angela Nugent at the contact information above by December 1, 2008, so that the information may be made available to the Panel for their consideration prior to the teleconference. Written statements should be supplied to the DFO in the following formats: one hard copy with original signature (optional), and one electronic copy via e-mail (acceptable file format: Adobe Acrobat PDF, MS Word, MS PowerPoint, or Rich Text files in IBM-PC/Windows 98/2000/XP format).

Accessibility: For information on access or services for individuals with disabilities, please contact Dr. Nugent at the phone number or e-mail address noted above, preferably at least ten days prior to the teleconference, to give EPA as much time as possible to process your request.

Dated: November 5, 2008.
Anthony F. Maciorowski,
Deputy Director, EPA Science Advisory Board Staff Office.

Attachment C: Teleconference Agenda

**U.S. Environmental Protection Agency – Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
Oxides of Nitrogen (NO_x) Primary Review Panel
Public Teleconference
December 5, 2008
1:00 a.m. to 3:00 p.m. Eastern time
Agenda**

Purpose: to review EPA's completed Risk and Exposure Assessment (REA) to support the review of the NO₂ Primary National Ambient Air Quality Standard (NAAQS)

1:00 p.m.	Convene the planning teleconference; take roll	Dr. Angela Nugent, EPA SAB Staff Office, Designated Federal Officer
1:05 p.m.	Agenda review	Dr. Jonathan Samet, Chair
1:10 p.m.	REA Chapter 10 Overview and NAAQS Update	Dr. Scott Jenkins, EPA OAR
1:20 p.m.	Public Comments	TBA
1:30 p.m.	Report from panel workgroup on exposure	Dr. Douglas Crawford-Brown, Workgroup chair
1:45 p.m.	Panel discussion	CASAC Panel
2:45 p.m.	CASAC Review/Acceptance of panel report and identification of next steps	Dr. Jonathan Samet
3:00 p.m.	Adjourn	Dr. Angela Nugent

Attachment D
Presentation: NO₂ Primary NAAQS Review:
Final Risk and Exposure Assessment Document

Slide 1

 United States Environmental Protection Agency
Office of Air Quality Planning and Standards

NO₂ Primary NAAQS Review:
Final Risk and Exposure Assessment Document



Office of Air and Radiation
Office of Air Quality Planning and Standards

Slide 2

 United States Environmental Protection Agency
Office of Air Quality Planning and Standards

Timeline for NO₂ Rulemaking

Major Rulemaking Milestones	Projected Date
ANPR Signed	January 9, 2009
ANPR Published	January 16, 2009
Proposal	June 26, 2009*
Final	January 22, 2010*

*These dates reflect a 1-month extension that has been agreed to by the plaintiffs but has not yet been officially entered by the court

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Slide 3

 United States Environmental Protection Agency

Office of Air Quality Planning and Standards

Overview of Major Changes Made From 2nd Draft REA

- Changes in analyses
 - Made our evaluations of alternative standards consistent, such that all alternative standards are now based on 1-h daily maximum NO₂ concentrations (chapter 7)
 - Air quality health characterization is now based on the number of times the daily maximum 1-hour NO₂ concentration exceeds benchmarks rather than number of hours with exceedances (chapter 7)
 - Ambient monitors separated into 3 near-road distance categories (≤ 20 m; > 20 m and < 100 m; ≥ 100 m) rather than the two done previously (< 100 m; ≥ 100 m) (chapter 7)
 - Enhanced uncertainty analyses including...
 - A sensitivity run that estimated on-road concentrations using a lognormal distribution (section 7.4.6)
 - AERMOD evaluation of the vertical concentration gradient (section 7.4.4)
 - APEX model sensitivity runs using alternative inputs (section 8.12.2)
 - Tables summarizing the qualitative analysis of uncertainty for the air quality and Atlanta exposure analyses (tables 7-31, 8-17)
- Topics for which discussions have been expanded and/or modified
 - Representativeness of the Atlanta results for the rest of the U.S. (8.11)
 - NO₂ monitoring network (sections 2.2.1 and 7.2.3)
 - Distinction between potential health benchmark levels and alternative standards (sections 4.5.3, 5.5, 6.2)
 - Justification for focusing on health endpoints with causal and likely-causal judgments in the ISA (sections 4.5.1, 10.3.1)
 - Consideration of indoor studies (sections 4.3.2, 4.5.2, 10.3.1)

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Slide 4

 United States Environmental Protection Agency

Office of Air Quality Planning and Standards

Overview of Major Changes Made From 2nd Draft REA: Addition of Chapter 10

Purposes of chapter 10:

- Provides a framework for the policy assessment that will be included in the ANPR
- Presents the analyses and approaches that will be used in considering whether to retain or revise the NO₂ NAAQS
- Considers the scientific evidence and the exposure-/risk-based information specifically as it relates to the issues of...
 - Adequacy of the current standard
 - Indicator
 - Averaging time
 - Form
 - Level

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Slide 5

 United States Environmental Protection Agency

Office of Air Quality Planning and Standards

Final REA: Conclusions on Adequacy of the Current Standard

- The scientific evidence clearly calls into question the adequacy of the current standard to protect public health and supports consideration of a short-term NO₂ standard that would provide increased health protection for sensitive groups
 - Causality judgments in ISA provide stronger support for effects associated with short-term exposures than long-term exposures
 - ISA concludes that the evidence supports a direct effect of short-term NO₂ exposure on respiratory morbidity at ambient concentrations allowed by the current NAAQS
- Exposure- and risk-based results reinforce the scientific evidence in supporting the conclusion that consideration should be given to revising the current standard so as to provide increased public health protection
 - Results of exposure and risk analyses indicate that appreciable health risks could occur in a hypothetical scenario in which air quality were to just meet the current standard

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 United States Environmental Protection Agency

Office of Air Quality Planning and Standards

Final REA: Conclusions on Averaging time

- The primary focus of an NO₂ standard should be to protect against short-term exposures
 - Conclusions in the ISA support the importance of protecting against respiratory effects associated with short-term exposures
 - Epidemiologic studies have reported associations with both 1-h (daily max) and 24-h (average) NO₂ concentrations
 - Controlled human exposure and animal toxicological studies have reported effects following NO₂ exposures of shorter duration than 24 hours (e.g., 1-h to 3-h)
- A standard based on 1-h daily maximum NO₂ concentrations could provide protection against health effects associated with short-term exposures and potential effects associated with long-term exposures
 - Analysis of air quality suggests that a 1-h (daily max) standard could provide protection against 24-h concentrations
 - A 1-h (daily max) standard of 100 ppb or below could maintain annual average NO₂ concentrations below current standard level
- An annual standard is not an effective or efficient approach to protecting against short-term exposures
 - A standard based on annual average concentrations would likely require more control than necessary in some areas and/or less control than necessary in others

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United States
Environmental Protection
Agency

Office of Air Quality Planning and Standards

Final REA: Conclusions on Form and Level

- For 98th and 99th percentile forms (and a 1-h daily maximum averaging time), the scientific evidence supports a range of levels from 50 ppb to 200 ppb
 - Based on key U.S. epidemiologic studies and controlled human exposure studies of airway hyperresponsiveness
- When the scientific evidence is considered in conjunction with exposure and risk results, the strongest support is for standards based on 98th/99th percentile 1-h daily maximum NO₂ concentrations between 50 and 100 ppb
 - This represents a range of levels that is consistent with the scientific evidence and that would be expected to provide improved public health protection relative to that provided by the current annual standard

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**Comments of Deborah Shprentz
Consultant to the American Lung Association on
EPA's Risk and Exposure Assessment (REA) to Support the Review of the
NO₂ Primary National Ambient Air Quality Standard
EPA-452/R-08-008a November 2008
Chapter 10: Evidence- and Exposure/Risk -Based Considerations
Related to the Primary NO₂ NAAQS**

CASAC Meeting December 5, 2008

The American Lung Association offers these comments on the policy options for revision the NAAQS for nitrogen dioxide (NO₂) discussed in chapter 10 of the Risk and Exposure Assessment (REA)..

In the REA, EPA suggests eliminating the annual average standard and replacing it with a 1-hour daily maximum concentration (98th or 99th percentile form) in the range of 50 to 200 ppb, with strongest support for a standard level between 50 and 100 ppb.

The American Lung Association recommends EPA:

- Add a 1-hour standard with a level set below 50 ppb using a tighter form than proposed here; and
- Retain, but strengthen the annual average standard.

Range of Potential 1-Hour Standards Should Be Changed

EPA relies on the Delfino et al., (2002) study to define a lower end of the range, focusing on the 98th and 99th percentile 1-hour daily maximum NO₂ concentrations in this study. We recommend that EPA look at the mean concentrations at which effects occurred (as well as 1 standard deviation below the mean) and set a standard below this level that incorporates a margin of safety to protect against the adverse effects.

The respiratory morbidity observed in this study did not just occur at the high end of the distribution. The adverse effects reported in this study occurred at the mean concentration, as well as above and below the mean. A standard based on the highest concentrations during the study period cannot possibly be protective of public health. A more appropriate statistic to focus on would be that mean concentration of 23.7 ppb.

Table 1 below notes the mean 1-hour daily maximum NO₂ concentrations for the other key epidemiological studies identified in Chapter 10. These studies clearly identify

adverse health effects such as emergency room visits and hospital admissions for respiratory causes at concentrations currently occurring in the U.S. Mean concentrations for all but one of these studies are about or below 50 ppb, suggesting that the standard must be set below this level to allow for a margin of safety.

Table 1: Mean 1-hr Daily Max NO₂ Concentrations Compared to 98th Percentile

Study	Mean 1-hr Daily Max (ppb)	98 th Percentile
Delfino	23.7	50
Peel (study period 1)	45.9	87
Peel (study period 2)	43.2	85
Jaffee	51	86
Ito	52	94
Ostro	71-75	180 -170
Linn	72	178
NYC - Manhattan	50	86
NYC - Bronx	49	88

Source: Thompson R, Jenkins S. Memo to NO₂ NAAQS Review Docket, “Air Quality Statistics for Cities Referenced in Key U.S. Nitrogen Dioxide Epidemiology Papers”

We note that the highest mean concentration reported in this set of studies is 75 ppb. With that as the data boundary, these studies cannot be used to justify an upper end of the range of 100 ppb.

Further, we note that there no data are offered to suggest that a uniform relationship exists between mean and 98th percentile concentrations in regions throughout the United States.

The upper ranges considered in the REA have no basis in the evidence and should be eliminated from further consideration. The meta-analysis of the clinical studies reports adverse effects such as increased airway hyperreactivity at concentrations of 100 ppb, which is the lowest level that was studied. This suggests that the upper end of the range of 100 ppb cannot possibly be protective of public health because there is no margin of safety, and that the 200 ppb level is completely unjustified. Additionally, most controlled human exposure studies do not include severe asthmatics or young children, so the regulatory levels must be set below the lowest observed adverse effect levels.

Form of the 1-Hour Standard Should Be Strengthened

The Lung Association favors a no exceedance form of the standard as opposed to a 98th percentile form, which allows 7-8 exceedance days each year to be excused from nonattainment determinations. EPA seems hyper-focused on the “stability” of the

Attachment E

standard at the expense of precautionary protection of health—stability being defined areas that show consistency in their nonattainment status. The purpose of a short-term standard should be to prevent short-term spikes. Instead, the Agency suggests a 98th or 99th percentile form of the standard that would permit multiple exceedances each year. Furthermore, the Agency suggests that nonattainment be measured based on three years of monitoring data. This approach accounts for meteorological variation from year to year that can affect attainment determinations, creating the perverse situation where a standard based on peak exceedances allows 21 or more exceedances days in a three-year period to be completely ignored.

Annual Average Standard Should be Retained and Strengthened

The Lung Association concurs with EPA's conclusion that the current annual average standard is insufficient to protect public health with an adequate margin of safety. However, we believe that the annual standard should be strengthened, as well as supplemented with a short-term 1-hour standard.

EPA's review of the scientific evidence in the ISA concludes that there is "suggestive" evidence of respiratory morbidity, specifically decrements in lung function growth associated with long-term exposure to NO₂. In light of this suggestive evidence, it would be prudent to retain and strengthen annual average standard. We note that based on a review of the same evidence considered by EPA, in 2008, California decided to establish a new annual average standard for NO₂, at a far lower concentration than the current NAAQS.

Improvements Needed in Monitoring

The current monitoring network is not sufficient. It fails to detect the maximum concentrations of NO₂ to which people may be exposed. The REA indicates that only 58 of 489 total NO₂ monitors are sited in areas of expected peak concentrations. More critically, it is evident that monitors are not routinely located near roadways where the REA indicates that the highest exposures are expected. Any revisions to the NAAQS must be accompanied to changes to the monitor siting criteria to ensure that attainment is measured against monitors that reflect peak exposures.

**Comments on Chapter 10 of the Final Risk and Exposure Assessment to Support the Review of the
NO₂ Primary National Ambient Air Quality Standard
(Docket ID. No. EPA-HQ-2006-0922)**

**Julie E. Goodman, PhD, DABT
Gradient Corporation, Cambridge, MA**

on behalf of the American Petroleum Institute

December 1, 2008

Chapter 10 of the *Risk and Exposure Assessment to Support the Review of the NO₂ Primary National Ambient Air Quality Standard* (hereafter referred to as the "REA") assesses the adequacy of the current nitrogen dioxide (NO₂) primary National Ambient Air Quality Standard (NAAQS) of 0.053 ppm (annual average) and alternative primary NO₂ standards (US EPA, 2008a). This assessment is based on the scientific evidence provided in the NO₂ *Integrated Science Assessment for Oxides of Nitrogen* (hereafter referred to as the "ISA") and the exposure and risk characterization data presented in the REA (US EPA, 2008a,b). US EPA concluded that "the scientific evidence reasonably supports a range of standard levels from 50 ppb to 200 ppb, with strong support for a level at or below 100 ppb" based on fewer NO₂-related emergency department (ED) visits, on average, than those associated with just meeting the current standard. US EPA based this conclusion on epidemiology studies focused on these concentrations, and noted that this is also supported by "1) evidence from controlled human exposure studies of airway hyper-responsiveness in asthmatics, 2) controlled human exposure and animal toxicological studies of impaired host-defense systems and increased risk of susceptibility to viral and bacterial infection, and 3) controlled human exposure and animal toxicological studies of airway inflammation" (US EPA, 2008a). The REA fails to consider several issues, discussed below, which suggest that clinical and epidemiology studies do not provide a sufficient scientific basis for establishing a 1-hr standard of 0.05 to 0.1 ppm NO₂.

1. Studies assessing the association between 1-h daily maximum levels of NO₂ close to 0.1 ppm or 0.2 ppm and respiratory morbidity do not support causation.

US EPA (2008a) primarily relies on six studies to support an appropriate upper end of the range of the 1-h daily maximum NO₂ standard. Four of these focused on maximum 1-h NO₂ levels of approximately 0.1 ppm (Peel *et al.*, 2005; NYDOH, 2006; Ito *et al.*, 2007; Tolbert *et al.*, 2007). The REA reports:

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Positive and statistically-significant associations were observed in several key US epidemiologic studies associated with 1-h daily maximum levels of NO₂ close to 0.1 ppm (Peel *et al.*, 2005; NYDOH, 2006; Ito *et al.*, 2007; Tolbert *et al.*, 2007) (see Figure 5-1). In multi-pollutant models, effect estimates remained statistically-significant in the study by Ito and positive, but non-significant, in the other studies.

This statement is misleading. There were several single-pollutant models in these studies that did not produce statistically significant effects. For example, the association between NO₂ and ED visits for asthma in the Peel *et al.* (2005) study was not statistically significant. In addition, there was a "key" study identified in Chapter 5 (Jaffe *et al.*, 2003) for which there were no statistically significant risks based on single-pollutant models that was not discussed in Chapter 10. Also, the risk estimates that were statistically significant in the studies noted above were not robust; that is, they were small in magnitude and their lower 95% confidence intervals (95% CIs) were close to 1. Both null results and the strength of significant associations should be considered in a proper weight-of-evidence analysis, but the REA does not do this. It should also be noted that statistical significance in these models did not fully account for all uncertainties, such as measurement error and exposure misclassification. Had these uncertainties been accounted for, it is possible that the risk estimates would not have been statistically significant. Finally, and perhaps most importantly, Chapter 10 of the REA does not give appropriate weight to the correlation of NO₂ with other co-pollutants, or that the study by Ito *et al.* (2007) was the only study reporting statistically significant effects in multi-pollutant models. Moreover, despite reporting significant effects using a multi-pollutant model, Ito *et al.* stated: "NO₂ may be a good indicator of more air pollution from local combustion sources. NO₂ is sometimes referred to as a surrogate marker of traffic-related air pollution." They suggested that it may be a surrogate for ultrafine particles or an agent "that may or may not be measured regularly and yet has some potential health effects."

In addition to the studies assessing health effect at NO₂ concentrations around 0.1 ppm, the REA relies on two studies with the highest 1-h NO₂ concentrations. Regarding these studies, US EPA (2008a) states:

Positive and statistically-significant NO₂ effect estimates were also observed in the two key US studies associated with the highest 1-h NO₂ concentrations (Linn *et al.*, 2000; Ostro *et al.*, 2001). These studies were associated with 98th and 99th percentile 1-h daily maximum NO₂ concentrations from 0.18 ppm to 0.21 ppm. These studies did not evaluate multi-pollutant models. Therefore, they do not provide additional support for an

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independent association between NO₂ and respiratory morbidity beyond that provided by the studies noted above.

It is notable that the REA acknowledges that these studies are not useful for assessing the causal association between short-term NO₂ exposure and respiratory morbidity because effects were not evaluated in multi-pollutant models. This is not consistent with their evaluation of studies assessing 1-h daily maximum levels of NO₂ close to 0.1 ppm, for which statistically significant effects were not found in multi-pollutant models except those described by Ito *et al.* (2007), but for which US EPA still considered to provide evidence of positive associations with NO₂. The REA should put more emphasis on multi-pollutant models, particularly when results differ from single pollutant models.

In sum, there is no weight-of-evidence assessment in Chapter 10 of the REA. US EPA (2008a) does not consider all data (statistically significant and not) equally, nor does it consider the uncertainties associated with exposure measurements and the likelihood that associations between respiratory morbidity and short-term NO₂ may actually be attributable to other factors. Thus, these epidemiology studies do not provide sufficient evidence for an upper end of the range of the 1-h daily maximum NO₂ standard.

2. The study by Delfino *et al.* (2002) does not provide sufficient evidence for determining an appropriate lower end of the range of levels for a standard.

One of two primary factors US EPA (2008a) considered for determining the lower end of the range of levels for the standard that are supported by the evidence was the study by Delfino *et al.* (2002). Regarding this study, US EPA states:

[T]he study by Delfino *et al.*, (2002) provides evidence for associations between short-term ambient NO₂ concentrations and respiratory morbidity in a location where NO₂ concentrations were well below levels in most other key US epidemiologic studies. This study reports positive associations between 1-h and 8-h (only 8-h associations were statistically-significant) levels of NO₂ and asthma symptoms in a location where the 98th and 99th percentile 1-h daily maximum NO₂ concentrations were 0.05 and 0.053 ppm, respectively.

In fact, the study by Delfino *et al.* (2002) does *not* provide sufficient evidence for determining the lower end of the range for several reasons. There were only 22 asthmatic children in this study and analyses stratified by medication use (on/off) were conducted using only 10 and 12 children, respectively. These small numbers could have lead to unstable estimates and spurious results. As with several other

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studies, Delfino *et al.* (2002) relied on fixed site monitors to determine levels in individuals, and this could have lead to exposure misclassification, also leading to spurious results (and at the very least, led to a higher degree of uncertainty that was not accounted for). Eight-h max NO₂ was statistically significantly correlated with every other independent variable assessed in this study (*i.e.*, 8-h max O₃, 1-h max PM₁₀, 24-h mean PM₁₀, 1-h max NO₂, 12-h daytime fungi, 24-h pollen, max temperature, and 24-h mean relative humidity) and 1-h max NO₂ was statistically significantly correlated with all of these except 8-h max O₃ (see Table 3, Delfino *et al.*, 2002). Any statistically significant associations observed between 8-h NO₂ and asthma symptoms may have been attributable to one of these other factors. Finally, Delfino *et al.* (2002) stated that their sensitivity analysis "identified the need for both a greater amount of data to model the shape of the exposure-response curve and better modeling strategies to determine that shape." Given this high level of uncertainty, the Delfino *et al.* (2002) study is not appropriate for determining the lower end of the range of the standard.

3. Clinical studies do not support a causal association between short-term NO₂ exposure and increased airway hyper-responsiveness.

Overall, results from the clinical, controlled-exposure studies do not provide clear evidence that there is a causal association between short-term (*i.e.*, less than 2 hours) exposure to NO₂ and increased airway hyper-responsiveness in individuals with asthma. US EPA's determination that increased airway hyper-responsiveness to non-specific bronchial challenges occurs at near ambient concentrations (0.1 – 0.3 ppm) relies primarily on US EPA's unpublished meta-analysis of controlled exposure studies (Section 3.1.3.2 of the ISA, US EPA, 2008b). US EPA's analysis is based on a meta-analysis published by Folinsbee (1992), and excludes studies that used specific allergen challenges, but includes an additional, more recent study that used a non-specific bronchial challenge. US EPA's meta-analysis also focuses on results involving resting exposures to NO₂, for which the response was greater than for studies that involved NO₂ exposures during exercise. US EPA's determination is questionable in that there is no clear relationship between NO₂ concentration and airway hyper-responsiveness for concentrations up to 1.0 ppm; the majority of the studies included in the meta-analysis do not show any statistically significant or biologically meaningful effect due to NO₂ exposure; the greater response for subjects at rest contradicts results from other studies and does not have a readily explainable biological basis; and the weight-of-evidence from more recent studies does not indicate that NO₂ exposure up to a concentration of at least 0.4 ppm has a significant effect on airway hyper-responsiveness either for individuals with or without asthma.

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A key tenet in establishing a causal relationship between an exposure and a subsequent response is that the magnitude of the response should increase as exposure increases. Yet, as shown in Figure 1, there is no clear relationship between NO₂ concentration and non-specific airway hyper-responsiveness for the studies included in the Folinsbee (1992) meta-analysis.

Figure 1a

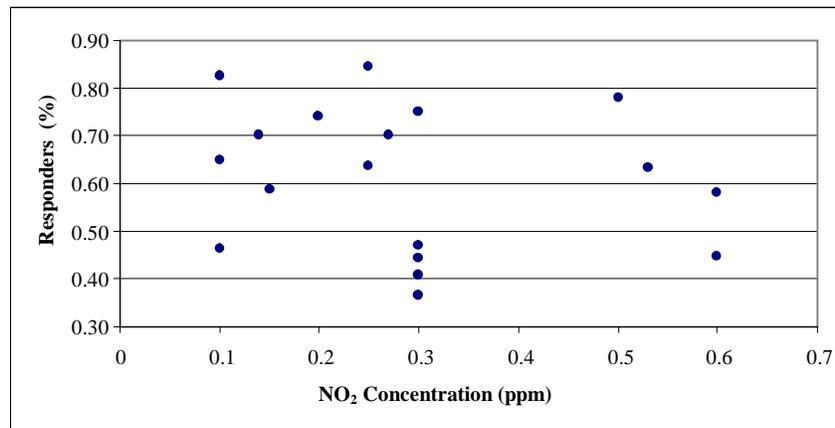


Figure 1b

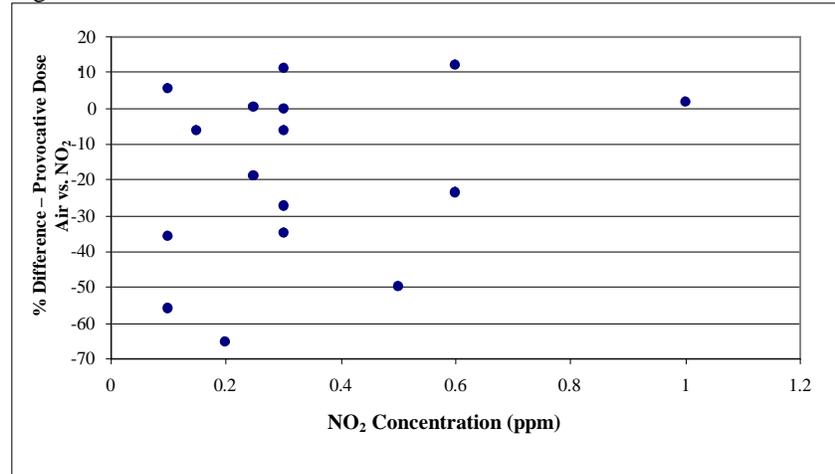


Figure 1. Top panel (a) shows the percent of study subjects who responded to NO₂ exposure with increased airway hyper-responsiveness (relative to the number of subjects who responded with both increased and decreased airway hyper-responsiveness but excluding those with no change) as a function of NO₂ concentration. Bottom panel (b) shows the percent difference in the provocative dose required for an airway response following exposure to either air or NO₂, as a function of NO₂ concentration. Data from individual studies are plotted as individual circles, based on Folinsbee (1992). Note that in Figure 1a, the percent of positive responders is overestimated because subjects whose airway response did not differ between air and NO₂ were excluded, and because it likely includes subjects whose change in responsiveness was within the range of normal intra-individual variability. Figure 1b excludes results from two studies, at 0.2 and 0.8 ppm, with a difference between air and NO₂ of 0.02 and -0.06, respectively, because Folinsbee did not provide data on the magnitude of the response.

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Importantly, the lack of a concentration-response relationship for the studies included in the Folinsbee (1992) meta-analysis is similarly borne out in individual studies from the Folinsbee analysis that have evaluated more than one NO₂ concentration, none of which show a concentration-response between NO₂ exposure and airway hyper-responsiveness (*e.g.*, Avol *et al.*, 1988; Bylin *et al.*, 1988; Jorres and Magnussen, 1990; Linn *et al.*, 1986; Rasmussen *et al.*, 1990, as cited in Folinsbee, 1992; Roger *et al.*, 1990). Further, the lack of a concentration-response for the studies included in the Folinsbee meta-analysis is understandable when evaluating the individual studies, the majority (15 of 20) of which did not show differences in response that were either statistically significant or biologically meaningful.

In the Folinsbee (1992) meta-analysis, a statistically significant relationship between NO₂ and airway hyper-responsiveness is observed only for subjects who were exposed at rest, but not while exercising. This counter-intuitive observation contradicts results from many controlled exposure studies which find that exercise enhances airway response to inhaled pollutants (*e.g.*, Bauer *et al.*, 1986; Linn *et al.*, 1985; Rubinstein *et al.*, 1990; Sheppard *et al.*, 1981). To explain the inconsistency between the meta-analysis and results from other studies, Folinsbee cites a study by Inman *et al.* (1990), in which responsiveness to methacholine is reduced *during* exercise; as well as a study by Freedman *et al.* (1988, as cited in Folinsbee), in which methacholine-induced bronchoconstriction is reduced more rapidly with exercise. However, in the studies cited by Folinsbee, exercise *preceded* the methacholine challenge (*i.e.*, Jorres and Magnussen, 1991; Kleinman *et al.*, 1983; Roger *et al.*, 1990; Strand *et al.*, 1996). Hence, the studies by Inman *et al.* and Freedman *et al.* that Folinsbee cites do not necessarily explain the paradox observed by Folinsbee of a greater effect on airway responsiveness at rest *vs.* with exercise.

As with many of the studies included in the Folinsbee analysis, more recent studies similarly do not indicate that short-term exposure (30 minutes to 6 hours) to NO₂, at levels ranging from 0.2 to 0.4 ppm, affects airway hyper-responsiveness (*e.g.*, Barck *et al.*, 2005; Jenkins *et al.*, 1999; Strand *et al.*, 1998; Witten *et al.*, 2005). These more recent studies evaluated airway response to naturally occurring allergens, including plant allergens (*e.g.*, birch, grass, timothy) and house dust mites.

Taken together, the clinical studies do not support a causal association between short-term NO₂ exposure and increased airway hyper-responsiveness.

4. US EPA overestimated the percentage of asthmatics who may experience NO₂-related airway hyper-responsiveness.

US EPA estimated the percentage of asthmatics who may be sensitive to NO₂-induced hyper-responsiveness based on the percentage of positive responders (*i.e.* individuals with increased airway hyper-responsiveness following exposure to NO₂) relative to the number of positive responders plus the number of negative responders (*i.e.*, individuals with decreased airway hyper-responsiveness following NO₂ exposure), as reported by Folinsbee (1992). However, the studies in the Folinsbee meta-analysis also included data for individuals whose response did not differ between NO₂ and air, and who presumably would not be sensitive to NO₂-induced hyper-responsiveness. For example, the study by Orehek *et al.* (1976) included data for three individuals whose response did not differ between NO₂ and air. By excluding this data, US EPA overestimated the percentage of individuals with asthma who may be susceptible to NO₂-related airway hyper-responsiveness.

A second way in which US EPA may have overestimated the number of individuals potentially sensitive to NO₂-induced hyper-responsiveness is by classifying as positive responders individuals whose response was within normal range of intra-individual variability. As US EPA correctly notes in the REA (US EPA, 2008a), the Folinsbee meta-analysis does not account for the magnitude of response. Yet it is important to distinguish responses which may be due to normal day-to-day variability from responses which are truly due to NO₂ exposure. Potential intra-individual variability can be estimated roughly based on responses of subject number 16 in the study by Orehek *et al.* (1976), who was exposed twice to air and twice to NO₂. Using this estimate of intra-individual variability, there at least six individuals classified as positive responders whose responses may have been due to normal variability rather than to any effect of NO₂.

A third way in which US EPA may have overestimated the number of individuals potentially susceptible to NO₂-induced hyper-responsiveness is by limiting their analysis to non-specific airway hyper-responsiveness, following challenge with pharmacological agents such as methacholine and carbochol, high concentrations of sulfur dioxide (SO₂), or cold air. In their own, unpublished meta-analysis, US EPA (2008b) has excluded studies from the Folinsbee (1992) analysis that used specific challenges (*i.e.*, allergens, such as ragweed), and has added a more recent study by Strand *et al.* (1996) that used a non-specific histamine challenge. Moreover, both of the studies that used SO₂ challenges assessed responsiveness to SO₂ using hyperventilation, which by itself can increase airway hyper-responsiveness

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(discussed in US EPA, 1993). Non-specific challenges to methacholine, carbachol, and high concentrations of SO₂ may overestimate responses to relevant challenges, such as ragweed, grass, and cold air, that individuals may actually be exposed to in their daily lives. Among studies that used specific allergen challenges (*i.e.*, ragweed, grass) or cold, which are more relevant than challenges with carbachol, methacholine, or hyperventilated SO₂, a significant effect of NO₂ on hyper-responsiveness was observed only in the study by Bauer *et al.* (1986). The enhanced response to NO₂ in the study by Bauer *et al.* may be at least partly due to use of a mouthpiece for exposing subjects to NO₂. As discussed by Sheppard *et al.* (1984), mouthpiece exposures tend to over-estimate responses relative to exposures involving more natural, oronasal breathing.

By excluding individuals whose responses did not differ between NO₂ and air, by not accounting for intra-individual variability, and by limiting their analysis to non-specific airway hyper-responsiveness, US EPA overestimated the percentage of asthmatics who may experience NO₂-related airway hyper-responsiveness.

5. Evidence from epidemiological and clinical studies does not consistently support a linear no-threshold dose-response association between short-term NO₂ exposure and respiratory morbidity.

With regard to the epidemiological evidence, US EPA (2008a) primarily relies on section 5.3.2.9 (p. 5-15) of the ISA, which concludes that the NO₂ epidemiologic studies provide "little evidence of any effect threshold." In Chapter 4 of the ISA, US EPA (2008b) states:

[O]f the epidemiology studies that attempted to look at the shape of the concentration-response below 50 ppb, one indicated that effects were weaker at lower levels (Hajat *et al.* 1999), and one showed a steeper log-linear relationship at lower doses (Burnett *et al.* 1997c). The remainder found that a linear function best described the data (Burnett *et al.* 1997a,b; Jaffe *et al.* 2003; Tenias *et al.*, 1998; Castellsague *et al.*, 1995). These results do not provide adequate evidence to suggest that nonlinear departures exist along any part of this range of NO₂ exposure concentrations.

US EPA (2008b) suggests several reasons why "it is difficult to identify any threshold that may exist." These are described in Chapter 5 of the ISA, where US EPA (2008b) states:

Factors that made it difficult to identify any threshold that may exist included: interindividual variation; additivity of pollutant-induced effects to the naturally occurring

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background disease processes; additivity to health effects due to other environmental insults having a mode of action similar to that of NO₂; exposure error; and response measurement error. Low data density in the lower concentration range as a result of limited monitoring is a particular problem in terms of measurement error. Additionally, if the concentration-response relationship was shallow, identification of any threshold that may exist will be more difficult to discern.

This statement is only partially correct. Some of these factors, such as a shallow concentration-response curve and low data density, may mask a threshold if one exists, as the ISA correctly notes. The other factors will not confound the identification of a threshold, but may change the shape of the concentration-response curve. It is conceivable that US EPA is implying that these other factors will lead to a linear low-dose concentration-response curve which, by definition, has no threshold. This view was recently put forth by White *et al.* (2008), who suggested that interindividual variation, exposure misclassification, and additivity-to-background will “tend to smooth and linearize the dose-response relationship.” In reality, however, this is not always the case (Rhomberg, 2008). Interindividual variation may broaden the concentration-response curve, but it will not linearize it (as suggested by White *et al.*, 2008). Exposure misclassification may also flatten a concentration-response curve, and may mask what may in fact be a steeper curve. Additivity-to-background may support a linear model, but only under certain situations. It is incorrect to assume it will always do so, and the REA has not assessed whether it does or does not in this situation.

Although several studies cited in the ISA reported that a linear model provided the best fit to the data, these data have many uncertainties (*e.g.*, exposure misclassification, measurement error), few of which are accounted for in statistical models. Even if a linear model best describes the reported data, it is plausible that a non-linear model would have better described the data were these uncertainties taken into account. Because of the many uncertainties, the currently-available NO₂ epidemiology data are simply not robust enough to determine whether a linear no-threshold dose-response model describes the association between short-term NO₂ exposure and respiratory morbidity.

While it may be difficult to discern whether or not the epidemiology data support a linear, no threshold concentration-response relationship between NO₂ and morbidity, the clinical data do not support a linear relationship between NO₂ exposure and airway hyper-responsiveness, as discussed in Section 3. Because some of the uncertainties in epidemiology studies, such as exposure misclassification, are controlled in the clinical studies, it is much easier to discern the nature of concentration-response

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relationship for clinical studies. As noted, neither a meta-analysis of the Folinsbee studies, nor individual studies that evaluated more than one NO₂ exposure concentration, provide evidence that the NO₂ concentration-response relationship is linear, with no threshold. Jenkins *et al.* (1999), who evaluated NO₂-induced airway hyper-responsiveness following a specific allergen challenge with house dust mite, similarly concluded that there may be a threshold for the effects of NO₂ on airway responses:

These results suggest that the pollutant-induced changes in airway response of mild atopic asthmatics to allergen may be dependent on a threshold concentration, rather than the total amount of inhaled over a period of time.

Taken together, the evidence from epidemiological and clinical studies does not consistently support a linear no-threshold dose-response association between short-term NO₂ exposure and respiratory morbidity.

6. Conclusion

In conclusion, neither epidemiology nor clinical studies provide a sufficient scientific basis for establishing a 1-hr standard of 0.05 to 0.1 ppm NO₂. Although statistically significant associations were observed between NO₂ concentrations of approximately 0.1 ppm and ED visits in some (but not all) studies, this association remained significant when exposure to other pollutants was accounted for in only the study by Ito *et al.* (2007), who nonetheless concluded that NO₂ may be a surrogate for some other pollutant with potential health effects, rather than actually causing adverse health effects. The study by Delfino *et al.* (2002), which US EPA relies on for establishing the lower end of potential 1-hour standards at 0.05, is quite small (n = 22) and subject to similar limitations as those studies measuring risks at approximately 0.1 ppm. Thus, it is too uncertain to identify the nature of the concentration-response relationship with any confidence. Although increased airway hyper-responsiveness has been observed in some of the clinical studies at NO₂ concentrations of 0.1 ppm, the majority of clinical studies show no associations with airway hyper-responsiveness at this concentration, and no concentration-response association up to at least 0.4 ppm NO₂. Moreover, we determined that US EPA overestimated the percentage of asthmatics who may experience NO₂-related airway hyper-responsiveness. Finally, neither epidemiological or clinical studies consistently support a linear no-threshold dose-response association between short-term NO₂ exposure and respiratory morbidity. Taken together, the weight of evidence does not support changing the current NAAQS to a 1-hr standard of 0.05 to 0.1 ppm NO₂.

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