



**EPA** United States  
Environmental  
Protection Agency

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# **Integrated Review Plan for the Primary National Ambient Air Quality Standard for Nitrogen Dioxide**

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National Center for Environment Assessment  
Office of Research and Development  
and

Office of Air Quality Planning and Standards  
Office of Air and Radiation  
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## **DISCLAIMER**

This integrated review plan serves as a management tool for the U.S. Environmental Protection Agency's National Center for Environmental Assessment and the Office of Air Quality Planning and Standards. The approach described in this plan may be modified to reflect information developed during this review and to address advice and comments received from the Clean Air Scientific Advisory Committee and the public throughout this review. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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# 1. INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is conducting a review of the air quality criteria for nitrogen oxides (NO<sub>x</sub>) and the primary (health-based) and secondary (welfare-based) national ambient air quality standards (NAAQS) for nitrogen dioxide (NO<sub>2</sub>). The purpose of this document is to communicate the plan for reviewing the air quality criteria for NO<sub>x</sub> associated with human health affects and the primary NAAQS for NO<sub>2</sub>. The review of the secondary NAAQS for NO<sub>2</sub>, to be conducted in conjunction with the review of the secondary NAAQS for sulfur dioxide (SO<sub>2</sub>), will be addressed in a separate plan.

This review will provide an integrative assessment of relevant scientific information on NO<sub>x</sub> and will focus on the basic elements of the primary NO<sub>2</sub> air quality standard: the indicator, averaging time, form,<sup>1</sup> and level. These elements, which serve to define each ambient air quality standard, must be considered collectively in evaluating the health protection afforded by the standard. The current standard uses NO<sub>2</sub> as the indicator for the broader mix of gaseous nitrogen oxides in the ambient air. It is defined in terms of an annual averaging time, calculated as the arithmetic mean of hourly averages, and a level of 0.053 parts per million (ppm).

This review plan is organized into six chapters. Chapter 1 presents background information on the review process, the legislative requirements for the review of the NAAQS, past reviews of the NAAQS for NO<sub>2</sub>, and the scope of the current review. Chapter 2 presents the current review schedule. Chapter 3 presents a set of policy-relevant questions that will serve to focus this review on the critical scientific and policy issues. Chapters 4 through 6 discuss the planned scope and organization of the key assessment documents, the planned approaches for preparing the documents, and plans for scientific and public review of the documents. As the assessments proceed, the plan described here may be modified to reflect information received during the review process.

## 1.1 OVERVIEW OF THE REVIEW PROCESS

The Agency has recently decided to make a number of changes to the process for reviewing the NAAQS (described at <http://www.epa.gov/ttn/naaqs/>). In making these changes,

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<sup>1</sup> The “form” of a standard defines the air quality statistic that is to be compared to the level of the standard in determining whether an area attains the standard.

1 the Agency consulted with the Clean Air Scientific Advisory Committee (CASAC), which  
2 provides advice to the Administrator on key elements of NAAQS reviews, and the public. This  
3 new process, which is being applied to the current review of the NAAQS for NO<sub>2</sub>, contains four  
4 major components. Each of these components is described in this section.

5 The first component of the review process is the development of an integrated review  
6 plan. This plan presents the schedule for the review, the process for conducting the review, and  
7 the key policy-relevant science issues that will guide the review. This final integrated review  
8 plan has been informed by input from CASAC, outside scientists, and the public. For purposes  
9 of this review (and for the Agency's concurrent review of the SO<sub>2</sub> primary NAAQS), the 7-  
10 member CASAC has been supplemented by additional scientific experts, collectively referred to  
11 as the CASAC NO<sub>x</sub> and SO<sub>x</sub> Primary Review Panel (see appendix).

12 The second component of the review process is a science assessment. Under the new  
13 process, a concise synthesis of the most policy-relevant science will be compiled into an  
14 Integrated Science Assessment (ISA), which will be informed by input from CASAC, outside  
15 scientists, and the public. The ISA for this review of the air quality criteria for NO<sub>x</sub> will  
16 critically evaluate and integrate scientific information on the health effects associated with  
17 exposure to NO<sub>x</sub> in the ambient air. It will focus on scientific information that has become  
18 available since the last review and will reflect the current state of knowledge on the most  
19 relevant issues pertinent to the review of the primary NO<sub>2</sub> NAAQS. The ISA will be supported  
20 by more detailed information about the scientific literature, which will be compiled into a series  
21 of annexes. The ISA and its annexes will replace the Air Quality Criteria Document (AQCD)  
22 from previous NAAQS reviews.

23 The third component of the review process is a risk/exposure assessment, which will be  
24 informed by input from CASAC, outside scientists, and the public. This assessment will  
25 develop, as appropriate, quantitative estimates of human exposures and/or risks associated with  
26 current ambient levels of NO<sub>2</sub>, with levels that just meet the current standard, and with levels that  
27 just meet possible alternative standards. EPA will prepare a concise risk/exposure assessment  
28 report that focuses on key results, observations, and uncertainties.

29 The fourth component of the revised process is a policy assessment/rulemaking. Under  
30 the new process, a staff paper, such as that prepared in previous NAAQS reviews, will not be  
31 prepared. Rather, the Agency's views on policy options will be published in the Federal Register

1 as an advance notice of proposed rulemaking (ANPR). The ANPR will present a policy  
2 assessment and will be accompanied by supporting documents, such as air quality analyses and  
3 technical support documents, as appropriate. Taking into account CASAC advice and  
4 recommendations as well as public comment on the ANPR, the Agency will publish a proposed  
5 rule, to be followed by a public comment period. Taking into account comments received on the  
6 proposed rule, the Agency will issue a final rule to complete the rulemaking process.

## 8 **1.2 LEGISLATIVE REQUIREMENTS**

9 Two sections of the Clean Air Act (CAA) govern the establishment and revision of the  
10 NAAQS. Section 108 directs the Administrator to identify and list “air pollutants” that “in his  
11 judgment, may reasonably be anticipated to endanger public health and welfare” and whose  
12 “presence . . . in the ambient air results from numerous or diverse mobile or stationary sources”  
13 and to issue air quality criteria for those that are listed. 42 U.S.C. § 7408(a) & (b). Air quality  
14 criteria are intended to “accurately reflect the latest scientific knowledge useful in indicating the  
15 kind and extent of identifiable effects on public health or welfare which may be expected from  
16 the presence of [a] pollutant in ambient air . . . .” 42 U.S.C. § 7408(b).

17 Section 109 directs the Administrator to propose and promulgate “primary” and  
18 “secondary” NAAQS for pollutants listed under section 108. 42 U.S.C. § 7409 (a). Section  
19 109(b)(1) defines a primary standard as one “the attainment and maintenance of which in the  
20 judgment of the Administrator, based on such criteria and allowing an adequate margin of safety,  
21 are requisite to protect the public health.”<sup>2</sup> 42 U.S.C. § 7409(b)(1). A secondary standard, as  
22 defined in section 109(b)(2), must “specify a level of air quality the attainment and maintenance  
23 of which, in the judgment of the Administrator, based on such criteria, is required to protect the  
24 public welfare from any known or anticipated adverse effects associated with the presence of  
25 [the] pollutant in the ambient air.”<sup>3</sup> 42 U.S.C. § 7409(b)(2).

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<sup>2</sup> The legislative history of section 109 indicates that a primary standard is to be set at “the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population,” and that for this purpose “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group” [S. Rep. No. 91-1196, 91<sup>st</sup> Cong., 2d Sess. 10 (1970)].

<sup>3</sup> Welfare effects as defined in section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, “effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being.”

1           The requirement that primary standards include an adequate margin of safety was  
2 intended to address uncertainties associated with inconclusive scientific and technical  
3 information available at the time of standard setting. It was also intended to provide a reasonable  
4 degree of protection against hazards that research has not yet identified. See *Lead Industries*  
5 *Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), *cert. denied*, 449 U.S. 1042 (1980);  
6 *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), *cert. denied*, 455  
7 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with  
8 pollution at levels below those at which human health effects can be said to occur with  
9 reasonable scientific certainty. Thus, in selecting primary standards that include an adequate  
10 margin of safety, the Administrator is seeking not only to prevent pollution levels that have been  
11 demonstrated to be harmful but also to prevent lower pollutant levels that may pose an  
12 unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

13           In selecting a margin of safety, the EPA considers such factors as the nature and severity  
14 of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree  
15 of the uncertainties that must be addressed. The selection of any particular approach to  
16 providing an adequate margin of safety is a policy choice left specifically to the Administrator’s  
17 judgment. See *Lead Industries Association v. EPA*, 647 F.2d at 1161-62.

18           In setting standards that are “requisite” to protect public health and welfare, as provided in  
19 section 109(b), EPA’s task is to establish standards that are neither more nor less stringent than  
20 necessary for these purposes. In so doing, EPA may not consider the costs of implementing the  
21 standards. See generally *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472,  
22 475-76 (2001).

23           Section 109(d)(1) requires that “not later than December 31, 1980, and at 5-year intervals  
24 thereafter, the Administrator shall complete a thorough review of the criteria published under  
25 section 108 and the national ambient air quality standards . . . and shall make such revisions in  
26 such criteria and standards and promulgate such new standards as may be appropriate . . . .” 42  
27 U.S.C. § 7409(d)(1). Section 109(d)(2) requires that an independent scientific review committee  
28 “shall complete a review of the criteria . . . and the national primary and secondary ambient air  
29 quality standards . . . and shall recommend to the Administrator any new . . . standards and  
30 revisions of existing criteria and standards as may be appropriate . . . .” 42 U.S.C. § 7409(d)(2).

1 Since the early 1980's, this independent review function has been performed by the Clean Air  
2 Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board.

### 4 **1.3 HISTORY OF REVIEWS OF THE PRIMARY NAAQS FOR NO<sub>2</sub>**

5 On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for NO<sub>2</sub>,  
6 under section 109 of the Act, set at 0.053 parts per million (ppm), annual average (36 FR 8186).  
7 In 1982, EPA published *Air Quality Criteria for Oxides of Nitrogen* (EPA, 1982), which updated  
8 the scientific criteria upon which the initial NO<sub>2</sub> standards were based. On February 23, 1984,  
9 EPA proposed to retain these standards (49 FR 6866). After taking into account public  
10 comments, EPA published the final decision to retain these standards on June 19, 1985 (50 FR  
11 25532).

12 On July 22, 1987, EPA announced that it was undertaking plans to revise the 1982 air  
13 quality criteria (52 FR 27580). In November 1991, EPA released an updated draft air quality  
14 criteria document for CASAC and public review and comment (56 FR 59285). The draft  
15 document provided a comprehensive assessment of the available scientific and technical  
16 information on health and welfare effects associated with NO<sub>2</sub> and other oxides of nitrogen. The  
17 CASAC reviewed the draft document at a meeting held on July 1, 1993 and concluded in a  
18 closure letter to the Administrator that the document "provides a scientifically balanced and  
19 defensible summary of current knowledge of the effects of this pollutant and provides an  
20 adequate basis for EPA to make a decision as to the appropriate NAAQS for NO<sub>2</sub>" (Wolff,  
21 1993). The Air Quality Criteria Document for the Oxides of Nitrogen was then finalized (U.S.  
22 EPA, 1993).

23 The EPA also prepared a draft Staff Paper that summarized a NO<sub>2</sub> exposure assessment  
24 conducted by the Agency (McCurdy, 1994), summarized and integrated the key studies and  
25 scientific evidence contained in the revised air quality criteria document, and identified the  
26 critical elements to be considered in the review of the NO<sub>2</sub> NAAQS. The Staff Paper received  
27 external review at a December 12, 1994 CASAC meeting. CASAC advice and  
28 recommendations and public comments on the first draft Staff Paper were taken into account in  
29 the preparation of the second draft Staff Paper. The CASAC reviewed the second draft of the  
30 Staff Paper in June 1995 and concluded in a closure letter to the Administrator (Wolff, 1995) that  
31 the document provided a "scientifically adequate basis for regulatory decisions on nitrogen

1 dioxide.” In September of 1995, EPA finalized the Staff Paper entitled, “Review of the National  
2 Ambient Air Quality Standards for Nitrogen Dioxide: Assessment of Scientific and Technical  
3 Information” (EPA, 1995).

4 In October 1995, the Administrator announced her proposed decision not to revise either  
5 the primary or secondary NAAQS for NO<sub>2</sub> (60 FR 52874; October 11, 1995). A year later, the  
6 Administrator made a final determination not to revise the NAAQS for NO<sub>2</sub> after careful  
7 evaluation of the comments received on the proposal (61 FR 52852, October 8, 1996). The level  
8 for both the existing primary and secondary NAAQS for NO<sub>2</sub> is 0.053 parts per million (ppm)  
9 (100 micrograms per cubic meter of air [ug/m<sup>3</sup>]), annual arithmetic average, calculated as the  
10 arithmetic mean of the 1-hour NO<sub>2</sub> concentrations.

#### 11 12 **1.4 SCOPE OF THE CURRENT REVIEW**

13 As noted above, in reviewing the NO<sub>2</sub> NAAQS, EPA has historically focused its review  
14 of relevant scientific information on the broad category of nitrogen oxides, while finding it  
15 appropriate to specify the indicator of the standard specifically in terms of NO<sub>2</sub>. The nitrogen  
16 oxides include multiple gaseous (e.g., NO<sub>2</sub>, NO) and particulate (e.g., nitrate) species, both of  
17 which will be considered in characterizing the atmospheric chemistry of NO<sub>x</sub>. Although we  
18 anticipate that the majority of the information available to inform the current review, particularly  
19 with regard to human exposures and health effects, will be specifically for NO<sub>2</sub>, we will consider  
20 the other nitrogen oxides to the extent that information is available and relevant to the review of  
21 the NO<sub>2</sub> NAAQS. In addition, we will consider the possible influence of atmospheric pollutants  
22 other than the nitrogen oxides (e.g., sulfur oxides, carbon monoxide, ozone, particulate matter)  
23 on the role of the nitrogen oxides in health effects.

24 In considering what species of NO<sub>x</sub> are relevant to the review of the NO<sub>2</sub> NAAQS, we  
25 note that the health effects associated with particulate species of nitrogen oxides have been  
26 considered within the context of the health effects of ambient particles in the Agency’s review of  
27 the NAAQS for particulate matter (PM). Thus, the current review of the NO<sub>2</sub> NAAQS will focus  
28 on the gaseous species of nitrogen oxides and will not consider health effects directly associated  
29 with particulate species of nitrogen oxides. In the most recent review of the NAAQS for PM, it  
30 was determined that size-fractionated particle mass, rather than particle composition, remains the  
31 most appropriate approach for addressing ambient PM. This conclusion will be re-assessed in

- 1 the next review; however, at present it would be redundant to also use the NAAQS for NO<sub>2</sub> to
- 2 protect against the health effects of particulate nitrogen oxides.

## 2. REVIEW SCHEDULE

On December 9, 2005, EPA's National Center for Environmental Assessment in Research Triangle Park, NC (NCEA-RTP) announced the initiation of the current periodic review of the air quality criteria for NO<sub>x</sub> and the NO<sub>2</sub> NAAQS and issued a call for information in the Federal Register (70 FR 73236). Table 2-1 outlines the anticipated schedule for this review.<sup>4</sup>

**Table 2-1. Anticipated Schedule for the Review of the Air Quality Criteria for Nitrogen Oxides and the Primary NAAQS for NO<sub>2</sub>**

Stage of Review	Major Milestone	Draft Target Dates
Integrated Plan	Literature Search	Ongoing
	Federal Register Call for Information	December 2005
	Draft Integrated Review Plan	February 2007
	Workshop on science/policy issues	February 2007
	CASAC/public consultation on draft plan	May 2007
	Final Integrated Review Plan	August 2007
Science Assessment	First draft of ISA	August 2007
	CASAC/public review of first draft ISA	October 2007
	Second draft of ISA	February 2008
	CASAC/public review of second draft ISA	May 2008
	Final ISA	July 2008
Risk/Exposure Assessment	Assessment methodology	September 2007
	CASAC/public consultation on methodology	October 2007
	First draft risk/exposure assessments	February 2008
	CASAC/public review of first draft assessments	May 2008
	Second draft of risk/exposure assessments	August 2008
	CASAC/public review of second draft assessments	September 2008
	Final assessments	November 2008
Policy Assessment/Rulemaking	ANPR	December 2008
	CASAC review/public comment on ANPR	January 2009
	Proposed rulemaking	May 2009
	Final rulemaking	December 2009

<sup>4</sup> This schedule is provisional, subject to completion of the the settlement process and entry of an appropriate court order in *Center for Biological Diversity et al. v. Johnson* (D.D.C) Civ. No. 05-01814.

### 3. KEY POLICY-RELEVANT ISSUES

#### 3.1 HISTORICAL PERSPECTIVE

The last review of the NAAQS for NO<sub>2</sub>, completed in 1996, evaluated the need for both a short-term and a long-term standard. That review concluded that exposure to NO<sub>2</sub> is associated with a variety of acute, as well as chronic, health effects. Therefore, in considering the adequacy of the existing standard, the relationship between short-term and annual average ambient levels of NO<sub>2</sub> was evaluated. An analysis of this relationship indicated that areas of the United States that meet the existing annual standard for NO<sub>2</sub> would also not exceed short-term NO<sub>2</sub> levels of potential concern. This analysis, together with the uncertainty surrounding the evidence for health effects following short-term, low-level exposure to NO<sub>2</sub>, informed EPA's conclusion that the existing NO<sub>2</sub> primary NAAQS provided adequate protection from short-term health effects. Therefore, a separate short-term standard was not developed. The current level for both the primary and secondary NAAQS for NO<sub>2</sub> is an annual arithmetic average of 0.053 parts per million.

#### 3.2 ISSUES TO BE CONSIDERED IN THE CURRENT REVIEW

In this review, a series of policy-relevant questions will frame our approach to determining whether the current primary NAAQS for NO<sub>2</sub> should be retained or revised. The answers to these questions, and the resulting conclusions regarding the corresponding policy issues, will inform the decision of whether to retain or revise the current annual standard and/or whether to set a separate short-term standard.

The first step in reviewing the adequacy of the current primary NO<sub>2</sub> standard is to consider whether the available body of scientific evidence, assessed in the ISA, supports or calls into question the scientific conclusions reached in the last review regarding health effects related to exposure to NO<sub>2</sub> and other gaseous oxides of nitrogen (collectively referred to as NO<sub>x</sub> in this and subsequent sections of this plan) in the ambient air. This evaluation of the newly available scientific evidence will address a series of questions including the following:

- Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of NO<sub>x</sub> found in the ambient air?

- 1 • What do recent studies focused on the near-roadway environment tell us about health  
2 effects of NO<sub>x</sub>?
- 3 • At what levels of NO<sub>x</sub> exposure do health effects of concern occur?
- 4 • Has new information altered conclusions from previous reviews regarding the  
5 plausibility of adverse health effects caused by NO<sub>x</sub> exposure?
- 6 • To what extent have important uncertainties identified in the last review been  
7 reduced and/or have new uncertainties emerged?
- 8 • What are the air quality relationships between short-term and long-term exposures  
9 to NO<sub>x</sub>?

10  
11 If the evidence suggests that revision of the current standard might be appropriate, we will  
12 consider whether the available body of evidence supports consideration of alternative standards.  
13 The following questions will inform this determination.

- 14 • Is there evidence for the occurrence of adverse health effects at levels of NO<sub>x</sub> lower  
15 than those observed previously? If so, at what levels and what are the important  
16 uncertainties associated with that evidence?
- 17 • Do exposure estimates suggest that exposures of concern for NO<sub>x</sub>-induced health  
18 effects will occur with current ambient levels of NO<sub>2</sub> or with levels that just meet  
19 current, or potential alternative, standards? If so, are these exposures of sufficient  
20 magnitude such that the health effects might reasonably be judged to be important  
21 from a public health perspective? What are the important uncertainties associated  
22 with these exposure estimates?
- 23 • Do the evidence, the air quality assessment, and the risk/exposure assessment  
24 provide support for considering different standard indicators or averaging times?
- 25 • What range of levels is supported by the evidence, the air quality assessment, and the  
26 risk/exposure assessments? What are the uncertainties and limitations in the  
27 evidence and the assessments?
- 28 • What is the range of forms supported by the evidence, the air quality assessment, and  
29 the exposure/risk assessments? What are the uncertainties and limitations in the  
30 evidence and the assessments?

## 4. SCIENCE ASSESSMENT

### 4.1 SCOPE AND ORGANIZATION

The science assessment for NO<sub>x</sub> will consist of the ISA and its supporting annexes. The ISA will critically evaluate and integrate the scientific information on exposure and health effects associated with NO<sub>x</sub> in ambient air.<sup>5</sup> The annexes, which will summarize relevant studies, will provide a detailed basis for developing the ISA. The annexes will include scientific evidence in the discipline areas of epidemiology, toxicology, and dosimetry as well as human exposure and atmospheric science relevant to the review of the primary NAAQS. The ISA will draw from this evidence and synthesize the current state of knowledge on the most relevant issues pertinent to the review of the NAAQS for NO<sub>2</sub>. Information from other scientific fields will be integrated into the health effects evidence if it contributes to a better understanding of population exposure and/or risk or to a better understanding of the nature, sources, distribution, measurement, and/or concentrations of NO<sub>x</sub> in ambient air. The ISA discussions will be designed to focus on the key policy questions described in Chapter 3 of this document.

The focus of the ISA will be on literature published since the previous review of the air quality criteria for NO<sub>x</sub>. Key findings and conclusions from the 1993 Air Quality Criteria Document (AQCD) for NO<sub>x</sub> will be briefly summarized at the beginning of the ISA. The results of recent studies will be integrated with previous findings. Important older studies will be more specifically discussed if they are open to reinterpretation in light of newer data. Generally, only information that has undergone scientific peer review and that has been published (or accepted for publication) in the open literature will be considered. In human and animal toxicologic studies, emphasis will be placed on studies conducted at or near NO<sub>x</sub> concentrations found in ambient air. However, in recognition of the fact that toxicologic studies do not necessarily reflect effects in the most sensitive populations, studies at higher exposure levels will be included when they provide information relevant to previously unreported effects, evidence of the potential mechanism for an observed effect, or information on exposure-response relationships.

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<sup>5</sup> Note that evidence related to environmental effects of NO<sub>x</sub> will be considered separately in the science assessment conducted as part of the review of the secondary NAAQS for NO<sub>2</sub> and SO<sub>2</sub>.

## 1 **4.2 ASSESSMENT APPROACH**

### 2 **Introduction**

3 The NCEA-RTP is responsible for preparing the ISA and its annexes for NO<sub>x</sub>. Expert  
4 authors include EPA staff with an extensive base of knowledge in their respective fields and  
5 extramural scientists contracted to the EPA.

### 6 7 **Literature Search**

8 The NCEA-RTP uses a systematic approach to identify relevant studies for consideration.  
9 A Federal Register Notice is published to announce the initiation of a review and request  
10 information from the public. An initial publication base is established by searching MEDLINE  
11 and other databases using as key words the terms nitrogen oxides, nitrogen dioxide, NO<sub>x</sub>, NO<sub>2</sub>,  
12 HNO<sub>3</sub>, nitric acid, peroxyacetyl nitrate (PAN), or total reactive nitrogen. This search strategy is  
13 periodically reexamined and modified to enhance identification of pertinent published papers.  
14 Additional papers are identified for inclusion in the publication base in several ways. First, EPA  
15 staff reviews pre-publication tables of contents for journals in which relevant papers may be  
16 published. Second, expert chapter authors are charged with independently identifying relevant  
17 literature. Finally, additional publications that may be pertinent are identified by both the public  
18 and CASAC during the external review process. The studies identified will include research  
19 published or accepted for publication by a date determined to be as inclusive as possible given  
20 the relevant target dates in the NAAQS review schedule. Some additional studies, published  
21 after that date, may also be included if they provide new information that impacts one or more  
22 key scientific issues. The combination of these approaches should produce the comprehensive  
23 collection of pertinent studies needed to form the basis of the ISA.

### 24 25 **Criteria for Study Selection**

26 In selecting epidemiologic studies for the present assessment, EPA will consider whether  
27 a given study contains information on (1) short- or long-term exposures at or near ambient levels  
28 of NO<sub>x</sub>; (2) health effects of specific NO<sub>x</sub> species or indicators related to NO<sub>x</sub> sources (e.g.,  
29 motor vehicle emissions, combustion-related particles); (3) health endpoints that repeat or extend  
30 findings from earlier assessments as well as those not previously extensively researched; (4)  
31 populations that are susceptible and vulnerable to NO<sub>x</sub> exposure; (5) multiple pollutant analyses  
32 and other approaches to address issues related to potential interactions (e.g., are there synergistic  
33 effects of NO<sub>x</sub> with other pollutants), confounding (e.g., is NO<sub>x</sub> associated with health endpoints

1 independent of copollutants), and effect modification (e.g., is the effect of NO<sub>x</sub> on health  
2 endpoints modified by the presence of copollutants); and/or (6) important methodological issues  
3 (e.g., lag of effects, model specifications, thresholds, mortality displacement) related to NO<sub>x</sub>  
4 exposure effects. Among the epidemiologic studies, particular emphasis will be focused on  
5 those relevant to standard setting in the United States. Specifically, studies conducted in the U.S.  
6 or Canada will be generally accorded more text discussion than those from other geographic  
7 regions, as the potential impacts of different health care systems and the underlying health status  
8 of populations need to be accounted for in the assessment. In addition, emphasis will be placed  
9 on discussion of (1) new, multi-city studies that employ standardized methodological analyses  
10 for evaluating NO<sub>x</sub> effects, provide overall estimates for effects based on combined analyses of  
11 information pooled across cities, and examine results for consistency across cities; (2) new  
12 studies that provide quantitative effect estimates for populations of interest; and (3) studies that  
13 regard NO<sub>x</sub> as a component of a complex mixture of air pollutants and thus give consideration to  
14 the levels of other copollutants, correlations of NO<sub>x</sub> with these copollutants, and conduct  
15 multipollutant analyses.

16 A set of explicit criteria will also be used to select experimental studies for discussion.  
17 The selection of research evaluating controlled exposures to laboratory animals will focus  
18 primarily on those studies conducted at or near ambient NO<sub>x</sub> concentrations and those studies  
19 that approximate expected human exposure conditions in terms of concentration and duration,  
20 which will depend on the toxicokinetics and biological sensitivity of the particular laboratory  
21 animal examined. In discussing the mechanisms of NO<sub>x</sub> toxicity, studies conducted under  
22 atmospherically-relevant conditions will be emphasized, but studies at higher levels also will be  
23 considered, due to species-to-species differences and potential differences in sensitivity between  
24 study subjects and especially susceptible human populations.. For research evaluating controlled  
25 human exposures to NO<sub>x</sub>, emphasis will be placed on studies that (1) investigate effects on  
26 potentially susceptible populations such as asthmatics, particularly studies where subjects serve  
27 as their own control to compare responses following NO<sub>x</sub> exposure and sham exposure and  
28 where responses in susceptible individuals are compared with those in age-matched healthy  
29 controls; (2) address issues such as dose-response or time-course of responses; (3) investigate  
30 exposure to NO<sub>x</sub> separately and in combination with other pollutants such as O<sub>3</sub> and SO<sub>2</sub>;  
31 (4) include control exposures to filtered air; and (5) have sufficient sample size to adequately  
32 assess findings.

33

## 1 **Content and Organization of the ISA**

2 The organization of the ISA for NO<sub>x</sub> will be consistent with that used in the integrative  
3 chapter of the criteria document for O<sub>3</sub> (U.S. Environmental Protection Agency, 2006). The ISA  
4 will contain information relevant to considering whether it is appropriate to retain or revise the  
5 current annual standard and whether it is appropriate to consider setting a separate short-term  
6 standard. The content of the ISA will be guided by a series of policy-relevant questions that  
7 were derived from the previous review of the NAAQS for NO<sub>2</sub>, as well as policy-relevant  
8 questions based on new scientific information. These policy-relevant questions are specifically  
9 related to the scientific literature for NO<sub>x</sub>, as opposed to the broader questions presented in  
10 chapter 3 which were developed to guide the entire review. The policy-relevant questions that  
11 will guide development of the ISA are related to two overarching issues. The first issue is  
12 whether new evidence reinforces or calls into question the evidence presented and evaluated in  
13 the last NAAQS review. The second issue is whether uncertainties from the last review have  
14 been addressed and/or whether new uncertainties have emerged. The specific questions that  
15 stem from these issues are listed below by topic area.

16

17 A. Air Quality and Atmospheric Chemistry: The ISA will present and evaluate data related  
18 to ambient concentrations of NO<sub>x</sub>; sources leading to the presence of NO<sub>x</sub> in the  
19 atmosphere; and chemical reactions that determine the formation, degradation, and  
20 lifetime of NO<sub>x</sub> in the atmosphere.

- 21 • What are the strengths and weaknesses of various methods for measuring NO<sub>x</sub>?  
22 To what extent are these methods subject to interference from NO<sub>x</sub> oxidation products  
23 or other substances? Are there reaction products that might be toxicologically-  
24 significant, such as nitro-PAHs?
- 25 • Based on recent air quality and emissions data, what are current concentrations and  
26 emissions of NO<sub>x</sub>? What spatial and temporal patterns can be seen in the air quality  
27 data for NO<sub>x</sub>?
- 28 • Using air quality and emissions data on NO<sub>x</sub> and atmospheric chemistry models, what  
29 are likely policy relevant background concentrations of NO<sub>x</sub>?
- 30 • Because ambient monitoring data are spatially sparse for NO<sub>x</sub>, are there other  
31 techniques that can be used to better define the range of concentrations and the spatial  
32 and temporal variability of NO<sub>x</sub> over the U.S.? Are satellite retrievals or three

1 dimensional chemical transport models useful? Can satellite data be used on a regular  
2 basis to improve the characterization of NO<sub>x</sub> emissions?

3  
4 B. Exposure: The ISA will evaluate the factors that influence exposure to NO<sub>x</sub> and the  
5 uncertainties associated with extrapolation from ambient concentrations to personal  
6 exposures to NO<sub>x</sub> of ambient origin, particularly in the context of interpreting results  
7 from epidemiologic studies. The issues of uncertainty differ by the exposure period of  
8 interest as short-term exposure studies (e.g., population-level studies using time-series  
9 analyses, field/panel studies) rely on temporal variation in exposure while long-term  
10 exposure studies (e.g., longitudinal cohort studies) rely on spatial variability of exposure.

- 11 • What are the uncertainties when extrapolating between stationary NO<sub>x</sub> monitoring  
12 instruments and personal exposure to NO<sub>x</sub> of ambient origin, especially for  
13 susceptible groups? Issues include measurement error in outdoor ambient monitors,  
14 the use of centralized monitors for estimating community concentrations, and their  
15 use as a surrogate for personal exposure to NO<sub>x</sub> of ambient origin.
- 16 • What do NO<sub>2</sub> concentrations from centrally-located ambient monitors represent? To  
17 what extent do they provide an estimate of ambient exposures to NO<sub>2</sub> versus an  
18 indicator of exposure to other gaseous pollutants (including CO and HONO) and  
19 particle phase pollutants generated by traffic or other combustion sources?
- 20 • What is the exposure pattern for indoor sources such as gas stoves or indoor  
21 space/water heating sources (i.e., peak, repeated peak, and average NO<sub>x</sub>) and how  
22 does it relate to ambient NO<sub>x</sub> patterns?
- 23 • What data are available to interpret both short- and long-term NO<sub>x</sub> exposures (e.g., 1  
24 hour, 24 hours, 2 weeks, longer periods)? This includes such information as air  
25 exchange rates, indoor sources, distance to highways, and methods for measuring  
26 personal exposures to NO<sub>x</sub>.
- 27 • How do NO<sub>x</sub> exposures interact with other pollutant exposures, including PM and  
28 other gaseous copollutants?
- 29 • How do modeled predictions of NO<sub>x</sub> concentrations compare with monitoring results?  
30 Do quality assurance (QA) checks suggest that modeling is accurate? How do the

1 models perform at the tails of the distribution, in high concentrations areas and near  
2 roadways?

3

4 C. Health Effects: The ISA will evaluate the literature related to respiratory, cardiovascular,  
5 and other health effects of NO<sub>x</sub> exposure. Other health effects also may be evaluated.  
6 Health effects that occur following both short- and long-term exposures will be evaluated  
7 in epidemiologic, human clinical, and toxicologic studies. Efforts will be directed at  
8 identifying the lower levels at which effects are observed.

9

10 Short-Term Exposure:

- 11 • What do controlled human exposure, animal toxicologic, and epidemiologic studies  
12 indicate regarding the relationship between short-term, repeated exposures to NO<sub>x</sub> and  
13 health effects of concern (e.g., lung function decrements, respiratory symptoms,  
14 inflammation, cardiovascular health endpoints, emergency department visits, hospital  
15 admissions, mortality), including nature and time course, in healthy individuals and in  
16 those with preexisting disease states (e.g., asthmatics, cardiovascular disease) or  
17 preexisting susceptibility (e.g., genetic, biochemical)?
- 18 • How do results of recent studies expand current understanding of the relationship  
19 between repeated, short-term exposure to NO<sub>x</sub> and lung function changes or lung  
20 function development? What are the lowest levels of NO<sub>x</sub> at which these lung  
21 function effects are observed? What is the potential clinical relevance of these lung  
22 function effects?
- 23 • What are the effects of NO<sub>x</sub> exposure on small airway function in humans (e.g.,  
24 oxygen diffusion capacity, ventilation-perfusion mismatches) and what is the potential  
25 clinical relevance of these effects?
- 26 • What are the effects of NO<sub>x</sub> exposure on cardiovascular health in humans (e.g., heart  
27 rate variability, arrhythmias, endothelial function, risk of myocardial infarction) and  
28 what is the potential clinical relevance of these effects?
- 29 • What is the influence of NO<sub>x</sub> on host defense against infectious disease?

- 1 • Is exposure to NO<sub>x</sub> associated with mortality (total, respiratory or cardiovascular),  
2 hospital admissions, or emergency department visits as assessed using population-  
3 level datasets? What are the lowest ambient NO<sub>x</sub> concentrations at which these  
4 associations are observed? The utility of the statistical methods applied will be  
5 evaluated (i.e., time series studies). As discussed above, the potential effects of  
6 exposure error on epidemiologic outcomes will be evaluated.
- 7 • To what extent does exposure to NO<sub>x</sub> contribute to health effects beyond the  
8 respiratory and cardiovascular systems ?
- 9 • What is the nature of health effects following short-term exposure to multipollutant  
10 mixtures that contain NO<sub>x</sub> in comparison to exposure to NO<sub>x</sub> alone? Is there an  
11 interaction between NO<sub>x</sub> and other air pollutants in the atmosphere?
- 12 • To what extent does the pattern of NO<sub>x</sub> exposure (e.g., peak, repeated peak, average)  
13 influence our interpretation of the health effects evidence?
- 14 • Does exposure to NO<sub>2</sub> (or other NO<sub>x</sub>) perturb the biologic function of endogenous NO  
15 (e.g., by generating unwanted or excessive reactive nitrogen species)?
- 16 • What biomarkers of early effect may be used in the assessments? What detectable  
17 biological changes will be considered adverse health effects?
- 18 • Do new data provide evidence to examine different exposure indices or averaging  
19 times specifically addressing need for a short-term standard (i.e., 1 to 3 hours)?

20  
21 Long-Term Exposure:

- 22 • Does the scientific evidence support the occurrence of health effects from long-term  
23 exposure (e.g., months to years) at ambient levels that are lower than previously  
24 observed? If so, what uncertainties are related to these associations and are the health  
25 effects in question important from a public health perspective?
- 26 • How do results of recent studies expand current understanding of the relationships  
27 between repeated, short-term exposure to NO<sub>x</sub> and lung function or lung function  
28 development? What are the lowest levels of NO<sub>x</sub> at which these lung function effects  
29 are observed?

- 1 • Can long-term exposures to NO<sub>x</sub> result in chronic effects manifested as permanent  
2 lung tissue damage, reduction in baseline lung function, or impaired lung function  
3 development?
- 4 • To what extent does long-term NO<sub>x</sub> exposure promote exacerbation and development  
5 of asthma or other chronic lung diseases, cardiovascular diseases, and other  
6 conditions? What is the relationship between long-term NO<sub>x</sub> exposure and shortening  
7 of human life span via promotion of such diseases?
- 8 • To what extent does long-term exposure to NO<sub>x</sub> contribute to other health effects, e.g.,  
9 epigenetic and reproductive effects?
- 10 • How does long-term, low-level exposure to NO<sub>x</sub> affect an individual's sensitivity to  
11 short-term but higher concentration exposures?
- 12 • What annual and seasonal patterns of NO<sub>x</sub> exposure are most instrumental in  
13 promoting potentially harmful health effects?
- 14 • What is the nature of health effects following long-term exposure to multipollutant  
15 mixtures that contain NO<sub>x</sub> in comparison to exposure to NO<sub>x</sub> alone? Is there an  
16 interaction between NO<sub>x</sub> and other air pollutants?
- 17 • Do new data provide evidence to examine different exposure indices or averaging  
18 times specifically addressing the long-term standard?

19

20 D. Causality: The ISA will evaluate the evidence for and against causal relationships  
21 between observed health outcomes and NO<sub>x</sub> exposures. Key considerations in drawing  
22 conclusions about causality will be biological plausibility and coherence of the evidence.  
23 The ISA will place emphasis on studies conducted at typical ambient levels, except  
24 regarding evidence of biological plausibility and mechanisms, as these may only be  
25 observable in animal or human exposure study populations at higher levels than they  
26 might be observed in susceptible human populations.

- 27 • Does the evidence base contain new information to evaluate the case for or against  
28 causal relationships between health outcomes and NO<sub>x</sub> exposure?
- 29 • What information is available regarding the health impacts of a decrease in ambient  
30 levels of NO<sub>x</sub>?

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E. Uncertainties: The ISA will evaluate uncertainty in the scientific data, particularly in relation to observed epidemiologic findings.

- How does confounding by coexposure to other pollutants (e.g., O<sub>3</sub>, PM, SO<sub>2</sub>, and CO) and meteorological factors influence the uncertainty of the evidence base for both short- and long-term exposures?
- To what extent are the observed health effects associations attributable to NO<sub>x</sub> versus the pollutant mixtures that NO<sub>x</sub> may be representing? For example, the possibility that NO<sub>2</sub> ambient concentrations may serve as a surrogate for personal exposure to vehicle exhaust pollutants, including various other gases and particles, will be considered.
- What are the uncertainties due to other confounding factors in epidemiologic studies (e.g., demographic and lifestyle attributes, genetic susceptibility factors, occupational exposure, and medical care)?
- What is the shape of concentration-response models (e.g., linear vs. threshold models) and how does this influence public health impacts?
- What uncertainties surround the evidence for long-term effects such as life shortening and development/progression of disease?

F. Biological Mechanisms of Action: The ISA will evaluate the data investigating biological mechanisms of action for the health outcomes associated with exposure to NO<sub>x</sub>. One limitation in examining mechanisms using animal toxicologic studies is the inherent anatomic and physiologic differences compared to humans that result in possible differences in dosimetry and mechanisms of action, especially with high exposure studies.

- Is there new information related to the biological mechanism of action?
- What are the potential biological mechanisms underlying response to NO<sub>x</sub>, with a focus on physical-chemical characteristics, response pathway(s), and exposure-dose-response relationships?

- 1 • What are the inherent interspecies and interstrain differences in sensitivity to NO<sub>x</sub> and  
2 in NO<sub>x</sub> dosimetry in different regions of the respiratory tract and what are the  
3 implications of these differences?
- 4 • What are the interspecies and interstrain differences in basic mechanisms of lung  
5 injury and repair?
- 6 • What NO<sub>x</sub> reaction products can be found in the respiratory tract cells, tissues, or  
7 fluids that may serve as markers of NO<sub>x</sub> exposure?
- 8 • What are the effects of host factors such as age, gender, pre-existing disease, and  
9 genetic background on cellular and tissue responses to NO<sub>x</sub>-induced injury?
- 10 • Which NO<sub>x</sub>-induced health effects are sufficiently characterized to be quantitatively  
11 compared across species?
- 12 • What is the state of knowledge of laboratory animal-to-human extrapolation of  
13 effects? Is a credible qualitative extrapolation possible for short- and for long-term  
14 exposures?
- 15 • Do interactions with PM and other copollutants in the atmosphere influence the toxic  
16 potential of NO<sub>x</sub>?

17

18 G. Susceptible and Vulnerable Populations: The ISA will examine health outcome data to  
19 identify specific groups that are more susceptible (e.g., children, asthmatics, patients with  
20 COPD, genetic susceptibility) and/or vulnerable (e.g., outdoor workers, socioeconomic  
21 factors) to the adverse effects of NO<sub>x</sub> exposure than normal healthy adults.

- 22 • What host and environmental factors (e.g., demographic, socioeconomic, and genetic)  
23 are associated with susceptibility and/or vulnerability to short- and long-term  
24 exposure to NO<sub>x</sub>?
- 25 • Is preexisting respiratory or cardiovascular disease an important factor in  
26 susceptibility to mortality associated with exposure to NO<sub>x</sub> and does age also play a  
27 role in this relationship?
- 28 • Regarding morbidity health endpoints, to what extent are specific subgroups more  
29 susceptible and/or vulnerable than the general population to NO<sub>x</sub> exposure?

- 1 • What is the relationship, if any, between susceptibility to short- and long-term  
2 exposure to NO<sub>x</sub>?
- 3 • Do interactions with PM and other copollutants in the atmosphere affect the  
4 susceptibility and/or vulnerability of humans to NO<sub>x</sub>?

5

6 H. Public Health Impact: The ISA will present concepts related to the potential for defining  
7 adverse health effects. To accomplish this, the implications for public health of different  
8 health effects will be discussed. This will include, as appropriate, an estimation of the  
9 potential number of persons at risk for each health effect.

10

11 The ISA will be supplemented by a series of annexes, which will be focused on  
12 accomplishing two goals. The first goal will be to identify scientific research that is relevant to  
13 informing key policy issues. The second goal will be to produce a base of evidence containing  
14 all of the publications relevant to the NO<sub>x</sub> review. The annexes will provide information on (1)  
15 the chemistry of NO<sub>x</sub> and the related chemistry of SO<sub>x</sub>, as well as sampling and analytic methods  
16 for measurement of NO<sub>x</sub> and SO<sub>x</sub>;<sup>6</sup> (2) environmental concentrations and human exposure to  
17 NO<sub>x</sub>; (3) dosimetry; (4) toxicologic studies of NO<sub>x</sub> health effects in laboratory animals; (5)  
18 human clinical studies examining health effects following controlled exposure to NO<sub>x</sub>; and (6)  
19 epidemiologic studies of health effects from short- and long-term exposure to NO<sub>x</sub>. More  
20 detailed information on various methods and results for the health studies will be summarized in  
21 tabular form in the annexes. These tables will generally be organized to include information  
22 about (1) concentrations of NO<sub>x</sub> levels and averaging times; (2) description of study methods  
23 employed; (3) results and comments; and (4) quantitative outcomes for NO<sub>x</sub> measures.

24 In assessing the scientific quality and relevance of epidemiologic, animal toxicologic, and  
25 human controlled exposure studies, the following considerations will be taken into account:  
26 (1) to what extent are the aerometric data and exposure metrics of adequate quality and  
27 sufficiently representative to serve as credible exposure indicators; (2) were the study  
28 populations adequately selected and are they sufficiently well-defined to allow for meaningful  
29 comparisons between study groups; (3) are the health endpoint measurements meaningful and

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<sup>6</sup> This section will also provide information on SO<sub>2</sub> in order to support the reviews of the primary and secondary NAAQS for both SO<sub>2</sub> and NO<sub>2</sub>. The atmospheric chemistry of NO<sub>x</sub> and SO<sub>x</sub> are intricately linked.

1 reliable; (4) are the statistical analyses appropriate, properly performed, and properly interpreted;  
2 (5) are likely covariates (i.e., potential confounders or effect modifiers) adequately controlled or  
3 taken into account in the study design and statistical analyses; and (6) are the reported findings  
4 internally consistent, biologically plausible, and coherent in terms of consistency with other  
5 known facts. Consideration of these issues will inform our judgments on the relative quality of  
6 individual studies and will allow us to focus the assessment on the most pertinent studies.

7

### 8 **4.3 SCIENTIFIC AND PUBLIC REVIEW**

9 Drafts of the ISA will be reviewed by the CASAC NO<sub>x</sub> and SO<sub>x</sub> primary review panel and  
10 made available for public comment. The annexes to the ISA will also be made available to the  
11 CASAC panel in order to assist with their review; however, the panel will not be specifically  
12 charged with reviewing the annexes. The CASAC panel will review the draft document and  
13 discuss their comments in a public meeting announced in the Federal Register. Based on  
14 CASAC's past practice, EPA expects that key CASAC advice and recommendations for revision  
15 of the document will be conveyed by the CASAC Chair in a letter to the EPA Administrator.  
16 In revising the draft ISA for NO<sub>x</sub>, EPA will take into account any such advice and  
17 recommendations. EPA will also consider comments received from CASAC or from the public  
18 at the meeting itself and any written public comments. EPA anticipates preparing a second draft  
19 of the ISA for CASAC review and public comment. After appropriate revision, the final  
20 document will be made available on an EPA website and subsequently printed, with its public  
21 availability being announced in the Federal Register.

22

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Therefore, discussion of their combined chemistry is more effective and more efficient than a separate discussion of each pollutant.

## 5. RISK/EXPOSURE ASSESSMENT

### 5.1 OVERVIEW

The risk/exposure assessments for the current review of the primary NAAQS for NO<sub>2</sub> will be designed to estimate human exposures and to characterize the potential health risks that are associated with current ambient levels, with ambient levels that just meet the existing standard, and with ambient levels that just meet alternative standards that may be under consideration. The risk/exposure assessments will focus primarily on NO<sub>2</sub>, but will consider, to the extent relevant information is available, the broader array of gaseous nitrogen oxides present in the ambient air.

The risk/exposure assessments will draw upon the information presented in the ISA and its Annexes. This includes information on atmospheric chemistry, air quality, human exposure, the impact of local source emissions, and health effects of concern. In particular, the availability of concentration-response and/or exposure-response data from the health effects literature will impact the type of risk and exposure assessments that will be performed.

Risks and exposures will be assessed using a tiered approach where progression to a more sophisticated level of analysis will depend on the availability of data and on the anticipated utility of the results. For example, exposure may be assessed through the use of ambient air quality as a surrogate for exposure or by supplementing the existing ambient monitor data with local source concentration measures and/or model estimates, where appropriate. In addition, the exposure estimates may involve incorporating human activity data or possibly the development of individual exposure profiles. The particular form of the exposure assessment selected would generate ambient concentrations as well as exposure metrics that are consistent with the available information on health effects associated with NO<sub>2</sub> exposure.

Risks would also be characterized using a tiered approach where progression to a more sophisticated level of analysis would depend on the availability of data and on the anticipated utility of the results. For example, risks could be assessed through the identification of concentration levels anticipated to result in adverse health effects, termed health effect benchmarks. These health effect benchmarks could then be used to determine how often air quality concentrations or estimated exposures exceed concentrations associated with adverse health effects. Concentration-response functions, derived from epidemiological studies, and/or exposure-response functions, derived from human clinical studies, may also be combined with

1 estimated exposures to characterize NO<sub>2</sub> health risk as appropriate and to the extent such  
2 information is available.

3 The major components of the risk/exposure assessments are outlined below and will be  
4 described in greater detail in a Scope and Methods Plan. Preparation of this detailed plan is  
5 underway and coincides with the development of the first draft ISA to facilitate the integration of  
6 policy-relevant science into both documents. This draft Scope and Methods Plan will also be the  
7 subject of a consultation with the CASAC NO<sub>x</sub>/SO<sub>x</sub> primary standard review panel and will be  
8 made available to the public for review and comment. The draft risk/exposure assessments  
9 prepared based on the Scope and Methods Plan will be made final upon completion of the final  
10 ISA and following review by the CASAC NO<sub>x</sub>/SO<sub>x</sub> primary standard review panel and the  
11 public.

12

## 13 **5.2 OVERVIEW OF EXPOSURE ASSESSMENT FROM PRIOR** 14 **REVIEW**

15 In the previous review of the NAAQS for NO<sub>2</sub>, exposure was assessed using ambient  
16 monitor data as a direct surrogate for exposure. This assessment targeted long-term air quality  
17 trends as indicated by analysis of ambient monitoring data (US EPA, 1995). The annual  
18 standard of 0.053 ppm was retained to protect against long-term exposures and resultant health  
19 effects. However, the variability in ambient concentrations and the potential for exposure to  
20 short-term peak concentrations was also considered. Because at the time of the standard review  
21 a few studies indicated the possibility of adverse health effects due to short-term exposures of  
22 about 0.20 ppm, the frequency of 1-hour ambient concentrations in excess of 0.15 ppm to 0.30  
23 ppm was estimated (McCurdy, 1994). Two analyses were performed, one considered ambient  
24 monitor data from the Los Angeles Consolidated Metropolitan Statistical Area (CMSA) and the  
25 other included CMSA monitor sites not within Los Angeles across the U.S., using ambient  
26 monitor data from years 1988-1992 and screened for sites with at least one hourly exceedance of  
27 0.15 ppm in a year. Of the 107 monitoring values obtained using this criteria (a total of 31 were  
28 within the Los Angeles CMSA), 4 had annual average concentrations greater than the annual  
29 standard of 0.053 ppm, all of which were in the Los Angeles CMSA. Two separate predictive  
30 models were constructed that related the frequency of hourly concentrations above potential  
31 short-term health effect benchmarks to a range of annual average concentrations, including the  
32 current standard. Based on the results of this analysis, both CASAC (Wolff, 1995) and the  
33 Administrator (60 FR 52874) concluded that the minimal occurrence of short-term peak

1 concentrations at or above a potential health effect benchmark of 0.20 ppm indicated that the  
2 current annual standard would provide adequate health protection against short-term exposures.

### 4 **5.3 CURRENT EXPOSURE ASSESSMENT APPROACH**

5 A three-tiered approach to assessing exposure will be employed, beginning with an air  
6 quality analysis and progressing to a more refined analysis if appropriate. This approach will be  
7 informed by the previous review of the NAAQS for NO<sub>2</sub> (US EPA, 1995), and the current NO<sub>x</sub>  
8 ISA and relevant Annexes. Consideration will also be given to recent guidelines published by  
9 the World Health Organization (2005) and the NO<sub>2</sub> review conducted by the California  
10 Environmental Protection Agency (CalEPA, 2006a; 2006b, 2007).

11 The goals of the NO<sub>2</sub> exposure assessment are: (1) to estimate short- and long-term  
12 exposures to ambient concentrations through air quality and modeling analyses that consider  
13 current air quality for NO<sub>2</sub> and air quality levels just meeting the current and potential alternative  
14 NO<sub>2</sub> standards; (2) to develop quantitative relationships between long-term average and short-  
15 term peak concentrations; and (3) to identify key assumptions and uncertainties in the exposure  
16 estimates. The exposure assessment will be used to inform the characterization of population  
17 risks, as described in Section 5.4.

#### 19 **Air Quality Characterization**

20 The first step in assessing exposure will be to conduct an air quality analysis relying  
21 largely on ambient air quality data and the information provided in the ISA and relevant  
22 Annexes. In this analysis, the ambient NO<sub>2</sub> concentrations will serve as a surrogate for human  
23 exposure and will allow a comparison with the assessment performed in the previous review.  
24 This analysis will include information on NO<sub>2</sub> properties, current NO<sub>2</sub> air quality patterns,  
25 historic trends, policy-relevant background levels,<sup>7</sup> and potential exposure concentrations of  
26 concern. This analysis will provide a frame of reference for subsequent discussions of current  
27 and possible alternative standards. General steps in the process include the following.

- 28 • Obtain ambient monitoring data collected since the prior NAAQS review (e.g., 1995-2006)
- 29 • Estimate exposures considering long-term averaging metrics, such as that of the current NO<sub>2</sub>  
30 standard (i.e., the annual average) using recent monitoring data from individual sites (e.g.,  
31 years 2003-2006)

- 1 • Estimate concentrations and number of short-term peak exposures, given just meeting the  
2 current annual NO<sub>2</sub> standard and potential alternative standards (using all available data).
- 3 ○ Identify specific locations to evaluate, such as the Los Angeles Consolidated  
4 Metropolitan Statistical Area (CMSA), Houston, Phoenix, New York, or other  
5 location(s) that may contain higher than average number of peak hourly  
6 concentrations. Aggregate other CMSAs that are similar, and identify a similar rural  
7 grouping(s) to the extent relevant information is available. Criteria will be developed  
8 for selection of appropriate areas and groupings based on statistical comparisons of  
9 ambient concentrations and influence on ambient concentrations by local sources of  
10 NO<sub>2</sub> (e.g., motor vehicle traffic).
- 11 ○ Develop new prediction equations using ambient monitor data to approximate  
12 minimum, mean, and maximum number of peak exposure concentrations given the  
13 annual average concentrations, with just meeting the current and potential alternative  
14 annual standards for NO<sub>2</sub> at each location or grouping.
- 15 ○ Develop the relationship between annual average concentrations and other potential  
16 short-term health-relevant averaging times identified in the ISA, e.g., the daily  
17 average and annual average concentrations and between hourly peak concentrations  
18 and daily average concentrations.
- 19 • Evaluate the potential impact of local sources on NO<sub>2</sub> concentrations typically not measured  
20 by ambient monitors. This may involve the development of statistical relationships for use in  
21 estimating local source concentration contributions from ambient monitor data, or by  
22 concentration distributions that account for any expected contribution to ambient  
23 concentrations.
- 24 ○ Local sources may include, for example, motor vehicle emissions contributing to on-  
25 road and inside vehicle NO<sub>2</sub> concentrations, and indoor emissions of NO<sub>2</sub> while  
26 cooking with gas stoves.
- 27 ○ Estimate long- and short-term exposure surrogate concentrations, for the combined  
28 ambient air concentrations and local source concentrations, considering just meeting  
29 the current standard and any potential alternative standards.

30 The outcome of this air quality characterization includes the estimation of both short- and  
31 long-term exposure surrogate concentrations as represented by the ambient monitor and

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7 Policy-relevant background is defined as the distribution of NO<sub>2</sub> concentrations that would be observed in the U.S. in the absence of anthropogenic (man-made) emissions of NO<sub>2</sub> in the U.S., Canada, and Mexico.

1 estimated local source contribution for a given location. These exposure surrogate estimates can  
2 be used either to estimate the number of exceedances of potential health effect benchmarks, or  
3 used in a health effects model that employs concentration-response functions, where appropriate  
4 data are available (see Section 5.4).

## 6 **Screening-level Exposure Assessment**

7 A screening-level exposure assessment would be designed to better represent the  
8 relationship between ambient concentrations, local sources, and human exposure. The approach  
9 would involve the development of screening-level exposure metrics to estimate variability in  
10 human exposure by considering time spent in various locations, rather than assuming that  
11 ambient concentrations are equivalent to exposures. This screening-level exposure estimation  
12 would consider several factors, including those listed below, and would be conducted in areas  
13 identified/grouped for the air quality characterization.

- 14 • Factors that may contribute to greater personal exposures (short- and long-term) including  
15 the impacts of important sources of NO<sub>2</sub> (e.g., vehicle emissions, outdoor point sources such  
16 as gas utilities, indoor gas stove usage) and the impacts of human behavior (e.g., time spent  
17 outdoors, time spent on or near roadways).
- 18 • Factors that may contribute to lessened personal exposures (short- and long-term) including  
19 the decay of NO<sub>2</sub> indoors and inside motor vehicles, and the time spent indoors and inside  
20 vehicles.
- 21 • Population living in areas exceeding the screening-level exposure metrics.
- 22 • Exposure levels experienced by susceptible populations (e.g., asthmatic children) relative to  
23 those experienced by the general public.

24 Results of this analysis would include both short- and long-term exposure estimates for  
25 census tract level population/cohorts for a given location. These exposure estimates could be  
26 used either to estimate the number of exceedances of potential health effect benchmarks, or used  
27 in a health effects model that employs exposure-response functions, where appropriate data are  
28 available (see Section 5.4).

## 30 **Refined Exposure Assessment**

31 Although the above screening-level assessment represents an improvement over the  
32 assumption that exposures are equal to ambient concentrations, it relies on a number of  
33 simplifying assumptions which result in uncertainty in the exposure estimates. Depending on the

1 relationship between these screening-level exposure estimates and the exposure-response  
2 information, or potential health effect benchmarks for health effects of concern, more refined  
3 estimates of exposure may be developed. The purpose of a more refined exposure assessment  
4 would be to more realistically incorporate personal human attributes, such as time-location-  
5 activity patterns and human physiology. The general approach of this assessment would be to  
6 estimate population exposures to ambient NO<sub>2</sub> in a number of urban areas across the U.S.,  
7 identified above, and possibly including a rural area (generally not impacted greatly by local  
8 sources) as a reference group for the analysis. Areas included in the analysis would be selected  
9 with the goal of achieving variation in population, geography, demographics, climate, and NO<sub>2</sub>  
10 air quality. Exposure estimates would be generated for current NO<sub>2</sub> levels, for levels just  
11 meeting the current NAAQS, and for levels just meeting any potential alternative standards.

12 The exposure assessment would take into account several important factors including the  
13 magnitude and duration of exposures, frequency of repeated high exposures, and breathing rate  
14 of individuals at the time of exposure. Estimates could be developed for multiple indicators of  
15 exposure including (1) counts of people exposed one or more times to a given NO<sub>2</sub> concentration  
16 while at a specified breathing rate and (2) counts of person-occurrences of particular exposures,  
17 which accumulate across all people in the population of interest.

18 A new version of EPA's Air Pollutants Exposure (APEX) model (also referred to as the  
19 Total Risk Integrated Methodology/Exposure (TRIM.Expo) model) would be used in this  
20 analysis. APEX is a Monte Carlo simulation model that can be used to simulate a large number  
21 of randomly sampled individuals within each area thus generating area-wide estimates of  
22 population exposure. APEX simulates exposures in indoor, outdoor, and in-vehicle  
23 microenvironments while taking into consideration the movement of individuals through time  
24 and space. Human activity data needed for this analysis would be drawn from the Consolidated  
25 Human Activity Database (CHAD), which is developed and maintained by ORD's National  
26 Exposure Research Laboratory (NERL). A key issue would be the development of an approach  
27 for creating longitudinal activity sequences for individuals based on a cross-sectional activity  
28 database that includes 24-hour records.

29 Results of this analysis would include both short- and long-term exposure estimates for  
30 individuals within census tracts for a given location. These exposure estimates could be used  
31 either to estimate the number of exceedances of potential short- and long-term health effect  
32 benchmarks, or used in a health effects model that employs exposure-response functions, where  
33 appropriate data are available (see Section 5.4).

## 1 **5.4 RISK ASSESSMENT APPROACH**

2 A two-tiered approach to characterizing health risks will be employed. In a first tier  
3 analysis, potential health effect benchmarks that may be identified based on information in the  
4 ISA would be combined with surrogate or exposure estimates from the exposure assessment in  
5 order to characterize population health risks. In a second tier risk analysis, which would be  
6 conducted only if judged appropriate and if relevant data are available, an assessment using  
7 concentration-response or exposure/dose-response data would be conducted by combining this  
8 data with either ambient air concentration distributions or exposure concentration distributions,  
9 respectively.

10 The goals of a NO<sub>2</sub> risk assessment would be: (1) to estimate the number of people  
11 exposed to NO<sub>2</sub> concentrations above health effect benchmarks considering current air quality  
12 and air quality levels just meeting the current and potential alternative NO<sub>2</sub> standards; (2) to  
13 provide distributions of health risk estimates over a range of ambient NO<sub>2</sub> concentrations; and  
14 (3) to identify key assumptions and uncertainties in the risk estimates.

### 15 16 **Health Effect Benchmark Exceedances**

17 This type of risk characterization would use exposure estimates, along with potential  
18 health effect benchmarks that may be identified based on information in the ISA and relevant  
19 Annexes, to estimate (1) the number of individuals with exposures above levels expected to  
20 cause adverse health effects, and (2) the range of the benchmark exceedance for those  
21 experiencing exposures of concern. Multiple exposure scenarios can be considered, including  
22 exposure associated with current ambient air quality, with current air quality levels enhanced by  
23 including local source contributions, and/or with levels of NO<sub>2</sub> associated with just meeting the  
24 current and potential alternative standards. Depending on data available in the ISA and Annexes,  
25 the health effect benchmarks may also account for those individuals that may be particularly  
26 susceptible and/or vulnerable to the effects of NO<sub>2</sub>. The health risk characterization would  
27 require that averaging times be comparable for any estimated exposure concentrations and health  
28 metrics. For the purposes of this assessment, the approach is similar to calculating a hazard  
29 quotient which is the ratio of a weighted population exposure (or individuals in the case of the  
30 refined exposure assessment) to a health benchmark concentration.

## 1 **Exposure-Response and Concentration-Response Functions**

2           Incorporating exposure-response or concentration-response data in the risk  
3 characterization will depend on the availability of data from controlled human exposure studies  
4 and epidemiological studies respectively. In either case, quantitative relationships provided by  
5 the study or derived from the data presented in the study describe the change in concentration  
6 (either ambient or exposure) associated with a change in health response. These relationships are  
7 applied to estimate health risk.

8           Controlled human exposure studies involve volunteer subjects who are exposed to  
9 specified levels of NO<sub>2</sub> under controlled conditions for specified lengths of time. The responses  
10 measured typically include measures of lung function, such as forced expiratory volume in one  
11 second (FEV<sub>1</sub>), respiratory symptoms, airway hyperresponsiveness, and/or inflammation. These  
12 measures form the basis for the development of exposure-response (E-R) relationships. Since  
13 the data are generated in a controlled laboratory setting, they can be applied in any area where  
14 exposures are either measured or modeled.

15           In contrast, epidemiological studies typically provide estimated concentration-response  
16 (CR) relationships based on data collected in environmentally-relevant settings. Ambient NO<sub>2</sub>  
17 concentration is typically measured as the average of monitor-specific measurements, although  
18 personal exposures are occasionally measured. Common health responses for NO<sub>2</sub> have  
19 included associations with respiratory symptoms in asthmatic children, asthma emergency  
20 department visits, respiratory related hospital admissions and premature mortality. Again,  
21 depending on the type of health response function(s) available, ambient NO<sub>2</sub> concentration data  
22 would be used for characterizing risks, and are most appropriately applied in areas where the  
23 epidemiological study was performed. It should be noted that a risk characterization based on  
24 epidemiological studies also requires baseline incidence rates and population data for the risk  
25 assessment locations.

26           Based on our current understanding of the available evidence, we do not anticipate that  
27 there will be sufficient exposure-response data from controlled clinical studies to characterize  
28 health risk in this manner. However, there may be limited data available to develop C-R  
29 relationships from recently conducted epidemiological studies. Following review of the draft  
30 ISA and considering comments and recommendations by CASAC, the risk/exposure assessment  
31 scope and methods plan will be designed to include such a proposed approach to characterizing  
32 health risk if warranted.

## 1 **5.5 ASSESSMENT CRITERIA**

2 Criteria will be established to determine the level of detail warranted and the specific  
3 design of the assessments. The criteria will be designed to determine the value added to the  
4 assessment and for informing the NO<sub>2</sub> NAAQS decision. The factors identified below will be  
5 considered.

- 6 • results of the ambient air quality characterization
- 7 • weight-of-evidence, as provided in the ISA, from new clinical studies with relevant  
8 exposure-response data, particularly those conducted at or near current ambient  
9 concentrations
- 10 • weight-of-evidence, as provided in the ISA, from new epidemiological studies that evaluate  
11 the relationship between short- and long-term exposures and health outcomes
- 12 • new information regarding susceptible populations identified in previous reviews (e.g., those  
13 with pre-existing respiratory disease and children 5-12 years of age) or information regarding  
14 newly identified susceptible or vulnerable populations
- 15 • information and data defining the potential impact of roadway NO<sub>2</sub> concentrations on nearby  
16 residents and on specific microenvironmental concentrations (e.g., while traveling inside  
17 motor vehicles)
- 18 • analysis of exposure studies using non-routine monitoring, other local sources (e.g., power  
19 utilities, rail-yards, airports), and/or modeled NO<sub>2</sub> concentrations
- 20 • existence of the data required to perform the analyses in each tier of the assessment

## 22 **5.6 UNCERTAINTY AND VARIABILITY**

23 The uncertainty and variability inherent in estimates of exposure and risk will be  
24 characterized regardless of the type of risk/exposure assessment conducted. Uncertainty reflects  
25 the degree of confidence in the representativeness of models or model components. Variability  
26 can be described in terms of empirical quantities that are inherently variable across time and  
27 space or between individuals (Cullen and Frey, 1999).

28 A tiered approach to assessing uncertainty and variability in exposure and risk estimates  
29 will be employed, beginning with a qualitative analysis and progressing to a quantitative analysis  
30 only if warranted and if data are available to support such an analysis. The first step in the  
31 uncertainty analysis would be to identify the components of the assessment, determine whether  
32 uncertainty can be evaluated for each of those components, and provide a rationale for why this

1 is the case. The second step will be to perform a qualitative uncertainty analysis for the  
2 appropriate components of the assessment. This qualitative analysis will result in a matrix  
3 describing, for each area of uncertainty, both the magnitude (minimal, moderate, major) and the  
4 direction of influence (under- or over-estimate) on risk/exposure estimates. If sufficient data are  
5 available, and if the magnitude of uncertainty is judged significant, a quantitative assessment of  
6 uncertainty will then be performed for selected components of the assessment.

7         There are two primary sources of uncertainty that would be addressed in a quantitative  
8 analysis. The first is uncertainty associated with the model inputs (e.g., use of air quality data,  
9 time-location-activity diaries, microenvironmental factor distributions). The second is  
10 uncertainty associated with model formulation (e.g., simple algorithms or those incorporated in a  
11 more complex model). Each of these is generally described below using the APEX model as an  
12 example.

13         APEX is a Monte Carlo simulation model that explicitly incorporates the variability  
14 inherent in the model input data. A 2-dimensional Monte Carlo Latin hypercube sampling  
15 approach could be used as a combined variability and uncertainty analysis for APEX. A Monte  
16 Carlo approach entails performing a large number of model runs with inputs randomly sampled  
17 from specified distributions that reflect the variability and uncertainty of the model inputs. The  
18 2-dimensional Monte Carlo method allows for the separate characterization of variability and  
19 uncertainty in the model results (Morgan and Henrion, 1990). If this approach were taken,  
20 developing appropriate distributions representing both variability and uncertainty in model inputs  
21 (e.g., air exchange rates, NO<sub>2</sub> decay rates, physiological parameters) would be a key part of the  
22 effort.

23         In the case of model formulation, the preferred approach would be to compare model  
24 predictions with measured values, while having relatively complete knowledge of the uncertainty  
25 associated with input parameters. For the purpose of the exposure assessment, model estimated  
26 exposures would be compared with measured personal exposures, provided appropriate data  
27 exist (e.g., similar averaging times, population demographics, geographic locations). In the  
28 absence of measurements that can be used to estimate model uncertainty, the analysis must rely  
29 on informed judgment. The approach would be to partition the model formulation uncertainty  
30 into that of the components, or sub-models, of APEX (e.g., microenvironmental concentrations,  
31 ventilation estimates). For each of the sub-models, we would discuss the simplifying  
32 assumptions and the uncertainties associated with those assumptions. Where possible, we would  
33 evaluate these sub-models by comparing their predictions with measured data. Where this is not

1 possible, we would formulate an informed judgment regarding a range of plausible uncertainties  
2 for the sub-models.

3

#### 4 **5.7 SCIENTIFIC AND PUBLIC REVIEW**

5 The CASAC NO<sub>x</sub> and SO<sub>x</sub> primary review panel will be consulted on the risk/exposure  
6 assessment scope and methods plan at a public meeting. Drafts of the risk/exposure assessment  
7 will also be reviewed by the panel. The panel will review the draft document and discuss their  
8 comments in a public meeting announced in the Federal Register. Based on CASAC's past  
9 practice, EPA expects that key CASAC advice and recommendations for revision of the  
10 document will be conveyed by the CASAC Chair in a letter to the EPA Administrator. In  
11 revising the draft risk/exposure assessment for NO<sub>2</sub>, EPA will take into account any such advice  
12 and recommendations. EPA will also consider comments received from CASAC or from the  
13 public at the meeting itself and any written public comments. EPA anticipates preparing a  
14 second draft of the risk/exposure assessment for CASAC review and public comment. After  
15 appropriate revision, the final document will be made available on an EPA website and  
16 subsequently printed, with its public availability being announced in the Federal Register.

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## **6. POLICY ASSESSMENT/RULEMAKING**

Based on the information in the ISA and the risk/exposure assessment report, the Agency will develop an ANPR that reflects EPA’s views regarding the need to retain or revise the NAAQS for NO<sub>2</sub>. The ANPR will identify conceptual evidence-based and exposure/risk-based approaches for reaching public health policy judgments. It will discuss the implications of the science and risk/exposure assessments for the adequacy of the current standard, and it will present exposure information associated with alternative standards. The ANPR will also describe a range of policy options for standard setting including a description of the underlying interpretations of the scientific evidence and risk/exposure information that might support such alternative standards and that could be considered by the Administrator in making NAAQS decisions.

A final decision should draw upon scientific information and analyses related to health effects, population exposure and risks, and judgments about the appropriate response to the range of uncertainties that are inherent in the scientific evidence and analyses. The Agency’s approach to informing these judgments is based on a recognition that the available health effects evidence generally reflects a continuum consisting of ambient levels at which scientists generally agree that health effects are likely to occur through lower levels at which the likelihood and magnitude of the response become increasingly uncertain.

The use of an ANPR will provide an opportunity for CASAC and the public to evaluate the policy options under consideration and to offer comments and recommendations to inform the development of a proposed rule. Taking into account CASAC advice and recommendations as well as public comment on the ANPR, the Agency will publish a proposed rule. This proposal will be followed by a public comment period. Taking into account comments received on the proposed rule, the Agency will then issue a final rule to complete the rulemaking process.

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- 29
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1 **APPENDIX**

2  
3 **U.S. EPA SCIENCE ADVISORY BOARD**  
4 **CLEAN AIR SCIENTIFIC ADVISORY**  
5 **COMMITTEE MEMBERS**

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7 **FISCAL YEAR 2007**

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10 The Clean Air Scientific Advisory Committee (CASAC) has a statutorily mandated  
11 responsibility to review and offer scientific and technical advice to the Administrator on the air  
12 quality criteria and regulatory documents that form the basis for the national ambient air quality  
13 standards (NAAQS), which currently include standards for lead (Pb), particulate matter (PM),  
14 ozone (O<sub>3</sub>), carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>) and sulfur dioxide (SO<sub>2</sub>).  
15 To perform such reviews, in each case the Committee forms a review panel consisting of  
16 CASAC members augmented by selected consultants with expertise in scientific or technical  
17 areas pertinent to the given pollutant or pollutant class under review.

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