Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide

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Integrated Review Plan for the Primary National Ambient Air Quality Standards for Nitrogen Dioxide

U. S. Environmental Protection Agency

National Center for Environmental Assessment
Office of Research and Development
and
Office of Air Quality Planning and Standards
Health and Environmental Impacts Division

Research Triangle Park, North Carolina

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DISCLAIMER

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS/ABBREVIATIONS

AADT	Annual Average Daily Traffic
AERMOD	EPA's Air Dispersion Model
ANPR	Advanced notice of proposed rulemaking
APEX	EPA's Air Pollutants Exposure model
AQI	Air Quality Index
AQS	EPA's Air Quality System
CAA	Clean Air Act
CAPS	Cavity attenuated phase shift
CASAC	Clean Air Scientific Advisory Committee
CBSA	Core Based Statistical Area
CFR	Code of Federal Regulations
CO	Carbon monoxide
C-R	Concentration-response
EPA	Environmental Protection Agency
E-R	Exposure-response
FEM	Federal Equivalent Method
FEV_1	Forced expiratory volume in one second, volume of air exhaled in first second of exhalation
FR	Federal Register
FRM	Federal Reference Method
HA	Hospital admissions
HERO	Health and Environmental Research Online
HONO	Nitrous acid
HNO_3	Nitric acid
IRP	Integrated Review Plan
ISA	Integrated Science Assessment
$\mu g/m^3$	micrograms per cubic meter
m	Meters
ME	Microenvironmental
MSA	Metropolitan Statistical Area
NAAQS	National Ambient Air Quality Standards
NCEA	National Center for Environmental Assessment
NCore	National Core Monitoring Network
NO	Nitric oxide
NO_2	Nitrogen dioxide
NO_3^-	Nitrate
NO_X	$NO+NO_2$
NO_Y	Total oxides of nitrogen ($NO_X + NO_Z$)
NO_Z	Reactive oxides of nitrogen (e.g., HNO_3, HONO, PAN, particulate nitrates)
O_3	Ozone
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation

OMB	Office of Management and Budget
ORD	Office of Research and Development
PA	Policy Assessment
PAN	Peroxyacetyl nitrate
PM	Particulate matter
$PM_{2.5}$	In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 2.5 microns (µm); a measurement of fine particles
ppb	Parts per billion
ppm	Parts per million
QA	Quality assurance
QMP	Quality Management Plan
REA	Risk and Exposure Assessment
RIA	Regulatory Impact Analysis
RTP	Research Triangle Park
SES	Socioeconomic status
SO_2	Sulfur dioxide
TBD	To be determined

1 INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is conducting a review of the primary (health-based) national ambient air quality standards (NAAQS) for nitrogen dioxide (NO_2). This Integrated Review Plan (IRP) presents the planned approach for the review. This review will provide an integrative assessment of relevant scientific information for oxides of nitrogen and will focus on the basic elements that define the NAAQS: the indicator,[1] averaging time,[2] form,[3] and level.[4] The EPA Administrator will consider these elements collectively in evaluating the protection to public health afforded by the primary NO_2 standards.

This document is organized into eight chapters. Chapter 1 summarizes the legislative requirements for the review of the NAAQS (section 1.1), summarizes the review process (section 1.2), provides an overview of past reviews of the primary NO_2 NAAQS (section 1.3), and outlines the scope of the current review (section 1.4). Chapter 2 presents the status and schedule for the current review. Chapter 3 provides background on the key issues and uncertainties that informed the final decisions in the last review and presents a set of policy-relevant questions that will serve to focus this review on the critical scientific and policy issues. Chapters 4 through 7 discuss the planned scope and organization of key assessment documents, the planned approaches for preparing the documents, plans for scientific and public review of the documents, and specific ambient air quality monitoring considerations. Complete reference citations are provided in Chapter 8.

1.1 LEGISLATIVE REQUIREMENTS

Two sections of the Clean Air Act (CAA) govern the establishment, review, and revision of the NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to list those air pollutants that in her "judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare;" "the presence of which in the ambient air results from numerous or diverse mobile or stationary sources;" and "for which . . .

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[1] The "indicator" of a standard defines the chemical species or mixture that is measured in determining whether an area attains the standard. Nitrogen dioxide (NO_2) is the indicator for the oxides of nitrogen.

[2] The "averaging time" defines the time period over which ambient measurements are averaged (e.g., 1-hour, 8-hour, 24-hour, annual).

[3] The "form" of a standard defines the air quality statistic that is compared to the level of the standard in determining whether an area attains the standard. For example, the form of the current 1-hour NO_2 standard is the three-year average of the 98^{th} percentile of the annual distribution of 1-hour daily maximum NO_2 concentrations.

[4] The "level" defines the allowable concentration of the criteria pollutant in the ambient air.

[the Administrator] plans to issue air quality criteria…" Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in the ambient air . . ." 42 U.S.C. 7408(b). Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants for which air quality criteria are issued.[5] Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[6] A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[7]

The requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified.[8] Both kinds of uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that provide an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree. The CAA does not require the Administrator to establish a primary NAAQS at a zero-risk level or at background concentration levels, but rather

[5] As discussed in section 1.4 below, this document describes the review of the *primary* NO_2 standards. The *secondary* NO_2 standard will be separately reviewed in conjunction with review of the secondary sulfur dioxide (SO_2) standard.

[6] 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, 91st Cong., 2d Sess. 10 (1970).

[7] 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."

[8] See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981); *American Farm Bureau Federation v. EPA*, 559 F. 3d 512, 533 (D.C. Cir. 2009); and *Association of Battery Recyclers v. EPA*, 604 F. 3d 613, 617-18 (D.C. Cir. 2010).

at a level that reduces risk sufficiently so as to protect public health with an adequate margin of safety.[9]

In addressing the requirement for an adequate margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive group(s), and the kind and degree of uncertainties. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment.[10]

In setting standards that are "requisite" to protect public health and welfare, as provided in section 109(b), the EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, the EPA may not consider the costs of implementing the standards.[11] Likewise, "[a]ttainability and technological feasibility are not relevant considerations in the promulgation of national ambient air quality standards."[12]

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards . . . and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate . . . " Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria . . . and the national primary and secondary ambient air quality standards. . . and shall recommend to the Administrator any new . . . standards and revisions of existing criteria and standards as may be appropriate . . . ." Since the early 1980s, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC).[13]

1.2 OVERVIEW OF THE NAAQS REVIEW PROCESS

The current process for reviewing the NAAQS includes four major phases: (1) planning, (2) science assessment, (3) risk/exposure assessment, and (4) policy assessment and rulemaking. Figure 1-1 provides an overview of this process, and each phase is described in more detail

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[9] See *Lead Industries v. EPA*, 647 F.2d at 1156 n.51, *Mississippi v. EPA*, 723 F. 3d 246, 255, 262-63 (D.C. Cir. 2013).

[10] See *Lead Industries Association v. EPA*, 647 F.2d at 1161-62; *Mississippi v. EPA*, 723 F. 3d at 265.

[11] See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (2001).

[12] See *American Petroleum Institute v. Costle*, 665 F. 2d at 1185.

[13] Lists of CASAC members and of members of the CASAC Oxides of Nitrogen Primary NAAQS Review Panel are available at: http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument.

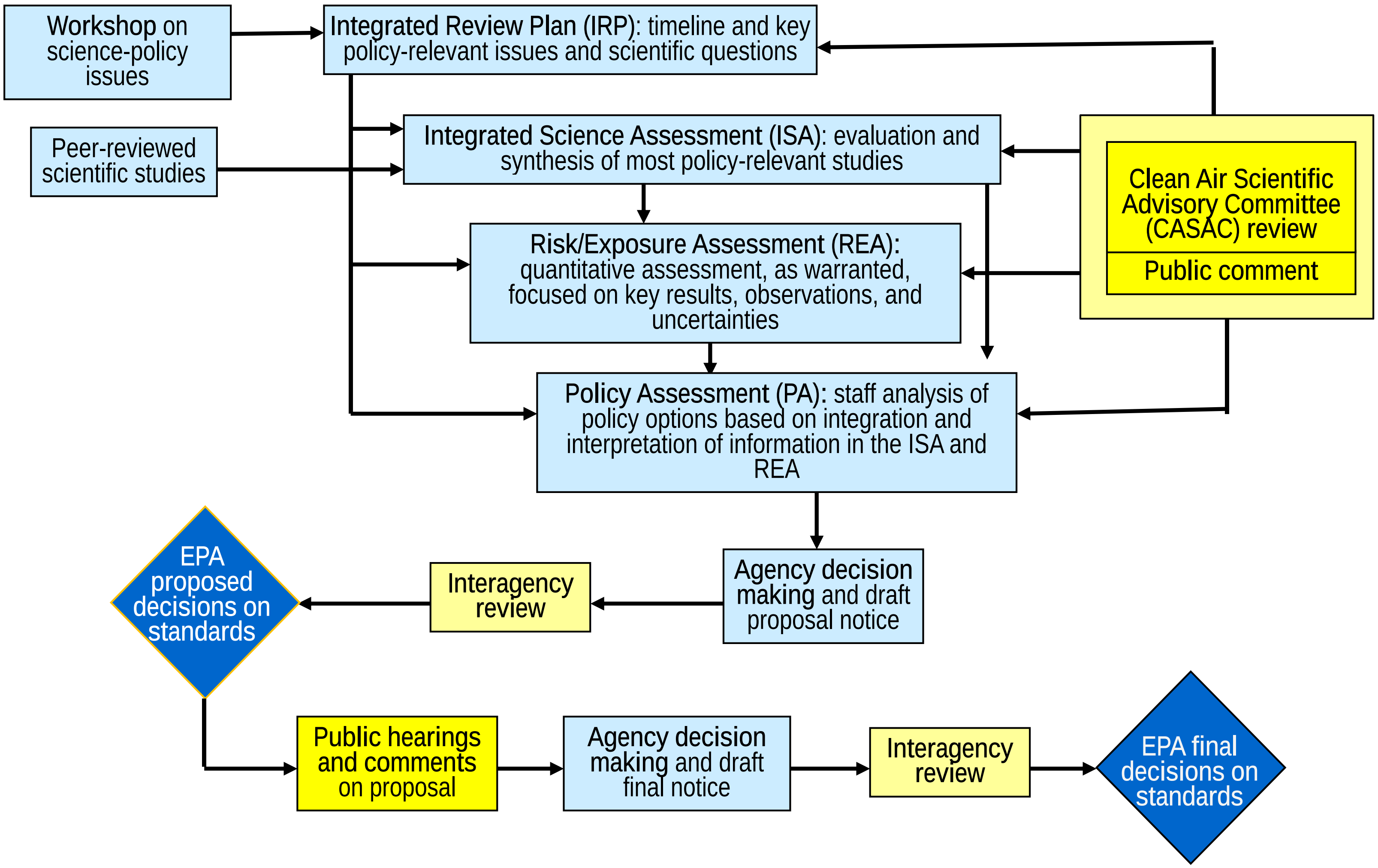

Figure 1-1. Overview of the NAAQS review process.

below.[14] The planning phase of the NAAQS review process begins with a science policy workshop, which is intended to identify issues and questions to frame the review. Drawing from the workshop discussions, a draft IRP is prepared jointly by the EPA's National Center for Environmental Assessment (NCEA), within the Office of Research and Development (ORD), and the EPA's Office of Air Quality Planning and Standards (OAQPS), within the Office of Air and Radiation (OAR).[15] The draft IRP is made available for CASAC review and for public comment. The final IRP is prepared in consideration of CASAC and public comments. This document presents the current plan and specifies the schedule for the entire review, the process for conducting the review, and the key policy-relevant science issues that will guide the review.

The second phase of the review, science assessment, involves the preparation of an Integrated Science Assessment (ISA) and, if appropriate, supplementary materials. The ISA, prepared by NCEA, provides a concise review, synthesis, and evaluation of the most policy-relevant science, including key science judgments that are important to the design and scope of exposure and risk assessments, as well as other aspects of the NAAQS review. The ISA (and any supplementary materials that may be developed) provides a comprehensive assessment of the current scientific literature pertaining to known and anticipated effects on public health and welfare associated with the presence of the pollutant in the ambient air, emphasizing information that has become available since the last air quality criteria review in order to reflect the current state of knowledge. As such, the ISA forms the scientific foundation for each NAAQS review and is intended to provide information useful in forming judgments about air quality indicator(s), form(s), averaging time(s) and level(s) for the NAAQS. The current review process generally includes production of a first and second draft ISA, both of which undergo CASAC and public review prior to completion of the final ISA. Chapter 4 below provides a more detailed description of the planned scope, organization, and assessment approach for the ISA and any supporting materials that may be developed.

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[14] The EPA maintains a website on which key documents developed for NAAQS reviews are made available (http://www.epa.gov/ttn/naaqs/). The EPA's NAAQS review process has evolved over time (Jackson, 2009). Information on the current process is available at: http://www.epa.gov/ttn/naaqs/review.html. As discussed in section 1.3 below, this process was generally followed in the primary NO_2 NAAQS review completed in 2010 with the exception that there was not a separate Policy Assessment document issued. Rather, the Risk and Exposure Assessment (U.S. EPA, 2008b) included a policy assessment chapter (i.e., Chapter 10).

[15] In this review of the primary NAAQS for NO_2, a draft plan for development of the ISA was prepared by NCEA prior to development of this draft IRP. The draft plan for development of the ISA was made available for public comment and was the subject of a consultation with CASAC (78 FR 26026; 78 FR 27234). Comments received during that consultation have been considered in preparation of chapter 4 in this draft IRP. Further comments received on this draft IRP will be considered in developing a final IRP and a second draft ISA.

In the third phase, the risk/exposure assessment phase, OAQPS staff considers information and conclusions presented in the ISA, with regard to support provided for the development of quantitative assessments of the risks and/or exposures for health and/or welfare effects. As an initial step, staff prepares a planning document (REA Planning Document) that considers the extent to which newly available scientific evidence and tools/methodologies warrant the conduct of quantitative risk and exposure assessments. As discussed in Chapter 5 below, the REA Planning Document focuses on the degree to which important uncertainties in the last review may be addressed by new information available in this review. Specifically, the document considers the extent to which newly available data, methods, and tools might be expected to appreciably affect the assessment results or address important gaps in our understanding of the exposures and risks associated with NO_2. To the extent warranted, this document outlines a general plan, including scope and methods, for conducting assessments. The REA Planning Document is generally prepared in conjunction with the first draft ISA[16] and is presented for consultation with CASAC and for public comment. When an assessment is performed, one or more drafts of each risk and exposure assessment document (REA) undergoes CASAC and public review. The REA provides concise presentations of methods, key results, observations, and related uncertainties. Chapter 5 below discusses consideration of potential quantitative human health-related assessments for this review.

The review process ends with the policy assessment and rulemaking phase. The Policy Assessment (PA) is prepared prior to issuance of proposed and final rules. The PA provides a transparent presentation of OAQPS staff analyses and conclusions regarding the adequacy of the current standards and, if revision is considered, what revisions may be appropriate. The PA integrates and interprets the information from the ISA and REA to frame policy options for consideration by the Administrator. Such an evaluation of policy implications is intended to help ‘‘bridge the gap’’ between the Agency’s scientific assessments, presented in the ISA and REA(s), and the judgments required of the EPA Administrator in determining whether it is appropriate to retain or revise the NAAQS. In so doing, the PA is also intended to facilitate CASAC’s advice to the Agency and recommendations to the Administrator on the adequacy of the existing standards and, as pertinent, on revisions that may be appropriate to consider, as provided for in the CAA. In evaluating the adequacy of the current standards and, as appropriate, a range of potential alternative standards, the PA considers the available scientific evidence and, as available, quantitative risk and exposure analyses together with related limitations and uncertainties. The PA focuses on the information that is most pertinent to evaluating the basic

[16]The current review of the primary NO_2 standards is an exception to this general schedule. As indicated in Table 2-1 below, the draft REA Planning Document will be made available for public comment and consultation with CASAC at approximately the same time as the CASAC review of the second draft ISA.

elements of national ambient air quality standards: indicator, averaging time, form, and level. One or more drafts of a PA are released for CASAC review and public comment prior to completion of the final PA.

Following issuance of the final PA and consideration of conclusions presented therein, the Agency develops and publishes a notice of proposed rulemaking that communicates the Administrator's proposed decisions regarding the standards review. A draft notice undergoes interagency review involving other federal agencies prior to publication.[17] Materials upon which the proposed decision is based, including the documents described above, are made available to the public in the regulatory docket for the review.[18] A public comment period, during which public hearings are generally held, follows publication of the notice of proposed rulemaking. Taking into account comments received on the proposed rule,[19] the Agency develops a final rule which undergoes interagency review prior to publication to complete the rulemaking process. Chapter 7 below discusses the development of the PA and the rulemaking steps for this review.

1.3 REVIEW OF AIR QUALITY CRITERIA FOR OXIDES OF NITROGEN AND STANDARDS FOR NITROGEN DIOXIDE

In 1971, the EPA added nitrogen oxides to the list of criteria pollutants under section 108(a)(1) of the CAA and issued the initial air quality criteria (36 FR 1515, January 30, 1971; U.S. EPA, 1971). Based on these air quality criteria, the EPA promulgated NAAQS for nitrogen oxides using NO_2 as the indicator (36 FR 8186, April 30, 1971). Both primary and secondary standards were set at 100 micrograms per cubic meter ($\mu g/m^3$) (equal to 0.053 parts per million (ppm)), annual average. Since then, the Agency has completed multiple reviews of the air quality criteria and primary standards, as summarized in Table 1-1.

[17] Where implementation of the proposed decision would have an annual effect on the economy of $100 million or more (e.g., by necessitating the implementation of emissions controls), the EPA develops and releases a draft regulatory impact analysis (RIA) concurrent with the notice of proposed rulemaking. This activity is conducted under Executive Order 12866. The RIA is conducted completely independent of the rulemaking process and, by statute, is not considered in decisions regarding the review of the NAAQS.

[18] All documents in the docket are listed in the www.regulations.gov index. Publically available docket materials are available either electronically at www.regulations.gov or in hard copy at the Air and Radiation Docket and Information Center. The docket ID number for this review is EPA-HQ-OAR-2013-0146.

[19] When issuing the final rulemaking, the Agency responds to all significant comments on the proposed rule.

Table 1-1. Primary national ambient air quality standards for oxides of nitrogen since 1971.

Final Rule/Decision	Indicator	Averaging Time	Level	Form
1971 36 FR 8186 Apr 30, 1971	NO_2	1 year	53 ppb[20]	Annual arithmetic average
1985 50 FR 25532 Jun 19, 1985	Primary annual NO_2 standard retained, without revision.			
1996 61 FR 52852 Oct 8, 1996	Primary annual NO_2 standard retained, without revision.			
2010 75 FR 6474 Feb 9, 2010	NO_2	1 hour	100 ppb	3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour concentrations
	Primary annual NO_2 standard retained, without revision.			

The EPA retained the primary and secondary NO_2 standards, without revision, in reviews completed in 1985 and 1996 (50 FR 25532, June 19, 1985; 61 FR 52852, October 8, 1996). In the latter of the two decisions, the EPA concluded that "the existing annual primary standard appears to be both adequate and necessary to protect human health against both long- and short-term NO_2 exposures" and that "retaining the existing annual standard is consistent with the scientific data assessed in the Criteria Document (U.S. EPA, 1993) and the Staff Paper (U.S.

[20] The initial standard level of the annual NO_2 standard was 100 µg/m^3 which is equal to 0.053 ppm or 53 parts per billion (ppb). The units for the standard level were officially changed to ppb in the final rule issued in 2010 (75 FR 6531, February 9, 2010).

EPA, 1995) and with the advice and recommendations of CASAC" (61 FR 52854, October 8, 1996).[21]

The last review of the air quality criteria for oxides of nitrogen (health criteria) and the primary NO_2 standard was initiated in December 2005 (70 FR 73236, December 9, 2005).[22,23] The Agency's plans for conducting the review were presented in the *Integrated Review Plan for the Primary National Ambient Air Quality Standard for Nitrogen Dioxide* (2007 IRP, U.S. EPA, 2007a), which included consideration of comments received during a CASAC consultation as well as public comment on a draft IRP. The scientific assessment for the review was described in the 2008 *Integrated Science Assessment for Oxides of Nitrogen – Health* Criteria (2008 ISA, U.S. EPA, 2008a), multiple drafts of which received review by CASAC and the public. The EPA also conducted quantitative human risk and exposure assessments, after consultation with CASAC and after receiving public comment on an analysis plan (U.S. EPA, 2007b). These technical analyses were presented in the *Risk and Exposure Assessment to Support the Review of the NO_2 Primary National Ambient Air Quality Standard* (2008 REA, U.S. EPA, 2008b), multiple drafts of which received CASAC and public review.

Over the course of the last review, the EPA made several changes to the NAAQS review process. An important change was the discontinuation of the Staff Paper, which traditionally contained staff evaluations to bridge the gap between the Agency's science assessments and the judgments required of the EPA Administrator in determining whether it was appropriate to retain or revise the NAAQS.[24] In the course of reviewing the second draft REA, however, CASAC expressed the view that the document would be incomplete without the addition of a policy assessment chapter presenting an integration of evidence-based considerations and risk and exposure assessment results. CASAC stated that such a chapter would be "critical for considering options for the NAAQS for NO_2" (Samet, 2008a, p.4). In addition, within the period

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[21] In presenting the rationale for the final decision, the EPA noted that "a 0.053 ppm annual standard would keep annual NO_2 concentrations considerably below the long-term levels for which serious chronic effects have been observed in animals" and that "[r]etaining the existing standard would also provide protection against short-term peak NO_2 concentrations at the levels associated with mild changes in pulmonary function and airway responsiveness observed in controlled human [exposure] studies" (61 FR 52854, October 8, 1996; 60 FR 52874, 52880, October 11, 1995).

[22] Documents related to the current review as well as reviews completed in 2010 and 1996 are available at: http://www.epa.gov/ttn/naaqs/standards/nox/s_nox_index.html.

[23] The EPA conducted a separate review of the secondary NO_2 NAAQS jointly with a review of the secondary SO_2 NAAQS. The Agency retained those secondary standards, without revision, to address the direct effects on vegetation of exposure to gaseous oxides of nitrogen and sulfur (77 FR 20218, April 3, 2012).

[24] Initial changes to the NAAQS review process included a policy assessment document reflecting Agency (rather than staff) views published as an advanced notice of public rulemaking (ANPR). Under this process, the ANPR would have been reviewed by CASAC (Peacock, 2006).

of CASAC's review of the second draft REA, the EPA's Deputy Administrator indicated in a letter to the CASAC chair, addressing earlier CASAC comments on the NAAQS review process, that the risk and exposure assessment would include "a broader discussion of the science and how uncertainties may effect decisions on the standard" and "all analyses and approaches for considering the level of the standard under review, including risk assessment and weight of evidence methodologies" (Peacock, 2008, p. 3). Accordingly, the final 2008 REA included a policy assessment chapter that considered the scientific evidence in the 2008 ISA and the exposure and risk results presented in other chapters of the 2008 REA as they related to the adequacy of the then current primary annual NO_2 standard and potential alternative standards for consideration (U.S EPA, 2008b, chapter 10).[25] CASAC discussed the final version of the 2008 REA, with an emphasis on the policy assessment chapter, during a public teleconference on December 5, 2008 (73 FR 66895, November 12, 2008). Following that teleconference, CASAC offered comments and advice on the primary NO_2 standard in a letter to the Administrator (Samet, 2008b).

As discussed in more detail in section 3.1 below, after considering an integrative synthesis of the body of evidence on human health effects associated with the presence of NO_2 in the air and the exposure and risk information, the Administrator determined that the existing primary NO_2 NAAQS, based on an annual arithmetic average, was not sufficient to protect the public health from the array of effects that could occur following short-term exposures to ambient NO_2. In so doing, the Administrator particularly noted the potential for adverse health effects to occur following exposures to elevated NO_2 concentrations that can occur around major roads (75 FR 6482). In a notice published in the *Federal Register* on July 15, 2009, the EPA proposed to supplement the existing primary annual NO_2 standard by establishing a new short-term standard (74 FR 34404). In a notice published in the *Federal Register* on February 9, 2010, the EPA finalized a new short-term NO_2 standard with a level of 100 ppb, based on the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour concentrations. The EPA also retained the existing primary annual NO_2 standard with a level of 53 ppb, annual average (75 FR 6474). The Agency's final decision included consideration of CASAC (Samet, 2009) and

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[25] Subsequent to the completion of the 2008 REA, EPA Administrator Jackson called for additional key changes to the NAAQS review process including reinstating a policy assessment document that contains staff analysis of the scientific bases for alternative policy options for consideration by senior Agency management prior to rulemaking (Jackson, 2009). As discussed in Chapter 7 of this document, a Policy Assessment will be developed for this review.

public comments on the proposed rule. The EPA's final rule was upheld against challenges in a decision issued by the U.S. Court of Appeals for the District of Columbia Circuit on July 17, 2012.[26]

Revisions to the NAAQS were accompanied by revisions to the data handling procedures, the ambient air monitoring and reporting requirements, and the Air Quality Index (AQI).[27] As described in section 6.2 below, one aspect of the new monitoring network requirements included requirements for states to locate monitors near heavily trafficked roadways in large urban areas and in other locations where maximum NO_2 concentrations can occur. Subsequent to the 2010 rulemaking, the EPA revised the deadlines by which the near-road monitors are to be operational in order to implement a phased deployment approach (78 FR 16184, March 14, 2013). As discussed in section 6.2 below, the near-road NO_2 monitors will become operational between January 1, 2014 and January 1, 2017.

1.4 SCOPE OF THE CURRENT REVIEW

Consistent with the review completed in 2010, this review will focus on health effects associated with gaseous oxides of nitrogen and the protection afforded by the primary NO_2 standards.[28] The gaseous oxides of nitrogen include NO_2 and nitric oxide (NO) as well as their gaseous reaction products. Total oxides of nitrogen include these gaseous species as well as particulate species (e.g., nitrates). Collectively, we refer to the total set of species as NO_Y (U.S. EPA, 2013b, section 2.2, Figure 2-1). Health effects associated with the particulate species are addressed in the review of the NAAQS for particulate matter (PM) (78 FR 30866, January 15,

[26] See *API v. EPA*, 684 F.3d 1342 (D.C. Cir. 2012).

[27] The current federal regulatory measurement methods for NO_2 are specified in 40 CFR part 50, Appendix F and 40 CFR part 53. Consideration of ambient air measurements with regard to judging attainment of the standards is specified in 40 CFR part 50, Appendix S. The NO_2 monitoring network requirements are specified in 40 CFR part 58, Appendix D, section 4.3. The EPA revised the AQI for NO_2 to be consistent with the revised primary NO_2 NAAQS as specified in 40 CFR part 58 Appendix G. Guidance on the approach for implementation of the new standard was described in the *Federal Register* notices for the proposed and final rules (74 FR 34404; 75 FR 6474).

[28] Section 108(c) of the CAA specifies that the air quality criteria relating to NO_2 include consideration of nitric and nitrous acids, nitrites, nitrates, nitrosamines, and other derivatives of oxides of nitrogen, including multiple gaseous and particulate species.

2013; U.S. EPA, 2009).[29] The EPA is separately reviewing the welfare effects associated with oxides of nitrogen and the protection provided by the secondary NO_2 standard in conjunction with a review of the secondary SO_2 standard (78 FR 53452, August 29, 2013).[30]

When referring to the group of gaseous oxidized nitrogen compounds as a whole, the ISA and other assessment documents developed in this review will use the term "oxides of nitrogen." In the last review, the EPA used "NOx" as the abbreviation for oxides of nitrogen. Based on the definition commonly used in the scientific literature, in this review, the abbreviation NO_X will refer specifically to the sum of NO_2 and NO concentrations (U.S. EPA, 2013b, section 2.2).

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[29] Additional information on the PM NAAQS is available at: http://www.epa.gov/ttn/naaqs/standards/pm/s_pm_index.html.

[30] Additional information on the ongoing and previous review of the secondary NO_2 and SO_2 NAAQS is available at: http://www.epa.gov/ttn/naaqs/standards/no2so2sec/index.html.

2 STATUS AND SCHEDULE

In February 2012, the EPA announced the initiation of the current periodic review of the air quality criteria for oxides of nitrogen and the primary NO_2 NAAQS and issued a call for information in the *Federal Register* (77 FR 7149, February 10, 2012). Also, as an initial step in the NAAQS review process described in section 1.2 above, the EPA invited a wide range of scientific experts (from EPA and outside organizations) to participate in a workshop to discuss the policy-relevant science to inform the development of this draft IRP. *Id.* These experts represented a variety of scientific disciplines, including epidemiology, human and animal toxicology, statistics, risk/exposure analysis, and atmospheric science. This public workshop was held February 29 to March 1, 2012, in Research Triangle Park, NC, and provided an opportunity for the participants to broadly discuss the key policy-relevant issues around which the EPA would structure this review of the primary NO_2 NAAQS and the most meaningful new science that would be available to inform our understanding of these issues.[31]

Based in part on the workshop discussions, the EPA developed the *Draft Plan for Development of the Integrated Science Assessment (ISA) for Nitrogen Oxides – Health Criteria* (U.S. EPA, 2013a)[32] and the draft IRP outlining the schedule, the process, and the policy-relevant science issues identified as key to guiding the evaluation of the air quality criteria for oxides of nitrogen and the review of the primary NO_2 NAAQS (U.S. EPA, 2014). The draft IRP was made available for review by the CASAC Oxides of Nitrogen Primary NAAQS Review Panel and for public comment (79 FR 7184, February 6, 2014). The CASAC discussed its review of the draft IRP at a public meeting on March 12, 2014 (79 FR 8701, February 13, 2014). Advice received from the CASAC on the draft IRP (Frey et al., 2014), as well as public comment on that draft document, were considered in developing this final IRP.

Table 2-1 outlines the schedule under which the Agency is currently conducting this review. The scope of the review and the key documents to be prepared during the review are discussed throughout the rest of this document. Based on the projected schedule presented in Table 2-1, the ISA will include consideration of new scientific studies published between January 2008 and August 2014. The EPA will also consider near-road NO_2 measurement data

[31] Workshop materials are available in the rulemaking docket accessible through http://www.regulations.gov, Docket ID number EPA-HQ-OAR-2013-0146.

[32] The EPA released a draft plan outlining the plans for developing the ISA for CASAC consultation and public review (78 FR 26026, May 3, 2013). The EPA held a consultation with CASAC on this draft plan during a public teleconference on June 5, 2013 (78 FR 27234, May 9, 2013). CASAC (Frey, 2013) and public comments on the draft plan were considered in developing Chapter 4 of the draft IRP (US EPA, 2014).

through August 2014 and additional data to the extent practicable as it becomes available through routine monitoring networks as discussed in section 6.2 below.

Table 2-1. Anticipated schedule for the current review.

Stage of Review	Major Milestone	Target Date
Integrated Review Plan (IRP)	Literature Search	Ongoing
	Federal Register Call for Information	February 10, 2012
	Workshop on science/policy issues	February 29 – March 1, 2012
	Draft plan for developing ISA	May 2013
	CASAC consultation on draft ISA plan	June 5, 2013
	Draft IRP	February 2014
	CASAC review of draft IRP	March 12-13, 2014
	Final IRP	June 2014
Integrated Science Assessment (ISA)	First draft ISA	November 2013
	CASAC public meeting for review of first draft ISA	March 12-13, 2014
	Second draft ISA	October 2014
	CASAC/public review of second draft ISA	December 2014
	Final ISA	April 2015
Risk/Exposure Assessment (REA)	REA Planning Document	November 2014
	CASAC consultation/public review of REA Planning Document	December 2014
	If warranted, First draft REA CASAC/public review of first draft REA Second draft REA CASAC/public review of second draft REA Final REA	TBD
Policy Assessment (PA)/Rulemaking	First draft PA	March 2015
	CASAC/public review of first draft PA	April 2015
	Second draft PA[33]	December 2015
	CASAC/public review of second draft PA	January 2016
	Final PA	June 2016
	Notice of proposed rulemaking	November 2016
	Notice of final rulemaking	August 2017

[33] The anticipated schedule presented in Table 2-1 includes preparation of two draft PAs for CASAC and public review. However, in NAAQS reviews where a new REA is not developed and where staff preliminarily conclude in a first draft PA that it is appropriate to consider retaining the current standards, without revision, the EPA may decide that there is no new substantive information that we would intend to add that would provide a basis for preparing a second draft PA. In NAAQS reviews in which the newly available information calls into question the adequacy of the current standard(s), a second draft PA is typically prepared to include staff consideration of potential alternative standards. If the Agency determines that a second draft PA is not warranted, CASAC and public comments on the first draft PA will be considered in preparing the final PA and the schedule adjusted accordingly.

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3 KEY POLICY-RELEVANT ISSUES

In each NAAQS review, an initial step is to address the following overarching question:

- **Does the currently available scientific evidence and exposure/risk-based information support or call into question the adequacy of the protection afforded by the current standard(s)?**

As appropriate, reviews also address a second overarching question:

- **What alternative standards, if any, are supported by the currently available scientific evidence and exposure/risk-based information and are appropriate for consideration?**

To inform our evaluation of these overarching questions in the current review, we have identified key policy-relevant issues to be considered. These key issues reflect aspects of the health effects evidence, air quality information, and exposure/risk information that, in our judgment, are likely to be particularly important to inform the Administrator's decisions. They build upon the key issues that were important in previous reviews.

Section 3.1 below describes the key considerations and conclusions from the last review with regard to the adequacy of the primary NO_2 standards (section 3.1.1) and with regard to the elements for a revised suite of standards judged in that review to provide requisite public health protection (section 3.1.2). Section 3.2 summarizes our general approach for reviewing the primary NO_2 standards in the current review and outlines the key policy-relevant issues. These issues are presented as a series of questions that will frame our approach to considering the extent to which the available evidence and information support retaining or revising the current primary standards for NO_2.

3.1 CONSIDERATIONS AND CONCLUSIONS IN LAST REVIEW

The last review of the primary NO_2 NAAQS was completed in 2010 (75 FR 6474, February 9, 2010). In consideration of health effects evidence and air quality and exposure/risk information available in that review, the EPA established a new short-term standard to provide increased public health protection, including for asthmatics and other at-risk populations,[34] against an array of adverse respiratory health effects that had been linked to short-term NO_2 exposures (75 FR 6498 to 6502; U.S. EPA, 2008a, sections 3.1.7 and 5.3.2.1; Table 5.3-1). Specifically, the EPA established a short-term standard defined by the 3-year average of the 98th percentile of the yearly distribution of daily maximum 1-hour NO_2 concentrations, with a level of 100 ppb. In addition to setting the new 1-hour standard, the EPA retained the annual standard with a level of 53 ppb (75 FR 6502). Together, the two standards were concluded to provide protection for at-risk populations and lifestages against adverse respiratory health effects associated with short-term exposures to NO_2 and effects potentially associated with long-term exposures. As discussed further in section 6.2 below, in conjunction with the revised primary NO_2 NAAQS, the EPA also established a two-tiered monitoring network composed of (1) near-road monitors which would be placed in locations of expected maximum 1-hour NO_2 concentrations near heavily trafficked roads in urban areas and (2) monitors located to characterize areas with the highest expected NO_2 concentrations at the neighborhood and larger spatial scales (also referred to as “area-wide” monitors) (75 FR 6505 to 6506, February 9, 2010).

Key policy-relevant aspects of the Administrator’s decisions with regard to the need to revise the primary NO_2 NAAQS, and with regard to the elements of the revised standard, are described below in sections 3.1.1 and 3.1.2, respectively. Areas of uncertainty identified in the last review are noted in section 3.1.3.

3.1.1 Need for Revision

The 2010 decision to revise the existing primary NO_2 standard was based on the extensive body of evidence published through early 2008 and assessed in the 2008 ISA (U.S. EPA, 2008a), including the assessment of the policy-relevant aspects of that evidence;[35] the quantitative exposure and risk analyses presented in the REA (U.S. EPA, 2008b); the advice and recommendations of CASAC (Samet, 2008b); and public comments (U.S. EPA, 2010). The scientific evidence included controlled human exposure studies providing evidence of airway

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[34] As used here and similarly throughout this document, the term *population* refers to persons having a quality or characteristic in common, such as a specific pre-existing illness or a specific age or lifestage, with lifestage referring to a distinguishable time frame in an individual’s life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth. Identifying at-risk populations includes consideration of intrinsic (e.g., genetic or developmental aspects) or acquired (e.g., disease or smoking status) factors that increase the risk of health effects occurring with exposure to oxides of nitrogen as well as extrinsic, nonbiological factors such as those related to socioeconomic status, reduced access to health care, or exposure.

[35] As noted in section 1.3 above, due to changes in the NAAQS process, the last review of the NO_2 NAAQS did not include a separate Policy Assessment. Rather, the REA for that review included a policy assessment chapter.

hyperresponsiveness in asthmatics following short-term exposures to NO_2 concentrations as low as 100 ppb and epidemiological studies reporting associations between short-term NO_2 and respiratory effects in locations that would have met the annual standard. The quantitative analyses presented in the 2008 REA included exposure and risk estimates for air-quality adjusted to just meet the annual standard. Based on the evidence and exposure/risk information, and based on CASAC's advice that "the current NAAQS does not protect the public's health and that it should be revised" (Samet, 2008b, p. 2), the Administrator concluded that the existing primary annual NO_2 standard alone was not sufficient to protect public health from the array of respiratory effects that had been reported following short-term exposures to oxides of nitrogen (75 FR 6488 to 6490, February 9, 2010).

As an initial consideration in reaching this decision, the Administrator noted that the evidence relating short-term (minutes to hours) NO_2 exposures to respiratory morbidity was judged in the ISA to be "sufficient to infer a likely causal relationship" (75 FR 6489; U.S. EPA, 2008a, sections 3.1.7 and 5.3.2.1).[36] This evidence included a large body of epidemiological studies reporting associations between short-term NO_2 concentrations measured at central-site monitors and respiratory-related symptoms, emergency department visits, and hospital admissions. Overall, the 2008 ISA characterized the epidemiological evidence as *consistent*, in that associations were reported in studies conducted in numerous locations with a variety of methodological approaches, and *coherent*, in that the studies reported associations with respiratory health outcomes that were logically linked together. In addition, a number of these associations were statistically significant, particularly the more precise effect estimates (U.S. EPA, 2008a, section 5.3.2.1). In studies that evaluated concentration-response (C-R) relationships, they appeared linear within the observed range of data with "little evidence of any effect threshold" (U.S. EPA, 2008a, sections 4.2 and 5.3.2.9). In considering the epidemiological evidence, the Administrator acknowledged that the interpretation of the studies was complicated by the fact that on-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include NO_2 but additionally noted that ISA analyses of co-pollutants generally found that NO_2 associations remained robust in multi-pollutant models (75 FR 6489).

The evidence also included controlled human exposure studies that evaluated airway hyperresponsiveness in asthmatics following short-term (30-minute to 2-hour) exposures to NO_2 concentrations at or above 100 ppb, as well as supporting evidence from animal toxicological

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[36]In contrast, the evidence relating long-term (weeks to years) NO_2 exposures to adverse health effects was judged to be either "suggestive but not sufficient to infer a causal relationship" (respiratory morbidity) or "inadequate to infer the presence or absence of a causal relationship" (mortality, cancer, cardiovascular effects, reproductive/developmental effects) (75 FR 6478).

studies (U.S. EPA, 2008a, sections 3.1.3 and 5.4). The EPA drew two broad conclusions regarding airway responsiveness in asthmatics following NO_2 exposures. First, NO_2 exposure may enhance the sensitivity to allergen-induced decrements in lung function and increase the allergen-induced airway inflammatory response following 30-minute exposures of asthmatic adults to NO_2 concentrations as low as 260 ppb. (U.S. EPA, 2008a, section 5.3.2.1, Figure 3.1-2). Second, exposure to NO_2 resulted in small but significant increases in nonspecific airway hyperresponsiveness in healthy and asthmatic adults. In asthmatics, the ISA concluded that such increases were observed following 1-hour exposures to 100 ppb NO_2 (U.S. EPA, 2008a, sections 3.1.3.2; 5.3.2.1). The EPA further concluded that the majority of asthmatics may experience NO_2-related airway hyperresponsiveness following short-term NO_2 exposures between 100 and 300 ppb (U.S. EPA, 2008a, Table 3.1-3; U.S. EPA, 2008b, p. 283). Enhanced airway responsiveness could have important clinical implications for asthmatics since transient increases in airway responsiveness following NO_2 exposure have the potential to increase symptoms and worsen asthma control (74 FR 34415, July 15, 2009; U.S. EPA, 2008a, sections 5.3.2.1 and 5.4). An update to a meta-analysis of data for nonspecific airway responsiveness that had been considered in the previous review provided support to the conclusions on exposure concentrations eliciting effects (Folinsbee, 1992; U.S. EPA, 1993, 60 FR 52818, October 11, 1995; U.S. EPA, 2008a, section 3.1.3.2, Tables 3.1-2 and 3.1-3).[37]

The exposure- and risk-based information summarized in section 5.1 below also informed the Administrator's decisions regarding adequacy of the then-existing primary annual NO_2 standard. Estimates were developed for (1) an "as-is" scenario which estimated the health risks associated with short-term exposure to NO_2 at actual recent air-quality concentrations, which were lower than what was permitted by the then-current annual NO_2 standard; (2) a "just meets" scenario which estimated the health risks associated with air quality adjusted upward to simulate just meeting the then-current annual standard; and (3) other scenarios for potential alternative standards.

The Administrator took note of the REA conclusion that risks estimated for air quality adjusted upward to simulate just meeting the current standard could reasonably be concluded to be important from a public health perspective, while additionally recognizing the uncertainties

[37]The updates made to the analysis were to remove the results of one allergen study and to add the results from a non-specific responsiveness study, and to discuss results for an additional exposure concentration (i.e., 100 ppb) (U.S. EPA, 2008a, section 3.1.3.2).

associated with adjusting air quality in such analyses (75 FR 6489).[38] For air quality adjusted to just meet the existing annual standard, the REA findings given particular attention by the Administrator included the following: “a large percentage (8 to 9%) of respiratory-related emergency department visits in Atlanta could be associated with short-term NO_2 exposures; most asthmatics in Atlanta could be exposed on multiple days per year to NO_2 concentrations at or above 300 ppb, and most locations evaluated could experience on-/near-road NO_2 concentrations above 100 ppb on more than half of the days in a given year” (75 FR 6489; U.S. EPA, 2008b, section 10.3.2). The 2008 REA additionally found that, under the “as is” scenario (i.e., recent air quality concentrations), individuals spending time on or near roads could expect to experience short-term NO_2 exposures above health effect benchmark levels of concern[39] multiple times per year.

In reaching the conclusion on adequacy of the then-existing standard, the Administrator also considered advice received from CASAC. In its advice, CASAC agreed that the primary concern in the review was to protect against health effects that have been associated with short-term NO_2 exposures. CASAC also agreed that the annual standard alone was not sufficient to protect public health against the types of exposures that could lead to these health effects. As noted in its letter to the EPA Administrator, ‘‘CASAC concurs with EPA’s judgment that the current NAAQS does not protect the public’s health and that it should be revised’’ (Samet, 2008b, p. 2).

Based on the considerations summarized above, the Administrator concluded that the then-existing NO_2 primary NAAQS was not requisite to protect public health with an adequate margin of safety and that the standard should be revised in order to provide increased public health protection against respiratory effects associated with short-term exposures, particularly for at-risk populations and lifestages such as asthmatics, children, and older adults (75 FR 6490). Upon consideration of approaches to revising the standard, the Administrator concluded that it was appropriate to set a new short-term standard, as described below.

[38] As described further in section 5.1 below, the 2008 REA considered air quality data from the existing network of ambient monitors as well as data from controlled human exposure studies and epidemiological studies to model exposure to NO_2 and to estimate health risks associated with short-term exposures. Additionally, recognizing that large segments of the public live, work, go to school, or travel on or near roads, the 2008 REA also estimated exposures that would occur in those particular locations.

[39] Health effect benchmark levels evaluated in the 2008 REA ranged from 100 to 300 ppb based on increased airway hyperresponsiveness in asthmatics (from controlled human exposure studies) (U.S. EPA, 2008b, section 6.2).

3.1.2 Elements of Revised Standard

In considering appropriate revisions in the last review, each of the four basic elements of the NAAQS (indicator, averaging time, level, and form) was evaluated. The rationale for decisions on those elements is summarized below.

3.1.2.1 Indicator

In previous reviews, the EPA focused on NO_2 as the most appropriate indicator for oxides of nitrogen because the available scientific information regarding health effects was largely indexed by NO_2. In the review completed in 2010, controlled human exposure studies and animal toxicological studies provided specific evidence for health effects following exposures to NO_2. In addition, epidemiological studies typically reported effects associated with NO_2 concentrations though the degree to which monitored NO_2 reflected actual NO_2 concentrations, as opposed to NO_2 plus other gaseous oxides of nitrogen, was recognized as an uncertainty (75 FR 6490, February, 9, 2010; U.S. EPA 2008b, section 2.2.3).

Based on the information available in the last review, and consistent with the views of CASAC (Samet, 2008b, p.2; Samet, 2009, p.2), the Agency concluded it was appropriate to continue to use NO_2 as the indicator for a standard that was intended to address effects associated with exposure to NO_2, alone or in combination with other gaseous oxides of nitrogen. In so doing, the EPA recognized that measures leading to reductions in population exposures to NO_2 will also reduce exposures to other oxides of nitrogen (75 FR 6490).

3.1.2.2 Averaging times

In considering the most appropriate averaging time(s) for the NO_2 primary NAAQS, the Administrator noted the available scientific evidence as assessed in the ISA, the air quality analyses presented in the REA, the conclusions of the policy assessment chapter of the REA, CASAC recommendations, and public comments received (75 FR 6490). Her key considerations are summarized below.

When considering averaging time, the Administrator first noted that the evidence relating short-term (minutes to hours) NO_2 exposures to respiratory morbidity was judged in the ISA to be "sufficient to infer a likely causal relationship" (U.S. EPA, 2008a, section 5.3.2.1) while the evidence relating long-term (weeks to years) NO_2 exposures to adverse health effects was judged to be either "suggestive but not sufficient to infer a causal relationship" (respiratory morbidity) or "inadequate to infer the presence or absence of a causal relationship" (mortality, cancer, cardiovascular effects, reproductive/developmental effects) (U.S. EPA, 2008a, sections 5.3.2.4-5.3.2.6). The Administrator concluded that these judgments most directly supported an averaging time that focused protection on effects associated with short-term exposures to NO_2.

As had been done in previous reviews of the NO_2 NAAQS, the Administrator next noted that it was instructive to evaluate the potential for a standard based on annual average NO_2 concentrations, as was the existing standard at the time of the 2010 review, to provide protection against short-term NO_2 exposures. To this end, the Administrator considered REA analyses that indicated a relatively large degree of variability in ratios of short-term (i.e., 1-hour and 24-hour) NO_2 concentrations to annual average concentrations, suggesting that a standard based on annual average NO_2 concentrations would not likely be an effective or efficient approach to focus protection on short-term NO_2 exposures. For example, these analyses indicated that in some areas the existing annual standard could allow 1-hour daily maximum NO_2 concentrations of about 400 ppb, while in other areas the annual standard could limit 1-hour daily maximum NO_2 concentrations to about 150 ppb. Thus, for purposes of protecting against the range of 1-hour NO_2 exposures, the Administrator agreed with the REA conclusion that a standard based on annual average concentrations would likely require more control than necessary in some areas and less control than necessary in others, depending on the standard level selected (75 FR 6491).

In next considering the level of support available for specific short-term averaging times, the Administrator noted that the policy assessment chapter of the REA considered evidence from both experimental and epidemiological studies. Controlled human exposure studies and animal toxicological studies provided evidence that NO_2 exposures from less than 1 hour up to 3 hours can result in respiratory effects such as increased airway responsiveness and inflammation (U.S. EPA, 2008a, section 5.3.2.7). She specifically noted the ISA conclusion that exposures of asthmatic adults to 100 ppb NO_2 for 1-hour can result in small but significant increases in nonspecific airway responsiveness (U.S. EPA, 2008a, section 5.3.2.1). In addition, the epidemiological evidence provided support for short-term averaging times ranging from approximately 1 hour up to 24 hours (U.S. EPA, 2008a, section 5.3.2.7). Based on this, the Administrator concluded that a primary concern with regard to averaging time is the degree of protection provided against effects associated with 1-hour NO_2 concentrations. Based on REA analyses of ratios between 1-hour and 24-hour NO_2 concentrations (U.S. EPA, 2008b, section 10.4.2), she further concluded that a standard based on 1-hour daily maximum NO_2 concentrations could also be effective at protecting against effects associated with 24-hour NO_2 exposures.

Based on the above, the Administrator judged that it was appropriate to set a new NO_2 standard with a 1-hour averaging time. She concluded that such a standard can effectively limit short-term (i.e., 1- to 24-hours) exposures that have been linked to adverse respiratory effects. She also retained the existing annual standard to continue to provide protection for effects potentially associated with long-term exposures to oxides of nitrogen (75 FR 6502). These decisions were consistent with CASAC advice to establish a primary short-term standard for oxides of nitrogen based on using 1-hour maximum NO_2 concentrations and to retain the current annual standard[40] (Samet, 2008b, p. 2; Samet, 2009, p. 2).

3.1.2.3 Levels

With consideration of the available health effects evidence, exposure and risk analyses, and air quality information, the Administrator set the level of the new 1-hour NO_2 standard at 100 ppb. This standard was focused on limiting the *maximum* 1-hour NO_2 concentrations in ambient air, including in locations near major roadways where the highest ambient NO_2 concentrations can occur in urban areas (75 FR 6474).[41] In establishing this new standard, the Administrator emphasized the importance of protecting against exposures to peak concentrations of NO_2, such as those that can occur around major roadways. Available evidence and information suggested that roadways account for the majority of exposures to peak NO_2 concentrations and, therefore, are important contributors to NO_2-associated public health risks.

In setting the level of the new 1-hour standard at 100 ppb, the Administrator noted that there is no bright line clearly directing the choice of level. Rather, the choice of what is appropriate is a public health policy judgment entrusted to the Administrator. This judgment must include consideration of the strengths and limitations of the evidence and the appropriate inferences to be drawn from the evidence and the exposure and risk assessments.

The Administrator judged that the existing evidence from controlled human exposure studies supported the conclusion that the NO_2-induced increase in airway responsiveness at or above 100 ppb presented a risk of adverse effects for some asthmatics, especially those with more serious (i.e., more than mild) asthma. The Administrator noted that the risks associated with increased airway responsiveness cannot be fully characterized based on available controlled human exposure studies, and thus she was not able to determine whether the increased airway responsiveness experienced by asthmatics in these studies was an adverse health effect. However, the Administrator concluded that asthmatics, particularly those suffering from more severe asthma, warrant protection from the risk of adverse effects associated with the NO_2-induced increase in airway responsiveness. Therefore, the Administrator concluded that the

[40] CASAC advised that "the findings of the REA do not provide assurance that a short-term standard based on the one-hour maximum will necessarily protect the populations from long-term exposures at levels potentially leading to adverse health effects" therefore, it recommended retaining the existing annual standard (Samet, 2008b, p. 2).

[41] In conjunction with this new standard, the Administrator established a 2-tiered monitoring network that included monitors sited to measure the maximum NO_2 concentrations near major roadways, as well as monitors sited to measure maximum area-wide NO_2 concentrations (see section 6.2 below).

controlled human exposure evidence supported setting a standard level no higher than 100 ppb to reflect a cautious approach to the uncertainty regarding the adversity of the effect. However, those uncertainties led her to also conclude that this evidence did not support setting a standard level lower than 100 ppb.

The Administrator also considered the more serious health effects reported in NO_2 epidemiological studies. She noted that a new standard focused on protecting against maximum 1-hour NO_2 concentrations in ambient air anywhere in an area, with a level of 100 ppb and an appropriate form (as discussed below), would be expected to limit area-wide[42] NO_2 concentrations to below those in locations where epidemiological studies had reported associations with respiratory-related hospital admissions or emergency department visits. The Administrator also concluded that such a 1-hour standard would be consistent with the REA conclusions based on the NO_2 exposure and risk information.

Given the above considerations and the comments received on the proposal, the Administrator judged it appropriate to set a 1-hour standard focused on limiting the maximum allowable NO_2 concentrations that can occur anywhere in an area, with a level of 100 ppb. Specifically, she concluded that such a standard, with an appropriate form as discussed below, would provide a significant increase in public health protection compared to that provided by the annual standard alone and would be expected to protect against the respiratory effects that have been linked with NO_2 exposures in both controlled human exposure and epidemiological studies. This includes limiting exposures at and above 100 ppb for the vast majority of people, including those in at-risk groups, and maintaining area-wide NO_2 concentrations well below those in locations where key U.S. epidemiological studies had reported that ambient NO_2 was associated with clearly adverse respiratory health effects, as indicated by increased hospital admissions and emergency department visits. The Administrator also noted that a standard level of 100 ppb was consistent with the consensus recommendation of CASAC.

In setting the standard level at 100 ppb rather than at a lower level, the Administrator also acknowledged the uncertainties associated with the scientific evidence. She noted that a 1-hour standard with a level lower than 100 ppb would only result in significant further public health protection if, in fact, there is a continuum of serious, adverse health risks caused by exposure to NO_2 concentrations below 100 ppb and/or associated with area-wide NO_2 concentrations well below those in locations where key U.S. epidemiological studies had reported associations with respiratory-related emergency department visits and hospital admissions. Based on the available

[42]As discussed above, area-wide concentrations refer to those measured by monitors that have been sited to characterize ambient concentrations at the neighborhood and larger spatial scales (see also section 6.2 below).

evidence, the Administrator did not believe that such assumptions were warranted. Taking into account the uncertainties that remained in interpreting the evidence from available controlled human exposure and epidemiologic studies, the Administrator noted that the likelihood of obtaining benefits to public health with a standard set below 100 ppb decreased, while the likelihood of requiring reductions in ambient concentrations that go beyond those that are needed to protect public health increased.

3.1.2.4 Forms

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. The Agency recognizes that for short-term standards, concentration-based forms which reflect consideration of a statistical characterization of an entire distribution of air quality data with a focus on a single statistical metric, such as the 98th or 99th percentile, can better reflect pollutant-associated health risks than forms based on expected exceedances. This is the case because concentration-based forms give proportionally greater weight to days when pollutant concentrations are well above the level of the standard than to days when the concentrations are just above the level of the standard. [43] In addition, when averaged over three years, these concentration-based forms are judged to provide an appropriate balance between limiting peak pollutant concentrations and providing a stable regulatory target, facilitating the development of stable implementation programs (75 FR 6492).

In the last review, the EPA considered two specific concentration-based forms (i.e., the 98th and 99th percentile concentrations), averaged over 3 years, for the new 1-hour NO_2 standard. The focus on the upper percentiles of the distribution was based, in part, on evidence of health effects associated with short-term NO_2 exposures from experimental studies which provided information on specific exposure concentrations that were linked to respiratory effects. The Agency proposed to adopt either a 99th percentile or a 4th highest form, averaged over 3 years, and also solicited comment on both 98th percentile and 7th or 8th highest forms, averaged over 3 years (74 FR 34430, July 15, 2008). Given the potential for instability in the higher percentile concentrations and the absence of data from the proposed two-tier monitoring network (e.g., around major roadways), CASAC, in a letter to the Administrator following issuance of the Agency's proposed rule, recommended a form based on the 3-year average of the 98th percentile of the distribution of 1-hour daily maximum NO_2 concentrations (Samet, 2009, p. 2).

In reaching her final decision in the last review, the Administrator recognized that the public health protection provided by the new 1-hour NO_2 standard was based in large part on (1) the approach used to set the standard and (2) the level of the standard in conjunction with the form of the

[43] Compared to an exceedance-based form, a concentration-based form reflects the magnitude of the exceedance of a standard level not just the fact that such an exceedance occurred.

standard (75 FR 6493). Given that the EPA set a new primary 1-hour NO_2 standard that focused on limiting the *maximum* allowable NO_2 concentration in ambient air, the Agency agreed with CASAC that an appropriate consideration with regard to form was the extent to which specific statistics could be unstable at locations where maximum NO_2 concentrations are expected (e.g., including near major roads).

Given the limited available information on the variability in peak NO_2 concentrations near important sources of NO_2 such as near major roadways, and given the recommendation from CASAC of the potential for instability in the 99th percentile concentrations, the Administrator judged it appropriate to set the form based on the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour NO_2 concentrations. *Id*. In addition, consistent with CASAC advice (Samet, 2008b, p. 2; Samet, 2009, p.2), the EPA retained the form of the annual standard (75 FR 6502).

3.1.3 Areas of Uncertainty

While the available scientific information informing the last review was stronger and more consistent than in previous reviews and provided a strong basis for decision making in that review, the Agency recognized that areas of uncertainty remained. These were generally related to the following: (1) understanding the role of NO_2 in the complex ambient mixture which includes a range of co-occurring pollutants (e.g., $PM_{2.5}$, ozone (O_3), CO, SO_2, other traffic-related pollutants); (2) understanding the extent to which monitored ambient NO_2 concentrations used in epidemiological studies reflect exposures in study populations and the range of ambient concentrations over which we continue to have confidence in the health effects observed in the epidemiological studies; (3) understanding the extent to which the magnitude and potential adversity of NO_2-induced respiratory effects reported in controlled human exposures studies can be characterized; (4) understanding the NO_2 concentration gradients around important sources, such as major roads, and relating those gradients to broader ambient monitoring concentrations; and (5) improving the characterization of NO_2 exposures and risk including alternative approaches for estimated risks associated with air quality simulated to just meet current or alternative standards.

3.2 GENERAL APPROACH FOR THE CURRENT REVIEW

The approach for this review builds on the substantial body of work done during the course of the last review, taking into account the more recent scientific information and air quality data now available to inform our understanding of the key policy-relevant issues. The approach described below is most fundamentally based on using the EPA’s assessment of the current scientific evidence and associated quantitative analyses to inform the Administrator’s judgments regarding primary standards for oxides of nitrogen that are requisite to protect public health with an adequate margin of safety. This approach will involve translating scientific and technical information into the basis for addressing a series of key policy-relevant questions using both evidence- and exposure/risk-based considerations.[44]

Figure 3-1 summarizes the general approach, including consideration of the policy-relevant questions which will frame the current review. The ISA, REA (if warranted), and PA developed in this new review will provide the basis for addressing the key policy-relevant questions and will inform the Administrator's judgment as to the adequacy of the current primary NO_2 standards and decisions as to whether to retain or revise these standards. This approach recognizes that the available health effects evidence generally reflects a continuum, consisting of ambient concentrations at which scientists generally agree that health effects are likely to occur, through lower concentrations at which the likelihood and magnitude of the response become increasingly uncertain. Furthermore, this approach is consistent with the requirements of the NAAQS provisions of the CAA and with how the EPA and the courts have historically interpreted the CAA. As discussed in section 1.1 above, these provisions require the Administrator to establish primary standards that, in the Administrator's judgment, are requisite to protect public health with an adequate margin of safety. In so doing, the Administrator seeks to establish standards that are neither more nor less stringent than necessary for this purpose. The CAA does not require that primary standards be set at a zero-risk level, but rather at a level that avoids unacceptable risks to public health. The four basic elements of the NAAQS (i.e., indicator, averaging time, form, and level) will be considered collectively in evaluating the health protection afforded by the current or any alternative standards considered.

We note that the final decision on the adequacy of the current standards and, if appropriate, potential alternative standards, is largely a public health policy judgment to be made by the Administrator. The Administrator's final decision must draw upon scientific information and analyses about health effects, population exposure and risks, as well as judgments about how to consider the range and magnitude of uncertainties that are inherent in the scientific evidence and analyses. As in the previous review, as well as other recent NAAQS reviews, the EPA will consider the implications of placing more or less weight or emphasis on different aspects of the scientific evidence and exposure/risk-based information to inform the public health policy judgments that the Administrator will make in reaching final decisions on whether to retain or revise the current standards in this review.

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[44] Evidence-based considerations include those related to the health effects evidence assessed and characterized in the ISA. Exposure/risk-based considerations draw from the results of the quantitative analyses.

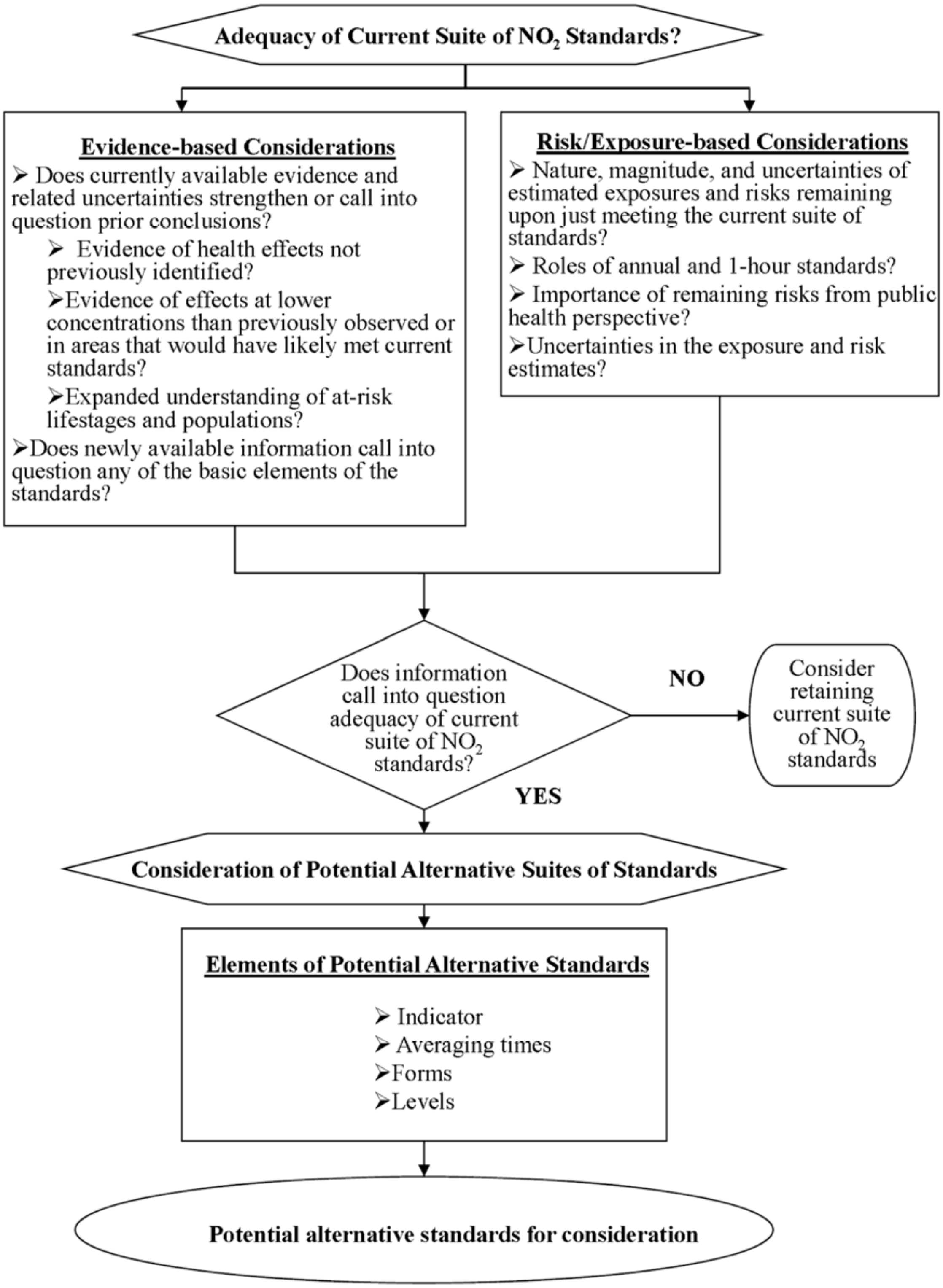

Figure 3-1. Overview of General Approach for Review of Primary NO_2 Standards

The initial overarching question in reviewing the adequacy of the current suite of primary NO_2 NAAQS is whether the available body of scientific evidence, assessed in the ISA and used as a basis for developing or interpreting any risk/exposure analyses, supports or calls into question the scientific conclusions reached in the last review regarding health effects related to exposures to oxides of nitrogen. The evaluation of the available scientific evidence and risk/exposure information with regard to adequacy of the current standards will focus on key policy-relevant issues by addressing a series of questions including the following:

- To what extent has new information altered the scientific support for the occurrence of health effects as a result of short- and/or long-term exposure to oxides of nitrogen in the ambient air?
    - What evidence is available from recent studies focused on specific chemical components within the broader group of oxides of nitrogen (e.g., NO_2, NO, NO_X) to inform our understanding of the nature of exposures that are linked to various health outcomes?
    - To what extent is key scientific evidence becoming available to improve our understanding of the health effects associated with various time periods of exposures, including peak (e.g., 1-hour) and long-term exposures (e.g., more than on month to years)?
        - At what pollutant concentrations do these health effects occur?
        - To what extent is new information available to improve our understanding of the range of ambient concentrations over which we continue to have confidence in the health effects observed in the epidemiological studies?
        - Is there evidence of effects at exposure concentrations lower than previously observed or in areas that would likely have met the current primary NO_2 standards?
        - To what extent are health effects associated with exposures to oxides of nitrogen, including NO_2, as opposed to one or more co-occurring pollutants (e.g., $PM_{2.5}$, CO, ozone, SO_2, other traffic-related pollutants)?
        - What are the important biological mechanisms and related modes of action for these health effects and are they consistent with biological mechanisms and modes of action characterized for oxides of nitrogen?
        - To what extent is new information available to improve the characterization of the magnitude and/or potential adversity of NO_2-induced respiratory effects reported in controlled human exposure studies?
    - Has new information altered our understanding of human lifestages and populations that are particularly at increased risk for experiencing health effects associated with exposure to oxides of nitrogen?

- What new information is available to inform our understanding of potential health effects in at-risk populations and lifestages living, working, playing or going to school near NO_2 sources (e.g., near roads)?
- To what extent is new information available regarding co-occurring risk factors that may be related to increased risk for experiencing health effects associated with exposure to oxides of nitrogen (e.g., children with asthma)?
- Is there new or emerging evidence of health effects beyond respiratory effects in asthmatics or effects in high exposure populations (e.g., people living, working, or going to school in near-road environments) that suggest potential additional at-risk lifestages and populations should be given increased focus in this review?
- Is there new information to shed light on the nature of the exposure-response relationship in different at-risk lifestages and/or populations?

- To what extent is new information available to improve our understanding of the NO_2 concentration gradients around important sources, such as major roads and combustion sources, and to relate those gradients to broader ambient monitoring concentrations?
- To what extent does risk or exposure information suggest that exposures of concern are likely to occur with recent ambient NO_2 concentrations or with concentrations that just meet the current primary NO_2 standards?
  - Are the estimated risks/exposures considered in this review of sufficient magnitude such that the health effects might reasonably be judged to be important from a public health perspective?
  - What new information is available to improve our understanding of exposure measurement error and the role of exposure in epidemiological inference, particularly for interpreting long-term exposure studies?
  - What are the important uncertainties associated with any risk/exposure estimates?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?
- To what extent does newly available information reinforce or call into question any of the basic elements of the current primary NO_2 standards?

If the evidence suggests that revision of the current standards might be appropriate, the EPA will address a second overarching question related to what alternative standards are appropriate for consideration. Specifically, we will evaluate how the scientific information and assessments inform decisions regarding the basic elements of the primary NO_2 NAAQS: indicator, averaging time, level, and form. These elements will be considered collectively in evaluating the health protection afforded by the current or any alternative standards considered. With regard to consideration of alternative standards, specific policy-relevant questions that will be addressed include the following:

- To what extent does any new information provide support for consideration of a different *indicator* for oxides of nitrogen in addition to or in place of NO_2?
- To what extent does the health effects evidence evaluated in the ISA, air quality analyses, and, if available, new REA provide support for considering any different *averaging times*?
- To what extent do air quality analyses and other information provide support for consideration of alternative standard *forms*?
- What range of alternative standard *levels* should be considered based on the scientific evidence evaluated in the ISA, air quality analyses and, if available, new REA[45]?
- What are the important uncertainties and limitations in the available evidence and assessments and how might those uncertainties and limitations be taken into consideration in identifying alternative standard *indicators, averaging times, forms and/or levels*?

[45] As outlined in Table 2-1 and discussed in Chapter 5 below, the REA Planning Document will consider the extent to which newly available scientific evidence and tools/methodologies warrant the conduct of new quantitative risk and exposure assessments. To the extent completely new assessments are not developed for this review, assessments from the last review may be interpreted in light of the newly available information in addressing the key policy questions for the review.

4 SCIENCE ASSESSMENT

The ISA comprises the science assessment phase of the NAAQS review process. As outlined in section 1.4 above, the purpose of the current review is to inform the review of the primary NO_2 standards only.[46] Hence, the ISA will focus on updating the air quality criteria associated with health effects evidence only.[47]

4.1 SCOPE OF THE ISA

The ISA provides an updated critical evaluation and synthesis of the current scientific literature pertaining to known and anticipated public health effects of gaseous oxides of nitrogen in the ambient air, including the nature of any remaining or newly identified uncertainties and limitations associated with the health evidence. The ISA will primarily focus on scientific evaluations that can inform the key policy questions described in section 3.2 above. Although emphasis will be placed on the discussion of the health effects information, other scientific information will also be presented and evaluated in order to provide a better understanding of the following issues: (1) the sources of oxides of nitrogen to ambient air; (2) measurement of and recent ambient concentrations of oxides of nitrogen including NO_2, including subsequent fate and transport in the environment; (3) important considerations related to characterizing potential population exposures to oxides of nitrogen; and (4) the validity of inferences that can be drawn about health effects related to exposure of oxides of nitrogen based on the methods used to assess population exposures and the influence of other factors (e.g., other pollutants in the ambient mixture) shown to be correlated with both oxides of nitrogen and health effects. The process for evaluating and synthesizing scientific literature and addressing key policy questions is detailed in the Preamble to the ISA.

The ISA is not intended to provide a detailed literature review but rather, will draw from the existing body of evidence to synthesize the current state of knowledge on the most relevant issues pertinent to the review of the primary NO_2 NAAQS. The ISA serves to revise the

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[46] As outlined in section 1.4 above, evidence related to potential welfare (e.g., ecosystem) effects of oxides of nitrogen will be considered separately in the science assessment conducted as part of the review of the secondary NAAQS for NO_2 and SO_2.

[47]In this review of the primary NAAQS for NO_2, as summarized in Chapter 2 above, a draft plan for development of the ISA was prepared by NCEA prior to development of the draft IRP. The draft plan for development of the ISA was made available for public comment and was the subject of a consultation with CASAC (78 FR 26026; 78 FR 27234). Comments received during that consultation were considered in preparation of chapter 4 in the draft IRP and the first draft ISA (U.S. EPA, 2013b). Further comments received on the draft IRP were considered in preparing this final IRP and will be considered in developing the second draft ISA.

scientific assessment available at the time of the last review. Thus, the ISA will build on the conclusions of the last review of the air quality criteria for oxides of nitrogen as presented in the 2008 ISA and focus on peer-reviewed literature published since that document[48] as well as on any new interpretations of previously available literature. Key findings, conclusions, and uncertainties from the 2008 ISA will be briefly summarized at the beginning of the ISA and of individual sections. Important older studies may be discussed in detail to reinforce key concepts and conclusions and/or if they are open to reinterpretation in light of newer data. Older studies also may be the primary focus in some subject areas or scientific disciplines (e.g., epidemiology, controlled human exposure, animal toxicology, atmospheric science, exposure science) where research efforts have subsided, and these older studies remain the definitive works available in the literature. Emphasis will be placed on studies that examine health effects relevant to humans and concentrations of oxides of nitrogen that represent the range of human exposures across ambient microenvironments (up to 5,000 ppb NO_2, which is one to two orders of magnitude above peak ambient concentrations as measured on roads). Other studies, generally at higher exposure concentrations, may be included if they contain unique data, such as previously unreported effects, evidence of the potential biological mechanism(s) for an observed effect, or information on concentration-response relationships.

4.2 ORGANIZATION OF THE ISA

The broad organization of the ISA for the health criteria of oxides of nitrogen will be consistent with that used in the recent assessments for other criteria pollutants (e.g., ISA for Ozone and Related Photochemical Oxidants, U.S. EPA, 2013c). The ISA will begin with a discussion of major legal and historical aspects of prior NAAQS reviews as well as procedures for the assessment of scientific information. An integrative synthesis chapter will summarize the key information for each topic area, the causal determinations for relationships between exposure to oxides of nitrogen and health effects, information describing the extent to which health effects can be attributable specifically to oxides of nitrogen, and other uncertainties related to the interpretation of scientific information. The integrative synthesis chapter also will discuss policy-relevant issues such as the exposure averaging times and lags associated with health effects, the concentration-response relationships including whether or not the evidence supports identification of a discernible threshold below which effects are not likely to occur, and the public health significance of effects associated with exposure to oxides of nitrogen. Subsequent chapters are organized by subject area (see draft outline of the ISA in Appendix A) and contain the detailed evaluation of results from recent studies integrated with previous findings (see

[48] For the current ISA, searches were conducted for studies published beginning in January 2008.

section 4.4 below for specific issues to be addressed). Sections for each major health effect category (e.g., respiratory effects) conclude with a causal determination about the relationship with relevant exposures to oxides of nitrogen. The ISA will conclude with a chapter that examines exposure and health outcome data to draw conclusions about potential at-risk lifestages and populations (as defined in section 3.1 above).

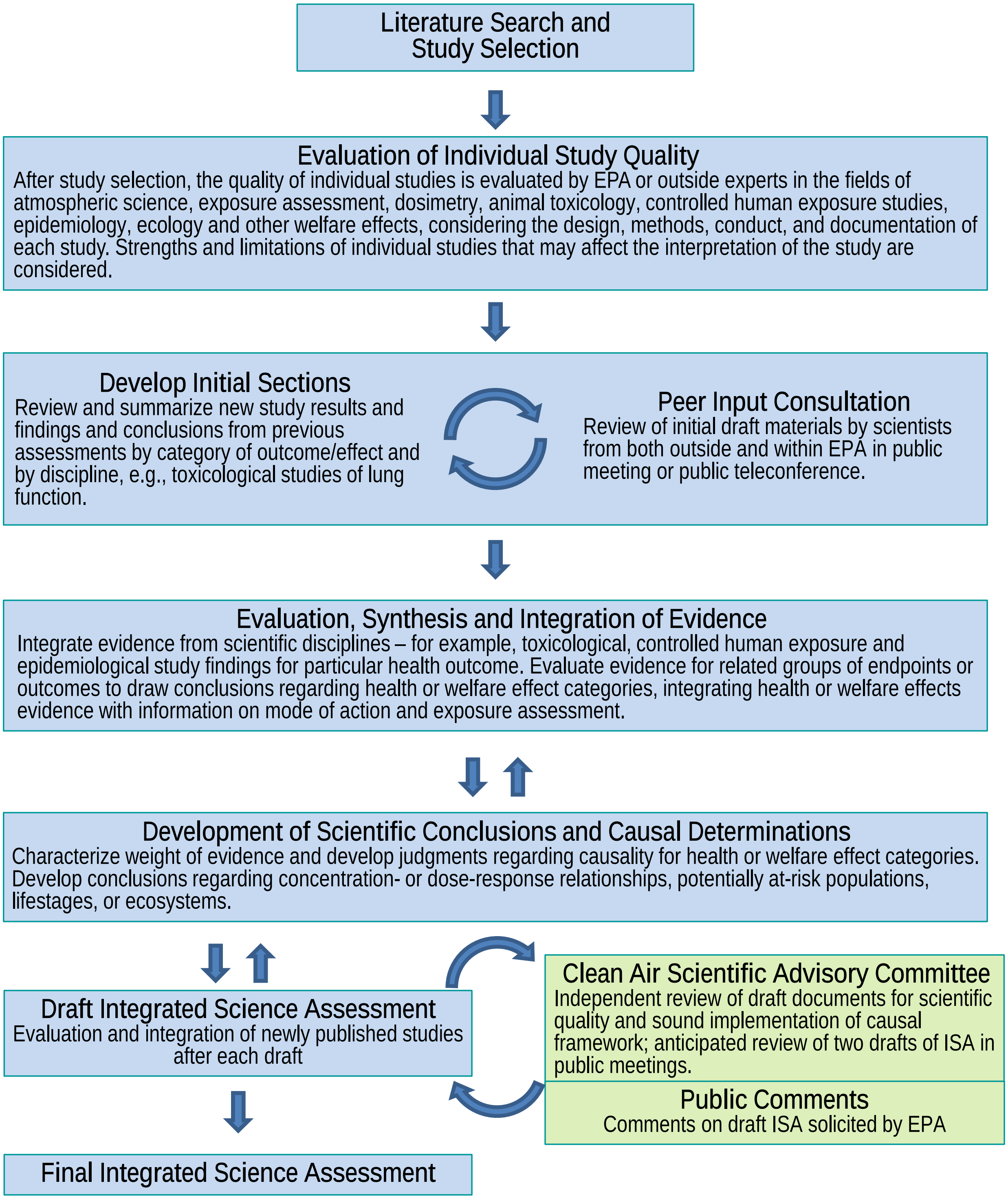
The ISA may be supplemented with other materials if additional documentation is required to support information contained within the ISA. These supplementary materials may include more detailed and comprehensive coverage of relevant publications and may accompany the ISA or be available in electronic form as output from the Health and Environmental Research Online (HERO) database developed by EPA.[49] Supplementary information that is available in the HERO database will be presented as electronic links in the ISA.

4.3 ASSESSMENT APPROACH

4.3.1 Introduction

The NCEA-RTP is responsible for preparing the ISA. In each NAAQS review, development of the science assessment begins with a "Call for Information" published in the *Federal Register*. This notice announces EPA's initiation of activities in the preparation of the ISA for the specific NAAQS review and invites the public to assist through the submission of research studies in the identified subject areas. This and subsequent key components of the process currently followed for the development of an ISA (i.e., the development process) are presented in Figure 4-1 and are described in greater detail in the Preamble to the ISA. Section 1.2 above briefly describes how the ISA fits into the larger NAAQS review process.
Important aspects of the development of the ISA are described in the sections below, including the approach for searching the literature and identifying relevant publications and informing specific policy-relevant questions that are intended to guide the assessment. These responsibilities are undertaken by expert authors of the ISA chapters which include EPA staff with extensive knowledge in their respective fields and extramural scientists solicited by the EPA for their expertise in specific fields. The process for scientific and public review of drafts of the ISA is described in section 4.5 below.

[49] For more information on the HERO database, see http://hero.epa.gov/.



Source: Modified from Figure II of the Preamble to the ISA (U.S. EPA, 2013b).

Figure 4-1. General process for development of Integrated Science Assessments.

4.3.2 Literature Search and Selection of Relevant Studies

The NCEA-RTP uses a structured approach to identify relevant studies for consideration and inclusion in the ISA. A *Federal Register* notice is published to announce the initiation of a review and request information, including relevant literature, from the public. In addition, the NCEA-RTP identifies publications by conducting a recursive multi-tiered literature search process that includes extensive manual and computer-aided citation mining of computer databases (e.g., PubMed, Web of Science) on specific topics in a variety of disciplines. The search strategies are designed *a priori* and iteratively modified to optimize identification of pertinent published papers. A broad search string is developed with keywords such as oxides of nitrogen, NO_X, NO_2, NO, nitric acid, peroxyacetyl nitrate, and total reactive nitrogen, and the specific syntax is tailored for each database. Papers are identified for inclusion in several additional ways: specialized searches on specific topics; relational searches that identify recent publications that have cited references from previous assessments; identification of relevant literature by expert scientists; recommendations from the public and CASAC during the call for information and external review process; and review of citations in previous assessments. These search methods are used to identify recent research published or accepted for publication since the 2008 ISA for Oxides of Nitrogen, i.e., starting in January 2008 through approximately two months before the release of the second external review draft of the ISA (target of October 2014, see Table 21). Studies published after that date may also be included in the ISA if they provide new information that impacts one or more key scientific issues. Studies published after the ISA cut-off date also may be considered in subsequent phases of the NAAQS review, after assessing whether they provide new information that impacts key scientific issues.

Once identified through the multipronged search strategy, ISA authors (EPA staff and extramural scientists) review studies for relevance. Inclusion criteria consist of epidemiological, toxicological, and controlled human exposure studies or reports that examine health effects in relation to exposure to gaseous oxides of nitrogen and studies or reports on sources, emissions, atmospheric chemistry, human exposure, dosimetry, or modes of action of gaseous oxides of nitrogen. To be included in the ISA, these studies and reports also have undergone scientific peer review and have been published or accepted for publication. Some publications retrieved from the literature search are excluded as not being relevant (e.g., do not meet aforementioned criteria) based on screening of the title or citation (e.g., not about air pollution, conference abstract) and are not documented further. For other publications, decisions about relevance require reading beyond the title. These publications are labeled as “considered” for inclusion in the ISA and are documented in the HERO database. On the HERO project page for the ISA for Oxides of

Nitrogen, documentation of references consists of bibliographic information and a label as to whether the reference is considered and/or cited.

From the group of "considered" references, studies and reports are selected for inclusion in the ISA based on review of the abstract and full text. The selection process is based on the extent to which the study is potentially policy-relevant and informative. Potentially policy-relevant and informative studies include those that provide a basis for or describe the relationship between oxides of nitrogen and effects, in particular, those studies that reduce uncertainty on critical issues. Also pertinent are studies that offer innovation in method or design or present novel information on effects or issues previously not identified. Uncertainty can be addressed, for example, by analyses of potential confounding or effect modification by copollutants or other factors, analyses of concentration-response or dose-response relationships, or analyses related to time between exposure and response. In keeping with the purpose to accurately reflect the latest scientific knowledge, a majority of the discussion in the ISA will describe studies published since the 2008 ISA. However, evidence from previous studies will be included to integrate with results from recent studies, and in some cases, characterize the key policy-relevant information in a particular subject area or scientific discipline. Analyses conducted by the EPA using publicly available data, for example, air quality and emissions data, also are considered for inclusion in the ISA. Individual study quality is not used as a criterion for study inclusion, and informative studies are not limited to specific study designs, model systems, or outcomes. The combination of approaches described above is intended to produce the comprehensive collection of pertinent studies needed to address the key scientific issues that form the basis of the ISA. References are cited in the ISA by a hyperlink to the HERO database and also are compiled into reference lists.

4.3.3 Evaluation of Individual Study Quality

After selecting studies for inclusion, individual study (from previous assessments or recently published) quality is evaluated by considering the design, methods, conduct, and documentation of each study but not considering whether the study results are positive, negative, or null. Further, the ISA forms independent conclusions about the strength of inference from study results weighing the authors' conclusions and independently evaluating study quality as detailed below and in the Preamble. This uniform approach aims to consider the strengths, limitations, and possible roles of chance, confounding, and other biases that may affect the interpretation of the results from individual studies. In assessing the scientific quality of studies, the following broad parameters are considered:

- How clearly were the study design, study groups, methods, data, and results presented to allow for study evaluation?
- To what extent are the air quality data, exposure, or dose metrics of adequate quality to serve as credible exposure indicators?
- Were the study populations, subjects, or animal models adequately selected, and are they sufficiently well-defined to allow for meaningful comparisons between study or exposure groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted? Do the analytical methods provide adequate sensitivity and precision to support study conclusions?
- Are likely covariates (i.e., potential confounding factors, modifying factors) adequately controlled for or taken into account in the study design or statistical analyses?
- Are the health endpoint measurements meaningful, valid, and reliable?

Additional considerations specific to particular scientific disciplines are discussed below.

Atmospheric Science and Exposure Assessment

Atmospheric science and exposure assessment studies focus on measurement, chemistry, fate, and transport of ambient air pollution as well as exposure to ambient air pollution using quality-assured field, experimental, and/or modeling techniques. The most informative measurement-based studies will include detailed descriptive statistics for high-quality measurements made at varying spatial and temporal scales. These studies will also include a clear and comprehensive description of measurement techniques and quality control procedures used. Quality control metrics (e.g., method detection limits) and quantitative relationships between and within pollutant measurements (e.g., regression model coefficients, intercepts, and fit statistics) should be provided when appropriate. Measurements including contrasting conditions for various time periods (e.g., weekday/weekend, season), populations, geographic regions, land use types (e.g., urban/rural), and proximity to various source sectors are particularly useful. The most informative modeling-based studies will incorporate appropriate chemistry, transport, dispersion, and/or exposure modeling techniques with a clear and comprehensive description of model science, evaluation procedures, and metrics.

Exposure measurement error, which refers to the uncertainty associated with the exposure metrics used to represent exposure of an individual or population, can be an important contributor to uncertainty in air pollution epidemiological study results. Exposure measurement error can influence epidemiological associations observed between ambient pollutant concentrations and health outcomes by biasing effect estimates toward or away from the null and/or widening confidence intervals around those estimates (Zeger et al., 2000). Factors that could influence error in exposure estimates include, but are not limited to, spatial patterns in ambient concentrations, non-ambient sources of exposure, topography of the natural and built environment, meteorology, air quality measurement instrument errors, model uncertainties, time-activity patterns, and the infiltration of outdoor pollutants into indoor environments. Additional information present in high-quality exposure studies includes location and activity information from diaries, questionnaires, global positioning system data, or other means, as well as information on commuting patterns.

Epidemiology

In evaluating the quality of epidemiological studies and strength of inference from their results, the EPA additionally considers whether a given study: (1) presents quantitative information on associations of health effects with short- or long-term exposures that represent ambient concentrations of oxides of nitrogen across various microenvironments; (2) examines health effects of multiple species of oxides of nitrogen; (3) assesses oxides of nitrogen as a component of a complex mixture of air pollutants (of primary interest are other pollutants emitted by motor vehicles, including carbon monoxide, PM and various inorganic and organic components) by considering concentrations of copollutants, correlations of oxides of nitrogen with these copollutants, potential copollutant interactions (e.g., synergistic effects of oxides of nitrogen with other pollutants), potential copollutant confounding (e.g., bias of associations observed between oxides of nitrogen and health endpoints by the effects of copollutants), and other methods to assess the independent effect of oxides of nitrogen; (4) examines other potential confounding factors or effect modifiers (e.g., socioeconomic status [SES]); and/or (5) examines exposure estimates that capture the spatial pattern of oxides of nitrogen in the study area. Also informative are studies that evaluate potential at-risk lifestages or populations; health endpoints not previously researched extensively; and important methodological issues (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement) related to the health effects of exposure to oxides of nitrogen. Among epidemiological studies characterized as high quality by these parameters, emphasis will be given to multicity studies that employ standard methodological analyses for evaluating effects of oxides of nitrogen across cities, provide overall estimates for effects by pooling information across cities, and examine consistency of results across cities. To address specific issues relevant to standard setting in the U.S., such as regional heterogeneity in effects, emphasis will be placed on studies that involve exposures and population characteristics that are relevant to current U.S. populations (e.g., studies conducted in the U.S. or Canada).

Controlled Human Exposure and Animal Toxicology

Controlled human exposure and animal toxicological studies experimentally evaluate the health effects of administered exposures in human volunteers and animal models under highly controlled laboratory conditions. Controlled human exposure studies are also referred to as human clinical studies. These experiments allow investigators to expose subjects or animal models to known concentrations of oxides of nitrogen under carefully regulated environmental conditions and/or activity levels. In addition to the general quality considerations discussed previously, controlled human exposure and animal toxicological studies will be evaluated with respect to details reported on the design, experimental procedures, and analytical methodology of each study with focus on: (1) characterization of the exposure concentration or inhaled dose, dosing regimen (e.g., duration), and exposure route; (2) characterization of the pollutant(s) (i.e., oxides of nitrogen species); (3) sample size and statistical power to detect differences; and (4) control of other variables that could influence the occurrence of effects. The evaluation of study design generally includes consideration of factors that minimize bias in results such as randomization, blinding and allocation concealment of study subjects, investigators, and research staff, and unexplained loss of animals or withdrawal/exclusion of subjects. Additionally, studies must include appropriate control groups and exposures to allow for accurate interpretation of results relative to the pollutant exposure. Emphasis is placed on studies that address concentration-dependent responses or time-course of responses. Also, with the recognition that controlled human exposure studies typically are conducted in young adults and healthy individuals, emphasis will be placed on studies that investigate potentially at-risk lifestages or populations (e.g., with pre-existing disease). In addition, consideration will be given to studies that investigate exposure to oxides of nitrogen separately and then simultaneously or sequentially with other pollutants such as particulate matter, sulfur dioxide, and ozone.

Controlled human exposure or animal toxicological studies involving exposures that approximate expected human exposures in terms of concentration, duration, and route of exposure are of particular interest. The ISA will define relevant NO_2 or NO exposures as those up to 5,000 ppb, which is one to two orders of magnitude above peak ambient concentrations as measured on roads. Studies using higher concentration exposures or doses will be considered to the extent that they provide information relevant to understanding mode of action or mechanisms, interspecies variation, or at-risk human lifestages and populations. *In vitro* studies may be included if they provide mechanistic insight for effects examined *in vivo* or in epidemiological studies. *In vitro* studies of NO_2 are particularly informative if conducted in anatomically relevant cells such as lung epithelium or other airway cells.

4.3.4 Integration of Evidence and Determination of Causality

As described in the Preamble to the ISA, the EPA uses a consistent and transparent basis for the integration of scientific evidence and evaluation of the causal nature of air pollution-related health effects in the ISA. For the evaluation of human health effects, the main lines of evidence are controlled human exposure, epidemiological, and toxicological studies, and evidence is integrated from previous and recent studies. Other information including mechanistic evidence, toxicokinetics, and exposure assessment may be highlighted if it is relevant to the evaluation of health effects and if it is of sufficient importance to affect the overall evaluation. The relative importance of different sources of evidence to the conclusions varies by pollutant or assessment, as does the availability of different sources of evidence for causality determination. In judgments of causality, scientists will also evaluate uncertainty in the scientific evidence, considering issues such as generalizing results from a small number of controlled human exposure subjects to the larger population; quantitative extrapolations of observed pollutant-induced pathophysiological alterations from laboratory animals to humans; confounding by co-exposure to other ambient pollutants, meteorological factors, or other factors; the potential for effects to be due to exposure to air pollution mixtures; and the influence of exposure measurement error on epidemiological study findings. Judgments of causality also are informed by the extent to which uncertainty in one line of evidence (e.g., potential confounding in epidemiological results) is addressed by another line of evidence (e.g., coherence with experimental findings, mode of action information). Thus, evidence integration is not a unidirectional process but occurs iteratively within and across scientific disciplines and related outcomes.

The EPA uses a framework to provide a consistent and transparent basis for classifying the weight of available evidence according to a five-level hierarchy: (1) causal relationship; (2) likely to be a causal relationship; (3) suggestive but not sufficient to infer a causal relationship; (4) inadequate to infer a causal relationship; and (5) not likely to be a causal relationship (U.S. EPA, 2013c, Table II). In the framework, key considerations in drawing conclusions about causality include consistency of findings for an endpoint across studies, coherence of the evidence across disciplines and across related endpoints, and biological plausibility, including key events within modes of action. As judged by these parameters, evidence that rules out chance, confounding, and other biases with reasonable confidence is sufficient to infer a causal relationship. Increasing uncertainty due to limited available information, inconsistency, and/or limited coherence and biological plausibility leads to conclusions increasingly lower in the hierarchy. Causal determinations are developed for major health effect categories (e.g., respiratory effects) or more specific groups of related outcomes and for the range of exposure concentrations of oxides of nitrogen defined to be relevant to ambient concentrations (e.g., up to 5,000 ppb NO_2). Findings based on higher exposure concentrations may be considered if they inform biological plausibility and potential modes of action and if biological mechanisms have not been demonstrated to differ based on exposure concentration. Causal determinations are based on the confidence in the body of evidence, considering study design and quality and strengths and weaknesses in the overall collection of previous and recent studies across disciplines. In discussing the causal determination, the EPA characterizes the evidence on which the judgment is based, including the weight of evidence for individual endpoints within the health effect category or group of related endpoints.

4.3.5 Quality Management

NCEA participates in the Agency-wide Quality Management System, which requires the development of a Quality Management Plan (QMP). Implementation of the NCEA QMP ensures that all data generated or used by NCEA scientists are "of the type and quality needed and expected for their intended use" and that all information disseminated by NCEA adheres to a high standard for quality including objectivity, utility, and integrity. Quality assurance (QA) measures detailed in the QMP are being employed for the current primary NO_2 NAAQS review, including the development of the ISA for the health criteria of oxides of nitrogen. NCEA QA staff is responsible for the review and approval of quality-related documentation. NCEA scientists are responsible for the evaluation of all inputs to the ISA, including primary (new) and secondary (existing) data, to ensure their quality is appropriate for their intended purpose. NCEA adheres to Data Quality Objectives, which identify the most appropriate inputs to the science assessment and provide QA instruction for researchers citing secondary information. The approaches utilized to search the literature and criteria applied to select and evaluate studies were detailed in the two preceding subsections. Generally, NCEA scientists rely on scientific information found in peer-reviewed journal articles, books, and government reports. The ISA also can include information that is integrated or reduced from multiple sources to create new figures, tables, or summation, which is subject to rigorous quality assurance measures to ensure their accuracy.

4.4 SPECIFIC ISSUES TO BE ADDRESSED IN THE ISA

The ISA for oxides of nitrogen will contain information relevant to considering whether it is appropriate to retain or revise the current primary NO_2 standards. Decisions on the specific content of the ISA will be guided by policy-relevant questions that frame the entire review of the primary NO_2 NAAQS as outlined in section 3.2 above. These policy-relevant questions are related to two overarching issues. The first issue is whether new evidence reinforces or calls into question the evidence presented and evaluated in the last primary NO_2 NAAQS review, with respect to factors such as the plausibility of health effects caused by exposure to oxides of nitrogen and concentrations of oxides of nitrogen associated with health effects. The second issue is whether uncertainties from the last review have been reduced and/or whether new uncertainties have emerged, especially regarding the potential for correlated traffic-related pollutants but not NO_2 independently to be responsible for health effects observed in association with NO_2. The ISA also will address a set of more specific policy-relevant questions related to the available scientific evidence that stem from these issues. These questions were derived from the last primary NO_2 NAAQS review, as well as from discussions of the scientific evidence that occurred at the February/March 2012 kickoff workshop for the current review (77 FR 7149, February 10, 2012); a CASAC consultation on the draft plan for development of the ISA (U.S. EPA, 2013a; 78 FR 27234, May 9, 2013; Frey, 2013); a public workshop that included review of initial draft materials for the ISA (78 FR 27374, May 10, 2013), and CASAC review of the draft IRP (Frey, 2014). The specific questions to be addressed in the ISA are listed below by topic area. In the ISA, most of these topic areas will be discussed in separate chapters or sections.

Atmospheric Science and Ambient Concentrations

The ISA will present and evaluate data related to ambient concentrations of oxides of nitrogen; sources leading to the presence of oxides of nitrogen in the atmosphere; and physical and chemical processes that determine the formation, degradation, and lifetime of oxides of nitrogen in the atmosphere. Key conclusions from the 2008 ISA were that motor vehicles and power plants are the major U.S. sources of NO_X emissions and that ambient concentrations of NO_2 display heterogeneity across spatial and temporal scales, are higher near roadways, and are correlated with ambient concentrations of several other traffic-related pollutants (U.S. EPA, 2008a, section 5.2.1). The formation and reactions of NO_2 are strongly influenced by volatile organic compounds and O_3. The relationships among these pollutants are critical to the understanding of ambient NO_2 concentrations. In the current review, with regard to air quality and atmospheric chemistry, specific policy-relevant questions that will be addressed include:

- What new information is available to inform our understanding of the atmospheric chemistry of oxides of nitrogen? How does new information characterize the role of atmospheric chemistry in determining relationships among oxides of nitrogen species? What new information is available with respect to formation of nitroaromatics and nitropyrenes, which have shown toxic effects and thus, may be important in assessing health effects from multipollutant exposures? How does the near-source environment (e.g., near major highways or large combustion sources) influence chemistry of oxides of nitrogen?

- What new information exists regarding characterization of sources of ambient oxides of nitrogen in both urban and rural environments? What are the relevant spatial and temporal scales for considering ambient emissions of oxides of nitrogen? What new information is available regarding existing and emerging sources of energy and impacts on emissions of oxides of nitrogen?
- To what extent have new methods been developed to improve measurements of oxides of nitrogen, particularly those that measure NO_2 directly? How have these new methods reduced interference problems in measuring oxides of nitrogen? What limitations still remain?
- Based on recent air quality and emissions data, what is known about recent emissions and resulting ambient concentrations of oxides of nitrogen? How have emissions and concentrations of NO_X and of NO_2 changed since the 2008 ISA? To what extent can new data sources (e.g., satellites) or air quality analyses be used to improve the characterization of ambient concentrations of oxides of nitrogen?
- What spatial and temporal patterns can be seen in ambient NO_2 and NO_X concentrations? In particular, what spatial and temporal patterns can be seen on a micro-scale near sources including major roadways and combustion sources such as power plants and biomass burning? What do ambient air quality characterizations (including examinations of the influence of meteorological parameters) indicate about spatial patterns on neighborhood, urban, regional, and national scales?
- Based on air quality and emissions data for oxides of nitrogen and atmospheric chemistry models, what are likely background concentrations of oxides of nitrogen in the absence of anthropogenic emissions?
- What new information is available to characterize the influence of meteorological parameters on micro- to neighborhood-scale concentrations of oxides of nitrogen?
- What information is available on interactions between oxides of nitrogen and copollutants in the atmosphere that may alter the spatial distributions of oxides of nitrogen?

Human Exposure

The ISA will evaluate the factors that influence exposure to ambient oxides of nitrogen and the measurement error and other uncertainties associated with extrapolation of ambient concentrations to personal exposures to oxides of nitrogen of ambient origin, particularly in the context of interpreting results from epidemiological studies. The evaluation will build upon the discussion in the 2008 ISA, which concluded that relationships between ambient concentrations and personal exposures were inconsistent and more poorly characterized for long-term than short-term exposures. Further, measurement error associated with using ambient NO_2 concentrations obtained from central site monitors as measures of short-term exposure in epidemiological studies tended to bias the magnitude of associations between ambient NO_2 and health effects toward the null (U.S. EPA, 2008a, section 5.2.2). The ISA will describe sources of potential exposure measurement error, the strengths and limitations of various exposure assessment method, and implications on inferences about epidemiological relationships observed between oxides of nitrogen and health effects. Exposure measurement error and its impact on the strength of epidemiological inference can depend on a number of factors including study design, the extent of spatial variability in ambient concentrations in the selected study areas, time-activity patterns of the study population, and the exposure assessment method. For example, exposure measurement error may differ by the exposure period of interest as most epidemiological studies of short-term exposure (e.g., population-level time-series studies, panel studies) rely on temporal variation in exposure while epidemiological studies of long-term exposure (e.g., longitudinal cohort studies) rely on spatial variability of exposure. The uncertainties related to exposure measurement error and impact on epidemiological inference will inform judgments about the confidence in the body of epidemiological results and in turn, causal determinations for the various health effect categories evaluated. In the current review, with regard to exposure assessment and implications on epidemiological inference about health effects, specific policy-relevant questions that will be addressed include:

- How have modeling techniques such as sub-grid scale modeling within chemical transport models, air quality dispersion models, and land use regression models been advanced in recent years? What new information is available regarding modeled estimates of spatially-resolved (at the micro-, middle-, and neighborhood scales) ambient NO_2 and NO_X concentrations used for exposure assessment?
- To what extent have hybrid modeling approaches that combine ambient concentrations with air quality models been recently developed to improve the spatial and temporal resolution of exposure estimates within a community? What advancements have been made regarding validation of hybrid models and their ability to estimate source attribution for exposures to NO_2 or NO_X?
- What are the relationships between oxides of nitrogen measured at stationary monitoring sites and personal short-term and long-term exposure? What evidence is available regarding these relationships in environments near roads or other sources?
- What new information exists about the relationship between NO, NO_2, and NO_X concentrations and indicators of near-source pollution including distance to sources (e.g., major roadways) and source activity levels (e.g., traffic counts)?
- What studies are available to examine the relationship between near-road oxides of nitrogen, on-road oxides of nitrogen, and in-vehicle exposures to oxides of nitrogen? Given the concern over short-term exposures at or less than one hour in duration, are the directly emitted NO_2/NO_X ratios sufficiently high such that on-road commuting NO_2 exposure is a significant component of total NO_2 exposure?

- To what extent is information available characterizing how well the current area-wide and near-road NO_2 monitoring sites represent exposures to populations living near major roads?
- What new information exists regarding characterization of error in assessment of short-term and long-term exposure of oxides of nitrogen and how it influences personal-ambient exposure relationships? What implications does exposure measurement error have on inference about epidemiological relationships observed between oxides of nitrogen and health effects? Do the implications vary according to factors such as exposure duration, study design, and exposure assessment method?
- What information is available regarding differences in exposure patterns for oxides of nitrogen and personal-ambient exposure relationships among various lifestages and specific groups within populations? What implications do these potential differences in exposure measurement error have on inferences about relationships with health effects observed in general population studies versus those conducted in specific lifestages and groups within the population (e.g., people with underlying health condition)?
- What are the implications for epidemiology for assessing health effects of exposures to oxides of nitrogen when there are instrumentation errors, such as interference in measurements of ambient NO_2 concentrations from other nitrogen compounds?
- What new information exists regarding exposure to oxides of nitrogen in a multipollutant context with other gaseous pollutants (e.g., carbon monoxide, nitrous acid), particle phase pollutants (e.g., ultrafine particles, black carbon, organic carbon, transition metals) generated by traffic or other combustion sources, or of a mixture of traffic-related pollutants?
    - To what extent do NO_2 measurements serve as surrogates of exposure to the other pollutants listed above? How does information about pollutant co-exposures aid in evaluation of copollutant confounding in epidemiological associations between oxides of nitrogen and health effects?
    - How do interactions among pollutants in the atmosphere influence exposure to oxides of nitrogen? How does information about pollutant interactions aid in evaluation of effect measure modification in epidemiological associations between oxides of nitrogen and health effects?
- What new information exists regarding indoor exposures to oxides of nitrogen, including those generated indoors and those that infiltrate from outdoors? What new information is available regarding how oxides of nitrogen are generated indoors?
- What new information is available regarding the interaction of indoor oxides of nitrogen with organic compounds emitted from home cleaning and deodorizing products to form organic nitrates indoors that may influence human exposure to NO_2?

Dosimetry and Modes of Action

The ISA will evaluate literature focusing on dosimetry and modes of action that may underlie the health outcomes associated with exposure to NO_2 and/or NO. These topic areas will be evaluated using both human and animal data. The 2008 ISA concluded that inhaled NO_2, at ambient-relevant concentrations, reacts with constituents of the epithelial lining fluid of the respiratory tract, including antioxidants, to form secondary reaction products (U.S. EPA, 2008a, section 2.6). These secondary reaction products initiate a cascade of events that are thought to be responsible for health effects observed in association with NO_2 exposure. Additionally, findings of NO_2-induced changes in airway responsiveness, airway inflammation, and lung host defenses were described as key mechanistic support for NO_2-related respiratory effects such as respiratory symptoms and emergency department visits. In the current review, specific policy-relevant questions related to dosimetry and modes of action that will be addressed include:

- What new information is available to inform our understanding of the potential biological mechanisms underlying responses to NO_2 and/or NO exposures at concentrations defined in the ISA to be environmentally relevant (up to 5,000 ppb, see section 4.3.4 above), with a focus on response pathway(s) and exposure-dose-response relationships?
- What information is available to characterize intra- and inter-individual variability in biological responses following exposure to NO_2 and/or NO?
- What are the effects of host factors such as lifestage, sex, pre-existing disease, genetic background, and physical activity on the uptake of NO_2 and/or NO and cellular and tissue responses as well as biological mechanisms that may underlie health effects associated with exposure to oxides of nitrogen?
- What information is available to discern the relative contributions to local NO_2 and/or NO of: (1) ambient exposures to NO_2 and/or NO; (2) dietary consumption of nitrite and nitrate which undergo transformation to NO; and (3) endogenous formation of NO_2 and/or NO?
- What NO_2 and/or NO reaction products, including oxides of nitrogen metabolites, can be found in the cells, tissues, or fluids of the respiratory tract and in the systemic circulation that may serve as markers of NO_2 and/or NO exposure and effect?
- What biological processes, from the molecular to whole organ level, can be qualitatively or quantitatively compared across species?
- To what extent can the inhalation dosimetry of NO_2 and/or NO be extrapolated between species, qualitatively or quantitatively?
- Do interactions between other inhaled pollutants and NO_2 and/or NO influence the mechanisms underlying the health effects of NO_2 and/or NO? If so, how might this information provide understanding of the potential for a copollutant to act as an effect measure modifier of health effects related to oxides of nitrogen?

Health Effects

In the 2008 ISA, the health effects evidence for oxides of nitrogen was largely indexed by studies of NO_2 with the bulk of the evidence provided by short-term exposure studies evaluating respiratory effects. The EPA will build on this assessment and evaluate the newly available literature related to respiratory, cardiovascular, reproductive, and developmental health effects, mortality, and cancer associated with exposure to oxides of nitrogen. Depending on data availability, other health effects also may be evaluated, for example, those related to the central nervous system or gastrointestinal system. The ISA will evaluate health effects that occur following both short- and long-term exposures as examined in epidemiological, controlled human exposure, and animal toxicological studies. Efforts will be directed at identifying the concentrations at which effects are observed, including those in potential at-risk lifestages and populations, and assessing the role of oxides of nitrogen within the broader mixture of ambient pollutants. The discussion of health effects also will be integrated with relevant information on dosimetry and modes of action. In the current review, with regard to consideration of health effects associated with short-and long-term exposure to oxides of nitrogen, specific policy-relevant questions that will be addressed include the following:

Short-Term (i.e., minutes to up to one month) and Long-Term (i.e., more than one month to years) Exposure

- What do studies across scientific disciplines (i.e., controlled human exposure, animal toxicological, epidemiological) indicate about the relationships of exposures to oxides of nitrogen with health effects that are examined in relation to both short-term and long-term exposure: respiratory effects, cardiovascular effects, and premature mortality?
- How does evidence for health effects associated with oxides of nitrogen compare among healthy individuals, those with pre-existing disease states (e.g., people with asthma or cardiovascular disease), particular lifestages, or groups characterized by other factors that potentially modify risk (e.g., genetic, nutritional)?
- At what ambient concentrations of oxides of nitrogen are associations with the various health effects observed in epidemiological studies most well characterized?
- To what extent does the scientific evidence support the occurrence of health effects of exposure to oxides of nitrogen at ambient concentrations that are lower than those previously demonstrated? If so, what uncertainties are related to these associations and are the health effects in question important from a public health perspective?
- What evidence is available regarding the shape of concentration-response relationships between exposure to oxides of nitrogen and various health endpoints?
  - Is there evidence to support the identification of a discernible threshold below which health effects will not occur?
- What evidence is available regarding the nature of health effects from interactions between oxides of nitrogen and other ambient air pollutants in comparison to health effects following exposure to oxides of nitrogen alone?
  - To what extent are the observed epidemiological health effect associations attributable to ambient oxides of nitrogen, another ambient pollutant, or to the pollutant mixtures that oxides of nitrogen may be representing? What information is

available specifically from studies conducted in populations spending time or living near roads or other sources? To what extent do findings from experimental studies provide biological plausibility for the effects observed in epidemiological studies?

Short-Term Exposure

- How do results of recent studies or new interpretations of previous findings expand our understanding of the relationship between short-term exposure to oxides of nitrogen and airway hyperresponsiveness or other lung function changes, inflammation, host defense against infection disease, respiratory symptoms, and asthma exacerbations?
- What new information is available on the effects of short-term exposure to oxides of nitrogen on acute cardiovascular events in humans such as myocardial infarction, stroke, increases in blood pressure, and arrhythmias?
- To what extent does short-term exposure to oxides of nitrogen contribute to premature mortality and health effects beyond the respiratory and cardiovascular systems?
- What is the extent of coherence of findings for effects such as hospital admissions, emergency department visits, and mortality with changes in lung function, airway hyperresponsiveness, heart rate variability, and vasomotor function? What other biomarkers of early effect may be used in the assessment of health effects?
- To what extent does information across epidemiological, controlled human exposure, and animal toxicological studies on the pattern of exposure to oxides of nitrogen (e.g., peak, repeated peak, average) provide understanding of the time course for changes in health effects? What information is available on time-activity patterns of study subjects such as time spent outdoors or activity levels that can aid in the understanding of nature of exposure or dosimetry of ambient oxides of nitrogen that are associated with health effects?
- To what extent do data across epidemiological, controlled human exposure, and animal toxicological studies provide information on health effects related to specific oxides of nitrogen (e.g., NO_2, NO) or averaging times of exposure to oxides of nitrogen that are relevant to the 1-hour standard? What data exist comparing associations of health effects among various short-term metrics of exposure to oxides of nitrogen (e.g., 1-hour versus 24-hour)?
- What information is available on the health effects of on-road or near-road commuting or occupational exposures to oxides of nitrogen on health outcomes?

Long-Term Exposure

- How do the results of recent studies expand our understanding of the relationships between long-term exposure to oxides of nitrogen and chronic respiratory effects manifested as a reduction in lung function, a reduction in lung development, or morphological changes?
- To what extent does long-term exposure to oxides of nitrogen promote exacerbation and development of asthma or other chronic lung diseases, cardiovascular diseases, and other conditions?

- To what extent does long-term exposure to oxides of nitrogen contribute to other health effects or changes in molecular and cellular processes, e.g., cognitive, behavioral, reproductive, developmental, cancer or epigenetic effects?
- What information is available on the effects of exposures to oxides of nitrogen on health outcomes in populations living near major roads or working on or near major roads?
- What information is available regarding the effect of long-term, low-concentration exposure to oxides of nitrogen on an individual's sensitivity to short-term but higher concentration exposures?
- What evidence is available regarding health effects related to long-term exposure windows other than annual or lifetime average (e.g., preconception, pregnancy average, pregnancy trimester average)? What data are available comparing associations of health effects among various long-term oxides of nitrogen exposure metrics (e.g., annual, seasonal, pregnancy average)?

Causality

In the 2008 ISA, the EPA concluded that the findings of epidemiological, controlled human exposure, and animal toxicological studies collectively provided evidence "sufficient to infer a likely causal relationship" between short-term NO_2 exposures and respiratory effects (U.S. EPA, 2008a, sections 3.1.7 and 5.3.2.1). In looking at a broader range of health effects associated with short- or long-term exposures to oxides of nitrogen, the 2008 ISA concluded there was evidence "suggestive but not sufficient to infer a causal relationship" between short-term NO_2 exposures and premature mortality and between long-term NO_2 exposures and respiratory effects (U.S. EPA, 2008a, sections 5.3.2.3 and 5.3.2.4). Furthermore, the 2008 ISA concluded that the scientific evidence was "inadequate to infer the presence or absence of a causal relationship" between short-term NO_2 exposures and cardiovascular effects as well as between long-term NO_2 exposures and cardiovascular effects, reproductive and developmental effects, premature mortality, and cancer (U.S. EPA, 2008a, sections 5.3.2.2, 5.3.2.5, and 5.3.2.6).

The causal determinations, based on the causal framework and integration of available evidence from previous and recent studies (see sections 4.3.3 and 4.3.4 above), were presented with a summary of the available evidence at the end of the sections for each broad health effect category and in the integrative synthesis chapter at the beginning of the ISA. In the current review, specific policy-relevant questions related to the causality determinations that will be addressed include:

- Does the evidence base from recent studies contain new information to support or re-evaluate the causal determinations made for relationships between NO_2 exposure and various health effects in the 2008 ISA?
- What is the strength of inference from epidemiological studies based on the extent to which they have:

- Examined exposure metrics that capture the spatial and/or temporal pattern of oxides of nitrogen in the study area
- Assessed potential confounding by other traffic-related pollutants and other factors?

- What information is available to support a rationale for forming causal determinations for other oxides of nitrogen (e.g., NO, NO_X)?
- What information is available regarding the health impacts of a decrease in ambient concentrations of oxides of nitrogen to inform causal determinations?

Uncertainties/Limitations

The causal determinations described above for the relationships between NO_2 exposure and health effects were informed by uncertainties and limitations in the evidence. The 2008 ISA noted the possibility that pollutants other than oxides of nitrogen within the broad ambient mixture were responsible for health effects observed in association with NO_2 and/or limited information from experimental studies to provide biological plausibility (U.S. EPA, 2008a, section 5.3). The 2008 ISA also described uncertainty related to the use of ambient NO_2 concentrations to represent personal ambient NO_2 exposure (U.S. EPA, 2008a, section 5.2.2). In each of the health effects sections and the integrative synthesis chapter, the ISA will evaluate uncertainties and limitations in the scientific data. These uncertainties also will inform causal determinations.

The ISA will evaluate potential confounding by other ambient pollutants in a hierarchical manner. Based on their stronger correlations with ambient oxides of nitrogen and consequent stronger potential for confounding, primary attention will be given to traffic-related pollutants such as carbon monoxide, fine particulate matter, black/elemental carbon, and ultrafine particles. The ISA also will evaluate potential confounding by other traffic-related pollutants such as volatile organic compounds and other criteria pollutants such as sulfur dioxide and ozone. To assess the independent effects of oxides of nitrogen, the ISA will examine whether epidemiological associations with oxides of nitrogen are found in copollutant models, which is the predominant method used in air pollution epidemiology to estimate the effect of one pollutant for a given concentration of a copollutant. The ISA also will evaluate whether oxides of nitrogen show interactions with copollutants or joint effects in associations with health outcomes. The assessment of potential confounding, interactions, or joint effects will draw upon results from health effects studies as well as available information on copollutant interactions in the atmosphere that influence the spatial distributions and modes of action for oxides of nitrogen and copollutants. In the absence of these aforementioned methods, the ISA will examine whether single-pollutant epidemiological associations with health effects in a given study differ between oxides of nitrogen and copollutants and examine the magnitude of correlation among pollutants.

Drawing from discussion about the strengths and limitations of various exposure assessment methods, the ISA will evaluate the strength of inference in epidemiological studies by considering information such as the exposure duration being examined, the extent of spatial and/or temporal variability in ambient oxides of nitrogen in the study area, the distribution of monitoring sites in the study area, the performance of exposure models used, and time-activity patterns of the study population. To the extent available, data from near-road monitoring networks will be used to characterize the spatial distributions in ambient NO_2 concentrations and human exposures, and in turn, the potential exposure measurement error in particular study areas based on the particular method of exposure assessment used. The adequacy of exposure assessment will be considered in weighing the quality of evidence, and in turn, forming causal determinations.

Epidemiological evidence is unlikely to completely address the aforementioned uncertainties. Any individual study is unlikely to evaluate all potentially correlated copollutants. And, the limitations of epidemiological methods to separate effects of highly correlated pollutants or separate the effects of more than two pollutants in the same model are well recognized. With respect to exposure measurement error, studies with personal ambient exposure measurements are not likely to be available. Thus, coherence with other lines of evidence are important to inform uncertainties in the epidemiological evidence regarding copollutant confounding and exposure measurement error. Controlled human exposure and toxicological studies that show effects on similar outcomes at relevant NO_2 exposures or effects on key cellular and molecular events in biological pathways leading to the health effect are important in providing biological plausibility. As well, epidemiological studies of indoor NO_2 are informative because relationships with copollutants may differ from those in outdoor environments.

In the current review, specific policy-relevant questions related to the evaluation of uncertainties/limitations that will be addressed include:

- To what extent are the observed health effect associations attributable specifically to ambient oxides of nitrogen versus only other pollutants contained in the broader air pollution mixture? For example, the ISA will consider the possibility that ambient concentrations of NO_2 serve not only as an indicator for oxides of nitrogen but as a surrogate for exposure to other vehicle exhaust gaseous and particulate pollutants.
    - What information about the independent health effects of exposure to oxides of nitrogen can be synthesized from the various lines of available evidence, for example, copollutant models, associations with other traffic-related pollutants, analysis of indoor NO_2, comparisons of results from locations with varying pollutant mixtures, studies of traffic proximity or intensity, and experimental studies?
    - How does confounding by co-exposure to other ambient traffic-related pollutants (e.g., particulate matter, carbon monoxide) or meteorological factors influence

relationships observed between health effects and both short- and long-term exposures to oxides of nitrogen? To what extent do other factors serve as potential confounding factors in epidemiological studies (e.g., age, SES, other exposures such as noise)?

- What information is available to assess the influence of exposure measurement error on uncertainty in epidemiological study results?
  - o How can the influence of exposure measurement error be assessed through the examination of various study designs, study populations, exposure assessment methods, spatial and/or temporal variability in ambient concentrations, spatial alignment of study population and ambient measurements, and analytical models?
  - o What information is available regarding the time-activity patterns of study subjects including time spent outdoors, spatial distribution of study subjects and ambient monitors, exposure assessment methods, potential interference in the measurement of NO_2 from other oxides of nitrogen in low traffic, downwind locations?

At-risk Lifestages and Populations

The ISA will evaluate an array of factors that may characterize potential at-risk lifestages or populations: intrinsic factors (biological factors such as age or genetic variants), acquired factors (e.g., pre-existing disease), extrinsic factors (nonbiological factors such as diet, low SES), and/or factors affecting dose or exposure (e.g., sex, age, outdoor activity or work, low SES, physical activity). The 2008 ISA discussed persons with pre-existing respiratory disease (e.g., people with asthma), children, and older adults as populations and lifestages potentially at greater risk of NO_2-related health effects (U.S. EPA, 2008a, section 5.3.2.8). Since completion of the 2008 ISA, the EPA has developed a framework to provide a consistent and transparent basis for classifying the weight of evidence for factors that may characterize at-risk lifestages or populations according to one of four levels: adequate evidence, suggestive evidence, inadequate evidence, and evidence of no effect (U.S. EPA, 2013c, Table 8-1). In this framework, key considerations in drawing such conclusions include consistency of findings for a factor within a discipline and, where available, coherence of the evidence across disciplines. Several lines of evidence inform conclusions about at-risk lifestages and populations but primarily includes observational or experimental studies that compare exposure to oxides of nitrogen or relationships with health effects among groups that vary by some characteristic such as pre-existing disease or age (i.e., exposure or effect modification). Also relevant are comparisons of results among observational or experimental studies that examine different population characteristics or time windows of exposure and experimental studies that examine health effects of oxides of nitrogen in a group with a particular characteristic (e.g., genetic background, pre-existing disease).

The various factors listed above may influence risk by increasing exposure, dose, or biological effect at a given dose, and some factors (e.g., SES) may contribute to risk in multiple ways. Conclusions will be drawn for the collective body of information available for a particular at-risk lifestage or population, not separately to classify risk due to increased exposure, dose, or biological effect. In the current review, with regard to at-risk lifestages and populations, specific policy-relevant questions that will be addressed include:

- Based on evidence integrated across studies and disciplines that examine factors that may increase exposure to oxides of nitrogen and/or risk of health effects related to exposure to oxides of nitrogen, what conclusions can be drawn about the presence of at-risk lifestages (e.g., the developing fetus, children, older adults) or populations and/or critical time windows of exposure?
- To what extent do living, working, attending school, or exercising near major roads or commuting on roads contribute to greater exposure to oxides of nitrogen and/or risk of related health effects? Given the concentration gradients observed for ambient oxides of nitrogen with distance to roads, what information is available regarding the sizes and sociodemographic characteristics of populations living near major roads?
- Which disciplines contribute information about particular at-risk lifestages and populations, and to what extent does limited or lack of information from specific disciplines produce uncertainty in conclusions about at-risk lifestages and populations?
- How does recent information compare with that evaluated in the 2008 ISA regarding people with pre-existing respiratory disease, genetic variants, or low SES as potential at-risk populations and children or older adults as potential at-risk lifestages?
- What information is available that provides insight as to whether a potential at-risk lifestage or population has higher exposure or dose of oxides of nitrogen, has a greater biological response to a given exposure, and/or experiences health effects at lower exposure concentrations?
- What is the extent of the coherence of evidence regarding potential at-risk lifestages or populations for both short- and long-term exposures to oxides of nitrogen?
- What quantitative information is available to characterize the magnitude of greater biological response or risk of health effects associated with exposure to oxides of nitrogen in a particular at-risk lifestage or population?
- What evidence is available regarding populations at increased risk because of co-occurring risk factors (e.g., young age, residence near major roads, lower SES, and asthma; older age and pre-existing cardiovascular disease)?

Public Health Impact

The integrative synthesis chapter at the beginning of the ISA will present concepts that integrate evidence on health effects and consequent public health significance to aid in the assessment of the public health implications of exposure to short- and long-term exposure to oxides of nitrogen. The discussion will include evaluation of the adversity of the health effects potentially associated with exposure to oxides of nitrogen. The assessment of public health impact also may include, as appropriate, an estimation of the sizes of potential at-risk lifestages and populations and discussion of the public health significance of the magnitudes of change in health outcomes characterized to result from ambient air exposure to oxides of nitrogen. Further, to the extent that evidence is available, the integrative synthesis chapter of the ISA will discuss what evidence is available regarding interrelationships among risk factors in a particular lifestage or population as described in the preceding section that may add to the understanding of the public health impact of exposure to oxides of nitrogen.

4.5 SCIENTIFIC AND PUBLIC REVIEW OF THE ISA

Drafts of the ISA will be made available for review by the CASAC and the public as indicated in Figures 1-1 and 4-1 and Table 2-1 above. Availability of draft documents will be announced in the *Federal Register*. The CASAC will review the draft ISA documents and discuss its comments in public meetings that will be announced in the *Federal Register*. The EPA will take into account comments, advice, and recommendations received from the CASAC and from the public in revising the draft ISA documents. The EPA has established a public docket for the development of the ISA.[50] After appropriate revision based on comments received from the CASAC and the public, the final document will be made available on an EPA website. A notice announcing the availability of the final ISA will be published in the *Federal Register*.

[50]The ISA docket can be accessed at www.regulations.gov using Docket ID number EPA-HQ-ORD-2013-0232.

5 QUANTITATIVE RISK AND EXPOSURE ASSESSMENT

Within the context of NAAQS reviews, a quantitative risk and exposure assessment (REA) is designed to estimate human exposure and health risks associated with existing and potential alternative standards. The appropriate scope of any REA will be informed by the availability of scientific information from the ISA as well as air quality information and information on data and models that may help to address important uncertainties or provide additional insights beyond those provided by previous REAs. As a result, the first step in the REA planning process is an assessment of the appropriate scope of the REA, which includes a determination of whether a distinct REA document is needed. As part of this planning process, we evaluate the 2008 REA in the context of the extent to which important uncertainties may be addressed by new information available since the previous review and the extent to which new information may change results of the 2008 REA in important ways or may allow for additional analyses that can address important gaps in our understanding of the exposures and risks associated with NO_2.

This phase of the NAAQS review begins with the preparation of a REA Planning Document and considers the extent to which newly available scientific evidence and tools/methodologies provide support for conducting quantitative risk and exposure assessments. To the extent warranted, the scope and methods for components of exposure/risk assessments will be described. As outlined in Table 2-1 above, the EPA plans to issue this REA Planning Document in November 2014. This document will be the subject of a CASAC consultation and will be made available to the public for review and comment. CASAC advice and public comments on the draft IRP (Frey, 2014) will be considered in developing the REA Planning Document. If warranted, one or more drafts of an REA will then be prepared and released for CASAC review and public comment prior to completion of a final REA.

The information newly available in this review will be considered in light of the comprehensive, complex and resource-intensive quantitative assessments of human exposure and health risks documented in the 2008 REA as discussed in section 5.1 below. As discussed in section 5.2 below, the REA Planning Document will consider the available scientific evidence, tools, and methodologies in light of areas of uncertainty identified in the 2008 REA and the potential for new analyses to provide notably different exposure and risk estimates, with lower associated uncertainty. The timeline for collection of ambient NO_2 measurement data within near-road environments under the recently revised monitoring requirements is recognized as an important consideration for the REA Planning Document. CASAC advice (Frey, 2014) and comments from the public on the draft IRP, as well as the availability of resources, will inform the development of the REA Planning Document.

5.1 OVERVIEW OF RISK AND EXPOSURE ASSESSMENT FROM PRIOR REVIEW

In the last review, as summarized in sections 5.1.1, 5.1.2, and 5.1.3 below, the EPA designed and developed three approaches to estimating exposures and health risks associated with a number of ambient air quality scenarios (i.e., recent air quality unadjusted, air quality adjusted to simulate just meeting the then-existing annual standard (i.e., annual average of 53 ppb), and air quality adjusted to simulate just meeting several potential alternative daily maximum 1-hour standards). Briefly, in the first approach ambient NO_2 concentrations (measured and modeled) were compared to 1-hour health effect benchmark levels derived from the controlled human exposure literature. In the second approach, modeled estimates of human exposures in an urban study area were compared to these same health effect benchmark levels. In the third approach, concentration-response relationships from an epidemiological study were used to estimate health impacts associated with ambient NO_2 concentrations in an urban study area. An overview of these approaches used and results generated in characterizing health risks is provided below.

The 2008 REA's health risk estimates were, in part, based on pre-2010 ambient monitor concentrations. Those monitors primarily measured NO_2 concentrations that were representative of a broad geographic area (e.g., area-wide ambient measurements)[51] rather than concentrations at specific locations where the highest concentrations of NO_2 were likely to be found (e.g., maximum or peak ambient measurements including near major roadways).

5.1.1 Ambient Air Quality Characterization

In the first approach, we compared 1-hour ambient NO_2 concentrations (1995 to 2006) with short-term health effect benchmark concentrations of 100, 150, 200, 250, and 300 ppb

[51] Area-wide monitors are defined as those sited at neighborhood, urban, and regional scales, as well as those monitors sited at either a micro- or middle-scale that are representative of many such locations in the same Core Based Statistical Area (CBSA) (40 CFR 58.1). The introduction and first use of the term "area-wide" was in the final rule for the last primary NO_2 NAAQS review as part of the NO_2 minimum monitoring requirements (75 FR 6504, February 9, 2010). The term was formally defined in the final rule for the most recent PM NAAQS review (78 FR 3235 and 3281 to 3282, January 15, 2013). The underlying spatial scales are defined in 40 CFR part 58 Appendix D, section 1.2(b).

NO_2[52] in order to identify the number of days a particular benchmark concentration was exceeded per monitor per year. All U.S. monitoring sites where NO_2 data had been collected were included in this analysis, and, as such, the results generated were considered a broad characterization of national air quality and potential human exposures that might be associated with these concentrations.[53] The available NO_2 air quality for 18 Core Based Statistical Areas (CBSAs) named study areas[54] and two aggregate study areas were separated into two six-year groups; one contained data from years 1995-2000, representing an historical data set; the other contained the monitoring years 2001-2006, representing recent ambient monitoring (U.S. EPA, 2008b, section 7.2.2).

Each of these monitoring year groups and study areas were evaluated considering the ambient NO_2 concentrations as they were reported and representing the conditions at that time (termed in that assessment "*as is*"). This served as the first air quality scenario evaluated as part of the air quality characterization. Further, within each year group and study area we categorized the monitors using their sited distance from a road: at or within 20 meters (≤ 20 m), between 20 and 100 meters (> 20 m to < 100 m), and at least 100 meters from a road (≥ 100 m).[55] These ambient monitor data were categorized in this manner to account for the potential influence of vehicle emissions on NO_2 concentrations measured at the monitors within close proximity to roadways (U.S. EPA, 2008b, section 7.2.3). There was potential for different concentration levels measured at each of these locations (i.e., near-road monitors versus those sited away from roadways) and thus potentially different exposure concentrations experienced by those persons

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[52] The 1-hour NO_2 health effect benchmark levels were based on NO_2 exposure concentrations associated with increased airway responsiveness in asthmatics and determined from 1 to 2 hour duration controlled human exposure studies. These benchmark values were used for the evaluation of both the NO_2 air quality concentrations and estimated NO_2 exposures.

[53] After applying a 75% data completeness criterion the final analytical data base included 627 monitors collecting ambient concentrations for 4,177 site-years of data (a valid monitoring day had ≥18 hourly measurements; monitors included in the analysis had ≥75% valid monitoring days in a year).

[54] At the time the assessment was conducted, we used the terms CMSA/MSA to describe the monitors associated with metropolitan statistical areas. We replaced that terminology here with CBSA to reflect current terminology. An initial pool of monitors was subset from the total set of monitors based on their belonging to specific CBSA. Then we selected study areas having annual mean NO_2 concentrations occurring at a minimum of one monitor at or above 25.7 ppb (i.e., the 90th percentile concentrations across all study areas and site-years) and/or had at least one reported 1-hour NO_2 level greater than or equal to 200 ppb (i.e., the lowest level of the potential health effect benchmarks indicated by the ISA at the time these study areas were identified for investigation in the 2008 REA). All remaining not included in this collection of named study areas were aggregated into either one of two groups: all other CBSA or all other non-CBSA.

[55] In our assessment, road distances to each monitor were generally determined using a Tele-Atlas roads database in a GIS application. The road types used to identify near-road monitors were those defined as: 1=primary limited access or interstate, 2=primary US and State highways, 3=Secondary State and County, 4=freeway ramp, 5=other ramps. Note only the monitors falling within the 18 identified study areas had estimated distances to these identified roads types, all other monitors (either characterized as 'other CMSA/MSA' or 'all other non-CMSA/MSA') were assumed to be ≥ 100 m from a road.

spending time in these locations. Then, for each ambient monitor, we summed the number of days per year that monitor recorded a daily maximum 1-hour concentration at or above the health effect benchmark levels and summarized this metric for each study area, year group, and roadway distance group, using descriptive statistics (e.g., means, maximums) (U.S. EPA, 2008b, section 7.2.5).

A second air quality scenario in the air quality characterization used the *as is* ambient monitoring data obtained from monitors sited ≥100 m from a road combined with an on-road concentration adjustment factor to estimate *on-road NO_2 concentration*s for each of the year-groups and study areas. This scenario was developed by recognizing that motor vehicles are important emission sources of NO_X and NO_2 and that people spend time inside vehicles while travelling on roadways. At that time, a strong relationship had been reported between NO_2 concentrations measured on roadways and NO_2 concentrations measured at increasing distance from the road, generally in the form of a first-order exponential decay (e.g., Cape et al., 2004). We derived an empirical distribution of on-road adjustment factors using data from published studies that reported on- and near-road NO_2 concentrations and NO_2 concentrations occurring at greater distances from a road (≥ 100 m).[56] Then, we probabilistically applied these on-road adjustment factors to NO_2 concentrations reported at monitors sited ≥ 100 meters from a road (and generally assumed to be at a background non-roadway influenced concentration) to approximate on-road NO_2 concentrations for each study area and monitor year. As described above, for the area-wide ambient monitor data, we counted the number of days per year an estimated daily maximum 1-hour on-road concentration exceeded the health effect benchmark levels and summarized these data using simple descriptive statistics (U.S. EPA, 2008b, section 7.2.4).

Additional summaries of exceedances of health effect benchmark levels were generated for the above two air quality scenarios (i.e., using the complete set of ambient monitoring concentrations at each of the three roadway distance categories and the simulated on-road NO_2 concentrations), though they differed in that the ambient concentrations were first adjusted to just meet the then-existing annual standard or alternative daily maximum 1-hour standards. Because the annual average 2001 to 2006 ambient concentrations[57] were below the level of the existing annual standard (i.e., < 53 ppb) as well as most of the potential daily maximum 1-hour standards

[56] See Table 7-10 of the 2008 REA for the specific values of distributions that were used and Appendix A, section 8 for the studies used and the derivation methodology (U.S. EPA, 2008b).

[57] Only the 2001 to 2006 ambient concentrations were used to evaluate the existing and alternative standard levels, the historical air quality data set with measurements from 1995 to 2000 was not used in this part of the assessment.

being evaluated, ambient concentrations were primarily adjusted *upwards* to reflect these additional air quality scenarios. A simple proportional adjustment approach was selected to simulate concentrations to meet a particular standard level, an approach supported by within-monitor comparisons of low and high NO_2 concentration years that largely demonstrated characteristics of a proportional relationship.[58] We note also that the *as is* air quality could be characterized in all study areas as falling within the evaluated alternative standard levels of 50 and 100 ppb (either a 98th or 99th percentile daily maximum1-hour concentration); thus simulating these particular air quality scenarios required the smallest proportional adjustment. Simulations of just meeting an alternative standard level of 50 ppb required a *downward* adjustment (U.S. EPA, 2008b, section 6.3.1). That said, the number of benchmark exceedances for *as is* air quality scenarios in each study area also fell within the range of that estimated considering the 50 and 100 ppb daily maximum 1-hour alternative standard scenarios.

5.1.1.1 Key Observations

- **Ambient monitoring NO_2 concentrations**: When considering any of the air quality scenarios, NO_2 concentrations and estimated number of exceedances of health effect benchmark levels were typically higher for monitors that were within 20 meters (m) of a roadway than when monitors were sited farther from a roadway (i.e., between 20 m and 100 m or ≥100 m from a road) (U.S. EPA, 2008b, section 7.3.1). As expected, fewer health effect benchmark exceedances were estimated to occur at the highest health effect benchmark level (300 ppb) when compared with the lowest health effect benchmark level (100 ppb). While results were generated for health effect benchmark levels ranging from 100 to 300 ppb in 50 ppb increments, the discussion in the 2008 REA focused only on the health effect benchmark levels of 100, 200, and 300 ppb.
    - **100 ppb health effect benchmark level**: When air quality was adjusted to simulate just meeting the then-existing annual standard (i.e., 53 ppb, annual average), most study areas were estimated to have, on average, 50 days or more per year with daily maximum 1-hour ambient NO_2 concentrations ≥ 100 ppb, while about 1/3 were estimated to have 100 days or more per year with daily maximum 1-hour ambient NO_2 concentrations ≥ 100 ppb. When air quality was adjusted to simulate just meeting alternative daily maximum 1-hour standard levels of 50 and 100 ppb (98th or 99th percentile in a year), far fewer days per year were estimated to have, on average, daily maximum 1-hour ambient concentrations ≥ 100 ppb (i.e., <10 days per year, on average) than compared with just meeting higher alternative daily maximum 1-hour standard levels of 150 and 200 ppb (generally tens to hundreds of days per year with

[58] Linear regressions were performed using the daily maximum 1-hour concentration distributions of each a low and high concentration year measured at the same ambient monitor and evaluated for model linearity and presence of statistically significant regression intercepts. Statistically significant linear regression slopes and model R^2 values strongly supported features of linearity. On a few occasions however, the presence of statistically significant regression intercepts and deviation from linearity at upper percentile concentrations tends to obfuscate a conclusion of proportionality existing at all monitors (Rizzo, 2008; U.S. EPA, 2008b, section 7.4.5).

daily maximum 1-hour ambient NO_2 concentrations ≥ 100 ppb) (U.S. EPA, 2008b, section 7.5).

- **200 ppb health effect benchmark level**: When air quality was adjusted to simulate just meeting the then-existing annual standard, only two study areas were estimated, on average, to have 10 or more days per year with daily maximum 1-hour ambient NO_2 concentrations ≥ 200 ppb. When air quality was adjusted to simulate just meeting alternative daily maximum 1-hour standard levels of 50 and 100 ppb (98^{th} or 99^{th} percentile in a year), only four study areas were estimated, on average, to have at least one day per year with daily maximum 1-hour ambient NO_2 concentrations ≥ 200 ppb.
- **300 ppb health effect benchmark level**: When air quality was adjusted to simulate just meeting the then-existing annual standard, only five study areas were estimated, on average, to experience any days with daily maximum 1-hour ambient NO_2 concentrations at central site monitors ≥ 300 ppb, and none of those study areas were estimated to experience more than 2 such days per year, on average. When air quality was adjusted to simulate just meeting alternative daily maximum 1-hour standard levels of 50 and 100 ppb (98^{th} or 99^{th} percentile in a year), only three study areas were estimated, on average, to have at least one day per year with daily maximum 1-hour ambient NO_2 concentrations ≥ 300 ppb.

- **Simulated on-road NO_2 concentrations**: Simulated on-road annual average NO_2 concentrations, estimated using an on-road adjustment factor, were on average, 80 percent higher than the respective ambient concentrations measured at distances ≥100 m from a road; thus, there were a greater number of days per year where estimated daily maximum 1-hour concentrations on roads exceeded the health effect benchmark levels.
  - **100 ppb health effect benchmark level**: In the majority of study areas, exceedances of the 100 ppb health effect benchmark level were estimated to occur on roadways for most days of the year when air quality was adjusted to simulate just meeting the then-existing standard. Most study areas were estimated, on average, to have between 100 and 300 days per year with daily maximum 1-hour on-road NO_2 concentrations ≥ 100 ppb. The mean number of days per year where estimated on-road concentrations were ≥ 100 ppb was always greater than that estimated using concentrations at ambient monitoring locations (e.g., up to 18 days per year for a standard level of 50 ppb, 257 for a standard level of 100 ppb, 343 for a standard level of 150 ppb, and 351 for a standard level of 200 ppb, based on the 98^{th} percentile of daily maximum 1-hour concentrations, averaged over three years).
  - **200 and 300 ppb health effect benchmark levels**: Even considering the higher health effect benchmark levels, most study areas were estimated, on average, to exceed these benchmark levels on roadways when air quality was adjusted to simulate just meeting the then-existing annual standard. Most study areas were estimated, on average, to have between 25 and 100 days per year with daily maximum 1-hour on-road NO_2 concentrations ≥ 200 ppb. All study areas evaluated, except one, were estimated to have on-road NO_2 concentrations ≥ 300 ppb. Four of these study areas

were estimated, on average, to experience an average of greater than 20 days per year with on-road NO_2 concentrations ≥ 300 ppb.

5.1.1.2 Key Uncertainties

An advantage of this approach to estimating potential health risk is its relative simplicity; however, there were a number of important uncertainties identified (US EPA, 2008b, section 7.4). One of the most important uncertainties overall was related to the spatial representation of the ambient monitors, hence part of the reasoning to revise ambient monitoring networks at the conclusion of the last primary NO_2 NAAQS review to include monitoring near roadways. To overcome this lack of near-roadway measurement data in the 2008 REA, and as briefly described above, we developed a simple statistical model using measurement data reported in a limited number of peer-reviewed studies to estimate on-road NO_2 concentrations. In doing so, this statistical model was characterized as having moderate or greater uncertainty in estimating on-road NO_2 concentrations, both in potentially under- and over-estimating the number of exceedances of health effect benchmark levels. In addition, the proportional adjustment applied to ambient air quality measurements to simulate just meeting the existing and alternative standards was characterized as another important uncertainty, particularly when adjusting concentrations upwards to meet or approach concentrations reflecting the existing primary annual NO_2 standard. Further, the selection of health effect benchmark levels used to characterize risk was based on controlled human exposure studies that used mild asthmatics. In the absence of information regarding the potential health response of persons characterized as having moderate or severe asthma, we characterized the health effect benchmark level selection as an important uncertainty.

5.1.2 Human Exposure Assessment

In the second approach, we used an inhalation exposure model to generate more realistic estimates of personal NO_2 exposure concentrations and compared those estimates of personal exposure to the health effect benchmark levels. The EPA's Air Pollutants Exposure model (APEX) probabilistically estimated individual exposures considering the time people spend in different microenvironments and the variable NO_2 concentrations that occur within these microenvironments across time, space, and microenvironment type, including estimation of on- and near-roadway exposure concentrations (U.S. EPA, 2008b, section 8.2). The EPA's air dispersion model (AERMOD) was used to estimate hourly NO_2 concentrations occurring at a census tract level and at roadway receptors, considering emissions from stationary, area-wide, and on-road mobile sources (U.S. EPA 2008b, section 8.4). This approach to assessing exposures at that time was more resource intensive than using ambient measurements as a surrogate for exposure as discussed in section 5.1.1 above; therefore, only one specific study area was selected for analysis (four counties comprising the core Atlanta, GA metropolitan statistical area, or MSA). Although the geographic scope of this analysis was restricted, the approach provided realistic estimates of NO_2 exposures, particularly those exposures associated with important emission sources of NO_X and NO_2, and served to complement the results of the broad NO_2 air quality characterization.

For the characterization of risks in the exposure modeling analysis, staff used the same range of short-term potential health effect benchmark levels described above in the air quality characterization summarized in section 5.1.1 (i.e., 1-hour NO_2 concentrations of 100, 150, 200, 250, and 300 ppb) and considered the same air quality scenarios (recent "as is" ambient concentrations and ambient concentrations adjusted to just meet the existing and potential alternative standards, though using only years 2001-2003).[59] Asthmatic school-age children (5 to 17 years of age) and all asthmatics (0 to 99 years of age) were considered the most important exposure study groups in this assessment based on their having potentially increased health risk to NO_2 exposure concentrations (U.S. EPA, 2008a, section 4.3). Exposure estimates for asthmatic school-age children were segregated from that estimated for the broader asthmatic population group because of their potential to have greater participation rate and time engaged in outdoor activities, thus possibly increasing their NO_2 exposures. When personal exposures for either exposure study group were simulated, the output of the analysis was an estimate of the number of individuals at risk for experiencing daily maximum 1-hour levels of NO_2 concentrations of ambient origin that exceeded particular health effect benchmark levels. An advantage of using potential health effect benchmark levels based on evidence from controlled human exposure studies to characterize health risks in this exposure modeling approach was that the effects observed in these studies clearly resulted from NO_2 exposure. This was in contrast to using health effects associated with ambient NO_2 concentrations in epidemiological studies (as discussed in the third approach described in section 5.1.3 below), which can also be associated with pollutants that co-occur with NO_2 in the ambient air.

5.1.2.1 Key Observations

- Estimated daily maximum 1-hour exposures at or above potential health effect benchmark levels using APEX were largely a function of roadway-related exposure concentrations (greater than 99 percent). Of these exposures, approximately 70 percent resulted from in-vehicle exposures, with the remainder associated with outdoor near-road exposures. Overall, when simulating air quality that just meets the then-existing annual

[59] This three-year period was selected to bound the most recent year of NO_X emissions data available (i.e., 2002) and used to model ambient concentrations at the time our exposure assessment was conducted (U.S. EPA, 2008b)

standard, virtually all asthmatics in Atlanta were estimated to experience six or more daily maximum 1-hour exposures per year to NO_2 concentrations above the highest health effect benchmark level evaluated (i.e., >300 ppb), indicating the extremely limited ability of the then-existing annual standard at that time to protect against daily maximum 1-hour exposures at or above any of the selected health effect benchmark levels (U.S. EPA, 2008b, section 8.10).

- **100 ppb health effect benchmark level**: For all air quality scenarios considered, more than 90 percent of all asthmatics in Atlanta were estimated to be exposed to concentration > 100 ppb at least one time per year. Of the daily maximum 1-hour alternative standard levels evaluated, 50 ppb was the only standard level estimated to reduce repeat daily maximum 1-hour NO_2 exposures above 100 ppb compared to recent air quality concentrations.
- **200 ppb health effect benchmark level**: Of all the air quality scenarios considered, only the 98th and 99th percentile daily maximum 1-hour alternative standards set at 50 ppb were estimated to reduce the percent of asthmatics exposed at least one time per year to concentrations > 200 ppb (by approximately 40 to 50 percent) relative to recent air quality concentrations.
- **300 ppb health effect benchmark level**: Of all the air quality scenarios considered, only alternative standard levels set at 50 ppb or 100 ppb were estimated to reduce the percent of asthmatics exposed at least one time per year to concentrations > 300 ppb (by approximately 80 percent and 15 percent, respectively) relative to recent air quality concentrations.

5.1.2.2 Key Uncertainties

The same important uncertainties exist for the exposure modeling results as described in section 5.1.1.2 above for the air quality characterization where similar approaches were used (i.e., proportional air quality adjustment approach and selection of health effect benchmark levels). One important uncertainty identified as specific to the exposure assessment was the AERMOD estimated concentrations used to represent the air quality surface across the Atlanta study area (U.S. EPA, 2008b, section 8.12). An evaluation with limited ambient monitor measurement data suggested a potential bias in overestimating ambient concentrations, potentially associated with uncertainty in mobile source emissions and/or diurnal profiles used as input (among other sources of uncertainty) (U.S. EPA, 2008b, section 8.4.8). Given the few monitors available and overall confidence in the AERMOD system and other input data, it was difficult to reasonably justify adjusting all estimated concentrations across the entire 4-county modeling domain based on the differing concentrations observed at the few monitor locations, thus they were used without adjusting for this observed difference. An additional uncertainty, though not specifically identified as an exposure uncertainty in the prior assessment, was the similar factors approach used to adjust 1-hour AERMOD ambient concentrations to estimate on- and near-roadways concentrations. While AERMOD estimated 1-hour NO_2 concentrations occurring on roadway link-based receptors, these on-road concentrations could not be used directly as an input to APEX based on its existing configuration. Thus, an on-road adjustment factor was developed from the AERMOD estimated on-road and census tract level concentrations (U.S. EPA, 2008b, section 8.7.2.5). These new on-road adjustment factor distributions used by APEX, along with the number of estimated on-road peak concentrations, were compared with those used for the air quality characterization (U.S. EPA, 2008b, section 8.4.8.3). The two similar, though independently developed, concentration adjustment approaches were found to be comparable across a wide range of estimated values, though they diverged at the upper percentiles of the distribution.[60] And finally, in a limited set of targeted exposure analyses, exposures were also modeled considering indoor source emissions (U.S. EPA, 2008b, section 8.7.2.1).[61] The characterization of indoor source emissions of NO_2 and estimated air exchange rates used to simulate indoor microenvironments was considered an important uncertainty.

5.1.3 Epidemiological-based Human Health Risk Assessment

In the third approach, respiratory-related l emergency department visits were estimated as a function of short-term ambient NO_2 concentrations measured at a fixed-site monitor representing ambient air quality for an urban area (U.S. EPA, 2008b, chapter 9). This health endpoint was selected because the 2008 ISA reported several epidemiological studies with observed positive associations between ambient NO_2 concentrations and emergency department visits and hospitalizations for all respiratory diseases and asthma (U.S. EPA, 2008a, section 3.1.6). In this type of risk estimation approach, concentration-response functions were based on findings from NO_2 epidemiological studies that relied on fixed-site, population-oriented, ambient monitors as a surrogate for actual ambient NO_2 exposures and were used to estimate the impact of daily maximum 1-hour ambient NO_2 concentrations, as measured at a single fixed-site monitor, on emergency department visits (U.S. EPA, 2008b, section 9.3). By focusing on a different health endpoint from the first two approaches described above, this epidemiological-

[60] See Figure 8-8 and Table 8-7 of the 2008 REA (U.S. EPA, 2008b, pp. 175 to 176). While the divergence between the two on-road concentration estimations was noteworthy, particularly at the upper percentiles of the distribution, important differences in the data used to develop the two approaches were likely a highly influential contributing factor. For example, the on-road adjustment factor used in the exposure modeling approach used 1-hour concentrations, while the on-road adjustment factor used in air quality characterization approach was developed from measurement data time averaged over 7 to 14 days. It is likely that the latter approach smoothes the distribution of possible concentration ratios by using the long-term time-averaged concentrations, though we believe it is reasonable to still highlight this issue here as an important uncertainty in the exposure assessment conducted for the last review.

[61] While potentially important in understanding health effects and the total exposure/health risk from NO_2, exposures resultant from indoor sources of NO_2 have limited relevance in understanding health risk associated with ambient concentrations.

based approach provided additional perspective on the potential public health impacts resulting from NO_2 exposures.

Because of the limited number of epidemiological studies reporting concentration-response (C-R) functions and the limited availability of other data needed for a quantitative risk assessment (e.g., baseline incidence rates), this type of health risk assessment was only conducted in one study area (Atlanta, GA) using C-R functions extracted from one study (Tolbert et al., 2007). The same general air quality scenarios described in section 5.1.1 above were evaluated (i.e., ambient concentrations *as is* and those adjusted to just meeting the then-existing annual and potential alternative daily maximum 1-hour standard levels), using ambient air quality data from 2005 to 2007, the most recent ambient monitoring data available at the time the assessment was conducted and similar to the years of air quality used in the epidemiological study in determining C-R functions (1993 through 2004) (Tolbert et al., 2007).

5.1.3.1 Key Observations

- **Health risks associated with just meeting the then existing annual standard**: Central estimates of annual NO_2-related respiratory emergency department visits associated with air quality adjusted upward to simulate just meeting the then-existing annual standard (based on 2006 to 2007 air quality data) range from 8.1 to 9.0 percent of total incidence (or 9,800 to 10,900 NO_2-related incidences per year) based on single-pollutant models and from 1.7 to 7.7 percent (or 3,100 to 9,400 NO_2-related incidences per year) based on two-pollutant models that included either CO, O_3, particulate matter 10 micrometers or less in diameter (PM_{10}), or a three pollutant model that included both O_3 and PM_{10}.
- **Health risks associated with just meeting alternative daily maximum 1-hour standards**: Central estimates of annual NO_2-related respiratory emergency department visits associated with air quality adjusted to simulate just meeting a 100 ppb, 1-h daily maximum, 98^{th} percentile standard (based on 2005 to 2007 air quality data) ranged from 3.9 to 4.3 percent of total incidence based on single-pollutant models and from 0.8 to 3.7 percent based on co-pollutant models. Central estimates of annual NO_2-related respiratory emergency department visits associated with air quality adjusted to simulate just meeting a 50 ppb, 1-h daily maximum, 98^{th} percentile standard (based on 2005 to 2007 air quality data) ranged from 2.0 to 2.2 percent based on single-pollutant models and from 0.4 to 1.9 percent based on the same above mentioned co-pollutant models.

5.1.3.2 Key Uncertainties

A few of the same important uncertainties exist for the health risk modeling results as described in sections 5.1.1.2 and 5.1.2.2 above for the air quality characterization and exposure modeling assessments where similar approaches were used (i.e., uncertainties related to the proportional air quality adjustment approach and the spatial representativeness of air quality data, in general). In addition, two uncertainties unique to the epidemiological-based health risk assessment approach recognized as important included (1) the appropriateness of the selected risk model (i.e., overall form for concentration-response functions and the presence or not of a threshold) and (2) the adequacy of the ambient NO_2 monitors to serve as a surrogate for population exposure (U.S. EPA, 2008b, section 9.6).

5.2 CONSIDERATION OF QUANTITATIVE ASSESSMENTS FOR THIS REVIEW

This discussion is focused particularly on considering the extent to which newly available scientific evidence and tools/methodologies are available to inform our understanding of the key areas of uncertainty identified in the 2008 REA as discussed in sections 5.1.1.2, 5.1.2.2 and 5.1.3.2 above. As outlined in Table 2-1 above, the EPA plans to release an REA Planning Document for consultation with CASAC and for public comments in November 2014 that will consider the extent to which new quantitative risk and exposure assessments will be appropriate to conduct in the current review. CASAC review and public comments on the draft IRP will be considered in developing the REA Planning Document (Frey, 2014).

Some key areas being considered by staff, including types of data, methodologies and tools, are identified and summarized below. Building upon each of the three approaches used to estimate exposure or health risk in the previous review, we summarize the potential areas where additional information, if available, would provide reasonable substance to address key uncertainties identified in the previous review. We then discuss the potential utility and impacts of this new information to improve upon the assessments performed in the prior review.

In evaluating the appropriateness of conducting new assessments, it is worth mentioning a few overarching considerations. For each of the three approaches used in the 2008 REA, the EPA staff used a mainly qualitative characterization of uncertainty that was supplemented with information generated from a number of targeted sensitivity analyses. Where appropriate data and methodologies are identified in the current review, it could be informative to conduct new sensitivity analyses of important model input variables (e.g., generate a broader range of risk estimates using alternative concentration-response functions) and perhaps better characterize uncertainty through quantitative analyses (e.g., propagate and evaluate uncertainties of varied model inputs through estimated exposure concentrations). Further detailed discussions regarding the types of analyses, data needed, and methods to be used, all taken in context with available resources, will be described in the REA Planning Document.

5.2.1 Air Quality Characterization

Table 5-1 summarizes the potentially important uncertainties where additional information, if available, would provide reasonable substance to the discussion of improving the air quality characterization performed in the prior review (U.S. EPA, 2008b, section 7.4).

Table 5-1. Information (data, methods, models, etc.) identified as potentially important and/or newly available to inform the air quality characterization for the current review.

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining from 2008 REA		Consideration of Potential Utility and Impact of Information Newly Available in This Review Could Have on Assessment
	Sub-group	**Description**	
Ambient Monitor Spatial and Temporal Representativeness	Near-Road Ambient Monitoring Data	There is a general lack of existing ambient monitoring data near-roads in most U.S. urban areas. This, combined with the potential for short-term high NO_2 concentrations occurring in these locations creates a significant uncertainty regarding how often on- and near-road NO_2 concentrations may exceed exposure levels of concern. This uncertainty served as a driver for revising ambient monitor siting.	The near-road monitoring network is to be developed in three phases: the first set of 52 monitors to begin measuring near-road NO_2 concentrations starting January 1, 2014, followed by the addition of 23 monitors by January 1, 2015, and phase III adding 51 monitoring sites (see section 5.2 of this IRP). Given this schedule, it is possible that there will be a lag in the availability of the newest near-road ambient monitor concentration data due to quality assurance reviews, potentially delaying the utilization of this new and important data in this NO_2 review.
	Long-term Exposures	The annual average standard of 53 ppb was retained in the last review due to some evidence suggesting NO_2 concentrations had a causal relationship with respiratory-related health effects. Newly identified for this review would be the consideration of how long-term, though spatially variable, ambient NO_2 concentrations could adversely affect health.	Model and data fusion techniques could improve the estimation of the spatial and temporal distribution of NO_2 concentrations across urban areas (not simply area-wide and on-road distinctions), generally accounting for increased emission sources and other influential factors within a defined spatial sector. There could be utility in estimating screening level long-term NO_2 concentrations if there were a newly defined long-term health effect benchmark level of interest.

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining from 2008 REA		Consideration of Potential Utility and Impact of Information Newly Available in This Review Could Have on Assessment
	Sub-group	**Description**	
Approach Used to Estimate On-Road NO_2 Concentrations	Exponential Relationship Used to Characterize Concentration Decline with Increasing Distance from Roads	Based on a literature review of all available studies (both U.S and non-U.S.) that measured both near- and away from road NO_2 concentrations conducted by OAQPS staff at the time of the last review, our analysis indicated that NO_2 concentrations decline with distance from a roadway; thus, an exponential relationship was used to derive our on-road adjustment factors. Variability in the form of the relationship could result in the derivation of different factors and potentially influence estimated on-road NO_2 concentrations, though of course any estimates will be dependent on the form and parameters describing the relationship.	We could use air quality models, e.g., AERMOD dispersion model combined with output from the photochemical model CMAQ, to characterize near-source gradients (roadways and combustion sources). In addition, we could evaluate alternative relationships (e.g., linear, biphasic, etc.), better characterize the distributions of on-road adjustment factors, and consider other factors used to define ambient monitors if there are studies newly available (modeling and/or measurement) that indicate alternative relationships exist outside of the range already considered in the 2008 REA. Further, in the absence of new data from the complete near-road monitoring network, additional information regarding near-road concentration gradients could be characterized from existing and new published literature and/or current ambient monitoring databases.
	Distribution of On-road Adjustment Factors	Two distributions of NO_2 on-road adjustment factors were derived and used in their empirical form, one for summer months ranging from 1.5 to 3.7 (median 1.9), the other non-summer months ranging from 1.2 to 2.5 (median 1.75).	
	Effect of Using Longer-term (weekly) Data versus Hourly Data to Estimate On-road Adjustment Factors	Data used to derive on-road adjustment factors were all from data collected over 1-week or longer term measurements. It is possible that there is variability in the derived relationship over different time-averaging periods and concentrations. Thus, there is uncertainty in application of the time-averaged derived distribution to accurately estimate variability in hourly NO_2 concentrations.	
	Definition of monitors minimally influenced by roadway emissions to use in the calculation of on-road concentrations	We used any ambient monitor that was > 100 meters from a road to estimate on-road concentrations. At that time, this distance alone was considered a reasonable criterion given the literature reviewed and patterns noted in the then-existing ambient monitoring data. As stated in the prior REA section 7.4.6, it is possible that some of the ambient monitors used to estimate on-road concentrations	

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining from 2008 REA		Consideration of Potential Utility and Impact of Information Newly Available in This Review Could Have on Assessment
	Sub-group	Description	
		could have been influenced by emissions from a non-road NOx source.	
Approach Used to Simulate Just Meeting Potential Air Quality Standard Scenarios	N/A	Six study areas (Los Angeles, Atlanta, New York, Philadelphia, Denver, and Chicago) were used to evaluate existence of a proportional relationship between high concentration and low concentration years. The proportional adjustment factors derived from the area design monitor was similarly applied to adjust all ambient monitors within a given study area. Deviation from proportionality (where it exists) at any monitor could result in either over or under-estimation of concentrations.	New, adjusted ambient air quality data sets could be developed if there are studies newly available that indicate alternative approaches to adjusting air quality exist that would generate demonstrably different data sets outside of those already considered in the 2008 REA. This could include additional analysis of ambient monitor data trends and air quality model based approaches.
Selection of Health Effect Benchmark Levels	N/A	A generally common and important uncertainty in controlled human exposure studies is the limited number of study subjects as well as limits to the type of pre-existing health conditions subjects may have, particularly if the health condition affords the subject with heightened effects sensitivity to the pollutant exposure. Further, there is a lack of exposure data from study groups at potentially at-risk lifestages (e.g., pregnant women, children).	New estimates of benchmark exceedances could be developed if there are studies newly available that indicate alternative health effect benchmark levels should be considered outside of the range already evaluated in the 2008 REA. This would also apply where any new health endpoints are identified beyond those associated with respiratory effects due to short-term exposures. Further, additional analysis of existing human exposure study data sets and an improved characterization of adversity could be possible using newly identified approaches or information.

The major uncertainties identified in section 5.1 above based on the 2008 REA were related to (1) ambient monitoring representativeness, (2) the approach used to estimate on-road NO_2 concentrations, (3) the approach used to estimate the existing and alternative air quality standard scenarios, and (4) the selection of health effect benchmark levels.

5.2.2 Human Exposure Assessment

In addition to some of the uncertainties identified and described above in section 5.2.1, three additional uncertainties were identified as specific to the exposure assessment conducted for the 2008 REA. The major uncertainties identified in section 5.1.2.2 above that warrant additional discussion here include (1) the use of unadjusted AERMOD estimated ambient NO_2 concentrations as input to APEX, (2) the factors approach used to estimate in-vehicle and near-road NO_2 concentrations, and (3) the limited input data used to estimate the contribution of a single source emission (indoor gas stoves) to a simulated person's total NO_2 exposure (Table 5-2).

Table 5-2. Information (data, methods, models, etc.) identified as potentially important and/or newly available to inform the exposure assessment for the current review.

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining from 2008 REA: Description	Consideration of Potential Utility and Impact of Information Newly Available in This Review Could Have on Assessment
Use of Unadjusted AERMOD Estimated Concentrations as Input to APEX	AERMOD was used to reasonably represent spatial variability in ambient NO_2 concentrations across an urban area where using limited monitor data alone cannot. Even though comparisons made with limited ambient monitoring data suggest AERMOD estimated ambient NO_2 concentrations may have been systematically over-estimated, concentrations were not adjusted for this potential upward bias.	We could further evaluate existing data generated for the 2008 REA (both the modeled exposures and ambient concentrations) to approximate the potential impact of developing a newly modeled alternative ambient concentration data set. In addition, we could use AERMOD, with recent improvements by EPA, to improve the quality and characterization of the ambient concentration data set for input to APEX.
Approach Used to Estimate In-Vehicle and Near-Road Microenvironmental (ME) Concentrations in APEX	In-vehicle and near-road NO_2 concentrations were estimated using a similar concentration adjustment approach described above for the air quality characterization, only differing in that the relationship between on-road and away-from-road receptor concentrations were estimated using AERMOD and that penetration/decay inside motor vehicles was accounted for by APEX. While the distribution of adjustment factors was stratified by time-of-day (11PM-6AM, 6AM-7PM, 7PM-11PM) and seasons (summer and not-summer) (U.S. EPA, 2008b, Table B-42), it is possible that use of a factors approach and randomly sampling from distributions occasionally leads to a mismatching of on-road adjustment factors and the away from road census block concentrations, leading to either over or under estimated on-road NO_2 concentrations. In addition, near-road NO_2 concentrations were considered at the same level as the estimated on-road concentrations without additional adjustment for their occurring at a given distance from the road. Note also, APEX estimated ME concentrations that varied across the study area based on workplace commutes of simulated individuals.	APEX has been recently modified to allow for a time series of on-road concentrations, and can be stratified by a geographic identifier, as an input to estimating in-vehicle exposure concentrations. Thus, APEX is capable of utilizing the AERMOD on-road concentrations themselves rather than using a factors-based approach. In the absence of having a time-series of on-road concentrations for potential study areas of interest, it is possible that new factors or concentration distributions could be developed and used to estimate near-road microenvironmental concentrations, where newly published data are identified.

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining from 2008 REA	Consideration of Potential Utility and Impact of Information Newly Available in This Review Could Have on Assessment
	Description	
Limited Input Data Used to Estimate Contribution of Indoor Source Emissions of NO_2 to Total Exposures	For a few APEX simulations, we estimated exposures associated with ambient NO_2 concentrations along with those associated with a single indoor emission source (gas stoves). The estimation was based on limited input data readily available to represent variability in the source emissions, population prevalence of gas stoves, frequency of source use per cooking event and times of occurrence, and indoor removal rates.	Estimation of total exposure to NO_2 (i.e., that arising from combined ambient, personal, and indoor sources) is an important consideration in understanding total NO_2-related health risk. However, the role and relevance of understanding the contribution of personal and indoor source emissions to exposures when setting ambient air quality standards would need to be further evaluated considering resource availability and in addressing other key assessment priorities.

5.2.3 Controlled Exposure-based Human Health Risk Assessment

One question to be raised for this review is whether or not there are newly identified controlled human exposure studies in addition to the studies previously considered in the 2008 REA that substantially expand our understanding of respiratory-related (or other) adverse health effects associated with short-term NO_2 exposures. If new studies are identified and adequate data are available to develop exposure–response (E-R) relationships, these functions could be combined with NO_2 exposures (e.g., output from a population-based exposure model) and thus, warrant conducting a quantitative risk assessment based on the controlled human exposure evidence. In addition, having new human exposure study data would not necessarily preclude a comparison of earlier approaches (e.g., meta-analyses) used to develop the health effect benchmark levels with any newly identified or alternative approaches identified in this review.

5.2.4 Epidemiological-based Human Health Risk Assessment

In addition to a few relevant uncertainties identified in section 5.2.1 above, two additional uncertainties were identified as unique to the epidemiological-based human health risk assessment conducted for the 2008 REA. The major uncertainties identified in section 5.1.3.2 above that warrant additional discussion here include (1) the selection of the C-R function and (2) the ability of the ambient NO_2 monitors to serve as a surrogate for population exposure. The risk assessment conducted in the last review focused on one health endpoint (i.e., respiratory-related emergency department visits) in one urban study area (Atlanta). An important issue in this review is whether or not additional information is available to consider conducting a quantitative risk assessment that would include additional health effect endpoints and/or additional urban study areas. The EPA's decisions regarding the conduct of and associated scope of an REA for this review can be informed by the ISA causality determinations,[62] in addition to the availability of appropriate data for quantitative analyses (e.g., availability of C-R functions, baseline incidence data, etc.). General criteria to be evaluated in identifying potential candidate studies to inform a quantitative risk assessment include the following:

- the study was a published, peer-reviewed study that had been evaluated in the ISA for the pollutant of interest and judged adequate by the EPA staff for purposes of inclusion in the risk assessment based on that evaluation;
- it directly measured, rather than estimated, the pollutant of interest on a reasonable proportion of the days in the study; and

[62] The strength of the ISA causal determinations serves as a preliminary screen in identifying health endpoints to consider in conducting our health assessments; historically, we have generally focused these assessments on health endpoints having either 'causal' or 'likely to be causal' determinations.

- it preferably included both single- and co-pollutant models.

Table 5-3 summarizes the potentially important uncertainties where additional information, if available, would provide reasonable substance to the discussion of improving the epidemiological-based human health risk assessment performed in the prior review.

Table 5-3. Information (data, methods, models, etc.) identified as potentially important and/or newly available to inform the epidemiological-based risk assessment for the current review.

Major Uncertainty or Limitation	Uncertainty/Limitation Remaining From 2008 REA	Consideration of Potential Utility and Impact that Information Newly Available in this Review Could Have on Assessment
	Description	
Form of Concentration - Response Functions	In the epidemiological-based health risk assessment, a single short-term NO_2 epidemiological study was used to estimate respiratory-related health risk (emergency department visits) in Atlanta (Tolbert et al., 2007). A log-linear form assuming no threshold was selected, and both single and co-pollutant models were employed. An additional study by Ito et al. (2007) conducted in New York City was also identified but due to time and resource constraints, was not included in the 2008 REA.	It is possible that new epidemiological-based health risk assessments in additional study areas could be performed using new or alternative C-R functions and potentially assuming alternative model specifications if such published studies are available.
Adequacy of the Ambient NO_2 Monitors to Serve as a Surrogate for Population Exposure	For the epidemiological-based health risk assessment developed from data reported in Tolbert et al. (2007), concentrations from a single ambient monitor were used to represent area-wide exposures.	While this is a common approach used in these types of assessments, it is possible that the effect of using a single monitor could be further evaluated where new studies have employed additional or alternative monitors in estimating health risk.

5.3 SCIENTIFIC AND PUBLIC REVIEW

The REA Planning Document will be distributed to the CASAC for their consideration and provided to the public for review and comment. The document will be the subject of a consultation with the CASAC at a public meeting or teleconference that will be announced in the *Federal Register*.

If, upon consideration of CASAC recommendations and public comments, the EPA concludes that development of a new REA, or updating or expanding the last assessment, is warranted, staff will take into account comments received from CASAC and the public in designing and conducting the assessment. In such a case, staff would prepare at least one draft of the assessment for CASAC review and public comment. Review would be conducted by CASAC and discussed at a public meeting that would be announced in the *Federal Register*. Based on past practice by CASAC, the EPA expects that key advice and recommendations for revision of the document would be summarized in a letter to the EPA Administrator. In revising the draft REA document, the EPA would take into account any such recommendations and also consider comments received from the public, both at the meeting itself and directly in writing. A final document would then be made available on an EPA website, with its public availability announced in the *Federal Register*.

If upon consideration of CASAC and public comments on the REA planning document, the EPA concludes that development of a new REA is not warranted, a REA will not be developed and the PA for this review will draw from the REA developed in the last review in light of analyses or assessments made in the REA planning document with regard to the current evidence pertaining to exposure and risk, as well as the evidence presented in the ISA and other documents prepared for the review. Review steps for the PA are described in section 7.1 below.

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6 AMBIENT AIR MONITORING

In the course of NAAQS reviews, aspects of the methods for sampling and analysis of the NAAQS pollutant, and the current network of monitors, including their physical locations and monitoring objectives, are reviewed. The methods for sampling and analysis of each NAAQS pollutant are generally reviewed in conjunction with consideration of the indicator element for each NAAQS. Consideration of the ambient air monitoring network generally informs the interpretation of current data on ambient air concentrations, and helps identify if the monitoring network is adequate to determine compliance with the existing or, as appropriate, a potentially revised NAAQS. This chapter describes plans for considering these aspects of the ambient air monitoring program for oxides of nitrogen which includes the indicator NO_2.

6.1 CONSIDERATION OF SAMPLING AND ANALYSIS METHODS

Generally, in order to be used for regulatory purposes, ambient NO_2 concentration data must be obtained using federal reference methods (FRMs) or federal equivalent methods (FEMs) which are designated by the Agency in accordance with 40 CFR part 53. As described in section 1.3 above, NO_2 is the indicator for the oxides of nitrogen NAAQS and has been routinely measured by chemiluminescent FRMs since the early 1980s.[63] However, in 2012 a photolytic chemiluminescent method became commercially available and was approved by the Agency as an FEM (77FR 32632, June 1, 2012). This new FEM is expected to be used to some degree in the ambient NO_2 monitoring network but is not expected to displace a majority of traditional chemiluminescence FRMs.

Both the chemiluminescent FRM and the photolytic chemiluminescent FEM are indirect measurement techniques for NO_2. In the chemiluminescent FRM, the analyzer can only detect NO in the sample stream and therefore utilizes a two-step process in determining the amount of NO_2 in ambient air. First, the analyzer determines the amount of NO in the sample air. Second, the analyzer re-routes air flow so that the sample air stream passes over a heated molybdenum oxide catalytic converter reducing a large majority (if not all) of the oxidized nitrogen species present in the sample stream to NO, before again measuring the amount of NO in the sample. The analyzer then subtracts the measured, actual ambient NO, determined in the first step, from the amount measured in the second step, allowing for the determination of NO, NO_2, and NO_X (where $NO_X = NO + NO_2$). This long-standing method is subject to interference (U.S. EPA, 2013b, section 2.4.1). This documented interference can produce a positive bias if higher

[63] See 40 CFR part 50, Appendix F.

oxidized nitrogen species such as nitric acid (HNO_3) or peroxyacetyl nitrate (PAN) make it to the converter, where they can be reduced by some degree to NO and subsequently counted as NO_2. While similar in the use of a two-step process of indirectly determining NO_2 concentrations as the chemiluminescent FRM, the photolytic-chemiluminescence FEM carries out the reduction of NO_2 to NO in a photolytic converter with a known converter efficiency rate. This method is more specific to NO_2 and, thus, is not subject to the same positive bias potential as the chemiluminescent FRM. Data produced by both of these FRM and FEM analyzers include NO, NO_2, and NO_X measurements which are all routinely logged by state and local agencies whom typically report the hourly average values to the EPA's Air Quality System (AQS).

The Agency is aware of a number of recent technological advances for direct measurements of NO_2 which are now or may become commercially available as FEMs (e.g., cavity attenuated phase shift (CAPS) spectrometry and cavity ring-down spectroscopy). The first of these new methods, CAPS spectrometry, had two models approved recently as FEMs (78 FR 67360, November 12, 2013; 79 FR 34734, June 18, 2014).[64] These new direct measurement techniques are specific to NO_2. This would create a notable, anticipated difference with the traditional chemiluminescent FRMs in that these direct measurement methods will only provide NO_2 data and will not provide NO or NO_X data. The Agency recognizes the advantages of these new direct measurement technologies including: (1) increased accuracy, via a lack of potential positive bias in measured values, and (2) increased confidence in monitored NO_2 values. However, there may also be potential drawbacks if these new methods largely replace the current network of FRMs and photolytic-chemiluminescent FEMs as there would potentially be a loss of monitored NO. As a result, the Agency seeks to determine what might be an appropriate balance between the use of the "old" and "new" methods. More specifically, the sampling and analysis issues to be considered during the current review include the following:

- To what extent are additional direct NO_2 measurements available for consideration as an FEM?
- If new, direct NO_2 measurement methods become available and integrated into the ambient network, what would be the anticipated impact to subsequent air quality data analyses by potentially losing NO and NO_X measurements?

6.2 CONSIDERATION OF AIR MONITORING NETWORK REQUIREMENTS

The majority of data used to determine compliance with the NO_2 NAAQS are obtained from monitors operated by state, local, and tribal air monitoring agencies. These monitors are

[64] For a complete list of designated reference and equivalent methods, seehttp://www.epa.gov/ttn/amtic/files/ambient/criteria/reference-equivalent-methods-list.pdf.

required due to either federal regulation contained in 40 CFR Part 58, Appendix D, state implementation plans, industrial permits, other state or local based requirements, or voluntary actions. The monitoring networks support three major objectives: (1) to provide air pollution data to the general public in a timely manner; (2) to support compliance with NAAQS and emissions strategy development; and (3) to support air pollution research studies.

A review of the available NO_2 monitoring network and data was performed as part of the primary NO_2 NAAQS review completed in 2010. In conjunction with revising the primary standards in that review, the Agency promulgated minimum monitoring requirements to support the implementation of a new primary 1-hour NO_2 standard. The minimum requirements consisted of the following: (1) near-road monitors which would be placed in locations of expected maximum 1-hour NO_2 concentrations near heavily trafficked roads in urban areas; (2) monitors located to characterize areas with the highest expected NO_2 concentrations at the neighborhood and larger spatial scales (also referred to as "area-wide" monitors) (75 FR 6505 to 6506, February 9, 2010); and (3) a specific set of monitors in areas with susceptible and vulnerable[65] communities exposed to NO_2 concentrations that have the potential to approach or exceed the standards (75 FR 6509). The near-road NO_2 monitoring requirements were novel at the time of promulgation and stemmed from findings that roadway-associated exposures account for a majority of exposures to peak NO_2 concentrations (75 FR 6514). The area-wide and the susceptible and vulnerable communities monitoring requirements each minimally required approximately 52 and 40 monitors, respectively, and were consistent with traditional monitoring approaches. This meant the existing network did not require significant modification in order to satisfy these two requirements. Sites satisfying these two monitoring network requirements were identified and documented or became fully operational on or before January 1, 2013. Conversely, the near-road NO_2 monitoring network did not exist at the time of promulgation, and the Agency acknowledged that it would have to be designed, funded, and installed in its entirety.

One near-road NO_2 monitor is required in each Core Based Statistical Area (CBSA) having 500,000 or more persons, per 40 CFR part 58, Appendix D, section 4.3.2. A second near-road NO_2 monitor is required in those CBSAs having either (a) 2,500,000 persons or more or (b) any CBSA having 500,000 or more persons that also has one or more road segments carrying 250,000 or greater Annual Average Daily Traffic (AADT) counts. At each of the near-road NO_2

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[65] The terms susceptible, vulnerable, sensitive, and at-risk are commonly used to characterize population groups or lifestages at greatest risk for experiencing health effects associated with exposure to a specific pollutant(s). In finalizing revisions to the NO_2 monitoring network in 2010, the EPA required that an additional forty monitors, nationally, be sited to focused "primarily on communities where susceptible and vulnerable populations are located" (75 FR 6510). In this review, the Agency will use the term "at-risk populations and lifestages" for those groups with characteristics that increase the risk of pollutant-related health effects.

sites, the monitors are subject to all requirements in 40 CFR part 58 and its appendices, which include specific siting criteria such as having the monitor probe placed "…as near as practicable to the outside nearest edge of the traffic lanes of the target segment; but shall not be located at a distance greater than 50 meters, in the horizontal, from the outside nearest edge of the traffic lanes of the target road segment" and having the monitor probe placed between 2 and 7 meters above the ground.

The near-road NO_2 monitors are required to be installed in three phases (78 FR 16184, March 14, 2013). The first phase required one monitor in any CBSA of 1,000,000 or more persons to be operational by January 1, 2014. We anticipate that 52 near-road sites will be added in Phase 1. The second phase is for any second monitor required in a CBSA (those having 2,500,000 or more persons or those having 500,000 or more persons that also have one more road segments carrying 250,000 or greater AADT counts) to be operational by January 1, 2015. We anticipate 23 near-road sites will be added in Phase II. The third phase is for those monitors in CBSAs having between 500,000 and 1,000,000 persons, which are to be operational by January 1, 2017. We anticipate 51 near-road sites will be added in Phase III.

By the end of 2013, the ambient NO_2 monitoring network was estimated to have 391 NO_2 monitors in operation nationwide (see Figure 6-1). This estimate does not reflect the impending additions of the three-phased implementation of the near-road NO_2 monitors. We anticipate 126 near-road sites will be operational on or before January 1, 2017, potentially resulting in more than 500 NO_2 monitors nationwide when the NO_2 network is fully operational.

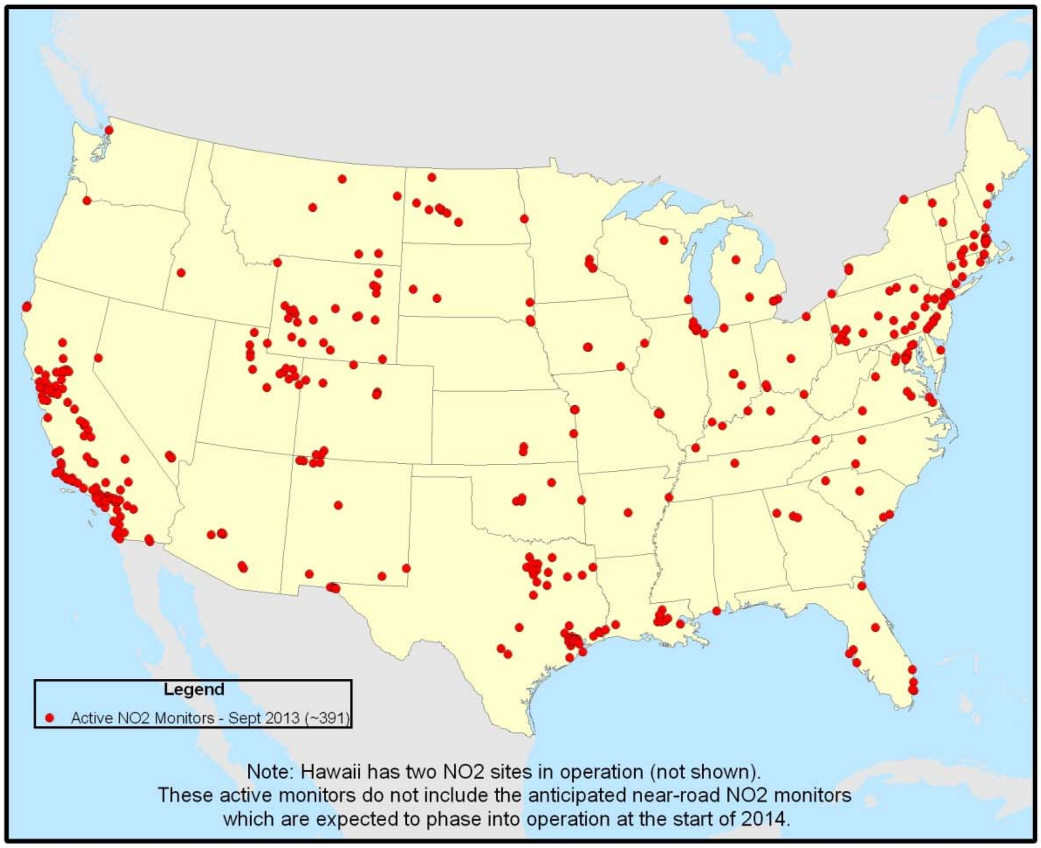

Figure 6-1. NO_2 Monitoring Network: Active monitors as of September 2013.

In the last review, there was limited near-road ambient NO_2 monitoring data. Analyses conducted as part of the 2008 REA (U.S. EPA, 2008b) along with public comment on the proposed rule were considered in reaching final decisions on how many and where near-road NO_2 monitors would be required. In particular, the 2008 REA considered estimates of on- or near-roadway exceedances in 17 urban areas associated with CBSA populations ranging from approximately 540,000 to 19,000,000 persons. Those analyses indicated that the areas under explicit consideration were estimated to experience NO_2 concentrations on or near roads that exceeded health benchmark levels.

In this review, the EPA will have the benefit of monitored near-road data for consideration in analyzing potential exposures and exceedances. Although the new near-road NO_2 monitoring network is not yet fully installed, data from newly operational monitors, plus data from more recent research efforts, may provide a clearer picture of what NO_2 concentrations are in the near-road environment, with the continued understanding that factors including traffic counts, fleet mix, congestion patterns, roadway design, terrain, and meteorology all play a major role in measured roadside NO_2 concentrations. The EPA plans to summarize the meta-data of near-road NO_2 monitoring sites (e.g., location, distance to road, probe height, target road AADT) to aid in the broad understanding of what the new near-road monitor data represent. The EPA also notes that many near-road NO_2 monitoring sites are expected to become multi-pollutant monitoring sites. For those CBSAs having 1,000,000 or more persons, both CO and $PM_{2.5}$ monitoring are required to be phased in from 2015 through 2017, at one site per CBSA (40 CFR part 58, Appendix D, sections 4.2.1 and 4.7.1). Further, the EPA has strongly encouraged state, local, and tribal air agencies to conduct multi-pollutant monitoring at near-road sites beyond those parameters that are required. Pollutants and metrics such as black carbon, ultrafine particles, toxics, ozone, meteorological parameters, and traffic counters and cameras have all been suggested for consideration (U.S. EPA, 2012). It is expected that many sites will have one or more of these additional measurements, which will increase the understanding of pollutant/traffic correlations, pollutant chemistry and fate, and provide information to improve our understanding of the role of oxides of nitrogen as a component of a complex mixture of air pollutants in the near-road environment.

Finally, with increasing availability of new near-road NO_2 monitoring data, the EPA anticipates that it may be in a position to re-evaluate the analyses underlying the minimum monitoring requirements promulgated in the 2010 revisions in this review. Any such analysis would be predicated on some framework or criteria to aid in the determination of whether a network design change is warranted and what modifications might be considered.

7 POLICY ASSESSMENT AND RULEMAKING

As outlined in section 1.2 above, the fourth and final stage of the NAAQS review is the preparation of a Policy Assessment (PA) and rulemaking notices. These two steps are described, respectively, in sections 7.1 and 7.2 below.

7.1 POLICY ASSESSMENT

The PA provides a transparent OAQPS staff analysis and staff conclusions regarding the adequacy of the current standards and potential alternatives that are appropriate to consider prior to the issuance of proposed and final rules. The PA integrates and interprets the information from the ISA and, if available, REA(s) to frame policy options for consideration by the Administrator. The PA is also intended to facilitate CASAC's advice to the Agency and recommendations to the Administrator on the adequacy of the existing standards or revisions that may be appropriate to consider, as provided for in the CAA. Staff conclusions in the PA are based on the information contained in the ISA; the REA, as available; and any additional staff evaluations and assessments discussed in the PA. In so doing, the discussion in the PA is framed by consideration of a series of policy-relevant questions drawn from those outlined in section 3.2 above, including the fundamental questions associated with the adequacy of the current standards and, as appropriate, consideration of alternative standards in terms of the specific elements of the standards: indicator, averaging time, level, and form.

The PA for the current review will identify conceptual evidence-based and risk/exposure-based approaches for reaching public health policy judgments. It will discuss the implications of the science and quantitative assessments for the adequacy of the current primary standards and for any alternative standards under consideration. The PA will also describe a broad range of policy options for standard setting, identifying the range for which the staff identifies support within the available information. In so doing, the PA will describe the underlying interpretations of the scientific evidence and risk/exposure information that might support such alternative policy options that could be considered by the Administrator in making decisions for the primary NO_2 standards. Additionally, the PA will identify key uncertainties and limitations in the underlying scientific information and in our assessments. The PA will also highlight areas for future health-related research, model development, and data collection.

In identifying a range of primary standard options for the Administrator to consider, it is recognized that the final decision will be largely a public health policy judgment. A final decision must draw upon scientific information and analyses about health effects and risks, as well as judgments about how to deal with the range of uncertainties that are inherent in the scientific evidence and analyses. Staff's approach to informing these judgments recognizes that the available health effects evidence generally reflects a continuum consisting of ambient concentrations at which scientists generally agree that health effects are likely to occur, through lower concentrations at which the likelihood and magnitude of the response become increasingly uncertain. This approach is consistent with the requirements of the NAAQS provisions of the CAA and with how the EPA and the courts have historically interpreted the CAA. These provisions require the Administrator to establish primary standards that are requisite to protect public health and are neither more nor less stringent than necessary for this purpose. As discussed in section 1.1 above, the provisions do not require that primary standards be set at a zero-risk level, but rather at a level that avoids unacceptable risks to public health, including the health of at-risk populations.[66]

Staff will prepare at least one draft of the PA document for CASAC review and public comment. The draft PA document will be distributed to the CASAC Oxides of Nitrogen Primary NAAQS Review Panel for their consideration and provided to the public for review and comment. Review by the CASAC will be discussed at a public meeting that will be announced in the *Federal Register*. Based on past practice by CASAC, the EPA expects that CASAC will summarize key advice and recommendations for revision of the document in a letter to the EPA Administrator. In revising the draft PA document, OAQPS will take into account any such recommendations and also consider comments received, from CASAC and from the public, at the meeting itself, and any written comments received. The final document will be made available on an EPA website, with its public availability announced in the *Federal Register*.

7.2 RULEMAKING

Following issuance of the final PA and the EPA management consideration of staff analyses and conclusions presented therein, and taking into consideration CASAC advice and recommendations, the Agency will develop a notice of proposed rulemaking. The proposed rulemaking notice conveys the Administrator's proposed conclusions regarding the adequacy of the current standards and any revision that may be appropriate. The EPA will submit a draft notice of proposed rulemaking to the Office of Management and Budget (OMB) for interagency review, to provide OMB and other federal agencies the opportunity for review and comment.

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[66] The at-risk population groups identified in a NAAQS review may include low income or minority groups. Where low income/minority groups are among the at-risk populations, the rulemaking decision will be based on providing protection for these and other at-risk populations and lifestages (e.g., children, older adults, persons with pre-existing heart and lung disease). To the extent that low income/minority groups are not among the at-risk populations identified in the ISA, a decision based on providing protection of the at-risk lifestages and populations would be expected to provide protection for the low income/minority groups.

After the completion of interagency review, the EPA will publish the notice of proposed rulemaking in the *Federal Register*. Monitoring rule changes associated with review of the primary NO_2 standards, and drawing from considerations outlined in Chapter 6 above, will be developed and proposed, as appropriate, in conjunction with this NAAQS rulemaking.

At the time of publication of the notice of proposed rulemaking, all materials on which the proposal is based are made available in the public docket for the rulemaking.[67] Publication of the proposal notice is followed by a public comment period, generally lasting 60 to 90 days, during which the public is invited to submit comments on the proposal to the rulemaking docket. Taking into account comments received on the proposed rule, the Agency will then develop a notice of final rulemaking, which again undergoes OMB-coordinated interagency review prior to issuance by the EPA of the final rule. At the time of final rulemaking, the Agency responds to all significant comments on the proposed rule.[68] Publication of the final rule in the *Federal Register* completes the rulemaking process.

[67] The rulemaking docket for the current primary NO_2 NAAQS review is identified as EPA-HQ-OAR-2013-0146. This docket has incorporated the ISA docket (EPA–HQ–ORD–2013–0232) by reference. Both dockets are publicly accessible at www.regulations.gov.

[68] For example, Agency responses to all substantive comments on the 2009 notice of proposed rulemaking in the last review were provided in the preamble to the final rule and in a document titled *Responses to Significant Comments on the 2009 Proposed Rule on the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (July 15, 2009; 74 FR 34404)* (U.S. EPA, 2010).

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APPENDIX A

DRAFT OUTLINE FOR INTEGRATED SCIENCE ASSESSMENT FOR OXIDES OF NITROGEN – HEALTH CRITERIA

Preamble	Process of ISA Development
(will be available online)	Literature Search
	Study Selection
	Evaluation of Individual Study Quality
	Evaluation, Synthesis, and Integration across Disciplines and Development of Scientific Conclusions and Causal Determinations
	EPA Framework for Causal Determinations
	Public Health Impact
	Approach to Classifying At-risk Factors
	Concepts in Evaluating Adversity of Health Effects
Preface	Legislative Requirements for the Primary NAAQS Review
	History of the Review of the Air Quality Criteria for the Oxides of Nitrogen and NAAQS for Nitrogen Dioxide
Executive Summary	
Chapter 1	**Integrative Summary**
1.1	ISA Development and Scope
1.2	Organization of the ISA
1.3	Sources of Oxides of Nitrogen to Human Exposure
1.4	Health Effects of Oxides of Nitrogen
	Causal determinations and key evidence for evaluated health effects including information related to dosimetry, modes of action, exposure assessment, and potential confounding factors
1.5	Evaluation of the Independent Effects of Nitrogen Dioxide
	Potential confounding by time-varying and individual- or population-level characteristics
	Potential confounding by copollutant exposures – multivariable models, indoor NO_2, traffic proximity and intensity, pollutant interactions or mixtures with oxides of nitrogen
1.6	Policy-Relevant Considerations
	NO_2 Exposure Metrics
	Lag Structure of NO_2-related Morbidity and Mortality Associations
	Concentration-Response Relationships and Thresholds
	Public Health Significance – Adversity of Effects, At-risk

[69]Sections for each of the major health effect outcome categories will include a review of the available evidence and conclude with the causal determination and summary of contributing evidence.

Chapter 6	**Integrated Health Effects of Long-term Exposure to Oxides of Nitrogen**[60]
6.1	Introduction
6.2	Respiratory Effects
6.3	Cardiovascular Effects
6.4	Reproductive and Developmental Effects
	Fertility, Reproduction, and Pregnancy
	Birth Outcomes
	Postnatal Development
6.5	Total Mortality
6.6	Cancer
Chapter 7	**Lifestages and Populations Potentially at Increased Risk for Health Effects Related to Exposure to Oxides of Nitrogen**
7.1	Introduction
7.2	Proximity to and Time Spent Near Major Roads
7.3	Genetic Factors
7.4	Pre-existing Disease/Conditions
7.5	Sociodemographic Factors (lifestage, socioeconomic status, race/ethnicity, sex)
7.6	Behavioral and Other Factors (diet, obesity, smoking, residential location)
7.7	Summary

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